Journal of Radiotherapy in Practice

cambridge.org/jrp

STereotactic Arrhythmia Radioablation: current status of the art. The old world and the new world connected

Mark Trombetta[1] and Joost Verhoeff[2]

[1]Allegheny Health Network, Drexel University College of Medicine, Pittsburgh, PA, USA and [2]University Medical Center: Utrecht, Utrecht, Netherlands

Editorial

Cite this article: Trombetta M and Verhoeff J. (2023) STereotactic Arrhythmia Radioablation: current status of the art. The old world and the new world connected. *Journal of Radiotherapy in Practice*. **22**(e67), 1–4. doi: 10.1017/S1460396922000401

Received: 10 October 2022
Revised: 10 December 2022
Accepted: 11 December 2022

Author for correspondence:
Mark Trombetta, Division of Radiation Oncology, Drexel University College of Medicine, 314 East North Avenue, Pittsburgh, PA 15212, USA.
E-mail: Mark.trombetta@ahn.org

Introduction

In 2017, the New England Journal of Medicine published the results of the highly unusual work of Washington University of St Louis Missouri (USA), purposely treating the human heart, a theretofore organ at risk (OAR), with radiation for a non-cancerous (but malignant nonetheless) arrhythmogenic focus of ventricular tachycardia (VT).[1] This was not a complete surprise since the literature had been populated with several foundational publications over the past decade.[2–5] However, for the radiation oncology profession which spent decades avoiding direct irradiation of the heart, this was nothing short of astounding.

We are now five years post-publication of the initial cohort and an estimated total number of patients treated with STereotactic Arrhythmia Radioablation (STAR) numbers still only in the hundreds of patients.

Current State of the Art

VT: knowing the enemy

Accurate and complete statistics are difficult to confirm in some countries; however, more than 300,000 persons in the United States die of VT annually as the most responsible entity for sudden cardiac death.[6] While prior myocardial infarction underlies VT most commonly, numerous non-infarct, structural causes also contribute to this event. Extrapolating these numbers across the known world, VT is a major cause of sudden death worldwide.

Limitations of the current state of the art: medications and endocardiac ablation

Medications such as amiodarone have been used with some success; however, the success is often short-lived and toxic. Neurotoxicity frequently becomes untenable, and drugs are often discontinued. As technology improves, many procedures show improved outcomes, including new types of cardiac ablation. However, the success rate is variable and depends on many factors[7] with success in only one-half to two-thirds of patients.[8,9] Causative factors for failure of intracardiac or epicardial ablation include inadequate depth of penetration of the ablative energy (usually less than 5 mm is possible), structural impediments such as cardiac valves (natural or mechanical), defibrillator or pacing leads, and an inability to completely localise and ablate a focal lesion. In this patient group where invasive ablation fails, the non-invasive treatment STAR is tested to prove safety and efficacy.

It must be remembered that this group of patients is among the highest risk for death or serious complication from poorly controlled VT or toxic therapy. As such, these patients poorly tolerate many therapeutic interventions such as extended ablation with its inherent risk of perforation, cerebrovascular insult and haemodynamic alterations due to procedural fluid and/or contrast overload. In a controlled low risk environment, intravascular cannulation and procedural intervention infrequently causes serious events. Not so with this palliative patient cohort, who frequently undergo STAR while in an intensive care unit and/or have multisystem instability. Currently, 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 conventional last resort may be more destructive and carries higher morbidity and risk.

Theories of the mechanism of action

Traditionally in the treatment of cancer, radiation is used to disrupt the DNA of a cell leading to apoptosis. The therapeutic ratio is achieved from the difference in repair capability between the normal tissue (capable of repair) and the target malignant tissue (less or incapable of repair).[10] Whether by direct DNA damage or the creation of free radicals or another state creating indirect

DNA damage, the traditional multi-fraction treatment allows repair of normal tissues between treatment fractions. This is not so in stereotactic radiation where a single very high dose is delivered irrespective of this repair process as there is no interfractional interval. Additionally, complete scarring of the target tissue is not the goal of STAR as eradication of the cardiac muscle (especially in a diseased substrate) could be counterproductive or lethal.

