Stereotactic Body Radiation Therapy (SBRT) in Hepatocellular Carcinoma

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Abstract

Purpose of Review Hepatocellular carcinoma (HCC) is a rising cause of mortality and morbidity, and although surgical resection is the preferred curative local therapy, < 30% of patients are candidates at diagnosis. This review discusses SBRT as an option in a variety of clinical scenarios.

Recent Findings Multiple retrospective and prospective studies demonstrate that stereotactic body radiation therapy (SBRT) is an effective bridge for transplant candidates and local therapy for patients with inoperable early-, intermediate-, or advanced-stage disease. SBRT is associated with excellent local control, and it is well-tolerated despite study cohorts enriched with patients who failed prior therapies and had poor baseline liver function.

Summary Additional randomized control trials are needed to determine the ideal treatment regimen and patient selection for SBRT.

Keywords HCC treatment · HCC radiation · HCC SBRT · HCC radiation

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer (~ 75–85% of liver cancers), the fifth most common cancer worldwide, and the third leading cause of cancer mortality [1, 2]. The incidence of HCC is driven by disparate risk factors in different parts of the world. As a result, HCC has increased in frequency in Europe and the USA while remaining stable in east Asian countries over the past few decades [3–6]. Chronic infection with hepatitis B and C viruses are major risk factors in Asia while chronic heavy alcohol use, obesity, and diabetes are the major drivers in the USA and Europe. Other risk factors include hemochromatosis, alpha-1-antitrypsin deficiency, and exposure to aflatoxin and mycotoxin in food [7]. Despite advances in screening for and diagnosis of HCC at earlier stages, management remains challenging.

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Disease staging guides the treatment of HCC. While over 18 staging systems have been developed for the categorization of HCC, Barcelona Clinic Liver Cancer (BCLC) is the most widely adopted system for management [8–12]. The BCLC system classifies HCC into 5 prognostic categories (very early, early, intermediate, advanced stage, terminal stage) based on tumor size, tumor burden, liver function based on Child-Pugh (CP) score, and performance status [10]. Patients with very early– and early-stage disease are preferentially treated with surgical resection, transplantation, and/or ablation. Surgical resection remains the primary curative treatment [13, 14]. Up to 75–80% of the liver can be safely resected in non-cirrhotic patients, and surgery has been shown to improve overall survival [15]. Intermediate-stage disease has historically been managed with chemoembolization, while advanced or terminal disease is generally treated with systemic therapy.

Despite improved radiographic screening and follow-up, ≤ 30% of patients are diagnosed with very early– or early-stage disease in the USA, and less than 5% of patients are good surgical candidates due to poor liver function, age, and/or other comorbidities [16, 17]. While patients with early-stage disease and poor liver function may be treated with orthotopic liver transplantation, patients often face long waitlists [18, 19]. Consequently, most patients with liver-confined HCC receive local therapies to achieve maximal tumor control while

preserving liver function. In the absence of surgical options, aggressive local therapy options including ablation therapies (e.g., radiofrequency (RFA), percutaneous laser (PLA), microwave (PVA), or cryo (CrA)) and arterial embolization techniques (e.g., transarterial chemoembolization (TACE) and transarterial embolization (TAE)) have historically played a large role in HCC management [20–23]. Recently, radiation therapy has been increasingly used for the management of HCC in patients who previously failed or are not candidates for surgery, ablation, and/or embolization. Stereotactic body radiation therapy (SBRT), in particular, promises precise, noninvasive, aggressive local therapy for HCC. Herein, we review the literature on the evolving use of SBRT to treat patients with HCC with an emphasis on patient selection, treatment, clinical outcomes, and associated toxicity.

