Received: 16 October 2019 | Revised: 5 November 2019 | Accepted: 13 November 2019

DOI: 10.1002/joa3.12283

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Noninvasive stereotactic radioablation for the treatment of atrial fibrillation: First-in-man experience

Pierre C. Qian MBBS[1] | Jose R. Azpiri MD[2] | Jose Assad MD[2] | Eric Noel Gonzales Aceves MD[2] | Carlos Erick Cardona Ibarra MD[3] | Cuauhtemoc de la Pena MD[3] | Miguel Hinojosa BS[3] | Doug Wong MD[4] | Thomas Fogarty MD[4] | Patrick Maguire MD, PhD[4] | Alice Jack BS[4] | Edward A. Gardner PhD[4] | Paul C. Zei MD, PhD, FHRS[1]

[1]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA

[2]Department of Cardiology, Christus Hospital, Monterrey, Mexico

[3]Department of Radiation Oncology, Christus Hospital, Monterrey, Mexico

[4]Cyberheart, Inc., Mountain View, CA, USA

Correspondence
Paul C. Zei, Brigham and Women's Hospital, 70 Francis Street, Boston, MA 02115, USA.
Email: pzei@bwh.harvard.edu

Funding information
The study received funding support by Cyberheart, Inc. PCQ was supported by a Bushell Travel Fellowship from the Royal Australasian College of Physicians.

Abstract

Purpose: Catheter ablation is an effective therapy for atrial fibrillation (AF). However, risks remain, and improved efficacy is desired. Stereotactic body radiotherapy (SBRT) is a well-established therapy used to noninvasively treat malignancies and functional disorders with precision. We evaluated the feasibility of stereotactic radioablation for treating paroxysmal AF.

Methods: Two patients with drug-refractory paroxysmal AF underwent pulmonary vein isolation with SBRT. After placement of a percutaneous active fixation temporary pacing lead tracking fiducial, computed tomography (CT) angiography was performed to define left atrial anatomy. A tailored planning treatment volume was created to deliver contiguous linear ablations to isolate the pulmonary veins and posterior wall. Patients were treated on an outpatient basis in the radioablation suite. Clinical follow-up was performed through at least 24 months after therapy.

Results: Both patients successfully underwent SBRT planning and treatment without significant early or long-term side effects up to 48 months of follow-up. One patient had AF recurrence after 6 months free of arrhythmia, while the second patient remains free of AF after 24 months with fibrosis detected on MRI scan consistent with the ablation lesion set. An incidentally noted small pericardial effusion occurred in one patient.

Conclusion: Stereotactic radioablation may be feasible for the treatment of drug-refractory AF. Further evaluation is warranted.

KEYWORDS

ablation, atrial fibrillation, new technology, noninvasive ablation, radioablation, stereotactic

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; CT, computed tomography; DOAC, direct oral anticoagulant; ECG, electrocardiogram; Gy, Gray; LA, left atrium; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; LV, left ventricle; MRI, magnetic resonance imaging; PA, posterior-anterior; pAF, paroxysmal atrial fibrillation; PTV, planned treatment volume; RAO, right anterior oblique; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SBRT, stereotactic body radiation therapy; VT, ventricular tachycardia; WACA, wide-area circumferential ablation.

Tweet: First-in-man treatment of atrial fibrillation using noninvasive stereotactic radioablation demonstrates feasibility.

1 | INTRODUCTION

Catheter ablation for atrial fibrillation (AF) has become a widely used approach for the treatment of symptomatic, drug-refractory AF.[1,2] A form of ablative energy is delivered through a catheter introduced into the atria via the venous vasculature to create scar and disrupt the postulated underlying arrhythmogenic substrate. Because the currently utilized energy forms of heating via radiofrequency energy or cooling via a balloon-delivered freezant require direct contact with the myocardial target, an invasive approach is required. The mainstay approach for catheter ablation for AF continues to be a durable electrical isolation of the pulmonary veins,[1,2] while appropriate and effective ablation targets beyond the pulmonary veins, particularly in patients with persistent AF, remain poorly defined.

Freedom from recurrent AF after catheter ablation varies widely, with reported arrhythmia-free survival ranging from as low as 20% to as high as 95%.[1,2] Several variables likely impact outcomes, including AF substrate (paroxysmal vs persistent AF), underlying cardiac pathology, the ablation technique and lesion set utilized, and the methods used to monitor AF burden and recurrence. Although catheter ablation is a reasonably safe and effective procedure, there are well-established risks of complications, including vascular injury, cardiac perforation, phrenic nerve injury, stroke, and most concerning, atrioesophageal fistula, which portend a high mortality rate.[1,2] As a result, there is ongoing interest in developing improved therapies for AF.

