Original Article

Treatment outcomes of helical tomotherapy for hepatocellular carcinoma in terms of intermediate-dose spillage

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Background: Although helical tomotherapy (HT) tends to increase intermediate-dose spillage by increasing of low-dose region, this has not been fully determined in the clinical setting. Therefore, we investigated treatment outcomes of HT for hepatocellular carcinoma (HCC) with respect to intermediate-dose spillage.

Methods: We retrospectively reviewed 20 HCC patients, who received high-dose radiotherapy (RT) using HT with radical intent between April 2014 and September 2017. In accordance with the Barcelona Clinic Liver Cancer (BCLC) classification, stage was 0 in 7 patients, A in 3 patients, B in 5 patients, and C in 5 patients. Baseline Child-Pugh class was A in 18 patients and B in 2 patients. The median tumor size was 2.5 cm (range, 1–11 cm). Helical intensity-modulated radiotherapy (IMRT) technique was applied in all patients: among these, 13 patients were treated with stereotactic body radiotherapy (SBRT). The median fraction size was 12 Gy (range, 2–15 Gy), and the median total dose was 50 Gy (range, 44–60 Gy). Intermediate-dose spillage was assessed by the Radiation Therapy Oncology Group recommendation from 22 HT planning data, as follows: R50% means the ratio of the 50% prescription isodose volume to the planning target volume (PTV).

Results: The median follow-up period after HT was 22 months. The local progression-free survival (LPFS) and progression-free survival (PFS) rates were 89% and 59% at 1 year, and 82% and 30% at 2 years, respectively. The overall survival rate was 100% at 1 year and 85% at 2 years, respectively. In terms of intermediate-dose spillage, minor or major deviations were noted in the R50% of 20 HT plans (91%). However, 1 patient (5%) experienced classic radiation-induced liver disease, and severe toxicity ≥ grade 3 was not reported.

Conclusions: Although HT for HCC tends to increase intermediate-dose spillage, the treatment results were favorable with that reported in other published studies.

Keywords: Dose constraints; hepatocellular carcinoma (HCC); helical tomotherapy (HT); radiotherapy (RT)

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and lead to major cancer-related deaths worldwide (1). As this neoplasm develops in patients with cirrhosis and additional comorbidities in most cases, the disease prognosis and the best treatment options may vary depending on the tumor burden, degree of liver dysfunction, and the patients' general conditions (2). Liver resection, liver transplantation, or radiofrequency ablation (RFA), all potential curative therapies for HCC, should be considered as the first-line treatment options when possible (3). However, about 30% of the patients initially diagnosed with HCC are appropriate for curative therapy. Locoregional treatment modalities, including transarterial chemoembolization (TACE), transarterial radioembolization, and external beam radiotherapy (RT), are considered for patients who are not candidates for curative therapy. Traditionally, RT for HCC has a limited role due to the low tolerance of the whole liver for radiation and the risk of radiation-induced liver disease (RILD), although HCC is a radiation-sensitive tumor (4). With advancements in RT techniques, including development of 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), the role of RT has expanded from a palliative to a curative intent aim, and treatment result has shown high rates of sustained local control in patients with varying states of HCC (5,6).

Helical tomotherapy (HT) is a unique rotational IMRT machine using a binary multileaf collimator (MLC) to rapidly open and close the apertures in front of the different beam elements in the fan beam. It uses a slow and continuous movement of the treatment couch with a quickly rotating X-ray source to make many rotations possible in a brief space of time utilizing a helical dose delivery technique analogous to the spiral computed tomography (CT) scanner (7). HT showed a significant improvement in the conformity index (CI) and homogeneity index (HI) for target volume coverage compared with 3DCRT and conventional MLC-mounted linear accelerator-based IMRT in HCC patients (8). However, the mean dose and low-dose region of the normal liver (NL), which is the critical constraint with respect to RT for HCC, increase in HT (9). It is not documented whether the rise in intermediate-dose spillage in the NL may increase the risk of RILD when HT is performed. One study reported the safety of lung SBRT using HT in terms of intermediate-dose spillage (10). Although all RT plans showed major or minor variations in the R50% [the ratio of the volume of 50% the prescription dose isodose to the volume of the planning target volume (PTV)], defined by the Radiation Therapy Oncology Group (RTOG) 0915 recommendation, only 8% of the patients experienced radiation pneumonitis (11).

