

Consensus Statement

Consensus on Stereotactic Body Radiation Therapy for Small-Sized Hepatocellular Carcinoma at the 7th Asia-Pacific Primary Liver Cancer Expert Meeting

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Keywords

Hepatocellular carcinoma · Stereotactic body radiation therapy · Survival · Radiation-induced liver disease

Abstract

Background: Stereotactic body radiation therapy (SBRT) is an advanced technique of external beam radiation therapy that delivers large ablative doses of radiation. In the past decade, many cancer centers have adopted SBRT as one mode of radically treating small-sized hepatocellular carcinoma (HCC), based on encouraging clinical outcomes. SBRT thus seems reasonable as first-line treatment of inoperable HCC confined to the liver. However, most of the clinical studies to date have been retrospective in nature, with key issues still under investigation. **Summary:** The above-mentioned publications were subjected to scrutiny, fueling discussions at the 7th Asia-Pacific Primary Liver Cancer Expert (APPLE 2016) Meeting on various clinical variables, such as indications for SBRT, therapeutic outcomes, treatment-related toxicities, doses prescribed, and specific techniques. The consensus reached should be of interest

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to all professionals active in the treatment of HCC, especially radiation oncologists. **Key Messages:** SBRT is a safe and effective therapeutic option for patients with small-sized HCC, offering substantial local control, improved overall survival, and low toxicity.

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Introduction

As diagnostic imaging and screening programs for hepatocellular carcinoma (HCC) have progressed, early-stage or small-sized tumors are being detected with greater frequency, enabling treatment locally via surgical resection, radiofrequency ablation (RFA), or transarterial chemoembolization (TACE). Recent technological advances offer precise and safe radiation delivery to multiple tumors in the body through image guidance. Given that the liver is a parallel organ, relatively high locally ablative radiation doses are tolerated. There is growing evidence for the usefulness of stereotactic body radiation therapy (SBRT) in the management of patients with primary liver cancer. The consensus presented herein was developed on the basis of recent evidence and expert opinions.

Definition

SBRT is a type of external beam radiation therapy technique requiring special equipment for use in patient positioning and delivery of high-dose radiation to body tumors (excluding the brain). Fewer fractions and sharp dose gradients spare normal tissues. This complex technique relies on the following: (1) stringent control of breathing motion, engaging 4-dimensional (4D) computed tomography (CT) scans to track respiration-induced hepatic movement, (2) extreme precision in patient positioning, and (3) image guidance for radiation delivery [1].

Early-stage HCC is defined as a solitary tumor ≤ 5 cm in maximum diameter or as multiple nodules (≤ 3 total) measuring ≤ 3 cm in maximum diameter, without vascular invasion/extrahepatic metastasis and with Child-Pugh A or B hepatic function. Not all tumors of small size are qualified as early stage because intrahepatic recurrences of HCC or Child-Pugh C score may apply [2, 3].

Indications for SBRT

SBRT may be an effective therapeutic option for early-stage or small-sized HCC, especially if surgical resection or percutaneous ablative therapies are difficult, unfeasible, or rejected. This approach is also used as a salvage treatment for tumor recurrence after local radical therapies or for residual cancer after surgical resection or percutaneous ablative attempts. In addition, SBRT may act as a bridge to liver transplantation or serve as an adjuvant treatment for intrahepatic tumors with incomplete iodized oil retention.

Outcomes of SBRT Use for HCC

Survival

SBRT has emerged as a promising noninvasive therapy in this setting. A limited number of clinical trials examining SBRT use in patients with HCC have been reported, yielding 3-year

Table 1. Outcomes of small-sized liver cancers after stereotactic body radiation therapy