Stereotactic body radiation therapy (SBRT) is a technology widely used to primarily treat malignancies and functional disorders.[3] Ionizing radiation in the form of photon energy is delivered to the target tissue via an external beam delivery system. The energy is delivered either by a source that is mounted on a robotically controlled arm or gantry that moves quickly around the patient. Up to several hundred high-energy beams are delivered at varying vectors to concentrate ablative energy within the target while sparing the surrounding tissues. Treatment delivery planning is based on imaging of the target with designation of a treatment zone using software associated with the delivery system. The software typically converts the physician's rendered plan into a radiation delivery protocol which then is delivered in a treatment suite under the direction of a radiation oncologist and radiation physicist. Stereotactic radioablation has been used to successfully treat a wide array of solid tumors including intrathoracic malignancies at an acceptable risk for collateral toxicity.[4–6]

The successful adaptation of stereotactic radioablation to target cardiac substrates has been reported.[7–9] The challenge of effective and safe ablative energy delivery to cardiac tissues is heightened because of the target motion resulting from both respiration and the cardiac contractile cycle. Despite this, effective and safe ablation has been reported in treating human intracardiac malignancy.[7] In a porcine model, the AV node and cavotricuspid isthmus have been targeted successfully, with demonstration of resultant conduction block.[8,10] More recently, successful clinical treatment of left ventricular myocardial substrate for malignant ventricular tachycardia has also been reported.[9,11,12] However, these prior applications of SBRT required a volumetrically simple target; essentially, a spheroid contour was desired. Whereas, the task of creating electrical isolation of the pulmonary veins requires a significantly more complex treatment volume if the current approach of wide-area antral pulmonary vein ablation remains the goal. Despite this complexity, the technology for delivering SBRT has, in theory, the inherent ability to translate any arbitrary treatment volume geometry imagined by the physician into reality in an automated fashion. As proof of this principle, in a canine and porcine model, targeting the right superior pulmonary vein with SBRT demonstrated dose-dependent efficacy in achieving electrophysiological conduction disruption and histological treatment effect.[13]

Safe and effective delivery of stereotactic radioablation to the left atrium (LA) in humans has not yet been reported. We postulated that a standard, widely clinically utilized stereotactic radioablation system could be configured to deliver safe and effective therapy to the LA to target the pulmonary veins in patients with drug-refractory paroxysmal AF.

2 | METHODS

Patients at Christus Hospital, Monterrey, Mexico were eligible for enrollment if they had (a) symptomatic AF documented by office ECG and/or ambulatory ECG monitoring (b) failed, or were intolerant of ≥1 Class I or Class III antiarrhythmic agent, or otherwise declined antiarrhythmic medications, and (c) were offered but refused referral to a large national or international center for catheter ablation of AF, electrophysiology laboratory facilities for which were unavailable locally. Informed consent was obtained, including specific reference to the experimental nature of the therapy, the unknown long-term effects of radiation therapy to cardiac and collateral tissues, the known risks and benefits of standard of care management alternatives such as conventional catheter ablation. Exclusion criteria included inability to provide informed consent, age <18 years, contraindication for radiation therapy including prior radiation therapy to the same body region, pregnancy, or significant vasculitidies or autoimmune disease, contraindication for anticoagulation, NYHA class IV congestive heart failure, or medical prognosis less than 6 months. The study protocol was approved by the local institutional IRB and Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), or Federal Commission for the Protection against Sanitary Risk. All aspects of the study adhered to the Declaration of Helsinki.

2.1 | Stereotactic radioablation treatment planning

The patients were treated in an ambulatory setting without interruption of antiarrhythmic medications or anticoagulation. In order to optimize target tracking during cardiorespiratory motion, an internal fiducial marker was placed transvenously in proximity to the left atrial target, specifically at the right atrial septum. Under fluoroscopic guidance and

via right internal jugular vein vascular access obtained using Seldinger technique, an active fixation unipolar pacing lead (Oscor, 6 French) was introduced into the right atrium and attached to the interatrial septum (Figure 1). In this fashion, no specific movement or breathing restrictions were required of the patients during treatment.

With the fiducial marker in place, patients underwent a planning contrast-enhanced cardiac computed tomography (CT) of the LA. A three-dimensional rendering of the LA was created using cardiac-specific contouring software (CardioPlan, Cyberheart) and used for identifying the treatment target. This target was then imported into the treatment planning software associated with the treatment system (CyberKnife, Accuray) and used to create the radiosurgical treatment plan. In this paradigm, the contouring software allowed the electrophysiologist to draw a computer rendering of the desired treatment volume. Once an acceptable graphic rendering of the treatment volume was created, the treatment planning software in turn then calculated the appropriate delivered radiation beams and their vectors. Next, the treatment plan was evaluated and modified as needed by a radiation oncologist, radiation physicist, and radiation therapist.

