주요간문맥종양혈전을 동반한 간세포암에 대한 다기관 체부정위방사선치료계획 비교연구(KROG 16-17)

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Multicenter Planning Comparison of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis (KROG 16-17)

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Background/Aims: To evaluate the technical feasibility of stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC) with the major portal vein tumor thrombosis (PVTT).

Methods: Ten institutions affiliated with the Korean Stereotactic Radiosurgery Group were provided the contours of four cases: the first case was the first branch PVTT with sufficient normal liver volume (NLV), the second was the first branch PVTT with insufficient NLV, the third was the main trunk PVTT at confluence level, and the fourth was the main trunk PVTT with entire length. The institutions were asked to make SBRT plans according to their current treatment protocols and to complete facility questionnaires.

Results: Based on institutional protocols, SBRT was feasible in nine institutions for the first case (32-60 Gy in 3-5 fractions), in eight institutions for the second case (32-50 Gy in 3-5 fractions), in seven institutions for the third case (35-60 Gy in 3-5 fractions), and in four institutions for the fourth case (35-42 Gy in 4-5 fractions). The other institutions recommended hypo- or conventional fractionation due to insufficient NLV or gastrointestinal organ proximity. With analysis of the SBRT dose to the central hepatobiliary tract, the major PVTT could theoretically be associated with a high risk of hepatobiliary toxicity.

Conclusions: Although SBRT is a technically feasible option for HCC with the major PVTT, there was a variability among the participating institutions. Therefore, further studies will be necessary to standardize the practice of SBRT for the major PVTT. (J Liver Cancer 2018;18:130-141)

Keywords: Hepatocellular carcinoma; Multicenter study; Portal vein; Stereotactic body radiotherapy; Survey

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INTRODUCTION

Hepatocellular carcinoma (HCC) is characterized by its propensity to invade the vasculature within the liver.¹ Hepatic vascular invasion of HCC is divided into microvascular invasion, and macrovascular invasion (MVI) which means gross invasion into the portal veins, hepatic veins, or the inferior vena cava in the liver.² Portal vein tumor thrombosis (PVTT), which is a tumor thrombus in the main portal vein and its branches, is the most common form of MVI, with an incidence ranging from 44% to 62% and a median survival time without treatment for only 2.7 months.^{3,4} Based on 2 phase III trials (SHARP and ORIENTAL Trials), sorafenib, a multikinase inhibitor, is the only approved standard treatment for advanced HCC, including PVTT.^{5,6} However, for PVTT subgroups, the recommendation of sorafenib as the only available treatment modality has been questionable due to the following reasons: the MVI site from these 2 phase III trials was unclear, a lower survival benefit was observed in the MVI subgroup, and sorafenib is expensive.⁷⁻⁹ A recent the American Association for the Study of Liver Disease guideline announced that it is not possible to recommend sorafenib alone over locoregional treatments for PVTT patients, as there remains inadequate evidence to inform the balance of benefit versus harm.¹⁰ Therefore, various treatment modalities or combination therapies are considered as alternative treatment options in clinical practice.¹¹⁻¹³

Radiotherapy (RT) is an effective treatment modality for killing tumor cells within the thrombus, performing recanalization, and rapidly relieving PVTT. These mechanisms can restore portal flow, improve liver functional reserves, and subsequently allow delivery of the therapeutic agents, via vessels, to the tumor. Many studies have shown the efficacy of conventional RT as a single treatment or in combination with other treatment modalities, including transarterial chemoembolization (TACE), in HCC patients with PVTT.^{1,14} A recent meta-analysis reported that the combination of RT and TACE induced higher objective response rates and superior overall survival than TACE alone, and the difference was statistically significant.¹⁵ In six of the eight studies in this analysis, only PVTT was treated with RT because intrahepat-

ic tumor tended to be large and multiple, and as such, repeated TACE was used to treat intrahepatic tumors. However, the tumors outside the RT field would quickly grow during RT. Therefore, the authors suggested that a more short-term fractionation regimen, such as stereotactic body radiotherapy (SBRT), may resolve this problem. Until now, only a few studies have reported SBRT for PVTT as an effective treatment modality with acceptable toxicity.¹⁶⁻²⁰ Considering the little clinical experience of treating PVTT with SBRT, and the highly individualized approaches that are taken for each clinical case, a wide variation in practice patterns among radiation oncologists is expected. Furthermore, the methodologies and technologies of SBRT for the treatment of major PVTT, such as the main trunk or the first branch which is centrally located on the liver, is more difficult to detect. Here, we conducted a multicenter planning study to compare current practices and evaluate the technical feasibility of SBRT for treating HCC with major PVTT.

