Radiotherapy and Oncology 133 (2019) 1–8

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Orignal Article

Dose escalation by intensity modulated radiotherapy in liver-directed concurrent chemoradiotherapy for locally advanced BCLC stage C hepatocellular carcinoma

Hwa Kyung Byun [a], Hyun Ju Kim [b], Yoo Ri Im [a], Do Young Kim [c], Kwang-Hyub Han [c], Jinsil Seong [a,*]

[a] Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul; [b] Department of Radiation Oncology, Gachon University Gil Medical Center, Incheon; and [c] Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 19 October 2018
Received in revised form 19 December 2018
Accepted 20 December 2018
Available online 11 January 2019

Keywords:
Hepatocellular carcinoma
Radiation dose–response relationship
Intensity modulated radiotherapy
Hepatic arterial infusion chemotherapy

ABSTRACT

Purpose: To evaluate the effects of dose escalation by intensity-modulated radiotherapy (IMRT) in liver-directed concurrent chemoradiotherapy for locally advanced Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma (BCLC-C HCC).

Materials and methods: During 2005–2016, 637 patients with BCLC-C HCC received RT with concurrent hepatic arterial 5-fluorouracil. Patients were divided into two groups according to the biologically effective doses for a tumor ($\alpha/\beta = 10$ Gy): <72 Gy (536 patients) and ≥72 Gy (101 patients). In each group, 128/536 (24%) and 94/101 patients (93%) used IMRT, respectively.

Results: The median follow-up for patients alive at the time of analysis was 36 months (range, 6–159 months). For ≥72 Gy and <72 Gy groups, the median overall survival (OS) was 21 and 13 months, respectively ($P = .002$). The 1-year local failure-free survival (LFFS) were significantly higher in high-dose group (95% vs. 79%; $P < .001$). After propensity score matching, high-dose group still had significantly better 1-year OS (62% vs. 51%; $P = .03$) and 1-year LFFS (95% vs. 78%; $P = .008$). In the multivariate model, RT dose was an independent predictor of LFFS and OS. The surgical conversion rate was significantly higher in high-dose group (20% vs. 12%, $P = .03$), with substantially increased median OS among patients who underwent surgery (104 months vs. 11 months; $P < .001$). There were no significant differences in gastrointestinal bleeding or radiation-induced liver disease.

Conclusions: In liver-directed concurrent chemoradiotherapy, radiation dose escalation by IMRT increased LFFS and OS for locally advanced BCLC-C HCC. It also increased the conversion rate to curative resection, which was attributable to increased OS.

Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage when the prognosis is extremely poor [1–3]. According to the Barcelona Clinic Liver Cancer (BCLC) guidelines, sorafenib is the only standard treatment for BCLC stage C (BCLC-C) [4]. However, the survival benefit after sorafenib treatment seems modest, based on two randomized trials that included Western and Asian-Pacific populations [5,6]. Moreover, since BCLC-C HCC is a heterogeneous group, the selection of treatment type may vary depending on the extent of vascular invasion or metastatic disease. Currently, there are still limited clinical data that make clear recommendations between systemic versus local therapy for this stage [7]. In this context, a wide range of treatment modalities is being explored to improve treatment outcomes for these patients [3]. Nevertheless, the treatment of BCLC-C HCC remains a significant clinical challenge because of its dismal prognosis.

Among the non-surgical treatments for HCC, external beam radiotherapy (RT) historically had a limited role because there were sparse randomized trial data supporting its safety and efficacy. However, recent advances have led to RT being listed in the National Comprehensive Cancer Network Guidelines as a locoregional treatment option for inoperable HCC [8]. In addition, RT

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; BCLC-C, Barcelona Clinic Liver Cancer stage C; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IMRT, intensity-modulated radiotherapy; SIB, simultaneous integrated boost; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; ITV, internal target volume; BED, biologically effective dose; LFFS, local failure-free survival; OS, overall survival; PSM, propensity score matching.

* Corresponding author at: Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.

E-mail address: jsseong@yuhs.ac (J. Seong).

https://doi.org/10.1016/j.radonc.2018.12.025
0167-8140/

has been recently suggested to be implemented in patients with advanced HCC by combining other locoregional or systemic therapy [9,10].

Combining RT with chemotherapeutic agents acting as radiosensitizers has been explored to increase the therapeutic ratio [11–13]. In our institution, concurrent chemoradiotherapy (CCRT) for advanced HCC has been performed for nearly two decades, and our treatment protocol consists of local RT plus hepatic arterial infusion chemotherapy using 5-fluorouracil, which we have termed "liver-directed CCRT." Several studies from our institution and other institutions have revealed that liver-directed CCRT provides favorable outcomes [11–14].

