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Cardiac arrhythmias and stereotactic radioblation: Pros and cons

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Cardiac arrhythmias and stereotactic radioblation: Pros and cons

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Editorial: Stereotactic radioablation of cardiac arrhythmias: pros and cons

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Editorial on the Research Topic
Cardiac arrhythmias and stereotactic radioblation: pros and cons

Ventricular tachyarrhythmias (VT) represent a life-threatening condition often observed in patients with structural heart disease, with consequent serious impact to patient survival and quality of life. The most common cause of recurrent monomorphic VT is the presence of an electroanatomic scar and related re-entry mechanisms. Particularly, radiofrequency catheter ablation (RFA) represents the gold standard for scar-related VT ablation, along with optimal medical therapy. The localization of an arrhythmic substrate inaccessible using catheter-based ablation techniques, usually due to a location deep on the endocardial or epicardial surfaces of the myocardium, is the most common cause of RFA failure (1). With regard to this, noninvasive stereotactic arrhythmia radioablation (STAR) uses stereotactic body radioablation therapy (SBRT) as a novel treatment modality for refractory VT (2, 3). Stereotactic body radioablation therapy delivers high-dose focused radiation in a single fraction of 25 Gy, allowing ablation through induction of myocardial scarring and a second mechanism related to reprogramming of electrical conduction (4). The procedure is completely noninvasive; therefore, it can be performed in patients with contraindications to invasive ablation procedures. Cardiac STAR should be performed at experienced centers, preferably within clinical trials, in cooperation between cardiac electrophysiologists and radiation oncologists and physicist. In this Research Topic of Frontiers in Cardiovascular Medicine, we aimed to report on three different themes such as:

- comprehensive review of the literature on STAR
- complex case reports, original research, and new studies on VT STAR
- new frontiers: STAR and atrial fibrillation (AF)

Comprehensive review of literature on STAR

In the first systematic review, Volpato et al. provided an overview of the available studies on VT STAR, describing the potential indications and technical aspects of this promising therapy. Particularly, STAR can be considered a true treatment for patients with structural heart disease who have recurrent VT or electrical storm despite optimal antiarrhythmic drug therapy and prior catheter RFA, or in case of contraindications to RFA, such as in

the case of mechanical aortic and mitral prosthetic valves. The purpose of the second systematic review by Franzetti et al. is to collect available evidence on the feasibility and efficacy of STAR in the treatment of AF. Particular attention should be paid to the safety rather than the efficacy of STAR, given the benign nature of AF. Uncertainties remain, especially regarding the definition of the treatment plan and the role of the target motion. In this setting, more information about the toxicity profile of this new approach is compulsory before applying STAR to AF in clinical practice.

Complex case reports, original research and new trials on VT STAR

In this Research Topic, we designed the observational study "VT-Art Consortium" in order to provide insight into the efficacy and safety of STAR through a matched pair analysis, in two groups of patients with VT undergoing radiation therapy versus conventional ablation.

Particularly, the early response to STAR may be unpredictable and probably does not reflect the final outcome of irradiation as demonstrated by preliminary results from the SMART VT trial using the volumetric modulated arc therapy technique and three 6 MeV flattening filter-free photon beam fields. Functional changes could appear relatively early, manifesting as a rapide decrease of VT burden, as well as transient exacerbation of the arrhythmia. The SMART-VT study is ongoing, and the clinical course of the two presented cases clearly indicates that the toxicity profile of the STAR can only be assessed as part of a comprehensive clinical trial.

Wight et al. analyzed long-term follow-up of STAR for refractory VT in advanced heart failure patients, with evidence of an immediate reduction in VT burden after treatment as an important bridge to transplantion in this particular clinical setting. We have also published a challenging case series on the feasibility of repeated STAR in recurrent VT, with good acute and mid-term safety.

Four case reports were included in our Research Topic: successful VT STAR in two complex cases, such as patient with pleurodesis and patient with multiple devices (valve prosthesis, biventricular defibrillator and contractility modulation device); histopathological examination of the irradiated ventricle with evidence of multifocal mosaic-like fibrosis; feasibility of ultrasound guidance with probe in parasternal viewing position during treatment. On this regard, in the single center study by Casula et al., a prototype of an automatic ultrasonographic imaging acquisition system was developed using an artificial intelligence algorithm to calculate cardiac displacement in real-time. In addition, Dvorak et al. proposed a new technique for geometry deformation margin with Cyberknife before STAR for better control of the risk of "target underdose".

New frontiers: STAR and atrial fibrillation

A prospective phase-II trial was designed to evaluate the safety of LINAC-based STAR (ClinicalTrials.gov: NCT04575662). Di Monaco et al. selected 5 elderly patients with refractory AF undergoing STAR, without evidence of acute toxicity.

Future directions

Non-invasive ablation of cardiac arrhythmias with STAR is generating considerable enthusiasm as an emerging treatment modality for VT. We consider this Research Topic a unique opportunity to share different views on this innovative treatment in electrophysiology. Current experience does not support the view that STAR can replace conventional catheter VT ablation. Larger prospective studies and randomized trials are needed to evaluate the efficacy and the long-term safety of this new treatment. Furthermore, considering STAR as an emerging treatment modality in heart failure patients undergoing heart transplantion, histopathological and molecular study could provide important data for the development of an accurate biological model of the antiarrhythmic effect of STAR.

Author contributions

All authors contributed to this editorial with substantial and direct review of the manuscript and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Paroxysmal Atrial Fibrillation in Elderly: Worldwide Preliminary Data of LINAC-Based Stereotactic Arrhythmia Radioablation Prospective Phase II Trial

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Treatment approach for elderly patients with atrial fibrillation (AF) is difficult. The present prospective phase-II trial evaluated LINAC-based stereotactic arrhythmia radioablation safety in this population. The reported data of the first 5 patients worldwide, showed no side effects, absence of AF episodes and without antiarrhythmic drugs. **Trial Registration:** ClinicalTrials.gov, identifier: NCT04575662.

