Digestive and Liver Disease 51 (2019) 445–451

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Phase I/II trial of helical IMRT-based stereotactic body radiotherapy for hepatocellular carcinoma

Jun Won Kim[a], Do Young Kim[b], Kwang-Hyub Han[b], Jinsil Seong[c,*]

[a] Department of Radiation Oncology, Gangnam Severance Hospital, Seoul, Republic of Korea
[b] Department of Internal Medicine, Severance Hospital, Seoul, Republic of Korea
[c] Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 31 January 2018
Received in revised form 2 August 2018
Accepted 7 November 2018
Available online 17 November 2018

Keywords:
Helical intensity-modulated radiotherapy
Hepatocellular carcinoma
Phase I/II trial
Stereotactic body radiotherapy

ABSTRACT

Background: To report the results of a phase I/II study of helical IMRT-based stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC).
Methods: Eligibility included Child–Turcotte–Pugh class A or B, ≤3 lesions, and cumulative tumor diameter ≤6 cm. Dose was escalated from 36 Gy to 60 Gy delivered in 4 fractions. Grade ≥3 gastrointestinal toxicities (CTCAE v3.0) or radiation-induced liver disease defined dose-limiting toxicity (DLT).
Results: Thirty-two patients were enrolled: seven in dose levels 1–2 (36–44 Gy) and 25 in levels 3–4 (42–60 Gy). Failures included 1 local, 14 outfield intrahepatic, 2 distant, 1 concurrent local and outfield, 1 concurrent outfield and distant, and 1 concurrent local, outfield, and distant. Nine had grade 3 hematologic toxicities and 5 had grade 2 hepatic toxicities; no patient experienced DLT. Two-year local control (LFFS), outfield intrahepatic control (OutFFS), and overall survival (OS) rates were 80.9%, 46.7%, and 81.3%, respectively. Dose levels 3–4 and pre-radiotherapy multi-segment recurrence were independent prognostic factors for LFFS and OutFFS, respectively. Two-year LFFS, OutFFS, and OS were significantly higher for patients who were treated with dose-levels 3/4 for tumor(s) involving single segment compared with the rest of the patients.
Conclusions: Helical IMRT-based SBRT was safe and effective, and patients with multi-segment recurrences prior to SBRT need to be closely followed.

1. Introduction

Stereotactic body radiotherapy (SBRT) delivers potent doses of highly conformal radiation to tumors in a small number of fractions, usually 5 or less, and has shown excellent local control for primary as well as metastatic liver malignancies [1]. Unlike metastatic liver tumors with a normal hepatic functional reserve, hepatocellular carcinoma (HCC) often presents with varying degrees of cirrhosis at the time of diagnosis, which limits the use of local treatments. SBRT delivers significantly higher doses of radiation to tumors than does conventional radiotherapy (RT), and by sharply reducing the radiation dose outside the target, minimizes radiation toxicity in the normal tissue surrounding the tumor [1]. Nonetheless, the safety and efficacy of SBRT in HCC patients with cirrhotic livers has not been fully explored in prospective trials.

Helical Tomotherapy (HT) (Accuray, Madison, WI) with megavoltage computed tomography (CT) for image guidance has shown its efficacy for locally advanced hepatocellular carcinoma [2]. HT is effective in treating multiple targets simultaneously [3], and the ability of HT to treat multiple intrahepatic tumors has been demonstrated [4]. Most clinical trials on liver SBRT allow up to 3–5 intrahepatic lesions for eligibility [5,6], and HT can be an effective tool for delivering SBRT with improved patient comfort and compliance.

We initiated a phase I/II study to evaluate the safety and efficacy of helical IMRT-based SBRT in the treatment of primary HCC. We have previously reported the phase I results [7], and we now report the final results of this phase I/II trial.

* Corresponding author at: Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
E-mail address: jsseong@yuhs.ac (J. Seong).
URL: http://mailto:jsseong@yuhs.ac (J. Seong).

https://doi.org/10.1016/j.dld.2018.11.004
1590-8658/

2. Materials

2.1. Eligibility

HCC was diagnosed either via biopsy or radiologically (characteristic findings of HCC on 2 imaging modalities or 1 imaging modality plus an α-fetoprotein level >200 ng/mL in high-risk patients) [8]. The diagnosis of liver cirrhosis was based on the histopathology or the clinical presentation and imaging (e.g., transient elastography) results [9].

All cases were presented at a multidisciplinary tumor board at our institution. SBRT was considered for primary HCC not suitable for surgery because it was technically or medically inoperable or because of the patient's refusal; lesions not suitable for TACE or RFA due to tumor hypovascularity or its location in the liver dome or near the major vessels; and recurrent tumor after multiple treatments including TACE and RFA. The inclusion criteria were as follows: ≥20 years of age; Eastern Cooperative Oncology Group performance status 0–2; maximum tumor diameter ≤5 cm (single tumor) or ≤6 cm (sum of 2 or 3 tumors); uninvolved liver volume >800 mL; tumor ≥1 cm from the stomach and/or bowel wall; and CTP class A or B cirrhosis. Patients also had to have adequate liver (total bilirubin <3 mg/dL, albumin >2.5 g/dL, normal ratio of prothrombin time to partial thromboplastin time, serum liver enzymes <3 times the upper limit of normal), renal and hematological functions. All patients gave informed consent prior to enrollment.