Except for cardiac stem cells, myocytes themselves do not undergo cellular division. As such, they are traditionally radioresistant cells. Cardiac and coronary artery radiation-induced damage following cancer therapy is well described in the literature.[11–13] Interestingly, extensive myocyte damage was not seen following STAR with the clinically used dose of 25 Gy as up to 80% cellularity was identified in explanted hearts.[14] In porcine models, doses higher than 32·5 Gy were needed to create scars.[15] Recently, Kim et al. have produced a report outlining a fascinating number of possible mechanisms.[16] In this sophisticated and intricate study, human-induced pluripotent stem cell-derived cardiomyocytes were monitored with a multi-electrode array recording system to use field potential duration as a surrogate for QT interval analysis. In summary, they identified the following: 1. Electrophysiologist (EP) changes may be due to ion channel function; 2. immediate EP changes such as decreased excitability, increased beat rate and cell-to-cell conduction slowing are restored within 1–2 days; 3. no acute cell death occurs following high dose irradiation. 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 remodelled absent cell death. We highly recommend a careful review of this paper.

Additionally, Zhang et al. at Washington University demonstrated that STAR may reprogramme the electrical conduction system without inducing cardiomyocyte dysfunction from transmural fibrosis through Notch reactivation.[17] Notch is a cell-surface receptor, and the Notch pathway regulates cell proliferation and cell death. In cardiomyocytes, Notch activation reprogrammes/reactivates cells contributing to electrical stability.

Original method

As originally reported,[1] localisation of the erratic arrhythmogenic focus was performed using a 256 lead EKG vest tightly approximated to the patient. From this vest, data (through the generation of a standard 12 lead EKG) are collected and then translated onto the 17-segment left ventricular heart model which correlates the electro-anatomic activity with an anatomically standardised region of the left ventricle to determine the focus of generated ectopy. The VT focus is segmentally identified by translating lead information to the anatomic subsection of the heart. From there, a cardiac CT can be used by translating regions of the heart to corresponding regions of the CT. This CT can be fused to a radiation treatment planning simulation CT which allows for traditional radiotherapy planning with one twist: part of the heart, previously an OAR becomes the target. Volumetric modulated radiation (VMAT) is then delivered to a stereotactic dose currently set at 25 Gy.

Problems with 17-segment model arrhythmia localisation

Immediately apparent is the potential inherent error of surface mapping of electrical currents generated from tiny foci deep within the cardiac muscle substrate. These electrical currents are not visible to any standard imaging device capable of accurate translation of the cardio-electric signal into a conventional radiotherapy treatment planning system. Some authors have also noted interobserver variability of the assignment of representative segments in correlation with the surface EKG.[18,19] At the second Washington University Symposium for Noninvasive Radioablation (SNORAD),[20] a concordance rate of identification among cardiologists, radiation oncologists (RO) and physicists was less than 70% for exact segment identification. Such variances lead to larger targets to ensure coverage of a target lesion identified by uncertainties inherent in the mapping systems. We have noted this in our in-house comparisons (yet to be published).

Alternative methods

Allegheny Health Network (AHN), in Pittsburgh, PA, USA has developed an alternative method of identifying and targeting the VT focus. A CARTO® 3 system (Biosense Webster, Irvine California) is used through a femoral catheterisation site to map the disrupted electrical potentials by directly contacting the intracardiac anatomy. Validated in-house software converts the electro-anatomic (EA) CARTO 3® maps to DICOM compatibility which can then be translated into conventional radiotherapy treatment planning systems. Either cardiac MRI (cMRI) or cardiac CT (cCT) is used to overlay the structural cardiac anatomy with the electrical anatomy. Cardiac MRI is preferred due to superior anatomic delineation; however, care must be taken with the cardiovascular implantable electronic device (CIED) in a high magnetic field. With this technique, it is imperative to enlist MRI imagers with extensive CIED experience. Depending on the presence or absence of image distortion related to the location of the implanted electrodes and the arrhythmogenic target, either cMRI or cCT is fused onto the CARTO 3® maps. At a joint planning conference, electrophysiologists (EP), RO and radiation physicists formulate consensus on the target and planning margins based on electro-anatomic mapping overlay as an alternative to application of the anatomic region of interest from 12-lead EKG localisation using the 17-segment model. The treatment is then delivered by VMAT or dynamic conformal arc therapy, depending on the target shape, usually in a two-arc plan. The delivery is confirmed by kilovoltage cone beam CT and is delivered within 10–15 total minutes. Most patients stay in house at least overnight depending on their fitness, although we have moved to outpatient treatment when possible.

