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A mid-treatment break and reassessment maintains tumor control and reduces toxicity in patients with hepatocellular carcinoma treated with stereotactic body radiation therapy

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Abstract

Background and purpose: Patients with hepatocellular carcinoma (HCC) commonly have underlying liver dysfunction with variable tolerance to liver stereotactic body radiation therapy (SBRT). We hypothesized that insertion of a 1-month mid-treatment break would allow us to adapt treatment to the individual patient response, thereby reducing toxicity without compromising local control (LC).

Materials and methods: We analyzed HCC patients receiving 3–5 fraction SBRT at our institution from 2005 to 2017. Over this time, patients were offered enrollment on prospective trials assessing individualized adaptive SBRT. Based on normal tissue complication probability and modeling of changes in liver function following a 1-month treatment break between fractions 3 and 4, patients could receive a total of 3 or 5 fractions. Patients not on trial received 3 or 5 fractions without a break. Toxicity was defined as a ≥2 point rise in Child–Pugh (CP) score within 6 months of SBRT.

Results: 178 patients were treated with SBRT to 263 HCCs. Median follow-up was 23 months. 86 treatments had a 1-month break. 1-Year LC was 95.4%; this was not different between patients treated with or without a break ($p = 0.14$). Controlling for tumor size and dose a break was not associated with inferior LC (HR: 0.58, 95%CI: 0.1–3.34, $p = 0.54$). 54 patients experienced a ≥2 point rise in CP score. Controlling for the number of prior liver directed therapies and mean liver dose, a treatment break reduced the odds of toxicity (OR: 0.42, 95% CI: 0.17–1.03, $p = 0.06$).

Conclusion: A one-month mid-treatment break and reassessment may reduce the odds of treatment related toxicity without compromising LC.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.07.027.

Keywords

Hepatocellular carcinoma; Stereotactic body radiation therapy; Local control; Toxicity

Stereotactic body radiation therapy (SBRT) is an effective treatment option for hepatocellular carcinoma (HCC) [1] with increasing utilization [2]. However, broad adoption has been limited over concerns regarding radiation induced liver toxicity [3,4], as many patients with HCC have underlying liver dysfunction secondary to cirrhosis and/or a history of prior liver directed therapies. While clinical features can aid in identifying patients at risk for toxicity [3], there remains significant variability and heterogeneity in an individual's tolerance to treatment which limits the ability to accurately predict which patients are at high risk for toxicity.

Our approach to mitigating this uncertainty in risk of toxicity has been to adapt treatment based on an individual's subclinical change in liver function in response to radiation. To achieve this, we have performed multiple consecutive prospective trials assessing the individual patient liver response to radiation through measurement of indocyanine green (ICG) retention [5]. ICG is exclusively cleared by the liver and excreted unchanged into bile, and as such, the rate of clearance provides a dynamic real-time assessment of liver function [6]. Early in our experience with ICG we discovered that increases in ICG retention, a direct indicator of worsening liver function, could be detected during treatment, with larger changes observed one-month post-treatment in patients who would eventually develop clinical manifestations of hepatotoxicity [7]. In an attempt to maximize the deliverable radiation dose and minimize the likelihood of toxicity, we began treating patients on trials in which patients received a 1-month treatment break and liver function re-evaluation following delivery of the first 60% of their planned total dose. Patients were most commonly planned to be treated with 5 fractions, and as such this 1-month break occurred between fractions 3 and 4. In this manner, we were able to assess individual's liver function in response to the initial portion of treatment, and then personalize any additional treatment after a 1-month break.

A potential shortcoming of this approach is that the 1-month treatment break may allow for tumor repopulation, and thereby result in inferior local control, particularly when compared to 5 consecutively delivered fractions. Furthermore, while our approach was conceptually designed to reduce toxicity, it is possible that any additional dose administered after the 1-month treatment break might increase the risk for treatment related toxicity. We, therefore, sought to assess the impact of a 1-month treatment break on tumor local control and treatment related toxicity, hypothesizing that when controlling for total delivered dose, the 1-month treatment break would decrease treatment related toxicity without loss of local control.

