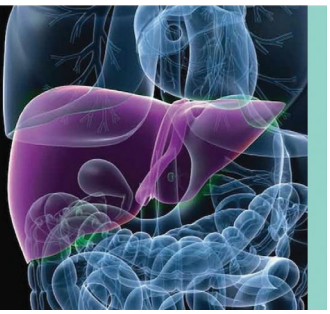


Radiation Therapies for the Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a leading cause of worldwide cancer mortality.[1] There is emerging favorable evidence behind the efficacy of radiation therapy in the form of transarterial radioembolization (TARE) and external beam radiation therapy for patients with HCC. Herein, we review the evidence for the use of these therapies, the assessment of treatment response, and the future directions needed for wider application of radiation therapy for the treatment of HCC.

TARE

TARE with yttrium-90-embedded glass or resin microspheres was given compassionate use approval by the US Food and Drug Administration in 1999, and with refinement in technique and patient selection, it has become an increasingly used form of locoregional therapy for HCC.[2,3] The principle behind TARE infusion is intra-arterial delivery of high-dose ionizing radiation into the tumor bed via the hepatic artery, with continuous radiation exposure as the yttrium-90 decays. TARE is typically conducted in a two-step process, with a ^{99m}technecium-labeled macroaggregated albumin mapping study prior to treatment to evaluate possible deposition of microspheres in extrahepatic sites, although patients with early-stage HCC (T1 or T2) may be able to avoid the mapping procedure.[4]

The efficacy of TARE has been evaluated across multiple stages of HCC (Table 1). In early-stage HCC, "radiation

Abbreviations: APHE, arterial-phase hyperenhancement; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CP, Child-Pugh; CR, complete response; HCC, hepatocellular carcinoma; HR, hazard ratio; LI-RADS, Liver Imaging Reporting and Data System; LR TR, LI-RADS Treatment Response; OS, overall survival; PR, partial response; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SD, stable disease; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TTP, time to progression.

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Potential conflict of interest: N.D.P. consults for Bristol Myers-Squibb, Exact Sciences, Eli Lilly, and Freenome. He advises Genentech, Eisai, Bayer, Exelixis, and Wako/Fujifilm. He received grants from Bayer, Target Pharmasolutions, Exact Sciences, and Glycotest.

Received August 31, 2020; accepted October 25, 2020.

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TABLE 1. KEY STUDIES OF TARE FOR THE TREATMENT OF HCC

Author (year)	n	Design	Intervention	Outcomes
Observational Cohorts				
Salem et al. (2018)[14]	N = 1000 BCLC stage A: 263 BCLC stage B: 152 BCLC stage C: 541 BCLC stage D: 44	Single-center prospective cohort	TARE	OS: CP class A: BCLC stage A: 47.3 months BCLC stage B: 25.0 months BCLC stage C: 15.0 months CP class B: BCLC stage A: 27.0 months BCLC stage B: 15.0 months BCLC stage C: 8.0 months
Early/Intermediate-Stage HCC				
Vouche et al. (2014)[5]	102 with solitary HCC ≤ 5 cm	Multicenter retrospective cohort	TARE segmentectomy	CR: 47% PR: 39% SD: 12% TTP: 33.1 months OS: 53.4 months
Salem et al. (2016)[7]	45 patients with CP class A cirrhosis and HCC: 24 underwent TARE and 21 underwent TACE	Randomized control trial	TARE versus TACE	Median TTP: TARE: >26 months TACE: 6.8 months OS: TARE: 18.6 months TACE: 17.7 months
Advanced-Stage HCC				
Vilgrain et al. (2017)[15]	459 patients with CP class A cirrhosis and BCLC stage C HCC: 237 assigned to TARE and 222 assigned to sorafenib	Randomized control trial	TARE versus sorafenib	OS: TARE: 8.0 months Sorafenib: 9.9 months
Chow et al. (2018)[16]	360 patients with CP class A cirrhosis and BCLC stage C HCC: 182 assigned to TARE and 178 assigned to sorafenib	Randomized control trial	TARE versus sorafenib	OS: TARE: 8.8 months Sorafenib: 10.0 months

segmentectomy" (treatment using TARE in an entire single liver segment) has been shown to be effective for local tumor control or as a bridge to resection, with a high level of pathological correlation for complete tumor response.[5] In a retrospective study of 70 patients treated with TARE with tumor size up to 5 cm, the median time to progression was 2.4 years.[6] There has been one randomized single-institution study comparing TARE versus transarterial chemoembolization (TACE) that consisted of 45 patients in total. Patients who received TARE had a longer time to progression (>26 versus 6.8 months), but there was no difference in OS (18.6 versus 17.7 months; $P = 0.99$).[7] Lower levels of evidence, including meta-analysis of observational cohort studies, have demonstrated conflicting results of TTP and OS between TACE and TARE.[8-10] TARE may be an effective bridge to liver transplantation for eligible patients, with outcomes comparable with TACE.[11,12] Overall TARE is well tolerated, with fatigue, abdominal pain, nausea/vomiting, and radiation-induced liver disease as the most common complications.[13,14] Common relative contraindications to TARE include hepatic dysfunction (e.g., hyperbilirubinemia), hepatofugal portal venous flow, and significant lung shunt fraction.

