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Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in Cirrhotic Liver

Hiroshi Doi, Hiroya Shiomi and Ryoong-Jin Oh

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Abstract

In the medically inoperable patients with solitary hepatocellular carcinoma (HCC), local therapies, such as radiofrequency ablation and transarterial chemoembolization, are used as alternatives. However, several factors, including anatomic and vascular variants, make procedures more challenging. Radiotherapy has historically been used as a palliative option for unresectable HCC. However, recent advances in modern radiotherapy, such as stereotactic body radiation therapy (SBRT), have dramatically increased the use of radiotherapy as a curative modality, particularly in cases ineligible for local ablation therapy or surgical resection. SBRT is a modern approach for delivering ablative high doses of irradiation in small volumes. SBRT in liver tumors, including HCC, provided local control with potential survival benefits in patients with inoperable status. However, the following issues remain to be addressed: the difference between primary and metastatic liver cancers; SBRT-related toxicity and prevention; pathological features of liver cancers; and potential SBRT strategies, including radiobiology-based SBRT and SBRT combined with immunotherapy. We summarized the effectiveness of SBRT and patient tolerance of the therapy. In addition, we present the current status and future perspective of SBRT as a treatment option for HCC.

Keywords: radiotherapy, stereotactic body radiation therapy, stereotactic ablative radiotherapy, hepatocellular carcinoma, cirrhosis, liver

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver [1]. Liver cancers have the seventh highest age-adjusted incidence rate in the world, with 0.8 million cases diagnosed a year [2]. The development of cirrhosis is associated with a high risk for developing HCC with most common risk factors including alcohol, viral hepatitis such

as hepatitis C virus (HCV), and nonalcoholic fatty liver disease (NAFLD). Due to the wide prevalence of HCC, it carries a significant economic burden on society at large, especially in the East Asian countries that have hepatitis B virus (HBV). Surveillance programs have also been implemented to screen for HCC in high-risk individuals, which is more cost-effective than the treatment of HCC. Hepatotropic viruses such as HBV and HCV have a strong association with the development of HCC; thus, the worldwide distribution of HCC mirrors the distributions of such viral infections [3]. Around 80–90% of HCC cases occur in the setting of underlying cirrhosis [4]. In addition, there is an incremental effect of the presence of more than one risk factor responsible for HCC as the presence of HBV/HCV coinfections increases the risk of HCC by two- to sixfolds. Similarly, alcohol abuse further increases this risk [5, 6]. Subsequently, we describe the role of radiotherapy in the treatment of HCC, including conventional to modern techniques, possible beneficial cases of radiotherapy, and future direction of liver stereotactic body radiation therapy (SBRT).

2. General approaches and conventional radiotherapy in the treatment of HCC

The initial approach in the management of HCC is to determine if either surgical resection or liver transplantation is feasible and best survival. The Barcelona Clinic Liver Cancer staging system is the most accepted staging system in clinical settings [7]. Orthotopic liver transplantation is the most efficient option for the treatment of HCC even though the insufficient number of donors makes challenging [8]. Therefore, local therapy is anticipated to be not only a bridging therapy but also a radical therapy in the treatment of HCC. Surgical resection is the standard local therapy for HCC [7]. Since the majority of HCC cases develop in cirrhotic patients, surgical interventions can become challenging, and the treatment has been directed toward liver transplantation. Other local therapies, such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), are used as alternatives in patients with HCC [7–9]. However, radical treatment for liver tumors can be challenging due to poor liver function, tumor location, and anatomical barriers. Furthermore, the preservation of residual liver function is required, as liver tumors have a high recurrence potential [9].

Radiotherapy is a local treatment modality and has also been used for palliative care in liver tumors. Conventional radiotherapy has been used approximately 50 Gy in a conventional fractionated schedule which could lead to a response rate as approximately 50–70% [10–14]. High doses of radiation, which are required for HCC, would sometimes exceed the levels tolerated by the background liver [15, 16]. However, modern radiotherapies, including stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), have recently attracted increasing attention as a therapeutic modality for various malignancies including HCC and have dramatically increased the use of radiation therapy as a curative modality [17–40]. However, certain issues regarding the current use of SBRT in HCC need to be addressed (e.g., ideal prescription doses, prevention of adverse events, and possible microscopic extension). In this chapter, we document the clinical utility and the present status of SBRT in the management of HCC, including clinical messages and pitfalls in liver cirrhosis and the probable treatment-related toxicities and their prevention, and summarize recent significant updates on biology-based SBRT strategies.

3. SBRT for HCC

The use of SBRT for extracranial tumors was developed by Blomgren et al. [17]. The major feature that distinguishes SBRT from conventional radiation treatment is the delivery of large doses of radiation in a few fractions, which results in a high biologically effective dose (BED). In addition, Zheng et al. have reported that a shortened delivery time could significantly increase the cell killing using *in vitro* experimentation [41]. The use of a high precision technique is critical to deliver a high dose of radiation to the target and keep rapid fall-off doses away from the target, thereby achieving a maximum treatment efficacy with minimal toxicity to normal tissues [42]. SBRT is now widely accepted as a treatment option for lung and liver tumors characterized by their small size and limited numbers [43].

Current advantages and challenges of SBRT in the liver are presented in **Table 1**. The clinical outcomes of SBRT for HCC in the previous reports are shown in **Table 2**. SBRT has been reported to provide 1-, 2-, and 3-year local control rates of 56–100, 53–95, and 51–92%, and 1-, 2-, and 3-year survival rates of 32–100, 55–100, and 21–82% for HCC, respectively [19–38]. **Figure 1** indicates the local control and overall survival after SBRT, $BED_{10} \geq 75$ Gy in ≤ 10 fractions (e.g., 40 Gy/4 fr), for HCC at our institute. **Figure 2** indicates a typical course of SBRT for HCC in cirrhotic liver. Recent reports indicated that SBRT was as effective as TACE and RFA, although there are only a small number of randomized trials examining the use of SBRT in HCC [34, 35, 38]. However, additional prospective studies involving large sample sizes are required to consolidate the evidences on SBRT with aim to standardize liver SBRT.

Advantages

- High possibility of local control
- Minimally invasive treatment modality, no requirements for anesthesia or injections
- High possibility to overcome anatomical limitations, including poorly defined tumors on ultrasound and tumors which are difficult to puncture
- No concern regarding the location close to major vessels, including the portal vein, inferior vein cava, and bile duct
- Possible to treat complicated forms of tumors, particularly using IMRT
- Short treatment term (usually within 2 weeks), possibility of benefit to the patient's quality of life and reduced medical cost
- Possibility to enhance the immune reaction to tumors

Current issues

- Poor outcomes and high possibility of toxicity with large tumors
 - Challenges involved in the treatment of tumors close to critical organs, such as the gastrointestinal tract
 - Effects of re-irradiation are unclear
 - Inaccuracy due to respiration and the presence of ascites
-

Abbreviations: SBRT = stereotactic body radiation therapy; IMRT = intensity modulated radiation therapy.

Table 1. Features of SBRT for liver tumors.

