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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (1): Hepatocellular carcinoma

Role of stereotactic body radiation therapy for hepatocellular carcinoma

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Abstract

The integration of new technologies has raised an interest in liver tumor radiotherapy, with literature evolving to support its efficacy. These advances, particularly stereotactic body radiation therapy (SBRT), have been critical in improving local control or potential cure in liver lesions not amenable to first-line surgical resection or radiofrequency ablation. Active investigation of SBRT, particularly for hepatocellular carcinoma (HCC), has recently started, yielding promising local control rates. In addition, data suggest a possibility that SBRT can be an alternative option for HCC unfit for other local therapies. However, information on optimal treatment indications, doses, and methods remains limited. In HCC, significant differences in patient characteristics and treatment availability exist by country. In addition, the prognosis of HCC is greatly influenced by underlying liver dysfunction and treatment itself in addition to tumor stage. Since they are closely linked to treatment approach, it is important to understand these differences in interpreting outcomes from various reports. Further studies are required to validate and maximize the efficacy of SBRT by a large, multi-institutional setting.

Key words: Hepatocellular carcinoma; Liver cirrhosis; Liver neoplasms; Radiation therapy; Stereotactic body radiation therapy

Core tip: The integration of new technologies has raised an interest in radiotherapy for hepatocellular carcinoma (HCC), with literature evolving to support its efficacy. These advances, particularly stereotactic body radiation therapy (SBRT), have been critical in improving local control or potential cure in liver lesions not amenable to first-line surgical resection or radiofrequency ablation. Active investigation of SBRT has recently started, yielding promising local control rates. However, information on optimal treatment indications, doses, and methods remains limited. In HCC, significant differences in patient characteristics and treatment availability exist by country. Further studies are required to validate and maximize the efficacy of SBRT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is currently the fifth most common solid tumor worldwide and the third leading cause of cancer-related death[1]. The definitive treatment for HCC has evolved primarily to be surgery, or-

thotopic liver transplantation, percutaneous ablation, or partial transarterial chemoembolization (TACE)[2]. However, in some patients, these therapies are not feasible. This review describes the evolution of and current practices for radiation therapy, with particular focus on stereotactic body therapy (SBRT) in treating these types of tumors in patients who are not candidates for definitive treatment. We also discuss the emerging role of SBRT as well as current outcomes, toxicities, and pathological and radiological findings after SBRT.

EPIDEMIOLOGY

The incidence of HCC is increasing in several developed countries, such as European nations and the United States, while in areas such as Japan and Singapore, the incidence of HCC seems to have stabilized or even fallen slightly[3,4]. The geographic variability in the incidence of HCC is largely explained by the distribution of hepatitis B and C viruses, and by the patterns of exposure to key risk factors in each population. The prevalence of such infections is being controlled by vaccination, which should also influence future trends in HCC occurrence. Heavy alcohol consumption, obesity, and diabetes are also risk factors and substantial causes of HCC in Europe and the United States.

The broad spectrum of HCC epidemiology and treatments is expected to affect prognosis. When referring to the literature on HCC treatment outcomes, it is important to carefully understand the differences in patient characteristics in each report, because these factors significantly affect outcomes as well as clinical application of various treatments.

STANDARD LOCAL TREATMENT OPTIONS FOR HCC

In HCC, prognosis is greatly influenced by underlying liver dysfunction and treatment itself, as well as tumor stage, while in other solid tumors, it is generally only related to tumor stage[2]. Unlike other cancers, many staging systems are used for HCC, including the Barcelona Clinic Liver Cancer (BCLC) staging[2], tumor-node-metastasis[5], Okuda[6], Cancer of the Liver Italian Program[7], and Japan Integrated Staging[8] scoring systems. Among these, the BCLC staging system considers the relevant parameters of all important dimensions and divides patients into very early/early, intermediate, advanced, and end-stage to recommend optimal treatment. Early-stage HCC patients are considered for potentially curative options such as resection, ablation, and transplantation. Patients with intermediate stage disease may benefit from TACE, whereas patients with advanced stage disease, or who cannot benefit from other options, are given sorafenib, an oral multikinase inhibitor, as the standard treatment.

Despite recent advances in early detection and diagnosis, only 30%-40% of patients with HCC may benefit from radical therapies. For patients who are not eligible for these curative therapies, two randomized trials have shown improved survival using TACE compared with symptomatic therapy alone[9,10]. However, TACE is somewhat controversial: a review from the Cochrane library that considered all randomized trials that compared TACE *vs* placebo, sham, or no intervention concluded that no firm evidence exists to support or refute TACE for patients with unresectable HCC[11]. In addition, the local control rate for TACE is inferior to those of resection and percutaneous ablation (82%-98% at 3 years)[12]. At best, the 3-year local control rate of superselective TACE was reported to be 65.3% in 123 patients with HCC < 5 cm in diameter[13]. Nevertheless, patients who have limited tumor burden but are not suitable for radical therapies usually undergo TACE despite its relatively low efficacy. Improving the outcomes of these patients is one of the major challenges in HCC management.

DIFFERENCE IN TREATMENT APPROACH BY COUNTRIES

The differences in patient characteristics or treatment availability by country are closely linked to the treatment approaches used in each county. Currently, early HCC diagnosis is increasingly feasible in countries with wider implementation of surveillance policies, which enables the application of curative treatments. Applicability of standard local treatments varies according to geographic distribution, with 50%-70% of cases in Japan being suitable for curative treatment, compared to only 25%-40% of cases in Europe and the United States, and 10% in Africa[14]. Once a high-risk cohort is identified, follow-up surveillance has contributed to early detection of HCC, although its efficacy appears to vary by country. In fact, in a recent Japanese cohort including 1432 patients, careful ultrasonography surveillance performed by highly skilled operators resulted in the average size of detected tumors being 1.6 cm ± 0.6 cm, with < 2% of the cases exceeding 3 cm[15].