Methods and materials

Patient selection

Through an institutional review board approved analysis, we identified all patients with HCC treated with 3 or 5 fraction liver SBRT at our institution from 2005 to 2017. This resulted in 178 patients treated on 221 occasions to 263 total tumors. Patients were allowed to have received prior liver directed therapy. All patients had HCC confined to the liver or limited (<5 cm) and stable extrahepatic disease. Patients treated on trial were required to have an Eastern Cooperative Oncology Group score ≤ 2. There were no limitations based on liver function other than having a total bilirubin <3 mg/dL and no limitations based on tumor size or vascular invasion.

Treatment and follow-up

Since 2003, our department has offered patients with HCC enrollment on prospective trials utilizing ICG to assess liver function prior to treatment as well as to assess changes in liver function mid- and post-treatment (, ,), with details of our treatment approach previously described [5]. Briefly, for patients electing to enroll on trial, a pre-SBRT ICG retention rate at 15 minutes (ICG-15) was measured at baseline, and a five, equal-sized, fraction treatment plan was created based on a normal tissue complication probability (NTCP) [8] threshold of <15%. Patients then received 3 of the 5 planned fractions on alternating days followed by a treatment break. One month after completing the first 3 fractions, ICG-15 was again assessed, and the dose for the final two fractions was determined based on a model incorporating the baseline and change in ICG retention at 1 month such that there would be at least a 90% probability that the patients ICG-15 post-completion of all treatment would not increase above 44%, as described previously [9]. For those with baseline retention >44%, a level associated with liver toxicity in large surgical series [10], or at high-risk for exceeding this threshold with delivery of fractions 4 and 5, only the first 3 fractions were delivered, with the dose for these first three fractions determined by our NTCP model. Conversely, patients receiving 5 fractions could receive 5 fractions with the same dose per fraction or 5 fractions with a reduced dose for fractions 4 and 5. A schema of this approach is provided in Supplemental Fig. 1. Patients with contraindications to receiving an ICG infusion (such as an iodine contrast allergy) or those electing against enrolling on trial were treated with 3 or 5 fractions on alternating days without a break. Our approach to treatment planning and delivery has previously been described [5], with dose prescribed to the isodose surface covering 99.5% of the planning target volume, with allowance for under coverage to meet normal tissue constraints.

Patients were typically seen in follow-up 4–6 weeks following completion of their final SBRT fraction at which time liver function was again assessed. Patients were then seen at 3 months, and 6 months post-treatment with repeat abdominal imaging (CT and/or MRI), and then followed every 3–6 months thereafter.

Endpoints

Local control (LC) was defined as the time from completion of SBRT until local progression of the treated lesion as defined by modified response criteria in solid tumors (mRECIST)

[11]. Censoring for LC occurred at the earliest of the last hepatic scan, liver transplant, or initiation of systemic therapy. Treatment related toxicity was defined as a ≥2 point increase in Child–Pugh score within 6 months of completing SBRT.

Statistical analysis

Comparisons of baseline characteristics between patients treated with and without a treatment break were performed using generalized estimating equation models. Cox proportional hazards models were used to model LC. A multivariable model with the percentage of biologically effective dose (BED) delivered after a 1-month treatment break and total delivered BED was used to assess the effect of a 1-month treatment break on the risk of local progression. This covariate value ranged from 0% (3 or 5 fractions with no break) to 40% (5 equal-sized fractions with a break between fractions 3 and 4). LC analysis was performed at the lesion level and toxicity at the treatment course level with use of robust standard errors to account for correlation between multiple lesions treated in the same patient and correlation between patients treated at multiple times, respectively. BED calculations were performed assuming an $\alpha/\beta = 10$ Gy and were not time adjusted. A logistic regression model was used to identify predictors of toxicity. The liver dose metric utilized in the toxicity models was the Liver exclusive of GTV mean dose (linear–quadratic–linear). Multivariable model selection was conducted using stepwise backward selection based on Akaike information criterion (AIC). We also used B-spline basis functions to model its relation to LC more flexibly without assuming either a linear or threshold effect.