Keywords: radioablation, stereotactic body radiotherapy, arrhythmia, atrial fibrillation (AF), elderly patients

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting more than 40 million individuals in the world, and elderly age is a prominent risk factor (1).

AF increased the risk of stroke and heart failure with a reduction in functional capacity (1). Current guidelines recommend Pulmonary Veins (PVs) isolation with catheter ablation (CA) in symptomatic patients refractory to antiarrhythmic therapy (AAT) (1).

In elderly, paroxysmal AF is difficult to treat with drugs, since they alternate sinus bradycardia and fast rate AF in the so-called tachy-bradi syndrome, and by CA due to the higher complication rate (1, 2). Thus, a non-invasive approach should be favorite.

Other ablation approaches have been implemented in cardiac arrhythmia, including stereotactic arrhythmia radioablation (STAR) or radiosurgery which is a safe and effective arm in the oncological and non-oncological scenario. STAR, using high-dose radiation, produced great biological cell kill death by multifactorial results (DNA double-strand breaks, apoptosis, vascular damage, ischemic cell-death) (3–5).

As we reported in a previous review, in field of preclinical research applied to STAR, several studies were conducted in animal models, showed also in porcine model the PVs isolation to treat AF could be achieved by radiosurgery with a conventional LINear ACcelerators (LINACs) (3).

Several STAR data were published for ventricular tachycardia, using different technologies, including LINACs or Cyberknife, but, as reported recently by Lydiard et al., "LINACs have not yet been used for AF treatments" (6).

Based on the latter background, a prospective phase-II trial was designed to evaluate safety of LINAC-based STAR (ClinicalTrials.gov: NCT04575662). We selected the elderly population with refractory AF due to the risk of recurrence of FA after the standard CA procedure and due to the risk of complication for these patients.

Here, the data of the first 5 elderly patients worldwide were preliminary reported.

METHODS

Inclusion criteria were: age more than 70 years; symptomatic paroxysmal AF; intolerance or non-response to AAT. All patients performed 1-week ECG-Holter monitoring (ECG-HM) (during AAT and AAT wash-out), a complete transthoracic echocardiogram, including the left atrial (LA) strain evaluation before STAR.

The study was approved by the local Ethics Committee and all patients signed informed consent.

The Transthoracic echocardiogram and atrial strain evaluation were performed. For 2D-STE analysis, a volumetric image of LA from the apical view was obtained and stored. An echocardiography core laboratory measured parameters related to LA Strain with a dedicated software (Philips, Epiq 7-Auto Strain Tomtec Application). To assess LA Strain we evaluated LA Reservoir-Strain (LASr) based on ED (End-Diastole) and Pre-A (pre-Atrial contraction), LA Conduit-Strain (LAScd) based on ED and Pre-A, LA Contraction-Strain (LASct) based on ED and Pre-A. LA area strain analysis was performed according to the methods previously described and according to the Task Force to standardize deformation imaging (7).

STAR procedures were shown in **Figure 1**. They were immobilized using a vac-lock bag and 3 Computed Tomography (CT, 1 mm slice-thickness), in the supine position were performed: basic free-breathing CT for dose calculation; 4-Dimension CT for moving evaluation; CT with contrast for anatomical accuracy (3–5).

Several Organs at Risks (OaRs) were contoured, making more attention to esophagus and main bronchus, for which a planning risk volume (PRV) was built. The clinical target volume (CTV) was identified by radiation oncologists and cardiologist and was defined as the area around PVs. From CTV, an internal target volume (ITV) was created to compensate heart and respiratory movement. Finally, the planning target volume (PTV) was defined adding 0–3 mm to the ITV, excluding the overlap area with OaRs/PRV, where PTV was cropped.

STAR was performed in free-breathing with a PTV prescription total dose (Dp) of 25 Gy/1 fraction. A "simultaneous