Reference (first author)	HCC status	Cases	Dose to tumors	Response, %				Overall survival, %			Local control, %				
				CR	PR	SD	PD	1 y	2 y	3 y	5 y	1 y	2 y	3 y	
Su [6], 2016	max. diameter ≤5 cm; BCLC A 55.3%, BCLC B 44.7%, CP A 86.4%, CP B 13.6%	132	42–46 Gy/3–5 Fx					94.1		73.5	64.3	90.9			
Wahl [7], 2016	max. diameter <3 cm 73.1%, 3 cm ≤ diameter < 5 cm 23.2%, diameter ≥5 cm 3.7%; CP A 68.7%, CP B 28.9%, CP C 2.4%	63	30 Gy/3 Fx to 50 Gy/5 Fx					74		46		97.4			83.8
Huertas [16], 2015	diameter ≤6 cm; CP A5–B8; ECOG ≤2; nodules ≤3; AJCC stage I 28.6%, II 68.8%, IIIa 1.3%, IIIb 1.3%	77	45 Gy/3 Fx, 2 Fx/week					81.8		56.6		99			99
Yamashita [45], 2014	AJCC stage I 37%, stage II 27%, stage III 8%, recurrence 14%, no stage 14%	79	BED ₁₀ = 96.3 Gy (75–106); 40 Gy/4 Fx to 60 Gy/10 Fx	45.6	35.4	11.4	5.1			52.9					74.8
Lo [46], 2014	BCLC A 5.7%, BCLC B 11.3%, BCLC C 83.0%	53	40 Gy/4–5 Fx	32.8	38.8	23.9	4.5			70.1		45.4			73.3 66.8
Sanuki [5], 2014	≤5 cm; T1 84.3%, T2 11.4%, T3 4.3%	185	CP A 40 Gy/5 Fx, CP B 35 Gy/5 Fx					95		83		70			99 93 91
Takeda [47], 2014	T1 68.3%, T2 15.9%, T3 15.8%	63	35–40 Gy/5 Fx	80.7	17.7	1.6	0			100		87			73 95 92
Yoon [4], 2013	diameter <6 cm; ≤3 nodules; CP A or B; normal liver volume >700 mL; distance between tumor and gastrointestinal >2 cm; 92 patients showed pretreatment failure	93	30–60 Gy/3 Fx	51.5	21.4	25.2	0			86		53.8			94.8 92.1
Jang [13], 2013	BCLC A 53%, BCLC B 29%, BCLC C 18%; diameter <7 cm	82	33–60 Gy/3 Fx					63		39					87
Bibault [14], 2013	BCLC A 62.7%, BCLC B 13.3%, BCLC C 24%; 51% treated with other therapies	75	24–45 Gy/3 Fx (median 45 Gy)					78.5		50.4					89.8 89.8
Park [48], 2013	diameter <6 cm; nodules ≤3; normal liver volume >700 mL; distance between tumor and gastrointestinal >2 cm	26	40–50 Gy/4–5 Fx	25	42.9	32.1	0			88.5		67.2			87.6
Buijold [49], 2013	BCLC A/B 34%, BCLC C 66%	102	30–54 Gy/6 Fx	11	43	44	2			55		34			87
Ibarra [50], 2012	tumor volume 334 (9.5–1,493) cm ³	21	30 Gy (7–15 Gy × 3 Fx)	10.5	15.8	31.6	42.1			87		55			68.4
Huang [8], 2012	median diameter 4.4 (1.1–12.3) cm; stage I 25%, stage II 17%, stage IIIa 33%, stage IIIb/IV 25%	36	37 (25–48 Gy)/4–5 Fx	22	36.6	39.0	2.4			64					87.6 75.1
Kwon [51], 2010	stage I 23 patients, stage II 16 patients, stage IIIa 3 patients	42	30–39 Gy/3 Fx	59.6	26.2	14.3	–			92.9		58.6			72 68

AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; BED, biologically equivalent dose; CP, Child-Pugh score; CR, complete response; Fx, fractions; HCC, hepatocellular carcinoma; max., maximum; PD, progressive disease; PR, partial response; SD, stable disease; y, year(s).