2.2 | Stereotactic radioablation treatment delivery

Treatment simulations were performed to ensure therapeutic radiation delivery of >25 Gy to the intended target without exceeding a maximum dose of 35 Gy, based on previous treatment experience,[9,11] while assurance of dosing within tolerances for surrounding structures.[14] The patient was then placed supine on the treatment platform and SBRT was delivered. Real-time imaging with planar x-rays was utilized to register the treatment plan using the fiducial marker as guidance. Next, the therapy was delivered as planned over the prescribed time course of approximately 90 minutes. No procedural sedation was required. Breaks in treatment were provided as needed for the patients, although none were needed. Immediately after treatment delivery, the fiducial marker was removed, and the patients were discharged home.

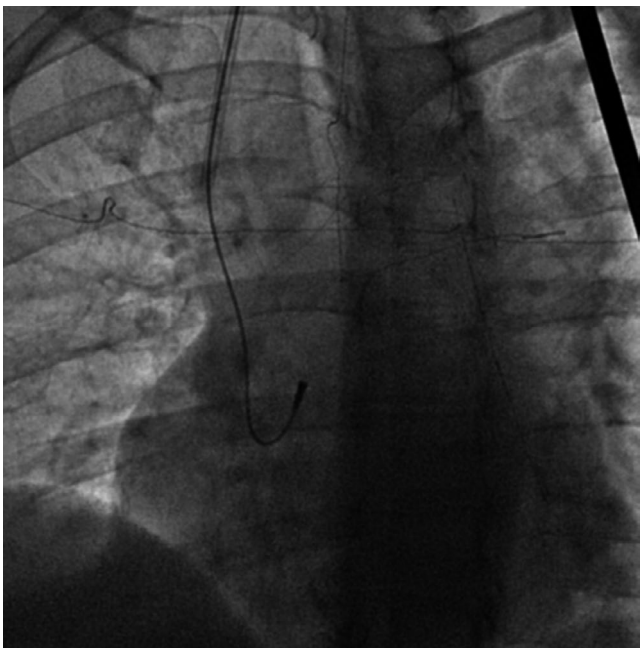

FIGURE 1 Placement of an internal fiducial point to improve radioablative accuracy. This shallow left anterior oblique projection fluoroscopic image demonstrates the position of the fiducial marker placed via right internal jugular vein access, and affixed to the right side of the interatrial septum, in close proximity to the left atrial target. Compensation for cardiorespiratory motion during radioablation is achieved by the external beam delivery system through tracking of fiducial movement using planar xray

2.3 | Clinical follow-up

Subsequent clinical follow-up protocol included monthly history, examination, and ECG, as well as imaging including baseline and repeat transthoracic echocardiography, chest CT, and cardiac MRI within the first 12 months. If clinically appropriate, antiarrhythmic medications were weaned, while anticoagulation was continued as clinically indicated according to CHA_2DS_2VASc score. As invasive mapping of the LA was not performed, there was no direct means to evaluate for pulmonary vein isolation. Moreover, given the time course for lesion maturation of weeks, periprocedural evaluation of electrophysiologic effects of radioablation was not feasible. Therefore, procedural efficacy at follow-up was assessed primarily via symptom reporting, ECG, and ambulatory ECG monitoring. Arrhythmia recurrence was reported with a blanking period of 3 months, given the expected time course for full treatment effect.

3 | RESULTS

Two patients, a 59-year-old man (patient 1) and a 55-year-old woman (patient 2), were treated. Baseline demographics for each patient are shown in Table 1. Both patients had paroxysmal, symptomatic, and drug-refractory AF; minimal comorbidities, save stroke in one patient, and hypertension in the other. Left ventricle (LV) function was normal, LA size was normal or mildly enlarged, and no valvular heart disease was present. Patients were both anticoagulated with direct oral anticoagulant (DOAC) agents, and neither had undergone prior cardioversion or catheter ablation.

3.1 | Design of the stereotactic radioablation lesion set

Radioablation treatment parameters for both patients are shown in Table 2. The designed lesion set for pulmonary vein isolation aimed to minimize radiation dosing to surrounding structures, in particular, the esophagus. The phrenic nerve could not be confidently identified on imaging. However, the

threshold for radiation injury to nerve tissue appears to be significantly higher than myocardium at 70-90 Gy according to clinical experience in radioablative treatment for trigeminal neuralgia.[15] For patient 1, a modified "box" lesion[16] set was planned. This included a contiguous lesion set encircling both right and left pulmonary vein (PV) sets and posterior wall. The lesion traversed anterior to both sets of PVs, the LA roof, and the inferior LA just posterior to the mitral valve. For patient 2, because of the rightward location of the esophagus near the right PVs, a pairwise wide-area circumferential ablation lesion set with a confluent overlap at the posterior wall was planned (Figures 2 and 3). These lesion sets were designed principally to minimize radiation dosing to the esophagus.