Bridge to Transplantation

Orthotopic liver transplantation is an alternative to definitive surgical resection for patients who meet the Milan Criteria (single tumor ≤ 5 cm or ≤3 nodules that are each ≤ 3 cm) but are ineligible for surgery due to impaired liver function [24]. This approach has the benefit of treating both hepatocellular carcinoma and comorbid liver disease. However, up to 20–30% of patients with HCC who are initially eligible for transplantation experience significant disease progression that invalidates their candidacy while awaiting the procedure [25, 26]. Local therapies such as RFA, TACE, and SBRT may offer these patients effective local control as a bridge to transplantation [27, 28].

Several studies have shown that patients who receive radiation therapy as a bridge to transplant achieved a > 70–100% radiographic LC and OS over a 5- to 8-month period [27, 29–33]. An early prospective series of 10 patients showed that conformal radiation therapy is an effective strategy for bridging to transplant [31]. Half of the patients received CRT after ineffective local control from previous treatment with RFA or TACE while the other half received CRT alone due to unsuitability for TACE or RFA based on tumor size or location. Ineligibility for RFA and TACE included thrombocytopenia, arterial occlusion, tumor multifocality, and necrosis of the biliary tree. All patients experienced a significant reduction in AFP and in-field tumor control with a median time to transplantation of 157 days after RT. Seven patients experienced partial radiographic response, an additional 2 achieving stable disease, and the final patient received a transplant after 1 fraction of treatment. Although CRT was well-tolerated in this report of select patients with mostly CP A and B liver disease, a similar volume of the treated liver has been associated with ~ 30% grade 3 or 4 toxicities in other series [22, 34, 35].

Subsequent studies explored the technique of SBRT as a method of limiting the volume of the liver treated while also dose-escalating to intensify treatment, improving both effectiveness and safety. In a retrospective review of 10 patients that received SBRT using Cyberknife to 11 HCC that were up to 5.5 cm and ultimately underwent transplantation (~median time of 151 days), all experienced a pathologic partial response with 3 fractions of treatment [30]. The cohort had an OS and DFS of 100% at 5 years with four patients experiencing mild toxicity including nausea, fatigue, or abdominal pain. A retrospective analysis summarizing the Memorial Sloan Kettering experience with SBRT bridge to orthotopic liver transplant showed a 3-year OS and DFS of 77% and 74% with a pathological response rate of 68% [32]. In this study, radiological response correlated poorly with pathological outcomes, and treatment failure due to recurrence was significantly associated with tumor size. Notably, 29% of patients experienced a worsening CP score before transplantation in a cohort where all patients had a CP-B7 or better. A larger phase I/II study from the University of Indiana further clarified the efficacy and tolerability of SBRT as a bridge to transplantation [36]. Twenty-three of the 60-patient cohort receiving SBRT for HCC were candidates for transplant. Ultimately, all candidates underwent transplantation and achieved 2 years of PFS and OS rate of 69% and 96%, respectively. Durable local control was achieved before and after transplant, as patients with progressive disease developed extrahepatic lesions. While SBRT in the total cohort was well-tolerated, 35% of patients developed grade 3 hematologic or hepatic toxicity. Notably, about 81% of patients who developed grade 3 toxicity had baseline grade 2 toxicity, and adverse toxicity was associated with worse underlying pretreatment liver function. Currently, SBRT treatments can be adjusted based on liver function to achieve the optimal balance for each patient.

How Does SBRT Compare with Other Local Therapy Modalities in Bridging Patients to Transplantation?

Princess Margaret Hospital conducted a respective review of 406 patients who received bridging therapies, 36 of which received SBRT while 99 patients received TACE, and 244 patients received RFA [37•]. Notably, patients treated with SBRT after failing RFA or TACE were placed in the SBRT group for analysis. The study showed no difference in the rates of transplantation completion (80 to 83%), transfusion requirement (median 2 units of packed RBCs), postoperative length of stay (10 days), or post-transplant 5-year overall survival (56–61%) between the three modalities. However, the pathological response of explanted tumors was lower with SBRT (13%) compared with RFA (49%) and TACE (24%). Multiple hypotheses have been posited for the lower rate of pathological response including variable time between bridge treatment and transplantation and delayed pathological response to tumors in response to RT. Also, patients were treated with a lower biologically effective dose than reported in

other studies. Despite the lower pathological response, the equivalent rate of transplant completion and peri-operative morbidity and mortality demonstrates that SBRT does not complicate surgery or worsen post-transplant outcomes.

