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ORIGINAL RESEARCH

Does HCC Etiology Impact the Efficacy of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma? An Asian Liver Radiation Therapy Group Study

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Background/Purpose: The Asian Liver Radiation Therapy Study Group has formed a large and detailed multinational database of outcomes following stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC). Here, we explored the potential impact of HCC etiology on SBRT efficacy. Tumor control probability (TCP) models were established to estimate the likelihood of local control (LC).

Methods: Data from 415 patients who were treated with SBRT for HCC were reviewed. Cox proportional hazards models were used to identify key predictors of LC. TCP models accounting for biologic effective dose (BED) and tumor diameter were generated to quantify associations between etiology and LC.

Results: Cox models demonstrated that hepatitis C virus (HCV) infection was associated with favorable LC following SBRT (HR=0.52, 95% CI 0.04–0.96, p=0.036). The 2-year LC rate for patients with HCV etiology was 88%, compared to 78% for other patients. Small tumor and high BED were also associated with favorable LC. TCP models demonstrated a 10–20% absolute increase in predicted LC across the range of SBRT doses and tumor sizes.

Conclusion: We found a novel association between HCV status and LC after SBRT for HCC that warrants further exploration. If validated in other datasets, our findings could help clinicians tailor SBRT schedules.

Keywords: tumor control probability, hepatocellular carcinoma, stereotactic body radiation therapy, hepatitis C virus

Introduction

Liver-directed treatment options for unresectable hepatocellular carcinoma (HCC) include trans-arterial chemo/radioembolization, radiofrequency ablation, percutaneous ethanol injection, and stereotactic body radiation therapy (SBRT). SBRT can deliver ablative therapy with high conformality while sparing most of the uninvolved liver[1,2] and has been demonstrated to yield local control (LC) rates ranging from 76% to 100%.[3–8] SBRT may be utilized effectively in combination with other liver-directed treatments or as monotherapy.[6,7,9,10]

Despite growing evidence supporting SBRT as an effective local treatment for HCC, concrete treatment guidelines (ie, patient selection and dose prescription) have not yet been established. We previously reported that the use of

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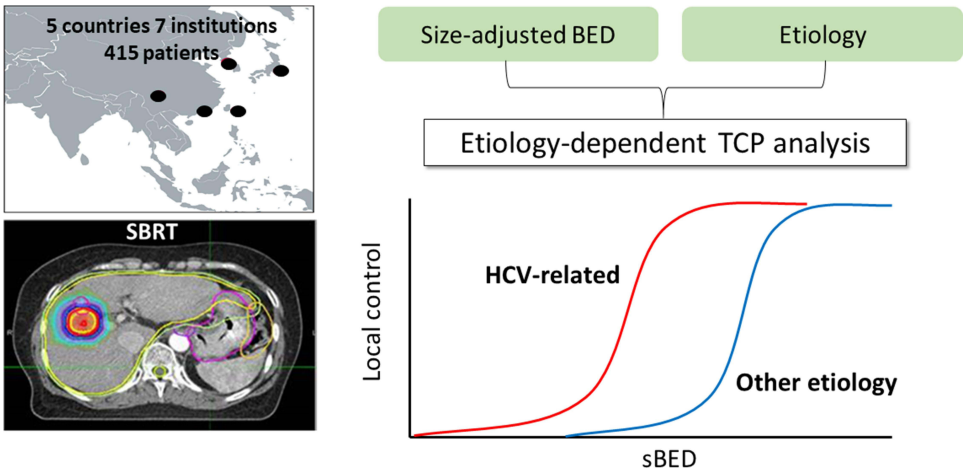
Graphical Abstract



a biologically effective dose (BED) above 100 Gy was associated with improved LC.[11] In that analysis, HCC etiology, characterized as hepatitis B or C virus infection compared to others, was not identified as a prognostic factor. More detailed analysis of predictors' tumor control probability (TCP) could further our understanding of SBRT efficacy and help clinicians balance the risks and benefits of various SBRT schedules.

Liver injury caused by chronic infection related to hepatitis B virus (HBV) or hepatitis C virus (HCV) accounts for 80% of HCC cases.[12] Overall, 2–5% of the patients with cirrhosis caused by HBV or HCV infection develop HCC annually. Various chemoprevention methods for decreasing the incidence of HCC in these patients, based on direct and indirect mechanisms which cause HBV-related or HCV-related HCC, have been investigated.[13,14] However, there are little data on the association between HCC etiologies and LC outcomes following SBRT.