Table 2. Comparison of overall survival for small-sized hepatocellular carcinoma treated with locoregional therapies

Treatment modality	3-year survival	5-year survival
Surgical resection	75–90% [9, 52]	40–75% [10, 52]
Laparoscopic resection	70–93% [54]	50–71% [54]
Radiofrequency ablation	54–67.2% [53]	40–67.9% [10, 55]
Liver transplantation	65–85% [59]	65–80% [59]
Stereotactic body radiation therapy	54–70% [4, 5]	64% [6]

Reference 4: the hepatocellular carcinoma was <6 cm across its longest diameter, and ≤3 lesions were presented. Reference 5: a single (either solitary or recurrent) hepatocellular carcinoma lesion; unfeasible, difficult, or refusal to undergo other surgery or percutaneous ablative therapies, tumor ≤5 cm. Reference 6: maximum diameter ≤5 cm. Reference 10: intrahepatic tumor with single nodule ≤5 cm or up to 3 nodules <3 cm. Reference 53: up to 2 nodules <4 cm. Reference 55: up to 3 nodules with a maximum diameter of 5 cm.

overall survival (OS) rates of 54–70% [4, 5] and a 5-year OS rate of 64% in small-sized HCC [6]. However, such efforts have been limited by small patient numbers and retrospective inclusion of nonsurgical patients. Published results of several retrospective studies (Table 1) have largely included instances in which surgical resection or percutaneous ablative therapies were difficult, unfeasible, or rejected, as well as some pools of intermediate or advanced-stage HCC. Herein, only patients receiving ≤10 fractions for HCC were reviewed.

A total of 224 patients with inoperable, nonmetastatic HCC received treatments at Michigan University Medical Center (RFA, 161; image-guided SBRT, 63). Inverse probability of treatment weighting was applied to adjust for imbalances in treatment assignment. In multivariate analysis, OS rates for RFA (1 year, 69.6%; 2 years, 52.9%) and SBRT (1 year, 74.1%; 2 years, 46.3%) did not differ significantly. Although based on retrospective data, SBRT nonetheless appears reasonable as first-line treatment of inoperable HCC, especially for tumors >2 cm [7].

With adjustment for presumptive prognostic factors, Huang et al. [8] used a Cox multivariable regression hazard model to compare OS curves of SBRT ($n = 36$) and non-SBRT ($n = 138$) patient groups (hazard ratio = 2.44; $p = 0.005$). The authors also compared the 2-year OS rates of SBRT recipients ($n = 28$) and matched controls ($n = 28$) (72.6 vs. 42.1%; $p = 0.013$), concluding that SBRT improved survival in patients with recurrent unresectable HCC.

In Table 2, survival data for patients with small-sized HCC are stratified by locoregional treatment modality. The current options for curative treatment of early-stage or small-sized HCC, namely liver transplantation, surgical resection, TACE, and percutaneous tumor ablation, all conform to established authoritative guidelines (i.e., Milan criteria, Barcelona Clinic Liver Cancer staging) [9]. Five-year survival rates of 50–80% are thereby achieved [10]. Given comparable outcomes (as shown), SBRT constitutes a viable alternative if such therapies fail or cannot be applied.

SBRT is also a suitable bridging therapy for patients with HCC awaiting liver transplantation. At the University of Rochester Medical Center, successful orthotopic liver transplantation was undertaken following SBRT (median, 6.3 months) in 11 of 18 patients with HCC (21 intrahepatic lesions). Recipients had small-sized HCC and Child-Pugh B or C liver function [11]. Similarly, 10 patients with HCC (11 lesions) underwent SBRT at Baylor University, administered as a bridge to liver transplantation. All patients subsequently received liver transplants [12]. SBRT may enable patients with HCC to remain eligible for curative transplantation pending organ availability.

