ORIGINAL ARTICLE

Description of multiparametric targeting techniques for stereotactic arrhythmia radioablation in refractory ventricular tachycardia: A quaternary medical center experience

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ABSTRACT

Background: Ventricular tachycardia (VT) is a potentially life-threatening arrhythmia which remains a major contributor to cardiac morbidity and mortality worldwide. Recently the use of stereotactic radiation has demonstrated efficacy, although standardization of methodology is lacking and variations in technique exist. In this paper, we discuss our outcomes as well as the various options available and the proposed indications for each.

Methods: 12-lead EKGs and device-obtained tracings were used to approximately localize the arrhythmogenic origin and to define the arrhythmic mechanism. When feasible, electrophysiology studies (EPS) with 3-D electroanatomic (EA) mapping during which a 3-D electroanatomic substrate map was created to delineate cardiac structures, identify areas of low voltage scar and confirm arrhythmic circuits. A 4-D cardiac magnetic resonance imaging (cMRI) or cardiac computed tomography (cCT) was performed to delineate cardiac geometry and structures. The Stereotactic arrhythmia radioablation (STAR) treatment plans delivered a total dose of 25 Gy in a single treatment fraction covering the entire arrhythmogenic target.

Results: Six of the nine patients showed a reduction in VT events at 6 weeks post STAR. One patient underwent cardiac transplantation two weeks following STAR. Excluding this patient from the analysis, all but one patient had a dramatic diminution in VT events (to 0) at 6 months post-procedure, including both patients with an LVAD. Six of the nine patients survived at least 4 months post procedure event free and 6 patients survive to date. The lone patient who did not respond died 13 months post procedure, however he had no further defibrillator discharges. Another patient died two months post procedure from uncontrolled multiple myeloma. One patient developed an asymptomatic pleural effusion, but no serious STAR-induced postoperative complications occurred.

Conclusions: STAR appears to be an effective therapy for refractory ventricular tachycardia, although long term data are still developing. Additional clinical trials and techniques are in development and STAR programs should be encouraged for additional well-equipped centers with experienced multidisciplinary clinicians.

Key Words: Radiation, Cardiac ablation, Ventricular tachycardia, Stereotactic, Arrhythmia

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1. Introduction

Ventricular tachycardia (VT) is a potentially life-threatening arrhythmia in patients with structural heart disease and heart failure. It remains a major contributor to cardiac morbidity and mortality worldwide and claims more than 300,000 lives annually in the United States.[1] Despite recent advances, the risk of VT in the overall population has remained unchanged largely due to improved post-MI survival.[1] Existing evidence suggests improved outcomes of death, VT storm, or appropriate implantable cardioverter defibrillator (ICD) discharge among patients undergoing catheter ablation versus those treated with escalation in antiarrhythmic drug (AAD) therapy.[2] Therefore, catheter ablation is often used as a primary therapy for VT, particularly in cases of recurrent, drug-refractory monomorphic VT arising from a specific substrate that can be targeted by mapping techniques.

Current catheter-based procedures for ablating VT rely on first creating detailed three-dimensional (3-D) electroanatomical maps (EAM) that incorporates both anatomic and functional electrical information in a real-time model of the endocardial and/or epicardial surface of the ventricles. Electrical activation during induced VT can also be studied, in combination with the 12 lead EKG and substrate map, to precisely localize elements of the VT circuit (entrance, isthmus, and exit sites). Comparatively, noninvasive mapping approach can only approximate the VT exit site.

Unfortunately, patients who fail or are unable to undergo standard VT ablation procedures have limited and unsatisfactory options. Alternative treatments such as ethanol ablation, bipolar ablation, needle catheter ablation, or sympathectomy/stellate ganglion block may not effectively treat the VT substrate, often due to anatomic limitations. Surgical ablation as a last resort may be more destructive and carries higher risk of morbidity and mortality. A non-invasive method such as Stereotactic Ablative Radiotherapy (STAR) aided by precise image-guided delivery offers an exciting potential for treatment of refractory VT.

In 2017, Cuculich et al. reported the use of stereotactic radiotherapy in five patients treated with promising results.[3] These authors used a 256 lead EKG vest placed on the patient to identify arrhythmia externally and correlated it with the 17-segment heart model. This technique is precisely described in the supplementary appendix of the original paper.[3] Additional published series and reports have confirmed these findings, including one from the initial authors in a larger cohort of patients.[4–9]

We initially reported the use of MRI/EA mapping in a case report study.[4] These EAMs are spatially accurate to a few millimeters resolution and define the VT target boundaries. We recognize that cMRI is unable to localize cardiac arrhythmia targets in some individuals (such as those patients where defibrillator or pacemaker leads obscure the target). We believe that multiparametric imaging and targeting capabilities are essential to a successful STAR program and are demonstrated in this retrospective work. Targeting methods that are image guided versus EKG guided have the potential to improve accuracy and reduce target volumes as localization becomes more precise.