The study protocol was approved by Institutional Review Board (IRB No. 4-2011-0650). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki declaration in 1975 (revised in 2000).

2.2. Treatment

Patients were immobilized using the Body Pro-Lok system (CIVCO, Coralville, IA), a vacuum cushion and an abdominal compression device used to reduce the amplitude of liver motion caused by breathing [10]. Images with the slice thickness of 1.5 mm were acquired using a 4-dimensional CT simulator (SOMATOM Sensation, Siemens, Germany) over 10 respiratory phases under shallow respiration. The simulation CT images were fused with images acquired via dynamic CT and magnetic resonance imaging (MRI) obtained for SBRT planning to optimize target delineation.

The gross tumor volume (GTV) included all tumors detected via dynamic CT and MRI, and summing the GTVs in all respiratory motion phases defined internal GTV (IGTV). The clinical target volume (CTV) was defined as the IGTV plus a 5-mm margin in all directions to allow incorporation of microscopic satellite lesions into the target volume. The planning target volume (PTV) was defined as the CTV plus a radial margin of 5 mm and a craniocaudal margin of 7 mm. Helical intensity-modulated radiotherapy (IMRT)-based SBRT planning was performed using a Hi-Art TomoTherapy Planning System (Accuray, Madison, WI). All plans were optimized to deliver at least 95% of the prescribed dose to 100% of the PTV, while keeping the maximum dose to the PTV below 105% of the prescribed dose. The dose constraints were as follows: ≥700 cc of total uninvolved liver receives <15 Gy; ≤2/3 of the right kidney receives >15 Gy; the maximum spinal cord dose is 18 Gy; and the maximum dose to the stomach or bowel is 24 Gy. All patients underwent SBRT with on-board mega-voltage CT (MVCT) for image guidance. In the phase I component of the trial, the dose was raised from 36 Gy in 4 fractions with increments of 8 Gy (4 × 2 Gy) for each dose level, until reaching a dose limiting toxicity (DLT). In the phase II component, the prescription dose was the highest dose achieved without DLT in the phase I component. Patients were treated every other day.

Preemptive antiviral therapy was provided for HBV carriers to prevent reactivation, according to the Korea Practice Guideline for the management of HCC [8].

2.3. Response evaluation

Patients were assessed during SBRT and after completion of treatment at 1 month, every 3 months for the first 12 months, and every 6 months thereafter. Dynamic liver CT or MRI was performed at each follow-up. The Modified Response Criteria in Solid Tumors was used to evaluate treatment response [11]. Local failure was defined as an infield recurrence or progressive disease. Outfield failure was defined as outfield intrahepatic metastasis, and distant failure as extrahepatic metastasis. Toxicity was graded in accordance with the Common Terminology Criteria for Adverse Events version 3.0. DLT was defined as a grade 3 or greater hepatic toxicity, a gastrointestinal toxicity occurring within 1 month of SBRT, or radiation-induced liver disease (RILD) requiring treatment in the absence of disease progression within 3 months of SBRT [12].

2.4. Study end points and statistics

The phase I component was designed as a prospective dose-escalation study. Initially, 3 patients received SBRT at the 3 lowest dose levels; if there was no DLT within 1 month after SBRT escalation to the next level was permitted. If toxicity occurred at a specific level, a minimum of 6 patients were treated at that level. The primary endpoint of the phase II component was the 1-year objective response (complete and partial) rate. The sample size for the phase II component was calculated using historical data to set the difference in the objective response rate at $p_1 - p_0 = 0.26$, presuming a minimal objective response rate (p_0) of 54% and an acceptable objective response rate (p_1) of 80% [5,13]. One-sided binomial test at α level of 5% and a power of 80% gave a sample size of 20, and assuming a drop-out rate of 10%, 23 patients will be required. The secondary endpoints were local control rate, progression-free survival (PFS), and overall survival (OS).

Local failure-free survival (LFFS), outfield intrahepatic failure-free survival (OutFFS), distant metastasis-free survival (DMFS), PFS, and OS rates were estimated using the Kaplan-Meier method. Survival rates were calculated from the last day of SBRT. The Cox regression method was used for multivariate analysis. A p value <0.05 was considered significant.

3. Results

3.1. Patients and treatment

A total of 10 patients were excluded from participating in the trial during the screening process: 5 patients had distance between target lesion and normal organ (bowel) less than 1 cm, one patient had a small liver volume (less than 800 cc), one patient had more than 3 lesions in pre-SBRT MRI, one patient had malignant portal vein thrombosis greater than 5 cm in its extent, one patient had pathology confirmation of cholangiocellular carcinoma, and one patient refused to participate in the trial.