Here, we perform a detailed analysis of predictors of LC following SBRT for HCC. Based on powerful associations between HCC etiology and LC, we present etiology-dependent TCP models.

Methods

Study Population

We retrospectively reviewed the data of 519 patients from seven institutions who were treated with SBRT between January 1, 2010 and December 31, 2016. Tumor with vascular invasion were excluded from the study because initial analyses demonstrated that vascular invasion was related to a high risk of local failure, with no evidence of a dose–response relationship when treating tumors with vascular invasion (Supplementary Figure 1). This study was performed in accordance with the provisions of the 1975 Declaration of Helsinki, which are ethical principles for medical research involving human subjects. Also, the study was approved by the Institutional Review Boards of every participating institution (Supplementary Table 1). The requirement for informed consent was waived due to the retrospective nature of the study. All confidential patient information is protected, and detailed information has been removed to ensure anonymity.

Stereotactic Body Radiation Therapy

Details about the techniques of SBRT used for the current cohort have been described previously.[7,11] In summary, either shallow breathing or breath holding was used for respiratory management. Gross tumor volume was defined in multi-phase contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Individualized dose pre-scriptions and pre-treatment image guidance were used for all patients. The planning target volume was covered by an

isodose of 70–95% with various SBRT planning techniques among institutions. Detailed information on prescription dose was summarized in Supplementary Table 2.

Follow-Up Evaluation

The primary study endpoint was local tumor progression, which was scored by the treating physicians based on serial imaging studies. Local tumor progression was defined based on the modified Response Evaluation Criteria in Solid Tumors. Contrast-enhanced lesions within the planning target volume observed in either dynamic contrast-enhanced CT (70.5%) or MRI (29.5%) were considered as tumor progression. Time to local tumor progression was defined from the date of SBRT initiation to the date of local failures or last follow-up.

TCP Modeling

First, the BED was calculated for each patient using a standard α/β ratio of 10 Gy. As in previous analyses examining outcomes following SBRT for lung cancer, size-adjusted BED (sBED) was defined as BED minus 10 times the maximal tumor diameter, in centimeters.[15,16] This variable was incorporated into a standard TCP model:

$$TCP = \frac{e^{[d-TCD50]/k}}{(1+e^{[d-TCD50]/k})}$$

d: sBED; TCD50: the dose required to achieve 50% tumor control; k: a fitting constant equal to 25 divided by the slope of the TCP curve at a dose equal to the TCD50.[17]

Patient data were sorted into four groups of equal size based on sBED, and the actuarial 2-year LC rate for each group was calculated. The TCP model was fitted to these data points using least-squares optimization. We utilized a bootstrap resampling method (5000 iterations) to characterize the distributions of model parameters and to formulate 95% confidence bounds for the TCP curve.[18] After statistical analyses demonstrated a powerful association between HCV etiology and LC, we conducted TCP modeling separately for patients with HCV versus patients with other HCC etiologies.

Statistical Analysis

The Pearson chi-squared or Fisher's exact test was used to compare categorical variables, along with the Mann–Whitney *U*-test for continuous variables stratified by HCV infection. LC rates were estimated using the Kaplan–Meier method. Univariable and multivariable Cox proportional hazards models were utilized to identify predictors of LC in the entire cohort and in patient subgroups. All analyses were performed using MATLAB (The Mathworks, Natick, MA, USA) and R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 415 patients met inclusion criteria for the current study. Patient, tumor, and treatment details are summarized in Table 1. The median age was 67 years (interquartile range [IQR], 59–76). The underlying liver diseases were HBV infection in 227 of the patients (54.7%) and HCV infection in 125 of the patients (30.1%). Regarding SBRT planning, the median gross tumor volume and planning target volume were 16.6 cm^3 (IQR, 3.9–50.2) and 52.2 cm^3 (IQR, 22.2–101.7), respectively. With a total dose of 48 Gy (IQR, 40.0–54.0), the median BED and sBED were 100 Gy (IQR, 80.0–116.0) and 70.0 Gy*cm (IQR, 46.0–92.5), respectively. There was no strong correlation among variables except for sBED, BED, and tumor size (Supplementary Figure 2).

After a median follow-up duration of 26.5 months (IQR, 14.7–43.7) following SBRT initiation for patients without local failure, 73 patients (17.6%) developed local failure. Median time to local progression for those patients was 9.1 months (IQR, 4.4–17.7). For all patients, the 2-year LC rate was 81.6% (95% confidence interval [CI], 77.5–85.8). In addition, the 2-year overall survival rate was 75.8% (95% CI, 71.4–80.4) and the median survival duration was 46.0 months (95% CI, 50.6–51.6, Supplementary Figure 3).

