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REVIEW

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Advances in radiation therapy for HCC: Integration with liver-directed treatments

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Abstract

HCC is the fourth leading cause of cancer-related mortality with increasing incidence worldwide. Historically, treatment for early disease includes liver transplantation, surgical resection, and/or other local therapies, such as thermal ablation. As a result of technical advances and high-quality prospective data, the use of definitive external beam radiotherapy with ablative doses has emerged. Intermediate-stage disease has been generally addressed with arterially directed therapies (eg, chemoembolization or radioembolization) and external beam radiotherapy, while advanced stages have been addressed by systemic therapy or best supportive care. The role of each local/locoregional therapy has rapidly evolved in the context of novel pharmacotherapies, including immunotherapies and antiangiogenic agents. The combinations, indications, and timing of treatments vary widely among specialties and geographies. Here, we aim to synthesize the best quality evidence available regarding the efficacy and safety of different liver-directed modalities, with a focus on recent prospective clinical data of external beam

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Liver Classification; EBRT, external beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; HAIC, hepatic artery infusion chemotherapy; IMRT, intensity-modulated radiation therapy; LDT, liver-directed therapy; LIRADS, Liver Imaging Reporting & Data System; MWA, microwave ablation; NCCN, National Comprehensive Cancer Network; OS, overall survival; PBT, proton beam radiotherapy; PFS, progression-free survival; RCT, randomized clinical trial; RFA, radiofrequency ablation; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

radiotherapy within the context of other available liver-directed therapies across Barcelona Liver Classification (BCLC) stages.

Keywords: HCC, liver-directed therapy, radiation therapy, stereotactic body radiation therapy

KEY POINTS

1. Due to technological advances, external beam radiotherapy (EBRT) has emerged as an effective treatment for early or intermediate-stage HCC, resulting in its inclusion in clinical guidelines.
2. Intensity-modulated radiotherapy (IMRT) allows precise delivery of higher targeted radiation doses to tumors while sparing surrounding normal organs, improving outcomes for early and intermediate-stage HCC in neoadjuvant, definitive, and adjuvant settings. Clinical trials have demonstrated its efficacy and safety, showing improved survival and disease control rates.
3. Stereotactic body radiotherapy (SBRT) delivers high radiation doses in a few fractions with enhanced precision and patient immobilization, improving outcomes in HCC. Studies show high local control and survival rates with minimal toxicity, making it an effective option for early to intermediate HCC. Recent data supports using SBRT for advanced HCC, highlighting its efficacy across different stages of the disease.
4. OLT and surgical resection are first-line curative treatments for early HCC. Retrospective studies show similar local control (LC) between SBRT and resection for small primary HCC, but prospective randomized studies are needed for confirmation.
5. Radiofrequency ablation (RFA) and microwave ablation (MWA) are effective for early HCC, offering similar outcomes to surgery in some cases. Studies comparing RFA and SBRT have shown mixed results, with SBRT providing better or comparable LC but more liver injury. A phase III trial found SBRT noninferior to RFA for recurrent/residual HCC.
6. Studies comparing transarterial chemoembolization (TACE) and SBRT suggest improved LC and fewer hospitalizations with SBRT, although overall survival (OS) rates do not differ. SBRT shows superior LC compared to TACE in some trials, but further confirmation is needed.
7. Transarterial radioembolization (TARE), using yttrium-90 microspheres, shows promising results for unresectable HCC and can improve outcomes compared to TACE. Comparative studies between TARE and SBRT are lacking, but older meta-analyses suggest better LC with SBRT. Personalized dosimetry in TARE improves outcomes, and emerging data support combining TARE with immunotherapy for enhanced effectiveness.
8. Combining EBRT with other liver-directed therapies like TACE significantly improves outcomes for patients with advanced HCC. Studies show enhanced median survival, progression-free survival (PFS), objective response rate, and time-to-progression compared to TACE or systemic therapy alone, indicating the potential benefits of integrated local treatments.
9. Combining radiation therapy with immunotherapy in HCC shows promising results, with improved PFS and OS rates. Clinical trials have demonstrated favorable outcomes and acceptable safety profiles, though more prospective data are needed to confirm these benefits and establish the synergy between radiotherapy and immunotherapy.
10. Liver-directed therapies for HCC improve patient outcomes and should be chosen through multidisciplinary discussions. Modern radiotherapy supports its inclusion as a key treatment option, emphasizing the need for tailored, patient-centered care through cross-disciplinary collaboration.

INTRODUCTION

HCC is the most common cause of primary liver malignancy (85%–90%) with over 900,000 new cases globally each year.[1] Because most patients have underlying cirrhosis or liver dysfunction, management of HCC is complex and requires a multidisciplinary approach.[2] Barcelona Clinic Liver Cancer Staging (BCLC) staging incorporates tumor burden, Child-Pugh score, and Eastern Cooperative Oncology Group (ECOG) performance status to guide treatment recommendations.[3–5] Patients with early-stage HCC (BCLC 0 or A) can undergo liver transplantation or surgical resection, with ablation (radiofrequency [RFA] or microwave ablation [MWA]) reserved for small, localized lesions in nonsurgical patients.[6] For patients with BCLC C HCC (portal invasion and/or metastases), systemic therapy is preferred. While advances in systemic therapy have increased overall survival (OS) for patients with advanced disease, prognosis remains poor.[7–12] For patients with intermediate disease (BCLC B), other liver-directed therapies (LDTs) are recommended including transarterial bland, chemo or

radioembolization (TAE, transarterial chemoembolization [TACE], or transarterial radioembolization [TARE], respectively), external beam radiotherapy (EBRT), and less commonly hepatic artery infusion chemotherapy (HAIC). These LDTs can be used for definitive treatment, as a bridge for liver transplantation, and palliatively in advanced stages (BCLC C or BCLC D).