The recent development of RT technologies, such as intensity-modulated radiotherapy (IMRT), has facilitated the safe and effective delivery of high doses to intrahepatic tumors [15,16]. With this technology, out institution has applied higher RT doses in liver-directed CCRT using a simultaneous integrated boost (SIB) technique. The present study aimed to evaluate whether RT dose escalation by SIB-IMRT in liver-directed CCRT could improve the local control and provide a survival benefit without increasing severe toxicity among patients with locally advanced BCLC-C HCC.

Materials and methods

Patient selection

We retrospectively identified 690 patients who underwent liver-directed CCRT for inoperable BCLC-C HCC between January 2005 and October 2016 at the Yonsei Cancer Center. The HCC diagnoses were based on the Korean Liver Cancer Study Group guidelines [17]. Patients were excluded based on the presence of distant metastasis (28 patients), previous or concurrent other malignancy (10 patients), a history of RT to the abdominal area (3 patients), and incomplete RT (range: 9–23 Gy) due to patient refusal (8 patients) and a poor general condition (4 patients). Thus, data from 637 patients were included in the final analyses. The retrospective protocol was approved by our institutional review board (4-2017-0855).

Treatment protocols

The definitions of target volumes and typical dose prescription are described in Supplementary Table 1. 5-mm margins around the gross tumor volume (GTV) and clinical target volume (CTV) were defined as the CTV and planning target volume (PTV), respectively. Tumor movement was included in the PTV by adding a generous margin in a craniocaudal direction before 2010. Four-dimensional computed tomography-based planning was adopted since 2010; the internal target volume (ITV) was delineated considering the tumor movement for every respiratory phase, and additional 5-mm margins around the ITV and CTV were defined as the CTV and PTV, respectively.

The RT doses were customized to maximize the dose delivered to the tumor while satisfying the normal organ dose constraints (Supplementary Table 2). For three-dimensional conformal RT, 45 Gy in 25 fractions was typically prescribed to the PTV. As IMRT was implemented for more patients, our practice pattern shifted to the delivery of higher doses of radiation. The GTV or ITV received a radiation dose of 50–75 Gy in 20–25 fractions using a central SIB technique, while the surrounding PTV received a lower radiation dose of 45–60 Gy in 20–25 fractions. For selected tumors with a sufficient distance from luminal organs, the GTV minus 1 cm was treated with an SIB of 100 Gy in 25 fractions (Fig. 1).

In cases with multiple tumors, the primary and adjacent tumors were irradiated, and lesions outside the target volume were treated using transarterial chemoembolization at the time of the

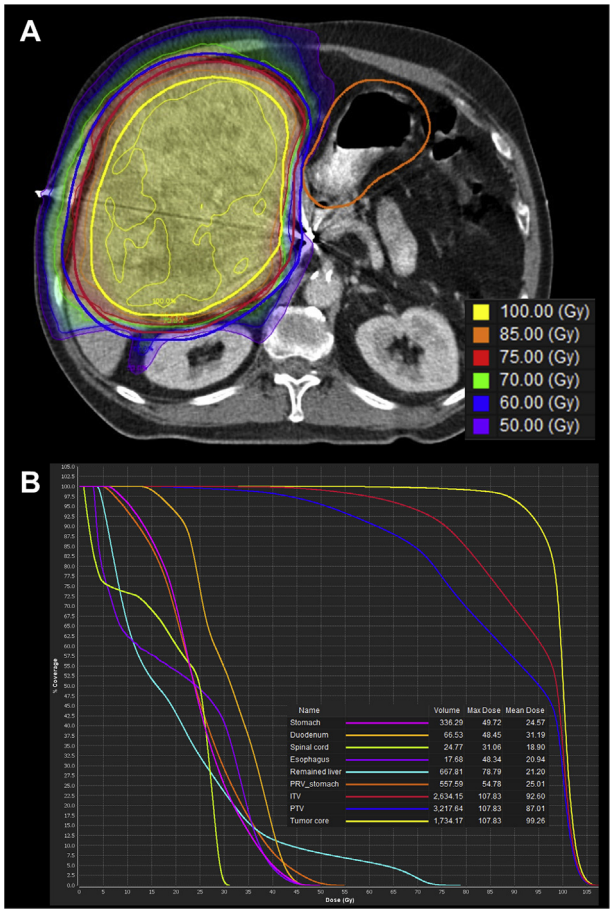

Fig. 1. A representative dose distribution using the simultaneous integrated boost technique at the level of the central axis (A) and its dose-volume histograms (B). Doses of 75 Gy and 60 Gy in 25 fractions were delivered to the internal target volume (ITV; red contour) and to the planning target volume (PTV; blue contour), respectively. Based on anatomic considerations, some patients received 100 Gy in 25 fractions to the gross tumor volume minus 1 cm, which was defined as the tumor core (yellow contour). The target volumes were subtracted from the planning risk volume (orange contour). During treatment planning, the organs at risk were considered the primary factor for constraining the target volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

arterial port insertion. If portal vein tumor thrombosis or regional nodal metastases were present, those were included in the RT field.