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Kwon et al. [19]	2010	Retrospective	42	33 (30-39) Gy/3 fr (70-85% isodose line covered the PTV)	69.2 (60-89.7)	29	1-year 72% 3-year 68%	1-year 92.9% 3-year 58.6%	35.7% G1 Constitutional symptoms 31.0% G1-2 Elevated liver enzyme 19.0% G1-2 Leukopenia 2.4% G1 hyperbilirubinemia and ALP	2.4% (1 patient) G4 Liver failure
Seo et al. [20]	2010	Retrospective	38	33-57 Gy/3 fr or 40-44 Gy/4 fr (60.5% patients received 39-57 Gy/3 fr)	69.3-165.3 or 80-92.4 (89.7-165.3)	15	1-year 78.5% 2-year 66.4%	1-year 68.4% 2-year 61.4% 3-year 42.1%	(57.9% G1-2 acute toxicities) 10.5% G1-2 hyperbilirubinemia 2.6% G1 albumin 5.3% G1 AST/ALT 2.6% G1 ALP 44.7% G1-2 Nausea, vomiting 7.9% G1 anorexia 13.2% G1-2 abdominal pain 2.6% G2 Paralytic ileus 2.6% G2 radiation dermatitis	2.6% G3 soft tissue toxicity (the right upper quadrate of the abdomen)

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Andolino et al. [21]	2011	Prospective	60	Child-Pugh A (60%): 44 Gy/3 fr Child-Pugh B (40%): 40 Gy/5 fr (80% isodose line, encompassing PTV)	Child-Pugh A: 108.5 Child-Pugh B: 85.5	27	3-year 90%	3-year 67%	n = 56 (93%) 23.2% G1-2 fatigue, nausea, and/or right upper quadrant discomfort	1.8% G2 chest wall toxicity 16.1% G3 liver enzymes elevation and/or hyperbilirubinemia 16.1% G3 thrombocytopenia 3.6% PT-INR 12.5% G3 albumin (17 patients of 21 patients with G3 hypoalbuminemia preexisting Grade 2 dysfunction) 1.8% G4 thrombocytopenia and hyperbilirubinemia 20.0% Child-Pugh classification progression
Kang et al. [22]	2012	Prospective	47	57 (42-60) Gy/3 fr (70-80% isodose line covered at least 97% of the PTV)	165.3 (100.8-180.0)	17	2-year 94.6%	2-year 68.7%	4.3% G3 hyperbilirubinemia (pre-existing Grade 1 or 2 hyperbilirubinemia and/or thrombocytopenia) 10.6% G3 Thrombocytopenia 4.3% G3 Ascites 6.4% G3, 4.3% G4 Gastrointestinal ulcer (3 of 5 patients had pre-existing ulcer, 2 patients experienced Grade 4 gastric ulcer perforation at 7 months and 10 months after SBRT)	

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Huang et al. [23]	2012	Retrospective	36	37 (25-48) Gy/4-5 fr (70-83% isodose line, encompassing PTV)	NA(31.2-105.6)	14	1-year 87.6% 2-year 75.1%	2-year 64%	36.1% G1-2 fatigue 25.0% G1-2 anorexia 13.9% G1-2 nausea/vomiting 5.6% G1-2 abdominal pain 2.8% G2, 2.8% G3 gastric ulcer (Both of 2 patients had gastritis before SBRT 2.8% G1 musculoskeletal	5.6% RILD (2 patients with Child-Pugh B)
Honda et al. [24]	2013	Retrospective	30	48 Gy/4 fr (86.7% of patients) or 60 Gy/8 fr (13.3% of patients) (isocenter prescription)	105.6 or 105.0	12.3	CR:96.3%	1-year 100% 2-year 100%	93.3% G1-2, 6.7% G3 leukocytopenia 96.7% G1-2, 3.3% G3 thrombocytopenia 100% G1-2 hemoglobin G1-2 hyperbilirubinemia G1 AST/ALT G1 ALP	3.3% Child-Pugh class progression

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Bae et al. [25]	2013	Retrospective	35	45 (30-60) Gy/3-5 fr (56–83% isodose line of the maximum dose or D95 prescription of 91–100% prescription doses for PTV)	101 (58–180)	14	1-year 69% 3-year 51%	1-year 52% 3-year 21%	(23% of patients experienced grade ≥ 3 toxicity) 8.6% G3 AST (1 patient also had grade 3 hyperbilirubinemia, all patients had pre-existing grade 2 elevation of AST or hyperbilirubinemia and experienced progression of intrahepatic HCC) 2.9% G3 Hepatic failure (1 month after SBRT) 2.9% G3 colonic ulcer (1 month after SBRT)	2.9% G4 Myelitis (18 months after SBRT, spine Dmax = 31 Gy/4 fr) 2.9% G3 gastric ulcer perforation (7 months after SBRT) 2.9% G5 duodenal ulcer bleeding (5 months after SBRT) 2.9% G4 colonic ulcer (3 months after SBRT)

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Bujold et al. [26]	2013	Prospective	102	36 (24-54) Gy/6 fr	57.6 (33.6–102.6)	31	1-year 87%	NA (median 17 months)	1.0% G3 fatigue 10.9% AST/ALT 3.0% G3, 2.0% G4 hyperbilirubinemia 1.0% G3 creatinine 2.0% G3 hemoglobin 1.0% G3 leukocytes 9.0% G3 platelets 29% (3-month), 6% (12-month) Child-Pugh class progression 46% (3-month), 17% (12-month) Child-Pugh score progression 1.0% G3, 1.0% G4, 4.9% G5 Liver failure 1.0% G5 cholangitis (HCC invaded the common bile duct) 1.0% G3, 1.0% G5 gastritis/gastrointestinal bleeding (G5 occurred 7.7 months after SBRT)	
Jang et al. [27]	2013	Retrospective	82 (95 HCC)	51 (33-60) Gy/3 fr (70–80% isodose line covered at least 97% of the PTV)	137.7 (69.3–180.0)	30	2-year 87% 5-year 82%	2-year 63% 3-year 39%	1.2% G3 hyperbilirubinemia (pre-existing G1) 2.4% G3 ascites 7.3% non-classic RILD (worsening of CTP score by ≥ 2, ≤ 3 months after SBRT, 2 of 6 with disease progression) 1.2% G3 soft tissue toxicity (this patient had a large tumor near the skin) 6.1% G3–4 GI toxicity (gastroduodenal ulcer in 2 patients, clonic ulcer in 1 patient, and gastroduodenal perforation in 2 patients, gastroduodenal perforation in 2 patients)	