METHODS

1. Case selection

The Korean Stereotactic Radiosurgery Group conducted a multicenter phase II study of SBRT for HCC with major portal vein invasion, which targeted PVTT of the main trunk or the first branch (NCT01850368). After reviewing the enrolled cases of this phase II study, four cases were retrospectively selected for our planning study. The first case was a patient with the first branch PVTT with sufficient normal liver volume (NLV). He was 56 years old and had multiple HCCs at the lateral segment of the liver, with PVTT at the left first branch, after right lobectomy and lung metastasectomy. In addition, lymph node enlargement was observed at the pericardiophrenic area. The tumor stage, according to the modified Union for International Cancer Control (mUICC), was IVB. The patient was a hepatitis B virus (HBV) carrier with liver cirrhosis, and a baseline liver function evaluation showed a Child-Pugh (CP) score of 7 and NLV of 1,339 mL. The second case was a patient with the first branch PVTT with insufficient NLV. He was 50 years old and had viable

HCC at the right posterior segment of the liver, with PVTT at the right first branch after 2 cycles of TACE. The mUICC stage of the patient was IVA. He was a HBV carrier with liver cirrhosis. The baseline liver function evaluation showed a CP score of 7 and NLV of 736 mL. The third case was a patient with the main trunk PVTT at confluence level. She was 58 years old and only had a viable tumor in the confluence level PVTT of the main trunk, after 2 cycles of TACE. The mUICC stage of the patient was III. She was a HBV carrier with liver cirrhosis. The baseline liver function evaluation showed a CP score of 5 and NLV of 1,248 mL. The fourth case was a patient with the main trunk PVTT with entire length. He was 73 years old and presented with a viable tumor in the entire-length PVTT at the main trunk, after 6 cycles of TACE. The mUICC stage of this patient was III. He was a HBV carrier with liver cirrhosis. The baseline liver function evaluation showed a CP score of 5 and NLV of 911 mL. Planning computed tomography (CT) images of each case are shown in Fig. 1.

2. Planning procedure

According to the phase II study protocol, the gross tumor volume (GTV) was defined as the PVTT that was visualized on the planning CT images and was considered equal to the internal target volume (ITV). In the longitudinal direction, the planning target volume (PTV) was defined as the ITV plus 4 mm, and as the ITV plus 2 mm in all other directions. As an important organ at risk (OAR), the NLV was defined as the total liver volume minus the GTV. The stomach, duodenum, and intestine were delineated by outlining all individual loops as several discontinuous structures, and the superior and inferior borders were defined as 2 cm beyond the superior and inferior extent of the PTV. In addition, the spinal cord, esophagus, and kidney were delineated as OARs. For this planning study, Digital Imaging and Communications in Medicine (DICOM) RT format files of the planning CT images and the structure set, including the PTV and OARs, were provided to 10 institutions that were affiliated with the Korean Stereotactic Radiosurgery Group. The institutions downloaded the DICOM files of the four cases from

a website and were asked to make SBRT plans according to their current treatment protocols as possible. Subsequently, the DICOM RT format files of radiation doses were uploaded to a website for review. In addition, the participating institutions were required to complete a facility questionnaire.

3. Data analysis

The DICOM files of each institution were imported into a MIM workstation (MIM Software Inc, Cleveland, OH, USA). All planning data were independently reviewed by 1 radiation oncologist and 1 physicist at Soonchunhyang University College of Medicine, Bucheon. Dosimetric quality was evaluated using a dose-volume histogram (DVH) analysis. The homogeneity index was defined as a dose at 2% of the PTV ($D_{2\%}$) minus a dose at 98% of the PTV ($D_{98\%}$) divided by the prescription dose. The conformity of the plans was assessed according to the conformity index (CI), which was defined as the ratio of the prescribed isodose volume to the PTV. To assess high-dose spillage, the percent ratio of the cumulative volume of all tissues outside the PTV receiving a dose of >105% of the prescription dose to the PTV was recorded as hot spot. To assess intermediate-dose spillage, the percent ratio of the maximum dose at 2 cm from the PTV to the prescription dose (D_{2cm} , %) and the ratio of the 50% prescription isodose volume to the PTV ($R_{50\%}$) were recorded. To evaluate variability of the CI, hot spot, D_{2cm} , and $R_{50\%}$ among the institutions, we used the NRG Oncology the Radiation Therapy Oncology Group (RTOG) 0915 protocol as the reference points (Supplementary Table 1). The maximal point dose (D_{max}) of the stomach and reverse NLV (rNLV, NLV receiving <X Gy) were derived from the DVHs. To assess the risk of hepatobiliary toxicity (HBT) $\geq$ grade 3 according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) version 4.03, we contoured the central hepatobiliary tract (cHBT) as a uniform 15-mm expansion of the PV as it extends from the splenic confluence to the first bifurcation of the left and right PV on the planning CT image, according to recommendations by the Stanford University.^{21,22} When the RT dose to the cHBT was converted to the biologically effective dose (BED) using