Although EBRT has long been available for treating HCC, technological advances have dramatically reduced the risk of major adverse events, namely radiation-induced liver damage, allowing for rigorous evaluation of ablative EBRT. Emerging evidence supporting the efficacy of EBRT for patients with early or intermediate HCC prompted its inclusion in clinical guidelines (eg, National Comprehensive Cancer Network [NCCN],[13] American Association for the Study of Liver Diseases [AASLD][14]). While the recommended preference remains for thermal ablation for nonsurgical patients with early-stage HCC, radiotherapy in the form of ablative EBRT or radioembolization (TARE) can be effective for intermediate or advanced diseases.

Radiotherapy can be classified into EBRT and internal RT.[15] EBRT mainly includes photon-based therapy with 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT), as well as proton and heavy ion radiotherapy.[16,17] Internal RT includes TARE and brachytherapy.[18–20]

Here, we review the available evidence of efficacy and safety for different types of radiotherapy and other LDTs. In addition, we present the current role and offer future perspectives regarding the potential of radiotherapy within the multidisciplinary treatment approach for HCC.

EBRT

Technological and treatment planning advances in radiotherapy delivery have markedly improved the therapeutic index for EBRT across several diseases, and the use of EBRT in patients with HCC has increased.[21] Early approaches using 3D-CRT to tumors up to 10 cm yielded promising initial results.[22–25] Modern EBRT techniques, such as IMRT and SBRT, combined with respiratory management can allow radiobiologically ablative doses to even very small lesions ($\leq$1 cm) with excellent local control rates (85-100%) in 7-15 fractions, in patients with unresectable HCC.[26,27]

IMRT

With IMRT, the treating physician defines the tumor volume and surrounding normal organs (eg, small bowel, uninvolved liver), and a treatment planning system uses “inverse planning” to modulate the radiation dose delivered from various beam angles.[28] Though more costly, computationally intensive, and requires sophisticated quality assurance, IMRT allows delivery of a higher targeted RT dose to a more conformal treatment volume when compared to earlier techniques. IMRT has been used for early and intermediate-stage HCC in both the neoadjuvant, definitive, and adjuvant settings.

Sun et al[29] conducted a small (n = 52) open-label randomized clinical trial (RCT) of patients with HCC and portal vein tumor thrombus after partial hepatectomy with or without thrombectomy to observation or postoperative IMRT (50 Gy in 25 fractions) and showed significantly improved OS outcomes in the RT arm.[29] A prospective, nonrandomized study of patients with HCC and microvascular invasion (MVI, BCLC C) offered better relapse-free survival (RFS) with postoperative IMRT compared to patients treated with best supportive care.[30] Neoadjuvant RT (50–60 Gy in 25–30 fractions) was recently evaluated in a prospective nonrandomized single-arm study and shown to be well tolerated. All patients (n = 38) showed either partial response or stable disease following RT.[31] The RAISE trial, a phase II multicenter RCT comparing adjuvant IMRT with active surveillance for patients with HCC and narrow margin ($\leq$1 cm) resection, reported a 2-year RFS of 78.4% compared to 57.4% for the surgery-only group ($p = 0.028$).[32]

In all, these studies showed that conventionally fractionated radiotherapy (~2–Gy per fraction of treatment) could be delivered safely and result in favorable outcomes for patients with HCC. With improved image guidance technology, investigators posited that, perhaps, higher RT doses per fraction could be safely delivered to further improve outcomes.

SBRT

SBRT is a conformal form of IMRT using high doses per fraction (typically 5 or fewer fractions) while implementing additional patient immobilization and image guidance. (IGRT).[33] SBRT has been studied in other malignancies with excellent results and is endorsed as a curative-intent strategy in lieu of surgical resection in several other cancers.[34,35] Stereotactic ablative radiotherapy (SABR) is used synonymously with SBRT, though it often implies that the dose/fractionation delivered is radiobiologically ablative[36] (Figure 1).

Evidence supporting the use of SBRT in HCC is summarized in Table 1. Most trials included patients with HCC with Child-Pugh A or B, and BCLC stage C. Several prospective single-arm phase 2 studies have shown 70% and 90% 3-year OS and local control (LC), with the use of SBRT and excellent toxicity profiles.[39,40,42,45–47] Bujold and colleagues reported on

