Editor's note: Please see related article, *Noninvasive Cardiac Radioablation at Washington University: Past, Present and Future Directions for the Treatment of Ventricular Tachycardia,* on page 10.

Healing Hearts: Evolution and Growth in Cardiac Radioablation

Mary Beth Massat

Stereotactic body radiation therapy (SBRT) may be more than a tool to target and destroy cancerous cells throughout the body. Data from a phase I/II prospective trial presented at ASTRO 2019 by clinicians at Washington University School of Medicine in St. Louis, Missouri, show promise for using SBRT to ablate cardiac tissue in patients with arrhythmias—including ventricular tachycardia (VT)—where other treatment options have failed.

The study of Electrophysiology (EP)-guided Noninvasive Cardiac Radioablation (ENCORE) for the Treatment of Ventricular Tachycardia is being led by Clifford Robinson, MD, associate professor of radiation oncology and cardiology, and Phillip Cuculich, MD, associate professor of cardiology and radiation oncology, at Washington University in St. Louis. They reported long-term follow-up data on 19 patients demonstrating a 78% reduction in VT episodes more than 2 years after the cardiac radioablation procedure. Overall survival was 74 percent after 1 year and 52 percent after 2 years. Six patients died from cardiac events and 3 died from noncardiac events.[1]

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Previously, Cuculich et al reported a 94% reduction in VT episodes in the first 6 months after cardiac radioablation treatment in a small cohort of 5 patients. The average treatment time was under 15 minutes and most of the patients stopped their antiarrhythmic medications a few weeks after treatment. The therapy combines electrocardiogram (ECG) data with computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging data to identify the precise area of the patient's heart causing the arrhythmia and then targets it with a single high dose of SBRT.[2] (**Figure 1**)

In a news release from the American Society for Radiation Oncology (ASTRO), Dr. Robinson said, "The results are very promising. The use of noninvasive radiation therapy is providing new hope for patients with life-threatening ventricular arrhythmias and limited treatment options." The cardiac radioablation technique could potentially help tens of thousands of people who suffer from arrhythmias and have tried other treatments without success.[3]

Current treatments to correct arrhythmias include medication, cardiac ablation using a catheter to scar or destroy the heart tissue causing the abnormal heart rhythm, and an implantable cardioverter defibrillator (ICD)—a small battery-powered device that detects irregular heartbeats and sends electric shocks to the heart to correct the problem.

ICDs do not prevent arrhythmias or VT, the most dangerous and life-threatening type of arrhythmia. The shocks also can be painful and frightening. Cardiac ablation, meanwhile, comes with high risks and may not provide long-term results, with success rates between 50% and 75%.[3,4] Additionally, cardiac ablation is not always an option because in some patients the catheter cannot reach the site in need of treatment, explains Paul C. Zei, MD, PhD, director, Comprehensive Atrial Fibrillation Program, Cardiac Arrhythmia Service, Brigham and Women's Hospital, and associate professor of medicine at Harvard Medical School, both in Boston, Massachusetts. For this patient population, cardiac radioablation can provide a real clinical need.