We repeated both LC and toxicity analyses using a propensity score analysis with an inverse probability treatment weighting (IPTW) [12,13]. This approach allows for a reduction of bias in the estimate of treatment effect in the setting of non-randomized treatment decisions. Patients with a Child–Pugh score ≥10 were excluded from this approach given the very small number of these patients. The probability (propensity) of receiving a treatment break was estimated from a multivariable logistic regression model as a function of gender, age at the time of treatment, presence of cirrhosis, portal vein thrombosis, number of prior liver directed therapies, tumor size, total BED delivered, hepatitis status, and baseline Child–Pugh score. Patient specific weights were then calculated as the inverse probability of being treated with their actual treatment break status. A Cox model with IPTWs was fit to compare the local control between the break and no break patients, and a logistic regression model with IPTWs was fit to assess the effect of a treatment break on toxicity. Statistical significance was evaluated at the 95% confidence level and all analyses were completed using R software version 3.3.3.

Results

Patient, tumor, and treatment characteristics

One-hundred and seventy-eight patients were treated with SBRT on 221 occasions to 263 HCCs. Median follow-up for all patients was 23 months. Table 1 displays baseline patient, tumor, and treatment related characteristics for all treatments, as well as for those delivered with or without a 1-month treatment break. In total 135 were given with 3 fractions only or 5

fractions without a 1-month treatment break (no treatment break group) and 86 were delivered with 5 fractions with a 1-month treatment break (treatment break group).

Local control

Nine HCCs demonstrated local progression. The estimated LC for all treated lesions at 1 and 2 years was 95.4% (95% CI: 91.8–99.2%) and 89.5% (95% CI: 82.4–97.3%), respectively (Fig. 1a). When comparing patients treated with and without a 1-month treatment break (Fig. 1b), patients treated with a break had numerically higher rates of LC at 1 and 2-years post-SBRT (98% vs 93%, and 93% vs 84%, respectively), but this difference was not statistically different (HR: 0.34, 95% CI: 0.07–1.51, $p = 0.15$). On univariate analysis of LC (Table 2), achieving a treatment BED ≥80 Gy was the only variable significantly associated with improved LC (HR: 0.16, 95% CI: 0.04–0.61, $p = 0.01$). Patients receiving a BED <80 Gy had 1 and 2-year rates of local control of 93% and 82%, respectively. Fig. 2 demonstrates the relationship between total BED delivered and estimated 1-year LC probability from a univariate model for LC. A total BED of 80 Gy was associated with a predicted 1-year LC of 95.4% (95%CI: 91.2–99.8%), with slight improvement in expected LC at a total of 100 Gy (97.5%, 95%CI: 94.3–100%).

We next sought to further assess the impact of a 1-month treatment break. Fig. 3a demonstrates the relationship between the percentage of BED received after a 1-month break, total BED delivered, and whether a tumor developed local progression, with the majority of progressions occurring in patients not receiving a treatment break. In a multivariate model controlling for the total BED delivered (Table 2), the percentage of total BED received after a 1-month treatment break was not associated with inferior LC (40% vs. 0% of total BED received after a 1-month break: [HR: 0.61, 95% CI: 0.15–2.45, $p = 0.48$]).

As a treatment break was not randomly assigned, we repeated analysis using IPTWs. After propensity weighting, baseline characteristics for patients treated with and without a treatment break were well balanced (Supplemental Table 1). In a weighted analysis controlling for total BED and tumor size, a treatment break was not associated with an increased risk of local progression (HR: 0.35, 95% CI: 0.06–2.08, $p = 0.25$) (Supplemental Table 2).

Treatment related toxicity

We next sought to evaluate the impact of a 1-month treatment break on the risk of treatment related toxicity. In total, 54 patients (27%) experienced a ≥2 point rise in their Child–Pugh score within 6 months following SBRT. Forty-nine patients had a 1-point increase, 85 had no change, and 9 had an improvement in score of 1 point. Thirty six percent of patients receiving only three fractions secondary to worsening liver function developed treatment related toxicity compared to 21% of patients who went on to receive fractions 4 and 5, although this difference was not statistically different (OR: 0.46, 95% CI: 0.16–1.34, $p = 0.14$). Patients only receiving 3 fractions were more likely to have cirrhosis, a greater number of prior liver directed therapies, and higher Child Pugh scores (all $p < 0.05$).