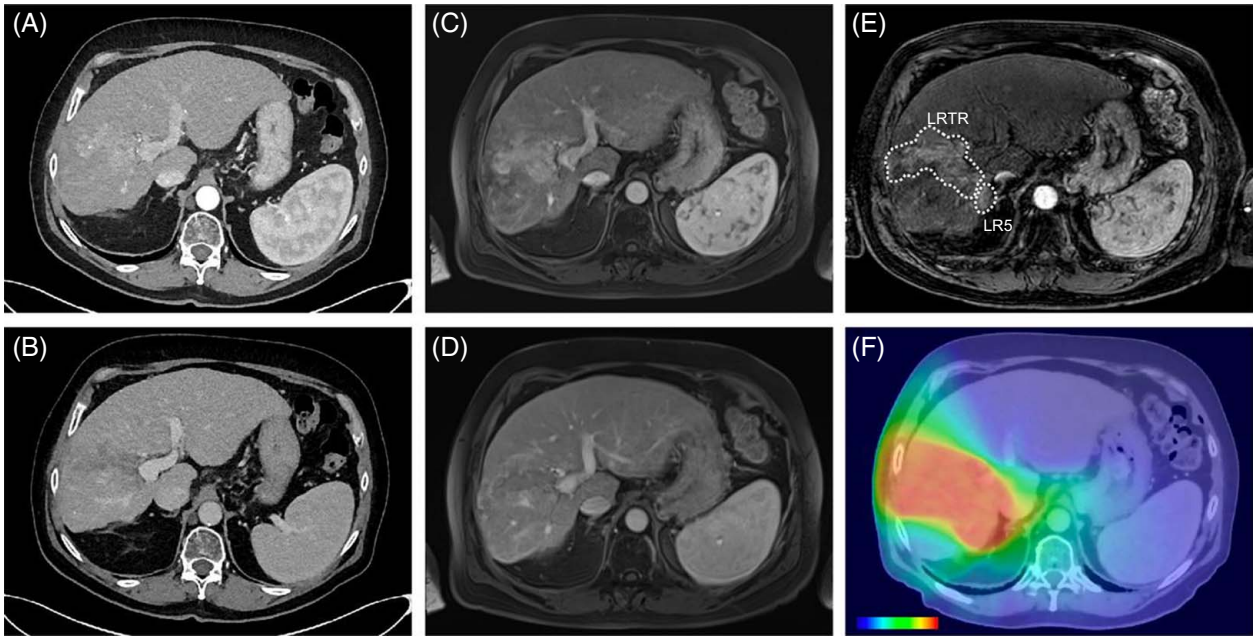

FIGURE 1 65-year-old-man with recurrent HCC and de novo HCC. (A) Arterial phase CT showing large (7.6×4.6 cm) LIRADS-TR (LR-TR) representing residual tumor lesion previously treated with TACE. (B) LR-TR equivocal lesion demonstrating wash out in venous phase (80 s). (C) T1 MR of gadobutrol (Gadavist) arterial (20 s) and (D) venous phase (70 s). (e) T1 MR of gadoxetate disodium (Eovist) arterial phase (20 s) showing LR-TR equivocal lesion and an additional LIRADS-5 lesion. (F) Dose color wash of stereotactic ablative radiotherapy encompassing both lesions to the prescribed dose of 45 Gy in 5 fractions (scale represents 0–49 Gy). Abbreviation: TACE, transarterial chemoembolization.

2 prospective studies evaluating 24–54 Gy in 6 fractions, including patients with large tumors (>7 cm median diameter) and 55% with tumor vascular thrombosis. This study showed 87% (95% CI: 78%–93%) 1-year LC and no radiation-induced liver damage at the dose levels evaluated.[46] Low, subablative doses (≤ 30 Gy in 6 fractions) appeared insufficient for LC (65% at 2 y), but for patients receiving ≥ 30 Gy in 6 fractions, LC was 85% at 2 years, demonstrating a need for minimum dose for local efficacy.

Rim and colleagues published a meta-analysis of 32 studies with 1950 patients with HCC and PVVT receiving 3D-CRT, SBRT, or TARE, and showed 1-year OS of 43.8%, 48.3%, and 46.5%, respectively (NS); 1-yr LC rates were 82.8%, 83.9%, and 57.5% respectively. In contrast to 3D-CRT and TARE, no grade ≥ 3 toxicities were reported in the SBRT studies. Radiation-induced liver damage episodes were not reported in the SBRT or TARE studies.[24] Jang and colleagues presented a phase II single-arm multicenter study of 65 patients with unresectable HCC treated with SBRT (45–60 Gy in 3 fractions). The 2-year and 3-year LC rates were 97% and 95%. Treatment was well tolerated, and progression-free survival (PFS) and OS rates were 48% and 84% at 2 years and 36% and 76% at 3 years.[39] Kimura and colleagues conducted a multicenter prospective study of 36 patients with previously untreated solitary primary HCC treated with SBRT. The 3-year OS was 78%, the 3-year local progression-free survival (LPFS) and LC were 73% and 90%, respectively. Grade 3 or 4 SBRT-related toxicities were observed in 4 patients (11%), and no grade 5 toxicities.[42]

NRG/RTOG 1112, a randomized phase III study was recently presented by Dawson et al.[44] Patients ($n=177$) with new or recurrent HCC unsuitable for resection, transplantation, ablation, or TACE were included. Most patients were BCLC C (82%), 74% had macrovascular invasion—a poor prognostic factor, and 4% had metastases. Patients were randomized to sorafenib versus SBRT followed by sorafenib. Median OS was 12.3 months with sorafenib and 15.8 months with SBRT/sorafenib (HR = 0.77, 1-sided $p=0.055$). After adjusting for performance status, M stage, Child-Pugh A5 versus 6, and degree of MVI, OS was statistically significantly improved for SBRT combined with sorafenib compared with sorafenib alone (HR = 0.72, 95% CI: 0.52–0.99, 2-sided Cox $p=0.042$). Median PFS (9.2 mo, 95% CI: 7.5–11.9 vs. 5.5 mo, 95% CI: 3.4–6.3; HR = 0.55, 95% CI: 0.40–0.75, 2-sided $p=0.0001$) and time to progression (TTP) rates (HR = 0.69, 95% CI: 0.48–0.998, 2-sided Gray's $p=0.034$) were also improved in the SBRT arm. Treatment-related grade ≥ 3 adverse events were not significantly different and were numerically higher in the sorafenib arm. The final complete report from this trial is pending.

