Review Article

Role of Radiotherapy in the Treatment of Hepatocellular Carcinoma

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Abstract

The role of radiotherapy in the treatment of hepatocellular carcinoma (HCC) has evolved over the past few decades with the advancement of technology and improved imaging. Radiotherapy can offer high local control rates in unresectable HCC, including cases with major vascular involvement, and can provide a modality to help bridge patients to potentially curative resection or transplantation. In metastatic cases, radiotherapy can provide good palliation. This review focuses on the common radiotherapy treatment modalities used for HCC, provides outcome comparisons of these radiotherapy techniques to outcomes with other treatment modalities for HCC, and highlights the discrepancy of the role of radiotherapy in HCC amongst the current available treatment guidelines.
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Introduction

In 2018, liver cancer is the second leading cause of cancer death in men and sixth leading cause of cancer death in women. Liver cancer is also the seventh most common-incident cancer worldwide.[1] The most common type of primary liver cancer globally is hepatocellular carcinoma (HCC). In many cases, HCC arises from underlying end-stage liver disease secondary to viral hepatitis or non-viral chronic liver diseases. The leading viral causes of HCC are hepatitis B virus and hepatitis C virus. The most common non-viral etiologies are alcohol use and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.[2,3] Despite the practice of primary prevention strategies and available antiviral treatments, cases of liver cancer and HCC are expected to increase. Finding effective treatments will be imperative.

Patients with limited tumor are eligible for curative treatments, including liver transplantation. However, liver transplantation is limited by various factors including availability of donor organs and strict criteria of liver transplantation for HCC patients. Other surgical options including surgical resection and novel surgical techniques to increase the available pool of organs for liver transplantation are reviewed elsewhere.[4,5]

A significant proportion of HCC patients are not eligible for curative treatments. Few systemic therapy options were available prior to the introduction of sorafenib. Sorafenib is currently the standard of care for patients with advanced HCC. In the SHARP and Asia-Pacific trials, sorafenib provided a survival benefit of about 2–3 months over the placebo group.[6,7] However, over the past 2 years, multiple molecular-targeted agents, including regorafenib, lenvatinib, cabozantinib and ramucirumab, offer alternative or additional options to sorafenib.[8] The REFLECT trial demonstrated noninferiority of lenvatinib to sorafenib as a first-line agent for HCC.[9] The RESORCE trial and CELESTIAL trials established the role of regorafenib and cabozantinib as second-line agents for patients refractory to sorafenib.[10,11] The REACH-2 trial validated the role of ramucirumab as a second-line treatment of advanced HCC.[12] Additionally, immune checkpoint modulators, such as nivolumab and pembrolizumab, have shown activity and efficacy in other malignancies and are now under investigation for HCC.[13,14]

As systemic therapies improve, local therapies have become more relevant and effective, even in advanced HCC cases. Local therapies that can help bridge patients to transplantation or offer palliative treatments include minimally invasive procedures, such as trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation (MWA), highly-focused ultrasound, and irreversible electroporation. These techniques are most effective in nodules less than 3 cm in diameter and can offer response rates greater than 80%.[4] With that said, more recent studies indicate that MWA has several advantages, including higher thermal efficiency, faster ablation time, less severe heat sink effect, and larger ablation zones compared to RFA. MWA can safely and effectively treat larger nodules, including those up to 8 cm in size.[15] When combined with effective systemic therapy, local therapies can offer improved outcomes than local therapies used alone. Evidence of this includes the TACTICS trial which demonstrated an increased progression-free survival with TACE plus sorafenib versus TACE alone.[16]

However, for locally advanced cases, minimally invasive procedures have limitations. For example, contraindications for TACE include impaired portal-vein blood flow due to portal-vein thrombus, malignant portal vein thrombosis, untreatable arteriovenous fistula, and impaired renal function.[17,18] RFA and MWA are contraindicated in patients with bleeding diathesis and can be difficult in tumors close to the diaphragm, gastrointestinal tract, pancreas, hepatic hilum, and major bile ducts or vessels.[19–21] Another local therapy

Keywords: Hepatocellular carcinoma; Liver cancer; radiotherapy; Radiation; Stereotactic body radiotherapy.
Abbreviations: 3DCRT, three-dimensional conformal radiotherapy; EBRT, external beam radiation therapy; HCC, hepatocellular carcinoma; IMRT, intensity modulated radiotherapy; MWA, microwave ablation; PBT, proton beam therapy; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; RILD, radiation-induced liver disease; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiation therapy; TACE, trans-arterial chemoembolization.
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that has shown promise either alone or in combination with both local and systemic therapies is radiotherapy. Various technological advances have allowed for more precise and dose escalated treatment regimens using radiotherapy. In this review, we will discuss the role of radiotherapy in HCC.