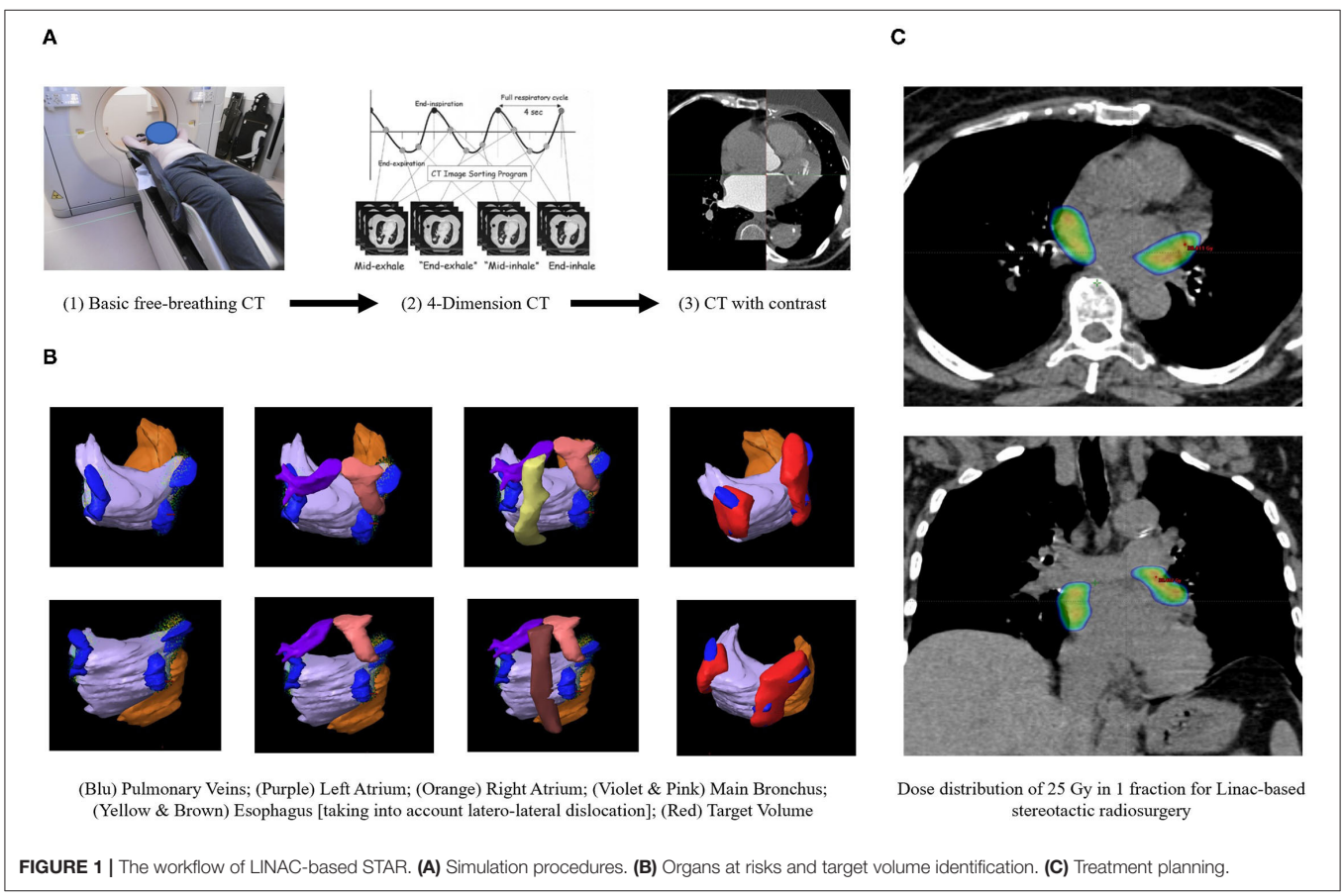

FIGURE 1 | The workflow of LINAC-based STAR. **(A)** Simulation procedures. **(B)** Organs at risks and target volume identification. **(C)** Treatment planning.

integrated protection" dose was realized to the interface between PTV-PRV to ensure the tolerability of critical structures (8). Flattening Filter Free (FFF), Volumetric Modulated Arc Therapy (VMAT) plan was generated, normalizing 100% Dp to 95% of the volume, while large intra-target dose heterogeneity D2% (PTV) < 150%Dp was accepted. The treatment was generated, optimized and delivered by TrueBeam^{TM} (Varian Medical System). Image-guided radiotherapy (IGRT) with Cone Beam CT and Surface-Guided RadioTherapy (SGRT) with Align-RT (Vision RT) were used to reduce set-up error and to monitor patients during fraction.

Follow-up consisted of clinical evaluation during and for 48 h after STAR. One-week ECG-Holter monitoring, transthoracic echocardiogram and clinical evaluation are performed 1, 3, 6, and 12 months after STAR.

The primary endpoint is the 1-month post-STAR safety, as complete STAR delivery and no acute treatment-related adverse events more than G3, assessed according to the Common Terminology Criteria for Adverse Events (version 5.0). Secondary endpoints were: reductions in AF episodes and in AAT, overall survival. The sample size planning is 20 cases based on 95% success for the primary endpoint, with a significant level of 5% and a power of 90%.

RESULTS

From May 2021 to January 2022, 11 elderly patients were enrolled, of which 6 were treated. AAT was stopped after enrollment.

For primary endpoint (side effects at 1 month after STAR), 5 patients completed treatment without acute treatment-related adverse events (>G1) and 1 patient has only 7 days of follow-up. The main STAR data are summarized in **Table 1**. The treatment plan was delivered with 3 no-coplanar arcs, in all cases. The mean Overall Treatment Time (OTT) was 3 min. Only patient-1 needed adaptive real-live radiotherapy due to the esophagus position, in fact at IGRT before STAR the esophagus position was completely different from CT simulation.

Four patients completed a 3 months FUP with transthoracic echocardiogram data. At baseline, LAV and LAA in PT-1 were significantly increased, in PT-2 moderately and in PT-3 slightly compared to the reference values. Strain parameters at baseline were also mild to moderate compromised or severely compromised compared to the reference values (**Table 2**).

The 1-week ECG-HM performed 1-month after procedure documented frequent atrial ectopy and atrial tachycardia without AF recurrences. A rare atrial ectopy without AF recurrences was documented at 3 months after procedure. No patients started AAT after radiotherapy. Regarding echocardiographic data, at 1-month follow-up in PT1-2-4 LASr (ED) and LASr (pre-A) were reduced with a prevalent reduction of the LASct component. In the PT-3, no significant reduction in the strain parameters was reported. At 3-month, a recovery trend of the global strain parameter was shown in PT1-2-4. At 1 and 3-months LAV and LAA were slightly reduced in all patients.

Patients 1–3 had a FUP of 6–7 months, Patient 4 a FUP of 3 months, Patient 5 a FUP of 1 month. For all treated patients with a mean follow-up of 4 months, no acute and late side effects were reported. Only one patient experienced G1 esophagitis (7 days from STAR), improved by 5 days of medical therapy.

DISCUSSION

Elderly patients affected by AF are a fragile population at higher risk of all CA procedural complications (1, 2), including vascular injury, cardiac perforation, phrenic nerve injury, stroke, and most concerning, atrio-esophageal fistula, which portend a high mortality rate and a higher rate of AF recurrences. For the latter reasons, in the clinical practice it is preferred to use pharmacological treatment rather than interventional procedures to treat AF in elderly.

STAR approach have been recently implemented, but no experience of LINAC has been published for AF (6). The present phase-II preliminary worldwide LINAC-STAR data on elderly patients showed: no acute toxicities; no AF episodes; no AAT use.

Three STAR-AF cases were published with Cyberknife technology, reporting an OTT of 90 min (9, 10). To optimize target tracking during cardiorespiratory motion, an internal fiducial marker was placed transvenously in proximity to the left atrial target (9). In 2 out 3 patients, AF occurred at 6-months from Cyberknife-STAR (9, 10).