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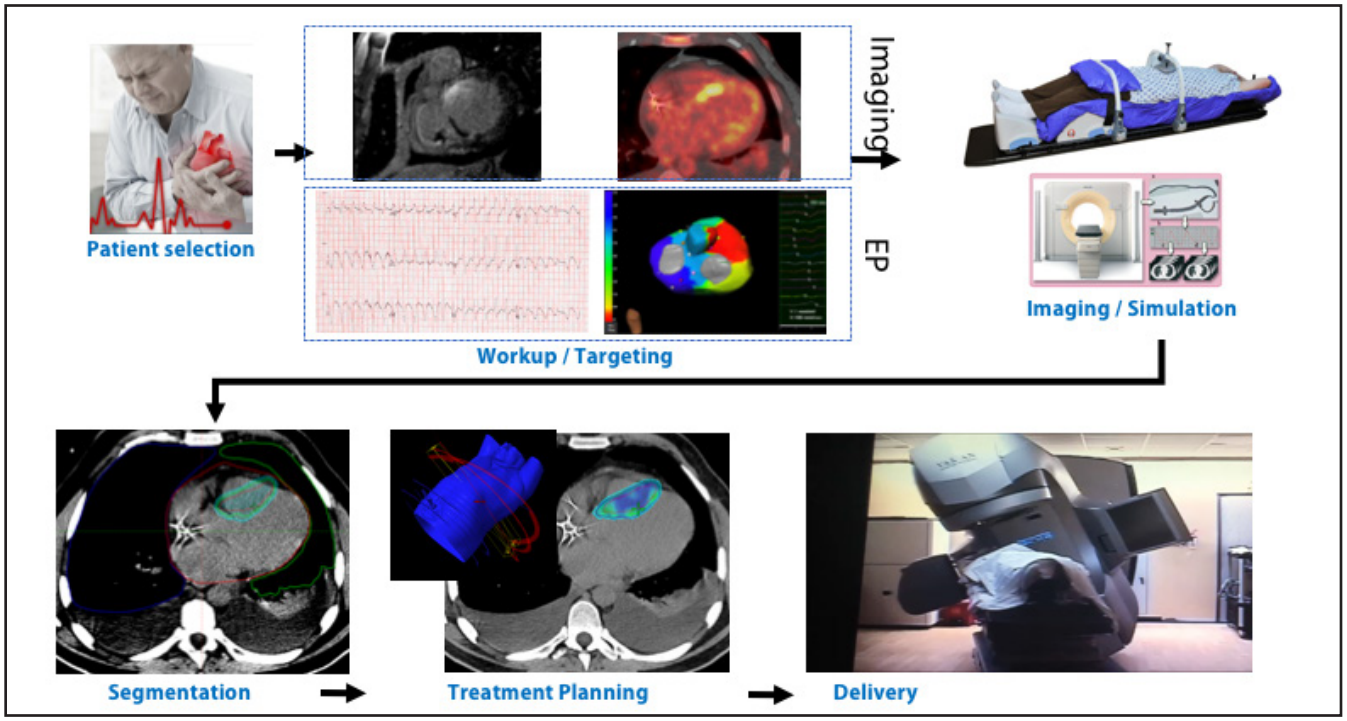

FIGURE 1. *Electrophysiology (EP)-guided noninvasive cardiac radioablation (ENCORE) fuses electrical electrocardiogram and imaging data to pinpoint scar tissue in a patient's heart responsible for the arrhythmias, then targets it with a single dose of stereotactic body radiation therapy. Used to treat ventricular tachycardia, ENCORE requires no general anesthesia and patients can return home immediately after treatment.[3] Credit: Clifford Robinson, MD*

technique and has a much shorter procedure time than catheter ablation," Dr. Zei says. "The tradeoff is there may be longer-term toxicity from the radiation; however, the procedural risk is vastly improved. The other big advantage is that it can address the shortcomings of catheter ablation by overcoming the barrier of getting ablative energy to the treatment site or treating a larger amount of tissue."

Additional Roots

While at Stanford University in California in 2012, Dr. Zei was one of the first clinicians to use CyberHeart's noninvasive method for performing cardiac radioablation on a patient under an Institutional Review Board-approved, compassion-use protocol. At that time, CyberHeart partnered with Accuray Inc. (Sunnyvale, California) to develop the technology for performing cardiac radioablation. In May 2019, Varian (Palo Alto, California) acquired CyberHeart and its intellectual property.

Dr. Zei and his colleagues at Stanford published data on the first CyberHeart procedure on a man in 2015, demonstrating feasibility of the technique. While the patient's VT returned, it was less frequent—52 episodes per month, 2 to 9 months postprocedure, compared to 562 episodes in the 2 months before the procedure. The cycle length was also slower: from 380-411 ms before the procedure, to 470 ms after the procedure.[5]

Of note, the complexity of planning this case went beyond the traditional considerations of using SBRT in the heart.