2. Materials and Methods

All patients were treated "off-label" under emergency compassionate care institutional guidelines which were monitored by the Institutional Review Board.

2.1 Arrhythmia localization

In our study, we employed a comprehensive approach to localize arrhythmogenic origins and characterize arrhythmic mechanisms. This involved the utilization of 12-lead electrocardiograms (EKGs) and device-derived tracings to provide an approximate localization of the arrhythmia. In cases where feasible, we conducted electrophysiology studies (EPS) with 3-D electroanatomic (EA) mapping techniques. During these procedures, we generated 3-D electroanatomic substrate maps, which allowed us to precisely delineate cardiac structures, identify regions with low voltage scar tissue, and validate putative arrhythmic circuits. Figure 1 demonstrates the CARTO® mapping.

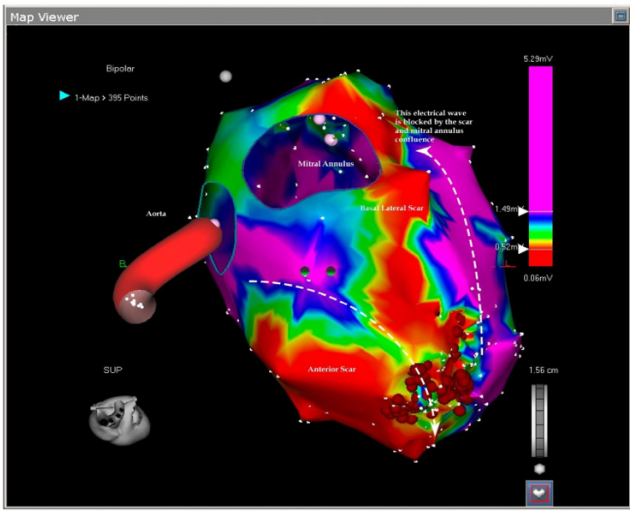

Figure 1. CARTO3® EP map. Myocardial infarction scars identified in red blush. Electro ablated areas represented by the dark red spheres inferiorly.

A 4-D cMRI was performed to delineate cardiac geometry and structures, as well as identify areas of myocardial scar or other abnormalities. The cMRI protocol was designed to

rapidly acquire images of the heart during end-expiration, with emphasis on the diastolic portion of the cycle when the cardiac muscle is at maximum thickness. A contrast enhanced cardiac computed tomography (cCT) is used to facilitate definition of cardiac structures if the patient cannot undergo cMRI scanning.

The electrophysiologist and medical physicist collaborated directly to ensure accurate translation of the mesh files onto the cardiac magnetic resonance imaging (cMRI) or cCT. This file transfer was then reviewed by the radiation oncologist.

2.2 STAR planning and treatment

Several days prior to treatment, all patients underwent a standard stereotactic body radiotherapy simulation, including the creation of a custom full-length immobilization device for the early patients. To allow for increased flexibility in target localization at the treatment interface, a Hexapod® (Elekta, Stockholm, Sweden) six degree of freedom table was incorporated into the workflow using a smaller immobilization bag. The scan is performed "arms up" unless the patient was unable to tolerate this position, then a slight modification in positioning was allowed. Once the custom immobilization device was made, a series of CT scans were acquired including a free-breathing CT and a respiration-correlated CT (4-D-CT) with a 2 mm slice interval, which provided information about the sum of cardiac and pulmonary motion. The EA mesh file data and 4-D cMRI were then fused to the simulation CT using MIM Maestro® software (MIMsoftware, Cleveland, Ohio; USA) (see Figure 2) or cCT. Cardiac motion cannot be gated for this therapy due to the overall treatment time required, and respiratory motion was managed by incorporating an internal target volume (ITV) which expanded the target along the respiratory motion course. Anterior, lateral, septal, apical, left ventricular summit, and right ventricular contouring was then performed. The gross target volume (GTV) for ablation was reviewed/confirmed by the electrophysiologist, the radiation oncologist and the medical physicist in during a joint multidisciplinary conference.

The treatment target volume was defined on the free-breathing CT scan using the Monaco® (Elekta, Stockholm, Sweden) treatment planning system (TPS). After outlining the GTV, an ITV was added to account for internal motion of the GTV caused by breathing and cardiac motion and assigned after review of the 4-D-CT and 4-D cMRI. Finally, an additional safety margin of 5 mm was added to the ITV for treatment planning to create a planning target volume (PTV), which accounted for any residual uncertainties in patient setup, motion, and delivery. This margin was adjusted to protect the organs-at-risk (OAR) (see Figure 3).

