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One-Year Outcomes Following Stereotactic Body Radiotherapy for Refractory Ventricular Tachycardia.

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Title

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One-Year Outcomes Following Stereotactic Body Radiotherapy for Refractory Ventricular Tachycardia.

Abstract:

Background:

Cardiac stereotactic body radiotherapy (SBRT) has emerged as a promising noninvasive treatment for refractory ventricular tachycardia (VT).

Objective: Describe the safety and effectiveness of SBRT for VT in refractory to extensive ablation.

Methods

After maximal medical and ablation therapy patients were enrolled in a prospective registry. Available electrophysiologic and imaging data were integrated to generate a plan target volume (PTV) All SBRT was planned with a single 25 gray fraction utilizing respiratory motion mitigation strategies. Clinical outcomes at 6 weeks, 6 months and 12 months were analyzed and compared to the 6 months prior to treatment. The VT burden (ICD shocks and ATP sequences) as well as clinical and safety outcomes were the main outcomes.

Results

15 patients were enrolled and planned. 14 underwent treatment with 12 surviving to the end of the 6-week period and 10 surviving to 12 months. From 6 week to 12 months there was recurrence of VT which resulted in either appropriate ATP or ICD shocks in 33% (4/12). There were significant reductions in treated VT at 6 weeks to 6 months (98%) and 12 (99%) months compared to the 6 months prior to treatment. There was a nonsignificant trend towards lower amiodarone dose at 12 months. 4 deaths occurred after treatment with no changes in ventricular function.

Conclusion

For a select group of high-risk patients with VT refractory to standard therapy, SBRT is associated with a reduction of in VT and appropriate ICD therapies over 1 year.

Introduction:

Cardiac stereotactic body radiotherapy (SBRT) has emerged as a promising therapy for patients with structural heart disease (SHD) and ventricular tachycardia (VT) which is refractory to standard antiarrhythmic drug (AAD) and catheter ablation therapy. Several centers have reported their experiences with different radiation platforms utilizing a similar dose of 25 Gy.[1–5] Outcomes have been mixed, likely reflecting differences in treatment modality, patient selection and methodology. The Hospital of the University of Pennsylvania has a large and unique VT referral population with an advanced ablation program utilizing noninvasive programmed stimulation (NIPS)[6] guidance. Additionally, the hospital serves a high-volume heart failure transplant and left ventricular assist device (LVAD) program. In this report, we describe our center's experience with SBRT as a treatment modality for refractory VT in patients with structural heart disease (SHD) refractory to or unable to undergo catheter ablation.

Methods:

A prospective registry was created as part of a University of Pennsylvania IRB approved protocol. The protocol prescribed SBRT treatment of patients with VT refractory to or not suitable candidates for standard medical or ablation therapy. Patients with acutely unsuccessful catheter ablation or with inducible clinical VT during noninvasive programmed stimulation (NIPS) were eligible. Once patients were identified at the treating physicians discretion, two electrophysiologists and one radiation oncologist met to confirm appropriateness. All patients were required to have failed optimal antiarrhythmic drug therapy and catheter ablation when not contraindicated. Clinical variables were collected and mortality risk scores such as PAINESD[7] were quantified.

EP study, Electroanatomic Mapping and VT Ablation:

Our methods for VT ablation have been previously described.[8] High density electroanatomic maps were created whenever possible to fully delineate bipolar and unipolar abnormalities as well as identify abnormal potentials. A representation of the aortic cusps was created to facilitate registration using intracardiac ultrasound integration or by point-by-point mapping. Late and abnormal potential mapping strategies were employed as well as entrainment, activation, and pace mapping strategies. Radiofrequency ablation was performed with open irrigated catheters using power control at 20-50 watts targeting 10% impedance drops for 1 to 5 minutes in duration per lesion. Adjunctive methods to enhance RF lesion depth such as bipolar ablation[9] and half-normal[10] saline strategies were employed at operators' discretion. Noninvasive programmed stimulation was performed in patients with acute success during VT ablation during the admission for VT ablation.

