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Clinical Investigation

Safety and Efficacy of Accelerated Hypofractionation and Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma Patients With Varying Degrees of Hepatic Impairment

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Summary

In this retrospective report of stereotactic body radiation therapy or accelerated hypofractionated radiation therapy for patients with varying degrees of hepatic

Purpose: To report the toxicities and outcomes for stereotactic body radiation therapy (SBRT) and accelerated hypofractionated radiation therapy (AHRT) in patients with Child-Pugh (CP) class A, B, or C and albumin-bilirubin (ALBI) score 1, 2, or 3 hepatocellular carcinoma.

Methods and Materials: We retrospectively reviewed the data from 146 patients with hepatocellular carcinoma who had undergone SBRT (50 Gy in 5 fractions) or AHRT (45 Gy in 18 fractions). The primary endpoint was liver toxicity, defined as an increase

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dysfunction, we identified that global hepatic functionality decline as measured by a Child-Pugh score decline of ≥2 within 6 months of radiation therapy was similar across baseline liver functionality groups. These data provide evidence for further prospective stereotactic body radiation therapy trials for patients with advanced liver dysfunction.

in the CP score of ≥2 within 6 months of radiation therapy. The secondary endpoints of ALBI change, overall survival, and local control were also calculated.

Results: The median follow-up was 23 months (range 1-59). Most received SBRT (72%), and 28% received AHRT. Of all 146 patients, 45 (31%) had a CP score elevation of ≥2 within 6 months of radiation therapy (RT) (27 patients [28%] with baseline CP-A/B7 and 18 [35%] with baseline CP-B8/B9/C cirrhosis; $P = .45$). On multivariate analysis, neither baseline CP nor ALBI score was predictive of toxicity. No patient with a decline in liver functionality of CP ≥2 within 6 months of RT returned to baseline at later time points. Eleven grade 4 toxicities were observed. The mean change in the raw ALBI score at ~6 months was similar for all baseline ALBI groups. Twenty-two patients underwent orthotopic liver transplantation after RT, 13 of whom had baseline CP-B8/B9/C liver functionality. For all patients, the 1- and 2-year treated-lesion local control was greater for SBRT than for AHRT (2-year 94% vs 65%, $P < .0001$).

Conclusions: The tolerability of SBRT or AHRT as measured by a CP score decline of ≥2 within 6 months of RT was similar across baseline liver functionality groups. Compared with AHRT, SBRT was associated with superior local control. Because the true tolerability of limited-volume RT for patients with CP-B or CP-C cirrhosis is unknown, prospective trials validating its safety and efficacy are warranted.

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer death in the world. HCC is newly diagnosed in ~700,000 people worldwide each year, with a similar number dying of the disease (1). In the United States, HCC is the fastest growing cause of cancer death, with nearly 30,000 deaths annually (2, 3).

The nonoperative management of HCC patients with severe hepatic dysfunction is controversial given their overall dismal prognosis from underlying liver disease. As a result, patients with poor liver function have been largely excluded from prospective and retrospective studies with only a few of Child-Pugh (CP) class C patients distributed among multiple studies with various treatment regimens (4-9). Given this, the safety, efficacy, and optimal radiation therapy (RT) dose-fractionation schedule for patients with the largest degree of hepatic dysfunction is currently unknown.

At Oregon Health and Science University, we have been treating HCC patients with advanced hepatic dysfunction with stereotactic body RT (SBRT; 50 Gy in 5 fractions) or accelerated hypofractionated RT (AHRT; 45 Gy in 18 fractions) since 2007. The purpose of the present study was to report the safety and efficacy of RT for HCC patients with varying degrees of hepatic impairment.

Methods and Materials

Eligibility criteria

The patients in this retrospective review included those with HCC who had completed either SBRT to 50 Gy in 5 fractions or AHRT to 45 Gy in 18 fractions to a single lesion from 2007 to 2015 with sufficient data to assess CP status after RT. The use of RT for HCC was decided by consensus of a multidisciplinary team and in the context of a specific institutional HCC treatment algorithm modified from the Barcelona Clinic Liver Cancer approach. Patients were included regardless of age, performance status, liver transplant candidacy, or number or type of liver-directed therapies before RT. The institutional review board approved the study before data collection.

Treatment planning and delivery

Patients underwent treatment simulation in the supine position with and without abdominal compression. A free-breathing 4-dimensional (4D) computed tomography (4D-CT) simulation was obtained with both early and delayed contrast-enhanced images. Breath-hold techniques were not used. Fiducial markers were placed for those patients without dense ethiodol uptake within the lesion to be treated.