Comparing the latter data with the present analysis, 2 differences should be highlighted.

In regards to target volume, the mainstay AF ablation approach is a PVs isolation, while appropriate/effective ablation targets, including atrial wall, remain poorly defined (1, 9, 10). In the Cyberknife cases, PVs and the left atrial posterior wall were irradiated, while in the present study, target was defined as the area around PVs. Moreover, higher dose was mainly located on the left lateral ridge, the area between appendage and left PVs (higher arrhythmogenesis area) (11).

In terms of TT, Cyberknife device is mounted on a robotic arm to deliver radiation to a tumor from different trajectories, while LINAC with a rotation of its gantry deliver high dose of radiation in a shorter time (3 vs. 90 min) (12). However, the shorter time is essential for reducing intrafraction motion, so in the present trial, due to the motion study and IGRT/SGRT monitoring, the introduction of fiducial was not necessary (3–5, 12).

Cyberknife device is mounted on a robotic arm to deliver radiation to a tumor from different trajectories, while LINAC with a rotation of its gantry deliver high dose of radiation in a shorter time (3 vs. 90 min).

Due to the innovation of this treatment for AF, sufficient data regarding procedural complications are not still available. However, previous studies reported STAR related complications during ventricular tachycardia treatment. In particular, a low

TABLE 1 | Patient characteristics and main treatment planning and dosimetric data.

	PT1	PT2	PT3	PT4	PT5
Clinical Characteristics					
Age (years)	77	70	82	89	79
Sex	Female	Female	Female	Male	Female
Cardiovascular risk factors	Dyslipidemia Hypertension	Dyslipidemia, Hypertension	Dyslipidemia, Hypertension	Hypertension	Hypertension
Other pathologies		Anxiety disorder Dysthyroidism	Dysthyroidism	Chronic Bronchitis, mild renal insufficiency	Dysthyroidism
Body Mass Index (Kg/m^2)	27	24	26	27	27
Time of onset of AF (years)	10	2	15	3	30
Maximum AF duration (hours)	10	14	12	24	24
Symptoms	Palpitations Lipothymia	Palpitations, Dyspnea	Palpitations	Palpitations, lipothymia	Palpitations, Dyspnea
1 week ECG Holter monitoring before radiotherapy (AAT wash-out)	7 AF episodes (max duration 11 min, mean ventricular rate 128b pm)	4 AF episodes (max duration 60 min, mean ventricular rate 138 bpm)	2 AF episodes (max duration 7 h, mean ventricular rate 142 bpm)	11 AF episodes (max duration 15 h, mean ventricular rate 171 bpm)	4 AF episodes (max duration 9 h, mean ventricular rate 153 bpm)
EHRA symptom scale	2b	2b	2b	2b	2b
Drug Therapy at enrolment	Atenolol 25 mg* Flecainide 200 mg* Apixaban 30 mg	Rivaroxaban 20 mg Amiodarone 200 mg* Bisoprololo 1.25 mg* L-thyroxine 50 mcg Olanzapine 2.5 mg Ramipril 2.5 mg Furosemide 25 mg Synvastatin 20 mg	Dabigatran 110 mg Losartan 50 mg Synvastatin 20 mg Ezetimibe 10 mg L-thyroxine 50 mcg	Bisoprolol 2.5 mg* Amiodarone 200 mg* Furosemide 25 mg Warfarin 5 mg	Flecainide 200 mg*, L-thyroxine 75 mcg Bisoprolol 2.5 mg*, Olmesartan 40 mg, rivaroxaban 20 mg, doxazosin 2 mg
Radiotherapy parameters					
CTV	15.4 cc	11.3 cc	25.3 cc	15.86 cc	15.8 cc
ITV	36 cc	33.2 cc	37.8 cc	44.5 cc	32.6 cc
PTV	53.5 cc	52.1 cc	59.1 cc	56.6 cc	49 cc
Prescription isodose	79%	75%	73%	74%	73%
D2%	30 Gy	31.8 Gy	31.9 Gy	32.6 Gy	32.2 Gy
Maximum dose to esophagus	13.8 Gy	13.2 Gy	11.8 Gy	13.2 Gy	15.4 Gy
Maximum dose to left bronchus	15.8 Gy	12.2 Gy	18.2 Gy	19 Gy	10.2 Gy
Maximum dose to right bronchus	13.7 Gy	20.6 Gy	4.5 Gy	5.9 Gy	8.5 Gy
Mean dose to heart minus PTV	5.2 Gy	3.7 Gy	4.8 Gy	4 Gy	3.7 Gy
OTT	3 min	3 min	3 min	3 min	3 min

**Drug stopped after enrollment. AAT, antiarrhythmic therapy; AF, atrial fibrillation; CTV, clinical target volume; EHRA, European Heart Rhythm Association; ITV, internal target volume; PRV, planning risk volume; PTV, planning target volume; OTT, Overall Treatment Time.*

percentage of complications was reported mainly within 90 days from STAR (heart failure exacerbation, radiation pericarditis and pneumonitis, nausea) and at long term follow up (mitral valve regurgitation worsening, pericardial effusions and gastro-pericardial fistula) (12).

Moreover, this analysis is the first to report clinical response. The frequent atrial ectopy and the atrial strain variations after procedure are probably indirect signs of effective atrial irritation due to radiotherapy. Some recent studies have shown the correlation between LA strain and atrial fibrosis, hypothesizing its prediction of the usefulness of ablation procedure (13). In this study, LAS parameters, based on ED and Pre-A, in three patients reduced 1-month after STAR. The LASct decreasing is related to atrial contraction phase of the cardiac cycle, probably due to acute irritation of the atrium immediately after STAR. The patient-3 showed no significant reduction in LAS parameters in the 1-month follow-up probably because atrial strain values were slightly reduced compared to normal. At the 3-month, a trend in recovery of LASr was found in the three patients. Finally, a reduction trend in LA volume and area was found in all patients

TABLE 2 | Main echocardiographic and ECG-HOLTER parameters.