Fig. 3b demonstrates the relationship between the percentage of BED received after a 1-month break, mean liver dose, and whether a patient experienced toxicity, with toxicity

occurring more frequently in patients treated without a treatment break. On univariate analysis (Table 3) there were no covariates significantly associated with an increased probability of treatment related toxicity. In multivariable analysis (Table 3), controlling for the number of prior liver directed therapies and mean liver dose the odds of toxicity decreased by a factor of 0.42 for those receiving 40% of their total BED after a 1-month treatment break (OR: 0.42, 95% CI: 0.17–1.03, $p = 0.06$), which was marginally statistical significant.

Analysis of toxicity was then repeated with an IPTW approach (Supplemental Table 3). In an IPTW logistic regression model controlling for the number of prior liver-directed therapies, and mean liver dose, receipt of a break was associated with a decreased risk of treatment related toxicity (OR: 0.35, 95% CI: 0.13–0.92, $p = 0.03$).

Discussion

We have found that a one-month mid-treatment break and reassessment did not lead to a loss of local control, but did appear to decrease the risk of toxicity in patients with HCC treated with SBRT. Controlling for the total BED delivered, a 1-month treatment break was not associated with inferior local control. Although approximately 30% of our patients had a Child–Pugh score of B or higher, only 27% percent of patients developed a ≥2 point rise in their Child–Pugh score within 6 months of completing SBRT. Controlling for the mean liver dose and number of prior liver directed therapies, a 1-month treatment break and reassessment reduced the odds of a ≥2 point increase in Child–Pugh score by greater than half (OR: 0.42). These results were replicated using an IPTW approach. These findings suggest that adapting treatment to the individual patient response may allow for maintaining high local control rates while decreasing the risk of toxicity compared to a population based approach.

At first, our finding that a 1-month treatment break did not impair local control may seem counterintuitive to radiobiologic principles as one would expect increasing treatment duration to result in a decrease in the total BED delivered [14]. While we noted improved local control with cumulative non-time adjusted BEDs greater than 80 Gy, our modeled predicted probability of 1-year local control for 3 equal fractions of 10 Gy, a total BED of 60 Gy ($\alpha/\beta = 10$ Gy), was greater than 80%. Similarly, the median prescribed dose in the largest prospective trial of SBRT for HCC, from the Princess Margret Hospital, was 36 Gy delivered in 6 fractions, which is a BED of 57.6 Gy ($\alpha/\beta = 10$ Gy), and this resulted in 87% 1-year local control [15]. Our overall rates of local control at 1- and 2-years post-treatment of 95% and 90% are also consistent with other modern series of SBRT for HCC [16–19]. Thus, it is likely that the near-ablative dose delivered with the first three fractions of SBRT in our patients receiving a 1-month treatment break provided sufficient tumor control to prevent significant tumor repopulation over a 1-month span.

Insertion of a 1-month treatment break with reassessment was associated with a greater than a 50% reduction in the odds of developing a 2+ rise in Child–Pugh, and our rate of toxicity compares favorably to those reported in the literature. Culleton et al. reported a 2+ rise in Child–Pugh score in 63% of patients with Child Pugh B or C disease [4], although some of

this difference in toxicity rates is likely explained by smaller tumor sizes and corresponding mean liver doses in our analysis. Similarly, when assessing this same definition of toxicity in patients with Child–Pugh A disease prospectively treated at the Princess Margaret Cancer Centre, 26% of patients of Child–Pugh A patients had a 2+ rise in their Child–Pugh score 3 months following SBRT. Although again our average tumor size and mean liver dose were less than that in the Princess Margaret experience, we considered rises in Child–Pugh score out to 6 months post-treatment as treatment related toxicity, thereby increasing the number of toxicity events observed in our analysis. Toesca et al. reported a 37.5% rate of a 2+ increase in Child–Pugh score within 1-year of SBRT in a cohort of 40 patients with HCC (median tumor size 5.1 cm), with 30% having documented Child–Pugh B disease [20]. While direct comparison to these series is limited by different tumor sizes, extent of underlying liver disease, and SBRT doses, our overall rate of treatment related toxicity of 27% appears to be less than anticipated given that nearly a third of our patients had a baseline Child–Pugh score of B or C, favoring our personalized adaptive approach.