Therefore, we investigated the treatment outcomes of HT for HCC in terms of intermediate-dose spillage. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2912).

Methods

Patient's selection

From April 2014 to September 2017, 26 HCC patients received HT for the liver tumor at Soonchunhyang University College of Medicine, Bucheon. We retrospectively reviewed the patients' medical records, and excluded some patients for the following reasons: (I) incomplete HT due to deterioration of ascites during RT (1 patient); (II) transfer to another hospital and loss of follow-up (2 patients); and (III) HT with palliative intent (3 patients). The remaining 20 patients, who received high-dose RT using HT with curative intent, were included in the current study. Seven patients were diagnosed with stage 0 according to the Barcelona Clinic Liver Cancer (BCLC) staging system, and they were treated with high-dose RT using HT because of refusal of surgery or inoperable status due to comorbidity. Three patients were classified as stage A and received HT because of abandonment of liver transplantation due to limitation of donor organ or unsuitable location for RFA. Five patients were Stage B and 5 were stage C. All patients underwent TACE, and follow-up CT images presented viable tumor after incomplete TACE. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the institutional review board (IRB) of Soonchunhyang University College of Medicine, Bucheon (2017-12-002-001). Because of the retrospective nature, the requirement of written informed consent was waived.

HT technique

All patients took planning CT scans with free breathing in the supine position with both arms raised above the head. A posterior vacuum-lock body fixation device was used for immobilization. To reduce respiratory movement, patients

were requested to take shallow breaths, and an anterior vacuum-sealed cover sheet or belt was applied. Contrast-enhanced CT with the helical mode (rotation time: 1 s) and subsequent CT scanning (rotation time: 1.5 s) were performed with a 3 mm slice thickness. All CT images were imported to a MIM workstation (MIM Software Inc., Cleveland, OH, USA). Gross tumor volume (GTV) was defined as enhancing lesions, including lipiodol-laden areas, on axial CT images. When necessary, liver dynamic enhanced CT and/or magnetic resonance imaging (MRI) were used to delineate the GTV accurately. The tumor volume used during HT planning was larger than the GTV according to the discretion of the treating radiation oncologist when identifying the borders of the tumor on 2 simulation CT images. This was referred to as the internal target volume (ITV). The PTV was defined as ITV plus asymmetric 3–10 mm margins in all directions to reduce the RT dose to the stomach, duodenum, intestine, or heart. An additional 2–5 mm margin was included in the longitudinal direction to compensate for uncertainties resulting from respiratory liver motion.

All structures were transferred to a Tomotherapy Hi Art II Planning System (Accuray Inc., Sunnyvale, CA, USA) for inverse treatment planning. HT plans were created with a pitch of 0.143–0.287, a modulating factor of 2 or 2.4, and a longitudinal aperture size of 1 or 2.5 cm. The final dose was calculated through the collapsed cone convolution superposition dose calculation algorithm. All plans were made using the helical-IMRT technique and subdivided into IMRT (≤7 Gy) and SBRT (>7 Gy) according to fraction size. SBRT or IMRT was individually applied according to the PTV, NL volume (NLV), and proximity to the gastrointestinal (GI) organ or central biliary tract. In cases with PTV <1 cm from the GI organ, we applied simultaneous integrated boost (SIB)-IMRT (12). At least 90% of the prescription dose should cover the PTV. In terms of liver constraints, at least 700 mL of the NLV did not receive a total dose >18 Gy [reverse V_{18Gy} (rV_{18Gy}), ≥700 mL] for SBRT, and the mean dose of the NL was ≤23 Gy for IMRT. The maximal dose (D_{max}) for the stomach and duodenum was ≤30 Gy for SBRT and ≤44 Gy for IMRT. The D_{max} for the remaining bowel was ≤33 Gy for SBRT and ≤60 Gy for IMRT. We selected the fractionation scheme considering a dose-volume histogram (DVH) for the normal organ. The total doses were converted into biologically equivalent dose (BED) for the equal comparisons of dose effects of various fraction sizes (α/β =10).