While the evidence is accumulating to support the use of SBRT in earlier-stage HCC, RTOG 1112 suggests that higher-risk patients, including those with vascular invasion, benefit from adding SBRT to sorafenib and the potential to extend this modality to bridge transplantation.[48–51] These data and others

TABLE 1 Evidence for SBRT in HCC

Trial	R/P	Phase	Inclusion	No of pts.	Arms	Primary endpoint	Dose/ fractions	LC	PFS (SBRT vs. another arm)	OS	Median OS (months)
Chan et al[37]	R	—	Advanced HCC, CP A, B, BCLC 0, A, B, C	16	SBRT	LC	45/10	3-yr LC: 91%		3-yr OS: 28%	23
Bush et al[38]	P	2	Patients with HCC eligible for transplant, CP A, B	69	PBT vs. TACE	OS	70.2/15	3-yr LC: ~62.5% vs. ~25% HR 5.64 (95% CI: 1.78–17.9, $p = 0.003$)	3-yr PFS: ~60% vs. 20% mPFS: NR vs. 12 mo ($p = 0.002$)	2-yr OS: 68% (95% CI: 0.54–0.86) vs. 65% (95% CI: 0.52–0.83) ($p = 0.80$)	~30 mo for both arms
Jang et al[39]	P	2	Unresectable HCC, CP A, B	65	SBRT	Severe toxicity	45–60/3	3-yr LC: 95%	3-yr LPFS: 36%	3-yr OS: 76%	
Durand-Labrunie et al[40]	P	2	Unresectable HCC, CP A, B	43	SBRT	LC at 18 months	45/3	18-mo LC: 98% (95% CI: 85%–99%)		18-mo OS: 72%	42
Kim et al[41]	P	3	Recurrent/ residual HCC, CPC A, B, BCLC 0, A, B, C	144	PBT vs. RFA	2-yr LPFS	66/10		2-yr LPFS: 92.8% vs. 83.2% (90% CI 0.7–18.4; $p < 0.001$)	2-yr OS: 88.8% vs. 92.9% ($p = 0.600$)	Not reached
Kimura et al[42]	P	2	Solitary primary HCC, CPC A, B, BCLC 0, A, B,C	36	SBRT	3-yr OS	40/5	3-yr LC: 90% (95% CI: 53%–90%)	3-yr LPFS: 73%	3-yr OS: 78%	Not reached
Comito et al[43]	P	3	Intermediate-stage HCC after incomplete response to TAE/ TACE, CP A, B, BCLC A, B	41	SBRT vs. TAE/ TACE	1-yr LC	30–75/3–10	1-yr LC: 84% vs. 23% ($p = 0.0002$; HR: 0.15; CI 95% 0.04–0.4)	Median PFS: 9 vs. 4 ($p = 0.016$)	mOS: 31 mo vs. 30 mo ($p = 0.472$)	31 mo vs. 30 mo
Dawson et al[44]	P	3	Unresectable HCC, CP A, B, C, BCLC B, C	177	SBRT vs. sorafenib	OS	40–50/5		Median PFS: 9.2 vs. 5.5 ($p = .0001$)		15.8 vs. 12.3 ($p = .0554$[a], 90% CI 11.4–19.2)

[a]After adjusting for PS, M stage, CP A5 versus 6, and degree of MVI, OS was statistically significantly improved for SBRT/S (HR = 0.72, 95% CI: 0.52–0.99, 2-sided Cox $p = 0.042$). ~ estimated from Kaplan-Meier curves. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh score; OS, overall survival; P, prospective; PBT, proton beam radiotherapy; PFS, progression-free survival; Pts, patients; R, retrospective; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization.

have led to the development of practice guidelines for the applications of radiotherapy,[52] especially SBRT,[53] that cite excellent LC, OS, and a low risk ($<10\%$) of late complications.

Although sorafenib remains a treatment option for patients with advanced HCC, it is unknown whether the improved outcomes with SBRT persist alongside new immunotherapy-based regimens, although preliminary data suggest it is safe.[54] Early separation of survival curves in RTOG 1112 hints that SBRT could serve as a treatment option for patients ineligible for immunotherapy. Studies combining immunotherapy and SBRT are actively being explored and detailed later in this review.

While most radiation treatments use photons, particle radiotherapy with protons and carbon ions has also been explored. Particles have the advantage of potentially delivering lower doses to non–tumor-bearing liver, which may decrease toxicity.[55] A single-arm prospective phase II trial in patients with locally advanced unresectable HCC and intrahepatic cholangiocarcinoma treated with ablative proton therapy (67.5 Gy in 15 fractions) showed 94.8% and 94.1% 2-year local control, respectively.[56]

SBRT VERSUS OTHER LIVER-DIRECTED TREATMENTS

Surgical resection

OLT and surgical resection are first-line curative treatments for early HCC. Several retrospective studies have compared SBRT with resection for the treatment of patients with small primary HCC and showed similar LC.[56,57] Confirmatory prospective randomized studies are needed before SBRT can be considered an alternative to resection in this patient population.

Local ablation therapy

RFA is also indicated for early HCC (BCLC 0 or A), although many centers prefer MWA, which is comparatively faster, exhibits less convective heat sink, and allows for larger treatment volumes. The SURF trial, a multi-institutional RCT in Japan, included 308 patients with small local HCC (≤ 3 cm, ≤ 3 nodules) and found no significant difference in RFS or 5-year OS between surgery and RFA.[58] Similarly, Ng et al[59] conducted an RCT comparing hepatic resection and RFA for early-stage HCC, finding no significant differences in tumor recurrence rates, 1-, 3-, 5-, and 10-year OS, or DFS between the groups. Two matched nonrandomized trials[60,61] comparing liver resection and MWA found similar 1-, 3-, and 5-year OS and RFS, but higher local recurrence with MWA, likely due to patient selection bias. In aggregate, these studies have established ablation with either RFA or MWA as definitive options, especially in patients ineligible for surgery.