Treatment differences by country are also prominent for organ transplantation. Orthotopic liver transplantation offers the best chance for cure, particularly in patients with decompensated liver disease. Excellent results can be achieved in patients with solitary HCC < 5 cm, or up to three nodules < 3 cm, and without extrahepatic or vascular spread, known as the Milan criteria[16]. However, the chance of transplantation is extremely limited in many countries due to the lack of sufficient liver donors. Furthermore, in contrast to western countries, Asia has cultural and religious barriers to organ donation from deceased individuals. The number of deceased donors per million population ranges from 0.07-6.5 among Asian transplantation centers, which is far below those of western countries (*e.g.*, 35.1 per million population in Spain and 25.2 per million population in the United States)[17].

RADIATION THERAPY FOR HCC

Historically, treatment with conventionally fractionated

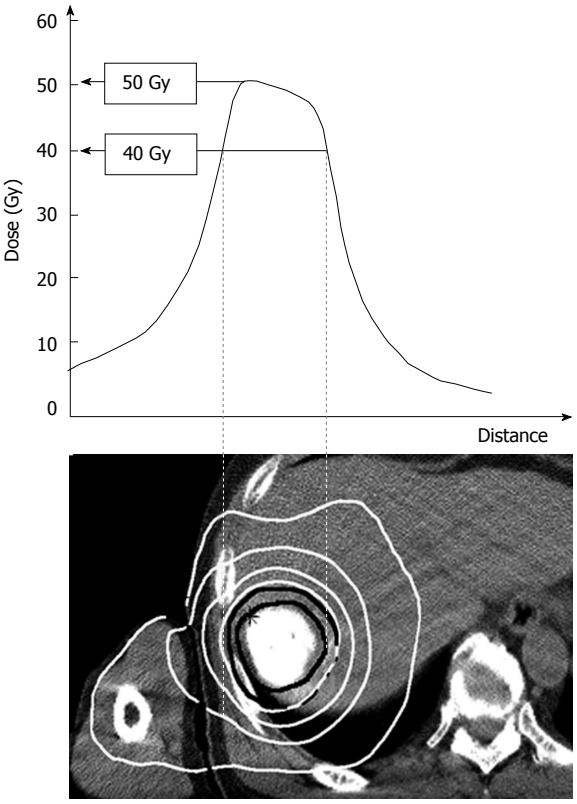

Figure 1 Dose distribution of stereotactic body radiation therapy for hepatocellular carcinoma at a dose of 40 Gy in 5 fractions, prescribed at the periphery of the target volume. The isodose lines (white solid lines) from inner to outer represent 40, 30, 20 and 10 Gy, respectively. The center of the tumor receives as high as 125% of the prescribed dose.

(1.8-2 Gy/fraction over several weeks) and 2-dimensionally-planned radiation is associated with high rates of local progression and short median survival duration. While a radiation dose-response has been observed in unresectable HCC, the delivery of high doses of radiation using conventional techniques has been limited by hepatotoxicity. Given these limitations, radiation therapy is usually not curative. Compared to other local therapies, the clinical data supporting evidence for radiotherapy in HCC patients are extremely limited[18].

As Dr. Dawson[19] descriptively discussed regarding how radiation therapy fit into the spectrum of liver cancer local therapies, HCC patients suitable for focal irradiation extend from very early to intermediate BCLC stage. For those who are unsuitable for resection, transplantation, or ablation, definitive radiotherapy or radiotherapy can be administered as a bridge to transplantation[20-22]. Definitive radiotherapy is also considered for those patients who are unsuitable for or refractory to TACE. For those patients who have portal invasion, systemic chemotherapy (*e.g.*, sorafenib) can be added to definitive radiotherapy.

SBRT

Numerous advances in external-beam radiation therapy allow for more accurate targeting, and make aggressive dose-fractionation strategies possible using techniques such as SBRT. Originally developed for the treatment of intracranial malignancies (*i.e.*, radiosurgery), SBRT has since been adopted for the treatment of extracranial diseases. For example, SBRT has been shown to be a highly effective and well-tolerated treatment in patients with medically inoperable or high-risk operable stage I non-small cell lung cancer[23].

The use of SBRT for liver malignancies was pioneered by Dr. Blomgren *et al*[24] at the Karolinska Institute, Stockholm in the early 1990s. SBRT refers to the use of stereotactic non-coplanar conformal radiation therapy intended for a small number of significantly larger fraction sizes (usually 8-12 Gy/fraction), while limiting the dose to adjacent normal tissues. The steep dose gradient within the target volume leads to tight conformity with steep and isotropic dose fall-off and high dose delivery to the target volume (Figure 1).

SBRT should be implemented with accurate patient repositioning, target localization, and control of breathing-related motion by breathing control devices such as abdominal compression, gating, and tracking systems, as well as some form of image-guided radiation therapy (IGRT) to improve set-up accuracy and treatment delivery[25].

Table 1 Eligibility criteria for different treatment modalities

	Surgery	Percutaneous ablative therapy	TACE	SBRT
Tumor size	< 5 cm (or more)	< 3 cm	> 3-5 cm	4 (or 5) cm
Number of tumors	< 3	Depends on location	1-multiple (> 4)	< 1-3
Location or characteristics	Depends on liver function	Away from large vessels or biliary system	Hypervascular lesions	Away from bowels
Local control (2 yr)	> 90%	> 90%	< 65%	> 90%
Level of evidence	High	Intermediate-high	Intermediate-high	Low
Invasiveness	High	Less	Less	None
Damage to the liver	High	Low	Low-moderate	Low-moderate

SBRT: Stereotactic body radiation therapy; TACE: Transarterial chemoembolization.