Univariate Cox proportional hazards models exploring predictors of LC are shown in Table 2. As expected, tumor size and BED were identified as potential predictors of LC. Unexpectedly, HCV infection was associated with a risk

Table 1 Patient and Tumor Characteristics

Variables		Total (N=415)
Age		67 [59–76]
ECOG PS	0	227 (54.7)
	1–2	188 (45.3)
Sex	Male	312 (75.2)
	Female	103 (24.8)
Etiology	HBV	227 (54.7)
	HCV	125 (30.1)
	Non-viral	63 (15.2)
ALBI score		−2.60 [−2.93 – −2.26]
ALBI grade	1	208 (50.1)
	2	198 (47.7)
	3	9 (2.2)
Previous treatment	Treatment-naïve	70 (16.9)
	Recurrent tumor	345 (83.1)
Number of previous treatments		2 [1–4]
Tumor size, cm		2.5 [1.5–3.9]
	≤3	261 (62.9)
	>3	154 (37.1)
Pre-treatment AFP, ng/mL		14.1 [4.9–102.0]
Gross tumor volume, cm^3		16.6 [3.9–50.2]
Planning target volume, cm^3		52.2 [22.2–101.7]
Total dose, Gy		48.0 [40.0–54.0]
Fractional dose, Gy		10.0 [8.0–12.0]
BED, Gy		100.0 [80.0–116.0]
sBED, Gy		70.0 [46.0–92.5]

Note: Values are presented as patient (%) or median [interquartile range].

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin–bilirubin score; AFP, alpha-fetoprotein; BED, biologically effective dose (α/β ratio of 10 is used for tumor control); sBED, size-adjusted biologically effective dose (defined as BED minus 10 times the tumor diameter in centimeters).

Table 2 Prognostic Factors for Local Control

		Univariable Analysis			Multivariable Analysis		
Variables	**(ref. vs)**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age	(continuous)	0.99	0.97–1.01	0.341			
ECOG PS	(0 vs 1–2)	1.60	1.01–2.53	0.046	1.53	0.96–2.44	0.076
Sex	(Male vs Female)	1.12	0.67–1.88	0.657			
Etiology	(HCV- vs HBV-related)	1.98	1.09–3.59	0.026	1.89	1.03–3.46	0.040
	(HCV-related vs Non-viral)	1.83	0.86–3.90	0.116	1.77	0.82–3.78	0.144
ALBI score	(continuous)	1.49	0.95–2.35	0.086			
Previous treatment	(Treatment-naïve vs Recurrent tumor)	1.22	0.64–2.33	0.536			
Pre-treatment AFP	(continuous, per doubling)	1.04	0.97–1.12	0.231			
Tumor size	(continuous)	1.14	1.04–1.26	0.005			
Tumor size	(≤3 vs >3 cm)	1.54	0.97–2.44	0.069			
BED	(≥100 vs <100 Gy)	2.22	1.34–3.69	0.002			
sBED	(≥70 vs <70 Gy)	2.12	1.30–3.46	0.003	2.23	1.36–3.64	0.001

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HCV, hepatitis C virus; AFP, alpha-fetoprotein; BED, biologically effective dose (α/β ratio of 10 is used for tumor control); sBED, size-adjusted biologically effective dose (defined as BED minus 10 times the tumor diameter in centimeters).

Table 3 Projected 2-Year Local Control Rates for Common Stereotactic Body Radiation Therapy (SBRT) Schedules and Selected Tumor Diameters, Based on Etiology of Hepatocellular Carcinoma

SBRT Schedule / Tumor Diameter	8 Gy × 6 Fractions		10 Gy × 5 Fractions		15 Gy × 4 Fractions	
	HCV-Related	Non-HCV-Related	HCV-Related	Non-HCV-Related	HCV-Related	Non-HCV-Related
2 cm	88%	75%	89%	78%	92%	86%
4 cm	85%	71%	87%	73%	91%	84%
6 cm	83%	66%	85%	69%	89%	80%

Abbreviation: HCV, hepatitis C virus.

reduction of nearly 50% compared to other HCC etiologies (HR compared to HBV = 0.52, 95% CI 0.04–0.96, p=0.036). Kaplan–Meier curves for LC for patients grouped by tumor size, BED, and HCC etiology are shown in Figure 1. The 2-year LC rate for patients with HCC etiology was 88%, compared to only 78% for other patients. Patient characteristics for etiology of HCC are detailed and compared in Supplementary Table 3. Although patients with HCV-related HCC were older, had decreased liver function, smaller tumor size, and target volume compared to those with non-HCV-related (either HBV-related or non-viral) HCC, there was no difference in sBED between two groups (median 70 Gy vs 73 Gy, p=0.334). In subsequent analysis based on underlying HCV infection status, sBED ≥70 Gy was related to LC in the HCV-related group and not in the non-HCV-related group (Supplementary Table 4).

