Role of External Beam Radiotherapy in Hepatocellular Carcinoma

Chien Peter Chen, MD, PhD

KEYWORDS

- Hepatocellular carcinoma • Radiotherapy • Radiation
- Stereotactic body radiotherapy • External beam radiotherapy
- Particle beam radiotherapy

KEY POINTS

- EBRT can provide comparable outcomes with similar safety profile as other loco-regional treatments for both resectable and unresectable HCC.
- For resectable HCC cases, EBRT can bridge patients to transplantation.
- In unresectable HCC patients, EBRT can provide high local control rates.
- EBRT can offer effective palliation in the metastatic HCC setting.
- Consideration of EBRT in the management of HCC should occur with a multidisciplinary treatment team.

INTRODUCTION

Liver cancer is the second leading cause of cancer death in men and sixth leading cause of cancer death in women.[1] The most common type of primary liver cancer globally is hepatocellular carcinoma (HCC) and causes include viral and nonviral etiologies, such as nonalcoholic fatty liver disease/nonalcoholic steatohepatitis and alcohol use.[2,3] Cases of HCC are expected to increase and effective treatments are imperative.

Patients with limited disease are eligible for liver transplantation. Due to limited availability of donor organs and strict criteria of liver transplantation, however, a significant proportion of HCC patients is not eligible for upfront curative treatments. Locoregional modalities with or without systemic therapies can help bridge patients to transplant. As for locally advanced and metastatic cases, radiotherapy and systemic therapies have improved and can offer effective palliation.[4] Systemic therapy options include molecular targeted agents.[5–11] Additionally, immune checkpoint modulators may have a role in HCC.[12–14]

Department of Radiation Oncology, Scripps Radiation Therapy Center, 10670 John Jay Hopkins Drive, San Diego, CA 92121, USA
E-mail address: chen.chienpong@scrippshealth.org

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As systemic therapies improve, local therapies have become more relevant. Local therapies for HCC include minimally invasive procedures, such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation, highly focused ultrasound, and irreversible electroporation.[15–17] For locally advanced cases, however, minimally invasive procedures can be limited by impaired portal-vein blood flow due to portal-vein thrombus, untreatable arteriovenous fistula, impaired renal function, bleeding diathesis, and tumor location (ie, protruding from the liver surface).[18–23]

Another local therapy, either alone or in combination with other locoregional and systemic therapies, is external beam radiotherapy (EBRT). Historically, EBRT had a limited role in treating the liver due to risk of radiation-induced liver disease (RILD). Classic RILD, which occurs within 4 months following radiotherapy, can present with fatigue, anicteric ascites, and hepatomegaly, with relatively normal liver function tests and normal bilirubin. Nonclassic RILD, which can occur within 3 months following radiotherapy, can present with jaundice and/or significant elevation of serum transaminases. Patients with underlying liver disease are at higher risk for nonclassic RILD.[24] Various technological advances have allowed for more precise and dose-escalated treatment regimens using radiotherapy. Given these developments, treatment guidelines for HCC have been updated. This review discusses the role of EBRT for HCC.

EXTERNAL BEAM RADIOTHERAPY TECHNIQUES

EBRT modalities include photon and particle beam radiation (**Table 1**). Photon-based EBRT involve x-rays whereas particle-based EBRT uses subatomic particles, such as protons, or heavier charged particles, such as carbon ions. Photon-based EBRT techniques include 2-dimensional radiotherapy (2DRT), 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and stereotactic body radiotherapy (SBRT). Particle-based EBRT techniques include 3DCRT and intensity-modulated proton therapy.

2DRT uses x-ray films to determine the appropriate positioning of radiation treatment fields via bony landmarks. Because no CT simulation is done, neither target volume nor critical organs at risk (OARs) are explicitly delineated. 2DRT allows for rapid treatment planning and treatment initiation. 2DRT is ideal for palliative situations.

Fig. 1 demonstrates the difference in dose distribution for the various EBRT techniques.