Concurrent continuous hepatic arterial infusion chemotherapy of 5-fluorouracil (500 mg/m^2/day) during the first and last week of RT was performed using a percutaneous hepatic arterial catheter inserted via hepatic arterial angiography. At 1 month after CCRT, hepatic arterial infusion chemotherapy using 5-fluorouracil (500 mg/m^2 on days 1–3) and cisplatin (60 mg/m^2 on day 2) was administered every 4 weeks for 1–14 cycles in accordance with the treatment response after CCRT and liver function [13].

Radiation dose analysis

All calculations regarding dose effects were performed using the biologically effective dose (BED) to account for the various fractionation schedules. The BED was calculated using an α/β value of 10 Gy, and patients were categorized according to whether they received a BED of <72 Gy (range: 41.4–71.9 Gy; 536 patients) or $\geq$72 Gy (range: 72–140 Gy; 101 patients). This cut-off point was determined based on the maximally selected rank statistics using

the Maxstat package (R package version 0.7–24) [18] and the maximum Yuden index in the receiver operating characteristic curve analysis [19].

Statistical analysis

Baseline characteristics between the two groups were compared using chi-square test, Fisher's exact test, or Student's *t*-test, as appropriate. The local failure-free survival (LFFS) and overall survival (OS) were defined as the time between the RT start date and the first event and analyzed using the Kaplan–Meier method and log-rank test. Cox's regression model was used for univariate and multivariate analyses of LFFS and OS. Factors with a *P*-value of <0.1 in the univariate analyses were included in the multivariate analysis (enter method). The dose–response relationships for local control and survival probability at 1-year after RT were analyzed using logistic regression. Propensity score matching (PSM) between the BED ≥72 Gy and <72 Gy groups was performed by using a 1:1 nearest neighbor (greedy-type) matching and a caliper width of a 0.2 standard deviation of the logit distance measure by using the R package "MatchIt" [20]. The matching covariates were selected on the basis of known clinical prognostic factors in prior studies [21–23], including performance status, tumor size, PTV, number of tumors, alpha-fetoprotein level, portal vein invasion, and RT modality (Supplementary Table 3). The balance in covariates was assessed using McNemar's test or McNemar-Bowker's test, as appropriate. Statistical significance was set at a 2-sided *P*-value of <0.05. Statistical analyses were performed using R software (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria) and SPSS software (version 23.0; IBM Inc., Armonk, NY, USA).

Results

Patient and tumor characteristics

The patient and treatment characteristics according to the BED ≥72 and <72 Gy groups are summarized in Tables 1 and 2, respectively. Significant inter-group differences were observed in Eastern Cooperative Oncology Group performance status ($P < .001$) and tumor size ($P = .01$; Table 1). In total, 514 patients (80.7%) underwent liver-directed CCRT as the initial treatment after diagnosis. The mean liver dose (corrected to 2 Gy fraction equivalent doses using an $\alpha/\beta = 8$ Gy [24]) was significantly lower in the BED ≥72 Gy group (20.1 Gy vs. 21.4 Gy; $P = .05$), which used significantly more IMRT (93.1% vs. 23.9%; $P < .001$; Table 2). There were no significant differences in the overall proportions of patients who received pre- and post-RT treatment, or in the classification according to treatment method, such as transarterial chemoembolization or sorafenib. The GTV/ITV was not significantly different between the groups, but the PTV was smaller in the BED ≥72 Gy group because smaller margins for the PTV were often used to meet the dose constraints. In addition, there was no correlation between the BED as a continuous value and GTV/ITV (Supplementary Fig. 1).

Effects of radiation dose on survival outcomes

The median follow-up of all patients was 13.5 months (range: 0.4–159.3 months), compared to 35.7 months (range: 6.3–159.3 months) among patients who were alive at the time of analysis. Among all patients, the median LFFS and OS was not reached and 13.7 months, respectively. For the BED ≥72 and <72 Gy groups,

Table 1
Clinical characteristics of all patients, patients who received a BED of <72 Gy, and patients who received a BED of ≥72 Gy.