Results

Conventional external beam radiation (EBRT)

Historically, external beam radiation therapy (EBRT) has had a limited role in treating malignant hepatic tumors due to risk of radiation-induced liver disease (RILD). "Classic" RILD typically occurs within 4 months following hepatic radiation therapy and patients can present with fatigue, anicteric ascites, and hepatomegaly with relatively normal liver function tests and normal bilirubin. "Non-classic" RILD can occur within 3 months of hepatic radiation with associated jaundice and/or significant elevation of serum transaminases. Patients with underlying liver disease, such as in patients with Child-Pugh score of B or C, are at higher risk for RILD that can manifest in a non-classic pattern.[22] Some early work on whole liver tolerance was from treatment of liver metastases in the RTOG 76-09 and RTOG 84-05 trials. The whole liver could be safely treated to 2100 cGy in seven fractions with daily fractionation or 3000 cGy in twenty fractions delivered b.i.d.[23,24] With these lower radiation dose regimens, EBRT only offered palliation.

However, partial liver treatment has provided insights to further dose escalation. Partial liver tolerance analysis from heavy ion treatments indicated that liver doses in excess of 3000–3500 cGE should be limited to 30% of the liver.[25] In 1991, Emami and co-workers 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 1/3 of the liver is associated with the same 5% risk of RILD.[26] 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 volume. Normal Tissue Complication Probability modeling showed that for primary hepatobiliary or liver metastases, mean dose of 5660 cGy (range 4050 cGy to 8100 cGy) was associated with a RILD complication rate of about 5%. Further model analysis demonstrated that a dose of 3200 cGy to the whole liver was associated with 5% risk of RILD, with no cases of RILD observed when the mean dose was less than 3100 cGy. Additionally, the liver radiation tolerance was lower with patients with HCC (5% risk of RILD with mean liver dose of 2800 cGy at 200 cGy per fraction) versus those with liver metastases (5% risk of RILD with mean liver dose of 3200 cGy at 200 cGy per fraction).[27–30] These studies have suggested that more focal radiation approaches, such as three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT), could offer local disease control with relatively low risk for RILD.

IMRT and 3DCRT are conventional EBRT radiation techniques that deliver optimized dose distributions in fractionated radiotherapy regimens. Both techniques utilize 3D images obtained by computed tomography to allow for target and avoidance structure, such as the normal liver tissue, delineation during radiation planning. IMRT is a more advanced EBRT technique than 3DCRT in that it uses modulated beams that allow for more improved target coverage, more conformal radiation dose distribution, and better radiation dose sparing of critical normal structures other than the liver. The main potential weakness is that IMRT may not spare as much normal liver in cases with large liver tumors greater than 6–8 cm.[31,32] Clinical studies comparing 3DCRT to IMRT for the treatment of HCC, which have included BCLC C or JIS Stage III and IVA patients, demonstrated higher local control and overall survival rates with IMRT. The radiation doses delivered ranged from 3600–6000 cGy at 180–500 cGy per fraction for 3DCRT and 4000–6600 cGy in 250–400 cGy per fraction for IMRT. Local control rates were 43% at 1 year and 28% at 3 years for 3DCRT and were 70% at 1 year and 47% at 3 years for IMRT, respectively. Overall survival for 3DCRT was 36% at 1 year and 14% at 3 years and for IMRT was 59% at 1 year and 33% at 3 years. Toxicity rates were similar between 3DCRT and IMRT, with RILD rates in 5% or less of patients.[33,34] Hence, these findings suggest the superiority of IMRT over 3DCRT in most cases.

Several recent studies have further demonstrated the efficacy of EBRT for definitive treatments as well as in the palliative setting. These studies included HCC patients with Child-Pugh class B and with portal vein tumor thrombosis (PVTT). Radiation doses ranged from 3000–7180 cGy in 180–600 cGy per daily fraction. Some of the studies allowed combined treatments, such as TACE or concurrent chemotherapy with capecitabine. Median follow-up ranged from 5–17 months. The objective relative response ranged from 43–74%, and the overall survival rate at 1 year ranged from 45–86% and at 2 years ranged from 23–69%. Grade 3 hepatotoxicity was observed in 0–13%. Combined treatments tended to increase severe toxicity with two fatalities, one of which occurred when IMRT was combined with TACE and the other when IMRT was combined with concurrent hepatic arterial infusion chemotherapy.[35–42] Additionally, although rare, EBRT can be effective for HCC accompanied by inferior vena cava invasion. A recent meta-analysis showed a pooled relative response of 59% with 2 year overall survival of 37%.[43] As for palliation, radiation can palliate symptoms from bone metastases and even lymph node metastases with response rates above 73%.[44–47]