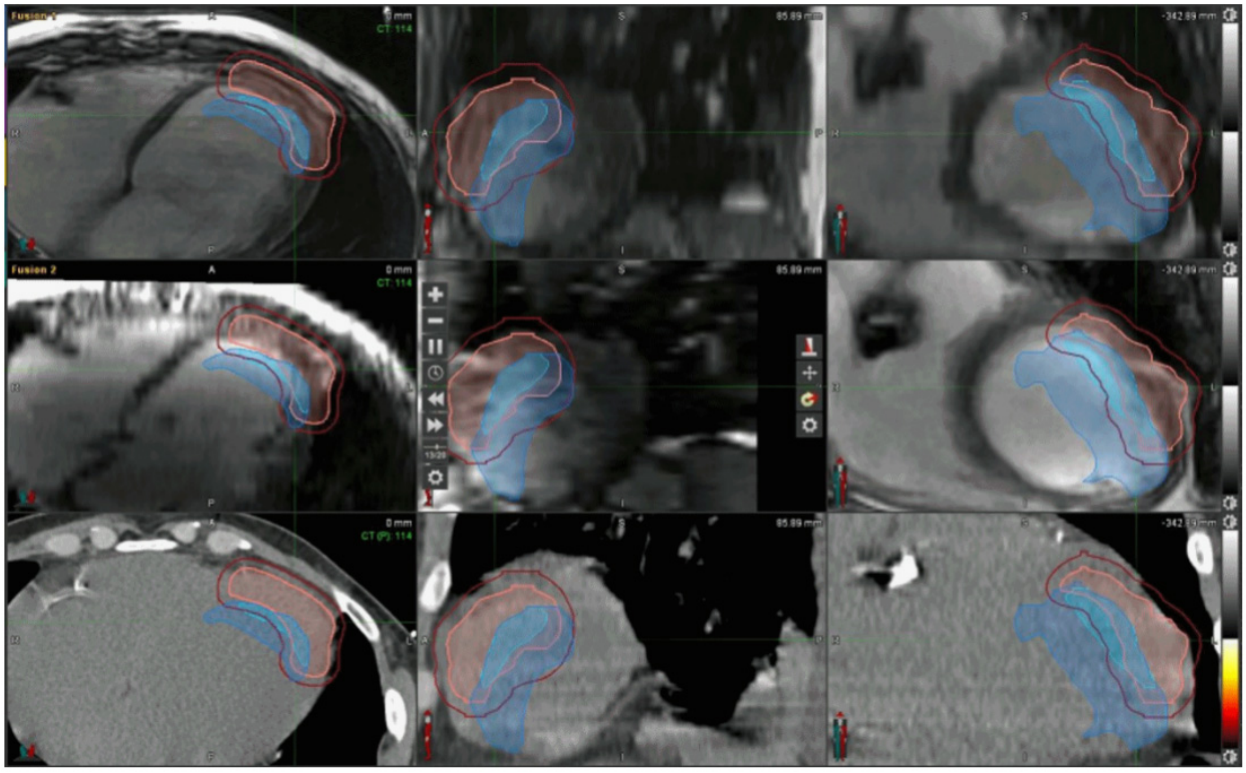

Figure 2. A plan for Patient 2 with ITV, PTV and isodose lines. The planned dose of 25 Gy is identified in translucent red. The "Hot spot" volume of 28.5 Gy is also identified (solid red).