	Total *N* = 637 *N* (% or range)	BED <72 Gy *N* = 536 *N* (% or range)	BED ≥72 Gy *N* = 101 *N* (% or range)	*P*[§]
Age, year, median	56 (27–84)	56 (27–84)	56 (34–83)	0.29
Sex				0.52
Female	82 (12.9)	71 (13.2)	11 (10.9)	
Male	555 (87.1)	465 (86.8)	90 (89.1)	
Viral etiology				0.80
B	513 (80.5)	431 (80.4)	82 (81.2)	
C	44 (6.9)	36 (6.7)	8 (7.9)	
Non-B, Non-C	80 (12.6)	69 (12.9)	11 (10.9)	
ECOG performance status				<0.001[*]
0	148 (23.2)	136 (25.4)	12 (11.9)	
1	461 (72.4)	387 (72.2)	74 (73.3)	
2	28 (4.4)	13 (2.4)	15 (14.9)	
Child-Pugh class				0.27
A	490 (76.9)	408 (76.1)	82 (81.2)	
B	147 (23.1)	128 (23.9)	19 (18.8)	
Tumor size, cm, median[#]	10 (1–22)	10 (1–20)	8 (1.9–22)	0.01
Number of tumor				0.10
Single	412 (64.7)	354 (66)	58 (57.4)	
Multiple	225 (35.3)	182 (34)	43 (42.6)	
Portal vein invasion site				0.10
No	171 (26.8)	137 (25.6)	34 (33.7)	
Single trunk only	292 (45.8)	255 (47.6)	37 (36.6)	
Double or main trunk	174 (27.3)	144 (26.9)	30 (29.7)	
Regional nodal involvement				0.17
No	553 (86.8)	461 (86)	92 (91.1)	
Yes	84 (13.2)	75 (14)	9 (8.9)	
AFP, ng/mL, median	407 (0.3–492,501)	511 (0.3–492,501)	168 (2–120,000)	0.35

BED, biologically effective dose; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein.
[*] Fisher's exact test.
[§] *P*-values were calculated for the comparison of the <72 Gy and ≥72 Gy groups.
[#] The maximum diameter of the largest tumor.

Table 2
Treatment characteristics of all patients, patients who received a BED of <72 Gy, and patients who received a BED of ≥72 Gy.

	All patients *N* = 637 *N* (% or range)	BED <72 Gy *N* = 536 *N* (% or range)	BED ≥72 Gy *N* = 101 *N* (% or range)	*P*[§]
Prescribed dose, Gy, median				
Total dose	45 (35.9–100)	45 (35.9–59.4)	75 (50–100)	<0.001
Fraction dose	1.8 (1.5–500)	1.8 (1.5–3.5)	3 (1.8–5)	<0.001
BED for total dose	53.1 (41.4–140)	53.1 (41.4–71.9)	97.5 (72–140)	<0.001
EQD2 for total dose	44.3 (34.5–116.7)	44.3 (34.5–59.9)	81.3 (60–116.7)	<0.001
Mean liver dose in EQD2, Gy, median	21.1 (3.6–34.4)	21.4 (3.6–34.4)	20.1 (7.4–30.7)	0.05
Volume, cm^3, median				
GTV/ITV[#]	594 (8–5768)	622 (8–3521)	452 (22–5768)	0.51
PTV	1111 (71–6907)	1214 (78–5153)	690 (71–6907)	0.002
Radiotherapy technique				
3D conformal	415 (65.1)	408 (76.1)	7 (6.9)	<0.001
IMRT	222 (34.9)	128 (23.9)	94 (93.1)	
Concurrent TACE	222 (34.9)	189 (35.3)	33 (32.7)	0.62
Pre-RT treatment				
All	123 (19.3)	101 (18.8)	22 (21.8)	0.49
TACE	104 (16.3)	84 (15.7)	20 (19.8)	0.30
RFA	24 (3.8)	18 (3.4)	6 (5.9)	0.21
Sorafenib[†]	8 (1.3)	6 (1.1)	2 (2.0)	0.62[*]
Surgical resection	21 (3.3)	18 (3.4)	3 (3.0)	1.0[*]
Other	10 (1.6)	10 (1.9)	0 (0)	0.38[*]
Post-RT HAIC	504 (79.1)	424 (79.1)	80 (79.2)	0.91
No. of cycle, median	2 (0–20)	2 (0–20)	3 (0–11)	0.59
Other post-RT treatment				
All	369 (57.9)	309 (57.6)	60 (59.4)	0.74
TACE	194 (30.5)	170 (31.7)	24 (34.8)	0.11
RFA	21 (3.3)	21 (3.9)	0 (0)	0.06[*]
Sorafenib[†]	197 (30.9)	169 (31.5)	28 (27.7)	0.45
Systemic chemotherapy	23 (3.6)	22 (4.1)	1 (1.0)	0.15[*]
Surgical resection	68 (10.7)	53 (9.8)	15 (14.8)	0.14
Liver transplantation	16 (2.5)	11 (2.1)	5 (4.9)	0.15[*]

BED, biologically effective dose; EQD2, equivalent dose in 2-Gy fractions; GTV, gross tumor volume; ITV, internal target volume; CTV, clinical target volume; PTV, planning target volume; IMRT, intensity-modulated radiotherapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; HAIC, hepatic arterial infusion chemotherapy; RT, radiotherapy.
[*] Fisher's exact test.
[§] *P*-values were calculated for the comparison of the <72 Gy and ≥72 Gy groups.
[#] The target volume was defined using GTV before 2010 and using ITV after 2010.
[†] The customary sorafenib dosage was 400 mg, twice daily.

the median LFFS was not reached and 88.6 months, the 1-year LFFS rates were 95.3% and 78.5% ($P < .001$), the median OS was 21.2 and 12.7 months, and the 1-year OS rates were 63.4% and 52.7% ($P = .002$), respectively (Fig. 2A and B). There were positive correlations between the BED as a continuous value and the 1-year probabilities of local control and survival (Supplementary Fig. 2).