TABLE 1 Baseline clinical characteristics of the treated patients

	Patient 1	Patient 2
Age	59	53
Gender	Male	Female
Hypertension	N	Y
Diabetes mellitus	N	N
Coronary artery disease	N	N
Peripheral artery disease	N	N
Stroke	Y	N
Congestive heart failure	N	N
CHA_2DS_2VASc score	2	2
AF duration	7 y	4 y
AF type	Paroxysmal	paroxysmal
AF symptoms	palpitations	palpitations
Anticoagulation	rivaroxaban	dabigatran
Failed antiarrhythmic medications	atenolol	atenolol
		amiodarone
		propafenone
Prior electrical cardioversion	N	N
Prior catheter ablation	N	N
Transthoracic echocardiogram		
Left ventricular ejection fraction	Normal	Normal
LA diameter (cm)	3.8	4.5
Presence of valvular disease	N	N
Baseline rhythm	sinus	sinus

3.2 | Delivery of radioablation dose

After fiducial marker placement and CT scan were performed, treatment planning and radioablative energy delivery was completed within 2 hours. The intended treatment plan was successfully delivered for both patients, with 89% and 96% of the planned treatment volumes receiving ≥25 Gy for patient 1 and 2, respectively (Figure 3), and acceptable average dose to nearby visceral tissues[14] (Table 2; Figure 3). Immediately after treatment, the fiducial markers were removed without complication. The patients tolerated the procedure well, with no immediate physical complaints nor observed complications.

3.3 | Clinical follow-up

In patient 1, no AF recurrence was seen during the first 6 months of follow-up; however, persistent AF occurred at 6 months. Because of prior intolerance of beta-blocker, the patient was placed on a rate control regimen of diltiazem. Owing to patient preference, no further attempts at rhythm control were performed. For patient 2, no recurrence of AF was seen on follow-up and monitoring. The patient continued on propafenone, having

TABLE 2 Stereotactic radioablation treatment delivery parameters

	Patient 1	Patient 2
Prescription dose (Gy)	25 Gy	25 Gy
Collimator size (mm)	Fixed 20 mm	Fixed 7.5 mm, 12.5 mm, and 20 mm.
Beams	241	269
Monitor Units (MU)	44 665	48 303
Treatment volume (ml)	48.87	54.5 ml
Mean delivered dose to target and nearby tissues (range)		
Targeted left atrial myocardium	35.21 (14.27-35.21) Gy	34.24 (16.99-34.25) Gy
Untargeted myocardium	12.62 (1.22-35.18) Gy	9.52 (1.93-34.25) Gy
Mitral valve	18.53 (15.06-22.93) Gy	10.87 (5.88-20.58) Gy
Pericardium	11.19 (1.19-35.18) Gy	7.31 (1.90-32.71) Gy
Lung	3.93 (1.00-30.94) Gy	3.52 (1.45-18.04) Gy
Esophagus	5.54 (1.18-16.65) Gy	4.61 (1.81-15.04) Gy
Spinal cord	3.25 (1.16-9.67) Gy	3.95 (1.71-6.62) Gy
Treatment time (min)	90	90