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Sanuki et al. [28]	2014	Retrospective	185	Child-Pugh A (74.1%): 40 Gy/5 fr Child-Pugh B (25.9%): 35 Gy/5 fr (70–80% isodose line, encompassing PTV)	Child-Pugh A: 72.0 Child-Pugh B: 59.5	24	1-year 99% 2-year 93% 3-year 91%	1-year 95% 2-year 83% 3-year 70%	4.9% mild fatigue 3.2% G3 laboratory abnormalities (prior to SBRT)	10.3% Child-Pugh score progression (by two points) 1.1% G5 liver failures (both 2 patients were classified as Child-Pugh B before SBRT) 3, 6 months after SBRT)
Takeda et al. [29]	2014	Retrospective	63	Child-Pugh A (69.8%): 40 Gy/5 fr Child-Pugh B (30.2%): 35 Gy/5 fr (70 or 80% isodose line, encompassing PTV)	Child-Pugh A: 72.0 Child-Pugh B: 59.5	31.1	1-year 100% 2-year 95% 3-year 92%	1-year 76% 2-year 87% 3-year 73%	*n = 63 7.9% mild fatigue 15.8% G3 subacute liver toxicity (6.3% before SBRT)	*n = 63 20.6% G3 liver toxicity
Yamashita et al. [30]	2014	Retrospective	79	48 Gy/4 fr (40 Gy/4 fr-60 Gy/10 fr)	96 (75-106)	15.9	2-year 74.1%	2-year 52.9%	n = 130 (79 HCC, 51 liver metastases) 2.3% G2 gastrointestinal toxicity (gastric inflammation in 2 patients 1 month after SBRT, gastric ulcer in 1 patient; 27 months after SBRT) 3.1% G3 gastrointestinal toxicity (duodenal ulcer 17 months, intestinal tract bleeding 5, 6 months, transverse colon ulceration 5 months, respectively, after SBRT) 0.8% G4 gastro-duodenal artery rupture (5 months after SBRT) 0.8% chest wall pain (combined with TACE)	

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events		
									Acute response	Late response	
Culleton et al. [31]	2014	Prospective	29	34.4 (20.9–48.7) Gy/6 (5-15) fr (Mean dose to PTV) or 30.9 (197-46.8) Gy/6 (5-15) fr (D95 prescription for PTV)	54.1 (28.2–88.2) 46.8 (26.2–83.3) (Calculated presupposed with 6 fractions)	NA	6-month 69.7% 1-year 55.5%	1-year 32.3% (median 7.9 months)	48.3% G1-2 fatigue 20.7% G1 nausea 10.3% G1-2 vomiting 10.3% G1-2 diarrhea 10.3% G1 abdominal pain 10.3% G1-2 abdominal distension Child-Pugh score progression (24.1, 24.1, 10.3% by 1 point, 2 points, 3 points, respectively, at 1 month after SBRT) 17.2% G3 thrombocytopenia (3 months after SBRT) 6.9% G3, 3.4% G4 transaminase elevation (1 month after SBRT) 3.4% G4 AST (3 months after SBRT)		
Huertas et al. [32]	2015	Retrospective	77 (97 HCC)	45 Gy/3 fr (prescribed to the 80% isodose line, encompassing PTV)	112.5	12	1-year 99% 2-year 99%	1-year 81.8% 2-year 56.6%	1.3% G1, 1.3% G2 asthenia 2.6% G1, 2.6% G2, 1.3% G3 ascites 1.3% G1 rib pain 1.3% G1 anorexia 2.6% G1 nausea 3.9% G1 epigastric pain 1.3% Classic RILD 3.9% Non-classic RILD 1.3% G5 Hematemesis	1.3% G2 asthenia 1.3% G1 radiation dermatitis 2.6% G1 nausea 2.6% G1, 3.9% G2, 3.9% G3 ascites 1.3% G2 colic ulcer 1.3% G3, 1.3% G4 gastric ulcer	

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Takeda et al. [33]	2016	Prospective	90	Child-Pugh A: 40 Gy/5 fr Child-Pugh B: 35 Gy/5 fr (prescribed to the 60–80% isodose line, encompassing PTV, D95 prescription for PTV)	Child-Pugh A: 72.0 Child-Pugh B: 59.5	41.7	3-year 96.3%	3-year 66.7%	2.2% transaminase elevation 5.6% thrombocytopenia 8.9% Child-Pugh score progression (by two points)	
Wahl et al. [34]	2016	Retrospective	63	30 or 50 Gy/3 or 5 fr (D99.5 prescription for PTV, the 75 to 85% isodose line encompassing PTV)	100 (NA)	13.0	1-year 97.4% 2-year 83.8%	1-year 74.1% 2-year 46.3%	1.6% G3 RILD 1.6% G3 gastrointestinal bleeding 1.6% G3 worsening ascites	8.3% G3 luminal gastrointestinal toxicity (at 2 years after SBRT) 3.3% G3 biliary toxicity (at 2 years after SBRT) *Child-Pugh score progression by average 1.2 points) (at 12 months after SBRT)
Su, et al. [35]	2017	Retrospective	82	42–48 Gy/3–5 fr (67 (57–80) % isodose line encompassing PTV)	NA (77.3–124.8) (Calculated presupposed with 42 Gy/5 fr–48 Gy/3 fr)	33.0	NA (one patient experienced local progression) (PFS; 1-year 81.4%, 3-year 50.2%, 5-year 40.7%)	1-year 96.3% 3-year 81.8% 5-year 70.0%	4.9% G1, 3.7% G2, 1.2% G3 nausea 1.2% G1, 1.2% G2, 2.4% G3 weight loss 3.7%, G1, 1.2% G2 fatigue 3.7% G1 hyperbilirubinemia 3.7% G1 ALT 4.9% G1 anemia 6.1%, 3.7% Child-Pugh progression (1, 2 points, respectively)	

Author [Ref]	Year	Prospective/retrospective	Patient number	Total dose/fraction (median, range)	BED ₁₀ (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Lo et al. [36]	2017	Retrospective	89	25–60 Gy/4-6 fr (40 Gy/5 fr (19 patients), 45 Gy/5 fr (18 patients), 50 Gy/5 fr (14 patients))	72 (40 Gy/5 fr), 85.5 (45 Gy/5 fr), 100 (50 Gy/5 fr)	NA	3-year 78.1%	1-year 45.9% 3-year 24.3%	24.7% G1, 4.5% G2 fatigue 13.5% G1, 2.2 G2 anorexia 13.5% G1, 12.4% G2, 1.1% G3 nausea/vomiting 4.5% G1 abdominal distension 19.1 G1, 7.9% G2, 2.2% G3 abdominal pain 3.4% G2, 2.2% G3 gastritis/gastric ulcer 2.2% G1, 4.5% G2 duodenal ulcer 1.1% G1, 2.2% G2 diarrhea 1.1% G1, 2.2% G2 dermatitis 11.2% RILD (1.1% classic RILD, 9.0% non-classic RILD (including 2 patients developed fatal non-classic RILD), 1.1% fulfilled the criteria of both types)	
Uemoto, et al. [37]	2018	Retrospective	121 (146 HCCs)	45 (30–64) Gy/5 (4-20) fr	80 (48–106)	21	2-year 91.5%, 5-year 89.8%	2-year 73.7%, 5-year 57.0%	0.7%≤G2, 0.7% G3 cholangiectasis 1.5% G1 pneumonitis 0.7% mucositis 0.7% G1 rib fracture 25.2% ascites 2.2 jaundice 1.5% pleural effusion (no hematological abnormality changed from the baselines)	

Abbreviations: NA = not applicable, HCC = hepatocellular carcinoma, SBRT = stereotactic body radiation therapy, NA = not applicable; BED = biologically effective dose, G = grade, PTV = planning target volume, AST = aspartate transaminase elevation, ALT = alanine transaminase elevation, ALP = alkaline phosphatase elevation, PT-INR = prothrombin time-international normalized ratio prolongation, RILD = radiation-induced liver disease, TACE = transcatheter arterial chemoembolization, PFS = progression-free survival.