We also performed PSM to compensate for the non-random assignments to each group. The patient characteristics before and after the PSM are summarized in Supplementary Table 3. Before the PSM, significant inter-group differences were observed in Eastern Cooperative Oncology Group performance status ($P = .003$), tumor size ($P = .002$), PTV ($P < .001$), and RT modality ($P < .001$). After the PSM, 94 matched pairs were created, and the two groups were well balanced (all $P > .05$). After PSM, the improved LFFS and OS in the high-BED group remained significant. For the matched BED ≥72 and <72 Gy groups, the median LFFS was not reached in both groups; the 1-year LFFS rates were 94.9% and 78.1% ($P = .008$), respectively; the median OS was 20.7 and 12.7 months, respectively, and the 1-year OS rates were 61.7% and 51.1% ($P = .03$), respectively (Fig. 2C and D).

Prognostic factors

The results of the univariate and multivariate analyses in all patients ($n = 637$) for LFFS and OS are summarized in Table 3. In multivariate analysis, LFFS was significantly associated with a BED of ≥72 Gy (hazard ratio [HR]: 0.33, 95% confidence interval [CI]: 0.16–0.67; $P = .002$) and regional nodal metastasis ($P = .02$). In addition, a BED of ≥72 Gy significantly predicted OS (HR: 0.75, 95% CI: 0.57–1.00; $P = .048$) in multivariate analysis, which was also predicted by the Child-Pugh class, tumor size, portal vein invasion, initial alpha-fetoprotein level, and concurrent treatment (all $P < .05$). When the BED was included as a continuous variable in the multivariate analysis, the same factors significantly predicted LFFS and OS, except that an increase in BED by 1 Gy showed marginal significance for OS ($P = .054$; Supplementary Table 4). Among the propensity-matched cohort ($n = 188$), a BED of ≥72 Gy was significantly associated with LFFS (HR: 0.35, 95% CI: 0.16–0.76; $P = .008$) and OS (HR: 0.62, 95% CI: 0.43–0.89; $P = .01$) in the multivariate analyses (Supplementary Table 5).

Surgical conversion

Among all patients, conversion to surgical treatment after liver-directed CCRT was performed in 84 patients: conversion to curative resection and liver transplantation was performed in 68 (10.7%) and 16 (2.5%) patients, respectively. In total, surgical treatment was performed for 19.8% of the BED ≥72 Gy group (20/101) and 11.9% of the BED <72 Gy group (64/536, $P = .03$). Compared to patients who did not undergo surgery, patients who underwent surgical treatment had a significantly increased median OS (103.8 months vs. 11.4 months; $P < .001$). Among the surgical subgroup, the 1-year OS rates for the BED ≥72 and <72 Gy groups were 95.0% and 96.9% ($P = .28$), respectively. Among the