In phase I component of the study, the dose was initially escalated to a maximum of 52 Gy (13 Gy/fraction), and the protocol was amended for further escalation to 60 Gy (15 Gy/fraction), which was the dose level used in phase II component (Table 1). In phase II component of the study, the trial was closed before reaching the target number owing to poor accrual. Between March 2012 and January 2015, 32 patients were enrolled (18 patients in phase I and 14 in phase II) with a total of 36 lesions treated. The number of patients enrolled in dose levels 1 (36 Gy), 2 (44 Gy), 3 (52 Gy), and 4 (60 Gy) was 4, 3, 8, and 17, respectively. The patients analyzed in this study

Table 1
Demographic and treatment data (n = 32).

Characteristics		No. of patients (%)
Sex	Female: Male	7: 25 (21.9: 78.1)
Age		Median 59.5 years (range 42–83)
Hepatitis etiology	B	23 (71.9)
	C	5 (15.6)
	nonB/nonC	4 (12.5)
BCLC stage	A	31 (96.9)
	C	1 (3.1)
UICC stage	T1N0	12 (37.5)
	T2N0	18 (56.3)
	T2N1	1 (3.1)
	T3N0	1 (3.1)
Child-pugh score	A (5)	28 (87.5)
	A (6)	4 (12.5)
Liver stiffness	Fibroscan (17/32)	Median 23.9 (12.1–75.0) kPa
AFP >9 ng/ml at RT	20 (66.7)	Median 13.5 (2.1–4656)
Portal vein thrombosis	No	32 (100)
Recurrence(s) prior to SBRT	In single segment	15 (46.9)
	In multiple segments	17 (53.1)
	None	6 (18.8)
Previous treatment to SBRT site	TACE	21 (65.6)
	TACE + RFA	3 (9.4)
	TACE + Sorafenib	1 (3.1)
	Lobectomy + TACE	1 (3.1)
Treatment-free interval		Median 3.5 months (range, 0.5–71)
Number of lesions treated with SBRT	1	29 (90.6)
	2	2 (6.3)
	3	1 (3.1)
Maximum tumor diameter		Median 2.1 cm (range 1.0–4.5)
Cumulative tumor diameter		Median 2.25 cm (range 1.0–4.5)
Dose per fraction/total dose	9 Gy/36 Gy	4 (12.5)
	11 Gy/44 Gy	3 (9.4)
	13 Gy/52 Gy	8 (25)
	15 Gy/60 Gy[a]	17 (53.1)

Abbreviations: RFA = Radiofrequency ablation; TACE = Transarterial chemoembolization; AFP = Alpha-feto protein; PIVKA = Proteins induced by vitamin K absence or antagonist-II; BCLC = Barcelona Clinic Liver Cancer; UICC = International union against cancer; SBRT = stereotactic body radiotherapy.
[a] Dose level 4 (15 Gy × 4 fractions) was added after no DLT was observed at level 3.

included those enrolled in dose levels 1 and 3 while the amended protocols were being approved.

The median age at the time of enrollment was 59.5 years (range, 42–83 years). Cirrhosis was related to hepatitis B virus (HBV) infection in 23 patients, hepatitis C virus (HCV) infection in 5 patients, and alcohol consumption in 4 patients. The CTP score was 5 in 28 patients and 6 in 4 patients. No patient had portal vein tumor thrombosis at the time of enrollment. Twenty-one patients received TACE, 3 patients received TACE and RFA, 1 patient received TACE and sorafenib, and 1 patient received lobectomy and TACE prior to receiving SBRT. The time interval between the last treatment and SBRT was median 3.5 (range, 0.5–70.6) months. Six patients received SBRT as initial treatment for a primary HCC or as salvage treatment for an intrahepatic metastatic lesion. Fifteen patients had a primary or recurrent tumor involving a single hepatic segment, and 17 patients had a recurrence tumor involving multiple segments prior to SBRT. All viable lesions at the time of enrollment were treated with SBRT, and the median cumulative tumor diameter was 2.1 cm (range 1.0–4.5 cm).

3.2. Toxicity

DLT was not reached in any of the patients. Table 2 shows the baseline toxicities, which worsened within the first 3 months after SBRT or before salvage treatment in cases of treatment failure. No grade 3 hepatic toxicities were detected; grade 2 hepatic toxicities included elevated aspartate transaminase levels in 2 patients, hypoalbuminemia in 2 patients, and hyperbilirubinemia in 1 patient. No grade 2 or higher gastrointestinal toxicities were noted. Grade 3 hematologic toxicities included leukocytopenia in 3 patients and thrombocytopenia in 6 patients; these toxicities were grade 2 at baseline in 8 of these patients.

Table 2
Treatment related toxicities within 6 months after SBRT.

