Radiofrequency Ablation Duration per Tumor Volume May Correlate with Overall Survival in Solitary Hepatocellular Carcinoma Patients Treated with Radiofrequency Ablation Plus Lyso-Thermosensitive Liposomal Doxorubicin

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ABSTRACT

Purpose: To determine whether burn time per tumor volume (BPV) (min/mL), where burn time is the total time during which radiofrequency (RF) energy is being applied, is correlated with hepatocellular carcinoma (HCC) treatment outcomes using RF ablation and lyso-thermosensitive liposomal doxorubicin (LTLD).

Materials and Methods: The HEAT study was a double-blind, randomized controlled phase III trial of RF ablation only versus RF ablation + LTLD in patients with HCCs 3–7 cm in diameter. Effect of BPV on progression-free survival and overall survival (OS) was analyzed.

Results: BPV demonstrated statistically significant differences between study groups for OS ($P = .038$, hazard ratio [HR] = 0.85), but not for progression-free survival ($P = .389$, HR = 1.059). In a separate analysis, treatment groups were independently analyzed to determine the effect of BPV within each individual group. OS improved as BPV increased for patients receiving RF ablation + LTLD ($P = .017$, HR = 0.836, confidence interval [0.722, 0.968]). This same association was not observed in patients receiving RF ablation only ($P = .57$, HR = 0.99).

Conclusions: BPV may be a useful metric for RF ablation + LTLD combination therapy for solitary HCC. The analysis suggested that the burn time for the tumor needs to be adjusted depending on the tumor volume. Because this is a post hoc study, the results are only suggestive and need to be confirmed with prospective studies.

ABBREVIATIONS

BPD = burn time per longest diameter, BPV = burn time per tumor volume, HCC = hepatocellular carcinoma, HR = hazard ratio, LTLD = lyso-thermosensitive liposomal doxorubicin, OS = overall survival, PFS = progression-free survival, RF = radiofrequency, TG = treatment group

Radiofrequency (RF) ablation has been widely used for unresectable hepatocellular carcinoma (HCC), but the application of RF ablation to tumors > 3 cm in diameter has not been as successful owing to technical limitations in creating a large enough treatment volume. This limitation results in incomplete treatment for tumors > 3 cm (1–6). Recurrence at

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the treatment margin suggests untreated residual microscopic disease beyond the ablation zone. Efforts to address tumor relapse resulting from undertreated margins have included alternative treatment methods, such as microwave ablation (7,8), or combining RF ablation with an adjunctive therapy, such as saline injection (9) or intravenous liposomal encapsulated doxorubicin. Lyso-thermosensitive liposomal doxorubicin (LTLD) (ThermoDox; Celsion Corp., Lawrenceville, New Jersey) was developed to release doxorubicin at temperatures $> 40°C$, which can potentially be used to deploy doxorubicin at the tumor margins during RF ablation. This synergistic combination of LTLD and RF ablation could possibly address RF ablation failure and disease recurrence on the tumor margins by depositing doxorubicin where it may be most beneficial. The safety and feasibility of combined systemic injection of LTLD and application of RF ablation (RF ablation + LTLD) have been shown in a phase I dose-escalation study for unresectable liver tumors (2).