The target and organs at risk were delineated on the untagged CT data set. The internal target volume (ITV) was defined by integrating information from pre-RT arteriograms, magnetic resonance imaging, and/or diagnostic triple-phase CT scans with the data from the 4D-CT simulation. The planning treatment volume (PTV) was created using a 5- to 10-mm circumferential expansion of the ITV. The choice of fractionation schedule (SBRT in 50 Gy in 5 fractions vs AHRT in 45 Gy in 18 fractions) was physician dependent and independent of the degree of hepatic dysfunction, with AHRT typically chosen for lesions in close proximity to critical organs at risk (ie, bowel, stomach, kidney, heart) or for lesions >5 cm. Free-breathing intensity modulated RT (IMRT), volumetric modulated arc therapy (VMAT), or 3-dimensional (3D) conformal RT (3D-CRT)

was delivered using a Varian Novalis Tx linear accelerator using 10-MV photon energy with daily image guidance. One patient received helical tomotherapy.

Follow-up protocol

The recommended follow-up protocol included regularly scheduled office visits and routine laboratory tests every 3 months after RT. Surveillance contrast-enhanced CT scans were ordered at the discretion of the treating physician.

Toxicity analysis

Liver toxicity was defined as an increase of the CP score of $\geq$2 at 6 months after RT. Toxicity observed after liver transplantation was not counted as toxicity in the analysis of the subgroups. In accordance with the 2010 QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) definition (10), the incidence of nonclassic radiation-induced liver disease (RILD) was also scored (defined as grade 4 aspartate aminotransferase or alanine aminotransferase elevation or an increase in CP score of $\geq$2 1 week to 3 months after treatment).

Study endpoints

The primary endpoint was an increase of the CP score of $\geq$2 within 6 months after RT. The secondary endpoints were raw albumin-bilirubin (ALBI) score decline (11), overall survival, and local control (defined as the absence of progressive disease within or at the PTV margin). The secondary endpoints were calculated from RT completion. Additionally, investigational toxicity data (ie, aspartate aminotransferase, alanine aminotransferase, thrombocytopenia) was scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (12).

Statistical analysis

Descriptive statistical analysis was conducted for all primary and secondary endpoints. The χ^2 test was used to assess whether the incidence of CP score elevation was different between the CP-B8/B9/C patients and CP-A/B7 patients and between the ALBI-1/2 patients and ALBI-3 patients. The Kaplan-Meier method was used to estimate the survival functions for overall survival (patients undergoing liver transplantation were excluded) and local control (patients undergoing transplantation were censored at transplantation). Group differences were examined using the log-rank test. The change in the raw ALBI score at $\sim$6 months after treatment was calculated, and group differences in the mean ALBI change were examined using analysis of variance. To assess for dosimetric predictors of CP decline at $\sim$6 months, logistic regression analysis of the multiple dose-volume histogram metrics and reverse metrics of liver spared certain doses (V15-spared [volume of liver minus ITV receiving $\geq$15 Gy] and V25-spared) was conducted. All data analysis was conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Patient and treatment characteristics

From 2007 to 2015, 146 patients met the inclusion criteria. The median follow-up period was 23 months (range 1-59). When classified by baseline CP score, 67, 60, and 19 patients had CP-A, CP-B, and CP-C cirrhosis, respectively. When classified by ALBI score, 23, 88, and 35 patients had ALBI-1, ALBI-2, and ALBI-3 liver functionality, respectively. Most patients were male (86%) and had hepatitis C (74%). The vast majority of patients (92%) had $\geq$1 previous liver-directed therapy. Of those therapies, 92% were transarterial chemoembolization (TACE) or transarterial embolization. Of the 146 patients, 22 ultimately underwent orthotopic liver transplantation after RT, of whom 13 had baseline CP-B8/B9/C liver functionality (Table 1).