INDICATIONS FOR SBRT

Although the indications for SBRT for hepatic malignancy have evolved, the role of SBRT in HCC is less clear. Future studies should focus not only on maximizing efficacy, but also on determining how SBRT should be used in the context of other previously established therapies. Careful patient selection is required and SBRT should be considered only after thorough discussion within a multidisciplinary team, with all legitimate treatment options also considered.

Eligibility criteria for different treatment techniques are outlined in Table 1. In general, SBRT and other local therapies can complementarily divide the roles between

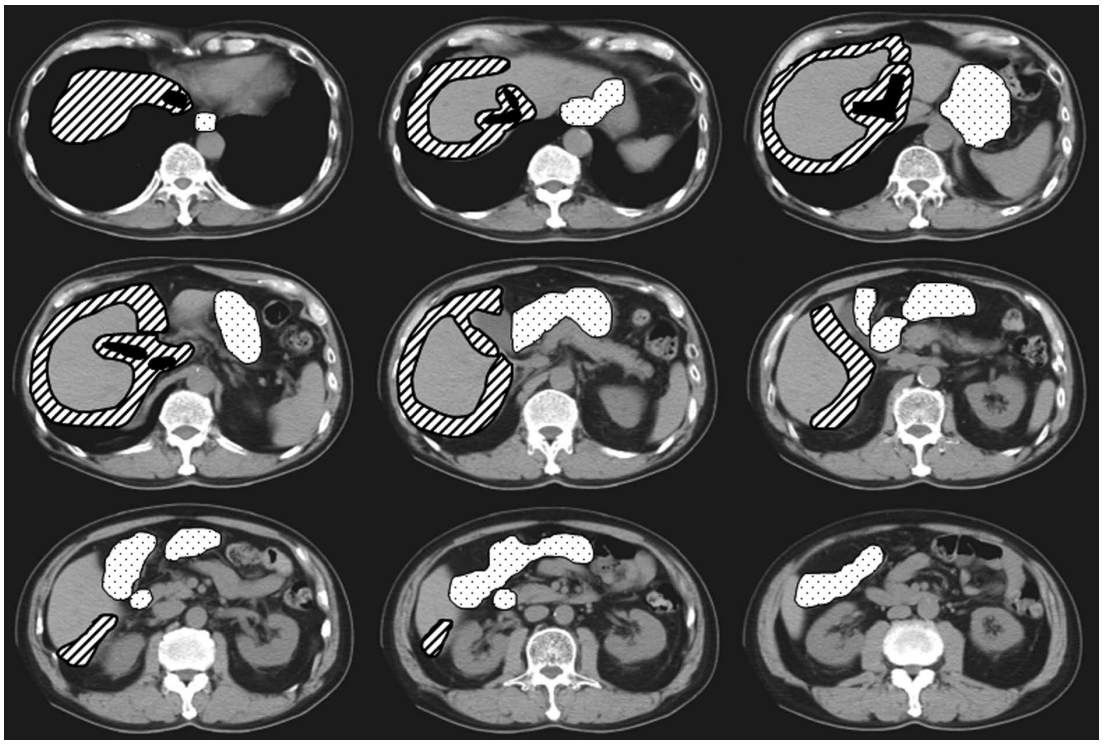

Figure 2 Computed tomography sections demonstrating typical locations treated with stereotactic body radiation therapy. Areas indicated with hatched lines can be safely treated with stereotactic body radiation therapy (SBRT), although these areas are difficult to approach for percutaneous ablation. Liver tumors located adjacent to the stomach and bowels (dotted areas) are not suitable for SBRT. Other unmarked areas can be treated either with SBRT or percutaneous ablation.

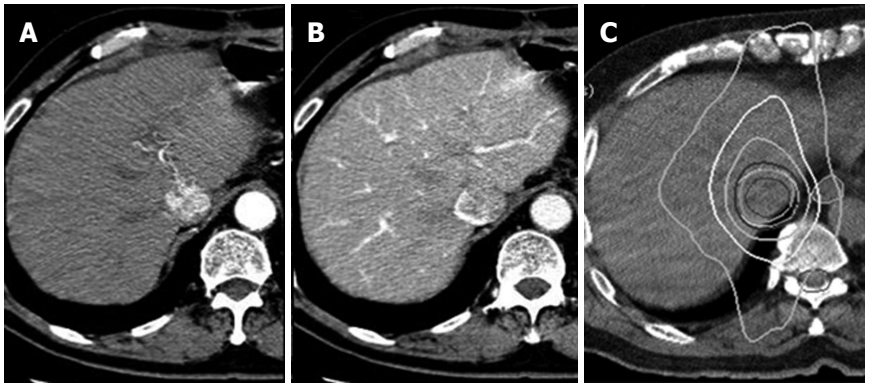

Figure 3 Hepatocellular carcinoma case that could not be effectively or safely treated with any treatment except for stereotactic body radiation therapy. The tumor invading the vena cava is enhanced in arterial phase and shows a defect in portal phase on dynamic computed tomography (A and B). An axial view of radiation dose distribution. The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively (C).

each modality. SBRT is feasible even for lesions that are not eligible for surgery or percutaneous ablation. For example, patients whose lesions are located in a central portal area or regions adjacent to great vessels or the biliary system are good candidate for SBRT[26]. In addition, lesions located just below the diaphragm or at the surface of the liver are also excellent targets for SBRT. Figure 2 illustrates typical liver locations for which SBRT can be safely delivered. SBRT is difficult to perform for lesions near the bowels due to the risk of gastrointestinal perforation, bleeding, and ulcer. Examples of patients who could not be treated with other local therapies but received SBRT are shown in Figures 3-5.