Failure definition and toxicity assessments

Regular follow up was undertaken at 1–2 months after the completion of HT and then at 3-month intervals using CT or MRI. Local failure (LF) was defined as either progressive disease according to the Modified Response Evaluation Criteria in Solid Tumors or regrowth in any direction beyond that reported in pre-HT images of the treated lesions. Local-progression-free survival (LPFS) was estimated from start date of HT to the date of LF or last follow-up. Progression-free survival (PFS) and overall survival (OS) was estimated from HT to the date of tumor progression recorded at any site, and the date of death from any cause or last follow-up. Hepatic toxicity was defined as classic RILD (i.e., anicteric hepatomegaly, ascites, or elevated alkaline phosphatase level more than twice the upper limit of the normal value) and non-classic RILD [i.e., elevation of liver transaminases more than 5 times the upper limit of the normal level, or a worsening of the Child-Pugh (CP) score ≥2 points], which occurred within 4 months after HT. Other toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and treatment-related severe toxicity was defined as grade ≥3 adverse events or classic/non-classic RILD.

Analysis of the dosimetric parameters and statistics

DVH analysis was used to assess dosimetric quality. To estimate the PTV coverage, doses at 95% of the PTV ($D_{95\%}$) were acquired. The HI was defined as $D_{2\%}$ of the PTV minus $D_{98\%}$ of the PTV divided by the prescription dose. CI was defined as the ratio of the prescription isodose volume to the PTV. To estimate high-dose spillage, the percent ratio of the cumulative volume of all tissues outside the PTV receiving a dose >105% of the prescription dose to the PTV (%) was calculated. To estimate intermediate-dose spillage, $R_{50\%}$ was calculated. To assess the risk of hepatic toxicity, the mean dose and rV_{18Gy} of NL were derived from the DVHs. Individual plans were evaluated using the RTOG 0915 recommendation as the reference points.

Statistical analysis

The Kaplan-Meier method was used to analyze survivals, and the log-rank test was applied to compare prognostic factors with survivals. All statistical analyses were undertaken using the SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA),

and a two-sided P<0.05 was considered statistically significant.

Results

Patient characteristics

The 20 patients were comprised of 16 males and 4 females, with an age ranging from 50 to 80 years (median, 64 years). Twelve patients (60%) were infected with hepatitis B virus. Except for 1 patient, all patients received various courses of previous treatments (range, 1–16 courses), including surgery, RFA, TACE, and RT. Baseline CP class was A in 18 patients and B in 2 patients. Concurrent hepatic arterial infusion chemotherapy was administered in 1 patient during HT. Median tumor size was 2.5 cm. Seventeen patients had single lesion and 3 patients had 2 lesions; 2 patients planned to receive HT for one lesion, in which RT target was partial, followed by TACE for another lesion. Seven patients received IMRT with a fraction size of 2–4.5 Gy and the total doses of 44–54 Gy/10–27 fractions, and 13 patients received SBRT with a fraction size of 11–15 Gy and the total doses of 44–60 Gy/4 fractions. Patients' characteristics are summarized in *Table 1*.

Treatment results

The median follow-up time from the date of HT administration was 22 months (range, 3–43 months). The 1-year and 2-year LPFS rates were 89% and 82%, respectively. The 1-year and 2-year PFS rates were 59% and 30%, respectively. The median OS was not reached, and the 1-year and 2-year OS rates were 100% and 85%, respectively. *Figure 1* shows survival graphs. On univariate analysis, the modified International Union Against Cancer tumor (mUICC-T) stage of 1 and 2, BCLC stage of 0 and A, tumor size ≤3 cm, PTV ≤80 mL, and fraction size >2.5 Gy were significantly favorable prognostic factors for LPFS. The mUICC-T stage, BCLC stage, tumor size, PTV, fraction size, and BED_{10} were significant prognostic factors for PFS. There was no significant prognostic factor for OS (*Table 2*).