These data demonstrate that SBRT is a safe and effective modality for preventing tumor progression in patients with HCC who are transplant candidates [32, 36, 38, 39]. Notably, SBRT cohorts performed well despite their enrichment with patients with poor liver function, challenging tumor location, larger tumor size, and failed local treatment. Most patients experienced minimal toxicity, though reported grade ≥ 3 toxicity rates range from 0 to $\sim 35\%$ [36, 39–41]. Compared with RFA and TACE, SBRT has been associated with equivalent or lower toxicity or hospitalization [37•, 42]. SBRT has been associated with worse liver function, though it is likely that patients with lower liver function reserve are treated SBRT since they no longer qualify for intra-arterial therapies. Despite multiple studies demonstrating the safety or efficacy of SBRT in preventing progression, there is limited specific data on the utility of downstaging patients [43], although it has been done. The delayed pathological response in prior series suggests that downstaging may take months to achieve, so that treating while a patient is still within transplant criteria may be a more effective strategy than downstaging.

While many of the retrospective cohorts used SBRT for patients who either were not candidates for or had failed other local therapy options, the prospective data suggest that SBRT may be a reasonable first-line option for bridging to transplantation. Additional prospective data are needed to clarify relative efficacy, toxicity, and surgical implications of SBRT compared with RFA and TACE. Historically, it has been challenging to compare the three modalities in a randomized trial. An ongoing clinical trial comparing TACE to SBRT at Lahey Clinic (Burlington, MA) as a bridge to transplant in patients with HCC may further clarify this question (NCT02182687).

Early-Stage Inoperable HCC

Patients with BCLC stage-A HCC have small (≤ 3 cm) tumors, limited tumor burden (≤ 3 foci), and normal to moderately compromised liver function (CP A or B) [10]. Many of these patients are ineligible for primary surgical resection or transplantation due to age and comorbidities. Curative options include aggressive local ablation therapies. RFA is the most commonly used ablation therapy modality and has the most accumulated evidence of its efficacy in treating HCC. Multiple randomized trials summarized in a recent Cochrane meta-analysis have demonstrated that treatment of HCC with RFA is associated with improved overall survival compared with treatment with percutaneous ethanol injection (PEI) [44]. However, RFA is not appropriate for lesions adjacent to large vessels (e.g., portal vein and hepatic artery branches), central biliary structures, stomach, bowel, or heart. Also, the efficacy

of RFA decreases with tumor size. SBRT does not have these treatment limitations and may be an effective modality for these patients.

SBRT has gradually gained popularity for treating patients with early-stage HCC who are not candidates for ablation therapy or failed primary ablation. In 2009, Romeo et al. reported a phase I/II study demonstrating the efficacy of SBRT as the primary treatment for eight patients with unresectable localized HCC who had not received other interventions. Patients with 1–2 lesions, ≤ 7 cm (total), KPS $> 80\%$, and CP A or B were treated in 3 or 5 sessions and achieved a 2-year local control rate of 82% [45]. While most patients tolerated treatment well, 1 patient with CP B liver function developed acute grade 5 liver failure. Overall, it demonstrated that SBRT may be effective primary local therapy in select patients. A recent larger phase I/II trial at the University of Indiana evaluated the efficacy SBRT for 59 patients with untreated HCC, ≤ 5 lesions (84% had 1 lesion), CP A or B, and ECOG 0–1 [46]. Primary treatment with SBRT achieved a response rate and 3y-LC in $\sim 90\%$ of patients. Better baseline liver function was associated with higher post-SBRT survival. CP A and B patients had a PFS of 22.3 months and 10 months and a median overall survival of 44.4 months and 17.0 months, respectively. Additional prospective trials further corroborate the efficacy of SBRT in achieving ~ 80–100% 2-year local control in patients with localized HCC (Table 1).

