CH CONVERGENCE HEPATOLOGY

Review Article

pISSN 3091-907X • eISSN 3092-3514

Convergence Hepatology 2026;2:1-15
https://doi.org/10.65633/ch.2026.2.1.1

Clinical Role of Radiotherapy in Hepatocellular Carcinoma: Evidence from Recent Prospective Studies and Meta-Analyses

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Received 2026. 3. 3.
Revised 2026. 4. 9.
Accepted 2026. 4. 14.

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Radiotherapy has long been investigated as a therapeutic modality in the management of hepatocellular carcinoma (HCC). Recently, updated clinical frameworks in the Barcelona Clinic Liver Cancer guidelines have allowed greater flexibility in integrating radiotherapy across disease stages. This review synthesizes contemporary prospective studies and systematic reviews/meta-analyses published over the past five years to clarify the current and emerging clinical roles of radiotherapy in real-world HCC management. Recent evidence highlights expanding applications of radiotherapy, including curative-intent stereotactic body radiotherapy in early-stage disease, consolidation after incomplete transarterial chemoembolization, perioperative strategies, and treatment of macroscopic vascular invasion. Radiotherapy is increasingly integrated with tyrosine kinase inhibitors and immune checkpoint inhibitors in advanced, oligometastatic, and oligoprogressive settings. In addition, particle therapies further broaden therapeutic options for liver-confined or anatomically challenging tumors. Collectively, contemporary data indicate that radiotherapy has evolved from a predominantly supportive modality to a versatile and increasingly evidence-based component of multidisciplinary treatment strategies for HCC.

KEYWORDS: Hepatocellular carcinoma; Radiotherapy; Prospective studies; Meta-analysis; Systematic review

INTRODUCTION

Liver cancer is the sixth most common cancer and the second leading cause of cancer-related death in South Korea, with approximately three quarters of cases attributable to hepatocellular carcinoma (HCC) [1,2]. HCC management involves a range of therapeutic modalities tailored to tumor stage, hepatic functional reserve, and treatment feasibility. Although external beam radiotherapy (EBRT) has been used across disease stages and is recommended by Asian guidelines [3], most international guidelines have not incorporated EBRT into their standard treatment algorithms [4,5]. In the 2026 update, the Barcelona Clinic Liver Cancer (BCLC) strategy introduced the CUSE (Complexity, Uncertainty, Subjectivity,

Emotion) framework to address therapeutic ambiguity and to move beyond a strictly linear stage-based algorithm [6]. By integrating clinical complexity, contextual feasibility, and patient-centered considerations into decision-making, the revised BCLC framework allows greater flexibility in treatment allocation. Accordingly, EBRT is now recognized as a therapeutic option across multiple stages within the CUSE framework, aligning more closely with the broader treatment paradigm reflected in several Asian guidelines. This narrative review aims to evaluate prospective studies and systematic reviews/meta-analyses published over the past five years to delineate emerging clinical evidence and research trends and to assess the potential applicability of radiotherapy in real-world clinical practice.

METHODS

Two databases, PubMed and Embase, were systematically searched for studies published between January 1, 2021 and February 8, 2026, using combinations of predefined search terms related to hepatocellular carcinoma, radiotherapy (including stereotactic body radiotherapy), and high-level evidence designs such as clinical trials, meta-analyses, and systematic reviews.

STEREOTACTIC BODY RADIOTHERAPY

SBRT vs. Local Ablative Therapies

Stereotactic body radiotherapy (SBRT) is a highly conformal radiotherapy technique delivering ablative radiation dose to tumors in a few fractions and is considered an alternative to surgery or ablative therapy based on practice guidelines [3,4,7,8]. There is growing evidence supporting the efficacy and safety of SBRT in newly diagnosed or recurrent HCC (Table 1). In a prospective, single-arm, multicenter phase 2 trial treating 33 newly diagnosed HCCs with a median tumor size of 2.3 cm (the STRSPH study), the 3-year local control (LC) rate was 93%, with grade 3 or higher SBRT-related nonlaboratory toxicities of 11% [9]. In a randomized controlled trial comparing SBRT and radiofrequency ablation (RFA) in 166 recurrent HCCs of less than 5 cm, SBRT showed significantly better LC than RFA (92.7% vs. 75.8% at 2 years), especially for tumors less than 2 cm, with no differences in progression-free survival (PFS) and overall survival (OS) [10]. Based on contemporary multicenter data and international practice guidelines, SBRT represents a curative-intent alternative to surgery in elderly or comorbid patients, those with marginal liver reserve, or patients who decline surgery [11,12]. SBRT may also offer superior LC compared with RFA for tumors adjacent to major intrahepatic vessels, centrally located lesions, or tumors that are technically difficult to access percutaneously. Notably, the 2026 BCLC update incorporates EBRT as a locoregional ablative option, reflecting these encouraging outcomes in early-stage disease [6].