The University Medical Center Utrecht; Utrecht, the Netherlands has developed and convened the Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entry tachycardia by a Multidisciplinary consortium (STOPSTORM).[21] One of the consortium partners (Lubeck University; Germany) has developed unique software for electro-anatomic correlation. This STOPSTORM review software (V 1·0) which is Microsoft Windows® based and runs in Matrix Laboratory (MATLAB®: versus R2021a) software (MathWorks, Inc., Natick Massachusetts, USA) is free to the public and open source. Within this software are two methods for registration of structures. The first, 2D–3D Registration, also uses electro-anatomic maps as above and the contours are manually overlaid onto reference structures such as the ascending aorta. The left ventricular (LV) maps and contours are then registered as related to the original reference structure (ascending aorta). The target is then defined on the LV map and translated from there onto the LV contour of the cardiac CT scan. The second method is the Bullseye 17-Segment registration, which is registered to the ascending aorta and LV and then manually co-registered to the 17-segment heart

https://doi.org/10.1017/S1460396922000401 Published online by Cambridge University Press

model. As the user chooses target segments, the software displays the selected segment on the cardiac CT. Treatment is then delivered.

Volume reduction

Not surprisingly, we expect volume and total dose per defined volume to be critical elements of the safe delivery of STAR. Preliminary results in comparison of techniques between EA mapping and 17-segment model overlay show mixed results.[18,19] There appears to be a definite volume reduction by EA mapping/fusion; however, interobserver variability between EP physicians and small numbers of patients treated to date with this technique makes formal quantification difficult. We expect that the direct mapping method and anatomically exact correlation with intracardiac EA mapping will diminish target volumes significantly compared to the 17-segment model method as the patient numbers expand.

Respiratory motion management

Currently, UMC Utrecht is developing a respiratory motion management protocol for MRI-guided radiotherapy. Due to breathing and cardiac contraction, the average motion of the heart within healthy subjects shows values of 10–17 mm (maximum 24 mm) in superior/inferior and 3–7 mm (maximum 12 mm) in anterior/posterior direction, respectively.[22,23] However, due to anatomical changes, for VT patients this is much lower, on the order of 3–5 mm in the SI, LR and AP directions, with maximum values up to 8 mm in the SI direction and 6·5 mm in the AP direction.[24,25] To manage this motion, an Internal target Volume (ITV) concept seems clinically feasible, although MRI-guided radiotherapy can optimise management of cardiorespiratory motion.

Cardiac motion management

Cardiac motion management, while critical in cMRI, may not be practicable currently, since the overall treatment times are measured in minutes, not seconds. In CT and MRI sequencing, slowing the cardiac rate enhances the images which are obtained within seconds. However, bradycardic manipulation is not practicable due to the relatively long delivery time which negates the benefit of motion control as current gating is not able to deliver sub-second photon bursts to account for cardiac muscle contraction. Additionally, cardiac physiologic manipulation may be risky in this high-risk population.

Initial results

To date at AHN and UMCU, we have treated 10 patients with a minimum of 8 weeks of follow-up. Eight of 10 had a diminution of VT episodes, including 7 who were completely event-free. One patient remained uncontrolled until his death thirteen months post-STAR. However, this patient had no further emergency defibrillations, and this should not be overlooked. One patient went from innumerable episodes post-massive lateral wall myocardial infarction to a single episode to date (12 months post-STAR). Another died VT free from rapidly progressive multiple myeloma 2 months post-STAR, and one underwent transplant two weeks post-STAR. The complete details will be published soon. In general, the time to efficacy has varied between studies, but recent reports demonstrate that the therapeutic effect of STAR can be expected in days to weeks.[24] This mimics our experience as we have seen reduction of VT episodes within days of therapy. To date, only one patient has developed an asymptomatic and minor ipsilateral pleural effusion thought to be resultant from STAR.