Toxicity		CTCAE v3.0 grade		
		1	2	3
Liver function	AST	12	2[a]	0
	ALT	5	0	0
	Albumin	0	2[b]	0
	ALP	4	0	0
	Bilirubin	2	1	0
	INR	1	0	0
Hematologic	Leukocytes	9	10[c]	3[d]
	Hemoglobin	6	1[e]	0
	Platelets	4	4[f]	6[g]
Gastrointestinal	Anorexia	7	0	0
	Nausea	3	0	0
Other	Fatigue	3	1	0
	Pain	3	0	0

Worsening toxicities due to SBRT are recorded; toxicities due to salvage treatment after treatment failure are not recorded.
Abbreviations: CTCAE = Common terminology criteria for adverse events; AST = Aspartate Aminotransferase; ALT = Alanine aminotransferase; ALP = Alkaline phosphatase; INR = International normalization ratio.
[a] One patient had grade 1 AST elevation prior to SBRT.
[b] One patient had grade 1 hypoalbuminemia prior to SBRT.
[c] Four patients had grade 1 leukocytopenia prior to SBRT.
[d] All patients had grade 2 leukocytopenia prior to SBRT.
[e] The patient had grade 1 anemia prior to SBRT.
[f] All patients had grade 1 thrombocytopenia prior to SBRT.
[g] Five patients had grade 2 and one patient had grade 1 thrombocytopenia prior to SBRT.

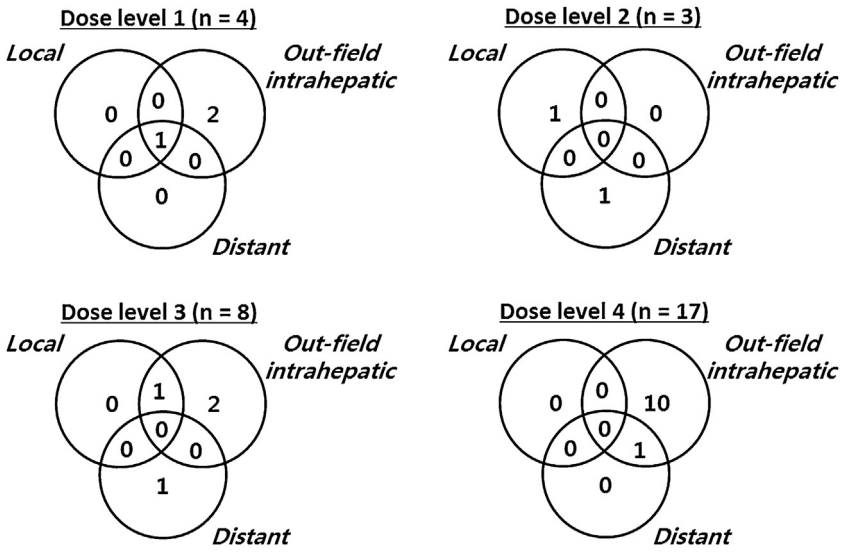

Fig. 1. Patterns of failure at dose levels 1, 2, 3, and 4.

Table 3
Factors influencing local control and outfield intrahepatic control.

Prognostic factors	Local control					Outfield intrahepatic control				
	UVA		MVA			UVA		MVA		
	95%CI	p	RR	95%CI	p	95%CI	p	RR	95%CI	p
Dose level		0.007			0.028		0.845			0.996
3–4	0.81–1.03		0.156	0.03–0.82		0.28–0.67		0.997	0.32–3.15	
1–2	0.06–0.80					0.06–0.80				
Age		0.143					0.684			
<60	0.48–0.95					0.20–0.71				
≥60	0.73–1.03					0.23–0.71				
Etiology		0.359					0.671			
Other	0.65–1.10					1.58–2.53				
HBV	0.61–0.95					0.12–0.77				
Pre-RT AFP		0.418					0.871			
<15 ng/ml	0.64–1.00					0.18–0.65				
≥15 ng/ml	0.60–1.00					0.28–0.79				
Cumulative diameter		0.495			0.752		0.739			0.962
≤2 cm	0.65–1.04		1.372	0.19–9.74		0.19–0.73		1.025	0.37–2.84	
>2 cm	0.59–0.97					0.25–0.70				
Single tumor		0.073			0.654		0.341			0.798
Yes	0.74–0.99		0.654	0.10–4.19		0.30–0.66		1.232	0.25–6.10	
No	0.20–0.87					0.20–0.87				
Multi-segments		0.041			0.101		<0.0001			0.001
No	0.81–1.06		0.148	0.02–1.45		0.51–0.96		0.140	0.04–0.45	
Yes	0.46–0.92					0.03–0.44				

Abbreviations: HBV = Hepatitis B virus; AFP = Alpha-feto protein; UVA = Univariate analysis; MVA = Multivariate analysis; RR = Relative risk; RT = radiotherapy.