SBRT vs. TACE

Beyond its role as an alternative to surgery or thermal ablation in early-stage disease, SBRT has also demonstrated superior local tumor control compared with transarterial chemoembolization (TACE)-based strategies. A multicenter randomized phase II trial (the TRENDY trial) comparing SBRT (n=12) with TACE using drug-eluting beads (n=16) demon-

Table 1. Prospective studies evaluating the role of stereotactic body radiotherapy

Studies	Major inclusion criteria	Treatments	Key findings
Sanuki et al., 2025 (STRSPH, phase II) [9]	No previous treatment for HCC, such as surgery, RFA, or TACE; Solitary tumor; Maximum size 1–5 cm; Child-Pugh A–B7	- SBRT (n=36, 40 Gy/5 Fx)	- Median tumor size 2.3 cm - OS[a] at 3 yr 82% - LC at 3 yr 93% - SBRT-related nonlaboratory toxicities ≥grade 3 11%
Xi et al., 2025 (phase III) [10]	Recurrent HCC; A single HCC ≤5 cm; Child-Pugh A	- RFA (n=83) - SBRT (n=83, 36-54 Gy/3 Fx)	- median diameter: 1.6 cm (RFA) vs. 1.7 cm (SBRT) - LPFS[a] better with SBRT (HR 0.45, *p*=0.014) - PFS or OS similar - acute and late adverse events similar
Méndez Romero et al., 2023 (TRENDY, phase II) [13]	Ineligible for surgery or ablation; BCLC A–B; 1–3 tumors; Cumulative diameter ≤6 cm; None or cirrhosis Child-Pugh A; BCLC A–B	- TACE-DEB (n=16): up to 4 sessions±ablation - SBRT (n=12): 48–54 Gy/6 Fx	TACE-DEB vs. SBRT - Median tumor size 3.0 vs. 3.5 cm - LC improved (43.6% vs. 100% at 2 yr, *p*=0.019) - TTP[a] similar: median 12 mo vs. 18.8 mo, NS - OS similar (median 36.8 vs. 44.1 mo, NS) - ≥grade 3 toxicity (treatment-related): 2 vs. 0 patients

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; SBRT, stereotactic body radiotherapy; OS, overall survival; LC, local control; LPFS, local progression-free survival; PFS, progression-free survival; TACE-DEB, transarterial chemoembolization with drug-eluting beads; BCLC, Barcelona Clinic Liver Cancer; TTP, time to progression; NS, not significant.
[a]Primary endpoint.

strated significantly improved LC in the SBRT arm (*p*=0.019), with 2-year LC rates of 100% versus 43.6%, respectively [13]. In a prospective observational study of patients with HCC not suitable for TACE, SBRT was associated with a significantly lower cumulative incidence of local progression compared with TACE (6% vs. 65% at 3 years) [14]. A contemporary meta-analysis comparing SBRT and TACE demonstrated comparable OS but significantly improved LC with SBRT (hazard ratio [HR] 0.25; 95% confidence interval [CI] 0.09–0.67; *p*=0.006), without excess severe toxicity [15].

As Bridging Therapy

Various locoregional therapies, including SBRT, have long been employed as bridging or downstaging strategies in patients awaiting liver transplantation. Although no randomized trials have evaluated SBRT in transplant candidates, accumulating prospective data suggest that it is both effective and safe. In a prospective study of patients on the transplant waitlist, SBRT (35–50 Gy in 5 fractions) achieved the highest LC (92.3% at 1 year), the highest pathological complete response (pCR) rate (48.1%), and the lowest dropout rates (15.1% and 23.3% at 1 and 3 years, respectively) compared with TACE and high-intensity focused ultrasound [16]. Similarly, a phase II nonrandomized trial reported objective response rates (ORRs) of 62.5–78.1% after SBRT (30–50 Gy in 5 fractions), with pCR observed in 75% of explanted livers [17]. In a prospective pilot study of 9 patients with Child-Pugh B8 or worse cirrhosis, SBRT (40 Gy in 5 fractions) achieved 100% LC at a median follow-up of 11.2 months [18]. Six patients (67%)

remained transplant eligible or underwent transplantation at 1 year, whereas three did not proceed to transplantation—two for non-tumor-related reasons and one due to minimal progression beyond the Milan criteria. Although one patient (11%) experienced grade 4 hepatic toxicity, there were no cases of nonclassical radiation-induced liver disease.