The Future

Dose reduction

While 25 Gy was set arbitrarily as a standard by researchers at Washington University in the initial cohort of patients treated,[1] it can be postulated that lower doses may be effective as well. Researchers in multiple sites are beginning to look at dose de-escalation, although 25 Gy may be the optimal dose based on preclinical and clinical results from two studies. In the first study by Kim et al.,[16] the electrical activity of cloned human-induced pluripotent stem cell-derived cardiomyocytes was studied after exposures to multiple-dose regimen of single fraction radiotherapy. Single doses of 20,25,30,40 and 50 Gy were delivered to the cells and compared to unirradiated cells as a control. Radiation was delivered using a conventional linear accelerator, and a multi-electrode array recording system was used to study the electrical alterations at the cellular level. This technique has been previously validated.[26] While this study did not define the mechanism of cell reprogramming as related to overall efficacy of radio-ablation, it demonstrated key findings: First, that cardiomyocytes can be remodelled by irradiation without causing cell death; second, that conduction velocity is slowed and then restored 1–2 days post-irradiation, and third that 25 Gy may be the ideal dose. We should note that, anecdotally, some centres have reported return of VT after 10 months, although the specifics of these issues are not clear at this time.

Additionally, the Swiss dose de-escalation DESIRED study delivered 20 Gy to the target;[27] however, the study was stopped early due to reduced efficacy. The results of these two studies seem to reveal that 25 Gy may indeed be the optimal dose.

Volume reduction

As with all radiation targets and OAR, volume is the foe of radiotherapy. With the defined EA map-based targeting described in both institutions, we expect to demonstrate comparative volume reduction differences among techniques. Currently, most STAR centres are considering volume reduction strategies.

Coronary artery sparing

With a large single dose of radiation delivered to the coronary substructure and the uncertainties related to cardiac motion, we realise that the coronary arteries, long described as vulnerable to irradiation,[28,29] are very likely to be OAR designees soon. Currently, work on coronary sparing is underway in several centres.

Use in non-ventricular arrhythmias

Currently, there are centres which have begun treatment of refractory atrial fibrillation. However, the published data to date are limited and in development.

Summary

STAR appears to be an effective therapy for ventricular tachycardia refractory to conventional therapies. Considering the paucity of therapies currently available (whether due to ineffectiveness or toxicity) and the magnitude of the problem worldwide, stereotactic ablation appears to show bright promise. The combined

https://doi.org/10.1017/S1460396922000401 Published online by Cambridge University Press

experience of the 'Old World' and the 'New World' presented here perhaps mimics a paradigm shift from the 'Old World' of invasive ablation to the 'New World' of STAR. Intense work and collaboration in this new and exciting sub-discipline of radiotherapy are rapidly producing evidence of therapeutic success. Stay tuned.