The RT characteristics are listed in Table E1 (available online at www.redjournal.org). Most patients underwent SBRT (72%), and 28% underwent AHRT. For the SBRT patients, 21 (20%), 70 (67%), and 14 (13%) underwent 3D-CRT, IMRT, or VMAT, respectively. For the AHRT patients, 4 (10%), 26 (64%), 10 (24%), and 1 (2%) underwent 3D-CRT, IMRT, VMAT, or helical tomotherapy, respectively. The median 'mean doses' to the liver minus the ITV was 640 cGy for SBRT patients and 926 cGy for AHRT patients. The CP class or ALBI score was not a clinical factor for the selection of 1 treatment regimen over another. No statistically significant difference was found in PTV size nor maximum dose to the PTV between the CP-A/B7 and CP-B8/B9/C patients or the ALBI-1/2 and ALBI-3 patients. However, for SBRT treatments only, the volume of the liver minus the ITV was smaller, the mean dose to the liver minus the ITV was greater, and the volume of the liver minus the ITV receiving $\geq$25 Gy was larger in the worst liver functionality groups (CP-B8/B9/C and ALBI-3; Table E2; available online at www.redjournal.org).

Toxicities observed

Of all 146 patients, 45 (31%) experienced toxicity determined by the primary endpoint (an elevation of CP score of $\geq$2 within 6 months of RT). Of the patients with baseline CP-A/B7 liver functionality, 27 (28%) experienced a CP elevation of $\geq$2 within 6 months after RT. In contrast, 18 patients (35%) with baseline CP-B8/B9/C functionality experienced toxicity ($P = .45$, Table 2). However, on post hoc exploratory analysis comparing more strictly CP-A only and CP-B/C, a statistically significant difference was found between the rates of observed toxicity ($P = .02$). Furthermore, 7 patients experienced a maximum CP progression of 4 points (5 with CP-B7 and 2 with CP-A6 baseline cirrhosis) and 10 patients

Table 1 Patient demographics and baseline HCC characteristics stratified by hepatic toxicity*

Variable	CP A/B7		CP B8/B9/C	
	No toxicity (n = 68; 72%)	Toxicity (n = 27; 28%)	No toxicity (n = 33; 65%)	Toxicity (n = 18; 35%)
Age (y)	63.3 ± 8.8	60.2 ± 6.3	62.3 ± 6.8	61.1 ± 6.1
Gender				
Male	58 (85)	23 (85)	28 (85)	18 (100)
Female	10 (15)	4 (15)	5 (15)	0 (0)
ALBI score				
1/2	64 (94)	22 (82)	14 (42)	11 (61)
3	4 (6)	5 (18)	19 (58)	7 (39)
Underlying liver disease				
Hepatitis B	2 (2)	4 (11)	0 (0)	1 (4)
Hepatitis C	47 (55)	23 (62)	23 (50)	16 (64)
Alcohol	25 (29)	9 (24)	18 (39)	6 (24)
NASH	6 (7)	1 (3)	2 (4)	1 (4)
Other/unknown	5 (6)	0 (0)	3 (7)	1 (4)
Portal vein thrombosis				
Yes	7 (10)	2 (7)	4 (12)	1 (6)
No	61 (90)	25 (93)	29 (88)	17 (94)
Previous liver-directed therapy				
0	3 (4)	0 (0)	7 (21)	2 (11)
1	23 (34)	11 (41)	12 (36)	7 (39)
2	16 (24)	10 (37)	8 (24)	5 (28)
3	10 (15)	3 (11)	6 (19)	3 (17)
≥4	16 (23)	3 (11)	0 (0)	1 (5)
AFP (ng/mL)	253.0 ± 757.3	104.0 ± 164.2	477.4 ± 1156.9	429.5 ± 963.5
Receiving OLT				
No	61 (90)	25 (93)	24 (73)	14 (78)
Yes	7 (10)	2 (7)	9 (27)	4 (22)
BCLC stage				
Stage A	6 (9)	0 (0)	1 (2)	0 (0)
Stage B	0 (0)	0 (0)	0 (0)	0 (0)
Stage C	59 (87)	27 (100)	16 (49)	14 (78)
Stage D	3 (4)	0 (0)	16 (49)	4 (22)

Abbreviations: AFP = α-fetoprotein; ALBI = albumin-bilirubin; BCLC = Barcelona Clinic Liver Cancer; CP = Child-Pugh; NASH = nonalcoholic steatohepatitis; OLT = orthotopic liver transplantation.
Data presented as mean ± standard deviation or n (%).
* Defined as CP elevation of ≥2 within 6 months of RT.

experienced a maximum CP progression of 5 points (1 with CP-A6, 4 with CP-B7, 3 with CP-B8, and 2 with CP-B9 baseline cirrhosis; Table 3). Using the QUANTEC definition of nonclassic RILD (CP score of ≥2 within 3 months of RT) (10), 33 patients (23%) developed toxicity. No patient with a decline in liver functionality of CP ≥2 within 6 months of RT returned to baseline at later points.