Figure 1. Planning computed tomography images in the axial, coronal, and sagittal planes. (A) The first branch PVTT with sufficient NLV. (B) The first branch PVTT with insufficient NLV. (C) The main trunk PVTT at confluence level. (D) The main trunk PVTT with entire length. The red, blue, yellow, and pink lines indicate the gross tumor volume, the planning target volume, the stomach, and the duodenum, respectively. PVTT, portal vein tumor thrombosis; NLV, normal liver volume.

a standard linear quadratic model with an α/β ratio of 10 (V_{BED10}), the $V_{BED10}40 < 37$ mL and the $V_{BED10}30 < 45$ mL of the cHBT were considered as the important cut-off point for HBT development.

This study was approved by the institutional review board (IRB No. K-1611-002-026). The need for written informed consent from the participants was waived because this study was a survey that used retrospective data of patients who were prospectively treated and we anonymized and de-identified all records and information prior to analysis so as not to infringe any patients' rights. This study was also conducted under the authorization and cooperation of the Korea Radiation Oncology Group (KROG 16-17).

RESULTS

1. Institutional protocols

Practice details for PVTB SBRT at the participating institutions are shown in Table 1. To create the PTV, 2 institutions added a 4-mm margin to the GTV or the ITV in the superior-inferior direction, seven institutions added a 5-mm margin, and one institution added a 7-10 mm margin. Most institutions contoured the gastrointestinal (GI) organ by outlining the individual wall loop. Seven institutions separately contoured the small bowel from the large bowel, while two institutions contoured the GI as a single organ. To minimize hepatic toxicity, all institutions agreed that the rNLV should be at least 700 mL, although the reference dose was variable. For the stomach, all institutions considered that the D_{max} to this organ was an important constraint, but the reference dose was variable. The number of SBRTs performed for HCCs per year was ≥ 24 in one institution, 11-13 in 5 institutions, 6-10 in two institutions, and 1-5 in two institutions. The ratio of SBRT application for PVTB of HCC was $< 10\%$ in four institutions, 10-20% in three institutions, 20-40% in one institution, 40-60% in one institution, and $> 60\%$ in one institution. In the clinical setting, the most common case that was consulted for RT was case 3, followed by case 1, case 2, and case 4, as shown (Fig. 2A). Among these cases, participating institutions selected cases 1 and 3 as showing the opti-

mal indications of SBRT for PVTB (Fig. 2B).

2. SBRT dose across 4 clinical cases

The practical SBRT dose schemes and PTV coverages for the 4 clinical cases are summarized in Table 2. From each institutional protocol, SBRT was feasible in 9 institutions for case 1, with 32-60 Gy in 3-5 fractions. However, one institution thought that SBRT was unsuitable for this case due to poor prognosis from multiple, uncontrolled HCCs and recommended 3-dimensional conformal radiotherapy (3DCRT) with 39 Gy in 13 fractions. For case 2, SBRT was feasible in eight institutions with 32-50 Gy in 3-5 fractions. Institution C felt that SBRT was unsuitable due to limitation of the NLV and recommended 3DCRT with 50.4 Gy in 28 fractions. Institution D thought that the NLV was insufficient and the right kidney was located near the PTV, and recommended 3DCRT with 45 Gy in 15 fractions. For case 3, SBRT was feasible in seven institutions, with 35-60 Gy in 3-5 fractions. The other institutions felt that SBRT was unsuitable due to the proximity of the GI organ, and recommended intensity modulated radiotherapy (IMRT) with 45-50 Gy in 10-25 fractions. For case 4, SBRT was feasible in four institutions, with 35-42 Gy in 4-5 fractions. The remaining institutions felt that SBRT was unsuitable due to the proximity of GI organ, and institution C also felt that the NLV was insufficient. These institutions recommended 3DCRT or IMRT, with 40-50.4 Gy in 10-28 fractions. With regard to high-dose spillage, the hot spot exceeded 15% in institution I for cases 1, 2, and 4, where the highest RT dose was prescribed to the PTV. In terms of intermediate-dose spillage, minor and/or major deviations of D_{2cm} and $R_{50\%}$ were noted in all participating institutions.