More recently, a phase III HEAT study was completed that aimed to show efficacy of RF ablation + LTLD for liver tumors with diameters between 3 and 7 cm. The study found no significant difference between the outcomes of groups receiving RF ablation only or receiving RF ablation + LTLD in terms of progression-free survival (PFS) (primary endpoint) and overall survival (OS) (secondary endpoint) (10). An initial post hoc subgroup analysis of 285 patients with a single tumor and dwell time (duration between needle-in and needle-out) > 45 minutes showed OS of patients receiving RF ablation + LTLD was improved compared with patients receiving RF ablation only (10). However, this dwell time included not only treatment burn time but also time for needle repositioning, which was not directly or mechanistically related to treatment efficiency. The primary mechanism for drug delivery with LTLD relies on rapid intravascular drug release from the liposomes while they are in circulation; this increases the intravascular drug concentration within the heated volume, which facilitates drug delivery across vessel walls through Fickian diffusion (11). To take best advantage of this formulation, it is necessary to deliver thermal ablation while the drug is circulating. Pharmacokinetic modeling of this drug suggests that applying thermal ablation during the period of time in which drug concentration is highest would maximize tissue drug deposition, provided that the thermal ablation were active for a prolonged and continuous duration before the serum drug levels declined (2). In this study, it was hypothesized that the burn time (ie, ablation duration, RF ablation energy "on") together with tumor volume plays an important role in the treatment of the HCC using RF ablation + LTLD. To test this hypothesis, HEAT study data were further analyzed retrospectively.

MATERIALS AND METHODS

Patient Population

In this post hoc study, data from the phase III HEAT study of LTLD were analyzed. The original double-blind, randomized controlled study compared RF ablation only versus RF ablation + LTLD in patients with HCC (10). Each participating site obtained approval by the institutional review board. The original trial included 701 patients with single or multiple HCCs between 3 and 7 cm in diameter (10). Owing to the nature of the LTLD pharmacokinetics and procedural variability (12), only data from patients with single tumors were analyzed in this study (n = 210 patients who received RF ablation only vs. n = 227 patients who received RF ablation + LTLD). The mean ± SD number of overlapping ablations was 3.69 ± 3.45. A univariate and multivariate Cox proportional hazard model was used to investigate the effect of burn time per tumor volume (BPV) (min/mL), where burn time is the total time during which RF energy is being applied, and tumor diameter on PFS and OS. Volume measurements (mL) were determined by outlining the tumor area in each computed tomography slice, multiplying by the slice thickness, and summing the values. Two radiologists from an independent contract research organization each measured tumor volumes. The average of the 2 values was used as the pretreatment tumor volume.

Statistical Analysis

To analyze the association between BPV and OS of the 2 treatment groups (TGs), hazard ratios (HRs) for different threshold values of BPV were calculated using RStudio (13). Also, Kaplan-Meier curves were plotted for 2 different BPV threshold values as examples. A Cox proportional hazards model of RStudio was used on 2 separate outcomes: OS and PFS (13). TGs (RF ablation only and RF ablation + LTLD), BPV, and burn time per tumor diameter were individually analyzed as input covariates using a simple Cox proportional hazard model. In addition, interaction of TG with BPV and tumor diameter was also tested in the complex multicovariate Cox proportional hazard model. To test Cox proportionality, Schoenfeld residuals were used to check nonzero slope, which indicates proportional hazard assumption is violated (14).

RESULTS

The volume measurements for the RF ablation only and RF ablation + LTLD groups (mean ± SD) were 35.3 mL ± 40.0 and 35.5 mL ± 38.5, respectively, with an average absolute measurement difference of 16.34%. Average burn times for TGs were not significantly different: 52.01 minutes versus 49.71 minutes for patients receiving RF ablation only versus patients receiving RF ablation + LTLD (2-sample t test h = 0, $P = .3927$, confidence interval [−8.30, 3.27]). In addition, burn time was plotted against tumor volume and tumor largest diameter (**Fig 1a, b**). The data were highly scattered and were analyzed further for association. The results indicated a quadratic relationship between tumor volume and burn time, as evidenced by the P value of the regression coefficients of tumor volume ($P < .0001$) and tumor volume squared ($P = .0088$). Similarly, burn time and tumor largest diameter were analyzed, and the results indicated a linear relationship between tumor largest diameter and burn time, as evidenced by the P value of the