One patient experienced classic RILD at 3 months after HT. Another patient experienced grade 2 rib fracture 16 months after HT, and the pain was relieved with oral medication. There was no severe toxicity above grade 3.

Analysis of the dosimetric parameters

The tumor was adjacent to the GI organs in 2 patients, who were treated with IMRT using 20 fractions. To compensate for the unexpectedly large interfractional and intrafractional variation of the GI organ, we conducted a re-plan after 15 fractions. Therefore, a total of 22 HT plans from 20 HCC patients were reviewed. Detailed contents for the dosimetric parameters are summarized in *Table 3*. The D_{max} of the PTV was located within the PTV in all cases. Considering that lower HI values indicate a more homogeneous target dose, SIB-IMRT plans had a more heterogeneous target dose. The CI had minor deviations in 5 plans (23%) and major deviations in 3 plans (14%). Major deviation of the high-dose spillage was occurred in 4 plans, all of which used SIB-IMRT techniques. A total of 20 plans (91%) had minor or major deviations for R50% in terms of intermediate-dose spillage. The NL constraints were satisfied for all patients. Classic RILD occurred in a patient with minor deviation for R50%.

Discussion

In comparison with other malignancies, various treatment guidelines for the HCC have been published worldwide based on different etiologies, medical insurance systems, and socioeconomic status among regions. Major guidelines, particularly in the West, including the BCLC staging system, suggest RT as an alternative treatment modality or limit RT only for the symptom palliation, or never mentioned RT (13). In real-world clinical practice, however, the University of Michigan reported that both RFA and SBRT are effective local treatment modalities for early stage HCC with 2-year LPFS rates of 80% and 84%, respectively (14). Two meta-analyses showed that TACE plus RT for unresectable HCC improved tumor response and OS compared with TACE alone (15,16). Based on these clinical evidence, some recently published guidelines, such as the National Cancer Comprehensive Network guideline 2020 version and 2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines, recommend RT as an equal locoregional modality with ablation or TACE (17,18). Since HT was developed as the first commercial system for planning and delivering IMRT, with the first patient being treated in 2002, the indication for HT has been expanded (19). The whole target is always covered by each beam in 3DCRT; the IMRT covers only a part of the PTV at a certain point using the dynamic delivery modes; thus, the interplay effects induced by the interplay between the interfractional movement of the moving organ and the dynamic dose delivery may result in target under-

Table 1 Patients' characteristics

Parameter	Median (range)/No. of pts
Age, years	64 [50–80]
Sex	
Male	16
Female	4
ECOG	
1	20
Hepatitis	
No	3
Alcohol	4
HBV	12
HCV	1
LC	
No	3
Yes	17
Previous treatment	
No	1
Surgery	3
RFA	3 (cycles of 1–3)
TACE	18 (cycles of 1–16)
RT	2
Baseline CP class	
A (5/6)	18 (10/8)
B (7/8)	2 (1/1)
Baseline AFP, ng/mL	9.9 [1.1–74596]
mUICC-T	
1	7
2	4
3	8
4	1
mUICC-N	
0	20
PVTT	
No	16
Yes	4
Combined treatment	
No	19
Yes	1
Tumor size, cm	2.5 [1–11]
PTV, mL	91.8 [14.6–586.3]
RT target	
All	18
Partial	2
RT technique	
IMRT	7
SBRT	13
Fraction size, Gy	12 [2–15]
Total dose, Gy	50 [44–60]
BED_{10}, Gy_{10}	105.6 [53.7–150.0]

HBV, hepatitis B virus; HCV, hepatitis C virus; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; RT, radiotherapy; CP, Child-Pugh; AFP, α-fetoprotein; mUICC, the modified International Union Against Cancer Stage; T, tumor; N, lymph nodes; PVTT, portal vein tumor thrombosis; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; BED_{10}, biologically effective dose when α/β ratio was assumed to be 10 Gy.