3. Sparing of OARs for 4 clinical cases

The DVHs of the NL, stomach, and cHBT, which are important OARs, are displayed in Fig. 3. For case 2, the RT dose, which irradiated to 700 mL of the rNLV, was significantly higher than RT doses of other cases in all institutions, because the NLV was 736 mL. For the stomach, the D_{max} was

Table 1. Practice details for stereotactic body radiotherapy to hepatocellular carcinoma with portal vein tumor thrombosis

	A	B	C	D	E	F	G	H	I	J
PTV margin	Lateral 3 mm Superior-inferior 5 mm	5 mm 5 mm	3 mm 5 mm	3 mm 5 mm	5 mm 5 mm	2 mm 4 mm	3-5 mm 7-10 mm	2 mm 4 mm	3 mm 5 mm	5 mm 5 mm
GI contour	IWC separating SB from LB	IWC as single organ	IWC separating SB from LB	IWC separating SB from LB	IWC as single organ	IWC of SB and PCC of LB	IWC separating SB from LB +5 mm	PCC	IWC separating SB from LB	IWC separating SB from LB
No. of fx	4 fx's	3 fx's	4 fx's	4 fx's	4 fx's	4 fx's	4 fx's	5 fx's	3 or 5 fx's	4 fx's
Normal liver constraint	$rV_{20Gy} \geq 700mL$	$rV_{7Gy \text{ or } 19.2Gy} \geq 700mL$	$rV_{7Gy} \geq 700 mL$	$rV_{19.2Gy} \geq 700 mL$	$rV_{19.2Gy} \geq 700 mL$	$rV_{19.2Gy} \geq 700 mL \text{ or } V_{10Gy} < 33\%$	$rV_{7Gy} \geq 700 mL$	$rV_{21Gy} \geq 700 mL \text{ or } V_{21Gy} < 33\%$	$rV_{7Gy} \geq 700 mL \text{ or } V_{21Gy} < 33\%$	$rV_{19.2Gy} \geq 700 mL$
Stomach constraint	$D_{max} < 30 Gy$	$D_{max} < 22.2 Gy$	$D_{max} < 35 Gy$	$D_{max} < 22.2 Gy$ $D_{10mL} < 16.5 Gy$	$D_{max} < 35 Gy$	$D_{max} < 35 Gy$	$D_{max} < 35 Gy$	$D_{max} < 35 Gy$	$D_{max} < 80 Gy$, EQD2	$D_{max} < 35 Gy$
Treatment machine	Infinity	CK	Cinac IX	Truebeam	RapidArc	RapidArc	Tomo	Truebeam	CK	CK
Gating application	No	Yes	No	No	Yes	No	No	No	Yes	No
Planning system	Monaco 5.0	Multiplan	Eclipse	Eclipse v11.0	Eclipse v8.6	Eclipse	Pinnacle	Eclipse v10.0	Multiplan	Multiplan 3.5
Calculation algorithm	Monte-carlo	Ray-tracing	AAA	AAA	AAA	AAA	CC	AAA	Ray-tracing	Ray-tracing
SBRT cases per 1 year	1-5 cases	11-23 cases	1-5 cases	11-23 cases	6-10 cases	≥ 24 cases	6-10 cases	11-23 cases	11-23 cases	11-23 cases
Ratio of SBRT to PVTT	20-40%	10-20%	10-20%	0-10%	40-60%	0-10%	0-10%	>60%	0-10%	10-20%

PVT, planning target volume; GI, gastrointestinal organ; IWC, individual wall contour; SB, small bowel; LB, large bowel; PCC, peritoneal cavity contour; fx, fraction; rV_{xGy} , normal liver volume receiving $<X$ Gy; reverse V_{xGy} : $D_{33\%}$, dose irradiated to 33% of normal liver volume; D_{max} , maximal point dose; EQD2, the equivalent dose of 2 Gy per fraction; CK, CyberKnife; AAA, anisotropic analytical algorithm; CC, CCre-calc.

13-31 Gy for case 1, 8-16 Gy for case 2, 17-29 Gy for case 3, and 27-36 Gy for case 4. According to the Stanford University guidelines that used to predict HBT, SBRT was feasible for case 1. However, SBRT application for case 4 could be theoretically associated with a high risk of HBT.

DISCUSSION

The current study showed that SBRT to the major PVTT was technically feasible, although the application rate of SBRT differed according to clinical situation. Six institutions applied fixed doses, regardless of the extent of PVTT, while four institutions applied different doses on a case-by-case basis. In general, fixed-dose prescription approaches are employed to administer the necessary minimum dose with sufficient efficacy (the minimum effective dose), and variable-dose prescription approaches are employed to deliver the maximum dose if dose constraints to the OAR are satisfied (the maximum tolerable dose).²³ The former concept may be reasonable to preserve liver function and permit additional treatment, while the latter concept may be suitable to maximize the PVTT response. Although some studies have reported that higher SBRT doses increased the PVTT response rate and improved survival, a dose-response relationship has not been determined in the clinical setting.¹⁹ Therefore, the optimal dose prescription for the major PVTT between fixed-dose and variable-dose should be evaluated. A hot spot