Medical therapy:

Antiarrhythmic drugs (AAD) were left to the discretion of the treating team. Given the patient population of refractory VT and the temporal delay seen with radiation therapy it was expected that AAD use would be intensified around the time of treatment. After the 6-week period from treatment AADs were reduced when appropriate.

Noninvasive Imaging:

Patients underwent a variety of imaging studies as a part of standard of care work up for refractory VT. including cardiac MRI, CT and PET imaging. Channel prediction software packages including ADAS Medical (Galgo Medical S.L. Barcelona, Spain) and MUSIC (Institut Hospitalo-Universitaire l'Institut de Rythmologie et Modélisation Cardiaque, Université de Bordeaux, France; and Inria Sophia Antipolis, France) were also utilized in selected cased. As needed, co-registration of CT, MR and PET was performed in Aria (Varian, Palo Alto, CA) and manual registration of electroanatomic maps was performed utilizing an approach based on alignment of aortic cusps, left ventricular apex and plane of the mitral annulus.

Radiation treatment planning and delivery:

Simulation—4D contrast CT based simulation planning was performed using a Siemens SOMATOM with 1-2 mm slice thickness. Except for patients where the left ventricular assist device (LVAD) drive line interfered with placement, a compression belt was used to limit respiratory excursion. To minimize the variability in heart position created by gastric distension, patients were simulated and treated with an empty stomach. Isocenter was marked using the free breathing scan. Initially, contrast was delivered during the free breathing scan, which was used for planning with the 4D scan for estimation of respiratory motion. For the final 7 patients, the contrast was given during the 4D scan so that it could be used directly for planning.

Gross target volume (GTV) determination— Our approach to targeting was multifaceted with emphasis on sites of clinical VT as opposed to "scar homogenization" or targeting the entirety of abnormal myocardium. Our emphasis is on sites of clinical VT. Electrophysiologic and EAM data is reviewed, and highest priority targets are identified. When invasive electroanatomic data was not present, non-invasive imaging and channel prediction was given priority. Figure 1.

Motion and uncertainty—After analyzing motion of the target substrate on 4D imaging, a custom expansion was determined to incorporate cardiorespiratory motion into the internal target volume (ITV). To account for set up uncertainty, this volume was uniformly expanded by 3 mm to create the planning target volume (PTV).

Planning, verification and delivery—Planning was performed using Varian Eclipse software for delivery on a Varian Truebeam Linac (linear accelerator) utilizing X-ray radiation with 25 gray dose. Planning constraints were developed by using the more conservative single fraction lung SBRT constraints. Treatments consisting of 3-4 non-coplanar arcs were delivered using cone beam CT image guidance. Abdominal compression devices were used in all patients to limit respiratory motion.

Assessment and follow up:

A prescribed follow up protocol included visits at 6 weeks, 6 months, and 12 months with echocardiogram between 3-6 months. Remote monitoring was utilized for all patients to monitor for VT. Medications were recommended to be reduced as possible.

Safety and heart failure status were assessed at all visits. Antiarrhythmic drug and amiodarone dosage were quantified.

VT efficacy was analyzed primarily by treated VT episodes: ATP sequences and appropriate ICD shocks. Inappropriate VT Treated VT episodes were compared in the 6 months prior to treatment, 0-6 weeks

following treatment, 6 weeks to 6 months following treatment and 6 months to 12-month interval. These intervals are based on prior studies of VT[11,12] and for the time course of radiation effects. For the analysis patients surviving a minimum of 6 months were included.

Statistical Methods:

SPSS (v 27.0 IBM Corp. Armonk, NY) and Graphpad Prism (v9, GraphPad Software, San Diego, CA) were used for statistical analysis. Normally distributed variables were reported as means with standard deviations. Non normally distributed variables were reported as medians with ranges. T-tests were used to assess significance of normally distributed, continuous variables. Non-normally distributed continuous variables, including VT burden, were assessed with the Wilcoxon matched pairs signed rank test. Fishers exact test and chi squared were used to analyze dichotomous variables.