Although 2DRT planning does not employ CT-based planning, to better illustrate the dosimetric differences among the various EBRT approaches, a 2DRT plan is superimposed on a planning CT scan of an example HCC patient. The dose distribution of a 2DRT plan involves higher relative dose (yellow) deposition not only in the target lesion but also in a significant proportion of the liver.

In 3DCRT, the tumor target and critical OARs are delineated on a planning CT. Multiple x-ray treatment fields are used and arranged around the target to optimize coverage of the target while minimizing dose to critical OARs, such as the liver, kidneys, and spinal cord. Each of the x-ray treatment fields can be shaped by collimators to block out critical OARs. Each treatment field has uniform radiation intensity. The shape and radiation dose rate of each x-ray field typically are fixed. **Fig. 1** illustrates a more conformal dose distribution in the 3DCRT plan compared with the 2DRT plan. Additionally, less of the critical OARs receives high dose, which can reduce toxicity.

IMRT represents a more advanced form of 3DCRT. IMRT plans involve delineation of a target and critical OARs. Multiple x-ray fields are used and collimators are utilized

Table 1
Comparison of external beam radiotherapy techniques

Technique	Pros	Cons
2DRT	Ease of planning Least expensive	Difficult to spare liver and other nearby critical organs Palliative in intent
3DCRT	Conformal dose distribution Some critical organ sparing Inexpensive	Longer treatment regimen (multiple weeks of treatment)
IMRT	More conformal dose distribution than 2DRT/3DCRT Higher LC than 2DCRT/3DCRT Potentially more sparing of critical structures than 3DCRT	Complicated planning Can involve patient immobilization, tumor tracking, image guidance Longer treatment regimen (multiple weeks of treatment) More expensive technique than 2DRT/3DCRT
SBRT	High fractional dose that can lead to LC than 2DRT/3DCRT/IMRT Superior dose distribution and thus potential decreased liver toxicity Short treatment regimen (2–5 fractions)	Complicated planning Requires patient immobilization, tumor tracking, image guidance More expensive technique than 2DRT/3DCRT
Proton/heavy ion (particle)	High LC Decreased integral dose that may lead to decreased liver toxicity	More susceptible to tissue heterogeneity and range uncertainty Significant financial and spatial investment required for particle therapy program High cost for particle therapy treatment package (most expensive of all EBRT options) Longer treatment regimen (multiple weeks of treatment)

to shape each treatment field. IMRT, however, uses nonuniform radiation intensity by modulating the shape of the treatment fields and utilizes inverse planning.[25] IMRT thus can achieve even more conformal dosimetric plans, which translates into less volume of critical OARs receiving high dose than with 3DCRT plans, as shown in **Fig. 1**. Due to the complexity of generating IMRT plans, IMRT does require more time for treatment planning and quality assurance.

SBRT is characterized by careful delineation of target and critical OARs, tight target margins, and strict dose constraints for OARs. SBRT uses potentially ablative doses in short treatment regimens. SBRT plans deliver high fractional doses, such as 500 cGy to 1000 cGy, often over 2 to 5 fractions. In contrast, fractionated EBRT treatment modalities, including 2DRT, 3DCRT, and IMRT, deliver lower doses per daily fraction, where typical daily doses are in the 180-cGy to 300-cGy range, over 2 weeks to 6 weeks. **Fig. 1** shows the superior dose distribution of SBRT over other photon-based modalities. Additionally, given the high fractional dose, SBRT can offer ablative potential and thus offer high local tumor control.[26] Due to the tight target margins, however, careful patient immobilization, advanced tumor tracking, image guidance, and respiratory management are critical for accurate delivery of SBRT plans.[27–29]