	PT1			PT2			PT3			PT4		
	BAS	**1M**	**3M**	**BAS**	**1M**	**3M**	**BAS**	**1M**	**3M**	**BAS**	**1M**	**3M**
LAV (ml)	64.2	62.7	61.5	97.8	83	81.4	68.1	63.5	50.3	94	92.3	90.4
LAA (cm^2)	20.9	21.5	22	28.5	25.6	25.1	20.1	21	18.2	26	25.8	24.9
LASr (ED)	13.2%	9.1%	15.4%	16.7%	13.3%	16%	27.7%	27.7%	22%	20%	16.5%	21.2%
LAScd (ED)	−8.2%	−5.6%	−4.5%	−9%	−9.7%	−4.5%	−8.2%	−6.7%	−5.8%	−16.2%	−15.4%	−12.9%
LASct (ED)	−5%	−3.5%	−11%	−7.7%	−3.6%	−11.5%	−19.5%	−21.1%	−16.2%	−7.9%	−1.1%	−8,2%
LASr (preA)	12.5%	8.8%	13.9%	15.5%	12.9%	14.3%	23%	22.9%	18.9%	21%	16.3%	20%
LAScd (preA)	−7.8%	−5.5%	−4%	−8.3%	−9.4%	−4%	−6.9%	−5.5%	−5%	−15.7%	−15.3%	−12.2%
LASct (preA)	−4.8%	−3.4%	−9%	−7.2%	−3.5%	−10.3%	−16.3%	−17.4%	−13.9%	−7.3%	−1.1%	−7.8%
LVEF (%)	55	55	58	55	55	55	55	55	58	45	45	49
Mitral valve regurgitation	Mild-Moderate	Mild-Moderate	Mild	Moderate	Moderate	Mild-moderate	Mild-Moderate	Mild-Moderate	Mild-moderate	Mild-moderate	Mild-moderate	Mild-moderate
Aortic valve regurgitation	-	-	-	Mild	Mild	Mild	Moderate	Moderate	Moderate	mild	mild	mild
Tricuspid valve regurgitation	Mild	Mild	Mild	Moderate severe	Moderate	Mild-moderate	Mild-Moderate	Mild-Moderate	Mild	Mild-moderate	Mild-moderate	Mild-moderate
Pericardial effusion	-	-	-	-	-	-	-	-	-	-	-	-

1-week ECG-Holter monitoring performed 1-month after STAR Data

	PT1	PT2	PT3	PT4
atrial ectopy	89,642 beats	27,675 beats	20,305 beats	58,004 beats
Atrial	19 episodes, max duration	73 episodes, max duration	5 episodes, max duration	26 episodes, max duration
tachycardia	2 h, meanVR 160 bpm	90 min; meanVR 146 bpm	12 min; meanVR 158 bpm	140 min; meanVR 147 bpm

ED, end diastole; LAA, left atrial area; LAScd, left atrial conduit strain; LASct, left atrial contraction strain; LASr, left atrial Reservoir strain; LAV, left atrial volume; LVEF, left ventricle ejection fraction; Pre-A, pre-atrial contraction; VR, ventricular rate.

probably because the maintenance of sinus rhythm improved ventricular performance with a reduction in the extent of mitral and tricuspid insufficiency and LA volume overload.

CONCLUSION

The present collected data are promising, showing the safety of LINAC-based STAR for AF for the first 5 patients. This new ablation approach could represent a valid non-invasive alternative for elderly who were excluded from catheter ablation. Prospective randomized trials are guaranteed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Interregionale; Policlinico di Bari - Bari. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD, FG, AF, and MG write the protocol study and have the idea. IB, FG, AS, RC, MC, and AF are the responsibility of radiotherapy and radiotherapy data. AD, MG, NV, FQ, and FT are responsible of cardiological data. GM and DD are responsible of radiological data. AD, FG, and AF write the paper. PG analyzed the statistical data. All authors corrected, improved the manuscript, and interpreted the results.

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CASE REPORT
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Case Report: Repeated Stereotactic Radiotherapy of Recurrent Ventricular Tachycardia: Reasons, Feasibility, and Safety

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Stereotactic body radiotherapy (SBRT) has been reported as an attractive option for cases of failed catheter ablation of ventricular tachycardia (VT) in structural heart disease. However, even this strategy can fail for various reasons. For the first time, this case series describes three re-do cases of SBRT which were indicated for three different reasons. The purpose in the first case was the inaccuracy of the determination of the treatment volume by indirect comparison of the electroanatomical map and CT scan. A newly developed strategy of co-registration of both images allowed precise targeting of the substrate. In this case, the second treatment volume overlapped by 60% with the first one. The second reason for the re-do of SBRT was an unusual character of the substrate–large cardiac fibroma associated with different morphologies of VT from two locations around the tumor. The planned treatment volumes did not overlap. The third reason for repeated SBRT was the large intramural substrate in the setting of advanced heart failure. The first treatment volume targeted arrhythmias originating in the basal inferoseptal region, while the second SBRT was focused on adjacent basal septum without significant overlapping. Our observations suggested that SBRT for VT could be safely repeated in case of later arrhythmia recurrences (i.e., after at least 6 weeks). No acute toxicity was observed and in two cases, no side effects were observed during 32 and 22 months, respectively. To avoid re-do SBRT due to inaccurate targeting, the precise and reproducible strategy of substrate identification and co-registration with CT image should be used.

Keywords: stereotactic body radiotherapy, ventricular tachycardia, electroanatomical mapping, failed catheter ablation, safety

INTRODUCTION

Current strategies of catheter ablation are effective in the prevention of recurrences of ventricular tachycardias (VTs) (1–3). Not frequently, catheter ablation may fail due to the inability to reach the critical part of the substrate (4, 5). The reasons include deep intramural location or failure to negotiate epicardial access (usually after previous surgery). Among the alternative treatment

strategies, stereotactic body radiotherapy (SBRT) was first reported in case reports or case series as an attractive option (6–8).