Table 2. Summary of studies of hepatocellular carcinoma.

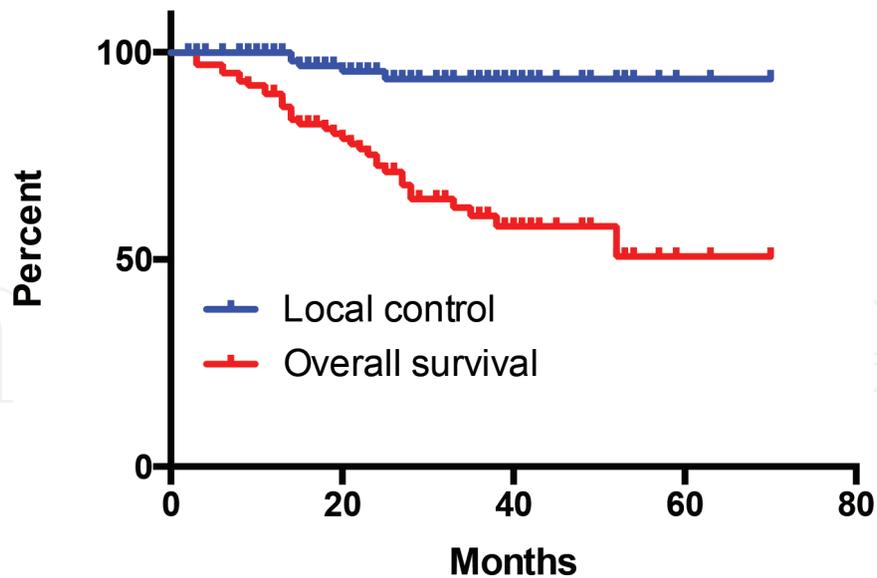


Figure 1. Local control and overall survival of HCC after SBRT. Local control (LC) and overall survival (OS) were described using the Kaplan Meier method in 100 patients with 116 HCCs underwent SBRT of $BED_{10} \geq 75$ Gy in ≤ 10 fractions, between July 2007 and August 2016 at Miyakojima IGRT Clinic (Osaka, Japan, approval no. 9). The 1-, 2- and 3-year LC rate was 100.0, 95.4 and 93.5%, respectively. The 1-, 2- and 3-year OS rate was 83.7, 72.6 and 60.5%, respectively. Abbreviations: HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy.

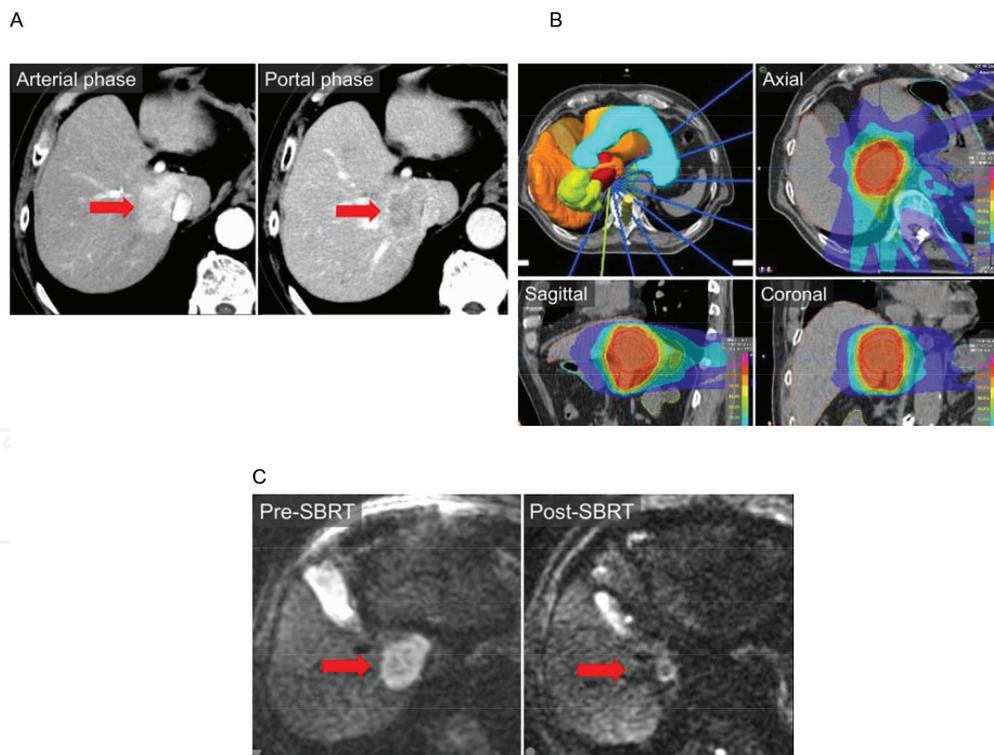


Figure 2. Typical course of SBRT for HCC in cirrhotic liver. An 86-year-old man developed HCC in S8. HCC with 50 mm in diameter existed (A, contrast-enhanced CT, arrowhead). SBRT of 40 Gy in four fractions ($BED_{10} = 80.0$ Gy) (B, treatment plan). The high intensity area that observed before SBRT in diffusion-weighted imaging of MRI (C, left) disappeared three months after SBRT (C, right). Abbreviations: HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; SBRT, stereotactic body radiation therapy; BED, biologically effective dose.

4. Radiotherapy in the management of HCC with tumor thrombus in vessels

Portal vein tumor thrombosis (PVTT), the most common form of macrovascular invasion of HCC, could propagate further, obstruct the whole vein lumen, and lead to poor prognoses ranging from only 2 to 4 months after supportive care [44, 45]. One of the treatment modalities is surgical resection that could lead to median survival time of 8–64 months, 1-, 2-, and 3-year overall survival rates of 31–87, 0–76, and 0–71%, respectively [46]. In addition, there is a potential survival benefit by surgical resection [47]. However, tumor thrombectomy can be associated with high morbidity and mortality rates, up to 23.7% [48]. TACE might be contraindicated for HCC patients with PVTT because of the potential risk of hepatic ischemic damages due to TACE. In addition, PVTT is not an indication for RFA because of the potential cooling effect and challenging status of percutaneous intervention.