Results

Patient population:

Fifteen patients underwent planning and fourteen underwent treatment. The baseline characteristics and treatments are detailed in Table 1. There were 5 deaths, 1 between planning and treatment and 4 in the 12 months following treatment. Patients were 65.0 ± 7.8 years old and mostly male (87%). The mean LVEF was 30.2 ± 3.6 and the mean PAINESD score was 13.6±7.4 (intermediate risk). 2(13%) patients had continuous flow left ventricular assist devices (LVAD) in place.

Invasive Electroanatomic and VT Ablation Data:

A mean of 2.1 catheter ablations were performed at University of Pennsylvania before SBRT with 4.7±2.1 inducible VTs. Bipolar ablation was used in 2(14%), half normal saline in 2(14%), and surgical cryoablation via thoracotomy in 1(7%). The average catheter-based ablation procedure duration was 6.8±1.9 hours with 4(29%) utilizing hemodynamic support. 6(43%) patients required critical care stay post ablation for vasopressor infusion to treat hypotension or mechanical ventilation/high-flow oxygen to treat hypoxia. Three (22%) experienced acute kidney injury and 1(7%) had an acute stroke.

Pretreatment imaging and SBRT planning/delivery:

Table 2 summarizes imaging modalities and volumes targeted. Thirteen (87%) patients had 3D electroanatomic mapping performed. Cardiac gated CTA was utilized in 93% (14) and cardiac MRI with and without wideband LGE sequences in 80% (12). 18-FDG PET was performed in 5 (33%). Channel prediction software was used in 40% (6). Treatment volume were 26.8 $\pm$ 9.8 cc, 45.6 $\pm$ 13.0 cc and 84.9 $\pm$ 24.4 cc for GTV, ITV and PTV, respectively. Dose constraints and dose to organs at risk, including cardiac substructures is included in the supplemental table 1.

VT outcomes

VT burden and characteristics are summarized in Table 3 and Figure 2 for those patients surviving at least 6 months. There was a significant percent reduction in treated VT, ICD shocks, and ATP sequences after treatment with SBRT compared to the six months prior (Table 3). Inappropriate therapies were not counted. Total treated VT episodes in the prior 6 months were 461, 6 weeks post treatment 58 (88% reduction p =.06), 6 weeks to 6 months 19 (98% reduction p<.001) and 5 in 6-12 months (99% reduction p <.001) . Any treated VT recurred in 33% (4) over the study period. Median (IQR) treated VT was

14(11-16.5) in the prior 6 months, 0(0-0) from 6 weeks to 6 months and 0(0-0) from 6-12 months. There was a significant reduction in treated VT and ICD shocks and treated VT from 6 weeks to 6 months and 6 to 12 months compared to pretreatment.

One patient required reintervention during the study period and subsequently underwent repeat catheter-based VT ablation. In the time after SBRT treatment the burden significantly decreased but after 5 months began experiencing an increase in burden. The VT cycle length (475 ms) and location (basal crux) at the procedure were similar in the pre and post radiation studies.

Clinical Outcomes and Safety:

Clinical outcomes and safety are summarized in Table 4. There were no observed cases of suspected radiation pneumonitis or pericardial effusion during the follow-up period. Although, one patient was observed to have a predominantly right sided aspiration pneumonia it was felt to be unlikely due to radiation given the clinical time course and location. There were no exacerbations of pulmonary disease in patients with or without COPD. There were also no observed acute gastrointestinal effects or known effects during follow up. There were no ICD malfunctions after SBRT. There were no LVAD or LVAD controller malfunctions.

Ejection fraction was compared at treatment and at 6 months and was not found to significantly differ (31.7±15 vs 31.8±11.6, p=0.96). QRS duration did not differ significantly at treatment and 6 months (141.6±32.7 vs 141.6±31.6, p=1). No new conduction block in the form of heart block or bundle branch block was observed. There was a non-significant decrease in daily amiodarone dose (400±174.8mg vs 225±190.9mg, p=0.12).