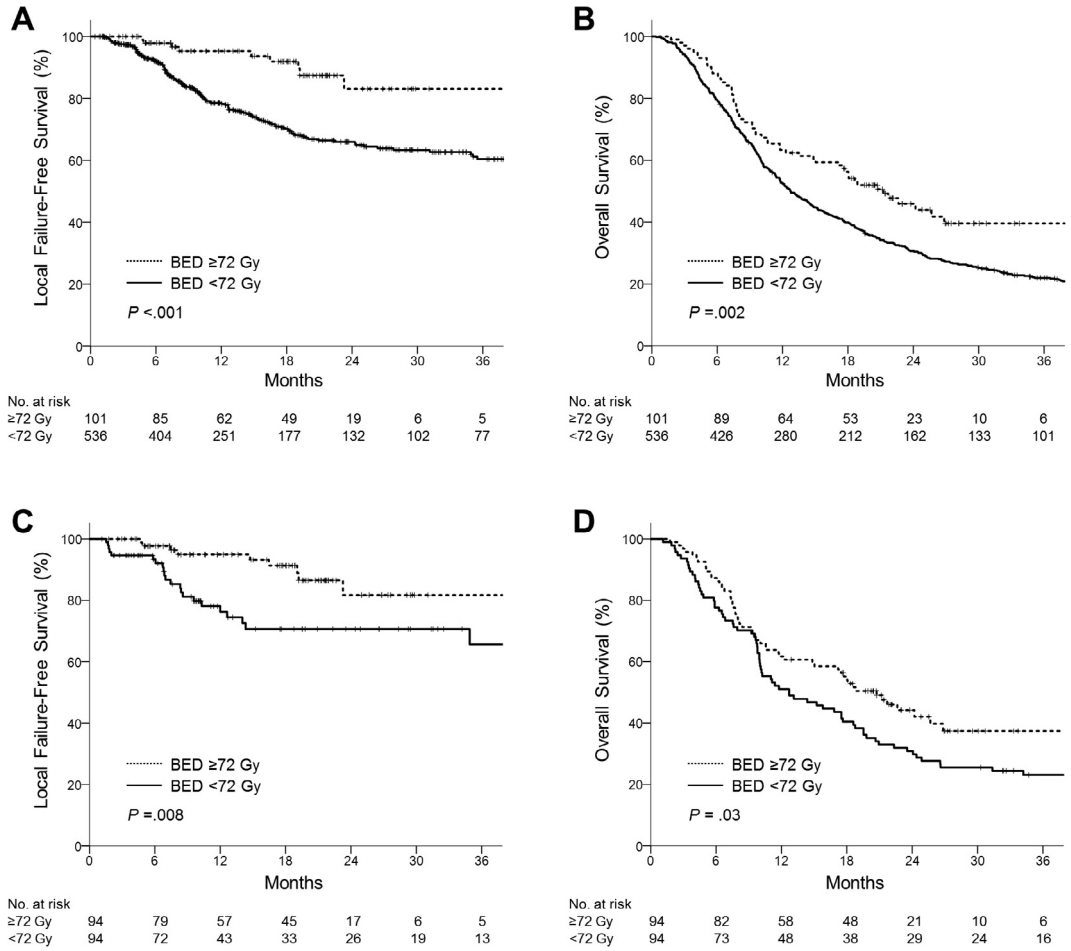

Fig. 2. Kaplan–Meier estimates of local failure-free survival (A) and overall survival (B) before the propensity score matching, as well as local failure-free survival (C) and overall survival (D) after the propensity score matching.

Table 3
Univariate and multivariate Cox regression models for local failure-free and overall survival in all patients ($n = 637$).

	Local failure-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥56 years vs. <56 years)	1.01 (0.73–1.39)	0.97			1.05 (0.88–1.24)	0.62		
Sex (Male vs. Female)	0.83 (0.53–1.32)	0.44			0.94 (0.73–1.21)	0.62		
Viral etiology (Hepatitis B/C vs. Non-B/C)	1.23 (0.74–2.04)	0.42			1.11 (0.85–1.45)	0.43		
ECOG performance status (1/2 vs. 0)	0.85 (0.59–1.22)	0.37			0.87 (0.72–1.06)	0.17		
Child–Pugh class (B vs. A)	1.48 (0.99–2.21)	0.06	1.29 (0.85–1.95)	0.23	2.37 (1.95–2.89)	<0.001	2.04 (1.66–2.49)	<0.001
Size of tumor (≥10 cm vs. <10 cm)	1.07 (0.78–1.49)	0.67			1.49 (1.25–1.77)	<0.001	1.29 (1.07–1.54)	0.006
Number of tumor (Multiple vs. Single)	1.10 (0.78–1.54)	0.59			1.24 (1.04–1.49)	0.02	1.15 (0.95–1.39)	0.14
Portal vein invasion (Yes vs. No)	1.41 (0.98–2.03)	0.06	1.30 (0.90–1.89)	0.16	1.67 (1.36–2.04)	<0.001	1.50 (1.22–1.84)	<0.001
Regional nodal metastases (Yes vs. No)	1.74 (1.15–2.65)	0.009	1.63 (1.07–2.49)	0.02	1.23 (0.96–1.58)	0.10		
AFP (≥407 ng/mL vs. <407 ng/mL)	1.35 (0.98–1.86)	0.07	1.27 (0.91–1.76)	0.16	1.71 (1.43–2.03)	<0.001	1.47 (1.23–1.75)	<0.001
Concurrent Treatment (HAIC + TACE vs. HAIC)	1.21 (0.87–1.69)	0.26			1.34 (1.12–1.60)	0.001	1.26 (1.05–1.52)	0.02
Treatment naïve (Yes vs. No)	1.34 (0.92–1.97)	0.13			1.14 (0.92–1.40)	0.24		
RT modality (IMRT vs. 3D-CRT)	0.70 (0.49–1.00)	0.05	0.99 (0.67–1.45)	0.95	0.89 (0.74–1.07)	0.22		
BED (≥72 Gy vs. <72 Gy)	0.30 (0.16–0.60)	0.001	0.33 (0.16–0.67)	0.002	0.65 (0.49–0.86)	0.003	0.75 (0.57–1.00)	0.05

ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; BED, biologically effective dose; HR, hazard ratio; CI, confidence interval.

non-surgical subgroup, the 1-year OS rates for the BED ≥72 and <72 Gy groups were 55.6% and 46.7% ($P = .04$), respectively.