Two large randomized controlled trials compared delivery of TARE versus sorafenib in patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC.[15,16] The SARAH trial, a multicenter trial in France of patients with previously unsuccessful TACE, showed no significant difference in survival between TARE and sorafenib (median 8.0 versus 9.9 months, respectively [hazard ratio [HR]: 1.15; 95% confidence interval [CI]: 0.94-1.41]).[16] The SIRveNIB Trial, completed in Asia among predominantly patients with hepatitis B infection, also showed no significant difference in survival between the two strategies (median 8.8 versus 10.0 months, respectively [HR, 1.1;

95% CI: 0.9-1.4]); however, patient quality of life was superior in both studies with TARE. Notable weaknesses of these studies include patient selection and limitations in the TARE delivered (i.e., lack of boosted radiation dosing); nevertheless, there is no evidence that TARE provides a survival benefit in unresectable HCC over systemic therapy, which is especially salient with the recent advent of more effective systemic therapies for HCC.[17]

The lack of controlled data supporting its efficacy has limited the widespread adoption of TARE; however, ongoing prospective trials will further define its role in the treatment of HCC across all BCLC stages.

STEREOTACTIC BODY RADIATION THERAPY

External beam radiation therapy is another emerging option for the treatment of HCC across BCLC stages and has evolved in recent years. Stereotactic body radiation therapy (SBRT) provides high-dose external radiation focused on the tumor while minimizing radiation damage to the surrounding liver parenchyma. Common adverse effects associated with SBRT include fatigue, anorexia, and liver decompensation. Patients with severe hepatic dysfunction have a relative contraindication to SBRT; however, there is some evidence that adaptive protocols that tailor radiation dosing to changes in liver dysfunction during treatment can help avoid significant decompensation in high-risk patients.[18,19]

The evidence behind the efficacy of SBRT comes largely from observational data (Table 2). In retrospective analyses in early-stage HCC, SBRT provides comparable local tumor control when compared with thermal ablation (83.8% versus 80.2% at 2 years), with superior control rates with tumors >2 cm (HR 3.35; $P = 0.025$.)[20,21] In comparison with TACE, SBRT is associated with superior tumor control for primary therapy (91% versus 23% at 2 years) and comparable with other therapies when bridging to transplant.[22,23] Finally, there are ongoing trials of SBRT combined with systemic therapies for patients with advanced HCC.[24] One randomized trial showed improved survival for patients who receive SBRT plus sorafenib versus sorafenib alone in 90 patients with

TABLE 2. KEY STUDIES OF SBRT FOR THE TREATMENT OF HCC

Author (year)	n	Design	Intervention	Outcomes
Early/Intermediate-Stage HCC				
Wahl et al. (2016)[20]	83 patients underwent SBRT and 161 patients underwent RFA	Retrospective cohort study	SBRT versus RFA	Freedom from local progression: 1-year: SBRT, 97.4%; RFA, 83.6% 2-year: SBRT, 83.8%; RFA, 80.2% 2-year OS: RFA, 53%; SBRT, 46%
Kim et al. (2019)[21]	105 patients underwent SBRT and 668 patients underwent RFA	Retrospective cohort study	SBRT versus RFA	Freedom from local progression (propensity matched): 2-year: SBRT, 74.9%; RFA, 64.9%
Sapir et al. (2018)[22]	114 patients underwent SBRT and 209 patients underwent TACE	Retrospective cohort study	SBRT versus TACE	Freedom from local progression: 1-year: SBRT, 97%; TACE, 47% 2-year: SBRT, 91%; TACE, 23% OS: SBRT, 34.9%; TACE, 54.9%; no significant difference in adjusted analysis ($P = 0.21$)
Sapisochin et al. (2017)[23]	Patients listed for liver transplantation: 36 patients underwent SBRT; 99 patients underwent TACE; 244 patients underwent RFA	Retrospective cohort study	SBRT versus TACE/RFA	Wait-list dropout: SBRT, 16.7%; TACE, 20.2%; RFA, 16.8% 5-year survival rate from listing: SBRT, 61%; TACE, 56%; RFA, 61%
Jackson et al. (2020)[19]	80 patients with CP class B cirrhosis underwent adaptive SBRT dosing tailored to liver function during therapy	Prospective cohort study	SBRT (single arm)	Freedom from local progression: 1 year, 92% 24% experienced radiation-induced liver decompensation within 6 months
Advanced-Stage HCC				
Yoon et al. (2018)[25]	90 patients with BCLC stage C HCC without extrahepatic metastases: 45 assigned to TACE+SBRT and 45 assigned to sorafenib	Randomized control trial	TACE+SBRT versus sorafenib	Time to progression: TACE+SBRT, 31.0 weeks; sorafenib, 11.7 weeks OS: TACE+SBRT, 55.0 weeks; sorafenib, 43.0 weeks