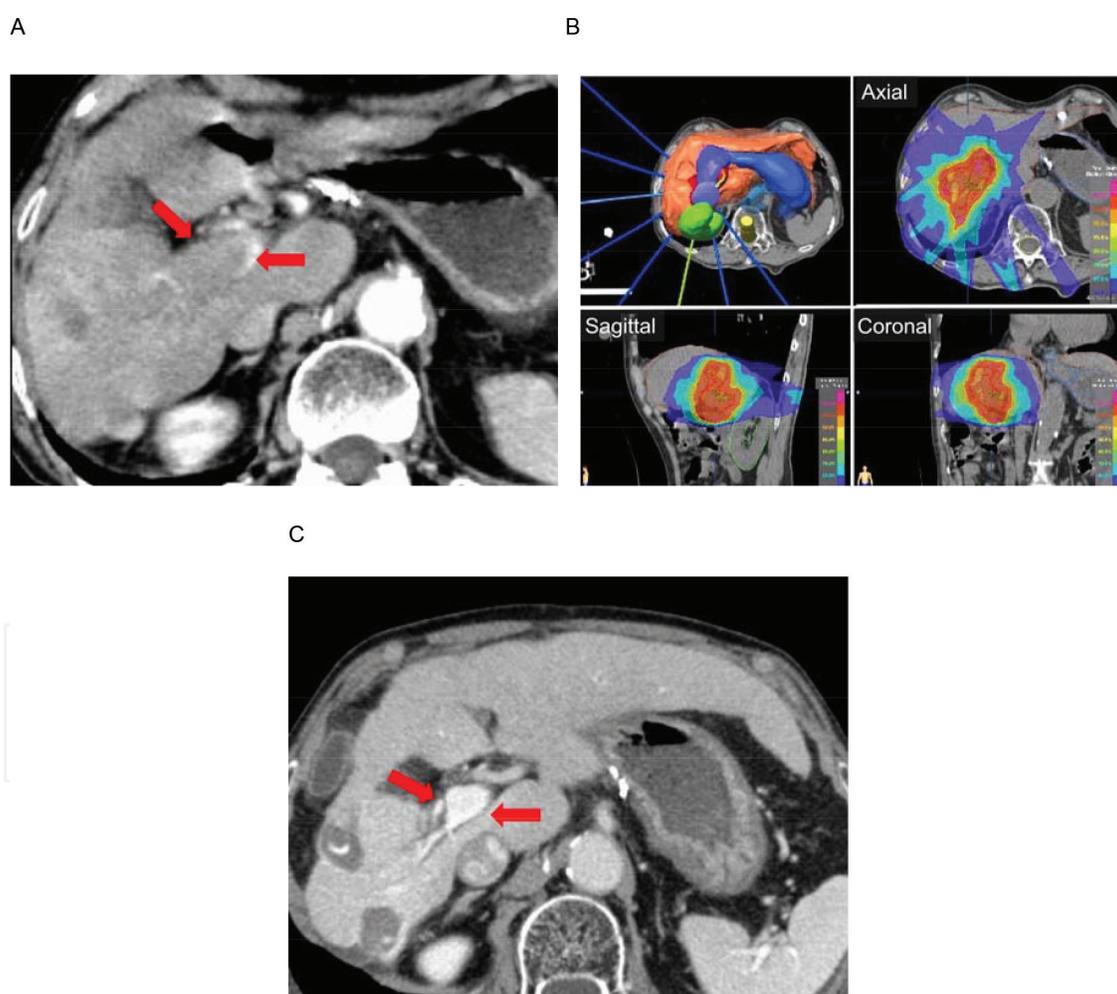


Figure 3. SBRT for PVTT. A 77-year-old man developed HCC due to hepatitis C with tumor thrombus in right portal vein (A, arrows, contrast-enhanced CT). The patient underwent SBRT of 60 Gy in 15 fractions ($BED_{10} = 84.0$ Gy) (B). The tumor thrombus disappeared after three months after SBRT. Contrast-enhanced CT indicates disobliteration of the right portal vein after SBRT (C, arrows). Abbreviations: SBRT, stereotactic body radiation therapy; PVTT, portal vein tumor thrombosis; HCC, hepatocellular carcinoma; CT, computed tomography; BED, biologically effective dose.

Although the efficacy of radiotherapy has been reported in patients with tumor thrombus using conventional schedule, the evidence of the survival benefit is insufficiently strong [39–41, 49–51]. In addition, Lin et al. have reported that radiotherapy can recanalize at a rate of 79% in 14 patients with PVTT [51]. However, there are only a few comparison studies among the techniques of radiotherapy [39, 51]. Matsuo et al. have reported, in a retrospective study, that the response rate of PVTT or inferior vena cava tumor thrombosis to radiotherapy was 67 and 46% in SBRT and 3D-CRT groups, respectively ($P = 0.04$) [39]. Moreover, SBRT has an advantage with regard to the shortened treatment term. Radiotherapy including SBRT may have the potential to be the standard technique of radiotherapy in the treatment of PVTT. **Figure 3** indicates a case of SBRT for HCC with PVTT.

Radiotherapy can overcome anatomical barriers such as major vessels and achieve a promising local control with minimal invasion. Therefore, a combined multimodal approach including radiotherapy would be needed in the treatment of the HCC with PVTT in order to maximize tumor control and to keep the normal liver damages due to treatment within a safe limit.

5. Prescription doses of SBRT for HCC

A dose-response relationship has been reported for conventional fractionated and stereotactic radiotherapy, although the best prescription dose of radiotherapy for HCC remains undecided [12, 27, 52].

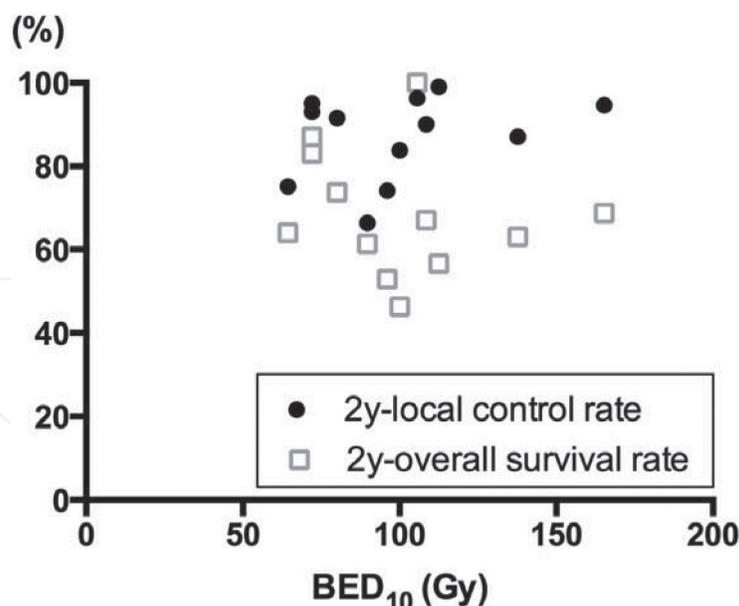


Figure 4. Dose-response relationship in SBRT for HCC. Previous reports that clearly indicates 2-year local control and overall survival were plotted in the scatter diagram [20–24, 27–30, 32, 34, 37]. X- and Y-axis indicates total doses radiotherapy in term of BED_{10} and the rates of 2-year local control and overall survival, respectively. No apparent dose-response relationship was observed in local control ($r = 0.2828$ and $P = 0.3732$) and overall survival ($r = -0.1872$ and $P = 0.5602$) at 2 years after SBRT. Abbreviations: SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; BED, biologically effective dose.