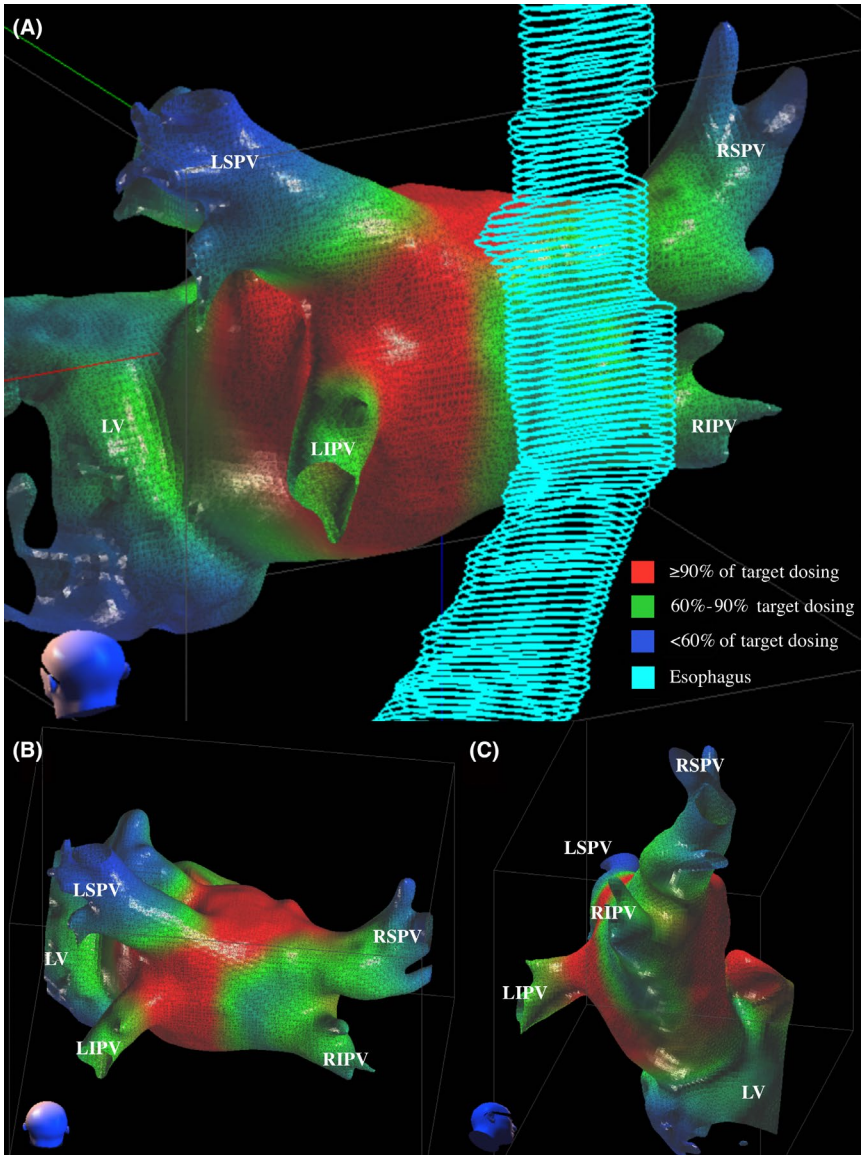

FIGURE 2 Anatomical considerations in tailoring the radioablative lesion set. Treatment dosing for Patient 2 is displayed on the 3D rendered left atrial volume using the radioablation treatment planning software (Cardioplan, Cyberheart, Inc and Cyberknife, Accuray Inc) Panel A shows a posterior-anterior projection of the left atrium with the esophagus in situ to demonstrate the arrangement of the lesion set to minimize esophageal dosing. Panel B and C are additional posterior-anterior and right lateral caudal views with the esophagus removed. Red signifies dosing at or above 90%, green (60%-90%) and blue (<60%) of the target dose of 25 Gy. LSPV:Left superior pulmonary vein; LIPV:left inferior pulmonary vein; RSPV:right superior pulmonary vein, RIPV:right inferior pulmomary vein; LV:left ventricle

weaned down to half dose during the follow-up period and remains on this antiarrhythmic given their previous difficulty with rhythm control and patient preference. No further AF has been reported at 2 years of follow-up. Both patients had continued DOAC therapy throughout the follow-up period. No adverse clinical effects have been reported, now approximately 3 years after initial therapy. In patient 2, routine transthoracic echocardiography at 6 months following treatment found a 4 mm global pericardial effusion without hemodynamic effects; this resolved with conservative management.

For patient 2, a cardiac MRI was performed before and at 1 year after SBRT delivery which showed a region of fibrosis not present on baseline imaging (Figure 4). The distribution of fibrosis in the septal and lateral left atrial walls was consistent with the SBRT lesion set delivered in this patient (Figures 1 and 2). No symptomatic nor occult complications were observed throughout the entire follow-up period to date and no change in cardiac function or valvular heart disease was observed (Table 3).

4 | DISCUSSION

In this study, first-in-man treatment of paroxysmal AF using stereotactic radioablation is described in two patients with indications for catheter ablation but a strong desire to undergo a less invasive procedure. We showed that it is possible to coordinate, plan, and accurately deliver a complex lesion set to the LA using stereotactic ablative therapy safely and effectively with a multidisciplinary team that includes cardiologists, electrophysiologists, and radiation oncologists and radiation physicists. No complications or longer term side effects of cardiac tissue irradiation were observed in either patient; one patient had reduction in AF burden and subsequent MRI imaging was consistent with left atrial radioablation induced fibrosis.