PERIOPERATIVE RADIOTHERAPY

Postoperative Radiotherapy

Adjuvant radiotherapy has been investigated predominantly in China as a strategy to reduce postoperative recurrence, particularly in patients with narrow resection margins, centrally located tumors, vascular invasion, or microvascular invasion. In centrally located HCC requiring narrow-margin hepatectomy, a prospective randomized trial showed a marginal improvement in recurrence-free survival (RFS) with adjuvant radiotherapy (5-year RFS 36.9% vs. 16.0%, p=0.03) and a significant RFS benefit in tumors ≤5 cm, with sustained long-term benefit observed in small tumors on extended follow-up [19,20]. In patients with portal vein tumor thrombus (PVTT), postoperative radiotherapy significantly improved survival, with median OS of 18.9 versus 10.8 months and markedly higher 1-year survival (76.9% vs. 26.9%, p=0.005) [21]. Prospective phase II data following narrow-margin hepatectomy demonstrated favorable outcomes with adjuvant radiotherapy, including 5-year OS and DFS rates of 72.2% and 51.6%, respectively, and absence of marginal recurrence, while propensity score–matched analysis confirmed improved OS (5-year 74.7% vs. 63.6%, p=0.045) and DFS (5-year 56.3% vs. 31.6%, p=0.001) with adjuvant radiotherapy [22,23]. Additional evidence from a randomized trial in microvascular invasion–positive disease showed that adjuvant SBRT improved DFS (5-year 56.1% vs. 26.3%, p=0.005) with a trend toward OS benefit, and intraoperative radiotherapy similarly improved recurrence-free outcomes after narrow-margin resection, particularly in patients with MVI [24,25]. Collectively, these studies indicate that adjuvant radiotherapy—delivered postoperatively or intraoperatively—may reduce recurrence and improve survival in selected high-risk patients.

Preoperative Radiotherapy

Neoadjuvant radiotherapy has been explored as a strategy to improve surgical outcomes in selected HCC populations with unfavorable anatomy or vascular invasion. In centrally located HCC, Tao et al. [26] reported that preoperative radiotherapy significantly improved postoperative disease-free survival, with 1-, 3-, and 5-year DFS rates of 74%, 55%, and 39%, respectively, compared with 44%, 28%, and 24% after surgery alone, and independently reduced recurrence risk (HR 0.42). In patients with PVTT, the randomized trial by Wei et al. [27] demonstrated superior survival with neoadjuvant radiotherapy (18 Gy in 3 fractions) followed by hepatectomy (p<0.001), with 1-year OS of 75.2% vs. 43.1% and significant reductions in mortality (HR 0.35, p<0.001) and recurrence (HR 0.45, p<0.001) compared with upfront surgery. A subsequent meta-analysis incorporating randomized and retrospective data similarly showed longer OS with preoperative radiotherapy [28]. More recently, Pan et al. [29] demonstrated promising efficacy of perioperative tislelizumab plus EBRT (45 Gy in 15 fractions) for macrovascular invasion, achieving a 30% ORR and major or complete pathological response in 66.7% of

resected patients. In parallel, ongoing prospective evaluation of radiotherapy (30 Gy in 10 fractions) combined with lenvatinib and sintilimab for PVTT-positive HCC reflects growing interest in immunotherapy–radiotherapy combinations [30]. Collectively, these data suggest that neoadjuvant radiotherapy, alone or in combination with systemic agents, may enhance resectability, reduce microscopic residual disease, and improve postoperative oncologic outcomes, supporting its consideration particularly in patients with high-risk or marginally resectable HCC.

TACE VERSUS TACE+SBRT/EBRT

Although Korean guidelines recommend the use of EBRT after incomplete TACE based on non-randomized studies [8], recent randomized studies support the efficacy and safety of EBRT or SBRT after incomplete TACE (Table 2). In a randomized phase III trial by Comito et al. [31] enrolling patients with an incomplete response after TAE/TACE, SBRT achieved significantly superior LC (84% vs. 23% at 1 year, p=0.002) and longer PFS (median 9 vs. 4 months, p=0.016) compared with repeated TAE/TACE. Chen et al. [32] compared TACE alone

Table 2. Randomized trials comparing transarterial chemoembolization alone versus transarterial chemoembolization plus radiotherapy

Studies	Major inclusion criteria	Treatments	Key findings
Comito et al., 2022 (Phase III) [31]	Incomplete response of unresectable HCC previously treated with one TAE/TACE cycle; BCLC A–B; Child-Pugh A–B	Arm A (n=19): repeated TAE/TACE Arm B (n=21): TACE #1 ⟶ SBRT (3–6 Fx)	TAE/TACE alone vs. TACE+SBRT - Median tumor size 2.5 cm - LC[a] improved (23% vs. 84% at 1 yr, p=0.002) - PFS improved (13% vs. 37% at 1 yr, p=0.035) - OS similar - No grade >3 toxicity
Féray et al., 2023 (TACERTE, phase II) [34]	Not eligible for surgery or percutaneous therapy; Child-Pugh A–B7; Maximum lesion size <9 cm	Arm A (n=64): 2–3 cycles TACE Arm B (n=56): TACE #1 ⟶ 3D-CRT (54 Gy/18 Fx)	- Mean tumor size: 5.4 cm - PFS[a] or OS similar in ITT analysis - PFS trend ↑ in Per-protocol analysis (HR 0.61) - More liver-related grade ≥3 AEs in arm B
Saad et al., 2024 (pilot study) [33]	Child-Pugh A; BCLC B; ≤3 HCC nodules, each up to 50 mm in diameter without vascular invasion; Inoperable or refusal of surgery; Unsuitability for RFA	Arm A (n=22): TACE alone Arm B (n=20): TACE #1 ⟶ SBRT (40 Gy/5 Fx)	- Mean tumor size: 4.4 cm (TACE) vs. 4.9 cm (SBRT) - LC better with SBRT (median 16 vs. 12, p=0.043) - PFS better with SBRT (median 16 vs. 11 mo, p=0.003) - OS or toxicities similar
Chen et al., 2025 (phase III) [32]	Not eligible for surgery or percutaneous therapy; ≤3 intrahepatic lesions; BCLC A–B; Child-Pugh A	Arm A (n=39): TACE alone (median 3 cycles) Arm B (n=35): TACE #2 ⟶ EBRT (55 Gy/15 Fx)	TACE alone vs. TACE+EBRT - Median tumor size 7.5 cm - LC improved (median LC: not reached vs. 13.1 mo, p<0.001) - PFS trend ↑ (median 11.6 vs. 15.4 mo, p=0.072) - OS[a] similar (median 36.8 vs. 47.1 mo, NS) - Toxicity similar