The CTP score worsened in 4 patients. In patient 1 (dose level 1), the CTP score increased from 5 to 6 1 month after SBRT and remained constant thereafter. In patient 2 (dose level 2), the CTP score increased from 5 to 6 at 3.5 months and returned to 5 at 6.5 months. In patient 3 (dose level 2), the CTP score increased from 5 to 6 at 1 month, further increased to 7 after salvage TACE, and returned to 5 at 30 months. In patient 4 (dose level 4), the CTP score increased from 6 to 7 at 13 months and remained constant thereafter. None of the 27 patients with HBV infection experience radiation-induced HBV reactivation.

3.3. Response and patterns of failure

SBRT resulted in a radiologic complete response (CR) in 29 patients (90.6%) and a partial response in 2 patients (6.3%). Twenty patients experienced disease progression, and the initial failure sites were as follows: 1 local, 14 outfield intrahepatic, 2 distant, 1 concurrent local and outfield, 1 concurrent outfield and distant, and 1 concurrent local, outfield, and distant. Fig. 1 shows patterns of failure at dose-levels 1 through 4. At dose level 1 (n = 4), 1 patient experienced concurrent local and outfield failure and lung metastasis, and 2 patients experienced outfield failure followed by local failure. At dose level 2 (n = 3), local failure was followed by outfield failure in 1 patient, and lung metastasis without intrahepatic failure occurred in another patient. At dose level 3 (n = 8), there was 1 outfield failure followed by local failure due to growth of the outfield failure into the treated area; 1 concurrent local and outfield failure due to tumor invasion of the portal tract; one outfield failure; and 1 distant failure. At dose level 4 (n = 17), concurrent outfield failure and lung metastasis followed by local failure due to growth of the outfield failure into the treated area occurred in 1 patient, and outfield failure without local or distant failure occurred in 10 patients.

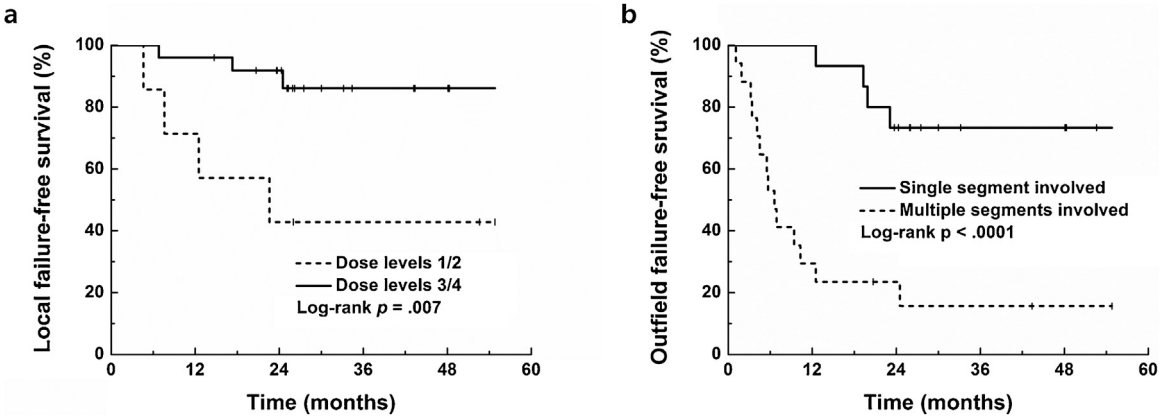

Fig. 2. Significant factors influencing local failure-free survival (a) and outfield failure-free survival (b).