There is always a waiting period between listing and transplantation, and this varies between institutions. Many therapies have been used as a "bridge" to transplantation, and SBRT has also been evaluated as a means to bridge to transplantation. As a bridging therapy, SBRT has been reported to be feasible and well tolerated[20,21,27]. Furthermore, it enables patients to remain on the list for frequently curative transplantation while waiting for donated livers to become available.

SBRT OUTCOMES AND OPTIMAL DOSES

Outcomes of SBRT for HCC are summarized in Table

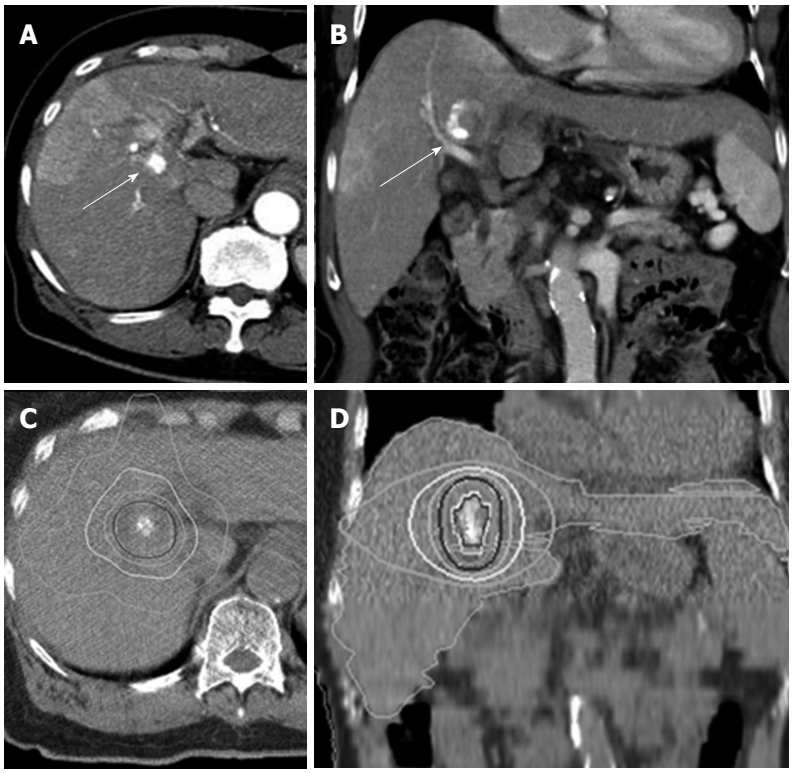

Figure 4 Case of hepatocellular carcinoma located in the hepatic hilum. Surgical resection would have required a right lobectomy. Percutaneous ablative therapy was impossible due to involvement of the biliary system and large vessels near the tumor. Axial and coronal views of a tumor with partial lipiodol deposit (A and B, arrows). Axial and coronal views of radiation dose distribution (C and D). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively.

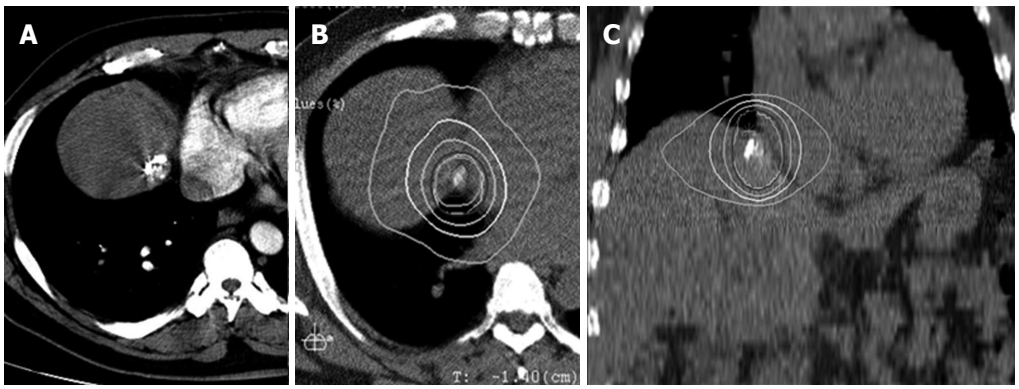

Figure 5 Case of hepatocellular carcinoma. Located adjacent to the right atrium (A). Axial and coronal view of radiation dose distribution (B and C). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively.

2[28-43]. A total of four prospective studies that exclusively evaluated HCC, as well as other retrospective studies demonstrated promising treatment effects (Table 3). The number of reports of successful SBRT studies had been increasing since 2006. Earlier studies involving SBRT for liver tumors included not only HCC but also cholangiocarcinoma and metastatic liver tumors, which made it difficult to compare the results between studies. Although the literature for SBRT is primarily composed of retrospective, small, single-institution series, SBRT has been associated with high local control rates, mostly in the range of 70%-90% at 1-2 years.

Various prescribed doses and treatment planning strategies are presently employed by different groups[28-43], and information about optimal treatment doses remains limited. Some studies employed SBRT alone, while others combined TACE as part of the treatment. Tumor size varied from 2-3 cm to approximately 5-7 cm. These differences are attributed to the geographic variability in HCC etiology and treatment availability, as previously mentioned. Therefore, the prescribed doses are expected to vary between studies even if only SBRT is used.