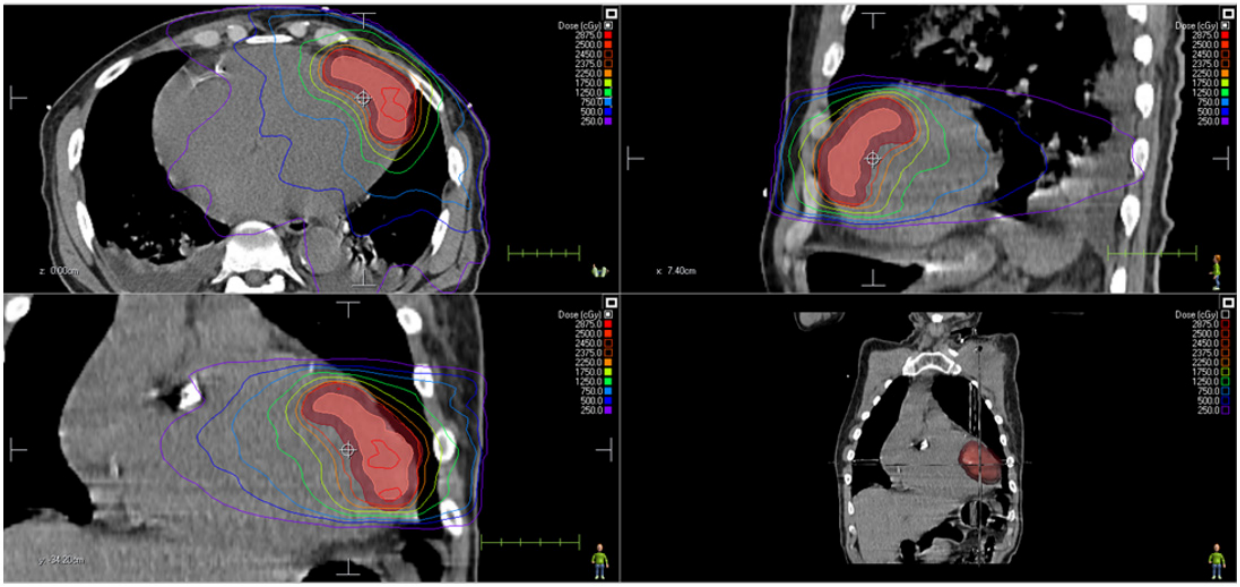

Figure 3. Patient 2 targeting showing appositional CARTO 3® LV map (translucent blue) with ITV (orange) and PTV (dark red)

Table 1. Dosimetric/treatment parameters for STAR

Target	
GTV	Up to 35 Gy max point dose
ITV	Up to 35 Gy max point dose
PTV	95% receives 95% of planned dose (23.75 Gy)
Organ at risk (OAR) Limits	
Spinal cord	< 0.35 cm^3 receives 10 Gy (max point 14 Gy)
	< 1.2 cm^3 receives 8 Gy
Esophagus	< 5 cm^3 receives 11.9 Gy (max point 15.4 Gy)
Stomach	< 5 cm^3 receives 17.4 Gy (max point dose 22 Gy)
Lung	Total bilateral limit: 1,500 cm^3 receives 7 Gy max point dose
Liver	< 700 cm^3 receives 11 Gy max point dose

The STAR treatment plans were generated in the TPS to deliver a total dose of 25 Gy in a single treatment fraction covering the entire region of the PTV. The orientation and direction of the radiation beams relative to the patient were selected with the goal of achieving maximal coverage of the PTV region while reducing the dose to surrounding normal tissue. Five patients were treated with three arcs while 4 patients were treated with two arcs. The selection of arcs was based upon minimizing dose to the OAR including the skin, esophagus, lungs, and spinal cord. The small bowel and stomach were included for ablative targets located near the apex of the heart. Beams were arranged using a dynamic conformal arc therapy (DCAT) or a volumetric modulated arc radiotherapy (VMAT) technique, depending on the target shape. A minimum of two arcs are recommended with this approach to minimize the overall time of delivery. A flattening free filter (FFF) was also used to reduce treatment time. Following review and approval, all plans were subjected to standard internal quality assurance prior to treatment delivery to ensure accurate delivery of the dose to the patient.

At the time of treatment, patients were placed in their custom immobilization device, aligned using the kilovoltage (kV) cone beam CT (CBCT) with additional verification of this alignment using kV orthogonal images of the heart, and treated without use of any additional imaging during the treatment delivery (see Figure 2). Table 1 lists the dosimetric parameters and OAR limits.

2.3 Peri-procedural device management

On the day of the radiotherapy procedure, we conducted comprehensive evaluations of the patients' defibrillators. These assessments included interrogation and appropriate programming, both before and after the radiotherapy session. After the treatment, we programmed the Cardiac Implantable Electronic Devices (CIEDs) to a detection zone that allowed for the detection of VT with a duration $\geq$ 20 ms slower than the slowest clinical or induced VT observed.

As part of routine clinical care, all CIEDs were subject to remote monitoring. We made efforts to maintain consistency in CIED detection and treatment parameters before and after the radiotherapy treatment. Consequently, all CIEDs, when present, were taken into account during the treatment planning phase. This inclusion was rigorously verified through intra-procedural dosimetry, and it is important to note that the radiation dose delivered to all devices remained below 200 cGy in total.

2.4 Post treatment care

In accordance with the clinical requirements of each patient, a decision regarding the appropriate care setting, whether outpatient or inpatient, was made. Once discharged from the hospital, patients were followed up after 1 month and then 3 months. Remote device checks were done every 2 months, per institutional protocol. During the initial post-procedural period, all prescribed medications, including oral anticoagulants, were maintained consistent with the pre-procedural regimen, with oral anticoagulation therapy being sustained for a minimum duration of one month. Adjustments or discontinuation of antiarrhythmic medications were implemented as clinically indicated.

3. RESULTS

In our study, a total of nine patients were included. These patients underwent 12-lead EKGs along with device-generated arrhythmia tracings to approximately localize the origin of the arrhythmia and elucidate its underlying mechanism. Among these nine patients, seven underwent $\geq$ 2 EP study coupled with 3-D EA mapping procedures. Notably, the ninth patient differed from the others, as he had not undergone a prior EP study. This was due to his recent experience of a substantial lateral wall myocardial infarction six weeks prior to the study, which resulted in his continuous hospitalization in the cardiac intensive care unit with a large left ventricular thrombus. Given his hemodynamic instability and physiological constraints secondary to the thrombus, it was deemed unsafe to subject him to an extended mapping procedure. Consequently, with the agreement of his medical power of attorney (his wife), an intervention was carried out in his case.