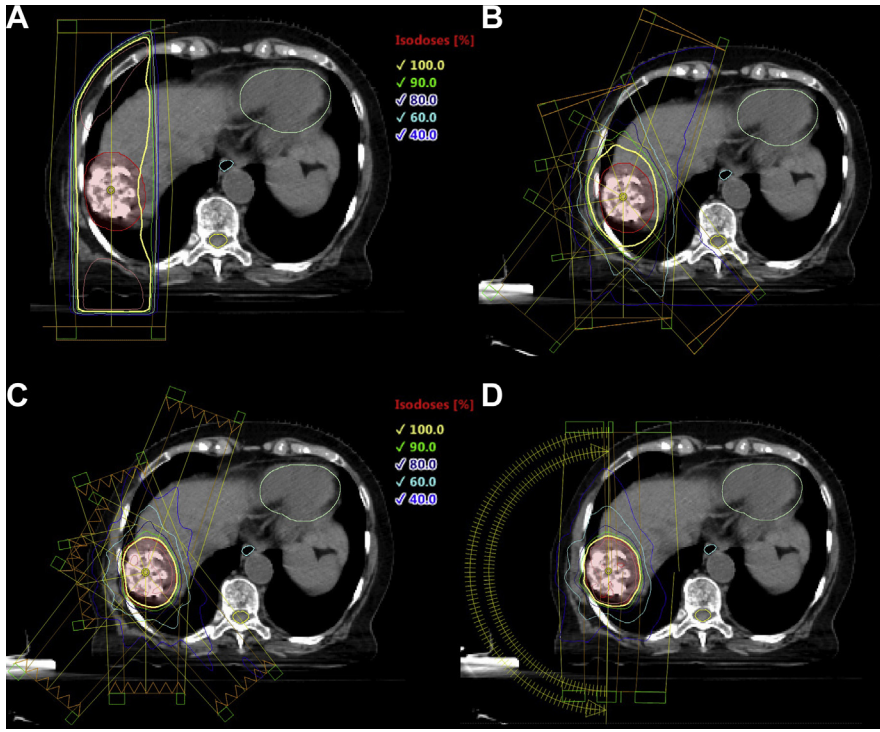

Fig. 1. Comparison of dose distribution for various EBRT techniques. Target is designated in red translucent color. Isodose lines represented by percent of total dose. (*A*). 2DRT (*B*). 3DCRT. (*C*) IMRT. (*D*) SBRT.

Similar to photon-based EBRT, charged particle therapy, such as proton beam therapy (PBT), can utilize 3-dimensional conformal and intensity-modulated approaches. Particle beam therapy, however, offers potential dosimetric advantages over some photon-based EBRT techniques. Charged particles have a finite range dependent on the initial charged particle energy. Particle EBRT uses simpler beam arrangements than photon EBRT. Particle EBRT thus can achieve decreased integral dose compared with photon EBRT. The effect of tissue heterogeneity and of range uncertainty, however, can negate or at least minimize the clinical advantages of particle-based radiotherapy. Additionally, particle EBRT requires significant financial and spatial investment, which have led to its limited availability and high cost.[30]

DOSE CONSTRAINTS

Regardless of the type of EBRT, whether photon based or particle based, dose constraints for the liver and nearby OARs must be respected. Early work on whole-liver radiation tolerance in patients treated for liver metastases was performed in the Radiation Therapy Oncology Group (RTOG) 76-09 and RTOG 84-05 trials. The whole liver could be treated safely to 2100 cGy in 7 daily fractions or 3000 cGy in 20 fractions delivered twice daily.[31,32] Partial-liver treatment, however, allowed for radiation dose escalation.[33] In 1991, Emami and coworkers[34] suggested baseline partial-liver tolerances. The whole-liver radiation dose associated with a 5% risk of RILD is 3000 cGy whereas a dose of 5000 cGy to one-third of the liver is associated with

the same 5% risk.[34] Models for RILD were developed and demonstrated that doses as high as 7260 cGy were safe if delivered to less than a third of the liver. normal tissue complication probability modeling showed that a mean dose of 5660 cGy was associated with a complication rate of approximately 5%. Additionally, the liver radiation tolerance was lower with patients with HCC versus those with liver metastases.[35–38] These studies suggested that focal radiation techniques could offer local disease control with relatively low risk for RILD.