In general, fixed doses are employed for relatively small tumors with a median diameter of approximately 3 cm, *e.g.*, 36 Gy/3 fractions or 40 Gy/5 fractions (Table 2). In contrast, modified doses are employed for relatively larger targets according to normal liver tolerance depending on tumor size and normal liver volume. Using normal tissue complication probability models[44], prescribed doses can be prospectively assigned while maintaining the same estimated risk of liver complication. With this approach, an iso-toxic SBRT regimen was developed at Princess Margaret Hospital at the University of Toronto[45]. The dose per fraction was determined based on

Table 2 Prospective studies of stereotactic body radiation therapy for hepatocellular carcinoma and other liver tumors

Ref.	Country	Patient number	Median volume, mL	Median size, cm	Median dose (range)/ fraction, Gy	Median follow-up (range), mo	Local control	Overall survival
Cárdenes *et al*[29]	United States (Indiana)	17	34 (8-95)	-	Variable CP-A: 36-48 Gy/3 fr CP-B: 40 Gy/5 fr	24 (10-42)	100%	75% (1 yr) 60% (2 yr)
Andolino *et al*[37]	United States (Indiana)	60	29 (2-112)	3.2 (1-6.5)	Fixed CP-A: 44 Gy/3 fr CP-B: 40 Gy/5 fr	27 (2-52)	90% (2 yr)	67% (2 yr)
Bujold *et al*[30]	Canada	102	117 (1-1913)	7.2 (1.4-23.1)	Variable 36 (24-54) Gy/6 fr	31 (2-36)	87% (1 yr)	Median 17 mo
Kang *et al*[31]	South Korea (Korea Inst. of Radiological and Medical Sciences)	47	15 (2-213)	2.9 (1.3-7.8)	57 (42-60) Gy/3 fr	17 (6-38)	95% (2 yr)	69% (2 yr)

CP: Child-Pugh.

Table 3 Retrospective studies of stereotactic body radiation therapy for hepatocellular carcinoma and other liver tumors

Ref.	Country	Patient number	Median volume (mL)	Median size, cm	Median dose (range)/ fraction, Gy	Median follow-up (range) (mo)	Local control	Overall survival
Choi *et al*[32], 2006	South Korea (The Catholic Univ. of Korea)	20	-	3.8 (2-6.5)	Fixed 50 Gy/5 or 10 fr	23 (3-55)	100%	70% (1 yr) 43% (2 yr)
Zhang *et al*[72], 2007	China (Hebei)	27	-	< 5 cm: 18% 3-5 cm: 41% > 5 cm: 41%	Median 40 (32-42) Gy/5 fr	10 (3-21)	22% (1 yr)	-
Choi *et al*[33], 2008	South Korea (The Catholic Univ. Korea)	31	25 (4-57)	-	Variable 33 (30-39) Gy/3 fr	11 (2-19)	100%	81% (1 yr)
Louis *et al*[34], 2010	Belgium	25	48 (7-363)	-	Fixed 45 Gy/3 fr	13 (1-24)	95% (1 yr)	79% (1 yr) 52% (2 yr)
Kwon *et al*[35], 2010	South Korea (The Catholic Univ. of Korea)	42	15 (3-82)	-	Variable 30-39 Gy/3fr	29 (8-4)	72% (1 yr) 68% (3 yr)	93% (1 yr) 59% (3 yr)
Seo *et al*[36], 2010	South Korea (Korea Inst. of Radiological and Medical Sciences)	38	41 (11-464)	-	Variable 33-57 Gy/3-4 fr	15 (3-27)	66% (2 yr)	61% (2 yr)
Huang *et al*[38], 2012	Taiwan	36	-	4.4 (1.1-12)	Variable 37 (25-48 Gy)/4-5 fr	14 (2-35)	88% (1 yr) 75% (2 yr)	64% (2 yr)
Honda *et al*[39], 2012	Japan (Hiroshima)	30	-	1.6 (1-3)	Fixed 48 Gy/4 fr or 60 Gy/8 fr	12 (6-38)	100%	100% (1 yr) 100% (3 yr)
Bae *et al*[40], 2013	South Korea (Korea Inst. of Radiological and Medical Sciences)	35	131 (21-2189)	-	Variable 45 (30-60) Gy/3-5 fr	14 (1-44)	69% (1 yr) 51% (3 yr)	52% (1 yr) 21% (2 yr)
Xi *et al*[41], 2013	China (Sun Yat-sen Univ.)	41	65 (± 48)	-	Variable 36 (30-48) Gy/6 fr	10 (4-25)	95%	50% (1 yr)
Sanuki *et al*[43], 2013	Japan (Ofuna)	185	8 (1.5-65)	-	Fixed CP-A: 40 Gy/5 fr/ CP-B: 35 Gy/5 fr/	24 (3-80)	91% (3 yr)	70% (3 yr)

CP: Child-Pugh.