Of the patient cohort, two individuals had indwelling left ventricular assist devices (LVADs) at the time of the study. In four patients, we were able to conduct a comprehensive 4-D cMRI to elucidate cardiac geometry and structural features, while also identifying regions of myocardial scar tissue and other anomalies. However, in two of these cases, the presence of intracardiac leads posed challenges by obstructing the intended imaging targets.

Six of the nine patients demonstrated a dramatic reduction in VT events at 6 weeks post STAR. One patient underwent cardiac transplantation two weeks following STAR. It is pertinent to mention that this particular patient had been on the transplant list due to pre-existing heart failure that predated the STAR intervention. When we exclude this transplanted patient from our analysis, it becomes evident that nearly all patients, except for one, experienced a significant decrease in VT events over the next 6 months, with some achieving complete freedom from VT (i.e., zero VT events). This positive outcome was observed even in the two patients who had LVADs in place at the time of the study.

Six out of the nine patients successfully survived for at least four months post-procedure without experiencing any VT events, and all six of these patients are currently alive. The single patient who did not respond to the treatment unfortunately passed away 13 months after the procedure. It is noteworthy that this patient did show some degree of response, as his VT episodes transitioned from being non-susceptible to anti-tachycardia pacing (ATP) termination (resulting in frequent shocks) to becoming ATP-terminable (no longer receiving shocks from his device. Another patient from our cohort died two months after the procedure due to uncontrolled multiple myeloma. This patient remained event-free until his demise.

In terms of postoperative complications, one patient developed an asymptomatic pleural effusion, but there were no instances of serious STAR-induced complications such as coronary artery issues, exacerbation of valvular heart disease, or damage to the cardiac conduction system. Detailed event status information for all patients is presented in Table 2.

Table 2. Patient event status

Patient number	Sustained VT episodes 90 days prior to STA	Total sustained VT episodes post STAR	VT episodes in 6 week "blanking period" post STAR	VT episodes post "blanking period" post STAR	6 weeks post
1	6	2	2	2	0
2	Innumerable	0	0	0	0
3	15	62	4	58	58
4	47	0	0	0	0
5	Innumerable	1	1	0	0
6	Innumerable	31	31	0	0
7	10	Innumerable	Innumerable	Transplanted	Transplanted
8	12	0	0	0	0
9	Sustained VT > 1 month	0	0	6	0

4. DISCUSSION

The landmark clinical work was pioneered by Cuculich and Robinson et al. and preclinical work dates back even farther.[3,5] Central to the use of STAR for cardiac ablation is a more critical understanding of the problem and the willingness to use traditional methods in non-traditional ways.

4.1 Catheter ablation of VT

Despite continued advances in ablation techniques, technologies, and our fundamental understanding of VT mechanisms, outcomes of initial VT ablation remain unsatisfactory (success rate reported at 53%-67% in patients with structural heart disease).[2,6] Failure of catheter ablation is often multifactorial, commonly related to difficult anatomic access, challenging catheter navigation, and inability to deliver an adequate transmural lesion. Patients with hemodynamic instability or significant comorbidities do not tolerate long invasive procedures. Moreover, serious complications remain high. Prolonged ablation times proportionally increase risks of perforation, tamponade, asymptomatic cerebral lesions, heart failure exacerbation and even cardiogenic shock.

4.2 Radiotherapy

Radiotherapy is an indispensable tool in the management of patients with cancer. Stereotactic radiosurgery utilizes image-guided, narrowly focused high-dose per fraction irradiation to target well-delineated tumors with ablative intent. For the purpose of STAR, delineation of the arrhythmogenic target while minimizing significant dose to OAR is critical to the success of treatment. When performing pre-treatment planning, an imaging scan [typically computed tomography (CT)] is obtained for radiation dose calculations along with evaluation of dose to nearby OAR.

4.3 Clinical experience with cardiac radioablation

To make the case for STAR, it must be considered that eligible patients have few alternatives and frequently are among the most critically ill with a tenuous life expectancy. For these patients, radioablation is currently done under an emergency classification.