Current dose constraints limit liver mean dose to less than 2800 cGy to achieve less than 5% risk of RILD for fractionated EBRT regimens. For SBRT, the quantitative analysis of normal tissue effects in the clinic constraints suggest keeping at least 700 cm^3 of liver receiving less than 1500 cGy for a 3-fraction SBRT regimen to achieve less than 5% risk of RILD. The American Association of Physicists in Medicine (AAPM) Task Group 101 constraints indicate at least 700 cm^3 of liver should receive less than 2100 cGy for 5-fraction SBRT regimens and less than 1920 cGy for a 3-fraction SBRT regimens.[39,40]

Evaluation for RILD includes Child-Pugh score (increase by 2 or more) and appropriate laboratory markers assessment, such as elevation of alkaline phosphatase (more than twice the upper limit of normal), of transaminases (greater than 5 times the upper limit of normal), and of total bilirubin as well as decrease in albumin and prothrombin time. Patients who may be inappropriate for radiation treatment include patients with liver reserve less than 700 cm^3, with active RILD, or with active connective tissue disorders, such as inflammatory bowel disease.

CURRENT GUIDELINES ON ROLE OF EXTERNAL BEAM RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA

Despite improved understanding and reduction of RILD risk with EBRT, many current guidelines suggest a limited role for radiation. The European Association for the Study of the Liver, American Association for the Study of Liver Diseases, and Japan Society of Hepatology guidelines do not include EBRT as a routine treatment of HCC.[41–43] In contrast, the Asian Pacific Association for the Study of the Liver guidelines indicates SBRT and charged particle therapy as reasonable options for patients who have failed other local therapies and could be considered for symptomatic bony metastases.[44] The Korean Liver Cancer Association guidelines indicates EBRT as an option in multiple settings, including HCC patients with portal vein tumor thrombus (PVTT), HCC patients with incomplete response to TACE, and HCC patients with symptomatic metastases.[45] The most liberal indications of radiotherapy occur in the Chinese guidelines, which suggests EBRT in multiple settings including adjuvant therapy for select patients with close margins.[46]

The discrepancy of recommendations for the role of EBRT is due partly to the lack of inclusion of radiation oncologists in the committees that develop treatment guidelines. With more recent evidence highlighting the efficacy of radiotherapy in HCC, the updated National Comprehensive Cancer Network guidelines includes radiotherapy as a treatment modality for HCC patients as follows[47]:

- Potentially resectable/transplantable patients with Child-Pugh class A or class B without portal hypertension but with adequate liver reserve
- Tumors 2 cm to 5 cm in diameter or 2 to 3 tumors less than or equal to 3 cm each without macrovascular invasion and no extrahepatic disease that are ineligible for transplant
- Unresectable HCC patients who are ineligible for transplant

- Inoperable patients, due to performance status or comorbidity, having local disease only or local disease with minimal extrahepatic disease
- Symptom control in the metastatic setting

COMPARATIVE OUTCOMES AMONG EXTERNAL BEAM RADIOTHERAPY MODALITIES

Three-Dimensional Conformal Radiotherapy and Intensity-Modulated Radiotherapy

3DCRT and IMRT are the main modalities used for fractionated EBRT regimens to treat HCC.

In the unresectable setting, including cases of PVTT, 3DCRT or IMRT provides good local control (LC) either alone or in combination with TACE or concurrent systemic therapy. The objective relative response (RR) ranged from 43% to 74% and the overall survival (OS) rate at 2 years ranged from 23% to 69%. Grade 3 hepatotoxicity was observed in 0% to 13%. Combined treatments tended to increase severe toxicity.[48–56] **Fig. 2** presents an unresectable, locally advanced HCC case treated with a combination of IMRT and sorafenib. Additionally, EBRT can be effective for inferior vena cava invasion.[57] In the resectable setting, adjuvant radiation has been considered in resectable or transplantable cases due to recurrence rates as high as 30%.[58–61] Microvascular invasion reduces disease-free and OS.[62] Postoperative radiotherapy has shown benefit in select scenarios. In posthepatectomy patients with tumors close to major vessels and close margins (<1 cm), adjuvant radiation significantly improved 3-year OS compared with patients who had close margin but did not receive radiation (OS, 64% vs 52%, respectively). The results of the adjuvant radiation group were comparable to results in patients who received wide margins (>1 cm).[63] Similarly, HCC patients with microvascular invasion receiving adjuvant radiation had improved relapse-free survival (RFS) and OS compared with TACE or conservative