HCC, hepatocellular carcinoma; TAE, transarterial embolization; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; SBRT, stereotactic body radiotherapy; LC, local control; PFS, progression-free survival; OS, overall survival; 3D-CRT, three-dimensional conformal radiotherapy; ITT, intention-to-treat; HR, hazard ratio; AEs, adverse events; RFA, radiofrequency ablation; EBRT, external beam radiotherapy; NS, not significant.
[a]Primary endpoint.

with TACE followed by EBRT and demonstrated significantly improved LC (median not reached vs. 13.1 months, $p<0.001$) without increased toxicity, although improvements in PFS and OS did not reach statistical significance. Similarly, Saad et al. [33] reported better LC with SBRT following TACE compared with TACE alone, without differences in OS and toxicity. Although PFS was not improved in the intention-to-treat analysis of the randomized trial by Féray et al. [34] a trend toward improved PFS was observed with the addition of EBRT after TACE in the per-protocol analysis. The higher incidence of liver-related severe adverse events may, in part, be attributable to the use of three-dimensional conformal radiotherapy rather than more advanced techniques such as intensity-modulated radiotherapy (IMRT). These data support the early consideration of EBRT or SBRT after incomplete TACE to increase LC in early or intermediate-stage HCC.

RADIOTHERAPY FOR MACROSCOPIC VASCULAR INVASION

Several prospective studies evaluating the role of radiotherapy in HCC with macroscopic vascular invasion have been published, following the Korean randomized trial comparing TACE plus EBRT with sorafenib, demonstrating superior PFS with TACE plus EBRT [35]. Guo et al. [36] randomized unresectable HCC patients with PVTT to RT prior to TACE or TACE followed by RT and demonstrated that RT prior to TACE achieved a marginal improvement in OS, with a recanalization rate of 61.6% at 3 months. OS and PFS were significantly better in the subgroup with Cheng's type III/IV PVTT [37] (Table 3). A prospective study by Dutta et al. [38] demonstrated that the pattern of PVTT recanalization after SBRT (22–50 Gy in 5 fractions) correlated with OS in HCC, with the longest survival observed in patients achieving complete recanalization, in a cohort in which 65% had Vp3–4 PVTT. Collectively, these findings suggest that PVTT recanalization following radiotherapy may restore portal venous flow, stabilize hepatic function, delay liver decompensation, and potentially enable subsequent locoregional therapies, thereby translating into improved survival outcomes in patients with advanced HCC.

The clinical benefit of combining radiotherapy with tyrosine kinase inhibitors has been explored in several studies (Table 4). The NRG/RTOG 1112 randomized phase III trial demonstrated that SBRT followed by sorafenib improved

Table 3. Prospective study evaluating the role of radiotherapy in hepatocellular carcinoma with macrovascular invasion

Studies	Major inclusion criteria	Treatments	Key findings
Guo et al., 2022 [36]	Unresectable HCC with PVTT; No distant or lymph node metastasis; Child-Pugh A–B7	Arm A (n=60): EBRT → TACE #1 Arm B (n=60): TACE #1 → EBRT (50 Gy [2–3 Gy per fraction] to primary & PVTT)	RT → TACE vs. TACE → RT - mOS[a] marginally better (15.4 vs. 11.5 mo, HR= 0.68, p=0.054) - mPFS improved (6.6 vs. 4.2 mo, HR 0.66, p=0.030) - Recanalization at 3 mo 61.6% vs. 43.4% - Based on PVTT types: significantly better OS and PFS in Cheng's type III/IV PVTT with RT → TACE, not in type I/II PVTT

HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; EBRT, external beam radiotherapy; TACE, transarterial chemoembolization; RT, radiotherapy; mOS, median overall survival; HR, hazard ratio; mPFS, median progression-free survival.
[a]Primary endpoint.