The experience with SBRT is gradually growing and several other case reports and prospective clinical studies documented a significant decrease in VT occurrences (9–19). However, even this strategy can fail for various reasons. Hence, the goal of this report was to describe a case series of re-do SBRT for VT recurrences, which is the first time in the literature.

METHODS

Since we used the same strategy of SBRT in all sessions, a brief description was provided here. The MultiPlan treatment planning system with sequential dose optimization and the CyberKnife radiosurgery system (both from Accuray, Inc., Sunnyvale, CA, USA) were employed as described previously (12). After image registration with two ECG-gated CT scans (in both systole and diastole), the internal target volume was calculated to account for heart contractions. For compensation of respiratory movements, the existing implantable cardioverter-defibrillator (ICD) lead was used as a surrogate marker. The tracking mode relevant to SBRT for VT is Synchrony using "fiducials". Based on the target surrogate, which is an ICD lead tip, in this case, a correlation respiratory motion model was created before the treatment. Such model was based on lead 3D locations extracted from a series of X-ray image pairs and corresponding respiratory phase signals from LED markers placed on the patient's chest. The created model was then used during dose delivery to control radiation source position and orientation to move together with the target (surrogate) while the beam was on. During treatment, the correlation model was updated with every new pair of X-ray images. In principle, this technology required minimum target volume expansion to cover respiratory motion-related target position variation during breathing so it has relatively better potency to spare normal tissue from dose.

CASE SERIES

Case 1

The first case was reported recently in detail as a case report, illustrating the need for precision in planned target volume (PTV) determination (20). Briefly, a 66-year-old man with a

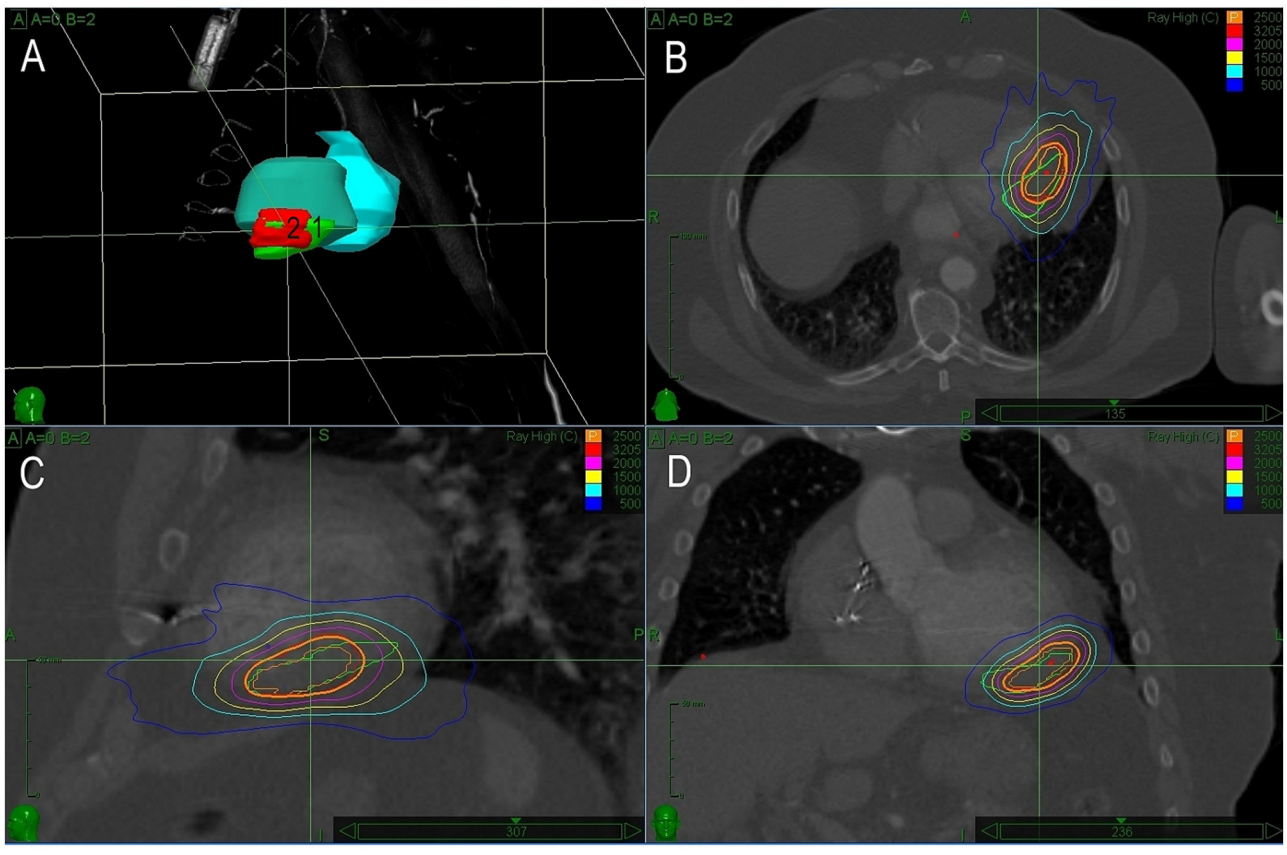

FIGURE 1 | A treatment plan for Case 1. **(A)** 3D reconstruction of planned treatment volumes for the first (1) and second (2) radiotherapy. **(B–D)** Depict sagittal, coronal, and axial views with isodose lines for both sessions of radiotherapy (green line shows target volume for the first and red for the second session). In this case, there is a significant overlap of both treatment volumes caused by inaccuracy in the planning of the first session.