Common Terminology Criteria for Adverse Events grade 4 toxicities within 6 months of RT were observed in 11 patients (4 with baseline CP-A cirrhosis, 5 with baseline CP-B cirrhosis, and 2 with baseline CP-C cirrhosis.). Grade 4 toxicities consisted of 1 gall bladder perforation, 4 cases of thrombocytopenia, 2 cases of hyperbilirubinemia, 2 cases of upper gastrointestinal bleeding, and 2 cases of encephalopathy; no definitive treatment-related deaths were seen. The incidence of grade ≥3 hyperbilirubinemia and hypoalbuminemia was greater in the CP-B8/B9/C patients (47% and 18%, respectively) and ALBI-3 patients (54%

Table 2 Baseline liver functionality and incidence of toxicity within 6 months of radiation therapy

Maximum Change in CP vs baseline	All patients (n = 146)	CP-A/B7 (n = 95)*	CP-B8/B9/C (n = 51)*	ALBI-1/2 (n = 111)†	ALBI-3 (n = 35)†
CP <2	101 (69)	68 (72)	33 (65)	78 (70)	23 (66)
CP ≥2	45 (31)	27 (28)	18 (35)	33 (30)	12 (34)

Abbreviations: ALBI = albumin-bilirubin; CP = Child-Pugh.
Data presented as n (%).
* $P = .453$ (Fisher exact test).
† $P = .676$ (Fisher exact test).

Table 3 Baseline liver functionality and maximum CP score change within 6 months of RT

Maximum CP change within 6 mo of RT	Baseline CP score							
	A5	A6	B7	B8	B9	C10	C11	Total
−2	0	0	0	0	0	1	0	1
−1	0	3	2	1	0	0	1	7
0	13	16	6	3	4	4	4	50
1	12	8	8	7	2	4	2	43
2	4	3	2	3	3	1	0	16
3	0	4	1	4	0	2	0	11
4	0	2	5	0	0	0	0	7
5	0	1	4	3	2	0	0	10
6	0	0	1	0	0	0	0	1
Total	29	37	29	21	11	12	7	146
Median FU (mo)	24.5	28.5	19.8	17.9	14.3	8.8	NR	

Abbreviations: CP = Child-Pugh; FU = follow-up NR = not reached; RT = radiation therapy.

and 25%, respectively) than in the CP-A/B7 patients (13% and 5%, respectively; $P < .05$) and ALBI-1/2 patients (15% and 5%, respectively; $P < .05$). For all other toxicity classes, no difference between liver functionality groups was seen (Table E3; available online at www.redjournal.org).

A waterfall plot was generated to show the change in the raw ALBI score between the score at ~6 months of follow-up (120-220 days after RT) and that at baseline. A negative score indicates improvement in the raw ALBI score, and a positive score indicates a decline (Fig. 1). For patients who had died before the 120- to 220-day window, the laboratory value as close as possible to the date of death was analyzed. For patients without laboratory values within the 120- to 220-day window, data as close as possible to the 220-day point were analyzed. Distribution of the raw ALBI score change over 6 months is given in Table E4 (available online at www.redjournal.org). For patients with a baseline score ALBI-1, ALBI-2, and ALBI-3, the mean decline of the raw ALBI score at approximately 6 months was 0.18, 0.35, and 0.25, respectively ($P = .25$).

Nondosimetric and dosimetric predictors of toxicity

The factors associated with toxicity are presented in Table 4. For CP-A/B7 and ALBI-1/2 patients, many of the liver minus the ITV dosimetric parameters for the SBRT subset were associated with toxicity on univariate analysis. For the ALBI-3 patients, the number of previous liver-directed therapies was significantly associated with toxicity.

In fitting the multivariable model (Table 5), we started by including every covariate from the univariate analysis with $P \leq .2$; only those covariates with a final P value $< .1$ were kept in the model. The treatment regimen variable (SBRT vs AHRT) was included but was removed owing to insignificant effects. In the multivariable model, baseline liver functionality was not predictive of toxicity within 6 months of RT. The mean dose to the liver minus the ITV (ALBI baseline classification only) was the only significant factor predictive of an increase in CP of ≥2 within 6 months of RT (Table 5).