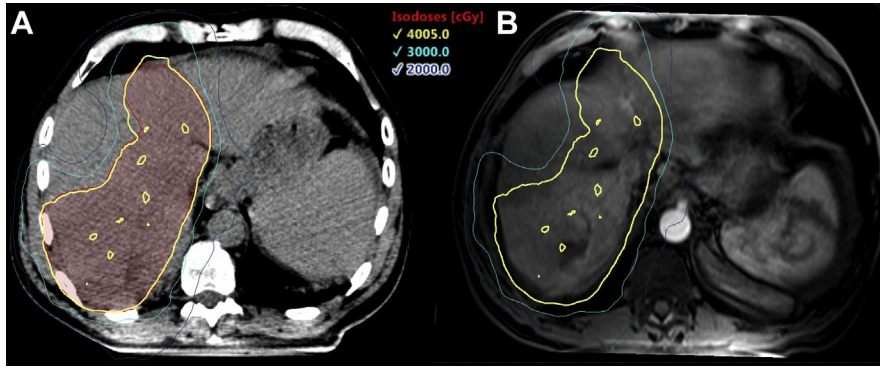

Fig. 2. IMRT for unresectable HCC. A 64-year-old man with a history of hepatis C–related cirrhosis developed an HCC with portal vein involvement and an AFP of 19,497 ng/mL. He was Child-Pugh A and was treated with IMRT (4005 cGy in 15 fractions) and sorafenib in 2014. (*A*) IMRT plan on planning CT. Isodose lines represented in absolute dose (cGy). (*B*) IMRT plan projected on pretreatment MRI abdomen. His AFP nadired to 6 and remained low with no recurrent disease until about 2 years post-treatment. His AFP increased to 19 and he underwent another course of IMRT in late 2016. He had control for another few years but ultimately progressed and went on nivolumab. He completed a third course of EBRT in 2019. Although, his HCC has since progressed locally, he remains alive as of August 2020.

management. The 3-year RFS rates for the adjuvant radiation, adjuvant TACE, and conservative management groups were 45%, 27%, and 11%, respectively. The 3-year OS rates for the adjuvant radiation, adjuvant TACE, and conservative management groups were 73%, 44%, and 28%, respectively.[64] Lastly, radiation can palliate symptoms from bone metastases and even lymph node metastases with response rates above 73%.[65–68]

Due to more conformal dose distribution and potential for dose escalation, IMRT can offer higher LC and OS rates than 3DCRT. LC rates (3-year 47% vs 28%, respectively) and OS rates (3-year 33% vs 14%, respectively) were in favor of IMRT. Toxicity rates were similar between 3DCRT and IMRT with RILD rates in 5% or less.[69,70] As for dose escalation, an IMRT simultaneous integrated boost approach achieved better objective RR (100% vs 62%, respectively; $P = .039$), LC at 2 years (86% vs 59%, respectively; $P = .119$), and OS at 2 years (83% vs 44%, respectively; $P = .037$) in the higher-dose group.[71] In cases of large liver tumors greater than 6 cm to 8 cm, however, IMRT can have higher integral dose whereby more volume of normal liver receives a low dose.[72,73] Depending on the size and location of the HCC target, careful selection of the appropriate EBRT modality is necessary.

Overall, fractionated 3DCRT or IMRT, either alone or when combined with other treatments, can offer good LC in unresectable HCC, including those with major vascular involvement, and can improve LC in select postoperative scenarios with microvascular invasion or close margins. In metastatic cases, EBRT can offer good palliation.

Stereotactic Body Radiotherapy

Recent studies have demonstrated the efficacy of SBRT in both resectable HCC and unresectable HCC.