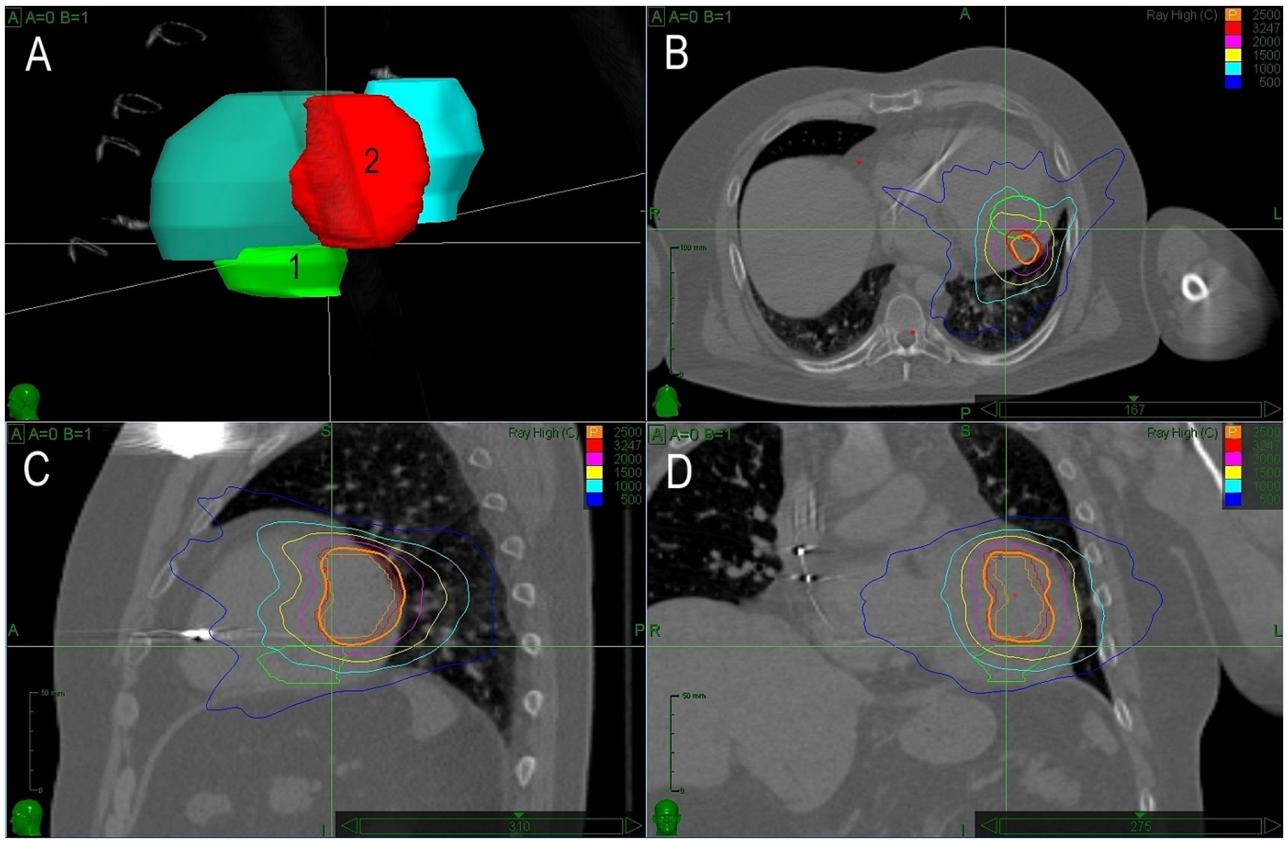

FIGURE 2 | The treatment plan for Case 2. Description of **(A–D)** is identical as in **Figure 1**. In this case, the second planned target volume covers an entirely different region.

history of coronary artery bypass graft surgery and primary prophylactic ICD implant (left ventricular ejection fraction of 35%) underwent catheter ablation for recurrences of slow VT. Clinical VT originated from a small reentrant circuit located intramurally and/or epicardially below the base of the posteromedial papillary muscle. Despite multiple endocardial ablation attempts, VT remained inducible and an attempt for percutaneous epicardial approach failed because of severe adhesions from previous cardiac surgery. The first SBRT session was planned based on a visual alignment of the presumed origin of VT from electroanatomical maps and CT images. A single fraction of 25Gy was delivered. For recurrences of VT episodes of the same ECG morphology, the patient underwent the second electrophysiology study and remapping 14 months later. Based on the electroanatomical mapping, the low voltage area caused by the previous SBRT was adjacent to the site of the earliest endocardial activity during VT. Additional RF ablation failed again to prevent the inducibility of VT and we used a newly developed co-registration method for the precise targeting of the SBR (20). Detailed maps were presented in a previously published case report (20). Briefly, there was only a small bipolar low voltage area after the first SBRT which was adjacent to the true exit of VT. Precise co-registration of the target in the second SBRT allowed to establish a smaller PTV amounting to 18 ml, including an additional 3 mm margin. The dice overlap of previous and new PTV was 0.68. The second session was performed 19 months after the first one. The same dose of 25 Gy was delivered (**Figure 1**). After transient early recurrences of slow VT, arrhythmias gradually disappeared within 3 months and the patient became arrhythmia-free for 32 months. No adverse effect of SBRT was observed during this period.