Retrospective studies comparing RFA and SBRT have shown mixed results.[62,63] Meta-analyses comparing SBRT to RFA report better or comparable LC with SBRT,[64–66] however more death and liver damage from SBRT.[67]

In 2021, Kim et al[41] published results from their phase III noninferiority study comparing ablative SBRT with protons (66 Gy in 10 fractions, $n=72$) to RFA ($n=72$) in patients with recurrent/residual HCC (<3 cm, ≤ 2 lesions) stratified by CP score and tumor stage. SBRT was noninferior to RFA on the primary endpoint of 2-year local PFS (92.8% vs. 83.2%, HR 0.73, $p=0.419$), as well as on secondary endpoints of PFS (2-y, 31.9% vs. 31.9%, HR 0.99, $p=0.958$) and OS (2-y: 91.7% vs. 90.3%, HR 1.07, $p=0.821$). Both treatments were well tolerated, with fewer grade 2 (7.5% vs. 20.3%) and grade 3 (0.0% vs. 16.1%) AEs in the SBRT with protons group, though there was a 32.5% incidence of grade 1 radiation pneumonitis following SBRT.

Transarterial embolization

Transarterial embolization (TAE), either bland or with chemotherapy (TACE), is a treatment for unresectable HCC. TACE has a 1A recommendation for stage B disease,[68] but some institutions prefer TAE due to lower costs and inconclusive comparative efficacy. Conventional TACE involves intraarterial administration of doxorubicin ($\pm$ cisplatin, and/or mitomycin C) mixed in lipiodol followed by blood flow occlusion with agents like Gelfoam, or bland microspheres.[69] Drug-eluting bead TACE (DEB-TACE) is also used to the same ends with reduced systemic toxicities. Since primary hepatic tumors are supplied by hepatic arteries, microspheres target tumoral tissue, causing cell death with minimal effects on the nonaffected liver.

In 2003, Llovet and colleagues performed a systematic review of randomized trials that included 7 trials with 545 patients assessing TACE in the treatment of unresectable HCC. Arterial embolization improved 2-year survival significantly compared with control, and sensitivity analysis showed the benefit for TACE with cisplatin or doxorubicin, but not TAE alone.[69] TACE represents a standard of care treatment, as illustrated by the 2022 BCLC Strategy publication,[6] and routine use in clinical practice. Contemporary data suggest TACE imparts a median survival of 25 months in properly selected patients. Studies comparing TACE and TAE show conflicting results.[70–73]

The LAUNCH trial, a phase III study of 338 patients with advanced HCC, reported that adding TACE to lenvatinib improved OS (17.8 vs. 11.5 mo, $p<0.001$)

and PFS (10.6 vs. 6.4 mo $p < 0.001$).[74] Treatment was well tolerated, with similar toxicities between groups, though grade ≥ 3 liver enzyme increases were statistically higher in the combination group. This was the first positive study confirming the role of local therapy in advanced disease.

An abstract of EMERALD-1, a phase III study compared TACE with or without durvalumab and bevacizumab for unresectable HCC eligible for embolization, reported improved PFS (HR 0.77, $p = 0.032$) in the combined TACE/durvalumab/bevacizumab with a manageable safety profile.[75]

Several retrospective and prospective studies have compared the outcomes of TACE to SBRT. Méndez Romero et al[27] recently published a multicenter randomized phase 2 trial, which prematurely closed due to slow accrual. In the ITT analyses, median TTP was 12 months for TACE and 19 months for SBRT ($p = 0.15$), median LC was 12 months for TACE and > 40 months (not reached) for SBRT ($p = 0.075$), and median OS was 36.8 months for TACE and 44.1 months for SBRT ($p = 0.36$). A post-hoc analysis showed 100% 1- and 2-year LC for SBRT, and 54.4% and 43.6% for DEB-TACE ($p = 0.019$), respectively. Comito et al reported a phase III randomized trial[43] comparing SBRT to TACE for intermediate-stage HCC after incomplete response following 1 TAE/TACE course, showing superior LC with SBRT (median not reached vs. 8 mo, $p = 0.0002$). While OS did not differ, the superior LC with SBRT suggests further confirmation is needed.

A phase III study by Bush et al[38] comparing ablative proton beam radiotherapy (PBT) (70.2 Gy in 15 fractions; n = 36) to TACE (n = 40) showed PBT had improved LC (HR 5.64, 95% CI: 1.78–17.9, $p = 0.003$), PFS (HR 3.62, 95% CI: 1.62–8.05, $p = 0.002$), liver control (HR: 3.18, 95% CI: 1.29–7.86, $p = 0.012$), fewer hospitalization days (166 for TACE vs. 24 for PBT), and lower costs for payors, without correction for capital equipment or amortization of PBT.

Liver-directed therapies are often used to bridge patients with HCC for liver transplant as well. An ITT analysis compared SBRT versus TACE or RFA as a bridge to transplant in patients with HCC. The 1-, 3- and 5-year survival from the time of transplant did not significantly differ between the groups.[76]

In summary, while there is no survival difference between TACE and SBRT, randomized data suggest improved LC and fewer hospitalization days with SBRT. Patient selection and institutional factors may influence treatment choice in this patient population.

Radioembolization

TARE, or selective internal radiation therapy (SIRT), uses arterial hypervascularity of HCC to deliver yttrium-90 (^{90}Y)-loaded glass (20–30 μm) or resin (20–60 μm) microspheres, to delay local progression and downstage HCC, allowing resection or transplantation.[77–79]

TARE is FDA-approved for unresectable, solitary HCC ≤ 8 cm with ECOG status 0 or 1, based on the LEGACY study, a single-arm, retrospective study showing an 88.3% overall response rate at 29.9 months median follow-up. Three-year OS was 86.6% for all patients, and 92.8% for patients who subsequently underwent resection or transplant.[80] Notably, patients included had no vascular invasion or extrahepatic disease.