Next, we subdivided the patients into 2 groups according to the raw ALBI decline to assess for any dosimetric predictors of overall liver function decline. The thresholds

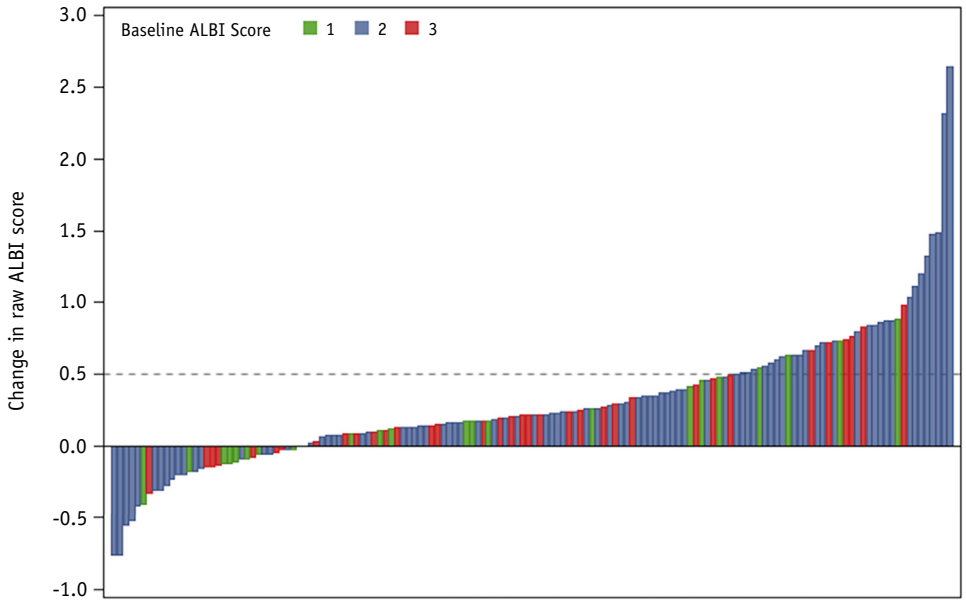

Fig. 1. Waterfall plot of 146 patients color-coded by baseline albumin-bilirubin (ALBI) score showing the change in raw ALBI score between the baseline measurements and ~6 months (window of ~120-220 days from radiation therapy). A negative score indicates an improvement in the ALBI score and a positive score, a decline in the ALBI score.

Table 4 Univariate analysis for predictors of toxicity (CP elevation of ≥2) within 6 months after radiation therapy