"In our planning, we had to consider cardiac motion in addition to respiratory motion in this patient," Dr. Zei explains. "There were also logistical challenges. Traditionally, a cardiologist or electrophysiologist doesn't work closely with a radiation oncologist. So that was a new working relationship with the added complexity of getting the patient in for pretreatment imaging, meeting to create the plan, and then scheduling the treatment."

After Dr. Zei left Stanford to lead the Comprehensive Atrial Fibrillation Program at Brigham and Women's Hospital, he continued to explore the potential for treating atrial fibrillation and VF on a Varian Edge radiosurgery system. Six patients have been treated at Brigham and Women's and he has also worked with groups in Texas, Japan, Mexico and Taiwan interested in performing the procedure, treating approximately 20 patients with this technique.

"One to 4 weeks after the procedure, we can see a real effect and that is quite consistent across the publications and in our own experience as well," Dr. Zei says. One limitation for cardiac radioablation, however, is the implanted ICD, which creates artifacts in the MR images of the heart used for treatment planning.

Gaining Momentum

At Allegheny General Hospital in Pittsburgh, Pennsylvania, radiation oncologists Athanasios (Tom) Colonias, MD, and Mark G. Trombetta, MD, were

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intrigued by results reported by Dr. Robinson in the initial 2017 *New England Journal of Medicine* article regarding SBRT to treat patients with refractory cardiac arrhythmias.[2] To learn more, Dr. Trombetta attended a September 2019 symposium at Washington University.

"There was tremendous interest compared to what I expected—approximately 300 people were in attendance," Dr. Trombetta says. "All over the world there are groups working to put this program together to offer it to their patients. However, most have not treated patients as it takes time to develop the technology and the planning."

Drs. Trombetta and Colonias identified a patient who could benefit at Allegheny General Hospital: a man who spent 30 days in the ICU with an uncontrolled heart rhythm. However, approximately 1 week before the procedure, the patient converted to a controlled heart rhythm and has remained in good condition.

"These are the highest risk patients whose alternative is sudden cardiac arrest and death," Dr. Trombetta says.

Vendor Updates

Interest in this procedure has also surfaced in Elekta's (Stockholm, Sweden) MR Linac Consortium, where Dr. Colonias is helping to spearhead a working group.

The Consortium group estimated that 100 patients worldwide have been treated with this procedure. While that number may have increased since the meeting, there is significant interest in exploring the use of Elekta's Unity for this procedure.

"Compared to CT-based planning, cardiac MRI with the right sequences will be a better modality to visualize the heart because of its superior imaging of infarcted soft tissue," Dr. Colonias says.

Adds Dr. Trombetta, "With a dedicated cardiac MRI system, we can see the area of infarct. That capability, or sequencing, is what we are working on to add to the Unity system. The procedure also requires electrical mapping, which can be done with intracardiac electronic mapping and intracardiac electrocardiography or by placing a vest on the patient that contains more than 200 electrode receivers. We need to identify the areas of involvement of the arrhythmia to target the therapy."

According to Dr. Colonias, cardiac radioablation is similar to other uses of SBRT in the body, with some minor adjustments. Drs. Colonias and Trombetta are working with their colleagues at Allegheny General Hospital to fuse the electrical data from the heart with the images used for treatment planning. Since intracardiac electronic mapping data are not DICOM compatible, the hospital team is looking at software revisions that could accomplish this task.

The DICOM-converted intracardiac electronic mapping data comes out in a mesh file providing graphic information that can then be overlaid on cardiac MR images to provide a more detailed vessel analysis that includes electrical activity. Sometimes, erratic heart pulses will go around a tightly ablated area, requiring the entire area to be treated with precision rather than using tiny pinpoint fields. This "fusing" of the electronic mapping and imaging data provides the information needed for radiation treatment planning.

Although there is much excitement surrounding cardiac radioablation, Drs. Colonias and Trombetta caution that more results on efficacy, toxicity and side effects are needed.

"These patients will die without intervention; however, we anticipate there will be significant toxicity and we need to quantify the side effects," says Dr. Colonias.