dosing (20). Theoretically, the physical properties of HT, composed of the rapid 360 degree rotating beams and slowly and continuously moving couch, may increase the interplay effects for moving organ compared to LINAC-based IMRT. A motion phantom study using HT validated that HT is an effective technique for treating moving tumors and hypofractionation (21). In the clinical setting, HT for 45 unresectable but confined intrahepatic HCC patients, with a median total dose of 54 Gy (2.2–5.5 Gy/fraction), showed an OS rate of 73% at 2 years (22). A phase I/II trial using HT-based SBRT for inoperable HCC ≤6 cm showed an LPFS rate of 81% and an OS rate of 81% at 2 years (23). The current study shows favorable treatment outcomes with an LPFS rate of 82% and an OS rate of 85% at 2 years. These findings suggest that HT for HCC is an effective treatment modality, regardless of the number of fractions.

Radiobiologically, the liver is a typical organ of a parallel

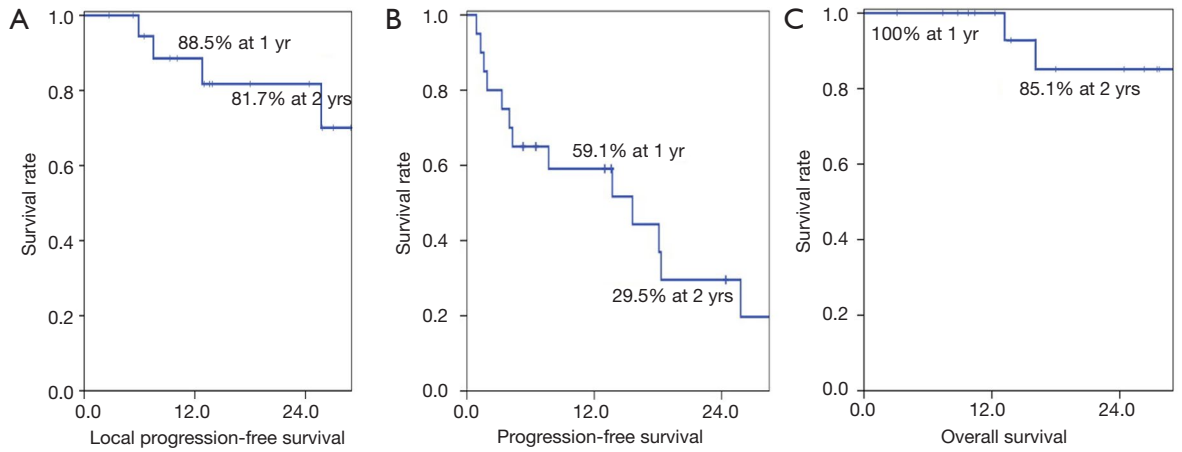

Figure 1 Local progression-free survival (A), progression-free survival (B), and overall survival (C) curves.

Table 2 Univariate analysis for parameters affecting local progression-free survival (LPFS), progression-free survival (PFS), and overall survival (OS)

Parameters	Variable	No. of pts	2-yr LPFS (%)	P value	2-yr PFS (%)	P value	2-yr OS (%)	P value
Age, years	≤60	7	83	0.447	51	0.066	100	0.885
	>60	13	83		15		73	
Sex	Male	16	77	0.322	25	0.237	91	0.369
	Female	4	100		50		67	
Baseline CP class	A	18	79	0.295	31	0.584	92	0.177
	B	2	100		0		50	
mUICC-T	1, 2	11	100	0.007	49	0.024	86	0.455
	3, 4	9	60		11		83	
BCLC stage	0, A	10	100	0.012	54	0.006	83	0.662
	B, C	10	65		10		86	
PVTT	No	16	85	0.109	31	0.774	79	0.965
	Yes	4	75		25		100	
RT technique	IMRT	7	71	0.081	0	0.057	60	0.051
	SBRT	13	89		46		100	
Tumor size, cm	≤3	12	100	0.005	52	0.000	88	0.982
	>3	8	54		0		80	
PTV, mL	≤80	10	100	0.011	60	0.000	86	0.871
	>80	10	60		0		83	
Fraction size, Gy	≤2.5	6	67	0.042	0	0.019	75	0.458
	>2.5	14	90		48		89	
BED_{10}, Gy_{10}	≤100	9	75	0.134	0	0.002	67	0.947
	>100	11	88		55		100	

CP, Child-Pugh; mUICC, the modified International Union Against Cancer Stage; T, tumor; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; PTV, planning target volume; BED_{10}, biologically effective dose when α/β ratio was assumed to be 10 Gy.