Based on the powerful association between LC after SBRT and HCC etiology observed in our dataset, we performed TCP modeling separately for patients with HCV-related HCC and for other patients. In patients with HCV infection, our bootstrap resampling technique yielded median optimal values of 140 and −240 Gy for k and TCD50, respectively. In patients with other HCC etiologies, median optimal values of 70 for k and −10 Gy for TCD50 were obtained, suggesting that HCV-related HCC is associated with favorable LC and a flatter dose–response curve. TCP modeling results are depicted in Figure 2, with HCV infection conferring a 10–20% absolute increase in predicted LC across the range of SBRT doses and tumor sizes included in this dataset (Table 3).

Discussion

Using a large, multinational database, we detected a powerful and unexpected association between HCC etiology and LC following SBRT, with favorable outcomes observed in patients with HCV infection compared to other patients. HCV etiology was associated with approximately 50% relative risk reduction and 10–20% absolute risk reduction for local recurrence following SBRT. Our findings, if validated in other datasets, could have broad implications in the implementation of SBRT for HCC.

To our knowledge, this is the first report demonstrating an association between HCV infection and favorable LC following SBRT for HCC. Reasons why this relationship has not been identified previously could include limited sample sizes in published analyses of outcomes following SBRT for HCC, small subsets of patients with or without HCV in those series, and lack of adjustment for other important prognostic factors, such as tumor size and BED. In previous reports from our group, patients with HBV and HCV infection were grouped together, masking the association between HCV infection and favorable LC.[7,11] To put our findings into context, we reviewed data from the HyTEC analysis of outcomes following SBRT for liver tumors.[19] Four HCC studies reported prevalence of HCV infection,[20–23] and there appears to be an association between HCV prevalence and estimated 2-year LC rate (Figure 3).

In keeping with practice patterns as SBRT for HCC was established,[19,24] a wide range of SBRT schedules was utilized to treat patients in our dataset. We employed TCP modeling to visualize the relationship between SBRT parameters and likelihood of local disease control. Because hepatitis C infection was identified as a powerful favorable prognostic factor with respect to LC, we derived models separately for patients with HCV-related HCC and other patients, demonstrating a 10–20% absolute difference in predicted 2-year LC rate based on HCC etiology. Validation studies using other large