To date, 3 RCTs evaluating TARE in advanced HCC have been published. The SARAH[81] (n = 459) and SIRveNIB[82] (n = 360) phase III trials compared TARE with ^{90}Y-resin microspheres versus sorafenib. SORAMIC (n = 424),[83] a randomized phase II trial, evaluated TARE combined with sorafenib versus sorafenib alone. None showed OS benefit of adding TARE; however, tumor response differences favoring TARE suggested further studies with personalized dosimetry software and super-selective TARE are needed.[84] Interpreting these trials with sorafenib as the control is challenging given contemporary reliance on immunotherapy-based regimens, and studies combining TARE and immunotherapy are ongoing.

The recently published AASLD guidelines[14] state that TARE or SBRT may be used as alternative therapies to thermal ablation for patients with BCLC stage A HCC who are not candidates for surgical resection, including those with tumors > 3 cm (Level 3, Strong Recommendation).

Although practice patterns in the US vary, TARE is often used over TACE, especially for lesions that are multifocal or have recurred after prior TACE/TAE treatment. In the TRACE phase II prospective RCT,[85] TARE was compared with TACE in patients with BCLC A or B HCC ineligible for surgery or ablation. Both median TTP (17.1 mo vs. 9.5 mo in the ITT group, $p = 0.002$), and median OS (30.2 mo vs. 15.6 mo, $p = 0.006$) were significantly improved with TARE. Salem et al[86] published a prospective phase II study comparing TACE with TARE in the treatment of HCC. Patients in the TARE group had significantly longer median TTP (> 26 mo) than patients in the TACE group (6.8 mo, $p = 0.0012$).

TARE has not been prospectively compared to SBRT for HCC and comparative studies are needed. However, the aforementioned meta-analysis by Rim and colleagues compared TARE, 3D-CRT, and SBRT, and showed 2-year LC rates of 57.5% (95% CI: 43.6–70.3), 82.8 (95% CI: 77.2–87.2), and 86.9% (95% CI: 81.0–91.2), respectively. These data suggest improved LC rates for either SBRT or 3D-CRT over TARE; however, numbers were small and TARE technique has improved since this analysis.[24]

Personalized dosimetry, which quantifies absorbed doses delivered to tumors relative to liver parenchyma, was assessed in the DOSISPHERE-01 phase II study (n = 93). This study compared standard dosimetry

(SDA) with personalized dosimetry (PDA) and was halted early due to positive interim results. Personalized dose escalation ($\geq$205 Gy) using ^{90}Y glass microspheres, while limiting doses to the healthy liver ($<$30 Gy) and lungs ($<$30 Gy), was feasible and improved objective response rates compared to standard dosimetry (120 ± 20 Gy). The study showed that there may be an advantage (ORR, OS) to tailoring the injected activity, based on scans using ^{99m}Tc-labeled macro-aggregated albumin (MAA) as a surrogate for the ^{90}Y glass microspheres, to maximize tumor dose so long as dose to organs at risk remains acceptable.[87] It is worth noting that while ^{99m}Tc-labeled MAA scans are widely used to estimate dosimetry before TARE, they have limitations in accurately predicting the actual delivered dose because these are surrogates of the therapeutic microspheres, not the microspheres themselves and biodistributions may, accordingly, differ. Posttreatment PET imaging, which measures the distribution of ^{90}Y microspheres, provides a more precise assessment of dosimetry but has the disadvantage of being available only after treatment (eg, retrospective vs. prospective dosimetry).

Concerns regarding DOSISPHERE-01 include the presence of patients with more advanced disease in the SDA arm and more censoring in the PDA group, potentially influencing results.[88] Nevertheless, this personalized dose-escalated approach warrants further study as recent retrospective trial suggests it may allow resection in patients with initially unresectable HCC (single large lesion, median size ~9 cm).[89]

Emerging data support the rationale for TARE with immunotherapy. Chew et al[90] correlated sustained clinical response with following immune activation using TARE. This was further confirmed by Rivoltini et al.[91] More recently, a prospective study combining TARE with pembrolizumab yielded a median OS of 27 months in patients with PVT, multifocal and diffuse disease, further confirming that radiation combined with immunotherapy deserves special focus.[92] The NASIR and SOLID trials further support the further exploration of combination in prospective randomized studies.[93,94] The ROWAN[95] and EMERALD-Y90[96] are prospective randomized and single-arm phase II trials, respectively, that are also investigating the combination.

EBRT COMBINED WITH OTHER LIVER-DIRECTED THERAPY

The efficacy of combined treatment with EBRT and TACE has been explored as well. A meta-analysis from 2015 demonstrated significantly improved median survival with the addition of SBRT to TACE compared to TACE alone.[56] An RCT by Yoon and colleagues compared TACE plus EBRT (30–45 Gy in 15 or 18 fractions, not ablative) versus sorafenib in patients with HCC with MVI. TACE was delivered every 6–8 weeks (median 4, IQR, 3–4). The combined treatment improved PFS (at 12 wk, 86.7% vs. 34.3%, $p < 0.001$), objective response rate (at 24 wk, 33.3% vs. 2.2%, $p < 0.001$), TTP (31 vs. 11.7 wk, $p < 0.001$), and OS (55 vs. 43 wk, $p = 0.04$) compared with sorafenib alone.[97] Again, these data suggest that local treatments, particularly in combination, may offer additional benefits over systemic therapy alone for certain patients with advanced HCC.