Toxicity

The treatment-related toxicities are listed in Table 4. Within 3 months after the completion of RT, the BED <72 Gy group had significantly more grade 3–4 hyperbilirubinemia ($P = .02$), while the BED ≥72 Gy group had significantly more thrombocytopenia ($P = .004$). No grade 5 laboratory toxicities were observed. There were no significant inter-group differences in classic and nonclassic radiation-induced liver disease, Child-Pugh score increase more than 2 points, and RT-induced gastroduodenal bleeding observed during the endoscopic examination.

Table 4
Treatment-related complications in the groups that received a BED of <72 Gy or ≥72 Gy.

	BED <72 Gy, *N* (%)	BED ≥72 Gy, *N* (%)	*P*
Liver function (Grade 3–4)[§]			
Albumin	17/515 (3.3)	3/98 (3.1)	1.0
Bilirubin	73/515 (14.2)	5/98 (5.1)	0.02
INR	4/515 (0.8)	0/98 (0)	1.0
AST	126/515 (24.5)	17/98 (17.3)	0.15
ALT	50/515 (9.7)	4/98 (4.1)	0.08
ALP	2/515 (0.4)	1/98 (1.0)	0.41
Hematologic (Grade 3–4)[§]			
Anemia	88/515 (17.1)	11/98 (11.2)	0.18
Leukopenia	156/515 (30.3)	24/98 (24.5)	0.28
Thrombocytopenia	145/515 (28.2)	42/98 (42.9)	0.004
RILD[#]			
Classic RILD	53/489 (10.8)	6/94 (6.4)	0.19
Nonclassic RILD	36/489 (7.4)	3/94 (3.1)	0.14
An increase in Child-Pugh score (≥2)[#]	45/489 (9.2)	6/94 (6.4)	0.38
Upper gastrointestinal bleeding (All grades)[†]	64/536 (11.9)	8/101 (7.9)	0.24
Grade 1–2	37	2	
Grade 3–4	26	6	
Grade 5	1	0	
Lower gastrointestinal bleeding (Grade 3–4)[†]	3/536 (0.6)	0/101 (0)	1.0[*]

BED, biologically effective dose; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; RILD, radiation-induced liver disease.

[*] Fisher's exact test.

[§] Acute laboratory toxicities were evaluated until the 3-month follow-up using the Common Terminology Criteria for Adverse Events (version 4.03). Twenty-four patients were excluded because they received additional transarterial chemoembolization within 3 months after the end of radiotherapy.

[#] Based on the definition of RILD, 24 patients were excluded because they received additional transarterial chemoembolization within 3 months after the end of radiotherapy, and 30 patients were excluded because they experienced intrahepatic progression within 3 months after the end of radiotherapy.

[†] Radiation-induced gastrointestinal bleeding was graded using the Common Terminology Criteria for Adverse Events (version 4.03).

RT-induced upper gastrointestinal bleeding occurred in 72 patients, including 64 and 8 patients in the low-BED and high-BED groups, respectively. Of 72 patients, 46 had gastric bleeding, 25 had duodenal bleeding, and 1 had both. The mean D_{max} of the duodenum in patients with duodenal bleeding was significantly higher than those without (Mean D_{max} ± standard deviation: 44.6 ± 9.7 Gy vs. 35.7 ± 15.8 Gy; $P = .002$). Similarly, the mean D_{max} of the stomach in patients with gastric bleeding was significantly higher than those without (42.3 ± 9.7 Gy vs. 33.5 ± 15.3 Gy; $P < .001$). One patient in the low-BED group whose duodenal D_{max} was 47 Gy died from duodenal bleeding at 3 months after the CCRT. In the other cases, complete hemostasis was achieved using argon plasma coagulation, hypertonic saline-epinephrine injections, or hemoclipping.

Discussion

The present study investigated whether RT dose escalation by SIB-IMRT in liver-directed CCRT could improve clinical outcomes among patients with locally advanced BCLC-C HCC. The results indicate that liver-directed CCRT using a BED of ≥72 Gy provided encouraging oncological outcomes, such as a 1-year LFFS rate of 95.3% and a median OS of 21.2 months.