There was 1 death between planning and treatment related to complications of VT storm and shock. There were 4 deaths in the 12 months following treatment. 2 deaths occurred 10 and 12 days after treatment and were related to aspiration pneumonia in one and complications of worsening heart failure in another and worsening cardiogenic shock. The pneumonia was felt to be unlikely a direct complication given the clinical history but possible that the treatment indirectly played a role. The case of worsening shock was possibly related to radiation however the indication for referral for SBRT was VT in a patient with advanced heart failure requiring inotropic and vasopressor support. The PAINESD score for both of these patients were in the high risk category 17 and 23 (high risk >= 15).

There were 2 deaths which occurred between 6 weeks and 12 months and were also possibly related to SBRT. The first occurred 7 months after treatment which occurred suddenly. No autopsy was performed, and the cause was undetermined. ICD interrogation showed no VT before death. The second occurred 3 months after treatment in a patient with LVAD and was related to progressive RV failure, cirrhosis, worsening quality of life, and a decision to enter hospice. RV failure and cirrhosis had been an issue prior to SBRT and the target was remote from the RV however a contributory effect cannot be ruled out.

Discussion:

VT is a challenging disease to study due to the waxing and waning nature[13,14] with background competing influences of heart failure, coronary artery disease, and medical therapy. Additionally, many

patients present with electrical storm or frequent VT requiring intensive therapy including bolus dosing of amiodarone which may further obfuscate short term outcomes. For these reasons we consider one-year outcomes more relevant than 6-month outcomes when assessing antiarrhythmic effect. Although not fully understood with respect to myocardial tissue there is an expected delay between radiation treatment and effect. In prior studies, a temporal delay between radiation and antiarrhythmic effect was observed usually occurring in the first 4-6 weeks[1,5]. Therefore, this period was reported separately.

This experience with SBRT in a challenging group of patients was notable for several findings. The first is a high rate of VT reduction in a high comorbidity cohort with aggressive ablation at a major center. Our institution had previously described those patients positive for clinical VT during NIPS experience VT recurrence rates of treated or sustained VT up to 70% at one year. [6 15] Although an imperfect control group, NIPS positive patients after ablation do match the clinical scenario although medical therapy is not controlled for. However, based on this comparison, we see a lower-than-expected overall recurrence rate of any treated VT (33%) at one year and therefore we believe there is an association with SBRT and antiarrhythmic effect based on this.

In comparison to other studies of SBRT for VT [1,3,5], our results are overall consistent but do show a greater reduction in VT burden and lower overall recurrence rate. Although it is challenging to draw conclusions from a heterogenous population there are several factors which may have contributed to these findings. Our group had mostly undergone extensive mapping and catheter-based ablations (93%, median 2 ablations, 6.8 hours per ablation) and MRI was highly utilized (93%). Excellent invasive and noninvasive data was therefore available which may have improved targeting of SBRT. Our group also utilized motion mitigation compression devices in all patients which may have improved delivery of radiotherapy. Another intriguing possibility is that there may be a synergistic relationship between recent ablation and radiosensitivity of VT substrate. The intense inflammation caused by RF energy in the surrounding myocardium persists for several weeks after ablation. These changes may alter oxygen levels and thereby radiosensitivity for example.

The safety of SBRT appeared to be excellent in the short term. There were no common short-term complications of effusion or pneumonitis. As reported with other studies there was no significant reduction of ejection fraction or change in cardiac conduction. There were several deaths which were likely mostly a reflection of the morbidity of the patients and is on par with other studies of catheter ablation.[16 17,18] The average patient had a PAINESD score of 14 which is nearly high risk (>= 15 high risk) and is associated with a high rate of death. [17,19] The 2 deaths occurring in the 6 weeks after treatment is similar to expected for a high risk PAINESD score.

SBRT does appear to have a significant delay in taking effect as compared to catheter ablation. Several patients who experienced VT in the first weeks after treatment went on to experience no VT for the next year after therapy. This period is clinically challenging for patients and providers and can lead to readmissions and long hospitalizations. Medication intensification or autonomic modulation[20] may be beneficial in bridging this period.