Table 4 Studies of liver tumors including hepatocellular carcinoma, cholangiocarcinoma, and liver metastasis

Ref.	Country	Study design	Tumors (patient number)	Median volume (mL)	Median size (cm)	Median dose (range)/fraction, Gy	Median follow-up (range) (mo)	Local control	Overall survival
Blomgren *et al*[24], 1995	Sweden	Retrospective	HCC+CCC/ metastasis (20/21)	22	-	Fixed 30 Gy/2-3 fr	11	HCC + CCC: 100% Metastasis: 95%	-
Tse *et al*[28], 2008	Canada	Phase Ⅰ	HCC/CCC (31/10)	173 (9-1913)	-	Variable Median 36 (24-54) Gy/6 fr	18 (11-39)	65% (1 yr)	48% (1 yr)
Herfarth *et al*[47], 2001	Germany	Phase Ⅰ-Ⅱ	HCC/CCC (4/54)	10 (1-132)	-	Dose escalation 14-26 Gy/1 fr	6 (1-26)	81% (18 mo)	-
Wulf *et al*[48], 2006	Switzerland	Prospective	HCC + CCC/ metastasis (5/51)	HCC+CCC: 14-516 Metastasis: 9-355	-	Variable Low dose: 30 Gy/3 fr or 28 Gy/4 fr High dose: 36-38 Gy/3 fr or 26 Gy/1 fr	HCC + CCC: 15 (2-48) Metastasis: 15 (2-85)	HCC + CCC: 100% Metastasis: 99% (1 yr), 66% (2 yr)	72% (1 yr) 32% (2 yr)
Méndez-Romero *et al*[49], 2006	The Netherland	Retrospective	HCC/ metastasis (11/34)	22 (10-322)	3.2 (0.5-7.2)	Variable No cirrhosis and ≥ 4 cm: 37.5 Gy/3 fr Cirrhosis and < 4 cm: 25 Gy/5 fr or 30 Gy/3 fr	13 (0.5-31)	94% (1 yr) 82% (2 yr)	HCC: 75% (1 yr), 40% (2 yr) Metastasis: 82% (1 yr), 54% (2 yr)
Iwata *et al*[50], 2010	Japan (Nagoya City University)	Retrospective	HCC/ metastasis (6/12)	-	2.3 (1.2-3.5)	Variable 50 or 55 Gy/10 fr	15	86% (1 yr)	94% (1 yr)
Goodman *et al*[51], 2010	United States (Memorial Sloan Kettering Cancer Center)	Phase Ⅰ	HCC/ metastasis (2/24)	33 (0.8-147)		Dose escalation 18-30 Gy/1 fr	17 (2-55)	77% (1 yr)	50% (2 yr)
Dewas *et al*[53], 2012	France	Retrospective	HCC + CCC/ metastasis (54/99)	32 (0.2-500)	3.3 (0.5-11)	Variable 45 Gy/3 fr	15 (12-18)	84% (1 yr) 75% (2 yr)	-
Ibarra *et al*[54], 2012	United States (Cleveland)	Retrospective, multicenter	HCC/CCC (21/11)	HCC: 334 (10-1914) CCC: 80 (31-819)	-	HCC: 22 (18-26) Gy/1 fr CCC: 30 (22-30) Gy/1 fr	13 (0.5-54)	84% (1 yr) 75% (2 yr)	87% (1 yr) 55% (2 yr)

CCC: Cholangiocarcinoma; HCC: Hepatocellular carcinoma.

the effective volume of normal liver irradiated (Veff). On a 6-fraction schedule, when the Veff was low (< 25%), doses of 54 Gy (9 Gy × 6) were delivered. For patients with a high Veff (25%-60%), doses from 30-45 Gy (5 to 7.5 Gy × 6) were delivered. In their phase I study of 102 HCC patients, the majority of whom had portal vein tumor thrombosis, the 1-year local control rate was 87%[30]. Univariate analysis revealed that higher SBRT doses were associated with higher local control (HR = 0.96; $P = 0.02$).

Both fixed-dose and variable-dose prescription approaches have their own rationale, and it is important to understand the differences in treatment intention (curative or semi-radical) and objectives (early or advanced). Two potential concepts may define the prescribed radiation dose: one is to deliver the maximum dose if dose constraints to the organs at risk are satisfied (the maximum tolerable dose); the other is to administer the necessary minimum dose with sufficient efficacy (the minimum effective dose, or, the ALARA: as low as reasonably achievable principal). The former concept appears to be suitable for larger tumors to maximize antitumor effects. In contrast, the latter concept may be reasonable for small HCCs, because intrahepatic recurrences frequently occur after treatment (68% in 5 years)[46] and they are repeatedly treated while underlying cirrhosis progressively develops over time.

It is also important to note that many reports include cholangiocarcinoma or metastatic liver tumors (Table 4); therefore, it is difficult to compare their survival with those who underwent resection and ablation[24,45,47-54]. While patients with liver metastatic disease have relatively normal liver function and tolerate radiation, patients with

HCC have pre-existing liver dysfunction, and radiation tolerance is less well established. In addition, radiosensitivity of these tumors appears to be different[55]. While metastatic lung tumors (particularly those from colorectal cancer) are reported to require dose escalation due to relatively low radiosensitivity[56], increasing the dose for HCC tumors may not be necessary. In fact, in a study of 185 patients with HCC (median diameter, 27 mm) treated with SBRT of 35 Gy or 40 Gy in 5 fractions, both local control (91% and 89%, respectively; Log-rank $P = 0.99$) and overall survival (66% and 72%, respectively; $P = 0.54$) rates were equivalent between the two dose groups[43].