	All patients (toxicity in 45/146)			CP-A/B7 (toxicity in 27/95)			CP-B8/B9/C (toxicity in 18/51)			ALBI-1/2 (toxicity in 33/111)			ALBI-3 (toxicity in 12/35)		
Univariate analysis	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, continuous (y)	0.96	0.91-1.01	.08	0.95	0.89-1.01	.11	0.97	0.88-1.06	.51	0.95	0.89-1.00	.07	0.99	0.90-1.10	.89
Gender (male vs female)	1.79	0.56-5.73	.33	0.99	0.28-3.48	.99	NE	-	-	1.30	0.33-5.16	.71	3.88	0.41-36.78	.24
Previous liver-directed therapy															
Continuous (n)	0.96	0.76-1.21	.72	0.91	0.68-1.20	.49	1.32	0.77-2.24	.31	0.83	0.62-1.12	.22	1.69	0.94-3.02	.08
<2 vs ≥2	1.57	0.49-2.02	.99	1.11	0.45-2.76	.82	0.74	0.23-2.34	.60	1.59	0.70-3.62	.27	0.22	0.05-0.97	.05
PTV (cm^3)															
Continuous	1.00	1.00-1.00	.72	1.00	0.99-1.00	.62	1.01	0.93-1.09	.89	1.00	1.00-1.00	.98	1.01	1.00-1.03	.11
<48.8 vs ≥48.8*	1.57	0.77-3.20	.21	0.80	0.33-1.96	.63	0.46	0.13-1.59	.22	0.68	0.30-1.54	.35	0.55	0.13-2.33	.41
Treatment (SBRT vs AHRT)	0.94	0.43-2.06	.89	2.07	0.63-6.81	.23	0.44	0.13-1.42	.17	1.05	0.42-2.61	.92	0.71	0.16-3.22	.65
Liver minus ITV†, continuous (cm^3)	1.00	0.99-1.00	.21	0.99	0.98-1.00	.05	1.01	0.99-1.02	.27	1.00	0.99-1.00	.30	0.99	0.97-1.02	.62
SBRT liver minus ITV															
Mean dose (continuous, Gy)†	1.01	1.00-1.02	.12	1.03	1.01-1.05	.01	0.99	0.96-1.02	.47	1.02	1.01-1.04	.01	0.97	0.94-1.01	.16
V5 (continuous, %)	1.02	0.99-1.05	.17	1.04	1.00-1.08	.04	0.99	0.95-1.04	.78	1.05	1.01-1.08	.01	0.94	0.87-1.02	.11
V15 (continuous, %)	1.03	0.99-1.08	.15	1.10	1.02-1.18	.01	0.95	0.86-1.05	.30	1.08	1.02-1.14	.01	0.93	0.83-1.05	.23
V25 (continuous, %)	1.08	0.98-1.19	.12	1.24	1.06-1.46	.01	0.90	0.73-1.11	.32	1.16	1.02-1.31	.02	0.89	0.70-1.13	.34
Volume spared 15 Gy (continuous, cm^3)†	0.99	0.98-1.00	.12	0.98	0.97-1.00	.01	1.01	0.99-1.04	.25	0.99	0.98-1.00	.05	1.01	0.98-1.04	.53
Volume spared 25 Gy (continuous, cm^3)†	0.99	0.98-1.00	.16	0.98	0.97-1.00	.01	1.01	0.99-1.03	.30	0.99	0.98-1.00	.09	1.01	0.98-1.03	.73
AHRT liver minus ITV															
Mean dose (continuous, Gy)†	1.01	0.99-1.02	.25	1.00	0.98-1.03	.90	1.01	0.99-1.04	.16	1.00	0.98-1.02	.80	1.05	0.99-1.11	.10
V5 (continuous, %)	1.01	0.99-1.05	.34	1.00	0.95-1.05	.94	1.03	0.99-1.07	.23	0.99	0.96-1.03	.76	1.10	0.97-1.25	.14
V15 (continuous, %)	1.03	0.98-1.07	.24	1.00	0.93-1.07	.98	1.06	0.99-1.13	.10	1.00	0.95-1.05	.86	1.44	0.67-3.10	.35
V25 (continuous, %)	1.06	0.96-1.16	.25	1.02	0.87-1.19	.85	1.08	0.96-1.22	.21	0.98	0.87-1.10	.71	1.24	0.98-1.56	.07
Volume spared 15 Gy (continuous, cm^3)†	0.99	0.98-1.01	.47	0.99	0.97-1.02	.68	1.00	0.97-1.02	.68	1.00	0.99-1.02	.74	0.92	0.84-1.01	.07
Volume spared 25 Gy (continuous, cm^3)†	1.00	0.98-1.01	.70	0.99	0.97-1.02	.60	1.00	0.98-1.02	.93	1.00	0.99-1.02	.66	0.93	0.85-1.01	.09

Abbreviations: AHRT = accelerated hypofractionated radiation therapy; ALBI = albumin-bilirubin; CI = confidence interval; CP = Child-Pugh; ITV = internal target volume; NE = not estimable owing to quasicomplete separation; OR = odds ratio; PTV = planning treatment volume; SBRT = stereotactic body radiation therapy; Vxx = volume of liver minus ITV receiving ≥xx Gy.

* Median = 48.2 cm; mean = 83.41 cm^3.

† OR expressed for a 10-unit change in the continuous variable.

analyzed were 0.5, 0.75, and 1.0 raw ALBI decline at approximately 6 months (120- to 220-day window) after RT. We then evaluated the association between ALBI decline and volumetric dose-volume histogram criteria (V5, V15, and V25) and volume-spared in cubic centimeters of liver (V15-spared, V25-spared) using logistic regression. None of these variables was significant enough to predict the ALBI decline at any of the threshold levels (0.5, 0.75, or 1.0; Table E5; available online at www.redjournal.org).