Another finding is that SBRT does not seem to be associated with dense fibrosis, a reduction in systolic function, wall motion abnormalities or conduction block as also reported by other groups.[4] However, we also did not see a shortening of the QRS duration as reported by others.[21] A good example of the effect of SBRT was the recurrence which required repeat ablation. The patient had near incessant VT which steadily declined after SBRT over the first 4 weeks and remained arrhythmia free for several

months on less medications before having a gradually increasing burden of VT. The repeat ablation showed an identical location of VT with the same morphology and cycle length. As such it seems that SBRT acts to modulate the electrophysiology of the VT substrate rather than ablate it which has important implications for dosing and the nature of the substrate being targeted.

Other observations include the usefulness of a collaborative approach to targeting. Generally, our targets were discussed as a group where all data was presented systematically. When a high-quality electroanatomic map was present this served as our primary guiding data. Channel prediction software was also useful in this role. Often the MRI abnormality encompassed an adjacent area to these maps and the PTV was expanded to encompass this.

SBRT has emerged as a clinically useful tool for patients with refractory VT primarily as a "bail out" or alternative therapy after catheter ablation. Looking forward, a role for SBRT can be seen emerging further upstream in patients at risk for acute decompensation during catheter ablation or challenging substrate. The exact mechanism of antiarrhythmic effect is unknown and therefore ideal dose of radiation still needs to be further elucidated. Additional studies are needed to refine the dosing and role of SBRT for treatment of VT.

Limitations:

There are several factors that make drawing conclusions challenging including: a highly heterogenous and morbid group, antiarrhythmic therapy and competing risks of heart failure and death from other causes. Antiarrhythmic dosing was left to physician discretion and not uniform. ICD programming was also left to physician discretion which could significantly affect the primary outcomes of treated VT.

Conclusions

SBRT for a select group of patients who have failed maximal traditional therapy is associated with a reduction in treated VT episodes over the following 12 months. Close collaboration between the treating electrophysiology and radiation oncology teams is critical for targeting. These results support a need for further randomized controlled trials.

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Age	**65.0 ± 7.8**
LVEF (%)	30.2 ± 3.6
ICMP	7(46%)
Male	13(87%)
PAINESD Score	13.6±7.4
LVAD	2 (13%)
VT storm	10(66%)
AAD use	15(100%)
Amiodarone	14(93%)
Amiodarone dose (daily mg)	400 ± 174
>= 2 AAD	9 (60%)
UPenn VT ablation #	2±1.1
Previous ablation	9(60%)
EP procedure time (hours)	6.8±1.9
#VTs induced	4.7±2.1
Supported Ablation (including LVAD)	4(29%)

Table 1. Patient and VT characteristics

IMAGING AND TREATMENT	
RADIOTHERAPY	
Gross Target Volume, CC	22.1(11.3-46.7)
Internal Target Volume, CC	26.2(47.0-70.3)
Planning Target Volume, CC	45.6(84.7-124.1)
Beam On Time M:S	3:27(2:37-4:35)
Immobilization	100%
IMAGING	
Invasive Electroanatomic	14(93%)
Cardiac Cta	12(80%)
Cmr	14(93%)
Pet	5(33%)
Channel Prediction	7(47%)

Table 2. Imaging and Target Volumes

	Prior 6 mo.	*0-6 wk.*	*6wk. - 6mo.*	*6 -12 mo.*	*6 wks - 12 mo.*
Total Treated VT	461	57	19	5	24
Median (IQR)	*14(11-16.5)*	*0(0-2.3)*	*0(0-0)*	*0(0-0)*	*0(0-0)*
Reduction vs prior 6 mo.	-	-	95.9%*	98.9%*	94.8%*
ICD shocks					
Total Shocks	44	6	0	0	0
Median (IQR)	*3(1-5.5)*	*0(0-0)*	*0(0-0)*	*0(0-0)*	*0(0-0)*
Reduction vs prior 6 mo.	-	-	100.0%*	100.0%*	100.0%*
ATP sequences					
Total ATP	418	19	2	5	7
Median (IQR)	*10(5-12.5)*	*0(0-0)*	*0(0-0)*	*0(0-0)*	*0(0-0)*
Reduction vs prior 6 mo.	-	-	99.5%*	98.8%*	98.3%*