above the NRG Oncology RTOG 0915 reference point was observed in one institution, which prescribed the highest SBRT dose. On the other hand, minor or major deviations of intermediate-dose spillage were observed in all participating institutions. Intermediate-dose spillage represents the steepness of the dose gradient outside the PTV for delivering a high dose to the tumor without OAR damage.²⁴ This is a distinct feature of SBRT and is used to evaluate SBRT plan conformity. However, the deviations shown in this study do not suggest suboptimal SBRT plans. First, although the RTOG reference value is widely accepted, it has not been clinically validated. One study reviewed the SBRT plans of 74 patients with lung cancers and analyzed treatment outcomes.²⁵ The $R_{50\%}$ was not met in any of the plans; 39% had minor variations and 61% had major variations. Nevertheless, the authors reported comparable survivals and minimal toxicities. Second, when a critical OAR is close to the PTV, reduction of the dose to the OAR could result in larger D_{2cm} and $R_{50\%}$ volume, particularly for the surrounding tissue on the side opposite the critical OAR.²⁶ Because the major PVTT is close to the duodenum, a rapid dose-reduction to the duodenum increases doses to the pancreas and the peritoneal cavity, which is a relatively radio-resistant organ, and expands the volume of D_{2cm} and $R_{50\%}$.

Author's survey shows that the NLV and the distances between GI organs and the PTV are critical factors for applying SBRT to major PVTT, although the reference points vary

Figure 2. Frequency of RT consultations for HCC patients with PVTT (A) and the optimal indications for SBRT (B) Responder can select multiple answer that were selected by participating institutions. RT, radiotherapy; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; SBRT, stereotactic body radiotherapy.

Table 2. Practical SBRT dose schemes and target coverage for 4 clinical cases

	A	B	C	D	E	F	G	H	I	J
Case 1: PTV=62 mL										
Dose (Gy)/ fx's	32/4	45/3	40/4	40/4	40/4	40/4	44/4	35/5	60/3	SBRT was not indicated
HI	0.1	0.2	0.1	0	0.1	0.1	0.1	0.1	0.2	
CI	1.2 [†]	1.1	1.1	0.9	1.1	0.9	1.1	1	1.3 [†]	
Hot spot* (%)	0	0	0	0	3	0	1	0	17 [†]	
D _{2cm} (%)	93.7 [†]	62.8	76.4 [†]	70.7 [†]	89.3 [†]	64.4	80.5 [†]	65.9 [†]	73.4 [†]	
R _{50%}	7.0 [†]	4.9 [†]	5.2 [†]	4.7 [†]	4.3 [†]	3.6	4.9 [†]	4.3 [†]	4.4 [†]	
Case 2: PTV=91 mL										
Dose (Gy)/ fx's	32/4	45/3	SBRT was not indicated	SBRT was not indicated	40/4	36/4	32/4	50/5	45/5	40/4
HI	0.1	0.3			0.1	0.1	0	0.1	0.2	0.2
CI	0.9	0.8			1	0.9	1.1	1	1.2 [†]	1
Hot spot (%)	0	0			0	0	0	0	10	0
D _{2cm} (%)	68.3	65.3			86.9 [†]	69.9	72.4 [†]	77.3 [†]	81.3 [†]	60.4
R _{50%}	4.4 [†]	4.3 [†]			3.6 [†]	3.5 [†]	3.5 [†]	3.6 [†]	4.6 [†]	4.1 [†]
Case 3: PTV=12 mL										
Dose (Gy)/ fx's	SBRT was not indicated	SBRT was not indicated	40/4	40/4	40/4	40/4	SBRT was not indicated	35/5	60/3	40/4
HI			0.1	0	0.1	0.1		0	0.2	0.2
CI			1.1	0.9	1.2 [†]	0.9		1	1.7 [†]	1.2 [†]
Hot spot (%)			0	0	2	0		0	41 [†]	1
D _{2cm} (%)			42	49.8	59.1 [†]	46.9		47.4	58.2 [†]	39.4
R _{50%}			4.7 [†]	4.2	5.4 [†]	5.1 [†]		4.4	6.1 [†]	5.3 [†]
Case 4: PTV=92 mL										
Dose (Gy)/ fx's	SBRT was not indicated	SBRT was not indicated	SBRT was not indicated	SBRT was not indicated	40/4	40/4	SBRT was not indicated	35/5	42/5	SBRT was not indicated
HI					0.1	0.1		0.1	0.3	
CI					1	0.9		1	1.4 [†]	
Hot spot (%)					0	0		0	23 [†]	
D _{2cm} (%)					76.8 [†]	67.2		75.1 [†]	88.1 [†]	
R _{50%}					3.9 [†]	3.6 [†]		3.7 [†]	4.6 [†]	

SBRT, stereotactic body radiotherapy; PTV, planning target volume; fx's, fractions; HI, homogeneity index, defined as D_{2%} of the PTV minus D_{98%} of the PTV divided by the prescription dose; CI, conformity index, defined as the prescription isodose volume to the PTV volume; D_{2cm}, the maximum dose at 2cm from the PTV; R_{50%}, the ratio of the 50% prescription isodose volume to the PTV.