Outcomes

The median survival stratified by CP score for those without liver transplantation was 22.3 months (95%

Table 5 Multivariable analysis for predictors of CP elevation of ≥2 within 6 months of RT classified by baseline CP score or baseline ALBI score

Multivariable model	OR	95% CI	*P* value
CP score			
Baseline liver functionality (low vs high*)	1.14	0.53-2.46	.731
Age (continuous)	0.95	0.90-1.00	.060
Mean liver minus ITV dose (continuous; Gy)	1.10	1.00-1.21	.057
ALBI score			
Baseline liver functionality (low vs high†)	1.02	0.44-2.37	.962
Age (continuous)	0.95	0.90-1.00	.059
Mean liver minus ITV dose (continuous; Gy)	1.10	1.00-1.21	.044

Abbreviations: ALBI = albumin-bilirubin; CI = confidence interval; CP = Child-Pugh; ITV = internal target volume; OR = odds ratio; PTV = planning treatment volume.
* Low = CP-A/B7; high = CP-B8/B9/C.
† Low = ALBI-1/2; high = ALBI-3.

confidence interval [CI] 14.8-35.4) for CP-A patients, 11.8 months (95% CI 7.9-15.9) for CP-B patients, and 5.6 months (95% CI 2.8-7.8) for CP-C patients. The median survival stratified by ALBI score was not reached for ALBI-1 patients (first quartile 22.2 months), 13.3 months (95% CI 11.0-16.6) for ALBI-2 patients, and 7.8 months (95% CI 3.9-9.4) for ALBI-3 patients (Fig. E1; available online at www.redjournal.org).

For all patients, the 1- and 2-year local control (LC) rates were greater in the SBRT group than in the AHRT group (1-year LC 97% vs 72%, $P < .0001$; 2-year LC 94% vs 65%, $P < .0001$; Fig. E2; available online at www.redjournal.org). When excluding patients with a PTV >115 cm^3 (equivalent to a 6-cm sphere) to objectively identify those patients who had received AHRT because of close proximity to critical organs at risk and not because of a large lesion size, the results were essentially unchanged, with SBRT still performing significantly better (1-year LC 97% vs 73%, $P < .0001$; 2-year LC 94% vs 66%, $P = .006$; Fig. E2; available online at www.redjournal.org).

Discussion

To the best of our knowledge, our study is the largest series in the published data examining the incidence of nonclassic RILD in patients with varying degrees of hepatic function. We did not identify a statistically significant difference between a CP score increase of ≥2 within 6 months after SBRT or AHRT for patients with decompensated liver functionality (CP-B8/B9/C or ALBI-3) compared with those with better compensated disease (CP-A/B7 or ALBI-1/2). Patients with poor hepatic function who might benefit most from local therapy are those bridging to potentially curative therapy (13) and those in need of lesion downsizing or size stability such that the transplantation requirements are met. In our series, 13 patients with CP-B8/B9/C cirrhosis underwent successful liver transplantation, of whom all were doing well with no evidence of disease at their last follow-up examination. Given the poor prognosis for CP-C patients who do not undergo curative transplantation (median survival <6 months) and the encouraging results for those who eventually did undergo transplantation, we now offer liver-directed therapy to patients with baseline CP-B8/B9/C cirrhosis only if they have been deemed eligible for transplantation (ie, bridge to transplantation).

A recently reported series from Princess Margaret Hospital in Canada reported that 26% of 101 patients with baseline CP-A cirrhosis and 7 of 13 patients with CP-B7 cirrhosis experienced CP ≥2 toxicity within 3 months of 6-fraction SBRT (14). Indiana University reported their phase 1 results of liver SBRT for patients with up to CP-B9 liver dysfunction. They reported that the only factor related to >1 grade ≥3 liver toxicity or death within 6 months after RT was the baseline CP score (15). A subsequent toxicity analysis of patients enrolled in their phase 1 and 2 trials was performed. Although their patient cohort was smaller than our cohort, they reported that 37% of CP-A patients and 29% of CP-B patients had CP score stability within 3 months of RT (16). Compared with our experience, in which no patients with toxicity returned to their baseline functionality, they reported that 14% of patients had a transient progression of CP score, with an eventual return to baseline within 3 months. Our rate of CP increase of ≥2 within 3 and 6 months of RT for all patients (23% and 31%, respectively) compares favorably with these experiences, with the exception that our analysis included patients with more severe cirrhosis.

Overall, our cohort of patients with unifocal tumors had a lower burden of hepatic disease compared with the Canadian and Indiana experiences, which might explain the lack of association seen between the baseline CP score and liver toxicity. Furthermore, our rate of portal vein thrombosis (10%) was lower than that in the Canadian (52%) or Indiana University (20%) experience. As a result, our median PTV (39 cm^3 for SBRT patients and 128 cm^3 for AHRT patients) and median mean liver dose (6 Gy for SBRT patients and 9 Gy for AHRT patients) were less than those in the Canadian experience (median total gross tumor volume ~100 cm^3, median number of gross tumor volumes >1, median mean liver dose 15-17 Gy) and Indiana experience (median PTV ~100 cm^3, 19% of patients with >1 and ≤5 lesions treated, mean liver doses not reported). As a result, our hypothesis-generating experience provides preliminary support for future studies of the safety of limited volume liver irradiation for patients with advanced cirrhosis.