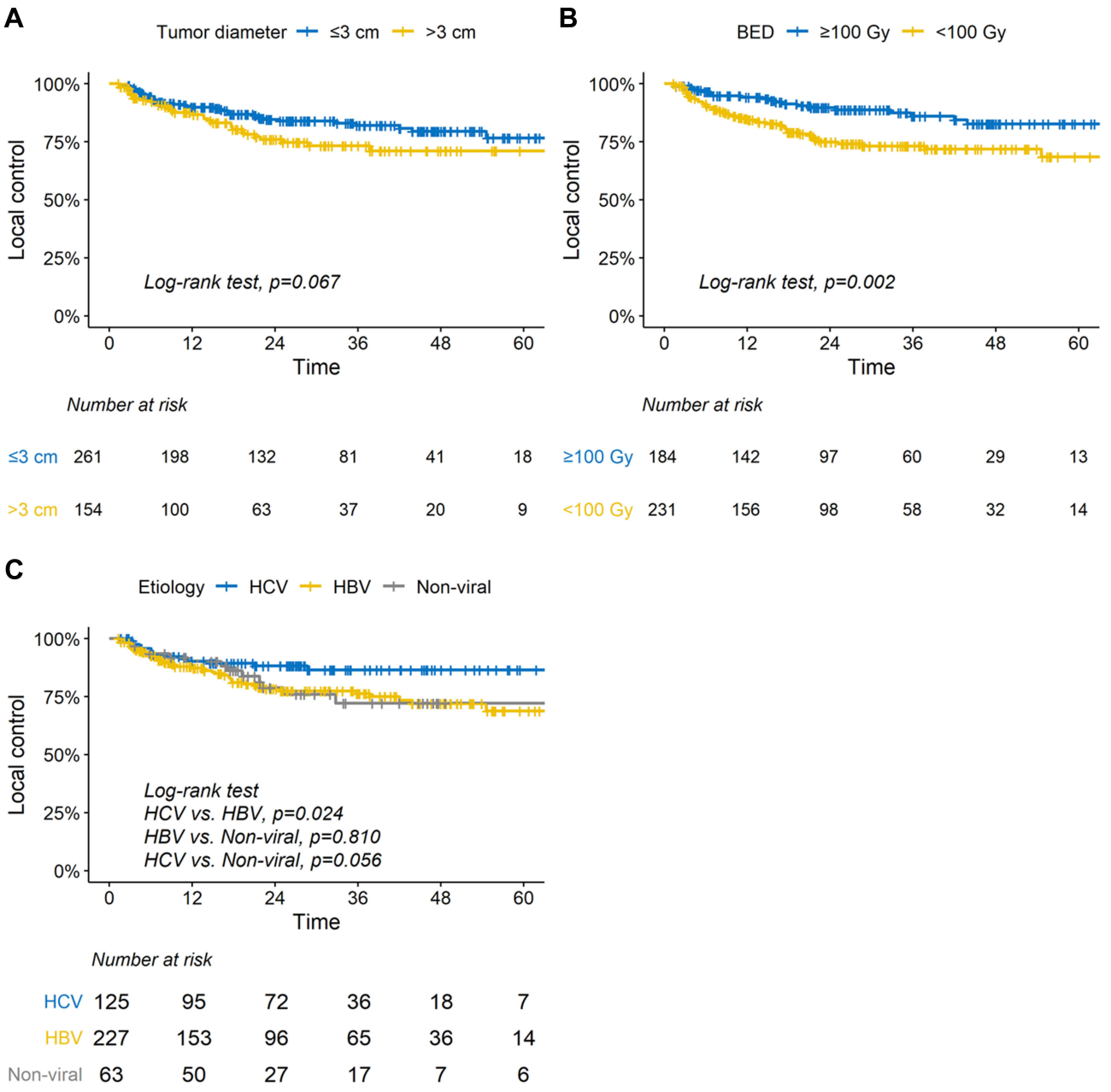


Figure 1 Kaplan–Meier curves for local tumor control following SBRT stratified by (**A**) tumor diameter, (**B**) biologically effective dose (BED), and (**C**) etiology.

datasets will be required to optimize our TCP model formulation, which was extrapolated from NSCLC SBRT series,[15,16] for characterizing outcomes following SBRT for HCC. Previous studies employing TCP modeling for HCC have been limited by small sample sizes (<100 patients).[21,25,26] If validated in additional cohorts, our etiology- and sBED-based TCP models may help clinicians in selecting patient-specific SBRT schedules to optimize the risk/benefit ratio.

HCV infection has not been established as a favorable prognostic factor in other HCC treatment settings. A meta-analysis of large studies employing sorafenib for treating advanced HCC did not indicate that hepatitis B or C infection influences treatment efficacy.[27] In a large series of patients treated with radiofrequency ablation for HCC, HCV infection was not associated with local disease control and was associated with reduced long-term survival rates.[28] A meta-analysis of nearly 5000 HCC patients who underwent surgery found that either HBV- or HCV-related HCC was a poor prognostic factor, and there was no difference in outcomes between HBV-related HCC and HCV-related HCC.[29] Integrative genomic analysis from the Cancer Genome Atlas Research Network has demonstrated that HCV-related HCC is associated with CDKN2A promoter