Due to the promising results of EBRT, there is recent interest in adjuvant radiation. For curative resectable or transplantable cases, recurrence rates can be as high as 30%.[48–51] Microvascular invasion is one factor that reduces disease-free and overall survival.[52] Interestingly, postoperative adjuvant radiotherapy may be beneficial in select scenarios. In post-hepatectomy patients with tumors close to major vessels and having close margins (<1 cm), adjuvant radiation significantly improved 3 year overall survival compared to that in patients who had close margin but did not receive radiation (overall survival 64% vs. 52%). The results of the adjuvant radiation group were comparable to results in patients who received wide margins (>1 cm).[53] Similarly, HCC patients with microvascular invasion receiving adjuvant radiation had improved relapse-free survival and overall survival compared to TACE or conservative management. The 3 year relapse-free survival for the adjuvant radiation, adjuvant TACE, and conservative management groups were 45%, 27%, and 11%, respectively. The 3 year overall survival for the adjuvant radiation, adjuvant TACE, and conservative management groups were 73%, 44%, and 28%, respectively.[54] Hence, EBRT has a role in select adjuvant settings for HCC patients.

Novel approaches using EBRT are also focusing on the role of dose-escalated regimens and combining EBRT with other therapies in advanced HCC cases. A recent study used a simultaneous integrated boost approach, whereby different target volumes are delineated and each target volume is

treated simultaneously to different doses. A planning target volume 1 and 2 were created for each patient. The planning target volume 1 and 2 were treated to 5500 cGy and 4400 cGy, respectively, in 22 fractions for the low-dose group. The high-dose group received 6600 cGy and 5500 cGy to planning target volume 1 and 2, respectively. Patients in the high-dose group achieved higher objective relative response (100% vs. 62%, $p = 0.039$), local control at 2 years (86% vs. 59%, $p = 0.119$), and overall survival at 2 years (83% vs. 44%, $p = 0.037$).[55] For locally advanced HCC, IMRT is combined with sorafenib in a phase II trial for unresectable HCC with or without PVTT. Radiation dose ranged from 4000–6000 cGy using 200 cGy per daily fraction. The 2 year overall survival rate was 32%.[56] Additionally, for unresectable HCCs, including those with PVTT, a combination of TACE and EBRT yielded improved outcomes compared to TACE alone. A meta-analysis of 25 trials demonstrated that TACE plus EBRT had a 1 year survival odds ratio of 1.36 and complete response odds ratio of 2.73 compared with TACE alone. The survival benefit was even higher at 5 years, with a 5 year odds ratio of 3.98 compared to TACE alone. However, there was increased risk for gastroduodenal ulcers in the TACE plus EBRT group, with an odds ratio of 12.8.[57]

Overall, EBRT, either alone or when combined with other treatments, can offer good local control in unresectable HCC, including those with major vascular involvement, and can provide a modality to help bridge patients to potentially curative resection or transplantation. In metastatic cases, EBRT can offer good palliation.

Stereotactic body radiation (SBRT)

SBRT is an EBRT technique whereby very high, potentially ablative doses are delivered to tumors in shorter durations than for conventional EBRT. SBRT may offer higher local control rates but also require advanced tumor tracking, image guidance, and respiratory management to minimize the risk of morbidity.[58–60]

Recently, a number of retrospective and a few prospective studies have revealed the efficacy of SBRT as a locally-ablative modality for HCC, as shown in Table 1. Most of the studies included patients predominantly with stage I-III (TNM) or BCLC A-B patients with a minority of patients with BCLC C stage. A large meta-analysis demonstrated that the pooled local control for SBRT was 87% and the 1 year overall survival was 80%. The pooled late toxicity rate was 6%.[61] More recently, SBRT was used as a bridge to transplantation in early stage inoperable HCC, with doses ranging from 3000–5400 cGy using a median fractional dose of 600 cGy. Median follow-up was 12 months. Post-SBRT liver explant revealed 27% complete response, 54% partial response, and 18% stable disease.[62] For HCC not eligible for transplant, SBRT can offer high rates of local control with radiographic freedom from progression of 80% with 3 year overall survival of 21%. Grade 3 toxicity was noted in 8% of the patients.[63]