A recent RCT found that combining SBRT with TACE and TKIs significantly improved 6-month PFS (78% vs. 36%, $p = 0.0245$) and OS (17.93 vs. 9.61 mo, HR = 1.869, $p = 0.017$) compared to TACE and TKIs alone in patients with unresectable HCC and portal vein tumor thrombus, with no severe safety concerns identified.

HAIC

HAIC, a less common transarterial-based locoregional therapy, usually involves multi-day delivery of FOLFOX (oxaliplatin, leucovorin, and fluorouracil) and has been evaluated in prospective RCTs. A phase III RCT by Li et al[98] compared FOLFOX-based HAIC (n = 159) to TACE (n = 156), showing superior median OS (23.1 vs. 16.1 mo, HR 0.58, 95% CI: 0.45–0.75, $p < 0.001$) and longer median PFS (9.6 vs. 5.4 mo, $p < 0.001$), with 2 treatment-related deaths in each group.[98] Lyu et al[99] compared FOLFOX-based HAIC (n = 130) to sorafenib (n = 132) in a phase III RCT in patients with a median tumor size of 11.2 cm, macrovascular invasion in 65.6%, showing improvement in median OS 13.8 months versus 8.2 months (HR: 0.41, 95% CI: 0.301–0.552, $p < 0.001$). These data suggest that escalating local therapy with HAIC can improve outcomes even in high-risk patients.

EMERGING RADIOTHERAPY APPROACHES

Palliative RT for end-stage disease

There is a role for RT in end-stage HCC as well. Dawson and colleagues recently published the Canadian Cancer Trials Group HE1 study, a phase III RCT comparing single fraction whole or near-whole liver palliative RT to best supportive care for the treatment of patients with painful HCC or liver metastases. The primary endpoint of pain control measured with Brief Pain Inventory was improved in 67% versus 22% of patients treated with RT or best supportive care, respectively ($p = 0.004$).[100]

Oligometastatic disease

SBRT is frequently used in oligometastatic disease as a local therapy in addition to systemic therapy,[101–103] and

even RTOG 1112 includes a small proportion of patients with extrahepatic disease (4%). A prospective phase II study has recently demonstrated good local tumor control rates and improved survival for patients with oligometastatic HCC treated with SBRT.[104] This approach can facilitate continuing systemic therapy by addressing oligoprogressive lesions. How modern systemic therapies, including immunotherapy, interact with radiotherapy is actively being investigated.

Radiation combined with immunotherapy

Immune checkpoint inhibitors have significantly improved PFS and OS in advanced HCC.[11,12] Salem and Greten[105] highlighted the rationale for combining locoregional therapies with immunotherapies in HCC, though prospective data are limited.

Along with the discovery of the abscopal effect—where RT to a single site induces responses in distant lesions—it has been suggested that the RT effect is closely influenced by the immune microenvironment.[106] Preclinical studies show irradiation triggers immunogenic cell death, releasing tumor-associated antigens and activating the immune system.[107,108] However, clinical results in several cancer types have been less than inspiring to date.[109–111]

A phase I trial of SBRT followed by nivolumab plus ipilimumab or nivolumab alone in advanced/unresectable HCC showed favorable outcomes for the combination, with a 57% response rate and 41.6 months median OS. The study faced slow accrual and 2 of 13 patients (15.4%) experienced dose-limiting toxicity, and grade 3 AEs were experienced by 8 patients (61.5%), which included 4 (30.8%) grade 3 hepatotoxicity.[112]

A prospective observational study treating 30 patients with conventionally fractionated radiation followed by atezolizumab and bevacizumab showed a 90% response rate. Grade 3-4 toxicities were seen in 8 (27%) patients and there were 9 (30%) who experienced a progression of Child-Pugh score of 2 points or greater. A median of 8 cycles were delivered after radiation, like what was achieved in the IMbrave150 study, suggesting safety of the combination.[113]

Results from a single-arm phase II study enrolling patients with recurrent or oligometastatic HCC (96% HBV associated) for treatment with ablative SBRT (54 Gy in 6) combined with sintilimab were recently reported. Twenty-five of the planned 30 patients had been enrolled, and the median follow-up was 21.9 months. The primary endpoint of PFS was 19.7 mo (95% CI: 16.9–not reached). Median OS was not reached, and the 1- and 2-year OS were 91.5% (95% CI: 80.8–100) and 83.2% (95% CI: 66.5–100), respectively. One- and 2-year LC rates were 100% and 90.9%, respectively. No grade 4 or 5 treatment-related AEs were reported. Grade 3 (n = 3, 12%) events included elevated gamma-glutamyl transpeptidase, thrombocytopenia, and myositis.[114]

A multicenter single-arm phase II study, including patients with HCC with portal vein tumor thrombus, demonstrated favorable treatment response and survival outcomes, along with an acceptable safety profile, for the combination of RT with sintilimab and bevacizumab. Patients obtained an ORR of 58.7% and a disease control rate of 100%.[115]

Ongoing trials are examining the efficacy of combining immunotherapy with EBRT for HCC.[116–118] We should reiterate and caution that prospective studies are sparse and, to date, lack demonstrable synergy between radiotherapy and immunotherapy.

While the role of combining SBRT or other LDTs with immunotherapy remains to be established in HCC, evidence from both RTOG 1112 and LAUNCH suggest that LDTs may be beneficial for patient outcomes when combined with systemic therapies.[74,119]

BRACHYTHERAPY

CT-guided high–dose-rate interstitial brachytherapy (HDRBT) is an ablative technique during which a radioactive source is inserted into the tumor through catheters. While brachytherapy is widely adopted by centers around the world, the evidence is mainly retrospective.[120,121]

Low–dose-rate brachytherapy (LDRBT) administered by ^{125} I seed Implantation is a treatment used for multiple cancer types including HCC.^{125} I seeds continuously release low energy γ-rays, which destroy tumor cells without endangering normal tissues.[122–124]

Retrospective data suggest that either definitive brachytherapy or dose escalation with brachytherapy appears to improve response rates.[19] While these results are promising, prospective data are needed to define any potential role of brachytherapy for HCC.