Bae et al. reported 85% local control rates at 2 years after an SBRT of 50 Gy in 10 fractions, 75 Gy in terms of biologically effective dose (BED) using the linear-quadratic (LQ) model assuming an $\alpha/\beta = 10$ Gy for tumors (BED_{10}) [53]. Lausch et al. have reported that the administration of a biologically equivalent total dose in 2-Gy fractions (EQD2) of 84 Gy ($BED_{10} = 100.8$ Gy) could achieve a 90% probability of a 6-month local control [54]. Jang et al. estimated that a 90% probability of a 2-year local control required 51.1 Gy in three fractions ($BED_{10} = 138.1$ Gy) [27]. Sanuki et al. and Takeda et al. reported a more than 90% 3-year local control rate with 40 Gy in five fractions ($BED_{10} = 72$ Gy) that was intended to enclose the planning target volume (PTV) by 80% isodose line of the maximum dose [28, 29]. **Figure 4** shows no dose–response relationship between a 2-year local control and overall survival rates and the total BED of SBRT with the range of prescription doses of ≥ 72 Gy. Notably, previous reports include various prescription definitions such as the prescription dose for the iso-center (isocentric prescription), a certain percent isodose line of the maximum dose (marginal prescription), and the dose to cover 95% of the PTV (D95 prescription). Based on these data, HCC has been treated with ≥ 80 Gy of BED_{10} and achieved a good local control at our institute as we hypothesized [37].

6. Adverse events of SBRT for HCC in cirrhotic liver, risk factors, and prevention

Manifestations of liver SBRT toxicity have fatigue, damage to the liver, gastrointestinal tract and biliary duct, cytopenia, dermatitis, and rib fractures (**Table 2**) [18–37]. Adverse events of radiotherapy depend on the treatment site, and the irradiated doses and volume and are categorized into either acute (typically within 3 months of radiotherapy) or late (months to years after radiotherapy), based on their time of onset [55]. The acute phase of radiation-induced injury is characterized by inflammation, in response to therapy, while the late phase is characterized by fibrosis and sclerosis of vessels leading to focal ischemia and chronic inflammation. To distinguish acute and late phases of toxicities is often difficult since liver damage with serum abnormalities can be observed weeks or months later after SBRT [16]. We summarize with focusing on the major toxicities in the liver, gastrointestinal tract, and central bile duct.

6.1. Liver toxicity

Liver toxicity, such as classic and non-classic radiation-induced liver disease (RILD), is one of the most common dose-limiting toxicities in liver radiotherapy [15, 16, 56, 57]. Clinical RILD occurs between 2 weeks and 7 months, typically within 4–8 weeks following hepatic radiotherapy. The patient presents with fatigue, weight gain, increased abdominal girth, hepatomegaly, anicteric ascites, and an elevation in alkaline phosphatase (over twice the upper limit of the normal values). Treatment options for RILD are limited, and the condition can become fatal due to liver failure [56, 58–61]. Non-classic RILD occurs in patients with underlying chronic hepatic disease, such as cirrhosis and viral hepatitis, and is characterized by jaundice and/or markedly elevated serum transaminases (over five times the upper limit of the normal values), developing between 1 week and 3 months after the completion of hepatic radiotherapy [19, 61]. The mean dose of less than 30 Gy has been considered as safe but radiation tolerance of the liver in a conventional radiotherapy [19]. However, the actual mean doses

appropriate for liver irradiation in SBRT have not been adequately investigated. Furthermore, radiotherapy has the potential to reactivate hepatitis B virus and differentiating patients may be necessary [62, 63]. There are differences in radiosensitivity between patients with normal and cirrhotic livers; cirrhotic liver may yield a higher radiosensitivity than normal liver [16, 57]. In addition, Child-Pugh B, particularly scores of ≥ 8 , was considered a significant risk factor for severe hepatic toxicity and poor prognosis [21, 31, 64]. Culleton et al. reported that 63% of 29 HCC patients with Child-Pugh B or C, receiving SBRT, declined Child-Pugh score by two points after 3 months [31].

As the liver is widely accepted as a parallel organ, a part of it can receive a high dose of irradiation as long as the functions as a whole organ are preserved [65–67]. Indeed, Schefter et al., Olsen et al., and Kang et al. used dose constraint, as the liver volume was >700 mL when the dose administered was less than 15 and 17 Gy in three fractions [22, 68, 69]. However, intrahepatic recurrence often occurs after a radical treatment for liver tumors because of chronic liver diseases, and such tumors have a chance to receive second radical treatment [9, 70]. Thus, the prediction of the volume of liver dysfunction is essential in order to spare the residual liver volume. After SBRT, focal dysfunction was noted in the irradiated background liver. Sanuki et al. have shown that the threshold dose of focal liver dysfunction was 30 and 25 Gy in five fractions in patients with Child-Pugh A and B, respectively, using magnetic resonance imaging (MRI) [71]. Similarly, Doi et al. have reported that focal liver dysfunction can occur at 40 and 70 Gy of BED₂ in the cirrhotic and normal liver, respectively, at a minimum dose [57]. **Figure 5** indicates a focal liver damage 3 months after SBRT. We have presented SBRT strategy with checkpoints to ensure safe treatment modality in SBRT for liver tumor [72]. To prevent RILD-related mortality, we evaluate the mean doses for the liver first and then analyze the potential loss of hepatic function in terms of BED (**Figure 6**).

6.2. Gastrointestinal injury

Ionizing radiation exerts an anticancer effect by reacting with molecular oxygen and water to generate reactive oxygen species that can attack deoxyribose in deoxyribonucleic acid (DNA). Sublethal doses of radiation can cause non-repairable DNA damage [73]. Intestine is a radiosensitive tissue because of the rapid turnover rate, and this can be a dose-limiting factor in SBRT. Gastrointestinal injuries including bleeding, ulcers, and perforations have been described, and the incidence of symptomatic gastrointestinal toxicities was less than 10% in majority of the previous reports (**Table 2**). However, severe toxicities, which can be lethal, have also been described in SBRT in the upper abdomen including liver [22, 30, 74–76]. Kang et al. have highlighted the possible association between severe gastrointestinal toxicity and the existence of mucosal ulceration prior to radiotherapy [22]. Barney et al. reported that the combination of SBRT and vascular endothelial growth factor inhibitor increased the risk of grade 3 or greater gastrointestinal toxicities [77]. Careful assessment is therefore required prior to the implementation of combined treatments, such as targeted therapy.

For the prevention of severe gastrointestinal injury, analyses of dose-volume responses have been reported. Kopek et al. recommended V21Gy ≤ 1 cc for the duodenum in abdominal SBRT in their analyses in 29 patients with cholangiocellular carcinoma (CCC) underwent SBRT (45 Gy/3 fractions) [78]. Bae et al. concluded that Dmax of 35 and 38 Gy in three fractions was associated with a probability of 5 and 10% severe gastroduodenal toxicity, respectively [79].