Additional studies have demonstrated that SBRT has a comparable or better efficacy compared with RFA or TACE. The University of Michigan reported a single-institution retrospective study of 224 patients with inoperable localized HCC treated with RFA ($\sim 70\%$ of cohort) or SBRT (30%) [54, 55]. The SBRT and RFA groups included a similar number of lesions treated and tumor sizes, and they demonstrated comparable 2-year LC rates ($\sim 80\%$) and overall survival at 1 year ($\sim 70\%$) and 2 years ($\sim 50\%$). Despite the enrichment with patients' adverse features in the SBRT (e.g., failed prior treatment, lower baseline liver function, higher AFP), it was associated with high 1-year LC rates (97.4.% vs. 83.6%). In addition, RFA was associated with worse local control for larger tumors (≥ 2 cm) compared with SBRT. These results suggest that SBRT is a good initial treatment option for patients with localized HCC.

SBRT achieves high rates of local control for localized HCC with reasonable toxicity [46, 50, 53]. Severe toxicity (grade ≥ 3) in recent reports ranged from 5 to 38% [46, 50, 52, 55–57], generally decreasing over time as experience with SBRT grows. The most commonly reported severe toxicities include worsening hematologic function and hepatic dysfunction. Less commonly patients experience severe nausea and fatigue. In addition to experience, the difference in the report rate of toxicity may result from institutional differences in patient selection, inherent differences in the sensitivity of the treated liver region to radiation, and dose-escalation and

Table 1 Prospective phase I and II trials of SBRT for HCC with > 20 patients

Study	n	CP score/BCLC Stage	Prior treatment	Tumor size (range)	Number of lesions	Outcomes	Grade ≥ 3 toxicity
Tse (2008)* [47]	31	CP A BCLC A-C	TACE 6% RFA 13% Other 61%	173 cc (9–1913)	≤ 3	1y-LC 65% 1y-OS 48%	26%
Kang (2012) [48]	42	CP A-B BCLC A-C	TACE 100%	2.9 cm (1–8)	NR	2y-LC 95% 2y-PFS 34% 2y-OS 69%	15%
Bujold (2013) [49]	102	CP A BCLC A-C	TACE 22% RFA 34% Surgery 9%	7.2 cm (1.4–23.1)	NR	1y-LC 97% med-OS 17 mo	25%
Lasley (2015) [46]	59	CP A-B BCLC NR	NR 15%	33.6 cc (2–107)	NR	*CP-A* 3-y LC 91% 3y-PFS 48% 3y-OS 61% *CP-B* 3y-LC 82% 3y-PFS 23% 3y-OS 26%	CP A: 10% CP B: 38%
Takeda (2016) [50]	90	CP A-B BCLC 0-C	TACE 28% RFA 3% Other: 17%	2.3 cm (1.0–4)	NR	3y-LC 96.3% 3y-OS 66.7%	11%
Feng (2018)* [51]	69	CP A-B BCLC NR	NR	3 cm (0–13)	NR	2y-LC 95% 2y-OS 28%	3%
Jang (2019) [52]	74	CP A-B BCLC 0-C	TACE 57%	2.4 cm (1.0–9.9)	≤ 2	3y-LC 95% 3y-PFS 36% 3y-OS 76%	3%
Durand-Labrunie (2020) [53]	44	CP A-B BCLC 0-A	None	2.8 cm (1.0–6.0)	1	1.5y-LC 98% 1.5y-OS 72%	31%

*Published study of SBRT with primary hepatocellular carcinomas and other tumors in the liver. Reported values are specifically for patients who received SBRT for HCC

BCLC Barcelona Clinic Liver Cancer, *CP* Child-Pugh, *LC* local control, *NR* not reported, *OS* overall survival, *RFA* radiofrequency ablation, *PFS* progression-free survival, *TACE* transarterial chemoembolization

fractionation. Notably, the population of patients receiving SBRT is usually enriched with patients with poor baseline liver function. The University of Indiana's prospective trial reported that severe toxicity was lower in patients with baseline CP A compared with CP B (11% vs. 38%) [46]. Other studies have reported high rates of toxicity in patients with CP B disease, and these patients should be treated with caution by experienced centers [58].