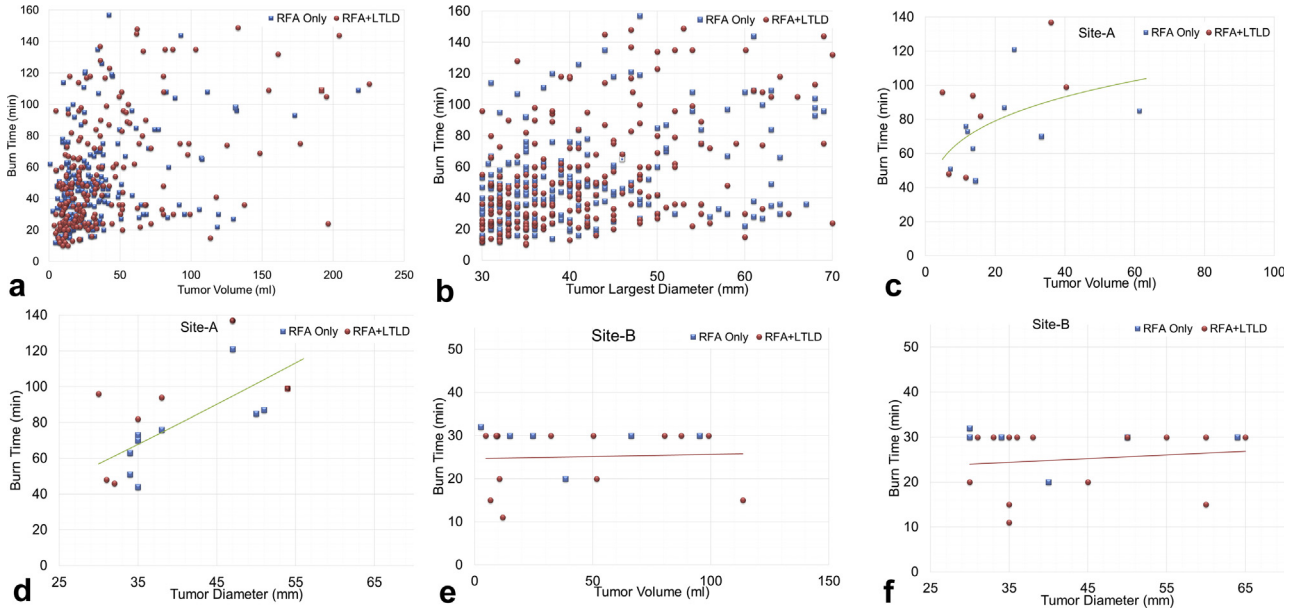

Figure 1. **(a–f)** Burn time versus tumor volume and tumor largest diameter. Aggregated data for burn time versus tumor volume **(a)** and tumor largest diameter **(b)** are highly scattered. There was a quadratic relationship between burn time and tumor volume and a linear relationship between burn time and tumor greatest diameter. Two sample sites showing burn time versus tumor volume **(c, e)** and burn time versus tumor diameter **(d, f)** with trend lines are shown. The first site **(c, d)** has an increasing burn time with both tumor volume and diameter. The relationship is linear for the diameter. In contrast, the second site has constant burn time without regard to increasing volume or diameter. RFA = RF ablation.

regression coefficient of largest tumor diameter ($P < .0001$). The P value for tumor largest diameter squared was $P = .1868$.

Each study site was examined individually to better understand their RF ablation treatment strategies and how operators were adjusting burn time depending on the tumor size. Results for burn time versus tumor volume and burn time versus tumor diameter from 2 different sites are shown as examples. The first site shows a trend in which the burn time increased as the tumor volume or diameter increased (Fig 1c, d). In contrast, the second site represents a site where burn time did not change as tumor diameter or volume increased (Fig 1e, f). Certain sites and certain operators demonstrated variability in terms of how and whether they adjusted the treatment times according to target tumor volumes. This practice pattern was measured and displayed using the graphic display, as a site-specific or operator-specific practice pattern plot.