Table 3 VT burden tabular format for patients >6 months n=12 indicates p<.01*

Safety			
New conduction block	0		
Pericarditis	0		
Pericardial effusion	0		
Radiation pneumonitis	0		
GI injury	0		
Pneumonia	1		
Deaths (total)	5		
Pretreatment	1		
Early < 4 weeks	2		
4 wks -12 mo	2		
Clinical Variables	**At tx**	**At 6mo**	**p**
Ejection fraction (%)	31.7±15	31.8±11.6	0.95
QRS duration (ms)	141.6±32.7	141.6±31.6	0.99
Amiodarone(mg) daily	400±174.8	225±190.9	0.12
Additional AAD	9	8	1

Table 4. Pre and post SBRT Safety and Clinical outcomes

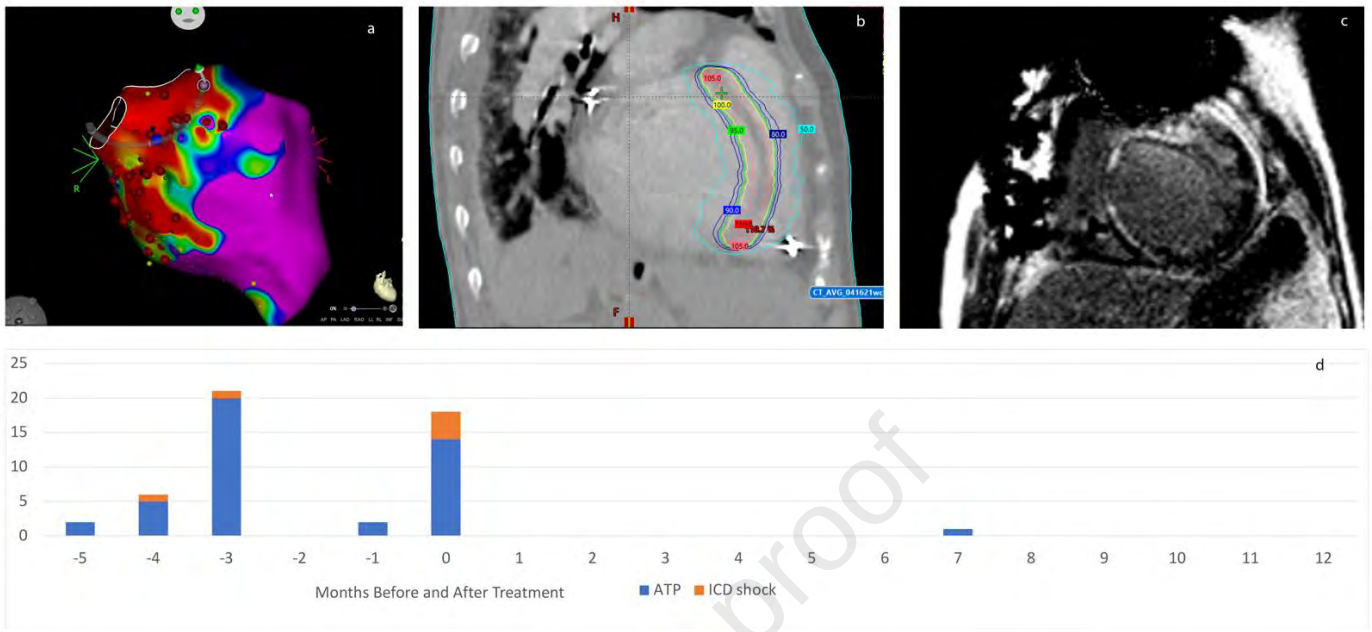


Figure 1

Treatment plan septal VT. Panel a. electroanatomic map showing bipolar voltage abnormality extending along the LV septum. B. Treatment plan with isodose lines targeting ventricular septum. C. Delayed enhancement MRI utilizing a wide band technique showing a basal septal abnormality. D. Treated VT episodes by month before and after treatment. 0-6 months was with 400 mg amiodarone and 6-12 months 200 mg daily. ICD programming was consistent throughout.