Further studies are needed to elucidate appropriate patient selection and dose and fractionation for SBRT, with particular attention to dose limits to the normal liver that minimize toxicity. Radiation treatments are already highly customized for patients based on a combination of metrics including mean dose to the liver and methods of preserving liver function as much as possible, but there is still much work to be done. These studies may further clarify which risk factors predispose these patients to grade three toxicity. In addition, prospective studies comparing SBRT to RFA would better define the efficacy of SBRT in improving LC, PFS, and OS among patients with inoperable localized HCC. Prospective trials would overcome the current patient selection bias that

increases the likelihood that patients with worse baseline liver function and performance will be treated with SBRT. The results of such a trial would further clarify the role of SBRT in the upfront management of these patients.

Intermediate-Stage HCC

Patients with BCLC stage-B HCC have large (>3 cm) tumors and/or multinodular tumors (> 3 foci) but have normal to moderately compromised liver function (CP A or B) [10]. Due to the increased tumor burden, BCLC stage-B HCC is not amenable to curative local therapy. Instead, these lesions are usually treated with arterial embolization techniques including transarterial embolization (TAE), transarterial chemoembolization (TACE), or transarterial radioembolization (TARE). These treatments exploit the preferential flow of blood from the hepatic artery to malignant lesions and the dual blood supply to the liver to infarct and potentially deliver cytotoxic chemotherapy or radiation beads to involved regions of the liver. This intervention is most appropriate for HCC that does not involve the main or lobar

branch portal vein thrombus, as embolization of these lesions would significantly compromise global hepatic function. In carefully selected patients, prospective trials show arterial embolization is superior to supportive care only, but these interventions only achieved an objective response rate on imaging of 22–39% at 6 months [21, 59–61]. As a result, there has been increased interest in the use of SBRT with intermediate-risk disease to improve the rate of local control.

Retrospective and prospective studies have demonstrated that SBRT improves local control in patients with intermediate-stage HCC. A single-institution phase I/II trial at Korea Cancer Center Hospital analyzed 41 patients with HCC treated with SBRT after prior treatment TACE (up to 5 times) and demonstrated a 2-year local control of 94% and progression-free survival of 33.8% [48, 62]. The majority of failures were out-of-field hepatic tumors, which may represent additional candidate lesions for SBRT. Repeat radiation for additional liver lesions requires great caution to minimize hepatic toxicity [63–65] but can be done. A small retrospective of analysis of 24 patients who received an additional course of Cyberknife SBRT for a new hepatic lesion at least 6 months after the first treatment demonstrated SBRT 3-y OS of 60.8% and 3y local control of 90.7% [64].

In addition to demonstrating efficacy, these studies have shown that SBRT has a favorable side-effect profile compared with arterial embolization. In general, SBRT is well-tolerated, associated with mild acute fatigue, loss of appetite, and potentially nausea for lesions located near the stomach. Reported grade ≥ 3 toxicity ranges from 5 to 30%. Long-term effects can include GI bleeds in patients with tumors near the bowel, but that risk is in the single digits. Recent studies have established that repeat SBRT is also well-tolerated. Sun J et al. reported that the most common adverse effect was fatigue, and only one patient experienced radiation-induced liver disease (RILD). Notably, the majority of patients in this cohort had CP A disease, suggesting that selection for better baseline function may have contributed to limited adverse effects of re-irradiation. In contrast, arterially directive therapy has been associated with up to 10–80% acute grade 3 toxicity, particularly in patients with alcoholic cirrhosis and central lesions.