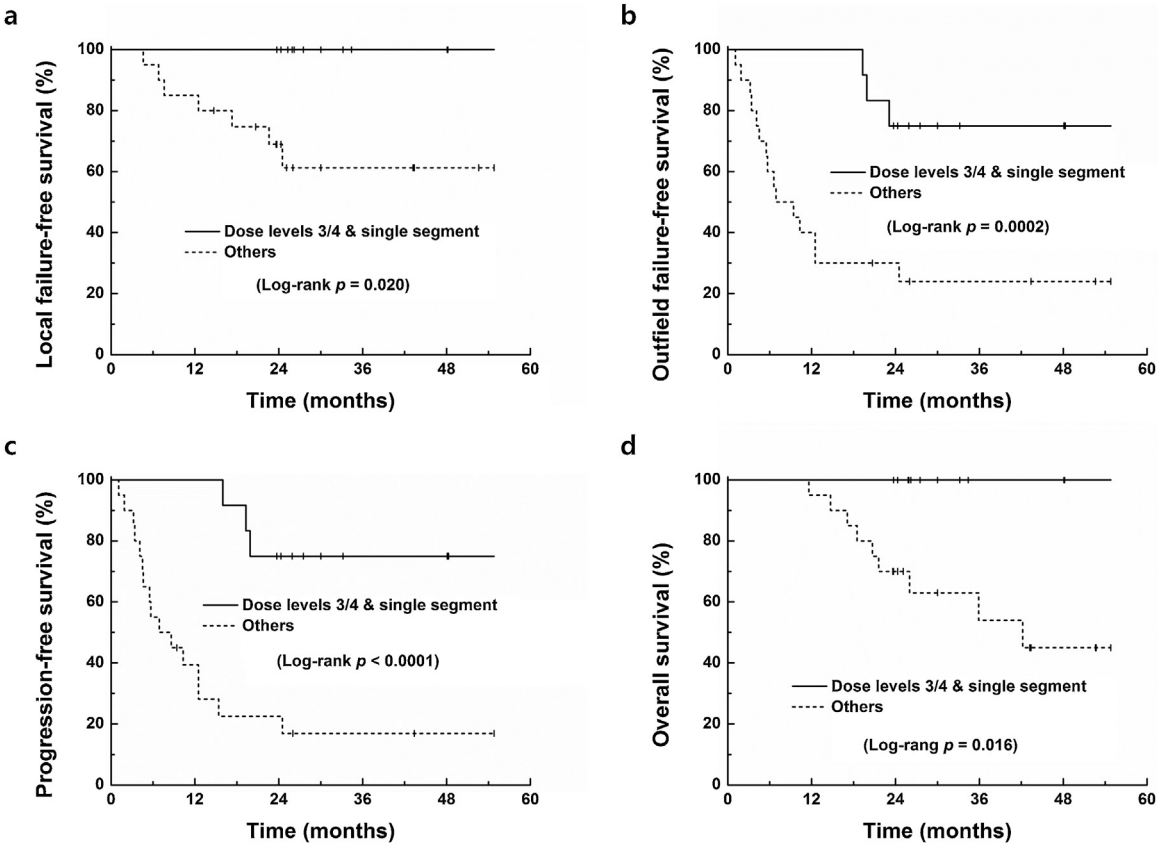

Fig. 3. Comparison of local failure-free survival (a), outfield failure-free survival (b), progression-free survival (c), and overall survival (d) between patients treated with dose-levels 3/4 for tumor(s) involving a single segment and the rest of the patients.

3.4. Survival and prognostic factors

The median follow-up time was 27 months (range, 12–55 months) for all patients, 39 months (range, 11.6–54.8 months) for patients in phase I, and 25.5 months (range, 14.7–30.0 months) for patients in phase II. One- and 2-year LFFS, OutFFS, DMFS, PFS, and OS rates were 90.6% and 80.9%, 62.5% and 46.7%, 93.8% and 84.2%, 62.3% and 42.7%, and 96.9% and 81.3%, respectively (Supplementary Fig. 1). Two-year local control rates at dose levels 1, 2, 3, and 4 were 25.0%, 66.7%, 87.5%, and 94.1%, respectively (results not shown). Dose levels 1–2 (vs. 3–4, p = 0.007) and pre-SBRT multi-segment recurrence (vs. single-segment recurrence, p = 0.040) correlated significantly with poor local control rates in the univariate analysis; however, only dose levels 1–2 independently influenced the local control rate (p = 0.028) in the multivariate analysis (Table 3 and Fig. 2A). Pre-SBRT multi-segment recurrence was the only factor that correlated significantly with poor outfield-intrahepatic control in both the univariate (p < 0.0001) and multivariate (p = 0.001) analyses (Table 3 and Fig. 2B).

We analyzed the treatment outcome of the patients with good prognostic factors. Two-year LFFS (100% vs. 68.9%, p = 0.020), OutFFS (75.0% vs. 30.0%, p = 0.002), PFS (75.0% vs. 22.5%, p < 0.0001), and OS (100% vs. 70.0, p = 0.016) were significantly higher for the patients who were treated with dose-levels 3 and 4 for primary or recurrent tumor(s) involving single segment (n = 12) compared with the rest of the patients (n = 20) (Fig. 3A–D).

4. Discussion

There are a few prospective studies on SBRT for HCC, with eligibility mostly limited to CTP class A patients. In sequential phase I and II trials, Bujold et al. treated 102 HCCs (median size, 7.2 cm; range, 1.4–23.1 cm) with 24–54 Gy in 6 fractions [13]. The 1-year local control rate was 87%; although enrollment was limited to CTP class A patients, there were 2 deaths possibly related to SBRT and a 29% increase in CTP score 3 months after treatment. The phase I/II trial by Mendez-Romero et al. included 8 HCC patients (6 CTP class A and 2 CTP class B) with a median tumor size of 6 cm (range, 2–8 cm) [14]. Patients with cirrhotic HCCs ≥4 cm received 25 Gy in 5 fractions or 30 Gy in 3 fractions, whereas those with cirrhotic HCCs <4 cm received 37.2 Gy in 3 fractions. The 2-year local control rate was 84%; 4 patients had grade ≥3 toxicity and 1 CTP class B patient experienced fatal RILD. In the phase I trial by Cardenes et al., doses were increased from 36 Gy to 48 Gy in 17 HCC patients (6 CTP class A and 11 CTP class B) with a median tumor size of 4 cm (range, 2–6 cm) [5]. The 1-year local control rate was 75%, and RILD occurred in 18% of the patients. The CTP score was the only factor associated with grade ≥3 hepatic toxicity or death within 6 months.