Several investigators have also investigated an RT dose–response relationship for intrahepatic malignancies. Park et al. [25] reported that the RT dose was the most significant factor associated with tumor response among 158 patients with HCC, based on response rates of 29.2% to <40 Gy, 68.6% to 40–50 Gy, and 77.1% to >50 Gy. Toya et al. [26] also reported a difference in the response rates of portal vein tumor thrombi among patients who received a BED of ≥58 Gy or <58 Gy (80.0% vs. 21.7%, $P < .001$). However, those two studies were performed many years ago, using limited RT doses [25,26]. A phase II trial of liver-directed CCRT (median RT dose: 60.75 Gy, 1.5-Gy fractions twice per day) for intrahepatic malignancies revealed that the total dose was the only significant predictor of survival [11]. A recent study from the MD Anderson Cancer Center also demonstrated that an ablative BED of ≥80.5 Gy substantially improved the 3-year OS rate among patients with inoperable intrahepatic cholangiocarcinoma (73% vs. 38%; $P = .02$) [16]. Those studies used higher RT doses, although the patients were not limited to having HCC [11,16]. In contrast, the present study only examined patients with locally advanced BCLC-C HCC who were treated with higher RT doses compared to the dose in previous studies [25–27]. Interestingly, among patients who received a BED of <72 Gy, there were no significant differences in LFFS and OS based on a BED cut-off of 53.1 Gy, which was the median BED among all patients (Supplementary Fig. 3). In addition, in the multivariate analysis for OS, a BED increase per 1 Gy lost its significance ($P = .054$; Supplementary Table 4). These findings may suggest that the traditional cut-off dose [25–27] is insufficient for achieving the maximum improvement in treatment outcomes and a much higher dose above the threshold BED of 72 Gy is needed to achieve it.

Two phase III randomized trials of sorafenib for BCLC-C HCC revealed a median OS value of 10.7 months in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial [5] and 6.5 months in an Asian-Pacific study [6]. In comparison, our results revealed a better median OS of 13.7 months in all patients and 21.2 months in the BED ≥72 Gy group. This favorable outcome in the current study may be partly explained by the patient selection: the SHARP and Asian-Pacific trials included large subgroups of patients with lung metastases (21% and 50%, respectively), whereas we excluded patients with distant metastases. However, patients with BCLC-C are a heterogeneous group and can have cancer-related symptoms, portal vein invasion, and/or extrahepatic spread, which can lead to broad variations in survival outcomes. For example, in the Japanese nationwide study, the 3-year OS rates were 51.6%, 38.9%, and 27.2% in patients with HCC

who have nodal metastases, locally advanced tumors, and distant metastases, respectively [28]. The wide variation in the survival of patients with BCLC-C HCC implies that they have heterogeneous clinical characteristics, and thus, different treatment modalities can be applicable depending on the extent of a patient's disease, and some patients with localized disease can benefit from more aggressive local treatment.

Considering surgical resection as a curative treatment for HCC patients, conversion to surgical treatment seems beneficial by providing a chance for cure to locally advanced stage C patients, although the percentage is limited. In a previous study from our group, 41 of 243 patients (16.9%) underwent curative resection after liver-directed CCRT, and these patients had improved OS [29]. In this context, a high-dose RT seems to contribute to improved OS by increasing the conversion rate to surgery (19.8% vs. 11.9%; $P = .03$), and by itself seems to improve OS, as shown in the non-surgical subgroup as well (1-year OS rates: 55.6% vs. 46.7%; $P = .04$).

Dose escalation during liver-directed CCRT was enabled by using a combination of modern RT techniques [15]. The central SIB to the hypoxic centers of large tumors was performed as well as simultaneous integrated protection to the abutting liver and luminal organ, which was facilitated by using IMRT [16,30]. Four-dimensional CT was used to reflect the tumor and normal organ movement for every respiratory phase in the RT planning. Daily CT image guidance was performed to ensure accurate localization. These techniques allowed for delivery of ablative doses to the tumors precisely while minimizing damage to the surrounding normal organs. In fact, the hepatic toxicity was not significantly different between the two dose groups. The toxicity rates were comparable to the historical data reporting an radiation-induced liver disease of 9.4%–19% [25,31–35] and a Child-Pugh score increase ($\geq$2 points) of 46% [36]. Moreover, although not significant, we observed that the RT-related toxicities could be lowered in the high-dose group, which can be explained by more use of IMRT and a lower mean liver dose in the high-dose group.

This study has several limitations. For example, given the retrospective design, unrecognized biases are possible, despite the fact that we performed multivariate analysis and PSM to correct for confounding factors. Another limitation is that the effect of liver-directed CCRT could have been decreased or biased because of pre- and/or post-RT treatment other than RT. However, no significant differences in these treatments were detected between the groups. Despite these limitations, our study also has several strengths. For example, the therapeutic effect of the high BED was supported by various endpoints, which included LFFS, OS, tumor marker response (Supplementary Data), and surgical conversion rate. In addition, we included a large number of patients with locally advanced BCLC-C HCC, who received relatively homogenous protocols at a single institution, and, to the best of our knowledge, this is the largest retrospective study of RT dose escalation for HCC.

In conclusion, RT dose escalation provided improved local control and a survival benefit among patients with locally advanced BCLC-C HCC, which could be attributed to the increased conversion rate to curative surgery in the high-dose group. Furthermore, modern RT techniques, such as SIB-IMRT, daily image-guided RT, and four-dimensional CT-based planning can be used to precisely and safely deliver tumoricidal doses. Therefore, we suggest that liver-directed CCRT with a BED of $\geq$72 Gy can be an effective treatment option for patients with locally advanced BCLC-C HCC.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.025.

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