OS compared with sorafenib alone in patients with HCC unsuitable for or refractory to locoregional therapies, without an increase in severe toxicities, with SBRT targeting all parenchymal and vascular HCC lesions [39]. Consistent with these findings, a phase II prospective study by Zhai et al. [40] reported favorable outcomes with concurrent sorafenib and radiotherapy in patients with portal or hepatic vein tumor thrombosis, achieving a median OS of 16.5 months and high in-field relapse-free survival of 85.4% at 2 years; OS and PFS were significantly better in cases without intrahepatic lesions outside the radiation field. Furthermore, a systematic review and meta-analysis including 11 retrospective studies demonstrated that EBRT combined with sorafenib achieved a median OS of 19.45 months and median PFS of 8.20 months with acceptable toxicity, supporting the survival benefit of this combination strategy [41]. In patients who are not candidates for immune-based regimens, treatment with tyrosine kinase inhibitors (sorafenib or lenvatinib) may be considered [4]; in this context, the addition of radiotherapy targeting intrahepatic tumors or PVTT may further improve clinical outcomes.

RADIOTHERAPY FOR OLIGOMETASTATIC DISEASE

Oligometastatic Disease

Oligometastatic disease is considered an intermediate state between localized and systemically metastasized disease, which has the potential for cure after salvage treatments [42]. Local therapies, including SBRT, have been used to treat oligometastatic tumors of solid tumors, as they have been associated with improvements in PFS and OS [43,44]. Even though

Table 4. Prospective studies evaluating the combination of radiotherapy and tyrosine kinase inhibitors

Studies	Major inclusion criteria	Treatments	Key findings
Dawson et al., 2025 (NRG/RTOG 1112, phase III) [39]	HCC unsuitable for and/or refractory to resection, ablation, or transarterial chemoembolization; BCLC B or C; Child-Pugh A; ≤5 liver tumors; Sum of tumor diameters ≤20 cm; Metastases ≤3 cm	Arm A (n=92): sorafenib Arm B (n=85): SBRT (27.5–50 Gy/5 Fx) → sorafenib (SBRT target: all parenchymal and vascular tumor)	Sorafenib vs. SBRT+sorafenib - Median sum tumor diameter 8.2 vs. 7.5 cm - Vp3, Vp4, or IVC 64% vs. 62% - Multiple tumors present: 56% vs. 63% - mOS[a] improved (12.3 vs. 15.8 mo, HR 0.72, p=0.04) - mPFS improved (5.5 vs. 9.2 mo, HR 0.55, p<0.001) - TTP superior (HR 0.69, p=0.03) - MVI response better (9% vs. 38%, p<0.001) - Disease control 45% vs. 75% - ≥grade 3 treatment-related toxicity similar (42% vs. 47%)
Zhai et al., 2025 (phase II) [40]	Presence of portal or hepatic vein tumor thrombosis; Child-Pugh A–B	Sorafenib+EBRT (40–66 Gy, 2-Gy fraction) (RT target: hepatic primary tumor and vein tumor thrombosis±regional lymph nodes)	mOS[a] 16.5 mo; mPFS 6.1 mo; median TTP 6.8 mo. ORR; 52.3% In-radiation-field relapse-free survival 85.4% at 2 yr Out-radiation-field relapse-free survival 26.3% at 2 yr

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; SBRT, stereotactic body radiotherapy; IVC, inferior vena cava; mOS, median overall survival; HR, hazard ratio; mPFS, median progression-free survival; TTP, time to progression; MVI, macrovascular invasion; EBRT, external beam radiotherapy; RT, radiotherapy; ORR, objective response rate.
[a]Primary endpoint.

systemic therapy remains the current standard treatment for metastatic HCC [4], accumulating evidence increasingly supports a potential role for radiotherapy in patients with oligometastatic HCC. In a systematic review and meta-analysis including 10 retrospective studies, metastasis-directed local therapies—such as surgery, RT, and RFA—were associated with favorable survival outcomes and high LC rates, with grade ≤3 complications occurring in less than 10% of patients [45]. Choi et al. [46] conducted a prospective phase II trial evaluating SBRT in 40 patients with 1–5 metastatic lesions. After a median follow-up of 15.5 months, the 2-year OS rate was 80%, and the 2-year time to local progression was 91.1%. The ORR was 75.8%, and the disease control rate reached 98.4%, with no grade ≥3 toxicities reported. Although the median PFS was 5.3 months—reflecting frequent out-of-field progression—the excellent in-field control highlights the ability of SBRT to achieve durable local tumor ablation with minimal impact on quality of life. Furthermore, Chen et al. [47] explored the combination of SBRT with the PD-1 inhibitor sintilimab in a phase II trial including 25 patients with recurrent or oligometastatic HCC. The median PFS was 19.7 months. The ORR was 96% (complete response in 68%), and the 1-year LC rate was 100%, while grade 3 adverse events occurred in only 12% of patients. However, despite these promising results, further prospective randomized studies are required to determine whether local therapies improve treatment outcomes in oligometastatic HCC.