In another recent study, SBRT delivered to HCCs involved 3750–4000 cGy at 800–1250 cGy per fraction. A little more than half (56%) of the HCC patients received combination TACE plus SBRT, whereas the rest received SBRT alone. This yielded a 1-year local control rate of 92%.[64] Of note, the addition of TACE to SBRT alone may not contribute much to local control or progression-free survival, especially for small HCCs. For small HCCs ineligible for resection or ablation, SBRT with or without TACE was examined. The 2 year overall survival and progression-free survival rates for the SBRT alone and SBRT plus TACE were 79% versus 80% and 49% versus 43%.[65] Overall, SBRT alone or in combination with other treatments can offer high control rates that are higher than conventional EBRT techniques.

When compared to other minimally invasive procedures, SBRT offers at least comparable if not more favorable efficacy profiles. Table 2 highlights the recent studies comparing the efficacy of SBRT versus other local treatments for stage I-III or BCLC A or B HCC patients. As a modality to bridging patients to transplantation, SBRT, TACE, and RFA had comparable outcomes in regards to the 5 year actuarial survival.[66] In a retrospective study of inoperable HCC patients, SBRT was compared to RFA. The SBRT group had lower pretreatment Child-Pugh scores, higher pretreatment alpha-fetoprotein levels, and greater number of prior liver-directed treatments. Despite this, SBRT provided a 2 year freedom from local progression of 97% compared to 84% for RFA. Larger tumor size was a predictor for freedom from local progression for RFA but not with SBRT. The acute grade 3 or higher complication rate was 5% versus 11% for SBRT versus RFA, respectively. The overall survival at 2 years was 46% versus 53% for SBRT versus RFA, respectively.[67] Similarly, after propensity score matching, the LC rate in HCC patients receiving TACE versus SBRT was comparable for local control, overall survival, and 1 year mortality.[68]

More recently, magnetic resonance-based strategies can offer improved assessment of SBRT treatment accuracy and can improve SBRT targeting. Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance images can visualize hepatic parenchymal changes. Post-SBRT Ge-EOB-DTPA-enhanced imaging can facilitate assessment of treatment accuracy.[69] As for real-time target tracking, magnetic resonance-linear accelerators (known also as MR-linacs) couple a magnetic resonance imaging scanner with a linear accelerator. The magnetic resonance-linacs can potentially track and visualize tumors in real time. Since magnetic resonance images can often better delineate HCCs compared to traditional computed tomography-based images, with real-time tracking, tumor margins used for radiation planning can be minimized. With smaller margins, magnetic resonance-linac-based radiation plans could offer lower doses to organs at risk and allow for dose escalation, which can lead to higher local control rates. In a recent multiinstitutional study, magnetic resonance-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.[70–72] SBRT, especially magnetic resonance-based SBRT, may help expand the role of radiotherapy in HCC treatment.

Particle therapy

Charged particle therapy, such as proton beam therapy (PBT) or carbon ion therapy, offers potential dosimetric advantages over conventional EBRT techniques. Charged particles have a finite range dependent upon the initial charged particle energy. For PBT, a large retrospective series of HCCs treated with hypofractionated regimens ranging from 5000–8400 cCGE using 350–500 cCGE per fraction demonstrated 5 year local control of 87% with 5-year OS of 23%.[73] In another study of PBT for unresectable HCC, PBT offered 2-year local control was 75% with 2 year overall survival of 55%.[74] As for