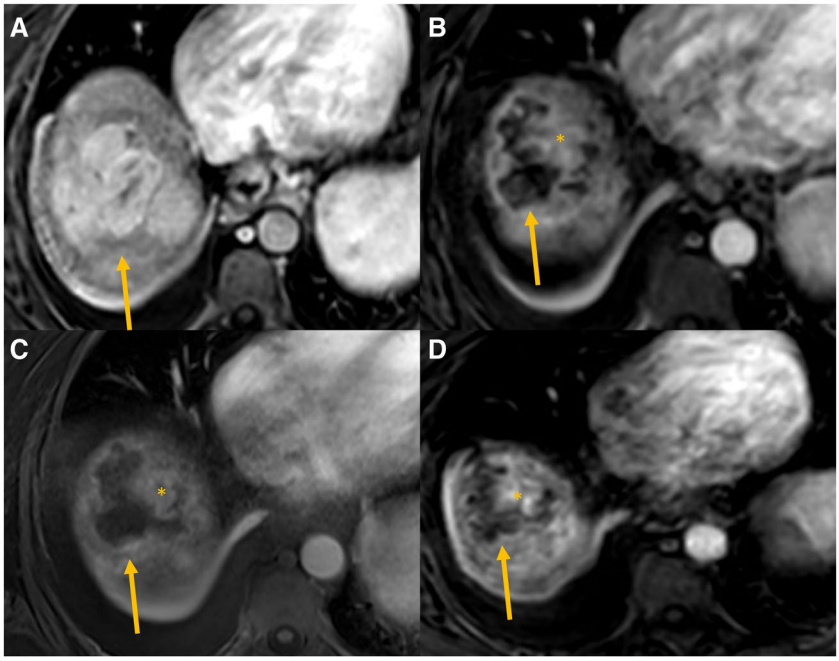


FIG 1 HCC, 7.2 cm, LI-RADS 5, in the dome segment 7/8 of the liver. (A) Large lesion demonstrating APHE and washout (not shown). Patient underwent TARE. (B) Three months after TARE, the lesion demonstrates large areas of nonenhancement, consistent with necrosis (asterisks). However, there is a persistent nodular area of enhancement (arrow), measuring 3.4 cm, LR TR Equivocal. (C) Imaging 4 months after TARE demonstrates persistent nodular enhancement, albeit smaller, measuring 2.5 cm, with overall regression of the treated tumor, LR TR Equivocal. (D) Imaging 6 months after TARE demonstrates persistent nodular enhancement, although smaller, measuring 2.1 cm, and overall continued regression in size of the treated tumor, LR TR Equivocal.

advanced HCC with macrovascular invasion (survival: 55 versus 43 weeks; $P = 0.04$).[25] There is additional observational data supporting the use of SBRT for local tumor control in patients with macrovascular invasion, including with extension into the inferior vena cava and right atrium, with 2-year survival rate up to 30% in one study from Korea.[26] As with TARE, early studies suggest that SBRT may provide an effective bridge to liver transplantation in eligible patients.[27]

Similar to TARE, prospective multicenter trials are needed to determine the role of SBRT in the HCC treatment algorithm and demonstrate its efficacy and safety, particularly given the technical expertise needed for effective administration of SBRT.

RADIOGRAPHIC EVALUATION AFTER LIVER RADIATION THERAPY

Response assessment after radiation-based therapies can be uniquely challenging to interpret because the imaging findings may not follow response criteria developed with other HCC therapies. Accurate interpretation of posttreatment imaging is important to prevent misdiagnosis of residual untreated disease and/or early retreatment. Posttreatment tumor shrinkage is often delayed, secondary to the cytostatic effects from radiation, which results in a delayed imaging response.[28]