Our analyses are not without limitation. This was a retrospective comparison, in that the use of ICG for treatment guidance was not randomly assigned, and as such, unknown confounders likely exist between patients treated with and without the use of ICG. In general, however, we tended to use ICG for patients with larger tumors and poorer liver function, which might tend to produce the opposite result to the one we observed. We further attempted to limit the bias associated with non-randomized treatment assignment by performing propensity score analyses with IPTW; however, it is likely that some bias remains given the retrospective nature of our analysis and non-randomized treatment assignment, and our findings should be interpreted with this in mind. Second, the extra effort required to use ICG could limit the implementation of our findings. We are conducting an analysis to determine if we can replace ICG with the Albumin Bilirubin score [21], which would facilitate broader adoption of our treatment method [21]. Additionally, only 12 patients received a total BED <50 Gy, so caution should be taken when interpreting our modeling of local control below total BEDs less than 50 Gy. Lastly, patient reported outcomes were not collected, and future work should incorporate both toxicity assessment and quality of life, as patient reported quality of life following liver SBRT has been shown to be associated with overall survival [22].

While our approach has allowed us to reduce the odds of treatment related liver decompensation, some patients receiving a 1-month treatment break still experience toxicity, and as such, incorporation of additional global and regional markers of liver function and response to SBRT will likely further decrease the incidence of toxicity. We have found that high serum levels of hepatocyte growth factor following a 1-month treatment break predicts subsequent liver toxicity, even in patients with normal tissue complication probabilities <1% [23,24], which has been confirmed by others [25]. Similarly, incorporation of mid-treatment increases in TGF-β1 can improve estimates of expected NTCP risk compared to dose-only models [26]. We have also found that gadoxetic acid-MRI can provide accurate assessment of regional liver function [27]. Incorporation of these global and regional assessments of liver function may improve our ability individualize treatment and reduce toxicity. Finally, moving forward, we plan to incorporate a utility based approach weighing the balance between improvements in local control from approximately 80% achieved with 3 fractions

only, to greater than 95% when additional dose is delivered with fractions 4 and 5, versus the increased risk of toxicity associated with delivering additional dose [28].

In conclusion, we demonstrate that insertion of a 1-month mid-treatment break with reassessment in patients with HCC appears to reduce the risk of treatment related toxicity without resulting in inferior local control. The probability of toxicity is reduced as the 1-month break allows for assessment of an individual's response to radiation therapy and thereby allows for dose reduction in patients with a subclinical decline in hepatic function following the first portion of treatment. Local control was not impaired by a 1-month break as the near-ablative doses delivered in the first three fractions are sufficient to provide 1-year local control in approximately 80% of patients. Our continuing efforts to develop an individualized adaptive approach should allow us to maximize local control while minimizing toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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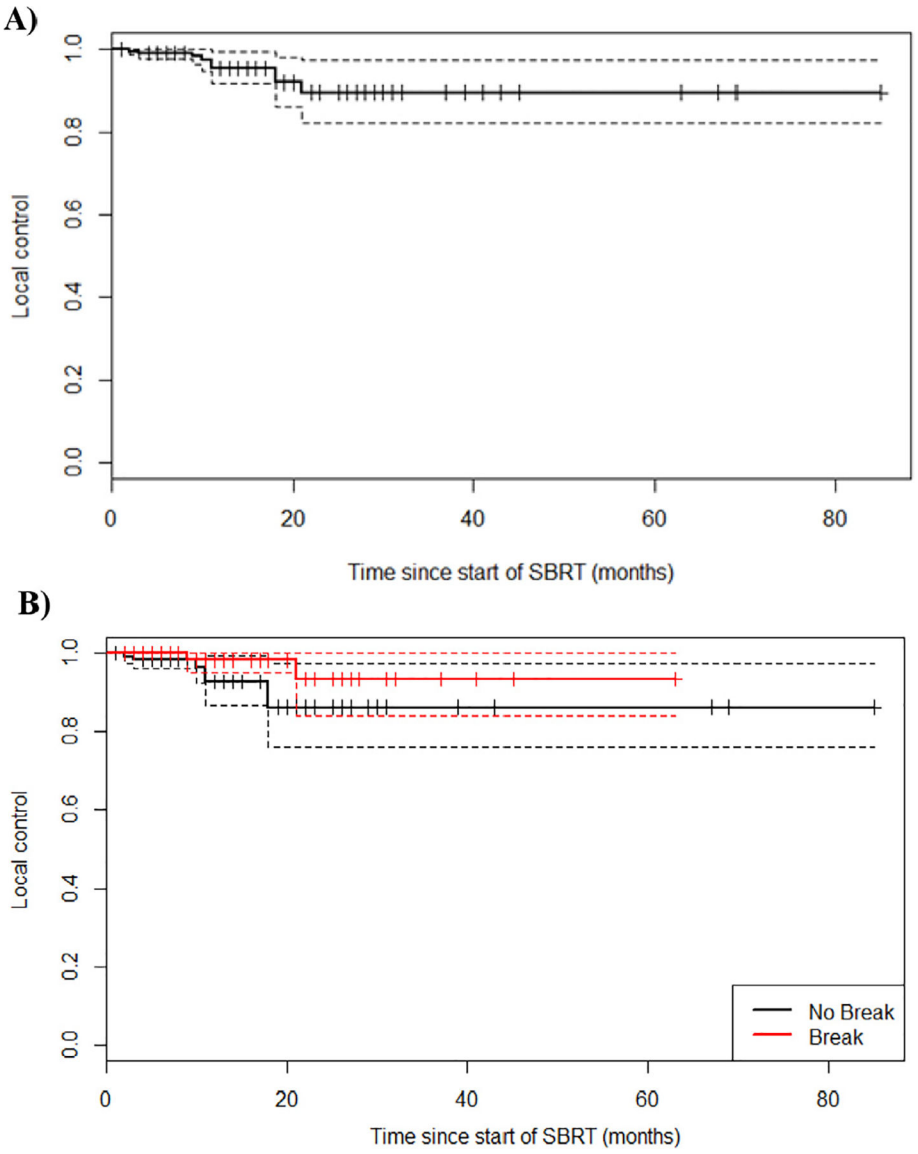