Our prospective study showed 1- and 2-year local control rates of 90.6% and 80.9%, respectively, which were equal to or better than those of previous trials [5,13,14]. There was a significant difference in the local control rate between dose levels 1–2 and 3–4. Three of 4 patients who received 36 Gy in 4 fractions and 1 of 3 patients who received 44 Gy in 4 fractions eventually experienced local failure. Two of 8 patients experienced local failure after receiving 52 Gy in 4 fractions; these failures were due either to the growth of the outfield failure into the treated region or recurrence along the portal tract encompassing the infield and outfield regions. No patient had experienced local failure after receiving 60 Gy in 4 fractions at the time of the analysis. What is encouraging in the current study is the absence of grade ≥3 hepatic toxicity and the CTP scores, which worsened only in 4 patients and only by 1 point. Our results suggest that 52 Gy in 4 fractions provide effective local control for HCC, provided that targets are well isolated from high-risk areas for tumor spread such as major vascular structures. Sixty-gray in 4 fractions can still be safely delivered for more radio-resistant tumors such as colorectal cancer metastases.

Several factors may be responsible for the low level of hepatic toxicity in the current trial. First, most of the patients were CTP-A5 (87.5%). Because CTP-A6 is associated with more inflammation and fibrogenicity than is CTP-A5, it has a higher potential for liver dysfunction. Wang et al. recommend that SBRT be performed with care in CTP-A6 patients with a prolonged prothrombin time [15]. Second, most of the patients had a single tumor with a small diameter (median, 2.1 cm), and the dose to normal liver volume may have been reduced. The median average dose to normal liver volume was 9.9 Gy (range, 3.0–14.3 Gy) in our trial, compared with 15.9 Gy (range, 4.3–21.4 Gy) and 10.7 Gy (range, 4.5–15.4 Gy) in the trials by Bujold et al. [13] and Cardenes et al. [5], respectively. HBV reactivation may further complicate hepatic toxicity among patients treated via chemotherapy or RT. Previous studies reported a 22–25% incidence of radiation-induced HBV reactivation after conventional RT [16,17]. No clinical studies involving SBRT for HCC, including ours, observed radiation-induced HBV reactivation, which may reflect under-reporting, effectiveness of preemptive antiviral therapy, or improved sparing of normal liver volume by SBRT compared with conventional RT. Huang et al. reported that the normal liver volume, the volume of liver receiving at least 20 Gy (V_{20}), and the mean liver dose all significantly correlated with HBV reactivation after conformal RT [16].

Factors possibly contributing to improved local control in the current trial include small tumor size, no major portal vein invasion, use of RT-planning MRI for accurate target delineation and detection of intrahepatic metastases not visible via dynamic liver CT, and the addition of a margin for coverage of microscopic satellite lesions. In previous SBRT trials, the CTV was identical to the GTV [5,14] or an optional 5–8 mm margin was added to the GTV to capture microscopic lesions [13]; however, MRI was not mandatory in these trials. Clinicopathologic studies of HCC have observed microscopic satellite lesions 5–10 mm from the gross tumor [18,19]. This emphasizes the importance of additional margins in local treatments, especially if treatment planning does not involve MRI. It is also worth noting that many of the patients enrolled in the current study received other treatments to the SBRT site(s) and the interval between the last treatment and SBRT was as short as 0.5 month (median 3.5 months). Multimodality treatment may well have led to the improved DFS and OS in these patients.

Despite high local control rates after SBRT, failures in the liver outside the PTV (outfield failure) remain a problem. SBRT for HCC is often initiated only after multiple attempts at local control in curative as well as palliative settings. For patients with a history of recurrence involving multiple hepatic segments, SBRT combined with regional or systemic treatments may improve PFS. It may also be used in cases of intrahepatic tumors incompletely treated via TACE [20] or in combination with TACE or sorafenib [21] for treatment of multiple HCCs. However, the safety and efficacy of the latter approach requires further evaluation before clinical application. In the meantime, we have shown significant improvements in local control, outfield intrahepatic control as well as patient survival when high-dose SBRT was delivered for primary or recurrent tumor(s) involving single segment only. Enrolment of patients may need to be restricted to these conditions if SBRT was to be used with a curative aim.

SBRT can provide an excellent local control without having to undergo invasive procedures and hospitalization. Improved QOL is certainly a major advantage of SBRT. The advantage of SBRT in terms of treatment cost is controversial, since the costs of SBRT and other treatment modalities vary tremendously among medical insurance systems. In Korea, SBRT certainly has an advantage over surgical resection considering the cost of operation and hospitalization. The cost of TACE or RFA are similar to SBRT while TACE and RFA also require short-term admission of the patient.

The current study used a relatively simple technique for SBRT of liver tumors: abdominal compression combined with 4-dimensional CT for simulation and MVCT for image-guidance. The efficacy of the Body Pro-Lok system in improving interfractional and intrafractional setup accuracy and minimizing respiration-related tumor movement during hypofractionated HT for intrahepatic HCC has been demonstrated [10]. Advantages of helical IMRT for treatment of liver tumors include its ability to effectively treat multiple targets simultaneously [4] and to improve tumor coverage [22]. Our protocol is easy to use and less time-consuming than other techniques for respiration-related liver motion; its potential benefits include shorter treatment set-up and delivery times and increased patient compliance.