Table 3. Toxicity of stereotactic body radiation therapy in hepatocellular carcinoma

Reference (first author)	Cases	Dose to tumors	Tech- nique	Dose constraints for organs at risk	Toxicity (common terminology criteria for adverse events)
Su [6], 2016	132	42–46 Gy/3–5 Fx	CK	duodenum 1 mL <25 Gy, stomach and small bowel 1 mL <25 Gy, each kidney 1/3 <15 Gy; liver Vtot-V15 Gy >700 mL; SC <15 Gy	G5 liver failure in 4 patients (3%), ≥G3 hepatic encephalopathy in 2 (2.3%), ≥G3 GI bleeding in 4 (3%), hepatic hemorrhage in 1 (0.8%)
Wahl [7], 2016	63	30–50 Gy/3–5 Fx	LA	duodenum 0.5 mL <24 Gy/3 Fx, 30 Gy/5 Fx; stomach 0.5 mL <22.5 Gy/3 Fx, 27.5 Gy/5 Fx; heart 0.5 mL <30 Gy/3 Fx, 35 Gy/5 Fx	G3 RILD in 1 patient, GI bleeding in 1 patient, worsening ascites in 1 patient; no death
Huertas [16], 2015	77	45 Gy/3 Fx	CK	liver V21 <33%, V15 <50%; stomach D _{max} <24 Gy, 5 mL <21 Gy; duodenum D _{max} <24 Gy, 5 mL <15 Gy; small intestine 0.5 mL <27 Gy, 5 mL <16 Gy; large intestine 1 mL <30 Gy, 20 mL <27 Gy; SCD _{max} <18 Gy; lung V20 <20 Gy; heart D _{max} <30 Gy	G2 colic ulcer in 1 patient (D _{max} = 45.6 Gy, V30 = 16 mL); gastric ulcer in 2 patients (D _{max} = 54 Gy, V24 = 9.5 mL); hematemesis in 1 patient
Culleton [56], 2014	29	30 Gy/6 Fx	LA	0.5 mL stomach <32 Gy, duodenum <33 Gy, small bowel <34 Gy, large bowel <36 Gy; liver VeffNTCP <22 Gy, rib <54 Gy	63% CP increase 2 points; G3 platelet decrease 14%; G3 transaminase increase 6.9%, G4 transaminase increase 3.4%
Sanuki [5], 2014	185	35–40 Gy/5 Fx	LA	liver V20 <20%, gastrointestinal <25 Gy/5 Fx, SC <25 Gy/5 Fx	CP increase 2 in 19 patients; G5 liver failure in 2 patients (all were CP B)
Lo [46], 2014	53	40 Gy/5 Fx (28–60 Gy/3–6 Fx)	CK	NR	none ≥G3 GI toxicity; 5 patients (9.4%) with RILD and 2 patients with fatal liver failure (death)
Yoon [4], 2013	93	30–60 Gy/3–6 Fx	LA	whole liver-V15 >700 mL, mean liver dose <13 Gy/3 Fx; esophagus and bowel 2 mL <21 Gy; gastric and duodenum 2 mL <18 Gy	septic shock due to insertion of the gold seeds occurred in 1 patient; ≥G3 hepatic toxicity in 6 patients; CP increase ≥2 in 9 patients; rib fractures in 2 patients (30 and 45 Gy in 3 Fx); biliary stricture in 1 patient
Jang [13], 2013	82	33–60 Gy/3 Fx	CK	whole liver-V15 or V17 >700 mL, mean SC <17 Gy; max. SC <22 Gy; esophagus <24 Gy	CP increase ≥2 in 6 patients (7%), G3 soft tissue toxicity in 1 patient (1%), G3 GI toxicity in 5 patients (6%) (ulcer in 3 patients, perforation in 2 patients)