Despite the evidence that SBRT added to TACE improved local control, the role of adding TACE to SBRT remains unclear and a prospective comparison study is needed. A retrospective analysis of 209 patients at the University of Michigan aimed to clarify outcomes of SBRT compared with TACE for patients with 1–2 tumors. SBRT was associated with much higher local control (2-year LC of 91% vs. 23%), though the SBRT cohort included slightly smaller lesions (2.3 cm vs. 2.9 cm). A recent meta-analysis suggests that SBRT combined with TACE compared SBRT alone is associated with higher 5-year survival and complete response rate [66]. However, the meta-analysis consists of 10 small retrospective studies with heterogeneously classified study cohorts and high heterogeneity between the reported outcomes. Thus, the results should be interpreted with caution.

Additional prospective studies are needed to further define the timing and sequencing of SBRT in patients with intermediate-stage HCC. A randomized, prospective, open-label, and phase II trial at the Erasmus Medical Center is investigating the efficacy of TACE versus SBRT and further clarifying the appropriate management for these patients. Other important questions include the efficacy of combination SBRT and TACE compared with individual therapies in treatment-naive patients, and the safety and efficacy of re-irradiation for disease progression. For the combination of SBRT and TACE, additional data is needed to identify the ideal sequencing of the two interventions.

Advanced-Stage HCC and Vascular Invasion

BCLC stage-C HCC is defined by macroscopic vascular invasion, mild to moderate impairment of liver function or performance status, or extrahepatic extension [10, 11]. Patients are at risk for decompensated cirrhosis, and portal hypertension due to portal venous thrombosis (PVT) is associated with worse overall survival [11, 49]. Thus, it is generally treated with systemic therapy. Multiple randomized trials have established sorafenib as the standard of care agent that improved survival compared with placebo [67–69]. A recent trial phase III trial has demonstrated the superior efficacy of atezolizumab and bevacizumab in first-line medical management on unresectable hepatocellular carcinoma [70]. In addition to systemic therapy, select patients with portal venous thrombosis (PVT) may benefit from locoregional therapies.

SBRT can be an effective treatment for patients with impaired liver function and/or macroscopic vascular invasion. Without local therapy, patients with advanced HCC treated with sorafenib have a 1-year overall survival of 30–45% [68, 69]. An early phase I at Princess Margaret Hospital of 31 patients with unresectable HCC and CP A liver disease treated with 6-fraction SBRT demonstrated a median survival of 11.6 months for patients with PVT and 17.2 months without PVT [47]. Additional studies have shown that SBRT is effective in patients with poor baseline liver function. In a prospective study at Princess Margaret Hospital, 29 patients with Child-Pugh B7 or B8 liver function and HCC with < 5 foci and total diameter < 10 cm treated with SBRT achieved a median survival of 7.9, which compares favorably to the median survival of ~ 4 months in prior series [58, 71]. A larger sequential phase I/II study evaluated the local control and survival in 102 patients who received SBRT for advanced HCC [49]. Over 60% of patients had multiple lesions, 55% of tumors were associated with tumor invasion of a major vessel, and the median diameter of the largest lesions was 7.7 cm. Treatment with SBRT was associated with a 1-year

local control of 87%, and radiation dose predicted improved local control on univariate analysis.

How Does Radiation Therapy Compare with Other Local and Systemic Therapy Interventions for Patients with PVT?

A meta-analysis pooled the data from prospective and retrospective studies of 2513 patients who received 3D CRT, transarterial radioembolization (TARE), or SBRT for HCC with PVT to analyze overall survival, response rate, local control, and toxicity [72]. The 1-year overall survival for the three modalities was similar (~ 44–48%). Notably, the local control rate associated with SBRT (86.9%) and 3D CRT (82.8%) was higher than TARE (57.5%), and the overall response rate was higher from SBRT (70.7%) than 3D CRT (51.3%) or TARE (33.3%). SBRT also improved patient symptoms. More than two-thirds of the patients treated with SBRT experienced improved abdominal distention and/or discomfort. A recent randomized trial compared local therapy with TACE and 3D CRT versus sorafenib in treatment-naive patients with liver-confined HCC with macroscopic vascular invasion [73]. Patients treated with TACE-RT had a significantly higher radiologic response rate (15% vs. 1%) at 24 weeks and progression-free survival (86.7% vs. 34.3%) at 12 weeks and a longer median overall survival (55 vs. 43 weeks) and time to progress (31 vs. 11.7 weeks). To date, no randomized control trials are comparing SBRT monotherapy to other local or systemic interventions for patients with advanced HCC with PVT. However, the pooled analysis shows that SBRT offers improved local control and progression-free survival, and the recent randomized trial demonstrates that local therapy options offer effective treatment in carefully selected patients with advanced liver-confined HCC with portal venous thrombosis.