RADIOPHARMACEUTICAL THERAPY

Cancer-targeted radiopharmaceutical therapy (RPT) leverages therapeutic emissions of unstable radioisotopes to exert anticancer effects and include FDA-approved agents for patients with lymphomas, neuroendocrine tumors, and prostate cancers.[125]

The radioiodine (^{131}I)-labeled antibody fragment (F(ab')$_2$), ^{131}I-metuximab, is specific to CD147 antigen, which is expressed in 60%–75% of HCC. Studies have shown efficacy of intraarterial administration in patients with unresectable HCC,[126,127] after ablation,[128] and as adjuvant treatment after liver transplantation[129] or after hepatectomy in patients with early HCC.[130]

Several groups are evaluating other targets present in HCC for possible RPT, including glypican-3

(GPC3)[131]; prostate-specific membrane antigen (PSMA),[132] which is also expressed on the neovasculature of HCC; and fibroblast activation protein (FAP) for which inhibitors (FAPi) have been developed and that can localize cancer-associated fibroblasts of HCC.[133]

CONCLUSIONS

Liver-directed therapies for HCC are important in improving the outcomes of patients. Choosing among these therapeutic options is best done in multidisciplinary discussions that consider patient-specific factors, underlying liver health, burden and location of the tumor, local expertise, and clinical infrastructure. Transplant is often the best curative option if feasible, otherwise, resection or ablation are preferred. Ablation has demonstrated comparable OS and RFS compared to surgery, offering an effective definitive local therapy in a single-day procedure for patients ineligible for resection. TACE and TARE have generally been used for larger or multifocal lesions, allowing for local control before transitioning to systemic therapy, and radiation segmentectomy for small lesions can yield a complete pathological response when personalized dose escalation is applied—a principle extrapolated from ablative EBRT.[134]

While radiation to the liver was once limited due to concerns of liver toxicity, modern studies indicate even with large total tumor burden or vascular invasion, external radiation can be administered safely with few side effects. In many cases, the adverse events profile is comparable to those documented in patients receiving systemic therapy alone[44] or TACE.[43,135]

In the modern era, there are prospective clinical trial data supporting that RT may play certain roles across a diverse set of HCC stages, from early and curative intent,[26] through intermediate,[26,43,119,135] to end-stage disease and palliative intent.[136] Other radiation approaches like brachytherapy and targeted radiopharmaceutical therapy are being investigated.

Importantly, while local control benefits are expected with LDTs, recent phase III trial results suggest that SBRT and TACE can be safely combined with systemic therapies with the potential for OS benefit. Given the growing evidence suggesting that ionizing radiation can synergize with immunotherapy, combinations with SBRT or TARE are being studied in prospective clinical trials.

With recent technological advances and prospective clinical trial data, modern radiotherapy may be added as a therapeutic option for LDTs to our armamentarium for HCC. Substantial progress has been made in predicting liver injury following radiation therapy, with a focus on quantitatively estimating the dose and volume tolerance of the liver, especially in patients with varying degrees of liver dysfunction. This progress has improved our understanding of liver tolerance to radiation, enabling safer and more effective treatments.

There are several limitations in our review and reflect existing and heterogenous treatment and assessment paradigms across the diverse specialties that care for patients with HCC. For example, the imaging features for appraising treatment response differ depending on the studies in question and which interventions are being evaluated. While thermal ablation and embolization techniques are typically evaluated by the early absence of arterial phase on imaging, radiation therapy often requires several months to achieve comparable imaging changes due to its gradual mechanism of action. This delayed resolution can result in the misinterpretation of early posttreatment imaging as persistent or progressive disease. Recognizing this difference is critical to avoid premature or inaccurate conclusions about treatment failure. The Liver Imaging Reporting & Data System (LIRADS) recently developed standardized imaging guidelines to assess treatment response that aims to account for the distinct response kinetics across the different liver-directed interventions. That said, it is clear that there is a critical need for better functional imaging strategies that can better discern treated, nonviable tumor tissue from the residual or recurrent viable tumor (eg, novel HCC-selective PET imaging agents[131]).

Notably, our review often referenced endpoints including “local control,” “progression-free survival,” and “objective response” as reported in the literature. This reflects a broader challenge in the field, where the endpoints differ across studies and specialties. Radiation oncologists tend to prioritize endpoints such as local control and PFS, whereas interventional radiologists often rely on objective response criteria. These discrepancies in outcome assessment and timeframes in assessing these endpoints create challenges when comparing results across studies and hinder the development of a cohesive framework for evaluating HCC treatments. Establishing unified response criteria and clinical trial reporting that integrate these varied perspectives is imperative in moving our field forward.

Ultimately, having several effective therapies available for local liver consolidation is good. Matching a specific patient with tailored treatment recommendations requires truly cross-disciplinary collaboration, ideally in the context of multidisciplinary disease management teams. When efficacy between treatments is comparable or where data are equivocal, such teams need to balance the benefit of a recommended treatment with a number of treatment-related visits, adverse event profile, cost-effectiveness, local expertise, and need for inpatient stays or outpatient visits to minimize the time burden on the patient. Using this patient-centered approach, clinicians can provide the best possible care for the diverse patient population with this very challenging disease.

CONFLICTS OF INTEREST

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