To avoid the unintended effect of the dissociated tumor volume and burn time covariates, BPV was suggested as a new parameter to use in the statistical analysis. Average BPV for TGs was not significantly different: 2.31 min/mL vs 2.42 min/mL for patients receiving RF ablation only and patients receiving RF ablation + LTLD (2-sample t test h = 0, $P = .55$, confidence interval [−0.27, 0.50]). Multiple covariate Cox survival analysis has been used to understand the interaction of different covariates (15) and the effects of these on survival. According to the Cox proportional hazard model, a secondary covariate may be a confounding or an effect modifier or neither. A confounding covariate (BPV/diameter) affects the outcome independent of the primary covariate (TGs). When BPV and diameter were included in the analysis, OS HR and P value did not change significantly compared with crude TG analysis, which suggests that BPV and diameter were not confounding covariates

Table 1. Cox Survival Analysis of the Covariates

Covariates	Output	*P* Value	HR	CI
(a) TG	TG	.445	0.895	0.674–1.189
(b) TG + BPV	TG	.416	0.888	0.669–1.181
	BPV	.149	0.942	0.868–1.022
(c) TG × BPV	TG	.290	1.249	0.827–1.887
	BPV	.591	0.987	0.939–1.036
	TG × BPV	.038	0.85	0.728–0.991
(d) TG + BPD	TG	.468	0.900	0.678–1.196
	BPV	.328	0.891	0.707–1.122
(e) TG × BPD	TG	.339	1.352	0.728–2.513
	BPD	.678	1.072	0.771–1.492
	TG × BPD	.147	0.711	0.448–1.127

Note–Cox analysis is presented for **(a)** TG only and **(b–e)** including multiple covariates BPV **(b, c)** and BPD **(d, e)** together with TG using overall survival. To check whether the secondary covariates (BPV and BPD) were confounding variables, summation operation was used **(b, d)**. Difference of *P* values and HRs was not statistically significant compared with crude model **(a)**, which suggested that BPV and BPD were not confounding variables. Interaction term for BPV was significant **(c)**, which means it is an effect modifier. The same effect was not observed for BPD **(e)**. Number of patients = 437; number of events = 191.

BPD = burn time per longest diameter; BPV = burn time per tumor volume; CI =confidence interval; HR = hazard ratio; TG = treatment group.

Table 2. Effect of BPV on Each Individual Treatment Group

Group	OS/PFS	*P* Value	HR	CI	Events (Deaths)	R^2
RF ablation only	PFS	.133	0.925	0.835–1.024	133	.02
	OS	.590	0.987	0.940–1.036	96	.002
RF ablation + LTLD	PFS	.637	0.98	0.90–1.066	133	.001
	OS	.017	0.836	0.722–0.968	95	.033

Note–Cox proportional hazard model to analyze the effect of BPV on each treatment group individually is presented. The results of the PFS analysis were not statistically significant in either group. Response of patients receiving RF ablation only (n = 210) to the increase of BPV was also not statistically significant. However, 1 unit increase of BPV (1 min/mL) increased the survival chance of patients receiving RF ablation + LTLD (n = 227), and the result was significant (*P* = .017, HR = 0.836).
BPV = burn time per tumor volume; CI = confidence interval; HR = hazard ratio; LTLD = lyso-thermosensitive liposomal doxorubicin; OS = overall survival; PFS = progression-free survival.

(Table 1a, b, d). Next, BPV and diameter were tested to determine whether they changed the effect of the TG. The interaction term for TG and BPV (TG × BPV) was significant (*P* = .038), and HR was 0.85, which suggested that BPV was an effect modifier (Table 1c). The result suggested that an increase in BPV improved survival of the patients receiving RF ablation + LTLD compared with patients receiving RF ablation only. The same analysis was repeated for burn time per tumor longest diameter, but it was neither confounding nor an effect modifier (Table 1d, e). In addition, effects of the mentioned covariates were not significant when PFS was considered (results not shown). Burn time alone was also checked to determine whether it was a confounding or an effect modifier covariate, but results showed that burn time was neither (TG + burn time: *P* = .457, HR = 0.897; TG × burn time: *P* = .164, HR = 0.993). Schoenfeld residuals were plotted to confirm that Cox proportional hazard assumption was valid in the analysis.