Jung [57], 2013	92	30–60 Gy/3–4 Fx	LA	distance between tumor and gastrointestinal >2 cm, mean liver dose <20.4 Gy	RILD: G2 in 11 patients, G3 or higher in 6 patients
Bibault [14], 2013	75	40–50 Gy/3 Fx	CK	normal liver >700 mL; liver V15 <50%, V21 <33%; gastric V21 <5 mL; duodenum V24 <0.5 mL; intestine V27 <0.5 mL	liver decompensated ascites in 5 patients (6.6%), duodenal ulcer G2 in 3 patients (4%), G4 in 1 patient (1.3%)
Park [48], 2013	26	40–50 Gy/10 Fx	LA	25% normal liver <50% prescribed dose; max. dose: esophagus and colon <35 Gy/10 Fx, stomach, duodenum, and SC <25 Gy/10 Fx	≥G3 hepatic toxicity in 1 patient (3.8%), CP increase 2 points in 1 patient (3.8%), rib fracture in 1 patient
Katz [11], 2012	18	50 Gy/10 Fx	LA	normal liver ≥1,000 cm ³ , 70% liver <27 Gy, mean liver dose 8.5 Gy (1–15.6 Gy)	none ≥G3 GI toxicity, G3 liver enzymes increased in 1 patient
Huang [8], 2012	36	37 (25–48) Gy/4–5 Fx	CK	liver volume >700 mL, mean dose <15 Gy; kidney V16 <33%/4 Fx, V18 <33%/5 Fx; SC max. <23 Gy/4 Fx, <25 Gy/5 Fx; heart max. <32 Gy/4 Fx, max. <35 Gy/5 Fx; stomach V25 <5 mL/4 Fx, max. <29 Gy/4 Fx, V27 <5 mL/5 Fx, max. <31 Gy/5 Fx; intestine V23 <5 mL/4 Fx, max. <27 Gy/4 Fx, V25 <5 mL/5 Fx, max. <29 Gy/5 Fx; large bowel V24 <5 mL/4 Fx, max. <28 Gy/4 Fx, V25 <5 mL/5 Fx, max. <29 Gy/5 Fx	G3 gastric ulcer in 1 patient, RILD in 2 patients who recovered with supportive care; ≤G2 GI toxicity such as vomiting in 5 patients, anorexia in 9 patients, fatigue in 9 patients, abdominal pain in 2 patients, musculoskeletal discomfort in 1 patient
Andolino [58], 2011	60	CP A 14 Gy × 3 Fx, CP B 8 Gy × 5 Fx	LA	CP A: 1/3 liver ≤10 Gy, ≥500 mL liver <7 Gy; CP B: 1/3 liver ≤18 Gy, ≥500 mL liver <12 Gy, SC <18 Gy; 2/3 right kidney <15 Gy, 1/3 left kidney <15 Gy; 0.5 mL intestine <12 Gy	56 patients completed SBRT, G1–2 nonhematologic toxicity in 13 patients (23%); G3 liver enzyme increase and/or hyperbilirubinemia in 9 patients (16%); G3 thrombocytopenia in 9 patients, G4 in 1 patient (G3 thrombocytopenia before SBRT); elevated INR in 2 patients; G3 hypoalbuminemia in 7 patients; CP A → B in 7/36 patients, CP B → C in 5/24 patients
Kwon [51], 2010	42	30–39 Gy/3 Fx	CK	liver V20 <50% prescribed dose, mean liver dose <18 Gy, stomach, intestine, bowel <21 Gy/3 Fx; 2/3 right kidney <15 Gy/3 Fx, SC <21 Gy/3 Fx	constitutional symptoms in 36%, G1 or 2 elevated liver enzyme in 30%, leucopenia in 18%; G4 liver failure in 1 patient (2.4%)