Table 3 Dosimetric parameters in 22 radiotherapy planning data

Plan	PTV (mL)	NLV (mL)	Total, Dose (Gy)	Fx dose (Gy)	PTV-D_{max} (%)	PTV-$D_{95\%}$ (%)	HI	CI	HDS (%)	R50%	NL-mean, dose (Gy)	rNL-18Gy (mL)	NL-V30Gy (%)
IMRT	60	699	45	4.5	117.5	102.4	0.1	1.2[a]	5.8	4.2	12.3	574	7.0
IMRT	127	1,010	50	2.5/2	133.3	100.7	0.3	1.1	3.9	3.8[a]	18.3	553	17.3
IMRT	135	1,371	54	2	105.4	99.7	0.0	0.9	0.0	3.6[a]	13.5	954	10.0
IMRT	147	987	50	3/2	164.8	102.0	0.6	2.1[b]	93.3[b]	7.9[b]	23.3	512	29.8
IMRT	216	920	44	2.7/2.2	131.0	100.9	0.3	1.4[a]	30.2[b]	5.1[b]	20.1	474	22.1
IMRT	410	1,117	37.5	3.5/2.5	154.3	104.9	0.5	1.9[b]	74.9[b]	5.9[b]	20.8[c]	686[c]	21.7[c]
IMRT	401	1,099	11	3.5/2.2	177.9	105.1	0.7	2.2[b]	106.7[b]	7.2[b]			
IMRT	581	1,036	33	3/2.2	150.5	103.5	0.5	1.1	5.9	4.1[b]	18.9[d]	637[d]	23.3[d]
IMRT	439	1,170	11	3/2.2	147.9	103.5	0.4	1.1	3.1	3.9[b]			
SBRT	15	980	48	12	105.5	100.1	0.0	1.3[a]	0.0	5.3[a]	5.9	903	2.6
SBRT	18	1,196	56	14	107.1	100.0	0.0	1.2[a]	0.0	7.1[b]	10.8	979	6.7
SBRT	28	1,360	60	15	104.1	100.0	0.0	1.1	0.0	4.8[a]	11.1	1,079	6.9
SBRT	29	812	52	13	106.1	100.0	0.0	1.2[a]	0.0	5.0[a]	7.4	715	6.2
SBRT	44	1,762	60	15	104.0	99.7	0.0	1.0	0.0	5.1[a]	4.8	1,595	4.5
SBRT	50	909	48	12	105.7	98.4	0.1	0.9	0.0	3.6	10.9	762	5.7
SBRT	57	1,502	52	13	105.1	99.8	0.0	1.0	0.0	4.5[a]	9.4	1,314	3.6
SBRT[e]	72	1,197	52	13	110.8	100.7	0.1	1.1	0.1	4.3[a]	11.2	971	7.1
SBRT	80	974	48	12	107.5	100.7	0.1	1.1	0.0	4.6[a]	10.6	773	8.0
SBRT	104	2,348	50	12.5	105.0	100.0	0.0	1.0	0.0	4.4[b]	12.6	1,728	9.0
SBRT	109	1,507	44	12/11	113.7	98.5	0.1	1.1	0.0	4.4[b]	12.5	1,245	5.0
SBRT	176	1,185	60	15	109.6	99.8	0.1	1.0	0.1	4.9[b]	16.9	834	18.6
SBRT	345	858	44	11	110.5	97.4	0.1	0.9	0.0	3.4[b]	10.7	716	6.5