* Means the ratio of the 105% prescription isodose volume outside PTV to the PTV; [†] Means minor variation; [‡] Means major variation according to NRG Oncology the Radiation Therapy Oncology Group (RTOG) 0915 protocol.

among institutions. Uncertainties remain regarding the optimal liver constraints, and prospective data are required to further define, although many clinicians, including authors in this study, apply a critical volume model (often rNLV of 700 mL).²⁷ The Princess Margaret Cancer Centre recently reported that PVTT was also associated with hepatic toxicity after SBRT for HCC.²⁸ Considering that HCC with PVTT is clinically associated with larger tumor size, higher tumor number, poorer tumor grade, and worse liver function, and these characteristics lead to poor prognosis, such as impaired liver function, intrinsic aggressiveness, reduced intolerance to anti-neoplastic treatment, and a high rate of developing complications related to portal hypertension, we should need more conservative liver constraints when using SBRT for HCC with the major PVTT.²⁹ With regard to GI organs, no standardized method for contouring has been evaluated. Although most clinicians in the current study separately contoured the individual walls for small and large intestines, this does not reflect the intrafrac-

tional and interfractional variations of the GI organ. A study that analyzed serial CT scans that were obtained during RT for prostate cancers reported that only 19.2% of GI organs always remain in the same location at each weekly CT.³⁰ Another study showed that contouring of the GI organ as a single peritoneal cavity was a significant predictor for small bowel toxicity, and the authors suggested that peritoneal cavity contouring was a reasonable surrogate for individual wall contouring.³¹ In addition, the duodenum is a small organ, in which relatively small differences in contouring can result in large discrepancies.³² Considering that the peritoneal cavity is easy and quick to contour on planning CT images, and that contouring has small variations between clinicians, further validation studies would be meaningful.

The HBT has recently gained attention as an important OAR after SBRT for HCC. The Stanford University announced 2 studies that predicted the HBT after SBRT for cHBT.^{21,22} These studies evaluated the dosimetric parameters

Figure 3. Dose-volume histogram of the normal liver (A), stomach (B), and central hepatobiliary tract (C) for the four cases which were planned with SBRT by participating institutions. SBRT, stereotactic body radiotherapy. rNLV, reverse normal liver volume, which receives <X Gy; D_{max} , maximal point dose; Gy_{BED10} , biologically effective dose using the standard linear quadratic model with an α/β ratio of 10; two asterisks refer to the reference point for predicting hepatobiliary toxicity, according to recommendations from the Stanford University.

Table 3. Clinical outcomes and survival in HCC with PVTT after SBRT

Study	No. of pts	Type of PVTT	SBRT target	SBRT dose median (range)	Combined treatment	ORR	Median survival	Overall survival at 1-year	Toxicity
Choi et al ¹⁶ (2008)	9	NS	PVTT	30 Gy (30-36)/3 fx's	TACE in 9 pts	44%	8 mo	43%	No Gr 3 toxicity
Xi et al ¹⁷ (2013)	33	1st or 2nd branch PVTT in 16 pts; main PVTT in 17 pts	PVTT +/- near HCC	36 Gy (30-48)/6 fx's	Sorafenib in 14 pts; TACE in 15 pts; RFA in 5 pts; surgery in 3 pts	76%*	24 mo in branch PVTT; 9 mo in main PVTT	92% in branch PVTT; 8% in main PVTT	Bilirubin ↑ of Gr 3 in 1 pt (2.4%)*
Kang et al ¹⁸ (2014)	101	1st branch PVTT in 67 pts; main PVTT in 34 pts	PVTT + HCC	40 Gy (21-60)/6 fx's	SBRT → TACE (A) in 34 pts; TACE → SBRT (B) in 37 pts; SBRT alone (C) in 30 pts	70%	15 mo in A; 15 mo in B; 12 mo in C	59% in A; 54% in B; 50% in C	CP class deterioration in 35 pts (35%); 11 pts (32%) in A; 15 pts (41%) in B; 9 pts (30%) in C
Matsuo et al ¹⁹ (2016)	38	Branch PVTT in 20 pts; main PVTT in 17 pts; NS in 1 pt	PVTT	42-55 Gy/10-15 fx's	TACE in 11 pts; TAI in 11 pts	67%*	11 mo*	49%*	No RILD. liver enzyme ↑ of Gr 3 in 1 pt (3%); bilirubin ↑ of Gr 3 in 1 pt (3%); albumin ↓ in 1 pt (3%); CP class deterioration in 1 pt (3%)
Lu et al ²⁰ (2016)	64	Branch PVTT in 36 pts; main PVTT in 28 pts	PVTT + HCC	40 Gy (35-45)/10-12 fx's	No	NS	6 mo	26%	AST/ALT ↑ ≥Gr 3 in 8 pts (13%); GTT ↑ ≥Gr 3 in 17 pts (27%); bilirubin ↑ ≥Gr 3 in 3 pts (5%)

HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; SBRT, stereotactic body radiotherapy; ORR, objective response rate including complete response and partial response; NS, not specified; TACE, transarterial chemoembolization; Gr, grade; RFA, radiofrequency ablation; CP class, Child Pugh class; TAI, transcatheter arterial infusion; RILD, radiation induced liver disease; AST, aspartate transaminase; ALT, alanine transaminase; GTT, gamma-glutamyl transpeptidase.

*Was evaluated in all patients including PVTT and inferior vena cava tumor thrombosis.

affecting HBT $\geq$ grade 3 according to the NCI CTCAE ver. 4.03, such as biliary stricture/obstruction, alanine transaminase/aspartate transaminase elevation, alkaline-phosphatase elevation, hepatobiliary infection, sepsis related to hepatobiliary infection, or hepatic failure. The authors suggested that $V_{BED10}40 < 37$ mL and $V_{BED10}30 < 45$ mL of cHBT were significant predictors for prevention of the HBT. Along with this observation, our planning study showed different probabilities of HBT according to the location of PVT: SBRT can be safely applied in case 1, SBRT ≤ 40 Gy can be applied in cases 2 and 3, and SBRT with 35–42 Gy can provoke considerable risk of HBT in case 4. However, HBT did not increase after SBRT to the main trunk PVT in published studies, as shown in Table 3. The discrepancies among the studies might be due to the following reasons. First, published studies were retrospective in nature. Therefore, selection bias may have occurred and the rates of HBT may have been underestimated. Second, HCC patients with PVT have poor survival rates, and as such, the patient may have died before HBT occurred. Third, each study evaluated toxicity with different definitions, which caused inconsistencies in reporting HBT. Finally, the dosimetric analysis at the Stanford University included patients with HCC and patients with cholangiocarcinoma. Patients with cholangiocarcinoma had significantly more biliary stents at the time of SBRT, and the related biliary infections were counted as HBT. In addition, discrimination between tumor progression and inflammatory or fibrotic changes that are caused by SBRT is sometimes difficult, particularly in the context of cholangiocarcinoma. Therefore, the risk of HBT in patients with HCC may have been overestimated. To confirm the safety of SBRT for cHBT, prospective studies focusing on major PVT are needed. We expect that our multicenter phase II study of SBRT for HCC with major PVT (NCT01850368) will provide answers.

In conclusion, our planning study shows that SBRT for HCC with the major PVT is a technically feasible option, particularly in cases with sufficient NLV and a gap from the GI organ. However, the SBRT dose needed to maximize local control and OAR constraints needed to minimize toxicity vary among institutions. Therefore, further studies will be needed to standardize the practice of SBRT for the major PVT.

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SUPPLEMENTARY MATERIAL

Supplementary data can be found with this article online <http://www.e-jlc.org/html/https://doi.org/10.17998/jlc.18.2.130>.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Chan SL, Chong CC, Chan AW, Poon DM, Chok KS. Management of hepatocellular carcinoma with portal vein tumor thrombosis: review and update at 2016. *World J Gastroenterol* 2016;22:7289-7300.
2. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. *Gastroenterology* 2009;137:850-855.
3. Zhang ZM, Lai EC, Zhang C, Yu HW, Liu Z, Wan BJ, et al. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. *Int J Surg* 2015;20:8-16.
4. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;29:62-67.
5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-390.
6. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25-34.
7. Bae SH, Park HC. Editorial on combination treatment beyond sorafenib alone for hepatocellular carcinoma with portal vein tumor thrombosis. *Transl Cancer Res* 2017;6(Suppl 3):S637-S642.
8. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et