Atrial fibrillation continues to be one of the fastest growing, most prevalent, and costly cardiac conditions.[2] Treatments directed at restoration and maintenance of sinus rhythm remain inadequate both in long-term single-procedure success rates

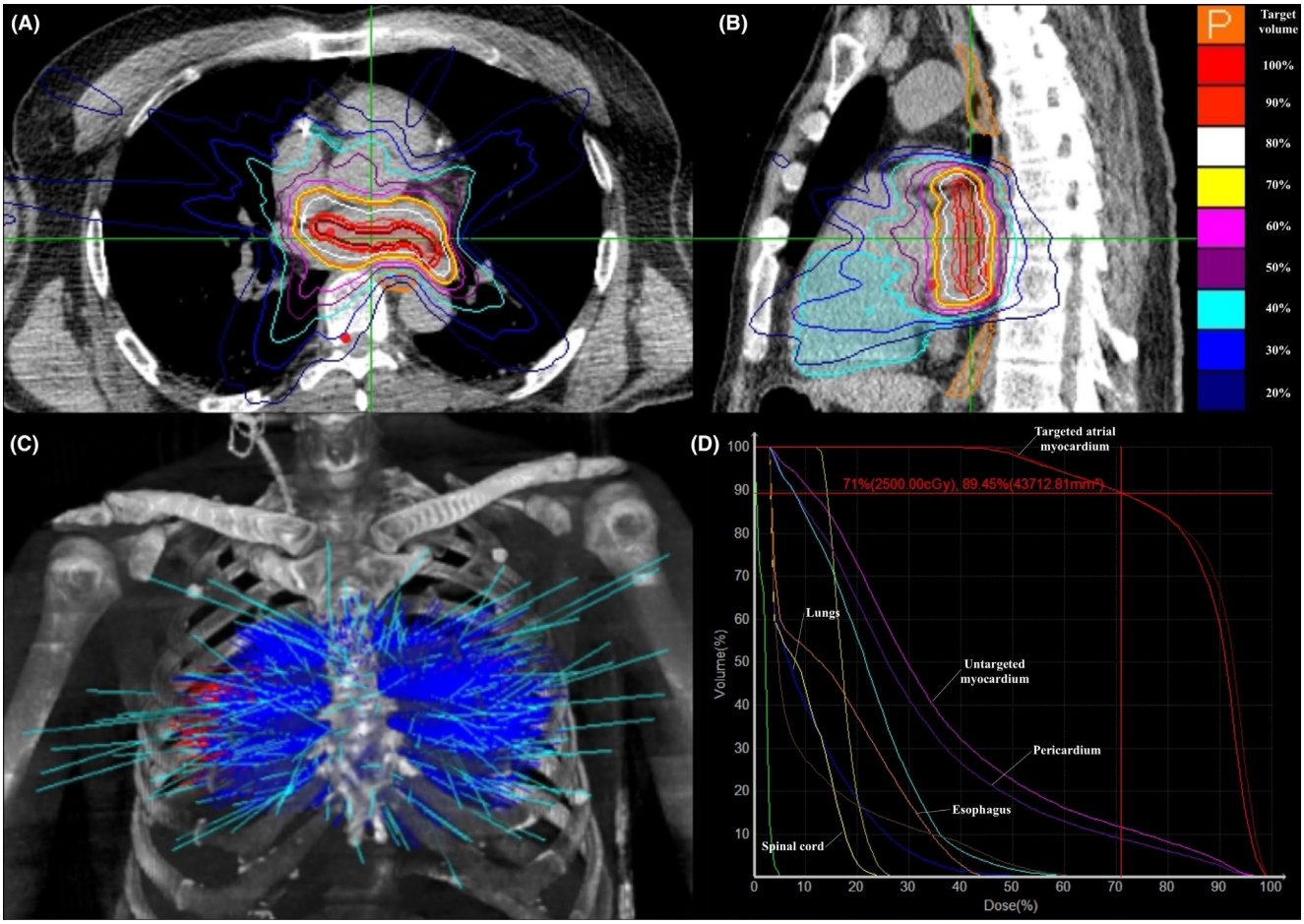

FIGURE 3 Planning and delivering steretotactic radioablation to the left atrium. Preprocedural CT scan of the chest obtained for patient 1; treatment volume planning requires defining a treatment volume using orthogonal imaging planes. Panel A and B show transverse and sagittal planes through the left atrium demonstrating radioablative isodose contours within and around the planned treatment volume, P, shown bounded by the orange line. Panel C demonstrates the calculated multiple beam angles used to deliver and concentrate radioablative energy within this treatment volume. Panel D shows the proportion of dose delivered to the targeted atrial myocardium and other key nearby visceral tissues as a function of tissue volume; it can be seen that approximately 89% of the target volume received at least 25 Gy

and economic considerations that limit access to health care. Stereotactic radioablation offers the potential to treat patients noninvasively, without anesthesia, and in an ambulatory setting, possibly lowering the barrier to therapy for many patients. In addition, the nearly ubiquitous presence of stereotactic ablation devices worldwide and the ability to plan treatment delivery digitally without a cardiac electrophysiology laboratory may allow access to therapy for many more patients in need on a global scale. Other applications of this approach may be in populations where conventional catheter ablation is indicated, but carries high risk, such as in severe heart failure,[17] or where left atrial access is prohibited by congenital abnormality, vascular occlusion, thrombus, or coagulopathy. Further evaluation is required to determine if this technology can provide acceptable clinical efficacy and side effect profile and further delineate its role and cost-effectiveness as an alternative modality to invasive catheter ablation therapy for the treatment of AF.