Table 1. Select studies of SBRT for HCC

Study	*n*	Stage	CP	SBRT details	Outcomes	Toxicities of grade 3+
Bujold *et al.*[93] (2013) Prospective (phase I/II)	102	BCLC A/B 34% BCLC C 66%	A 100%	Median 36 Gy in 6 fractions	Median OS 17m	30%
Culleton *et al.*[94] (2014) Prospective	29	BCLC B 7% BCLC C/D 93%	B 96% C 4%	30 Gy in 6 fractions	1y LC 87% 1y OS 55%	63% decline in CP score by >= 2
Lasley *et al*.[95] (2015) Prospective	59	TNM stage: I 80% II 10% III 3%	A 64% B 36%	48 Gy in 3 fractions (CP A) 40 Gy in 5 fractions (CP B)	CP A 2y LC 91%, 3y OS 61%, median OS 45m CP B 2y LC 82%, 3y OS 26%, median OS 17m	CP A 11% CP B 38%
Kang *et al.*[96] (2012) Prospective (phase II)	47	BCLC A 17% BCLC B 66% BCLC C 17%	A 87% B 13%	Median 57 Gy in 3 fractions (range 42–60 Gy)	2y LC 95% 2y OS 69% CR by 6m 38%, PR 38%	6%
Sanuki *et al.*[97] (2014)	185	TNM stage: I 84% II 11% III 4%	A 85% B 15%	CP A 40 Gy in 5 fractions CP B 35 Gy in 5 fractions	3y LC 91% 3y OS 70%	13% 1% grade 5 liver failure
Jang *et al.*[98] (2013)	82	BCLC A 52% BCLC B 29% BCLC C 18%	A 90% B 10%	Median 51 Gy in 3 fractions	2y LC 87% 2y OS 63%	3%
Yoon *et al.*[99] (2013)	93	NR	A 74% B 26%	Median 45 Gy (range 30–60 Gy in 3–4 fractions)	3y OS 54% HCC >3 cm 3y LC 76% HCC 2.1–3 cm 3y LC 93% HCC <= 2 cm 3y LC 100%	6.5%
Yamashita *et al.*[100] (2015)	79	I 36% II 26% III 9%	A 85% B 11% C 1%	Mode 45 Gy (range 30–60 Gy in 3–4 fractions)	2y LC 64% 2y OS 53%	0%
Hasan *et al.*[101] (2017)	40	BCLC 0 15% BCLC A 25% BCLC B 60%	A 100%	Mean 45 Gy (range 40–50 Gy in 4–5 fractions)	2y in field LC 98% 2y intrahepatic control 62% 2y OS 60% Path CR 62%	0%
Moore *et al.*[62] (2017)	23	BCLC A 100%	A 56% B 44%	Median 54 Gy in 3 fractions	CR 27%, PR 54%, SD 18% Median OS not reached for transplanted patients Median OS 23m for non-transplanted patients	4% developed RILD but underwent successful transplant
Qiu *et al.*[63] (2018)	93	AJCC: I 50% II 14% IIIA 23% IIIB 5% IV 9% CLIP: 0 29% 1 26% 2 32% 3 13%	A 54% B/C 46%	50–60 Gy in 5–10 fractions	CR 1%, PR 35%, SD 44%, PD 20% 3y OS 21% Median OS 8.8m	10%

Abbreviations: CP, Child-Pugh; CR, complete response; FFLP, freedom from local progression; HCC, hepatocellular carcinoma; LC, local control; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SBRT, stereotactic body radiotherapy, TNM, TNM classification of malignant tumors.

Table 2. Select studies comparing SBRT to other local liver treatments

Study	*n*	Stage	Modalities compared	SBRT details	Outcomes	Toxicities of grade 3+
Sapir *et al.*[102] (2018)	209	NR	SBRT vs TACE	Median BED 100 Gy	SBRT 2y LC 91%, 2y OS 55% TACE 2y LC 23%, 2y OS 35%	SBRT 8% vs TACE 13% (p = 0.05)
Mohamed *et al.*[103] (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%
Wahl *et al.*[67] (2016)	224	Mostly TNM Stage I/II	SBRT vs RFA	Median BED 100 Gy	SBRT 2y FFLP 84%, 2y OS 46% RFA 2y FFLP 80%, 2y OS 53%	SBRT 5% RFA 11%
Su *et al.*[104] (2017)	117	BCLC A 93% BCLC B 7%	SBRT vs Resection	42–48 Gy in 3–5 fractions	SBRT 5y OS 70%, 5y PFS 41% Resection 5y OS 64%, 5y PFS 40%	SBRT 3% (nausea, weight loss) Resection – 25% (hepatic pain, hepatic hemorrhage, weight loss)

Abbreviations: BED, biological equivalent dose; CP, Child-Pugh; CR, complete response; FFLP, freedom from local progression; HCC, hepatocellular carcinoma; IM, inside Milan; LC, local control; NN, no necrosis on pathological response; NR, not reported; OM, outside Milan; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; Y90, Yttrium-90 radioembolization.