After TARE, successfully treated tumors can demonstrate a range of imaging findings, including: (1) persistent intratumoral arterial-phase hyperenhancement (APHE), (2) geographic or nodular peritumoral APHE, (3) thin rim of peritumoral APHE, or (4) complete lack of enhancement (Fig. 1).[29] Importantly, persistent central arterial hyperenhancement can be seen longer than 3 months in tumors treated by TARE, with progressive decrease and eventual lack of enhancement over time. Imaging features suggestive of residual tumor after TARE include new or enlarging nodular or mass-like APHE within or around the treated tumor and growth over time, particularly more than 6 months after treatment.[29]

After SBRT, APHE with or without "washout" can persist for up to and occasionally greater than a year, although persistent APHE gradually decreases in intensity over time.[30] Early

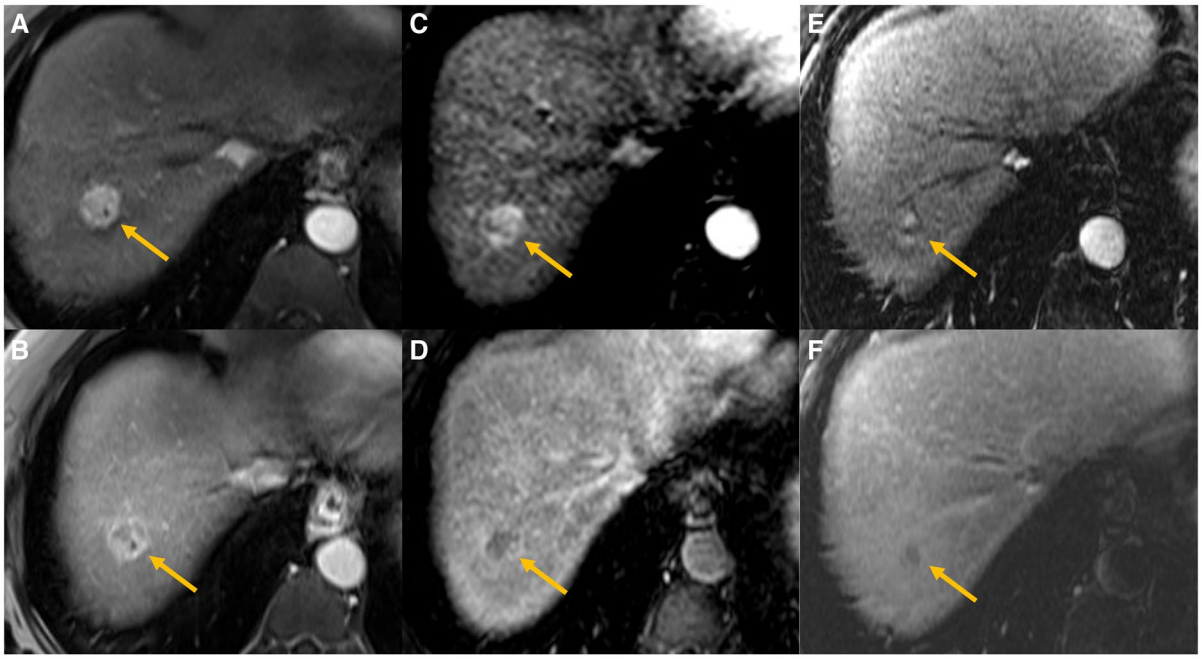


FIG 2 HCC, 2.4 cm, with APHE (A), washout appearance, and capsule appearance (B) is identified, LI-RADS 5. Patient undergoes SBRT for treatment. Three months after SBRT, the lesion measures 2.2 cm, with persistent APHE (C) and washout (D), LR TR Equivocal. (E) Five months after SBRT, the lesion continues to regress in size, with a 1.0-cm area of residual nodular APHE with washout appearance, LR TR Equivocal. (F) At 15 months after SBRT, there is no evidence of local progression based on clinical and imaging data.

posttreatment, geographic APHE surrounding the treated tumor is common and likely represents hyperemia; over time this converts to progressive delayed-phase geographic enhancement, likely secondary to radiation fibrosis, often associated with capsular retraction and peripheral intrahepatic biliary dilatation.[31] In addition, the treated tumor can gradually decrease in size as treatment response is evolving (Fig. 2).[30] Imaging features suggesting local disease progression after SBRT include increasing size of the treated tumor or new or increasing intensity of APHE after treatment.[10]

CONCLUSION

There are promising data regarding the use of TARE and SBRT in the treatment of HCC, with treatment outcomes comparable with other commonly used therapies for HCC. Radiation therapies are not currently included in guidelines as front-line therapies for HCC because of the lack of controlled data supporting their use. Prospective randomized control trials are needed across BCLC stages with attention to patient-reported outcomes, costs, and efficacy outside of expert centers, but in the interim, with proper expertise and patient selection, radiation therapies appear to be a viable and effective treatment option for HCC at multiple stages.

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