Fig. 1.

Local control following liver SBRT for (A) all patients and (B) for patients treated with and without a 1-month treatment break.

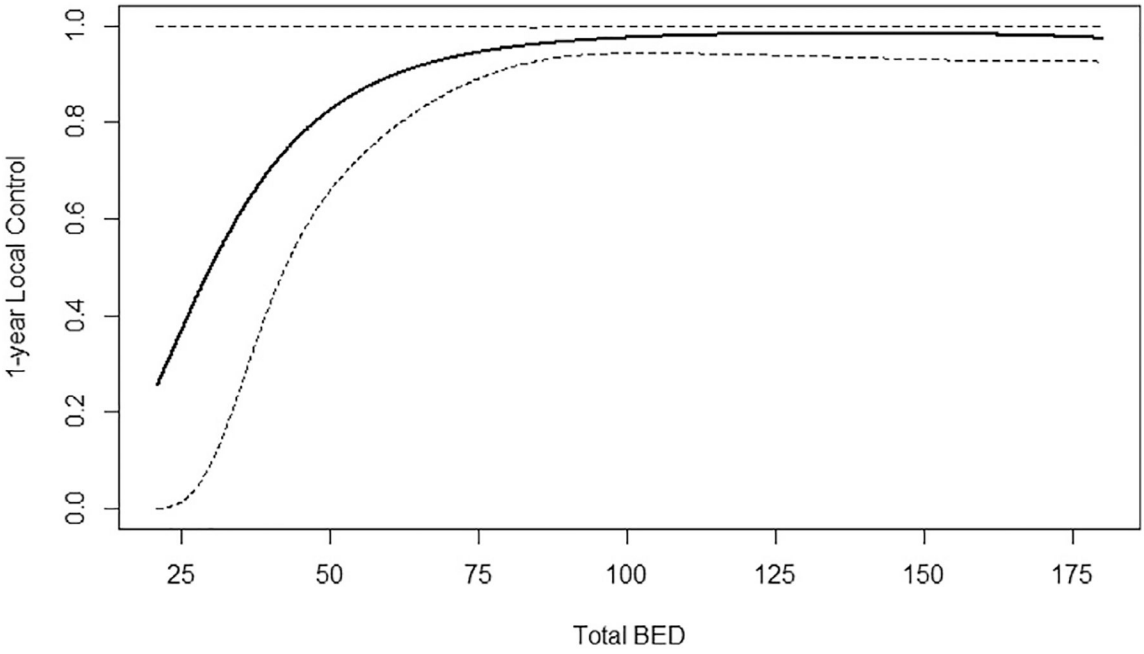
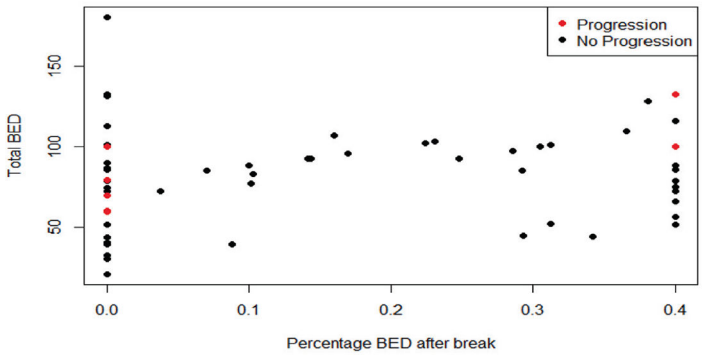