There was a difference between the 2 TGs when the BPV was increased (Table 1). To further investigate the details of BPV effect, each group (RF ablation only and RF ablation + LTLD) was independently analyzed to determine the effect of BPV within each individual group (Table 2). In this analysis, BPV was considered as the input covariate in the Cox survival analysis.

Cox univariate analysis was also performed by applying thresholds to the BPV and considering only the patients above the threshold value (Fig 2). As the threshold was increased, the hazard ratio became smaller, which was expected. Survival results with Kaplan-Meier survival curves demonstrated a significant difference with the addition of LTLD for the subset of patients analyzed who had single tumors and met specific thresholds of time per tumor volume (Fig 3a, b). For example, when only the patients with BPV > 2 min/mL were considered, HR was 0.7, which means 42.8% survival improvement for patients receiving RF ablation + LTLD compared with patients receiving RF ablation-only (Fig 3a). When the threshold was increased to 3.4 min/mL, HR was reduced to 0.5, and survival improvement became 100% (Fig 3b).

The percentage of the patient population that could be completely treated using a BPV of 2 min/mL, depending on the available burn time, is plotted in Figure 4. For example, if available burn time was 100 minutes, almost 80% of the tumors could have been treated using 2 min/mL BPV. Tumor volume versus longest diameter was plotted with fitted curve, and the right side of the plot provided corresponding burn time to optimize the LTLD effect. A magnified version of the plot was also provided for the tumor longest diameter from 35 mm to 55 mm (Fig 5).

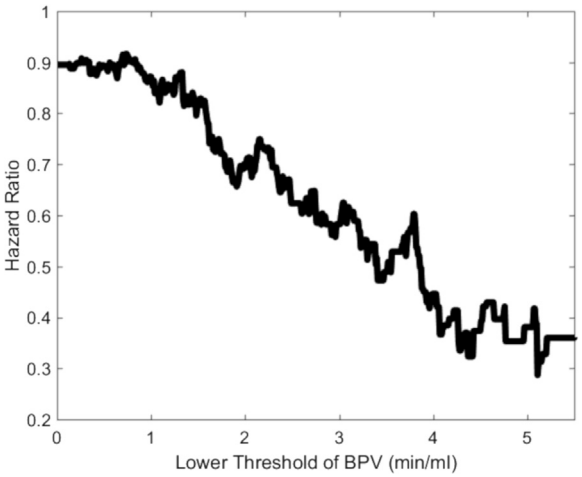

Figure 2. Hazard ratio versus lower threshold of BPV. As patients with smaller values of BPV were excluded, the hazard ratio decreased, representing improved benefit for patients receiving RF ablation + LTLD compared with patients receiving RF ablation only. When patients with < 2 min/mL BPV were excluded, the hazard ratio became 0.7, which meant survival of patients receiving RF ablation + LTLD improved 42.8% compared with patients receiving RF ablation only. With exclusion of patients with < 3.4 min/mL BPV, the hazard ratio and survival improvement for patients receiving RF ablation + LTLD became 0.5 and 100%, respectively, compared with patients receiving RF ablation only.

DISCUSSION

Although previous studies presented promising results for the RF ablation + LTLD combination (2), the results of the phase III HEAT study show no statistically significant difference between the 2 TGs for the primary (PFS) and secondary (OS) endpoints (10,16). However, the same study