Oligoprogressive Disease

Oligoprogression is defined as a clinical state in which a limited number of metastatic lesions (commonly ≤5 lesions in ≤3 organs) demonstrate radiographic progression after a period of disease control under ongoing systemic therapy, while the remaining disease sites remain stable or responsive [42]. This condition is biologically distinct from generalized progression and is thought to reflect the emergence of resistant tumor subclones at selected sites, thereby providing a therapeutic window for local ablative treatment while maintaining systemic therapy. In the phase II RADIANT trial, SBRT was delivered to all oligoprogressive lesions in 70 patients with solid tumors while systemic therapy was continued, resulting in approximately 53% of patients remaining free from systemic therapy change at 1 year [48]. More specifically in hepatocellular carcinoma, Hsu et al. [49] conducted a prospective phase II study in 35 patients with oligoprogressive HCC during first-line PD-1 inhibitor plus lenvatinib therapy and demonstrated a median PFS of 11.3 months, an ORR of 74.3%, and a 2-year OS rate of 84.9%, without significant deterioration in liver function. These results appear superior to those observed with traditional second-line strategies, supporting the concept that local ablation may delay the need to switch systemic therapy in patients with oligoprogressive lesions. Despite these promising results, larger randomized trials are warranted to validate the concept of ablating oligoprogressive lesions while maintaining ongoing systemic therapy.

COMBINATION OF IMMUNOTHERAPY AND RADIOTHERAPY

As immunotherapy-based combinations have become the current standard treatment for advanced HCC, accumulating clinical evidence supports the role of SBRT combined with

Table 5. Prospective studies evaluating the combination of radiotherapy and immunotherapy

Study	Patients	Major inclusion criteria	Treatments	Key findings
Chiang et al., 2024 (phase II) [51]	63	Unresectable HCC achieving CR after locoregional therapy+immunotherapy	Locoregional therapy (including SBRT/TACE)+immunotherapy; watch-and-wait after CR	CR 46%; 3-year OS[a] 75.5%; 3-year LC 90.5%
Li et al., 2022 (phase II) [52]	21	Unresectable HCC; BCLC B–C; Child–Pugh A–B	SBRT (30–50 Gy/10 Fx)+camrelizumab	ORR[a] 52.4%; mPFS 5.8 mo; mOS 14.2 mo; manageable toxicity
Juloori et al., 2023 (phase I) [53]	14	Advanced/unresectable HCC	SBRT (40 Gy/5 Fx) followed by nivolumab±ipilimumab	Favorable clinical outcomes with nivolumab and ipilimumab; ORR 57% vs. 0%; mPFS 11.6 vs. 4.7 mo; mOS 41.6 vs. 4.7 mo
Chen et al., 2023 [54]	20	Unresectable and/or disease progression after local treatment; BCLC B–C; Child–Pugh A	SBRT (24 Gy/3 Fx) followed by toripalimab+anlotinib	ORR 15%; DCR 50%; mPFS[a] 7.4 mo
Tang et al., 2025 (ReUNION-1, phase II) [55]	21	Anti–PD-1 refractory HCC; Child–Pugh A	SBRT (25–50 Gy/5 Fx) followed by sintilimab+bevacizumab biosimilar	Non-irradiated lesion ORR[a] 33.3%; DCR 66.7%; mPFS 6.2 mo; mOS 24.4 mo; LC 100% (irradiated lesion)
O'Kane et al., 2026 (PEMRAD, phase II) [56]	22	Progression on sorafenib; Child–Pugh A	SBRT (27.5–50 Gy/5 Fx)+pembrolizumab	ORR[a] 41%; mPFS 5.4 mo; mOS 12.6 mo; LC 91.2% with SBRT

HCC, hepatocellular carcinoma; CR, complete response; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; OS, overall survival; LC, local control; BCLC, Barcelona Clinic Liver Cancer; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; DCR, disease control rate; PD-1, programmed cell death protein 1.
[a]Primary endpoint.

immunotherapy across diverse HCC settings (Table 5) [6,50]. In locally advanced HCC, locoregional therapy, including SBRT, plus immunotherapy achieved a CR rate of 46%, with CR patients demonstrating favorable long-term outcomes, suggesting the potential for durable disease control with a watch-and-wait strategy [51]. In unresectable HCC, prospective studies of SBRT combined with PD-1 blockade reported meaningful response and survival outcomes [52], while intensified regimens incorporating dual checkpoint blockade demonstrated enhanced activity [53]. Additional multimodal strategies integrating SBRT with systemic agents have further shown signals of disease control in advanced disease [54]. Importantly, SBRT-based combinations also demonstrated activity beyond first-line settings, including immunotherapy-refractory disease and post-sorafenib populations, supporting the feasibility and clinical activity of immunotherapy plus SBRT across treatment-naïve, advanced, vascular-invasive, and refractory HCC scenarios [55,56]. Across prospective studies, the radiotherapy field has ranged from SBRT targeting a single index intrahepatic lesion to multi-target liver SBRT encompassing multiple hepatic tumors and macrovascular invasion, and in selected trials it has also extended to treat extrahepatic metastatic lesions [51-56]. Prospective randomized trials are warranted to clarify whether EBRT combined with immunotherapy confers a survival advantage over either modality alone, analogous to the survival benefits observed with TACE combined with immunotherapy and targeted agents in patients without extrahepatic metastases or major portal vein thrombosis, as demonstrated in the EMERALD-1 and LEAP-012 trials [57,58]. In parallel, dedicated investigations are also