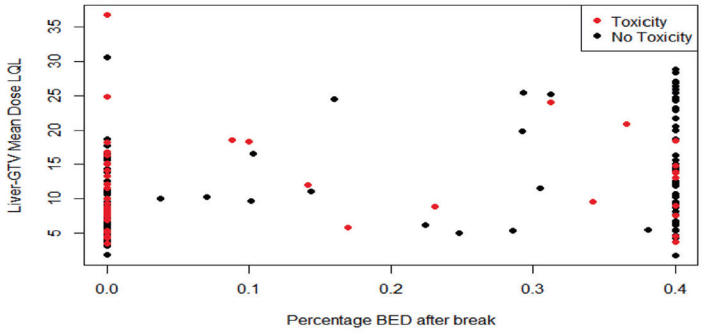
Fig. 2.
Probability of local control 1-year post-SBRT as a function of total BED delivered.

A)



% BED after break	0-0.1	0.1-0.2	0.2-0.3	0.3-0.4
Progression (n)	7	0	0	2
No progression (n)	127	3	8	77
Missing (n)	24	1	0	14

B)



% BED after break	0-0.1	0.1-0.2	0.2-0.3	0.3-0.4
Toxicity (n)	39	2	1	12
No toxicity (n)	82	2	6	53
Missing (n)	20	0	0	4

Fig. 3.

Local progression (A) and toxicity (B) as functions of SBRT dose (total BED) versus percentage of dose delivered after a 1-month treatment break.

Table 1

Baseline patient, tumor, and treatment characteristics (n = 221 hepatocellular carcinoma treatments).

	All (n = 221)	**No break (n = 135)**	**Break (n = 86)**	***P*-value**
Median age at SBRT (IQR)	64.8 (59.2–73.1)	64.5 (59.0–71.5)	66 (60.1–76.5)	0.17
Gender				
Male	175 (79.2%)	111 (82.2%)	64 (74.4%)	0.21
Female	46 (20.8%)	24 (17.8%)	22 (25.6%)	
Cirrhosis				
Yes	189 (85.5%)	120 (88.9%)	69 (80.2%)	0.11
No	32 (14.5%)	15 (11.1%)	17 (19.8%)	
Portal Vein Tumor Thrombosis				
Yes	38 (17.2%)	19 (14.1%)	19 (77.9%)	0.15
No	183 (82.8%)	116 (85.9%)	67 (22.1%)	
Median number of prior liver-directed therapies (IQR)	1.0 (0–3)	1.0 (0–2.5)	2.0 (0–3)	0.64
Baseline Child-Pugh score (pre-SBRT)				
A				
5	86 (38.9%)	36 (26.7%)	50 (58.1%)	<0.001
6	63 (28.5%)	39 (28.9%)	24 (27.9%)	
B				
7	25 (11.3%)	19 (14.1%)	6 (7.0%)	
8	22 (10.0%)	18 (13.3%)	4 (4.7%)	
9	13 (5.9%)	12 (8.9%)	1 (1.2%)	
C				
10	5 (2.3%)	5 (3.7%)	0	
11	1 (0.5%)	1 (0.7%)	0	
Unknown	6 (2.7%)	5 (3.7%)	1 (1.2%)	
Median Total Tumor size (IQR)	2.6 (1.8–4.1)	2.4 (1.6–3.5)	3.1 (2.1–5.5)	0.003
Median total BED (IQR)	79.2 (69.3–100.0)	74.2 (60.0–89.7)	100 (89.3–116)	<0.001
Median Mean Liver exclusive of GTV mean dose LQL (IQR)	10.4 (6.4–15.1)	8.4 (5.4–14.2)	13.1 (8.9–19.9)	<0.001
Treatment group				
3 fractions with high baseline ICG or no ICG assessment	85 (38.5%)	85 (63.0%)	0	