Other factors may also affect treatment outcomes. Some reports on SBRT for HCC use TACE as a part of their treatment, or for validation of tumor location in each treatment session by visualizing the tumor with lipiodol on computed tomography (CT), while other reports treat patients with SBRT alone. In addition, since patients in most of the series were previously treated by other standard therapies, outcomes of these patients are much worse than those in whom surgery is performed as the first treatment. While achieving high local control rates (approximately 90%-100% in 2 years) with SBRT, the 2-year overall survival rates, which range from 52%-69%, seem to be compromised, most likely due to the inclusion of large tumors or heavily pretreated patients with repeated recurrences. In a retrospective analysis of 63 patients who had previously untreated HCC with a median tumor size of 2.6 cm, SBRT delivered 35-40 Gy in 5 fractions yielded 2- and 3-year local control rates of 95% and 92%, respectively, with a median follow-up duration of 31.1 mo[57]. In this study, the overall survival rate was 73% in 3 years, which was comparable to outcomes treated with surgery or percutaneous ablation, considering these candidates were medically unfit for radical therapies. In the Japanese Nationwide Survey, the 3-year overall survival rates of patients with solitary tumors ≤ 2 cm and 2-5 cm treated with resection were 83%-90% and 70%-81%, respectively. Those treated with percutaneous ablation were 82%-88% and 66%-82%, respectively[58]. According to these results, it is indicated that a high local control rate for SBRT similar to other standard local therapies can achieve equivalent overall survival.

TOXICITIES AFTER SBRT

Radiation-induced liver disease (RILD) is a dose-limiting complication of liver irradiation. This could be an important issue, particularly in patients with HCC, primarily in the context of underlying liver cirrhosis. Originally, RILD was thought to involve anicteric hepatomegaly, ascites, and elevated alkaline phosphatase typically occurring 2-12 mo after therapy. This endpoint can occur in patients who have otherwise fairly well functioning pretreatment livers and can be fatal once it occurs ("classic" RILD)[59]. Caution must be exercised in patients with HCC derived from pre-existing liver disease, because patients with more severe liver disease are significantly less likely to tolerate radiation[60], which can manifest as "nonclassic" RILD. A review article by Pan *et al*[59] referred to nonclassic RILD as ≥ Grade 3 elevated liver transaminases or worsening of Child-Pugh score by ≥ 2. However, information about nonclassic RILD remains limited, and the clinical significance of such liver toxicities has not been validated, particularly for hypofractionated SBRT.

In general, SBRT can be performed safely. In sequential phase Ⅰ and Ⅱ trials of SBRT of 24 to 54 Gy in 6 fractions for 102 locally advanced HCCs, ≥ Grade 3 toxicity was observed in 30% of patients. In these trials, there were seven deaths (7%) possibly related to treatment (1.1-7.7 mo after SBRT)[28]. In a large retrospective study of 185 HCC patients treated with SBRT of 35 or 40 Gy in 5 fractions, acute but transient ≥ Grade 3 toxicities were observed in 24 (13.0%) patients, and grade 5 liver failure occurred in 2 patients (1.3%)[43].

Another major concern of SBRT-induced complications involves gastrointestinal toxicity. Gastric or duodenal ulcer or perforation has been reported[38,40]. Such toxicities can be avoided when the target is approximately > 2 cm from the bowels. If the target is less than that distance, the dose or fraction size that can be delivered safely to the target often needs to be decreased to respect the radiation tolerance. In contrast, it appears that SBRT can be safely delivered to tumors located within or near the biliary system[26].

PATHOLOGICAL AND RADIOLOGICAL FEATURES OF HCC AND NORMAL LIVER AFTER SBRT

Effect of SBRT to normal liver parenchyma

Normal liver changes after high-dose irradiation have been recognized to have the histopathologic features of veno-occlusive disease (VOD)[61,62]. Olsen *et al*[22] reported on the histopathologic features underlying focal liver reactions to irradiation in 2 patients who underwent surgical resection following SBRT. They identified areas of radiation injury as having histologic characteristic of focal VOD with centrilobular congestion and fibrosis. These distinct areas were observed with clear demarcation between the irradiated and nonirradiated liver.

Radiographic normal tissue changes caused by irradiation have been described after SBRT in the absence of clinical manifestations of RILD. Most notable is a well-demarcated focal hypodensity of liver parenchyma that appears in the first few months after SBRT on CT, often referred to as focal liver reaction to radiation[22,63-65] (Figure 6). They typically present as sharply demarcated areas from the surrounding liver tissue, which presents, often enhanced, in the portal-venous or late phases. According to a report on radiation-induced focal liver reactions in cirrhotic livers evaluated on dynamic CT, it began at a median of 3 mo, peaked at 6 mo, and disappeared about 9 mo later, and these appearances remained for more than 12 mo in at least one-third of patients[64]. It is im-

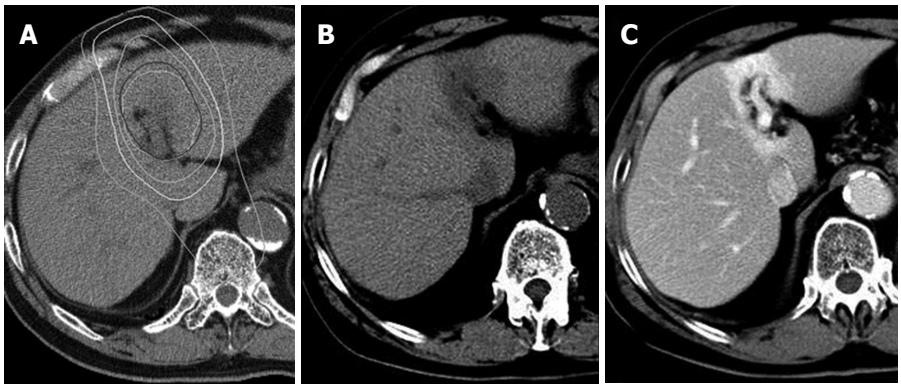

Figure 6 Typical focal liver reaction 3 mo after stereotactic body radiation therapy seen on computed tomography. An axial view of radiation dose distribution (A). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively. Pre-enhancement computed tomography shows a low-density lesion corresponding to a high-dose area (B). A well-demarcated enhancement due to contrast retention indicating congestion is seen in portal phase (C).