CK, CyberKnife; CP, Child-Pugh score; Fx, fractions; GI, gastrointestinal; INR, international normalized ratio; LA, linear accelerator; max., maximum; NR, not recorded; RILD, radiation-induced liver disease; SBRT, stereotactic body radiation therapy; SC, spinal cord; Vtot, total liver volume; V15, liver volume receiving 15 Gy; Veff, effective volume; NTCP, normal tissue complication probabilities.

Toxicity

In terms of acute adverse events, the most common subjective complaints are constitutional symptoms, including fatigue, poor appetite, and nausea. Slight elevation of liver enzymes and leukopenia/thrombocytopenia are the main objective findings. Once SBRT is completed, acute events typically resolve without specific treatment. Nonclassic radiation-induced liver disease (RILD) (liver enzyme elevation, ≥ 2 -point rise in Child-Pugh score) is also common during or after SBRT but is rarely fatal. As shown in Table 3, a summary of 15 reports and 1,063 patients with HCC undergoing SBRT, only 8 patients (0.8%) presented with grade 5 liver failure, and most fatalities from liver failure were linked with Child-Pugh B liver function. Caution is thus warranted in patients with Child-Pugh B status, ensuring low dose volumes.

Gastrointestinal (GI) toxicity is another concern, especially if tumors and luminal structures (esophagus, stomach, duodenum, or intestine) are closely situated. GI toxicities of grade 3 or higher were reported in 15 patients (1.4%) (Table 3). Other complications, such as rib fracture, chest or abdominal pain, biliary stricture, and musculoskeletal discomfort, were noted occasionally. However, toxicities in general were infrequent and mild.

Radiation Dose

Tumor Dose

SBRT is an ablative therapy using higher doses to destroy cancer cells. Delivery protocols have varied considerably (24–60 Gy/3–10 fractions). High-dose SBRT may increase local control and improve OS in patients with inoperable HCC. Jang et al. [13] cited respective 2-year local control/OS rates of 100/71, 78/64, and 64/30% ($p = 0.009/p < 0.001$) at doses >54 , 45–54, and <45 Gy, all in 3 fractions. SBRT dose was also found to be significantly prognostic of OS ($p = 0.005$) in multivariate analysis, and correlation analysis revealed a positive linear relationship between SBRT dose and local control ($R = 0.899$; $p = 0.006$)/OS ($R = 0.940$; $p = 0.002$) at 2 years. Wahl et al. [7] further documented local control rates of 97.4 and 83.8% at 1 and 2 years, respectively, using a median biologically equivalent dose (BED) of 100 Gy, assuming a 10 Gy α/β ratio. In most instances, $BED_{10} > 80$ Gy was delivered to tumors (Table 1). Dose and fractions were usually dictated by tumor size, organs at risk (such as whole liver), and luminal structures nearby. Unfortunately, no evidence has yet emerged to clearly support a minimum or maximum dose of SBRT for HCC. This issue merits further research.

Dose Constraints for Normal Liver

Su et al. [6], Yoon et al. [4], and Jang et al. [13] from Asia indicated that liver volume receiving 15 Gy (V_{15}) > 700 mL may lead to grade 3 or fatal RILD at doses of 30–60 Gy/3–6 fractions, but according to Bibault et al. [14] in France, no RILD was encountered at whole normal liver volume > 700 mL and $V_{15} < 50\%$, using 40–50 Gy/3 fractions. However, decompensated cirrhosis did develop 3 months later in 5 patients (6.6%). At normal liver volume < 700 mL and mean hepatic dose < 15 Gy (25–48 Gy/4–5 fractions), 2 of the 26 patients studied by Huang et al. [8] developed RILD, but both recovered with supportive care. Still, Katz et al. [11] reported no RILD at normal liver volume $\geq 1,000$ mL and mean dose < 15 Gy (50 Gy/10 fractions). Therefore, at least 700 mL of normal liver (Child-Pugh A) must receive < 15 Gy to minimize acute and late liver toxicities [15].

Dose Constraints for the GI Tract and Other Organs at Risk

GI bleeding is the most frequently encountered nonhepatic toxicity following SBRT. With delivery of < 25 Gy to 1 mL of duodenum, stomach, or small bowel, the rate of GI bleeding was