	All (*n* = 221)	No break (*n* = 135)	Break (*n* = 86)	*P*-value
3 fractions with large change in ICG preventing fractions 4 and 5	23 (10.4%)	23 (17.0%)	0	
5 fractions with no break (consecutive)	27 (12.2%)	27 (20.0%)	0	
5 fractions with a break with reduced dose for fractions 4 and 5	22 (10.0%)	0	22 (25.6%)	
5 fractions with a break with the same dose for fractions 1–5	64 (29.0%)	0	64 (74.4%)	

Abbreviations: SBRT = stereotactic body radiation therapy, IQR = interquartile range, BED = biologically equivalent dose, LQL = linear quadratic linear, ICG = indocyanine green.

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Table 2

Local progression univariate and multivariable analysis.

Variable	Univariate analysis			Multivariable analysis			Multivariable analysis		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Gender (female vs. male)	1.11	(0.22, 5.68)	0.90						
Age at SBRT	1.01	(0.96, 1.06)	0.69						
Portal vein tumor thrombosis	0.68	(0.08, 6.09)	0.73						
Number of prior liver-directed therapies	1.30	(0.88, 1.93)	0.19						
Tumor size (cm)	1.04	(0.89, 1.23)	0.62				1.02	(0.81, 1.29)	0.85
GTV (cm^3)	0.998	(0.994, 1.00)	0.35						
PTV (cm^3)	0.996	(0.99,1.01)	0.49						
Cirrhosis	2.06	(0.26, 16.5)	0.50						
Type of liver disease (HCV vs. other)	0.65	(0.16, 2.60)	0.54						
Total dose (Gy)	0.93	(0.85, 1.02)	0.14						
BED	0.97	(0.93, 1.01)	0.16	0.97	(0.93, 1.02)	0.21	0.97	(0.93, 1.02)	0.26
BED ≥80 Gy (vs. <80 Gy)	0.16	(0.04, 0.61)	0.01						
% BED delivered after break (40% vs. 0)				0.61	(0.15, 2.45)	0.48	0.58	(0.10, 3.34)	0.54

Abbreviations: SBRT = stereotactic body radiation therapy, GTV = gross tumor volume, PTV = planning tumor volume, HCV = hepatitis C virus, Gy = Gray, BED = biologically equivalent dose.

Table 3

Toxicity univariate and multivariable analysis.

Variable	univariate analysis			Multivariable Analysis		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Gender (Female vs. Male)	1.89	(0.87, 4.13)	0.11			
Age at SBRT	1.01	(0.98, 1.04)	0.50			
Portal Vein Tumor Thrombosis	1.04	(0.44, 2.49)	0.92			
Number of prior liver-directed therapies	0.87	(0.74, 1.04)	0.14	0.85	(0.70, 1.02)	0.08
Cirrhosis	2.76	(0.80, 9.54)	0.11			
Type of liver disease (HCV vs. Other)	1.35	(0.68, 2.71)	0.39			
Baseline Child-Pugh Score	0.95	(0.74, 1.21)	0.67			
Tumor size	1.08	(0.95, 1.22)	0.23			
Mean liver dose (Gy)				1.02	(0.96, 1.09)	0.53
% BED delivered after break (40% vs. 0)				0.42	(0.17, 1.03)	0.06

Abbreviations: SBRT = stereotactic body radiation therapy, HCV = hepatitis C virus, Gy = Gray, BED = biologically equivalent dose.