Given the limited clinical experience with stereotactic radiotherapy targeting cardiac arrhythmias, the ideal dosing regimen remains uncertain. Experience described in this report as well as prior reports describing treatment of VT[9,11] have consistently shown safety and, in general, effective arrhythmia reduction at 25 Gy treatment dose. Even in preclinical evaluations, treatment escalation did not demonstrate toxicity up to 35 Gy in a single-fraction dose.[10,13,18] Much of our current knowledge of the cardiotoxic effects of radioablation is derived from clinical observations in the radiation oncology literature after treatment of nearby noncardiac targets,[19,20] thus the long-term toxic effects of direct cardiac radioablation remain still largely unknown.

Although the stereotactic radioablative treatment itself was completely noninvasive, a temporary fiducial marker was placed on the right side of the interatrial septum to ensure accurate target tracking during cardiorespiratory motion. In theory, any discrete cardiac or pericardial structure that has adequate radiographic opacity as well as fixed translational distance and similar cardiorespiratory excursion as the intended target could be used as a fiducial marker; for example, cardiac valve calcification, coronary calcification or stents, and implanted permanent pacing lead electrodes. Alternative

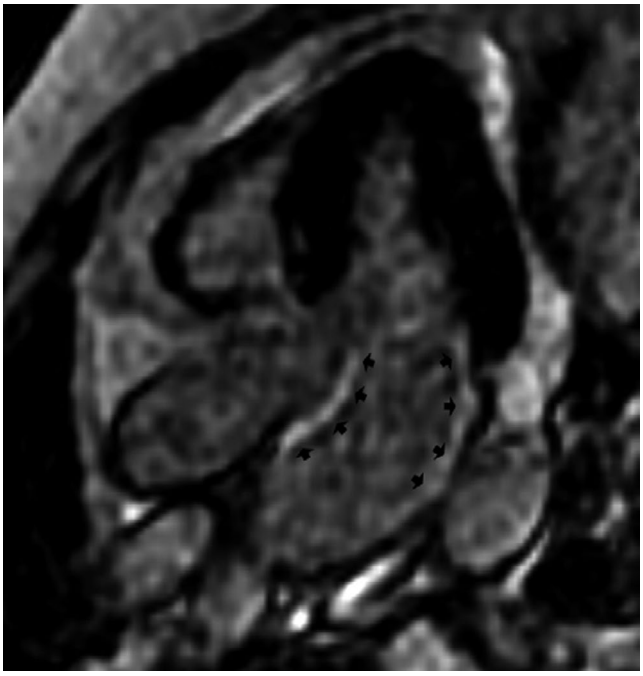

FIGURE 4 Cardiac magnetic resonance imaging demonstrating left atrial fibrosis in the radioablation treatment zone. Cardiac MRI for Patient 2, performed one year post stereotactic radioablation therapy, is shown. In this four-chamber view, areas of late gadolinium enhancement (arrows), consistent with fibrosis, are seen within the left atrium septal and laterally consistent with treatment areas

approaches to compensate for patient and cardiorespiratory motion include gated radioablative energy delivery or designating a larger treatment volume to encompass the range of expected motion, though the latter approach may increase exposure to critical structures such as the esophagus and more distal PVs. Evaluation of the merits of other approaches to compensate for cardiorespiratory motion during SBRT is warranted if a completely noninvasive procedure is intended.

5 | LIMITATIONS

The small number of treated patients limit generalizability of the observed results and more clinical experience is warranted to better understand the efficacy and safety of this treatment paradigm. Given patient preference in this study, invasive electrophysiologic testing could not be performed to demonstrate electrical block. Further studies in larger patient cohorts and where pulmonary vein isolation can be ascertained are required to overcome these limitations.

6 | CONCLUSION

In this first-in-man study, we demonstrated the feasibility of applying SBRT to accurately deliver a complex left atrial lesion set aiming to isolate the pulmonary veins and posterior wall in patients with symptomatic paroxysmal AF. Stereotactic radioablation is a widely available technology that can potentially provide a noninvasive alternative for delivering ablation therapy to control this highly prevalent and important condition. The translation to clinical practice of this imminently scalable approach depends on further studies to define optimal clinical dosing, procedural efficacy, and long-term safety.