Chen[4] recently presented a review of select SBRT studies and showed that SBRT offered 3 year LC as high as 90% and 3 year OS as high as 70%. SBRT also can serve as a bridge to transplantation in early-stage inoperable HCC, with doses ranging from 3000 cGy to 5400 cGy using a median fractional dose of 600 cGy. Post-SBRT liver explant revealed 27% complete response and 54% partial response.[74] **Fig. 3** presents a patient with cT1N0M0 HCC whereby SBRT served as a bridge to liver transplantation.

For HCC not eligible for transplant, SBRT provides high LC.[75,76] For small HCCs ineligible for resection or ablation, SBRT alone achieved a 2-year OS and PFS of 79% and 49%, respectively, compared with 80% and 43%, respective, with SBRT plus TACE.[77] **Fig. 4** presents a case of a patient ineligible for transplantation but had a small HCC who underwent definitive SBRT. Overall, SBRT alone or in combination with other treatments can offer high control rates for both resectable and unresectable HCC cases.

Particle External Beam Radiotherapy

Most particle-based EBRT experience for HCC has been with PBT. A large retrospective series of HCCs treated with hypofractionated regimens demonstrated 5-year LC of 87% with 5-year OS of 23%.[78] Other recent studies, including a recent review of PBT for HCC, reported 3-year LC 70% to 88% and a 3-year OS ranging from 45% to 65%.[79–81] As for heavy charged particles, such as carbon ions, they can offer higher radiobiological effectiveness and linear energy transfer than conventional x-rays and even protons. Carbon ion therapy for HCC can provide 5-year LC rates of 81% to 96%, with late grade 3 toxicity in 3% to 4% range.[82,83] A recent review of charged particle therapy reported actuarial LC rages ranging from 71% to 95% at 3 years and OS

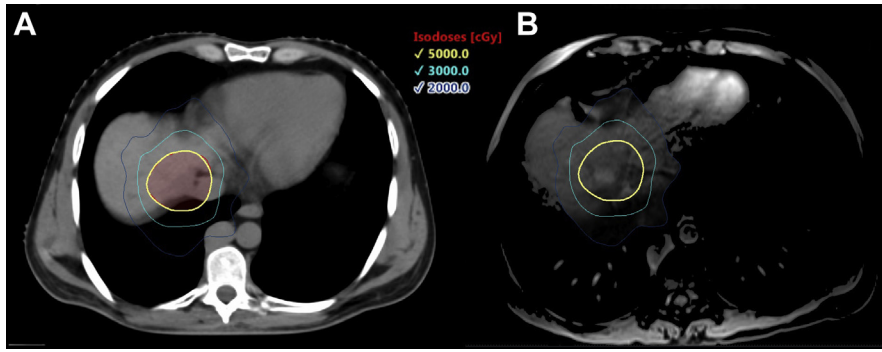

Fig. 3. SBRT as bridge to transplantation. A35-year-old man with a history of Budd-Chiari–related cirrhosis who developed a cT1N0M0 HCC next to the right liver dome. AFP was 1872. He underwent TACE in 7/2018 but subsequent imaging and post-TACE AFP of 1613 indicated residual disease. He completed a course of SBRT involving 5000 cGy in 5 fractions. (*A*) SBRT plan on planning CT. Isodose lines represented in absolute dose (cGy). (*B*) SBRT plan projected on pretreatment MRI abdomen. The patient's AFP nadired to 2.8 in June, 2019, and he underwent transplant on June 26, 2019. Post-transplant pathology showed 100% necrosis with complete response.

at 5 years ranging from 25% to 42%. Late grade 3 or higher adverse events occurred in only 2% of patients.[84] A meta-analysis comparing charged particles and SBRT, however, showed that comparable outcomes with no advantage in survival or LC with particle therapy.[85] Despite the similar outcomes, given the significant cost associated with construction and operations of particle beam facilities, particle EBRT for HCC may be appropriate in select cases, such as previously irradiated patients.