Few studies have assessed treatment-related toxicity using the more objective ALBI score, which has been tested in a large international cohort of patients with HCC (11). Investigators at Stanford University recently reported their retrospective findings on the decline in the ALBI score after

SBRT in a cohort of 60 patients with CP-A and CP-B HCC and cholangiocarcinoma (17). They reported that for the HCC subgroup, the mean ALBI decline was 0.15 at 1 month and 0.35 at 12 months after RT, with a statistically significant correlation of worse overall survival for those patients with an ALBI decline of 0.5 after SBRT. Again, our multivariate analysis was unable to determine any differential intolerability to treatment according to the baseline characteristics, with patients with any baseline liver functionality at equal risk of toxicity.

In our study, we attempted to identify liver function-specific dosimetric predictors of CP decline, with the hope of developing practical constraints for inclusion in further prospective protocols for this sensitive population. However, our rigorous analysis did not identify a statistically significant dosimetric or critical volume constraint predictive of a CP decline of $\geq$2 within 6 months of RT.

The LC after RT for HCC has been widely reported. Princess Margaret Hospital has the largest prospective experience with 1- and 2-year LC rates of 87% and 74% (18). Multiple other retrospective series have reported similar, or better, control rates (19, 20). The SBRT doses in the Princess Margaret trial ranged from 24 to 54 Gy in 6 fractions, with no apparent dose response identified on multivariate analysis (18). Largely because of concerns of intolerance to critical nearby organs, our institutional paradigm from 2007 through 2015 included fractionated treatment of lesions close to the bowel or stomach to 45 Gy in 18 fractions (AHRT) rather than our standard ablative dose of 50 Gy in 5 fractions (SBRT). In the present study, we have found statistically significant superior LC rates for our SBRT regimen compared with AHRT, with a 2-year LC rate of 94% versus 65%, respectively.

We hypothesized that the larger fraction sizes used in SBRT are particularly effective for these hypervascular lesions, resulting in irreparable damage to the microvasculature through the indirect effects of the high-dose per fraction RT (21, 22). Furthermore, an analysis of 431 patients distributed among 13 studies presented in abstract form only by the American Association of Physics in Medicine Working Group for SBRT identified no dose—response relationship for primary liver tumors with biologically effective doses of 60 to 263 Gy (23). Given this, we have altered our institutional protocol by favoring a more dose-reduced and bowel-tolerant SBRT regimen instead of AHRT for lesions in close proximity to at-risk organs.

The present retrospective single-institution report had several limitations. Our survival and LC outcomes might not be generalizable because only patients with a relatively low tumor burden were identified for analysis. Just as with most retrospective studies, the precise causes of death are challenging to discern; thus, we could not completely rule out that some of these patients did not die of some element of RILD. Furthermore, our typical treatment paradigm consists of TACE with ethiodol before SBRT. Although the benefits of residual ethiodol uptake within the tumor for targeting purposes under volumetric image guidance is undoubted, pretreatment with TACE might have affected the liver tolerance to subsequent SBRT or AHRT and contributed to our LC secondary to localized radiation enhancement (24). Additionally, because only patients who completed an entire treatment regimen were included for analysis, it is plausible, although unlikely, that a subset of patients had ended treatment early owing only to intolerable toxicity. Finally, just as with all studies of this patient population, no consensus has been reached regarding the best toxicity endpoint, because it is difficult to ascertain treatment-related RT-induced toxicity from decompensation resulting from progression of underlying liver disease, with a possibility that many of the toxicities observed were not attributable to liver RT.

Conclusions

For HCC patients with advanced liver dysfunction, the tolerability of RT as measured by a CP score decline $\geq$2 at 6 months was similar across all baseline liver functionality groups. Furthermore, compared with AHRT, SBRT was associated with superior LC. Because the results of the present study cannot dispel the generally accepted notion that patients with advanced cirrhosis must be treated with caution, future prospective trials validating the safety and efficacy of hypofractionated RT are warranted.

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