There is an increasing body of clinical experience with cardiac radioablation. We previously noted the landmark study of 2017 where five patients with high-risk, refractory VT showed a reduction from VT baseline of 99.9%.[3] Subsequent additional publications supported optimism for cardiac radioablation of VT as an effective therapy with a reasonable safety profile. Robinson et al. reported a Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia (ENCORE-VT), which prospectively examined the safety and efficacy of noninvasive targeting coupled with a single dose of stereotactic body radiotherapy (SBRT) for patients with refractory VT. A total of 19 patients were enrolled to receive SBRT in the ambulatory setting which was accomplished in an average time of 15 minutes. The treatment achieved a dramatic reduction in several measures of VT burden. Of 18 evaluable patients, any reduction in VT or premature ventricular contractions occurred in 17 (94%), with a concurrent reduction in antiarrhythmic medication. The median number of VT episodes decreased from 119 (4–292) in the 6 months before ablation to 3 (0–31) in the 6 months after ablation. ICD shocks were also significantly reduced from a median of 4 (0–30) to 0 (0–7), as were ATP therapies from before ablation 81 (0–292) to after ablation 3.5 (0–29). No acute toxicity was observed. Delayed pericarditis/effusion (28%) and pneumonitis (11.1%) occurred, which were generally responsive to medical therapy.[6]

A case series and numerous successful case reports have also supported ongoing research into cardiac radioablation.[4,7,8,10,11] However, with limited numbers of patients and a lack of long-term safety and efficacy data, this treatment remains investigational.

4.4 Mechanism of action

Radiation is used to disrupt the DNA of a cell, although the mechanism of benefit here has not been conclusively identified. In oncologic use, complete eradication of the target tumor is the desired outcome. The therapeutic ratio is achieved from the difference in repair capability between the normal tissue (capable of repair) and the target tissue (less or incapable of repair).[12] However, eradication of the target tissue is not the goal of STAR as destruction of the already diseased myocardium could incur severe morbidity or even death.

Myocytes do not undergo cellular division and radiation-induced cardiac injury is well described in the literature.[13,14] However, in one study, myocyte damage was not seen following STAR, with up to 80% cellularity identified.[15] While the actual mechanism of action is unknown, Kim et al. postulate that the overall summation was that the elimination of the erratic focus may occur in the cardiomyocytes themselves, suggesting that the post STAR electrical properties of cardiomyocytes can be remodeled without cell death.[15] Zhang et al. have demonstrated that STAR may act to reprogram the electrical conduction system without inducing cardiomyocyte death or functional loss through Notch reactivation. In cardiomyocytes, the cell surface receptor Notch reprograms/reactivates cells contributing to electrical stability.[16–18]

4.5 Rationale for further investigational study

Despite the successes that have been reported in the literature, a consensus and generalizable framework does not yet exist for administering STAR. Without consistency in process and treatment delivery, the size, and locations of identified VT ablation targets can vary tremendously between patients and ablation facilities, making difficult proper analysis of the successes and failures of cardiac SBRT. There are several process issues that need to be considered:

1. Precisely identifying the target site.

Target delineation is based on some combination of arrhythmia mapping (either noninvasive or invasive) and 3-D imaging. Although conventional diagnostic CT imaging is utilized for data capture and calculation, it often offers inadequate and imprecise soft tissue visualization of the cardiac anatomy. Cardiac MRI can also be incorporated by electronic fusion onto a radiotherapy CT-treatment planning scan. Importantly, most current methods of registering imaging data to define radioablation targets are CT based and rely on a visual consensus reached by the treating physicians, which can lead to over or under estimation of the actual target volume.

2. Determining a safe dose to a designated PTV volume is critical to maximization of success with minimization of risk.

We believe that EA mapping and cMRI based translation directly correlate to increased accuracy and increased precision which additionally translates to lesser volumes for ablation. Radiation complications are inextricably linked to volume, and we believe this approach may lead to reduction of long- and short-term complications, although more study is needed to make definitive conclusions. Determining an optimal prescription dose is critical and data are limited in this regard. The current standard dose delivered at Washington University of 25 Gray was adopted from the first human case report by Loo et al. as a safe dose.[8] Escalation above 25 Gy (30 Gy or more) led to greater scar formation with potentially more efficacy and toxicity, as reported by Kiani et al.[17] Kim et al. demonstrated a trend toward decreased efficacy when using pluripotential extra-corporeal stem cells with doses of less than 25 Gy.[15]

4.6 Comparison of planning methods

A. 17 segment-based planning

The American Heart Association 17 segment left ventricular model with EKG correlate was the initial model reported by Cuculich et al.[3] The workflow for STAR planning based on this model was further described in 2019.[6] As a non-invasive and proven targeting system, it remains the standard to which others are compared. It requires minimal investment, has a high rate of patient acceptance (as a non-invasive methodology) and incurs the least risk among various methods. While proven effective, the model has its detractors and drawbacks. The system relies on surface-based mapping and not direct and precise electrical conductivity mapping such as done with the CARTO3® system.[21] The model is relative to the actual cardiac anatomy and boundary definitions are imprecise in that regard (see Figure 4). In a study by Oh et al., multiple and independent EP physician correlation was widely inconsistent, bolstering this as a possible source of error.[22]