COMPARATIVE OUTCOMES OF EXTERNAL BEAM RADIOTHERAPY AND OTHER LOCOREGIONAL TREATMENTS

EBRT provides at least equivalent outcomes and safety profiles as other locoregional treatments for HCC (**Table 2**).[4] As a bridging modality to transplantation, SBRT, TACE,

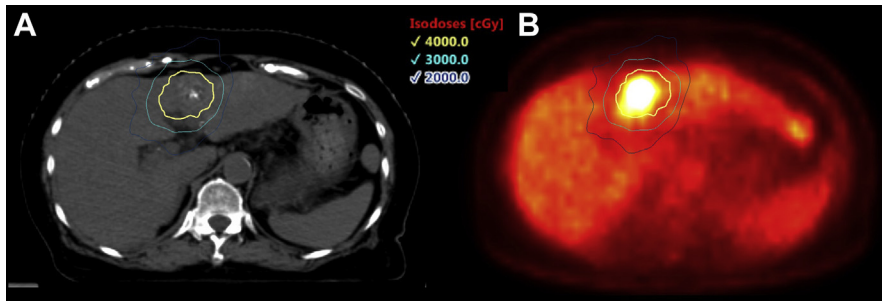

Fig. 4. SBRT for HCC ineligible for transplantation. A 74-year-old woman with NASH cirrhosis developed a left liver lobe HCC with AFP of 736. She completed TACE followed by SBRT (4000 cGy in 5 fractions) in March, 2016. (*A*) SBRT plan on planning CT. Isodose lines represented in absolute dose (cGy). (*B*) SBRT plan projected on pretreatment PET, which demonstrated an FDG (Fluorodeoxyglucose [^{18}F]) avid HCC. The patient's AFP normalized by 6 months post-treatment and has remained in the normal range.

Table 2
Select studies comparing stereotactic body radiotherapy to other locoregional treatments for hepatocellular carcinoma

Study	n	Stage	Modalities Compared	Stereotactic Body Radiotherapy Details	Outcomes	Toxicities (Grade 3+)
Sapir et al,[105] 2018	209	NR	SBRT vs TACE	Median BED, 100 Gy	SBRT: 2-y LC, 91%; 2-y OS, 55% TACE: 2-y LC, 23%; 2-y OS, 35%	SBRT, 8%, vs TACE, 13% (P = .05)
Su et al,[90] 2017	117	BCLC A, 93% BCLC B, 7%	SBRT vs resection	42–48 Gy in 3–5 fractions	SBRT: 5-y OS, 70%; 5-y PFS, 41% Resection: 5-y OS, 64%; 5-y PFS, 40%	SBRT, 3% (nausea, weight loss); resection, 25% (hepatic pain, hepatic hemorrhage, weight loss)
Wahl et al,[87] 2016	224	Mostly TNM stage I/II	SBRT vs RFA	Median BED, 100 Gy	SBRT: 2-y FFLP, 84%; 2-y OS, 46% RFA: 2-y FFLP, 80%; 2-y OS, 53%	SBRT, 5% RFA, 11%
Mohamed et al,[106] 2016	60	IM, 78% OM, 22%	SBRT vs TACE vs RFA vs Y90 as bridge to transplant	Median, 50 Gy (range 45–60 Gy); Y90, average dose, 109 Gy	SBRT: PD, 4%; NN, 14% TACE: PD, 5.5%; NN, 4% RFA: PD, 0%; NN, 20% Y90: PD, 11%; NN, 0%	SBRT, 0% TACE, 11% RFA, 22% Y90, 0%

Abbreviations: BED, biological equivalent dose; BCLC, Barcelona clinic liver cancer; CP, Child-Pugh; CR, complete response; IM, inside Milan; NN, no necrosis on pathologic response; NR, not reported; OM, outside Milan; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; Y9-90 radioembolization.