Despite the increased risk of hepatic decompensation and poor functional status of patients with advanced-stage HCC, SBRT is generally well-tolerated. The meta-analysis of retrospective and prospective studies reported a grade 3 or higher toxicity of 0 to 10% [72]. Other prospective studies reported grade 3 or higher toxicity of 26 to 36% [47, 49, 51, 58]. The most common severe adverse effects included transaminitis and liver failure, and in one trial, the percentage of patients experiencing liver deterioration in the absence of tumor progression after 1 year was 6% for CP class and 17% of CP score. Notably, 11% of patients in the sorafenib group required dose reduction due to toxicity while no patients required dose reduction in the TACE-RT group.

Additional studies are needed to further define the appropriate treatment for patients with advanced HCC. Randomized trials are needed to validate the efficacy and safety of SBRT compared with other local therapy modalities. In addition, future studies should aim to clarify the ideal combination of RT, arterial embolization, and/or systemic therapy that

improves disease control and overall survival while minimizing toxicity [74]. After all, the studies presented herein suggest that carefully selected patients with BCLC patients may be effectively managed with local therapy with delay or omission of systemic therapy. Three randomized trials of patients with advanced HCC have already reported no survival benefit from sorafenib alone compared with TARE with or without sorafenib [28, 75, 76]. Additional studies to clarify the selection between local and systemic therapy options are particularly important in light of recent studies demonstrating improved disease control and survival with immunotherapy [70]. Currently, there are several ongoing randomized trials investigating sorafenib with or without TACE (NCT01829035 and NCT01906216) or sorafenib with or without SBRT (NCT0173093 and RTOG 1112). Recent advances in the systemic therapy options will require careful analysis of these study results to determine the role of local therapy as first-line systemic therapy options evolve.

Patient Experience

It is also important to understand patients' experiences with receiving SBRT. Treatment planning begins with a 1-h simulation consisting of a CT scan with intravenous contrast of the liver in the treatment position. Patients lie flat with their hands above their heads or at their sides and behind their bodies, depending on the treatment machine. Several techniques including breath-hold, respiratory gating, and fiducial tracking may be used to control for tumor motion during the respiratory cycle to minimize the rim of the normal liver that receives radiation. Planning typically takes 1.5 weeks due to its complexity and requirement for many quality assurance steps. Treatment usually requires patients to lie still in the treatment position for 20 to 60 min. Patients usually receive 3 to 5 sessions of treatment over 1–1.5 weeks. These treatments are conducted as an outpatient and do not require hospitalization or anesthesia. Most patients drive themselves to treatment and tolerate the treatment very well, even coming for treatment during their lunch break from work. While on treatment, patients are monitored weekly for acute toxicity, which could include mild nausea for tumors near the stomach. Quality of life has been studied during and after treatment and is minimally impacted [77, 78].

Post-SBRT Monitoring

What is the anticipated course after SBRT? Monitoring patients after SBRT is critical for assessing disease response and the need for additional treatment, particularly since patients can develop new lesions within the liver due to the field cancerization effect. The post-treatment disease control depends on the baseline performance status, tumor size, biological markers, and liver function. Better baseline liver function

(CP A vs. CP B and C), lower albumin-bilirubin index (ALBI), and lower pretreatment AFP are associated with better survival and fewer acute and late grade 2 toxicity after SBRT [79]. Smaller tumors are associated with increased radiographic response to SBRT, decreased disease progression, and overall survival.