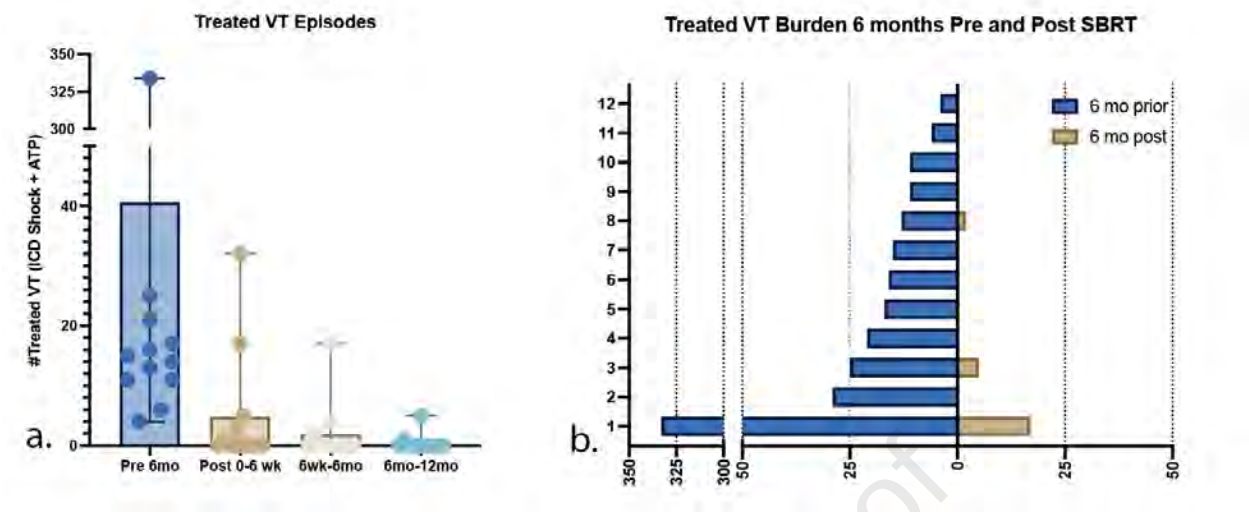
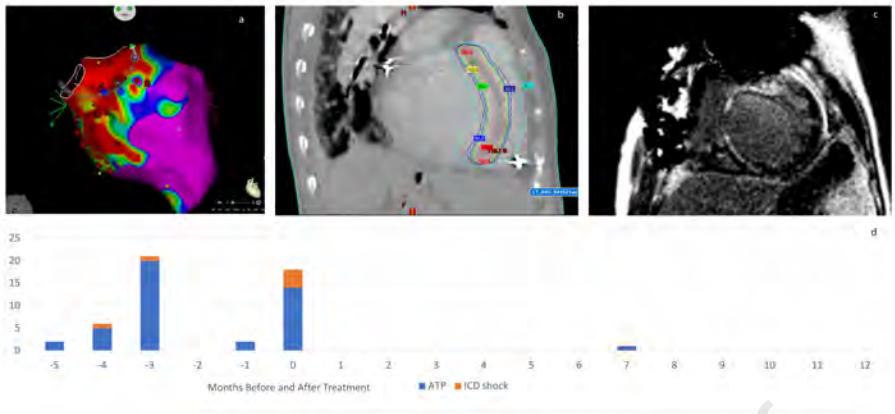
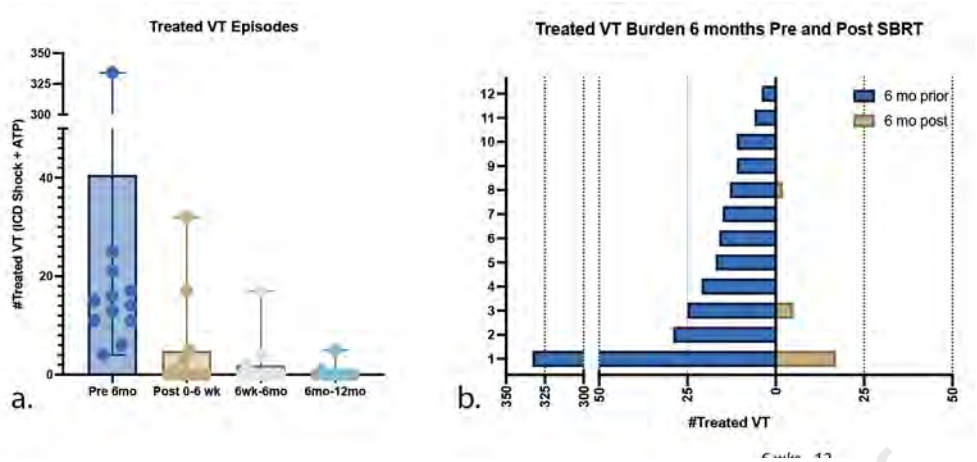