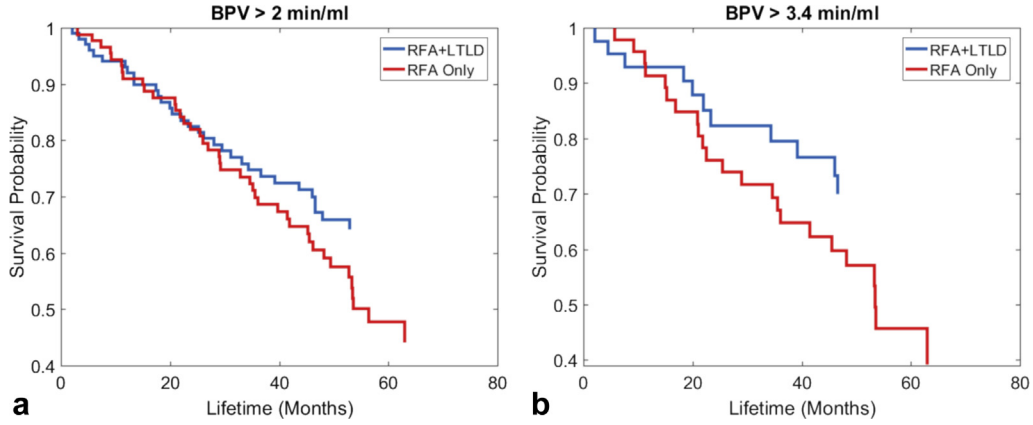

Figure 3. Kaplan-Meier plots for patients treated with BPV > 2 min/mL **(a)** and > 3.4 min/mL **(b)**. **(a)** Hazard ratio was 0.7 when the threshold was 2 min/mL, reflecting a 42.8% survival improvement for patients receiving RF ablation + LTLD compared with patients receiving RF ablation only. **(b)** For BPV threshold of 3.4 min/mL, hazard ratio was reduced to 0.5, and survival improvement became 100%. RFA = RF ablation.

reported that patients receiving RF ablation + LTLD had better OS compared with patients receiving RF ablation only when only a subgroup of patients treated > 45 minutes of dwell time were considered (10,16).

The phase III HEAT study failed to meet the study endpoints when analyzed with conventional metrics. However, consideration of the mechanisms of action for this drug-device combination therapy supports analysis with a custom metric for critical evaluation of efficacy. In general, post hoc analyses may be inconclusive, may be unreliable, or may convey a low level of data. However, this study may merit unique consideration and guide future studies, given the supportive preclinical mechanistic data for this drug plus device approach.

This work not only revealed a different perspective and implications of the HEAT trial but also illustrated the importance of study design in drug-device combination therapies in general, especially combination therapies that depend on standardization of a variably subjective therapy, such as thermal ablation. Although RF ablation is present in many algorithms for HCC management, the variability of the application or delivery of this therapy is frequently ignored or underrepresented. Specifically, there is a variability of practice patterns and an inherent lack of uniform technical guidance and instructions for use for RF ablation duration. Although an association between burn time and both tumor volume and tumor largest diameter was present, this link was not enforced or prospectively designed in practice, as evidenced by the widely scattered values (**Fig 1a, b**). This degree of scatter and the demonstrated link between burn time and outcome highlight the importance of more tightly defined standardization of technique. This may be especially true for any operator-dependent procedure such as RF ablation. Based on the mechanism of drug-device combination action, this work suggests that appropriately extended RF ablation durations for larger volume tumors is required to increase efficacy of LTLD + RF ablation in terms of survival. Furthermore, BPV can be used to normalize and stratify the subjective variability among different operators and different sites based on practice patterns. This normalization may have broad implications for the field of combination drug-device therapies.

In this study, only patients with a single tumor were considered owing to the technical variability of the RF ablation + LTLD procedure in patients with multiple tumors as well as the fact that the timing of the LTLD injection and RF ablation is critically important for maximizing the local drug release and optimizing the pharmacokinetics of LTLD combined with RF ablation (2,12). The optimal combination of drug and device requires synchronization of the device use and the known temporal profile of the drug pharmacokinetics. Ablating multiple tumors in 1 session ensures that either none of the tumors receives optimum treatment or only 1 tumor can be treated properly by RF ablation + LTLD, as the subsequent tumors will be exposed to lower levels of serum drug. Therefore, patients with multiple tumors were excluded from the analysis.