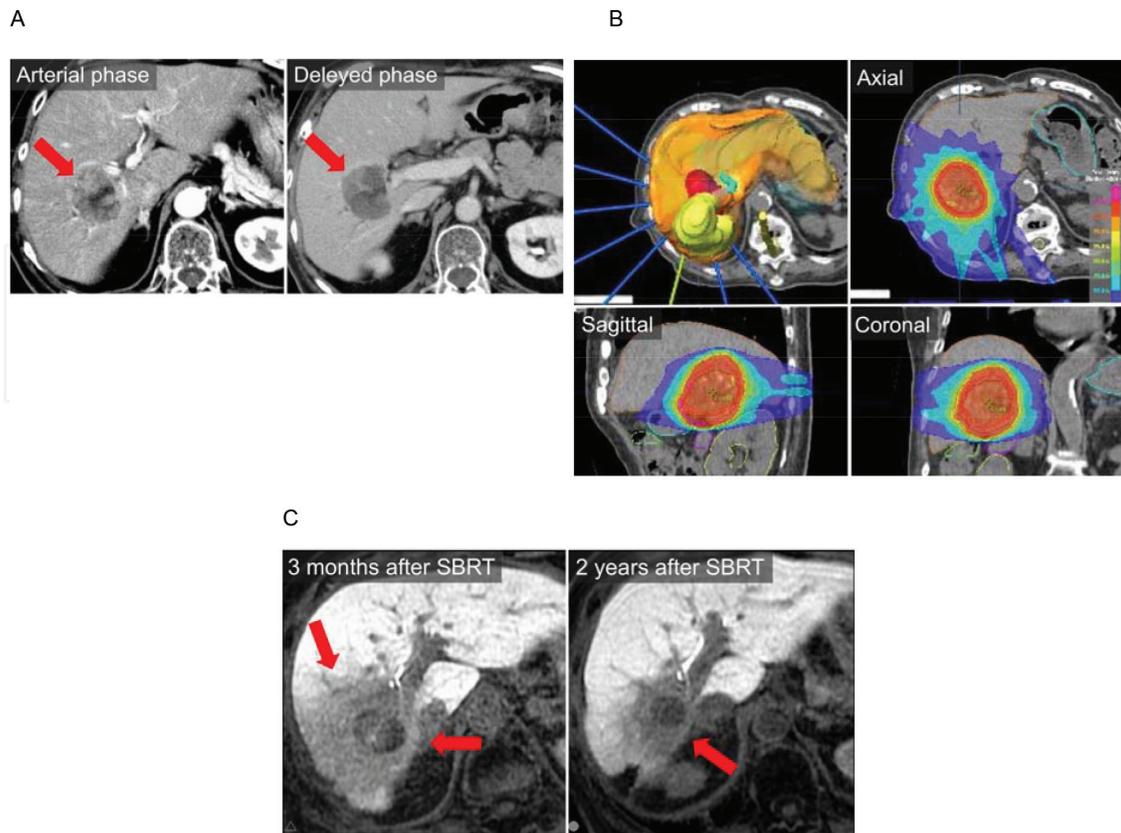


Figure 5. Focal liver dysfunction after SBRT in the follow-up MRI. A 77-year-old woman developed HCC due to hepatitis B. (A) Contrast-enhanced CT images indicate HCC in S7 area. Arterial phase showed patchy high density area (arrow, left) and contrast washed-out was observed later in delayed phase (arrow, right). (B) SBRT of 55 Gy in 10 fractions ($BED_{10} = 85.3$ Gy) was performed for the tumor. (C) Low intensity area was found in accordance with the irradiated area of treatment plan in Gd-EOB-DTPA enhanced-MRI three months after SBRT (left, arrows) and focal liver atrophy was observed later (right, arrow). Abbreviations: SBRT, stereotactic body radiation therapy; MRI, magnetic resonance imaging; CT, computed tomography; HCC, hepatocellular carcinoma; BED, biologically effective dose; Gd-EOB-DTPA, gadolinium ethoxybenzyl-diethylenetriamine pentaacetic acid.

Kavanagh et al. recommended that the volume of stomach receiving >22.5 Gy should be ideally minimized to <5 cc, with D_{max} of <30 Gy in three fractions [80]. Sanuki et al. suggested that SBRT could be performed with the avoidance of severe toxicities when the target had a distance of >2 cm from the bowel [81]. An increased number of fractions may reduce BED for normal tissues in SBRT for liver tumors close to the gastrointestinal tract [57]. Since there are no established strategies for the prevention and treatment of radiation-induced gastrointestinal injury, efforts should be required to minimize radiation doses for gastrointestinal tracts [82].

6.3. Central hepatobiliary tract toxicity

Eriguchi et al. documented asymptomatic bile duct stenosis in 2/50 patients, receiving >20 Gy in five fractions to the central liver [83]. One of these patients received SBRT on two occasions to the central liver tumors and developed abnormalities in liver enzymes. The abnormal region visible on a computed tomography scan corresponded to the site irradiated up to a cumulative maximum dose of 88 Gy in two sessions of SBRT. The authors concluded that SBRT for liver tumors in the hepatic hilum was feasible with minimal biliary toxicity.

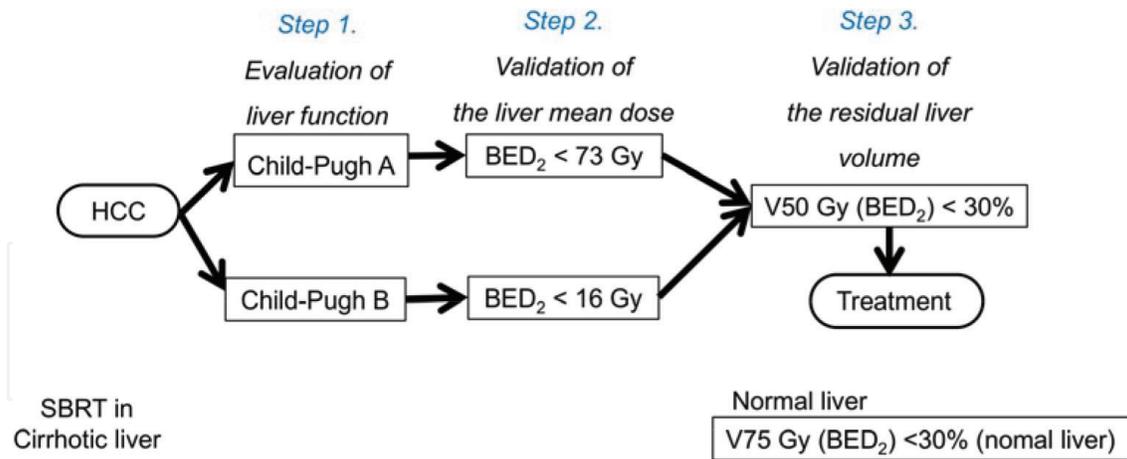


Figure 6. The current recommended treatment protocol to provide a safe SBRT for HCC in cirrhotic liver. To minimize the risk of radiation-induced liver disease and liver damage, two different checkpoints were included. Herein, we propose a safe treatment protocol for SBRT of liver tumors. First, liver function is evaluated according to the Child–Pugh classification (Step 1). Next, the liver doses are evaluated to prevent RILD. A mean BED_2 of less than 73 and 16 Gy for the whole liver should be maintained to prevent RILD in patients with Child–Pugh A and B liver function, respectively (Step 2). Finally, the volume of hepatic dysfunction is assessed to estimate the residual liver volume (Step 3). Abbreviations: SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; BED, biologically effective dose.