Table 6. Prospective studies evaluating the combination of radiotherapy and immunotherapy in hepatocellular carcinoma with vascular invasion

Study	Patients	Major inclusion criteria	Treatments	Key findings
Hu et al., 2023 [60]	60	HCC with Cheng's type II–IV PVTT; Child-Pugh A –B	Arm A: Camrelizumab/apatinib Arm B: Camrelizumab/apatinib plus SBRT (40 Gy/5 Fx) targeting PVTT and contiguous primary hepatic lesion	SBRT vs. non-SBRT: mOS[a], 12.7 vs. 8.6 mo; mPFS, 4.6 vs. 2.5 mo; ORR, 47.5% vs. 20%; DCR, 72.5% vs. 40%
Wang et al., 2023 [61]	30	Unresectable HCC with extrahepatic PVTT; Child-Pugh A –B	Atezolizumab/bevacizumab plus EBRT (52–56 Gy in 2-Gy fractions) targeting extrahepatic PVTT	ORR[a] 76.6%, mPFS 8.0 mo, mOS 9.8 mo
Kim et al., 2024 (NEXTRAH, phase II) [64]	50	Unresectable HCC with vascular invasion in the portal vein, hepatic vein, or inferior vena cava; Child-Pugh A	Nivolumab plus EBRT or PBT (30–50 Gy/10 Fx) targeting vascular invasion and surrounding involved regions	ORR 36%; DCR 74%; mPFS[a] 5.6 mo; mOS 15.2 mo
Zhu et al., 2024 (phase II) [62]	46	HCC with Cheng's type I–III PVTT; Child-Pugh A; Largest tumor size ≤10 cm; Number of tumors ≤3	Sintilimab/bevacizumab plus EBRT (30–50 Gy/10 Fx) targeting all lesion including primary tumor and PVTT	ORR[a] 58.7%; DCR 100%; mPFS 13.8 mo; mOS 24.0 mo
Mo et al., 2025 (phase II) [63]	24	Unresectable HCC with Vp3–4 PVTT; Child-Pugh A–B7	Cadonilimab/lenvatinib plus SBRT (30–40 Gy/5 Fx) targeting PVTT and immediately adjacent tumor tissue (1-cm margin)	ORR[a] 38.1% (Primary liver lesions) and 76.2% (PVTT); DCR 100%; mPFS 6.8 mo; mOS 13.4 mo

HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; SBRT, stereotactic body radiotherapy; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; DCR, disease control rate; EBRT, external beam radiotherapy; PBT, proton beam therapy.
[a]Primary endpoint.

needed to define the optimal radiotherapy target volume and treatment extent, including whether irradiation should be limited to index lesions or expanded to encompass multifocal intrahepatic disease and macrovascular invasion [59].

In HCC with PVTT, emerging evidence indicates that radiotherapy combined with immunotherapy may improve outcomes in this poor-prognosis population (Table 6). Hu et al. [60] conducted a multicenter, open-label, non-comparative randomized trial enrolling 60 systemic treatment–naïve patients with HCC and PVTT to camrelizumab/apatinib with or without SBRT, demonstrating superior outcomes in the SBRT cohort, with median OS of 12.7 vs. 8.6 months and median PFS of 4.6 vs. 2.5 months. The addition of SBRT also improved ORR and disease control rate, with manageable toxicity. In addition, prospective multimodal studies combining radiotherapy with PD-1/PD-L1 blockade and anti-angiogenic therapy have consistently reported encouraging antitumor activity in PVTT populations [61-63], while concurrent delivery of radiotherapy with nivolumab further supports the feasibility of integrating radiotherapy and immunotherapy in patients with macrovascular invasion [64]. Zhu et al. [62] delivered radiotherapy to all intrahepatic lesions, with the GTV including both the primary tumor and PVTT, reflecting the rationale that PVTT control may restore portal flow and reduce dissemination, whereas reduction of intrahepatic tumor burden may enhance and prolong the systemic benefit of immunotherapy. However, the optimal target volume remains undefined, as these prospective studies did not report outcomes stratified by radiotherapy target-volume strategy (e.g., PVTT-only vs. PVTT plus primary tumor vs. broader

intrahepatic coverage). Collectively, these findings provide a clinical rationale for integrating radiotherapy with immunotherapy to improve thrombus response and overall disease control in PVTT, although the optimal target-volume strategy has yet to be established in prospective comparative trials.