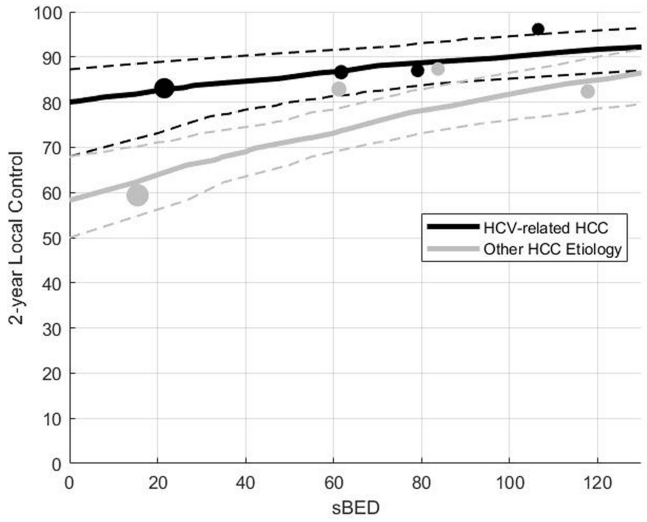


Figure 2 Tumor control probability modelling results for actuarial 2-year local control with size-adjusted biologically effective dose (sBED) for patients with hepatitis C virus (Black) and hepatitis B or non-viral etiology (grey).
Notes: Each circle represents the outcomes of tumors after sorting by sBED. Circle size is proportional to sample size. The solid curve depicts the results of model fitting using all available data. Dotted lines indicate 95% confidence intervals for tumor control probability as a function of sBED.
Abbreviation: sBED, size-adjusted biologically effective dose (calculated from BED minus 10 times the maximal tumor diameter (cm).

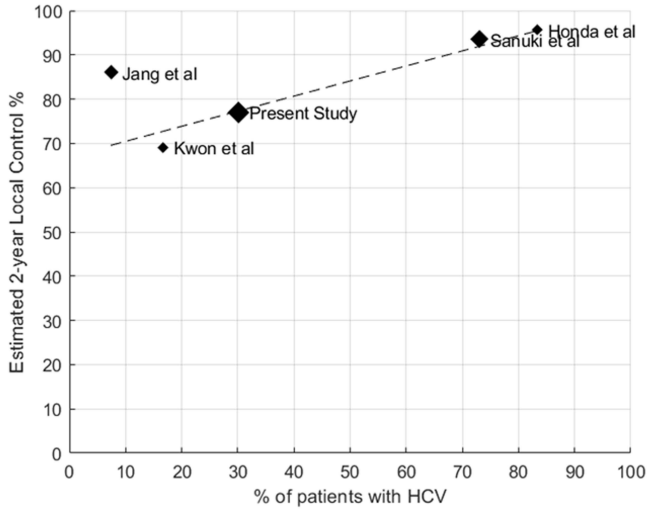


Figure 3 Scatter plot of 2-year actuarial local control rate versus percentage of patients with hepatitis C in studies included in the HyTEC analysis as well as in the present study. Marker sizes are proportional to study sample sizes. The dotted line depicts the results of weighted linear regression, excluding the present study.
Abbreviation: LC, local control.

silencing and TERT promoter mutations.[30] Furthermore, HCV-related HCC demonstrated better survival outcomes than non-viral or HBV-related HCC did when treated with atezolizumab with bevacizumab.[31] Recently, non-viral HCC, mostly related to non-alcoholic steatohepatitis, showed decreased immune response and survival outcomes after immune checkpoint inhibitor.[32,33] Considering the notion that large fractional dose of SBRT elicits immune-mediated cell death, improved LC outcomes of HCV-related HCC in the current cohort might stem from immune response.[34,35] These and other potential mechanisms for differential radiosensitivity among HCC patients warrant further study.

Limitations of our study include absence of central review for defining local failures and limited follow-up duration for many patients. As in most prior studies examining LC following SBRT and implementing TCP modeling, we did not formally account for the competing risk of mortality occurring before local disease recurrence in our statistical methods. This is the first report of TCP models using sBED in HCC. We found that current TCP as a function of sBED predicted

2-year LC more accurately than TCP as a function of BED in the current data (Supplementary Figure 4). As mentioned previously, the TCP model formulation used in this analysis was initially developed using NSCLC data, and validation studies are needed to validate its use in HCC and characterize optimal model parameters. In addition, further study with detailed information on etiology of HCC including not only viral-related but also non-alcoholic steatohepatitis could reveal the radiosensitivity according to the etiology of HCC.

In conclusion, we have identified a novel association between HCV infection and favorable LC outcomes following SBRT for HCC. Also, current etiology-dependent TCP modeling hypothetically provided the size-adjusted dose–response relationship according to HCV status in patients treated with SBRT. Our TCP models require further validation with an external dataset including multiple events to confirm its usefulness in clinical practice. We hope our TCP models could be used as a reference for decision-making by physicians before planning SBRT.

Abbreviations

BED, biologically effective dose; CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; LC, local control; MRI, magnetic resonance imaging; SBRT, stereotactic body radiation therapy; TCP, tumor control probability.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Nitin Ohri reports personal fees from Merck, personal fees from AstraZeneca, personal fees from Genentech, outside the submitted work. The authors report no other conflicts of interest in this work.

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