NLV, normal liver volume; HI, homogeneity index ($D_{2\%}$ of the PTV minus $D_{98\%}$ of the PTV divided by the prescription dose); CI, conformity index (CI), defined as the ratio of the prescription isodose volume to the PTV; HDS, high dose spillage (cumulative volume of all tissue outside PTV receiving a dose >105% of the prescription dose; R50%, the ratio of the 50% prescription isodose volume to the PTV; rNL-18Gy, NLV receiving <18 Gy; NL-V30Gy, NLV receiving 30 Gy. [a], minor deviation according to RTOG 0915 protocol; [b], major deviation according to RTOG 0915 protocol; [c,d], Two patients changed treatment plan during HT. Therefore, we divided dosimetric parameters for PVT but summarized dosimetric parameters for normal liver as organ at risk; [e], dosimetric parameter for a patient with classic RILD.

architecture model. Although RILD mostly occurs if the critical volume of the NL damaged is over a threshold, the risk may be additionally increased by dose distribution of the functional reserve and subunit radiosensitivity (24). HT achieves better CI and HI than 3DCRT at the expense of a greater low-dose bath (9). This low-dose bath may impact the partial volume tolerance of the NL and may increase the risk of RILD even if the same mean dose of the NL is irradiated. At present, with modern RT technology, experts recommend that attention must be paid to the specific isodose distribution, including that for intermediate doses such as 20–30 Gy, during treatment planning evaluation (25). However, the tolerance of the NL by intermediate-dose spillage from HT has never been clinically validated despite many dosimetric studies. We could find a clue from the lung, another typical organ of a parallel architectural model. One institution began lung SBRT with HT since 2008 and applied constraints from the RTOG 0915 recommendation (10). They noticed that many SBRT plans with HT for the lung did not meet R50% and assessed the clinical validity of

R50% in 74 patients (81 lesions and 79 plans). All plans had major deviations (39%) or minor deviations (61%) from R50%. However, treatment-related toxicity was minimal: 2 patients (3%) experienced chest wall pain; 6 patients (8%) experienced radiation pneumonitis (grade 1–2 in 4 patients, grade 3 in 1 patient, and grade 5 in 1 patient). One patient with grade 5 radiation pneumonitis underwent multiple lung surgeries and high-dose RT for lung cancer before SBRT, and fatal toxicity might be induced from surgeries and underlying poor lung function. The authors concluded that HT is a safe SBRT modality for lung cancer, despite not being able to meet R50%. Our study also showed that 20 HT plans had minor deviations (41%) or major deviations (50%) from R50%, although all patients met the NL constraints. Among these, only 1 patient with minor deviation of R50% experienced classic RILD and subsequently recovered. This suggests that the increase in intermediate-dose spillage from a greater low-dose bath by HT is not related to the increase of hepatic toxicity if the NL constraints are met, and that HT for HCC is a safe treatment modality.

There were several limitations in this study. First, we applied R50% for both SBRT and IMRT cases. Actually this constraint was made for measurement of the steepness of the dose gradient for SBRT. Considering that IMRT is used for large-sized HCC or HCC located near GI organ or central biliary tract, R50% for IMRT does not reflect intermediate-dose spillage, although linear interpolation is permitted for unspecified values of PTVs. However, this might be the best method because R50% by the RTOG recommendation is the only accepted value in the world to assess intermediate-dose spillage. Second, this study was a retrospective analysis with a small sample size. Therefore, selection bias may arise, and the rate of treatment-related toxicity may be underestimated. Although we found that deviation of R50% from the desired value did not increase the risk of hepatic toxicity, further studies based on a large population will be needed to confirm the result.

In conclusion, the current study reported an LPFS rate of 82% and an OS rate of 85% at 2 years, respectively, using HT. These treatment results are comparable with those published in other published studies using different RT machines, and support that HT is an effective treatment modality. In terms of intermediate-dose spillage, minor or major deviations from the desired R50% were noted in 91% of HT plans. However, the only 1 patient (5%) experienced classic RILD and this supports that HT is a safe treatment modality. Although this is the first study to validate the clinical significance of unmet R50% by HT for the treatment of HCC, additional studies based on larger populations will be needed.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2912

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the institutional review board (IRB) of Soonchunhyang University College of Medicine, Bucheon (2017-12-002-001). Because of the retrospective nature, the requirement of written informed consent was waived.

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