B. cMRI-based planning

In general, CT and MRI have demonstrated complimentary imaging abilities as opposed to exclusive domains. Magnetic resonance imaging has demonstrated superiority of visualization over CT in areas such as the parenchymal brain, liver, and pelvis, while CT imaging is superior in areas such as the lung and boney regions. As an example, brain imaging by MRI is generally superior to CT, while the base of skull and boney cranial structures are generally the domain of CT. It is similar for CT and cMRI based imaging in STAR, but for different reasons. Metallic devices such as CIED leads near a ventricular target may preclude the use of cMRI as targets may be unable to be identified due to cMRI imaging voids. Additionally, the CIED itself precludes imaging in certain centers. Strict cMRI based protocols must be developed to safely image and treat patients with magnetic resonance-based devices.[23] The AGH procedure is partly outlined above, however additional steps are taken in the acquisition of certain sequences such as selecting imaging sequences with a specific absorption rate (SAR) of 2 or less to prevent thermal injury to the myocardium and minimizing the total patient time in the MRI bore depending at least partly on the SAR. Certainly, cMRI unquestionably exhibits enhanced capabilities in visualizing cardiac anatomical structures and has the potential to reveal myocardial scarring following cardiac injury, specifically in the context of infarction, through the application of gadolinium-based contrast enhancement. It is worth noting that on numerous occasions, the infarcted area can serve as the locus for arrhythmogenic events. A minor drawback of this approach is similar to that noted with CT. An additional image is overlaid upon the planning CT which may introduce co-registration uncertainties following image fusion.

C. cCT based planning

Cardiac CT with iodinated contrast presents an attractive image-based alternative to superficial electrical mapping as the cardiac anatomy can be clearly defined, especially in the presence of a well-timed infusion of a specified volume

of iodinated contrast media. However, pure CT imaging alone lacks an electrical correlate. As such, invasive electro physiologic mapping must be developed within the patient temporally proximal to the time of ablation to identify the anatomic site of arrhythmia, unless the 17-segment method is used as an alternative. We prefer CT when cMRI images are distorted or obscured by implanted devices if the target can be clearly identified. Additionally, some systems such as the CARTO3® system are not DICOM compatible and the mesh data files must be translated by verified software to allow an overlay with the CT. A second step of fusing the CT to a radiation planning CT introduces additional possibilities for positional error due to limitation of image registration. This being said, correlative imaging provides a structural platform familiar to the radiation oncologist, medical physicist and dosimetrist.