patients with PVTT and vascular invasion, PBT can also provide 2 year overall survival rates greater than 40%.[75,76] A recent review of PBT for HCC reported 3 year local control rates of 70–88% and 3 year overall survival rates ranging from 45–65%.[77] Additionally, heavy charged particles, such as carbon ion, have higher radiobiological effectiveness and linear energy transfer than conventional x-rays or even protons. The higher radiobiological effectiveness and linear energy transfer of heavy ions can theoretically produce greater outcomes, but the use of heavy ion treatments is limited by the significant cost associated with construction and operations of such facilities. However, carbon ion therapy for HCC can offer 5 year local control rates of 81–96%, with late grade 3 toxicity in the 3–4% range.[78,79] More recently, a review of charged particle therapy cited actuarial local control rates ranging from 71–95% at 3 years and overall survival at 5 years ranging from 25–42%. Late grade 3 or higher adverse events occurred in only 2% of patients.[80] However, a meta-analysis comparing charged particles and SBRT showed that the outcomes were comparable, with no advantage in survival or local control with particle therapy.[61] Charged particle therapy does provide some potential advantages over conventional EBRT techniques but further investigation is needed.

Selective internal radiation therapy (SIRT)

SIRT involves the injection of microspheres with β-emitting radioisotope, commonly 90Yttrium. SIRT has been useful in treating large lesions more than 7 cm in diameter and tumors with vascular invasion. Disease control rates as high as 70–80% have been achieved.[81] However, adverse events including radiation pneumonitis, pulmonary fibrosis due to hepato-pulmonary shunts, post-radioembolization syndrome, which involves abdominal pain, fever, and nausea, and radioembolization-induced liver disease have been observed.[82,83] Additionally, for PVTT, SIRT may not be as effective as other radiation modalities. In a recent meta-analysis of HCC with PVTT, the pooled response rate for SIRT was 33% versus 51% for 3DCRT and 71% for SBRT. The pooled 1 year overall survival rates for SIRT, 3DCRT, and SBRT were 38%, 44%, and 46%, respectively.[84] In another recent study comparing SIRT to SBRT involving unresectable HCC, no difference was noted in overall survival or disease-specific survival.[85] Hence, proper patient selection is paramount for SIRT.

Conclusions

Radiotherapy has evolved rapidly over the past two decades. With advancements in technology, including improved image guidance and dose escalation with partial liver treatments, high local control rates with relatively low toxicity have been achieved with the various radiotherapy modalities. Additionally, as systemic therapies improve, loco-regional therapies become more relevant. Multiple clinical trials utilizing EBRT alone or in combination with other treatment modalities, which include systemic or local therapies, are underway.[86]

Despite the evidence of the effectiveness of radiotherapy in HCC, guidelines have continued to suggest a limited role for radiation. The recently updated European Association for the Study of the Liver guidelines indicate that EBRT is under investigation and that there is no evidence to support its routine role in the management of HCC.[87] The American Association for the Study of Liver Disease guidelines from 2018 do cite some studies involving EBRT but overall, radiotherapy was not recommended in essentially all scenarios.[88] The Japan Society of Hepatology guidelines also do not mention radiotherapy in the treatment of HCC.[89] The main

reason for lack of inclusion of radiotherapy in management guidelines was the lack of randomized trials.

In contrast, the Asian Pacific Association for the Study of the Liver guidelines indicate that SBRT and charged particle therapy are reasonable options for patients who have failed other local therapies. Radiotherapy could also be considered for symptomatic bony metastases.[90] The Korean Liver Cancer Society guidelines describe the best and alternative options for various clinical settings based on the modified Union for International Cancer Control staging. EBRT is indicated as options in multiple settings including Child-Pugh class A or "superb B" and the irradiated total liver volume receiving greater than 3000 cGy is less than 60%, unresectable HCC not amenable to other local treatments, HCC patients with incomplete response to TACE when dose-volume criteria are met, HCC patients with PVTT when dose-volume criteria are met, and for palliation in metastatic HCC.[91] The most liberal indications of radiotherapy occur in the guidelines in China. The Chinese guidelines suggest a potential role for radiotherapy in multiple settings including locally advanced disease with PVTT, as a bridging treatment for HCC patients awaiting transplantation, adjuvant therapy for select patients with close margins, and palliative treatment for recurrent or metastatic disease.[92]

With more evidence of the efficacy of radiotherapy in HCC, the updated National Comprehensive Cancer Network guidelines (version 5.2018) have included radiotherapy as a treatment modality for HCC patients that are unresectable or ineligible for transplant. Given the variability of recommendations from different guidelines, a multidisciplinary team involving hepatology, surgical oncology, medical oncology, and radiation oncology should ideally convene to make the appropriate treatment recommendations for each HCC patient.

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Conflict of interest

The author has no conflict of interests related to this publication.

Author contributions

Performed the manuscript writing, critical revisions, and all administrative duties related to the preparation of this article (CPC).

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