PALLIATIVE RT FOR PRIMARY HCC

Current guidelines recommend palliative radiotherapy for symptomatic primary HCC as well as for extrahepatic metastatic lesions, based on several prospective and retrospective studies [3,65]. In a retrospective cohort of patients with symptomatic HCC treated with a single 8-Gy fraction, half of the patients experienced symptomatic improvement, with a median duration of symptom relief of 3 months [66]. More recently, the randomized phase III CCTG HE1 trial compared radiotherapy plus best supportive care (BSC) with BSC alone in patients with painful hepatic cancer, of whom 35% had HCC [67]. A single 8-Gy fraction significantly improved hepatic pain compared with best supportive care alone, with 67% versus 22% of evaluable patients achieving at least a 2-point reduction in worst pain intensity at 1 month (p=0.0042). Radiotherapy was well tolerated without treatment-related mortality, and 3-month OS was numerically higher in the radiotherapy arm (51% vs. 33%; HR 0.56, 95% CI 0.30–1.05, p=0.068).

ADVANCED RADIOTHERAPY TECHNOLOGIES

Advances in RT Technology

Radiotherapy for HCC has evolved considerably over recent decades, enabling increasingly precise and individualized treatment delivery. The transition from conventional techniques to three-dimensional conformal radiotherapy and subsequently to IMRT and SBRT has enabled improved dose conformality and dose escalation while reducing irradiation of uninvolved liver tissue [68,69]. Moreover, various respiratory motion management techniques—including respiratory gating, breath-hold approaches, and real-time tumor tracking—and image-guided radiotherapy using cone-beam computed tomography or magnetic resonance imaging are currently employed to reduce radiation exposure to the normal liver and surrounding organs [68,70,71]. Taken together, these advances have expanded the clinical applicability of radiotherapy in HCC by reducing radiation-related toxicities.

Particle Therapy

Proton beam therapy (PBT) has emerged as a promising modality for HCC owing to its favorable dose distribution characterized by the Bragg peak, which delivers a high tumor dose while minimizing irradiation of uninvolved liver parenchyma and adjacent organs. Recent prospective evidence supports its clinical efficacy across disease settings. A phase II study of image-guided PBT for operable or ablation-eligible solitary HCC demonstrated excellent long-term outcomes with 5-year OS of 70% and LC of 92%, alongside minimal severe toxicity and preserved quality of life, suggesting its potential role as an alternative curative option [72]. Randomized evidence comparing PBT with other locoregional therapies has emerged: a phase III trial reported non-inferior local PFS compared with RFA in small recurrent tumors [73], while a randomized comparison with TACE demonstrated similar OS

with improved PFS and LC, along with fewer hospitalizations and lower overall treatment cost [74]. Model-based analyses indicate that the dosimetric advantage of PBT is particularly relevant in patients with larger cumulative tumor diameter, central or hilar tumor location, or multifocal disease due to reduced predicted hepatic toxicity [75]. Japanese large prospective registry data involving more than 500 patients confirmed favorable real-world outcomes with a 3-year LC rate of approximately 90% and low rates of severe late toxicity [76].

Consistently, a recent systematic review and meta-analysis encompassing over 1,800 patients reported pooled 3- and 5-year local PFS rates of 88% and 86%, respectively, with low rates of grade ≥3 hepatic toxicity (1%), classic radiation-induced liver disease (2%), and non-classic RILD (1%), supporting durable tumor control with preservation of liver function [77]. In summary, these findings suggest that PBT represents an effective and safe modality across the spectrum of liver-confined HCC, with particular potential advantages in anatomically challenging tumors or in patients for whom preservation of hepatic reserve is critical.

Carbon-ion radiotherapy (CIRT) offers distinct biological advantages over photon and proton therapies owing to its high linear energy transfer and increased relative biological effectiveness, which may enhance tumor cell kill even in hypoxic or radioresistant tumors. Early prospective evidence in HCC has shown encouraging outcomes. A phase I dose-escalation study reported favorable long-term results with 1-, 3-, and 5-year OS rates of 91%, 82%, and 67%, respectively, and excellent LC (94.4% at 5 years) without dose-limiting toxicity [78]. Similarly, a prospective study evaluating a four-fraction regimen demonstrated promising LC and survival outcomes with minimal severe toxicity and preserved liver function [79]. Despite these encouraging findings, available evidence is primarily derived from small prospective cohorts without randomized comparisons, and uncertainties persist regarding optimal patient selection, treatment protocols, and comparative effectiveness relative to other advanced radiotherapy modalities. Therefore, further multicenter prospective studies and randomized trials are warranted to clarify the clinical role of CIRT.

CONCLUSION

Modern radiotherapy techniques have expanded the therapeutic landscape of HCC through improved precision and safety. Prospective and randomized studies have demonstrated meaningful improvements in local control and survival across early-stage, advanced-stage, and vascular-invasion disease. Integration with systemic therapies, including targeted agents and immunotherapy, represents a particularly promising strategy. Particle therapies further enhance treatment options in anatomically challenging or liver-limited disease. Future multicenter randomized trials are needed to refine optimal indications, target volumes, and combination strategies.

ACKNOWLEDGEMENTS

None.

FUND

None.

ETHICS STATEMENT

Consent for publication is not required, as this submission does not include any images or information that could identify any individual.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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