3.0% (4/132) [6]. This incidence declined to 1.6% at doses <24 Gy in 3 fractions or 27.5 Gy in 5 fractions per 0.5 mL [7], and GI ulcers developed in 3.9% (3/77) [16]. At <21 Gy/3 fractions delivered to 5 mL of stomach or <24 Gy/3 fractions delivered to 0.5 mL of duodenum, GI toxicity was minimal (grade 2, 3/75; grade 4, 1/75) [14]. Doses <25, <24, and <23 Gy, respectively delivered to 5 mL of stomach or intestine in 36 patients were associated with a single instance of gastric ulcer [8]. GI dose constraints should be considered for neighboring hepatic tumors. Compounding the effects of radiation, patients with underlying cirrhosis are at risk of gastroduodenal bleeding or ulcers. Yet, fatal GI toxicity (bleeding, ulceration, or perforation) was rarely reported (Table 3), largely because most doses delivered to 1 mL of esophagus, stomach, duodenum, or intestine were <24 Gy/3 fractions or <30 Gy/6 fractions. In other words, fatal GI toxicity was avoidable with appropriate constraints.

No data on radiation-induced injury to the kidney, heart, or spinal cord were available, these organs being remotely situated. In tumors located close to ribs, whole-rib doses should be <30 Gy/3 fractions [4].

Combination with Other Therapies

Jacob et al. [17] retrospectively compared TACE alone and TACE plus SBRT as treatment of HCC in patients with tumor diameters ≥ 3 cm. Local recurrences were significantly reduced and OS improved by combined treatment. Honda et al. [18] also recorded a rise in complete responses upon addition of SBRT to TACE in patients with solitary HCC ≤ 3 cm, and in patients subjected to SBRT after incomplete response to TACE, the survival outcomes registered by Paik et al. [19] approached those of complete TACE responders or curative measures. SBRT as adjuvant therapy may well improve the efficacy of TACE, but no clinical data at present suggest that TACE improves the efficacy of SBRT in early-stage HCC.

SBRT may also serve as a salvage treatment for residual or recurrent HCC after surgical resection or RFA. However, significant toxicity has resulted from SBRT and sorafenib in combination, with no added benefit. Thus, a regimen of concurrent SBRT and sorafenib is not recommended outside a clinical trial in locally advanced HCC [20]. Patients with hepatitis B virus reactivation and concomitant serum hepatitis B virus DNA elevation or biochemical abnormalities of the liver are advised to receive antiviral therapies prior to SBRT.

SBRT Technique

Simulation and Target Delineation

Dynamic contrast-enhanced CT is the preferred imaging modality for treatment planning. If tumors are not well visualized on CT scan, fusion of pretreatment diagnostic magnetic resonance imaging and planning CT images is required. 4D CT simulations are used in patients treated via nonbreathhold technique to gauge gross tumor volume and internal target volume. In SBRT, gross tumor volume, clinical target volume, internal target volume, and planning target volume are stipulated by ICRU Report 62 [21]. Although subclinical extension of HCC is a known phenomenon [22], clinical target volume margin is generally not critical in SBRT, because falloff exposure will likely eradicate any existing microscopic disease. If respiratory gating is applied, internal target volume is the sum of all gross tumor volumes within the predefined gating window. Planning target volume margin is a technique- and center-specific geometrical variation. The entire liver and both kidneys, as well as the spinal cord, duodenum, and stomach, are delineated and should be contoured as organs at risk.

Immobilization

Patient immobilization and control of organ motion are crucial for the success of SBRT in this setting. A variety of body frame systems are available, most relying on vacuum cushions, with or without abdominal compression [23, 24].

Methods controlling breathing motion include active breathing control (ABC), abdominal compression, respiratory gating, and real-time tumor tracking. ABC involves a modified spirometer, with two pairs of flow monitors and scissor valves to control respiration. Activation is triggered at a predefined lung volume, “freezing” all breathing motion for 15–20 s by closing both valves. ABC-assisted SBRT is quick, generating the smallest planning target volume by comparison. However, pretreatment training is required, and it may be unsuitable for some patients, especially those with reduced lung function [25].

Abdominal compression is a convenient mean of reducing tumor motion by applying a compressive plate or a breath belt during both planning CT and treatment. High levels of forces are required to compress the abdomen [26], and subxiphoid compression is advised for better breathing management, reducing craniocaudal liver motion to within 5 mm [27]. However, liver deformation and gross tumor volume positional deviation are important consequences of abdominal compression, necessitating rigid liver-to-liver registrations to minimize variations [28].