and RFA had comparable outcomes for 5-year actuarial survival.[86] For inoperable HCC cases treated with either SBRT to RFA, SBRT provided higher 2-year freedom from local progression (FFLP) (97% vs 84%, respectively) despite the SBRT group having more patients with unfavorable factors, such as lower pretreatment Child-Pugh scores, higher pretreatment α-fetoprotein (AFP) levels, and greater number of prior liver-directed treatments. Larger tumor size was a predictor for FFLP for RFA but not with SBRT. Acute grade 3 or higher complication rate was lower for SBRT (5% vs 11%, respectively). Two-year OS was comparable (46% vs 53%, respectively).[87] Similarly, the LC rate in HCC patients receiving TACE versus SBRT was comparable for LC, OS, and 1-year mortality.[88] When EBRT is combined with other locoregional treatments, higher OS can be achieved. A meta-analysis of 25 trials demonstrated that TACE plus EBRT had a 5-year survival OR of 3.98 compared with TACE alone. There was increased risk for gastroduodenal ulcers, however, in the combined modality, with an OR of 12.8.[89] Even in resectable cases, EBRT can offer favorable outcomes as resection. Su and colleagues[90] compared SBRT versus resection, and 5-year OS and PFS were virtually identical.

Selective internal radiation therapy (SIRT) has been useful in treating large lesions and tumors with vascular invasion.[91] Adverse events, however, including radiation pneumonitis, pulmonary fibrosis due to hepatopulmonary shunts, postradioembolization syndrome, and radioembolization-induced liver disease, have been observed.[92,93] In patients with PVTT, the pooled response rates for SIRT were 33% versus 51% for 3DCRT and 71% for SBRT. The pooled 1-year OS rates also was higher for EBRT modalities.[94] In another recent study comparing SIRT to EBRT involving unresectable HCC, there was no difference in OS or disease-specific survival.[95] Hence, proper patient selection is paramount for SIRT compared with EBRT approaches.

SUMMARY

With advancements in technology, including improved image guidance and dose escalation with partial-liver treatments, high LC rates with relatively low toxicity have been achieved with various EBRT modalities. As systemic therapies improve, locoregional therapies, such as EBRT, will become more relevant. Multiple clinical trials utilizing EBRT alone or in combination with other treatment modalities, which include systemic or local therapies, are under way.[96]

In regard to the future role of EBRT in HCC management, accurate tumor localization and visualization techniques may allow for further dose escalation and better outcomes. Magnetic resonance (MR)-based strategies, such as gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRIs, can offer more precise EBRT targeting and assessment of treatment accuracy.[97] MR linear accelerators (MR-linacs), which couple an magnetic resonance imaging (MRI) scanner and linear accelerator, can track and visualize tumors in real time. Because MRIs can better delineate HCCs compared with planning CT-based images, MR-linacs, with real-time tracking, can allow for tighter tumor margins, lower OAR doses, and dose escalation. In a recent multi-institutional study, MR-guided liver SBRT was performed using a median delivered dose of 5000 cGy in 5 fractions. With a median follow-up of 21.2 months, the freedom from local progression was 100% for HCC. No grade 4 or greater gastrointestinal toxicities were observed.[98–100] SBRT, especially MR-based SBRT, may help expand the role of radiotherapy in HCC treatment.

Neoadjuvant therapy has been used to downstage disease and to evaluate treatment response prior to resection for other solid malignancies. For HCC, transarterial

radioembolization, and TACE, systemic therapy have been suggested as possible neoadjuvant approaches.[101] In a recent randomized, multicenter study involving patients with resectable HCC and PVTT, neoadjuvant radiotherapy involving 3DCRT of 1800 cGy in 6 fractions resulted in a significantly improved 2-year OS of 27% versus 9% in hepatectomy alone.[102] As for the safety of preoperative EBRT, Hasan and colleagues[103] showed that preoperative EBRT (median of 4000 cGy in 5 fractions) resulted in 39% complete response with no increase in postoperative mortality or length of stay after transplant. Neoadjuvant EBRT presents another potential indication for EBRT in the management of HCC.

Due to the increased evidence of efficacy and safety of EBRT for HCC, treatment algorithms have started to incorporate EBRT.[47,104–106] There remain many guidelines that continue to ignore EBRT as a treatment modality of HCC. Given the variability of recommendations from different guidelines, a multidisciplinary team involving hepatology, surgical oncology, medical oncology, and radiation oncology ideally should convene to make the appropriate treatment recommendations for each HCC patient.

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DISCLOSURE

The authors have nothing to disclose.

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