Previous studies showed that the survival benefit for the patients receiving LTLD in the phase III HEAT study was found only for a subgroup of patients who were treated with a dwell time > 45 minutes (10). Dwell time may not be the best measure for the completeness of treatment because it includes both burn time and time for electrode repositioning between ablation treatments, thus including time while the RF ablation system is off and being subject to wide variations in practice patterns and techniques. BPV may be a parameter directly related to completeness of the treatment because RF ablation "on" duration is the major RF ablation variable adjusted by interventional radiologists according to the tumor size. BPV standardizes total burn time depending on the tumor volume and yields a normalized metric for comparison and verification of adequacy of technique.

The longest diameter is the usual standard for liver and other tumor size measurements as well as treatment planning. Burn time per longest diameter was found not to be a confounding or effect modifying covariate (**Table 1**).

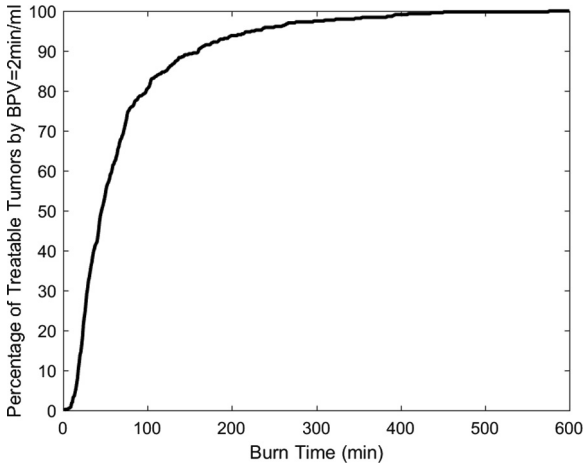

Figure 4. Percentage of patient population that could be treated with a BPV of 2 min/mL depending on the available burn time. As the available time for treatment increases, the percentage of patients who may be treated with the defined value of BPV increases. If BPV of 2 min/mL is used, approximately 80% of the patients can be treated in < 100 minutes.

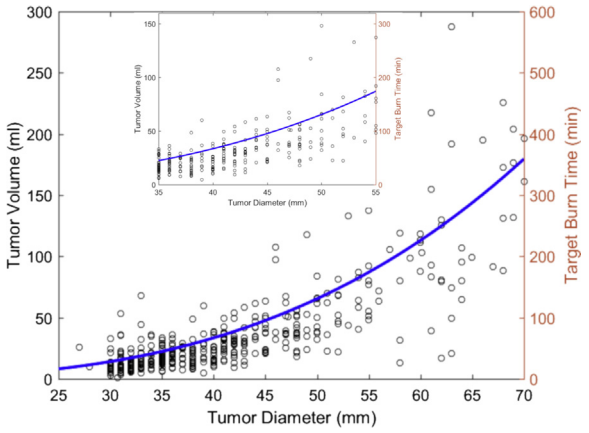

Figure 5. Tumor volume versus tumor longest diameter versus target BPV of 2 min/mL as an example. The blue curve is the fit of the tumor volume versus tumor longest diameter. Target burn time was calculated by multiplying the value of tumor volume in the fitted curve by the sample BPV value of 2 min/mL. The inset is a magnified detail for diameters 35–55 mm.

Although further investigations are crucial, tumor volume may be a better way to characterize the size of the tumor and determine the requisite burn time to ensure successful tumor coverage and overall successful local treatment. Therefore, BPV is the more consistent parameter to more accurately reflect the effects of duration of ablation, especially for the patients receiving RF ablation + LTLD.