TABLE 3 Clinical treatment outcomes

	Patient 1	Patient 2
Treatment Date	October 2014	April 2016
PV isolation approach	WACA	WACA
Additional ablation lesions	Box (roof line, inferior line)	Roof and posterior wall ablation
Follow-up duration to date (mo)	48	24
AF Recurrence	Y	N
Time to AF recurrence (mo)	6	N/A
Symptoms at last follow-up, compared to preablation (1 = worse, 2 = unchanged, 3 = improved)	3	3
Additional ablation procedures performed?	N	N
Adverse events		
Myocardial ischemia	N	N
Vascular access complication	N	N
Organized atrial tachyarrhythmias	N	N
Pericardial tamponade	N	N
Stroke, TIA	N	N
AE fistula	N	N
Pneumonitis or bronchitis	N	N
Dysphagia or odynophagia	N	N
Posttreatment follow-up TTE (12 mo)		
Left ventricular ejection fraction	Normal	Normal
LA diameter	4.6	4.5
Presence of valvular disease	N	N

CONFLICT OF INTEREST

PCZ: research support, consulting (Cyberheart); DW, EG, PM, AJ: employees (Cyberheart); TF: equity interest (Cyberheart); Others: none to report.

ORCID

Pierre C. Qian https://orcid.org/0000-0003-1447-4680

TWITTER

Paul C. Zei @paulzei

REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B,, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothoracic Surg. 2016;50:e1–88.
2. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. J Arrhythm. 2017;33:369–409.
3. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand. 1951;102:316–9.
4. Videtic GMM, Hu C, Singh AK, Chang JY, Parker W, Olivier KR, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927). Int J Radiat Oncol Biol Phys. 2015;93:757–64.
5. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol. 2011;6:2036–43.
6. Macia IGM. Radiobiology of stereotactic body radiation therapy (SBRT). Rep Pract Oncol Radiother. 2017;22:86–95.
7. Soltys SG, Kalani MY, Cheshier SH, Szabo KA, Lo A, Chang SD. Stereotactic radiosurgery for a cardiac sarcoma: a case report. Technol Cancer Res Treat. 2008;7:363–8.
8. Sharma A, Wong D, Weidlich G, Fogarty T, Jack A, Sumanaweera T, et al. Noninvasive stereotactic radiosurgery (CyberHeart) for creation of ablation lesions in the atrium. Heart rhythm. 2010;7:802–10.
9. Loo BW, Soltys SG, Wang L, Lo A, Fahimian BP, Iagaru A, et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. Circ Arrhythm Electrophysiol. 2015;8:748–50.
10. Lehmann HI, Deisher AJ, Takami M, Kruse JJ, Song L, Anderson SE, et al. External arrhythmia ablation using photon beams: ablation of the atrioventricular junction in an intact animal model. Circ Arrhythm Electrophysiol. 2017;10:e004304.
11. Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, et al. Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia. N Engl J Med. 2017;377:2325–36.
12. Robinson CG, Samson PP, Moore KMS, Hugo GD, Knutson N, Mutic S, et al. Phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation for ventricular tachycardia. Circulation. 2019;139:313–21.
13. Zei PC, Wong D, Gardner E, Fogarty T, Maguire P. Safety and efficacy of stereotactic radioablation targeting pulmonary vein tissues in an experimental model. Heart rhythm. 2018;15:1420–7.
14. Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2010;76:326–32.
15. Régis J, Tuleasca C, Resseguier N, Carron R, Donnet A, Gaudart J, et al. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. J Neurosurg. 2016;124:1079–87.
16. Kumagai K, Muraoka S, Mitsutake C, Takashima H, Nakashima H. A new approach for complete isolation of the posterior left atrium including pulmonary veins for atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18:1047–52.
17. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018;378:417–27.
18. Bode F, Blanck O, Gebhard M, Hunold P, Grossherr M, Brandt S, et al. Pulmonary vein isolation by radiosurgery: implications for non-invasive treatment of atrial fibrillation. Europace. 2015;17:1868–74.
19. Adams MJ, Lipshultz SE, Schwartz C, Fajardo LF, Coen V, Constine LS. Radiation-associated cardiovascular disease: manifestations and management. Semin Radiat Oncol. 2003;13:346–56.
20. Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys. 2010;76:S77–85.

How to cite this article: Qian PC, Azpiri JR, Assad J, et al. Noninvasive stereotactic radioablation for the treatment of atrial fibrillation: First-in-man experience. *J Arrhythmia*. 2019;00:1–8. https://doi.org/10.1002/joa3.12283