Figure 2. VT burden (patients with survival >6 months) . Per time interval (a). 6 months before and after treatment excluding blanking period (b).





Supplemental: Dose constraints vs planned dose

Structure	Constraint	Dose	Max dose	Min dose
PTV_2500	D95%[Gy]≥23.75	24.32 +/- .45	25.11	23.8
	D99%[Gy]≥22.5	23.09 +/- 1.5	24.7	19.2
ITV_2500	D95%[Gy]≥ 23.75	25.41 +/- .58	26.6	23.8
	D99%[Gy]≥22.5	25.06 +/- .79	26.4	22.6
GTV	D95%[Gy]≥ 23.75	25.6 +/- .49	26.7	24.3
	D99%[Gy]≥22.5	25.29 +/- 64	26.5	23.4
Spinal Cord	D0.35cc [Gy]≤5	2.66 +/- .88	3.9	0.995
	D1.2cc [Gy]≤8	2.45 +/- 82	3.64	0.912
	D0.03cc [Gy]≤10	2.87 +/- .93	4.29	1.09
Esophagus	D5cc [Gy]≤10	4.38 +/- 2.1	8.74	1.62
	D0.03cc [Gy]≤15	7.32 +/- 3.3	14.5	3.62
Stomach	D10cc [Gy]≤5	1.47 +/- 1.2	3.84	0.201
	D0.03cc [Gy]≤10	4.73 +/- 3.7	11.94	0.271
Heart	D500cc [Gy]≤25	5.71 +/- 2.6	11.1	2.57
	D0.03cc [Gy]≤29	27.29 +/- .55	28.5	26.3
	mean [Gy]≤15	6.68 +/- 1.5	9.5	3.79
Heart-PTV_2500	D500cc [Gy]≤25	4.61 +/- 2.6	9.84	1.27
	D0.03cc [Gy]≤29	25.72 +/- .80	27.5	24
	mean [Gy]≤15	6.54 +/- 3.7	19.4	3
Great Vessels	D10cc [Gy]≤10	6.54 +/- 4.5	20.6	0.17
	D0.03cc [Gy]≤15	11.44 +/- 5.5	25.8	0.24
Cardiac Substructure	Constraint	Dose	Max dose	Min dose
Left atria	mean [Gy]≤15	4.36 +/- 2.0	8.03	1.19
	D0.03cc [Gy]≤15	17.0 +/- 7.3	26.2	5.12
Right atria	mean [Gy]≤15	3.01 +/- 1.4	5.28	0.89
	D0.03cc[Gy]≤15	13.0 +/- 8.3	26.3	3
Left ventricles	mean [Gy]≤15	9.18 +/- 1.82	13.1	6.52
	D0.03cc [Gy]≤15	27.2 +/- .59	28.4	26
Right ventricles	mean [Gy]≤15	7.97 +/- 4.6	14.9	1.08
	D0.03cc [Gy]≤15	21.9 +/- 8.5	27.9	4.89
LAD	mean [Gy]≤15	9.45 +/- 5.6	21.4	2.12
	D0.03cc [Gy]≤15	15.2 +/- 7.8	27.8	3.58
Left Coronary Artery	mean [Gy]≤15	10.3 +/- 9.2	25.1	0.198
	D0.03cc [Gy]≤15	14.4 +/- 12	26.5	0.217
Right Coronary Artery	mean [Gy]≤15	3.12 +/- 2.5	9.84	0.304
	D0.03cc [Gy]≤15	5.95 +/- 4.13	15.9	0.478