References

1. Cuculich P S, Schill M R, Kashani R et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. N Engl J Med. 2017; 377: 2325–2336.
2. Ipsen S, Blanck O, Oborn B et al. MO-A-BRD-08: radiosurgery beyond cancer: real-time target localization and treatment planning for cardiac radiosurgery under MRI guidance. Med Phys. 41: 410. doi: 10.1118/1.4889111.
3. Loo B W, Soltys S G, Wang L et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. Circ Arrhythm Electrophysiol. 2015; 8(3): 748–750. doi: 10.1161/CIRCEP.115.002765.
4. Cvek J, Neuwirth R, Knybel L et al. Cardiac radiosurgery for malignant ventricular tachycardia. Cureus 2014; 6: 7.
5. Loo B W, Soltys S G, Lei W et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. Circ Arrhythm Electrophysiol. 2015; 8: 748–750. doi: 10.1161/CIRCEP.115.002765.
6. Sapp J L, Wells G A, Prakash R et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. N Engl J Med. 2016; 375: 111–121.
7. Gianni C, Mohanty S, Trivedi C et al. Alternative approaches for ablation of resistant ventricular tachycardia. Card Electrophysiol Clin. 2017; 9: 93–98.
8. Sacher F, Tedrow U B, Field M E et al. Ventricular tachycardia ablation: evolution of patients and procedures over 8 years. Circ Arrhythm Electrophysiol. 2008; 1: 153–161.
9. Tung R, Vaseghi M, Frankel D S et al. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: an International VT Ablation Center Collaborative Group study. Heart Rhythm 2015; 12: 1997–2007.
10. Aguilar M, Quian C, Boeck M et al. The rapidly developing area of radiocardiology: principles, complications and applications of radiotherapy of the heart. Can J Cardiol. 2021; 37: 1818–1827.
11. van Leeuwene-Segarceanu E M, Bos W J, Dorresteijn L D et al. Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease. Cancer Treat Rev. 2011; 3: 391–403.
12. Ruiz C R, Mesa-Pabon M, Soto K et al. Radiation-induced coronary artery disease in young patients. Heart Views 2018; 1: 23–26.
13. van Nimwegen F A, Schaapveld M, Cutter D J et al. Radiation dose response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol. 2016; 3: 235–243.
14. Chang J H, Cha M. Early period high dose irradiation effect on heart: cell to human. Unpublished data presented to SNOSTORM, 2022.
15. Blanck O, Bode F, Gebhard M et al. Dose-escalation study for cardiac radiosurgery in a porcine model. Int J Radiat Oncol Biol Phys. 2014; 89(3): 590–598. doi: 10.1016/j.ijrobp.2014.02.036. Epub 2014 Apr 18.
16. Kim J S, Choi S W, Park Y et al. Impact of high-dose irradiation on human iPSC-derived cardiomyocytes using multi-electrode arrays: implications for the antiarrhythmic effects of cardiac radioablation. Int J Mol Sci. 2022; 23: 351. doi: 10.3390/ijms23010351.
17. Zhang D M, Navara R, Yin T et al. Cardiac radiotherapy induces electrical substrate reprogramming in the absence of transmural fibrosis. Nat Commun. 2021; 12(1): 5558. doi: 10.1038/s41467-021-25730-0.
18. Oh S, Shaw G, Thosani A, Liu E, Trombetta M G, Sohn J. Target Volume Comparison Between Clinicians Comparing the traditional 17-Segment Model and Direct Registration of Electroanatomic Maps in Stereotactic Arrhythmia Radioablation for Refractory Ventricular Tachycardia. Blue Ribbon e Poster presentation to the 64th annual meeting of the American Association of Physicists in Medicine Washington, DC; July 10–14th.
19. Boda-Heggemann J, Blanck O, Mehrhof F et al. Interdisciplinary clinical target volume generation for cardiac radioablation: multicenter benchmarking for the RAdiosurgery for VENtricular TAchycardia (RAVENTA) trial. Int J Radiat Oncol Biol Phys. 2021; 110(3): 745–756. doi: 10.1016/j.ijrobp.2021.01.028. Epub 2021 Jan 27.
20. Second annual Symposium for Noninvasive Radioablation (SNORAD) Symposium Exercise. St Louis, Missouri, USA, 2019.
21. https://www.stopstorm.eu/en/project.
22. Lydiard S, Pontré B, Lowe B S et al. Cardiac radioablation for atrial fibrillation: Target motion characterization and treatment delivery considerations. Med Phys. 2021; 48: 931–941.
23. Ipsen S, Blanck O, Lowther N J et al. Towards real-time MRI-guided 3D localization of deforming targets for non-invasive cardiac radiosurgery. Phys Med Biol. 2016; 61: 7848–7863.
24. Prusator M T, Samson P, Cammin J et al. Evaluation of motion compensation methods for noninvasive cardiac radioablation of ventricular tachycardia. Int J Radiat Oncol Biol Phys. 2021. doi: 10.1016/j.ijrobp.2021.06.035.
25. Knutson N C, Samson P P, Hugo G D et al. Radiation therapy workflow and dosimetric analysis from a phase 1/2 trial of noninvasive cardiac radioablation for ventricular tachycardia. Int J Radiat Oncol Biol Phys. 2019; 104: 1114–1123.
26. Zwartsen A, de Korte T, Nacken P et al. Cardiotoxicity screening of illicit drugs and new psychoactive substances (NPS) in human iPSC-derived cardiomyocytes using microelectrode array (MEA) recordings. J Mol Cell Cardiol. 2019; 136: 102–112.
27. Verhoeff personal correspondence with Etienne Pruvot re: STARTRAK and DESIRED trials. https://stopstorm.eu/en/centre-hospitalier-universitaire-vaudois-chuv.
28. Heidenreich P A, Kapoor J R. Radiation induced heart disease: systemic disorders in heart disease. Heart 2009; 95(3): 252–258. doi: 10.1136/hrt.2008.149088.
29. Martinou M, Gaya A. Cardiac complications after radical radiotherapy. Semin Oncol. 2013; 40(2): 178–185. doi: 10.1053/j.seminoncol.2013.01.007.

https://doi.org/10.1017/S1460396922000401 Published online by Cambridge University Press