5. Conclusion

In conclusion, helical IMRT-based SBRT was safe and provided effective local control for HCC in cirrhotic patients. Patients with multi-segment recurrences prior to SBRT should be monitored closely for outfield failures.

Conflicts of interest
None declared.

Funding

This study was supported by the National Nuclear R&D Program through a National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (Grant number; NRF-2017M2A2A7A02070426).

Acknowledgements

This study was selected as one of the Top 20 scoring posters in the "Gastrointestinal-GI" track at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO), San Diego, CA, September 2017.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.11.004.

References

[1] Mendez Romero A, de Man RA. Stereotactic body radiation therapy for primary and metastatic liver tumors: From technological evolution to improved patient care. Best Pract Res Clin Gastroenterol 2016;30:603–16.
[2] Yoon HI, Lee IJ, Han KH, Seong J. Improved oncologic outcomes with image-guided intensity-modulated radiation therapy using helical tomotherapy in locally advanced hepatocellular carcinoma. J Cancer Res Clin Oncol 2014;140:1595–605.
[3] Lee IJ, Seong J, Lee CG, Kim YB, Keum KC, Suh CO, et al. Early clinical experience and outcome of helical tomotherapy for multiple metastatic lesions. Int J Radiat Oncol Biol Phys 2009;73:1517–24.
[4] Lee TF, Chao PJ, Fang FM, Su TJ, Leung SW, Hsu HC. Helical tomotherapy for single and multiple liver tumours. Radiat Oncol 2010;5:58.
[5] Cardenes HR, Price TR, Perkins SM, Maluccio M, Kwo P, Breen TF, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol 2010;12:218–25.
[6] Rule W, Timmerman R, Tong L, Abdulrahman R, Meyer J, Boike T, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol 2011;18:1081–7.
[7] Kim JW, Seong J, Lee IJ, Woo JY, Han KH. Phase I dose escalation study of helical intensity-modulated radiotherapy-based stereotactic body radiotherapy for hepatocellular carcinoma. Oncotarget 2016;7:40756–66.
[8] Korean Liver Cancer Study G, National Cancer Center K. KLCSG-NCC Korea practice guideline for the management of hepatocellular carcinoma. Gut Liver 2014;2015(9):267–317.
[9] Seo YS, Kim MY, Kim SU, Hyun BS, Jang JY, Lee JW, et al. Accuracy of transient elastography in assessing liver fibrosis in chronic viral hepatitis: a multicentre, retrospective study. Liver Int 2015;35:2246–55.
[10] Hu Y, Zhou YK, Chen YX, Shi SM, Zeng ZC. Clinical benefits of new immobilization system for hypofractionated radiotherapy of intrahepatic hepatocellular carcinoma by helical tomotherapy. Med Dosim 2017;42:37–41.
[11] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.
[12] Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237–48.
[13] Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 2013;31:1631–9.
[14] Mendez Romero A, Wunderink W, Hussain SM, De Pooter JA, Heijmen BJ, Nowak PC, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase i-ii study. Acta Oncol 2006;45:831–7.
[15] Wang PM, Chung NN, Hsu WC, Chang FL, Jang CJ, Scorsetti M. Stereotactic body radiation therapy in hepatocellular carcinoma: Optimal treatment strategies based on liver segmentation and functional hepatic reserve. Rep Pract Oncol Radiother 2015;20:417–24.
[16] Huang W, Zhang W, Fan M, Lu Y, Zhang J, Li H, et al. Risk factors for hepatitis B virus reactivation after conformal radiotherapy in patients with hepatocellular carcinoma. Cancer Sci 2014;105:697–703.
[17] Kim JH, Park JW, Kim TH, Koh DW, Lee WJ, Kim CM. Hepatitis B virus reactivation after three-dimensional conformal radiotherapy in patients with hepatitis B virus-related hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2007;69:813–9.
[18] Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, et al. Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. Cancer 2002;95:1931–7.
[19] Ikeda K, Seki T, Umehara H, Inokuchi R, Tamai T, Sakaida N, et al. Clinicopathologic study of small hepatocellular carcinoma with microscopic satellite nodules to determine the extent of tumor ablation by local therapy. Int J Oncol 2007;31:485–91.
[20] Kang JK, Kim MS, Cho CK, Yang KM, Yoo HJ, Kim JH, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. Cancer 2012;118:5424–31.
[21] Brade AM, Ng S, Brierley J, Kim J, Dinniwell R, Ringash J, et al. Phase 1 trial of sorafenib and stereotactic body radiation therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2016;94:580–7.
[22] Lee IJ, Seong J. The optimal selection of radiotherapy treatment for hepatocellular carcinoma. Gut Liver 2012;6:139–48.