With respiratory gating, SBRT dose is delivered only in specific phases of the respiratory cycle to avoid unnecessary dosing of normal tissue and underdosing of the target. Treatment time is longer with gating, but it is an acceptable alternative to ABC. The Real-Time Position Management System or the Exac Trac Adaptive Gating System are commonly used.

Image Guidance

Various imaging modalities are integrated into radiation treatment systems, offering image guidance strategies to produce volumetric and/or planar imaging at the time of treatment delivery and to reduce the negative impact of geometrical changes that may occur [29]. For SBRT in HCC, two available clinical systems enabling tracking of and compensation for patient-specific tumor motion during treatment are the gimbals-based Vero platform and the robot-based CyberKnife [30]. Due to limited tumor visualization in treatment CT scans and X-ray fluoroscopic images, gold fiducial markers are often implanted in liver tissue surrounding tumors to reduce residual setup errors [31], assess breathing motion [32], and track tumor position dynamically [33].

Image-guided radiation delivery is fundamental to SBRT. At present, a number of applications, such as CyberKnife, helical tomotherapy, and volumetric-modulated arc radiotherapy, are SBRT capable [34].

Treatment Plan

During the past decade, various techniques have been devised for SBRT of HCC. Compared with other methods (3D conformal radiotherapy or intensity-modulated radiation therapy), SBRT plans have very high dose drop speeds around targets and high conformal doses to targets. Tumor volumes are also smaller. Hence, a small grid size (typically 2 mm) is recommended for dose calculation [1], and at least 5–9 noncoplanar or coplanar fields should be used for conventional treatment planning [35]. Small-size beam shaping devices may improve conformity of target dose distributions [1]. In some protocols, tissue heterogeneity corrections are included in dose calculations (RTOG1112). Various indices can be applied to evaluate and report plan quality (e.g., conformity index, R50%, D 2 cm, and heterogeneity index) [1]. The gradient index (same as R50%) reflects the dose gradient around the planning target volume [36], impacting nearby normal tissue. Hot spots within the target are generally considered a mark of steep dose gradient and are clinically desirable. Considering the differ-

ences among techniques or protocols, it is essential to report the prescription dose in details (e.g., isodose covering planning target volume to a particular volume).

Post-SBRT Images

Tumor

HCC responsive to SBRT appears nonenhanced on imaging, which may be more useful than size reduction in evaluating treatment outcomes during the first 6–12 months (supporting EASL rather than RECIST criteria) [37]. Response rates in hypervascular HCC have increased during follow-up radiologic imaging for as much as to 2 years after completion of SBRT [38].

Liver

In patients receiving SBRT for HCC, follow-up CT liver dynamics were classifiable as follows: type 1, hyperdensity in all enhanced phases; type 2, hypodensity in arterial and portal phases; and type 3, isodensity in all enhanced phases [39, 40]. Features in the enhancement group (type 1) changed significantly over time, most patients qualifying as Child-Pugh A. In the nonenhancement group (type 3), Child-Pugh B was a significant element [39, 40]. The incidence of arterial hypervascularity in irradiated hepatic parenchyma may gradually increase for 6 months after SBRT, potentially interfering with accurate assessment of treatment response. Lack of washout on delayed phase in hypervascular areas helps distinguish SBRT-related change from residual/recurrent HCC [41]. Focal liver reaction to SBRT (not to be misread as recurrent HCC) has a threshold dose of 30 Gy/5 fractions for Child-Pugh A and 25 Gy/5 fractions for Child-Pugh B [42, 43] or 20 Gy/3 fractions [44]. Of note, uncertainty exists between the imaging changes, the pathological fibrosis, and the serological data. These doses will help predict potential loss of liver tissue after SBRT.

Conclusion

In conclusion, SBRT is a safe and effective therapeutic option for patients with small-sized HCC, offering substantial local control, improved OS, and low toxicity.

Disclosure Statement

The authors declare no conflicts of interest.

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