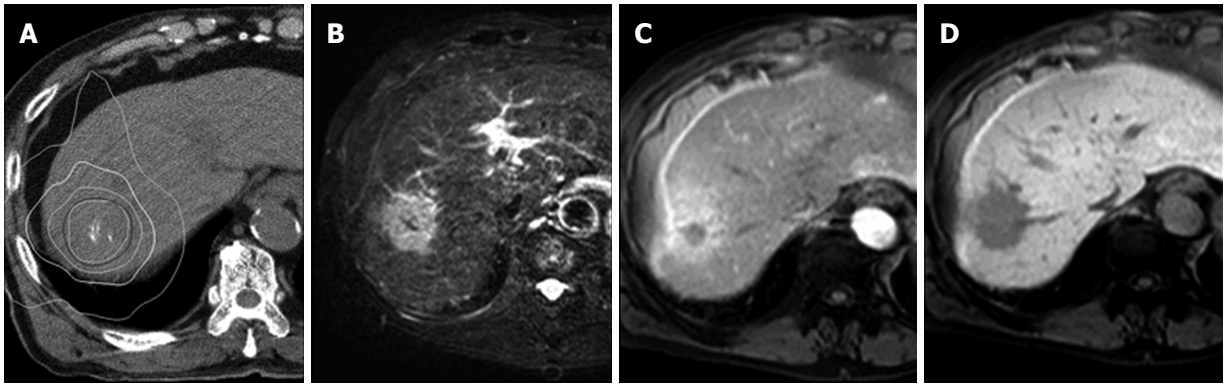

Figure 7 Typical focal liver reaction 4 mo after stereotactic body radiation therapy seen on gadoxetate acid-enhanced magnetic resonance imaging. An axial view of radiation dose distribution (A). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively. A T2-weighted image shows a high-intensity area corresponding to a high-dose area (B), which is seen as an enhanced area in early phase after injection of gadoxetate acid (C). The hepatobiliary phase shows a well-demarcated low-intensity area (D).

portant that this type of reaction following SBRT to the liver is recognized, and it should not be misinterpreted as local recurrence, because the duration of tumor viability after SBRT overlaps with this time period[63,65].

Focal liver reaction has primarily been evaluated using CT, and it can also be recognized on magnetic resonance imaging (MRI). The role of the contrast agent gadoxetate acid (Gd-EOB-DTPA) for MRI in the detection and characterization of HCC has been an area of active laboratory and clinical research[66,67]. After intravenous injection, Gd-EOB-DTPA is gradually taken up by hepatocytes and is eventually excreted *via* the biliary pathway. Hepatocyte-phase Gd-EOB-DTPA-enhanced MRI can be used for the detection or characterization of hepatic lesions and potentially for the measurement of hepatocyte function. Figure 7 shows a clear demarcated focal liver reaction corresponding to a highly-irradiated area, seen as low signal intensity of adjacent liver parenchyma typically observed 1-6 mo after treatment in hepatobiliary phase images (15-20 min after Gd-EOB-DTPA injection).

Effect of SBRT to tumor

SBRT as a bridging therapy to orthotopic liver transplantation provided an opportunity to study the histopathologic features of tumors treated with SBRT[20,21,27]. According to these studies, this therapy can achieve a complete response rate of 27%. In contrast, most SBRT series reported a local control rate of 70%-100%, which implies that the effect of SBRT takes a considerable time to cause tumor cell death. Such discrepancy appears to be attributable to the difference in evaluation time; the interval between bridging SBRT to liver transplantation was approximately 4-7 mo while radiological response rate evaluation was performed at a median follow-up of approximately 12-24 mo. In fact, a retrospective study described the long-term imaging appearance of 42 small hypervascular HCCs following SBRT[68]. In this study, the complete response rate increased from 24% (n = 10) at 3 mo to 67% (n = 28) and 71% (n = 30) at 6 and 12 mo, respectively. The 2-year local control rate was 97% and the overall complete response rate at maximum follow-up was 93% (n = 39), yet three enhanced tumors persisted for more than 2 years without evidence of progression. Cautious and continuous observation until tumor regrowth is required to evaluate the true effect of this treatment.

FUTURE RESEARCH DIRECTIONS

The most common site of first recurrence was the liver outside the irradiated volume, providing the rationale for studies combining regional or systemic therapies with SBRT. The Radiation Therapy Oncology Group (RTOG) has initiated a phase Ⅲ study of sorafenib *vs* SBRT followed by sorafenib in HCC (ClinicalTrials.gov identifier, NCT01730937). Eligible patients have locally advanced HCC that is unsuitable for resection, transplantation, or radiofrequency ablation, or is unsuitable for TACE or refractory to TACE (BCLC Intermediate [B] or Advanced [C]). Dozens of additional clinical trials utilizing SBRT for HCC are being conducted around the world, suggesting that it is a promising and actively investigated treatment option. Among these studies, a Japanese multicenter group is conducting a study of SBRT for previously untreated solitary HCC patients who are unfit for resection or ablation (primarily BCLC stage 0 and A). The results should provide new information about the effect of SBRT as an alternative option for early HCC.

In addition to conformal photon external-beam delivery, data suggest improved outcomes with proton or charged-particle therapies[69-71], particularly for large tumors. The optimal indication needs to be defined for SBRT and particle-beam therapies to separate the specific roles for each modality.

While the early outcomes of SBRT use in unresectable HCC are encouraging, further studies are required to validate these favorable results. A large, multi-institutional phase Ⅱ study should be performed to evaluate the efficacy and toxicity of SBRT for unresectable HCC, as well as the feasibility of this treatment in a multi-institutional setting.

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