The good news is that most modern linacs using image guidance with appropriate immobilization devices should be able to deliver cardiac radioablation. Since most treatment planning systems rely on CT simulation data, Dr. Trombetta is working on a protocol to convert these treatments to the Elekta Unity once the system is installed at Allegheny General Hospital.

Although preliminary data are intriguing, many questions remain regarding long-term response and optimizing precision in the delivery and workflow of cardiac radioablation. Elekta is investing resources to explore the technique, both with conventional linacs and the company's MR linac, Elekta Unity, including the working group with Dr. Colonias.

"We were blown away by the initial results presented in both the *New England Journal of Medicine* article and at the ASTRO session last year," says John Christodouleas, MD, vice president of Medical Affairs and Clinical Research, Elekta. "Currently, the most important work is happening at the individual institutions but there are at least a few multi-institutional registries gathering data on disease control and toxicity."

From a research and development standpoint, Elekta is focused on building a foundation of knowledge for radiation oncologists and cardiologists to create a strategy addressing challenges in clinical workflow.

"For this to be successful, it will require the expertise of both communities—radiation oncology and cardiology," he adds. "Both communities will also need to collaborate clinically and technically to make this option available to patients who have very few options left."

Although a conventional linac was used by Washington University in St. Louis, Dr. Christodouleas sees potential for MR linacs. The downside of a conventional linac is it doesn't visualize soft tissue very well and can't visualize the tissue while the beam is on. With the high doses being delivered in the reported cases, soft-tissue visualization and motion management will likely be key to avoiding healthy heart tissue. Dr. Christodouleas points out that in addition to cardiac and respiratory motion, the heart may drift while the beam is on and that could be the most important type of motion to manage as the heart may not drift back to its original position.

"The promise of Elekta Unity is to use soft-tissue diagnostic quality imaging to target the region of interest and to continue imaging the patient while the treatment beam is on," Dr. Christodouleas explains. "If there is a change in position, the provider can hold the beam or track it."

MRI could also potentially be used to assess biologic response, particularly if fractionated treatments are used in the future. The plan used at Washington University in St. Louis was not fractionated, rather it was conducted in 1 treatment session.

According to Deepak Khuntia, MD, senior vice president and chief medical officer at Varian, after acquiring the assets to CyberHeart, Varian created a business entity for cardiac radioablation.

"With the CyberHeart asset and intellectual property, we are looking to create an SBRT solution for cardiac radioablation," Dr. Khuntia says. "This is different from most products Varian has brought to market because it is considered by the FDA to be class III and, therefore, has a more stringent regulatory pathway."

First, however, Varian is focused on assembling the right team to develop an end-to-end solution that addresses technical and workflow considerations as well as regulatory and reimbursement requirements.

"Our cardiac radioablation technique will require a different set of solutions than what currently exists," Dr. Khuntia explains. The institutions that have performed cardiac radioablation have utilized a variety of platforms and have developed in-house solutions for the technique.

"If we want a technology that is available to all clinics and not just academic or large tertiary care institutions, then we need to develop a commercial-grade, scalable solution," he adds.

Dr. Khuntia expects that electrophysiologists will drive this technique, including identifying patients who would benefit, requiring Varian to examine treatment planning from their perspective. Radiation oncologists are accustomed to looking at targeting tools and software with cross-sectional anatomic slices; electrophysiologists, however, view anatomy 3-dimensionally, prompting the need for software updates that provide information in a familiar form.

"This information is not just the electrical signals but also the anatomic and physiologic information," he explains. "Sometimes, a PET scan is used in evaluating arrhythmias. So, how we take that information along with a 12-lead EKG and possibly 4D-gated MR, and reconstruct it into a tool that can help an electrophysiologist target the area of abnormality, still needs to be determined."

While additional multisite, prospective studies and longer-term results are needed to validate the safety and efficacy of cardiac radioablation, patients who have run out of treatment options for their arrhythmia or VT and have undergone cardiac radioablation are reported to be doing well.

"We are on the heels of something quite exciting," Dr. Khuntia says.

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