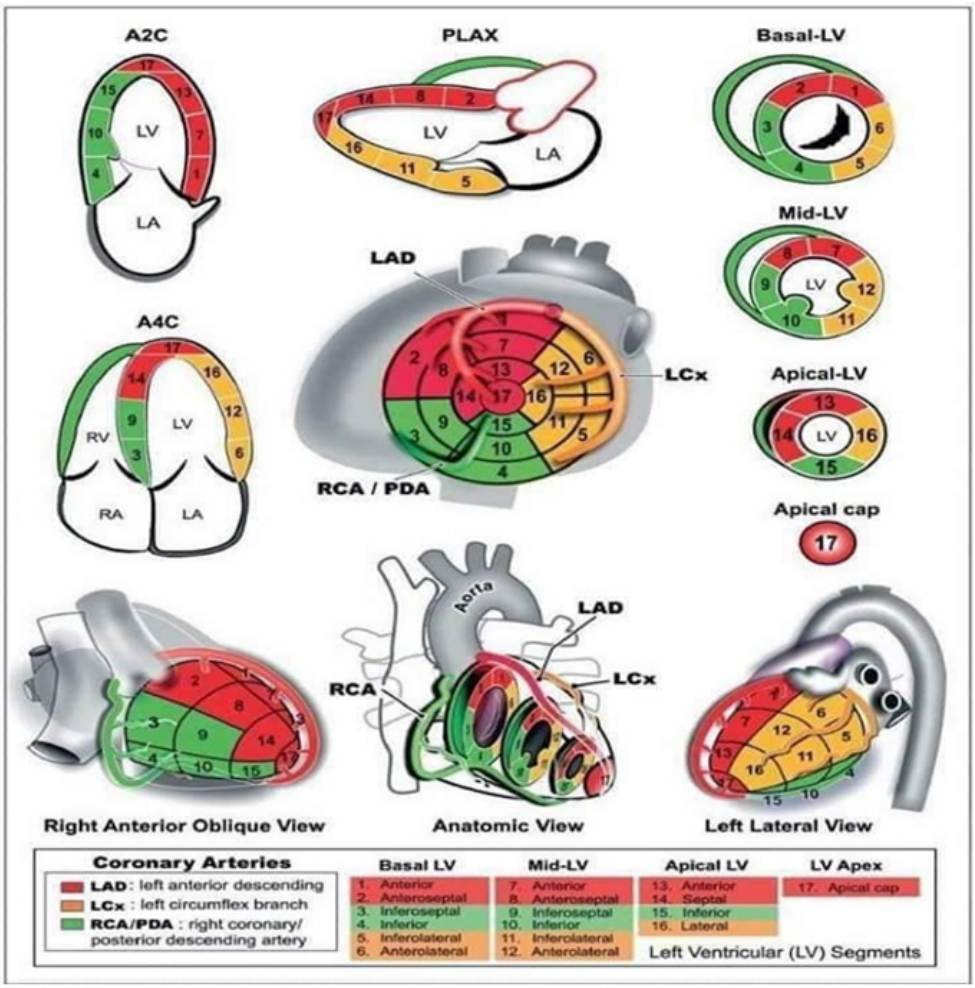

Figure 4. The 17 segment LV model with correlates

4.7 Future plans

We have evaluated the intricacies of the procedure, unique precautions, workflow requirements, and enhanced staffing needs, and have developed a dedicated process to migrate our STAR procedure to an MRI/linear accelerator-based approach for those patients able to be accurately imaged by cMRI. Migration an MRL such as the Unity® (Elekta AB, Stockholm, Sweden) device has the capability of MRI imaging, planning and treatment delivery which eliminates a translational step from cMRI to planning CT. Additionally, the real time imaging will allow intraprocedural monitoring of the target and, we believe, increased accuracy of delivery and decreased target volumes. Respiratory management is an active area of study, most notably by researchers J. Verhoeff and M. Fast et al. [University Medical Center Utrecht]. Additionally, we are developing a planning protocol to minimize dose to the coronary arteries; specifically, the left sided vessels which are frequently near the target volume. As one would expect, these vessels have been chronically affected by coronary vascular disease which many times has precipitated the VT. Finally, we have developed a "Bridge to Transplant" program similar to that used by others in other organ sys-

tems. We expect that some patients, even though successfully treated with STAR, will require transplantation to follow due to extensive cardiac dysfunction frequently found in these patients prior to STAR. We may also have to prepare for transplantation due to long term dysfunction related to STAR which is as yet unknown due to the nascent nature of this procedure.

4.8 Potential risks and intricacies of STAR

Ablative radiation leads to a complex cascade of acute and chronic tissue effects, including microvascular endothelial cell apoptosis, oxidative injury, inflammation, and fibrosis. Post-procedure symptoms may include fatigue, hypertension, nausea, dizziness, dyspnea, and pneumonitis.[10] Some of the most severe toxicities may not manifest until many years after treatment). Late cardiac toxicities have been best described in patients treated with radiotherapy for lymphoma and breast cancer due to long life expectancies in these patients.[12] Exposing large portions of the heart to high doses of radiation can lead to a significant increase in rates of coronary artery, valvular and pericardial disease, conduction abnormalities, and cardiomyopathy. However, modern computerized treatment planning, coupled with more advanced delivery techniques may minimize unintended effects and significantly reduce the risks of cardiac toxicity.

Electroanatomic mapping includes transmural puncture and intracardiac mapping which has inherent risks. Additionally, the intracardiac anatomy is not simply a series of "balloons." There is an intricate fibromuscular network with valvular structures as well as their associated papillary muscles and chordae tendineae which must be navigated with special skill.

Radiotherapeutic delivery is complicated by both cardiac and respiratory motion which much be considered. Currently gating is not possible and with treatment delivery in the 15–20-minute range, as well as the impaired state of these patients in general, breathing management and induced cardiac bradycardia are impractical and potentially unsafe. The lowest efficacious dose has yet to be established, but dose de-escalation protocols are in development.

Additionally, long term risks cannot be adequately identified due to the nascent nature of the therapy and the overall life expectancy of patients with severe cardiac dysfunction which make up the entire patient cohort. From a financial standpoint, widespread application of STAR is difficult, as currently there are no Centers for Medicare and Medicaid codes for billing. And finally, since this paper was submitted two prospective European trails have been published defining additional targeting methodology. We recommend a review of their work.[24,25]

5. Conclusion

STAR appears to be an effective therapy for refractory VT, although long term data are still developing. Multiparametric planning techniques exist, each with their individual strengths and weaknesses, all of which should be considered depending on patient circumstance. Additional clinical trials and techniques are in development and STAR programs should be encouraged for additional well-equipped centers with experienced multidisciplinary clinicians.

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Authors contributions

Dr Trombetta was the primary author and provided radiotherapy direction and planning assistance. Drs Liu, Shaw, Thosani contributed to the manuscript writing, provided electrophysiologic therapy and data acquisition as well as treatment planning assistance. Dr Oh provided computer program development, manuscript writing and planning assistance as well as quality control. Drs Biederman and Doyle provided technical MRI assistance, concept development and manuscript composition. Dr Gupta provided manuscript finalization. All authors provided critical review and refinement.

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Conflicts of Interest Disclosure

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.

Informed consent

Obtained.

Ethics approval

The Publication Ethics Committee of the Sciedu Press.

The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

Provenance and peer review

Not commissioned; externally double-blind peer reviewed.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DATA SHARING STATEMENT

No additional data are available.

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