The analysis showed that each unit (1 min/mL) increase of BPV increases survival rate of patients receiving RF ablation + LTLD by 17.6% compared with patients receiving RF ablation only (**Table 1c**). This result was confirmed by separating the TGs, inputting BPV, and running a crude analysis (**Table 2**). The result showed that survival of patients receiving RF ablation + LTLD improved as BPV was increased. Every unit increase in BPV improved survival rate of patients receiving RF ablation + LTLD by 19.6% (1/0.836 = 1.196), which indicated that BPV may be critical for the survival rate of patients receiving RF ablation + LTLD, as the drug deposition increases with extended burn time as reflected by extended BPV. Analysis using BPV demonstrated a survival benefit when comparing RF ablation only versus RF ablation + LTLD in solitary HCCs with diameter between 3 and 7 cm. For unknown reasons, such survival benefit was not statistically significant when PFS was considered.

The effect of BPV increase was not statistically significant in the patients receiving RF ablation only ($P = .590$, HR = 0.987). This result may explain why prolonged treatments may not have produced the same amount of cell killing in the periphery of the ablated zone compared with RF ablation + LTLD, which defines whether the drug provides benefit or not. A general guideline for duration of liver RF ablation does not exist because the technical specifications of the different RF ablation systems vary. Duration of RF ablation may change depending on tumor shape, vascularization, and size as well as the RF ablation system and other operator factors. It is intriguing that specific centers and specific operators were clustered according to practice patterns or a practice phenotype. Such a tool (with future validation of metrics) may prove useful for training or screening out outlying and underperforming or nonuniform operators or sites.

Extended duration of anesthesia required for treating large tumors may increase procedural risks, but this is true for RF ablation alone as well. A feasibility analysis showed that if the operators had 100 minutes of burn time, almost 80% of the patients with single tumors in this study could have been treated > 2 min/mL (**Fig 4**). Using the target burn time plots, one can determine how long RF ablation needs to be performed. For example, if an interventional radiologist aims to ablate a single tumor using 2 min/mL with a single electrode, ablation of a 45-mm-diameter tumor (approximately 50 mL volume) would require 100 minutes (**Fig 5**). Feasibility of delivering the burn time is an important part of the treatment planning. To achieve 2 min/mL burn time, patients with a 70-mm tumor would need to be treated for nearly 360 minutes, which is not realistic (**Fig 5**). Use of multiple electrodes may address this limitation.

The main limitation of this study is that it was a post hoc analysis. Although the data were derived from a randomized, double-blind investigation that was both multiinstitutional and international in scope, the reported measure was not included in the original analysis plan. RF ablation device, electrode, and power variations were beyond the scope of this article and were not included in the analyses. One additional limitation of this study is the variability introduced by the use of 3 different RF ablation vendors, which may introduce a risk of comparing noncomparable data. For this reason, the study was limited to the subset of solitary tumors, which may improve

standardization across the study. Also, the basic mechanisms of RF ablation in the range near 500 kHz rely on the same mechanistic principles, regardless of the shape of the RF ablation probe or the presence of water cooling. Thus, similar dependency on thermal conductivity is present in all RF ablation systems as well as the requisite minimal treatment time per volume tumor metric, which is the central hypothesis of this work. These results need to be confirmed in a prospective clinical trial that controls for these device and operational parameters. Any post hoc subpopulation or subgroup study may be subject to more risk for confounding variables (eg, asymmetric Eastern Cooperative Oncology Group Performance Status or sample selection bias). However, a large randomized well-controlled trial with this as an endpoint defined a priori will be less prone to these biases.

In conclusion, analysis using the parameter BPV demonstrated a survival benefit when comparing RF ablation + LTLD versus RF ablation only in solitary HCC 3–7 cm in diameter. Device-drug combination studies need to be optimized and customized, depending on the interaction of the device and drug. The data suggest that BPV may be used to filter survival curves for significant differences and may also identify different performing or potentially underperforming operators or sites. Such a metric may have implications for future studies of this device-drug combination therapy. Defining rational metrics based on mechanisms of action may play a role in standardization and normalization of human factors during clinical trial design.

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