Assessing patient response to SBRT is challenging and requires a radiologist familiar with both HCC and post-radiation imaging. A handful of radiology-pathology correlation studies in the transplant setting have been useful to characterize imaging changes in response to therapy. As opposed to a treatment like RFA or TACE, in which response (complete necrosis) can be judged at the 4–6-week mark, patience is required to appreciate a radiation response (Fig. 1). Generally, early follow-up (3–6 months) can show a zone of hyperemia including and surrounding the tumor on the arterial phase, related to edema from treatment. This will improve up to 12 months, with decreased tumor enhancement and size. Explant pathologic studies have shown that persistent enhancement does not mean that tumors are still viable, so there is no need to jump in with additional treatment unless the AFP is rising [80–82]. Portal venous washout can persist up to 12 months after treatment as well, improving over time [30, 39, 41, 80, 83, 84]. The zone of washout can increase, due to changes in the function of liver parenchyma around the tumor, reflecting the high dose radiation zone. Thus, the typical metric for response is a lack of progression or local control [85, 86]. Scans will continue to improve for 6–12 months, and AFP will reassuringly also fall [28, 70, 75, 76]. However, these findings can persist for more than 1 year in up to 1/3 of patients, and it is important to ensure that they are distinguished from local recurrence or progression, to avoid subjecting patients to unnecessary subsequent treatments.

In addition to monitoring for disease response, patients require surveillance for toxicity. Although the treatment is generally well-tolerated, one of the most severe adverse effects includes RILD. It manifests as anicteric hepatomegaly, ascites, and elevated liver enzymes (i.e., ALP >> ALT and AST) about 2 weeks to 3 months after SBRT. Delaying liver MRI to 3 to 6 months after treatment can help ensure sufficient time for normal parenchyma recovery and adequately diagnosed RILD [87, 88]. Compared with conventional radiation performed decades ago, the risk of RILD is decreased with SBRT limiting radiation dose to the normal parenchyma [89–91]. A recent release nomogram may help predict the risk of post-treatment radiation-induced hepatitis [92]. Additional adverse effects that require monitoring include GI toxicity (gastric and duodenal ulcers or perforation), although the incidence is quite rare [93, 94].

Conclusion

This review synthesized current data on the indications, patient selection, outcomes, and post-treatment monitoring of SBRT. The data show that SBRT is a safe and effective treatment for patients who are not candidates for definitive surgical management. Retrospective and prospective series have shown that SBRT can effectively bridge patients to transplantation and achieves excellent local control in patients with early-stage inoperable, intermediate stage, and advanced disease. Unlike other local treatment modalities, SBRT is appropriate for patients with unfavorable locations (e.g., adjacent to the heart, bowel, or central biliary structures; or invading large vessels). Emerging data demonstrate that it is safe to provide repeat radiation for patients who have intrahepatic progression, either to the same lesion or a new one, with proper consideration of remnant liver function. Although patients who receive SBRT often have worse baseline performance status compared with other local therapy modalities, SBRT is well-tolerated and associated with few grade ≥3 toxicities compared with other local therapy options. Prospective trials of SBRT in comparison with and combination with other local and systemic therapies are needed to clarify the optimal role of SBRT for patients with HCC.
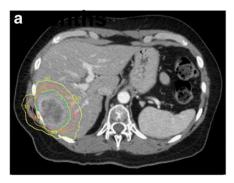

Fig. 1 Axial CT scans of the abdomen with contrast depicting stereotactic body radiation therapy (SBRT) to a solitary hepatocellular carcinoma (**a**) and the radiographic evolution of the lesion at 3 months (**b**) and 15 months (**c**) after treatment. The radiation dose gradient is represented by the colored lines in **a**. Red = 50 Gy (prescription dose). Orange = 40 Gy. Yellow = 30 Gy

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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