- al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012;57:821-829.
9. Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 2012;48:1452-1465.
10. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358-380.
11. Korean Liver Cancer Study Group (KLCSG), National Cancer Center Korea (NCC). 2014 KLCSG-NCC Korea practice guideline for the management of hepatocellular carcinoma. *Gut Liver* 2015;9:267-317.
12. National Comprehensive Cancer Network. NCCN categories of evidence and consensus [Internet]. Fort Washington, PA (USA): National Comprehensive Cancer Network; [cited 2017 May 25]. Available from: https://www.nccn.org/professionals/physician_gls/categories_of_consensus.asp.
13. Rim CH, Seong J. Application of radiotherapy for hepatocellular carcinoma in current clinical practice guidelines. *Radiat Oncol J* 2016;34:160-167.
14. Bae BK, Kim JC. The response of thrombosis in the portal vein or hepatic vein in hepatocellular carcinoma to radiation therapy. *Radiat Oncol J* 2016;34:168-176.
15. Zhao Q, Zhu K, Yue J, Qi Z, Jiang S, Xu X, et al. Comparison of intra-arterial chemoembolization with and without radiotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a meta-analysis. *Ther Clin Risk Manag* 2016;13:21-31.
16. Choi BO, Choi IB, Jang HS, Kang YN, Jang JS, Bae SH, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer* 2008;8:351.
17. Xi M, Zhang L, Zhao L, Li QQ, Guo SP, Feng ZZ, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. *PLoS One* 2013;8:e63864.
18. Kang J, Nie Q, Du R, Zhang L, Zhang J, Li Q, et al. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. *Mol Clin Oncol* 2014;2:43-50.
19. Matsuo Y, Yoshida K, Nishimura H, Ejima Y, Miyawaki D, Uezono H, et al. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. *J Radiat Res* 2016;57:512-523.
20. Lu XJ, Dong J, Ji LJ, Xiao LX, Ling CQ, Zhou J. Tolerability and efficacy of gamma knife radiosurgery on hepatocellular carcinoma with portal vein tumor thrombosis. *Oncotarget* 2016;7:3614-3622.
21. Osmundson EC, Wu Y, Luxton G, Bazan JG, Koong AC, Chang DT. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. *Int J Radiat Oncol Biol Phys* 2015;91:986-994.
22. Toesca DA, Osmundson EC, Eyben RV, Shaffer JL, Lu P, Koong AC, et al. Central liver toxicity after SBRT: an expanded analysis and predictive nomogram. *Radiation Oncol* 2017;122:130-136.
23. Sanuki N, Takeda A, Kunieda E. Role of stereotactic body radiation therapy for hepatocellular carcinoma. *World J Gastroenterol* 2014;20:3100-3111.
24. Yang J, Fowler JF, Lamond JP, Lanciano R, Feng J, Brady LW. Red shell: defining a high-risk zone of normal tissue damage in stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2010;77:903-909.
25. Amin NP, Nalichowski A, Campbell S, Hyder J, Spink R, Konski AA, et al. Helical therapy is safe for lung stereotactic body radiation therapy despite limitations in achieving sharp dose gradients. *Technol Cancer Res Treat* 2017;16:1173-1178.
26. Bae SH, Kim MS, Jang WI, Kim KB, Cho KH, Kim WC, et al. Quality assurance for a multicenter Phase II study of stereotactic ablative radiotherapy for hepatocellular carcinoma ≤5 cm: a planning dummy run. *Jpn J Clin Oncol* 2017;47:535-542.
27. Murray LJ, Dawson LA. Advances in stereotactic body radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol* 2017;27:247-255.
28. Velec M, Haddad CR, Craig T, Wang L, Lindsay P, Brierley J, et al. Predictors of liver toxicity following stereotactic body radiation therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2017;97:939-946.
29. Yin J, Bo WT, Sun J, Xiang X, Lang JY, Zhong JH, et al. New evidence and perspectives on the management of hepatocellular carcinoma with portal vein tumor thrombus. *J Clin Transl Hepatol* 2017;5:169-176.
30. Sanguineti G, Little M, Endres EJ, Sormani MP, Parker BC. Comparison of three strategies to delineate the bowel for whole pelvis IMRT of prostate cancer. *Radiation Oncol* 2008;88:95-101.
31. Banerjee R, Chakraborty S, Nygren I, Sinha R. Small bowel dose parameters predicting grade ≥ 3 acute toxicity in rectal cancer patients treated with neoadjuvant chemoradiation: an independent validation study comparing peritoneal space versus small bowel loop contouring techniques. *Int J Radiat Oncol Biol Phys* 2013;85:1225-1231.
32. Baldini EH, Abrams RA, Bosch W, Roberge D, Haas RLM, Catton CN, et al. Retroperitoneal sarcoma target volume and organ at risk contour delineation agreement among NRG sarcoma radiation oncologists. *Int J Radiat Oncol Biol Phys* 2015;92:1053-1059.