Osmundson et al. analyzed 96 patients with liver tumors, including 20 CCCs, who received different schedules of SBRT, and reported that the incidence of hepatobiliary toxicity \geq Grade 2 and 3 was 24.0 and 18.8%, respectively [84]. Furthermore, CCC, biliary stent, $V_{BED_{10}} 72 \geq 21$ cc, $V_{BED_{10}} 66 \geq 24$ cc, and $D_{meanBED_{10}} \geq 14$ Gy to central hepatobiliary tract were associated with hepatobiliary toxicity [81]. The same groups reported radiation-induced pathological changes of the bile duct in resected surgical specimens 25 months after SBRT and concluded that liver toxicity should be considered while treating central liver lesions [85]. The same group has also reported a dose-volume association between \geq Grade 3 hepatobiliary toxicity and doses for central biliary tract and suggested $V_{BED_{10}} 40 < 37$ cc and $V_{BED_{10}} 30 < 45$ cc as dose-volume constraints in SBRT for primary liver tumors [86].

The anatomical structures in the hepatic hilum make radical treatment for liver tumors, such as surgery and RFA, more challenging. In such a scenario, SBRT can be a better option in comparison to other modalities, and to the best of our knowledge, there is no apparent consensus on the use of SBRT with few reports addressing this point. Further studies are required to determine the dose constraints for the bile duct, as there can be potential dose constraints due to the central hepatobiliary tract toxicity.

7. Current issues and future perspective of liver SBRT

Liver SBRT is a well-established and promising treatment for a limited number of small tumors. We have set out the difference between primary and metastatic liver cancers, considering the occurrence and prevention of toxicities. However, further questions regarding the pathological features of liver cancers, and potential SBRT strategies, including radiobiology-based SBRT and SBRT combined with immunotherapy, have not yet been fully addressed.

7.1. Potent strategies of SBRT based on radiation biology

Brown et al. reported that a greater endothelial cell damage and vascular damage, leading cancer cell apoptosis, can be caused by SBRT, and reoxygenation can increase antitumor effect in fractionated radiotherapy [87]. Shibamoto et al. concluded that reoxygenation could be promoted by a 72-h break period in SBRT [88]. No prospective clinical trials exist in terms of evaluation of the benefit of a break in SBRT. However, a longer overall treatment time (e.g., 1–2 fractions per week: 2-week schedule) may yield better local control outcomes in SBRT [89, 90]. SBRT for larger tumors has still unclear roles and is challenging because they are usually in exclusion criterion. In addition, large tumor size (≥ 2 –4 cm) has been reported to be a predictive factor for poor outcomes after SBRT for HCC [23, 30, 32]. Further biological assessment might yield potential factors that improve treatment outcomes such as escalated doses, treatment schedule with a break, combined therapy with ideal chemotherapy, individualized treatment, and particle therapies.

7.2. Potential needs of clinical tumor volume margin in liver SBRT

Definition of clinical tumor volume (CTV) is the volume that includes both gross and microscopic disease and is created by adding several mm to 1.5 cm to gross tumor volume (GTV), in order to allow for microscopic extension. However, CTV is frequently equal to GTV in SBRT [91]. It is still poorly understood whether CTV margins are necessary, as there are limited reports of microscopic extension of liver tumors as premises for radiotherapy. HCC is characterized by direct invasion and a potential high presence of daughter nodules around the tumor that may lead to locoregional recurrence [92]. Wang et al. reported that the potential maximum margin extending beyond the gross tumor margin was 8.0 mm, although 94.7% of patients with HCC had a microscopic extension of ≤ 3.5 mm [93]. Wang et al. analyzed 149 resected HCCs with a mean diameter of 5.8 cm (range: 1.0–22.0 cm) and found that microinvasion was not present in 47.0% patients [94]. Microinvasion distances of ≤ 2 mm were found in 96.1% of patients with tumor dimensions of ≤ 5 cm. Uemoto et al. have first reported that a larger margin to GTV inclined to improve local control and survival outcomes in clinical data, suggesting the benefit of CTV margins [37]. Further clinical translational studies should be conducted in order to assess the optimal CTV margins.

7.3. Current knowledge of Immuno-SBRT

Regression of tumors outside the radiation field after local radiotherapy, due to systemic induction of antitumor immunity, is called the abscopal effect [95]. SBRT combined with immune checkpoint inhibitor has recently resulted in unexpected clinical complete responses from distant sites from the irradiated areas, in various malignancies [96–98]. Recently, synergistic effects of radiotherapy combined with immunotherapy have been reported in both preclinical and clinical studies, with the high possibility of the abscopal effect, which may significantly change the treatment strategies for metastatic diseases [96–105]. However, the optimal treatment schedule and doses in the combined setting of radiotherapy and immunotherapy are poorly understood at present. Young et al. reported an enhanced efficacy of immune-radiotherapy administered concurrently with radiotherapy [101]. In a meta-analysis of preclinical data, Marconi et al. reported that the probability of abscopal effects is 50% when a BED of 60 Gy is generated [102]. Moreover, SBRT may provide smaller target volumes, and in a clinical trial involving patients with pancreatic cancer, Wild et al. found that hypofractionation

could minimize the toxic effects on circulating lymphocytes [106]. By expanding its application range from small tumors to metastases, SBRT might have good potential to achieve newer objectives in systematic disease, although further investigations are required.

8. Advantages of particle therapy in treatment for HCC in cirrhotic liver

The use of particle therapy, such as proton and carbon ion therapy for liver tumors, is a promising strategy to increase the dose of radiation without a concurrent increase in toxicity. Particle therapy exhibits a narrow Bragg peak at a defined depth for a defined energy [73]. Particle therapy can provide high concentrations of radiation doses to the target by positioning individual Bragg peaks to coincide with the areas of the target. In photon radiotherapy, the doses that the liver receives have a strong positive relationship with the irradiated target volume, and unacceptable higher doses might be irradiating to the background liver in the treatment of large live tumors [72]. Particle therapy can reduce the liver volume that receives low to intermediate doses, resulting in the reduction of mean liver doses with an advantage of target conformity [107, 108]. In addition, carbon ion therapy offers the added potential benefit of an increased relative biological effectiveness and a lower oxygen enhancement ratio due to the high linear energy transfer that may improve responses in hypoxic areas of tumors, which are more resistant to photon radiotherapy [73]. A relevant clinical consideration is that particle therapy can benefit relatively large tumors, such as >3 cm (particularly >5 cm) and patients with poor liver function, which are limiting for SBRT [109].

9. Conclusions

For HCC, SBRT is safe and effective, with excellent local control achieved. Tumors that are relatively small and distant from gastrointestinal tissues are strong candidate for SBRT in curative intent. Therefore, novel strategies should be developed based on new knowledge of biological responses to radiation therapy. State-of-the-art liver SBRT remains a pioneering strategy in multimodal therapy.

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Conflict of interest

None.

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