Case 2

The second case of a patient with cardiac fibroma triggering recurrent VTs of different morphologies was reported after the first successful SBRT in 2017 (10). Briefly, it was a 34-year-old patient diagnosed with an intramyocardial tumor (60 x 40 x 25 mm) located in the inferolateral wall of the left ventricle. The patient presented with several morphologies of VT. The patient underwent exploratory surgery, but the excision of the tumor was impossible for its size. Only far-field signals were recorded above and around the tumor. Empirical epicardial cryoablation around the tumor was performed with transient suppression of VTs. Subsequent electroanatomical mapping and pace mapping identified two regions responsible for two residual clinical VTs. One had a reentrant character with an exit in the lateral wall, which was close to the summit. This VT was non-inducible after catheter ablation. The other VT became

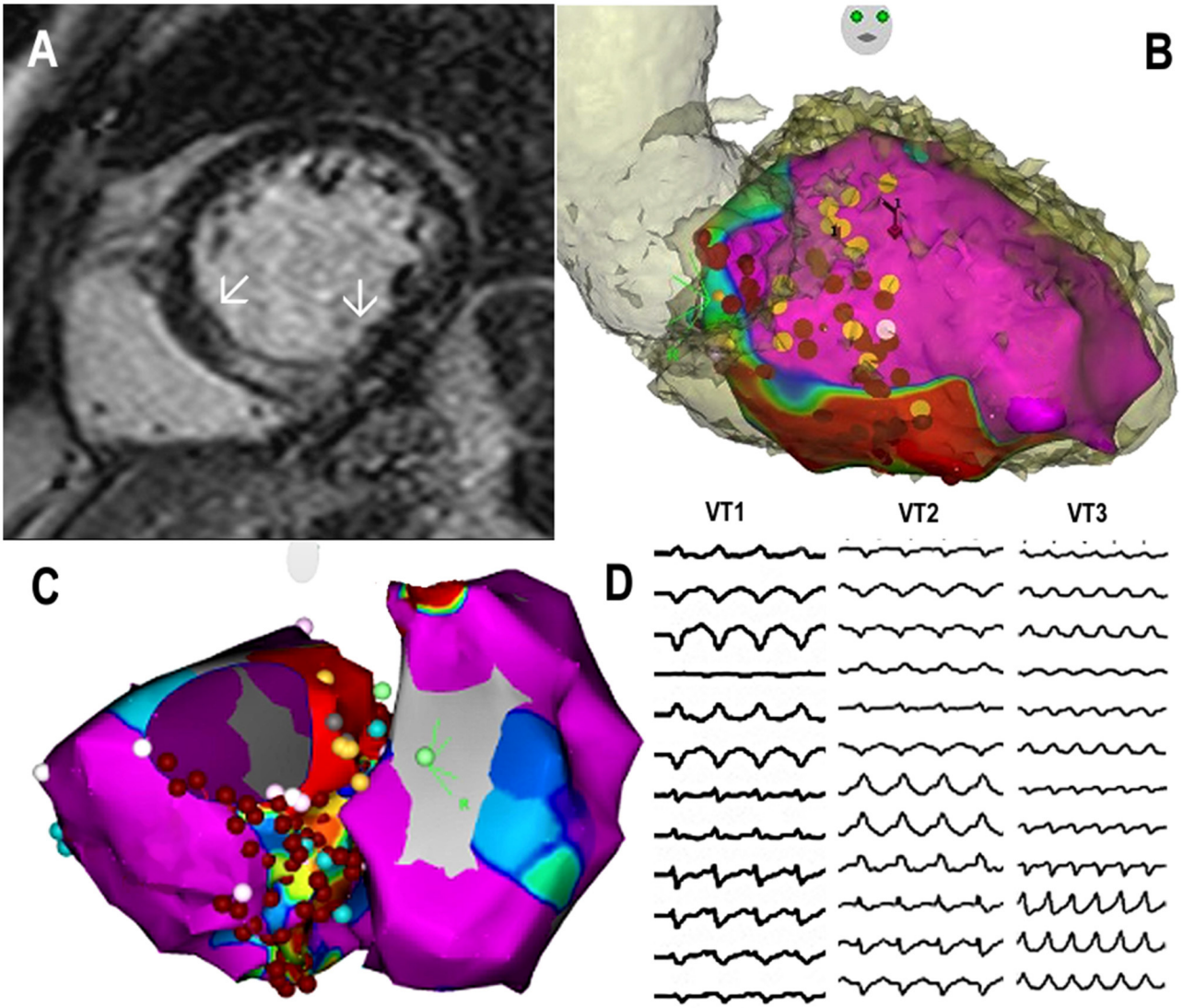

FIGURE 3 | Clinical findings from Case 3: **(A)** MRI with late gadolinium enhancement within the basal septum and adjacent inferior wall (arrows); **(B)** electroanatomical bipolar voltage map merged with CT angiogram of the left ventricle in right anterior oblique (RAO) view, displaying low voltage inferoseptally and ablation points in this region and at midseptal level before 1st stereotactic body radiotherapy (SBRT); **(C)** electroanatomical bipolar voltage maps obtained during third catheter ablation before 2nd SBRT, showing a larger area of low voltage in the entire basal septum up to outflow tract with ablation points; **(D)** ECG recordings of dominant ventricular tachycardia (VT) morphologies: VT1 and VT2 before the first SBRT, VT3 before the second SBRT. Note change in the exit from the low septum to high septum for VT3.

incessant and originated in a region between the septum and posteromedial papillary muscle. It had characteristics of focal VT with a source located deep in the wall, adjacent to the tumor. The patient was referred for SBRT. PTV was determined based on tumor location and visual comparison with electroanatomical maps. SBRT was performed with 25 Gy to the 75% isodose line. After the procedure, VT disappeared gradually within 6 months. The patient was without any arrhythmia for the next 22 months. However, the patient remained on amiodarone which had to be stopped due to amiodarone-related thyrotoxicosis. After successful treatment of this condition, the patient was without arrhythmias for the next 10 months. Then, the patient returned with an electrical storm and one morphology of VT. Electrophysiological study induced sustained VT from the anterolateral basal part of the ventricle. Electroanatomical bipolar voltage map showed normal values and pacing revealed slowed conduction in this region. Ablation did not prevent the inducibility of VT due to the deep location of the substrate. The second session of SBRT was planned and conducted based on precise integration of data from electroanatomical mapping and CT. PTV for the second SBRT was applied on the opposite side of the tumor and there was no overlap with the first radiotherapy site. The size of the tumor remained the same. After the second SBRT (25 Gy, PTV 62.2 ml; **Figure 2**), the patient

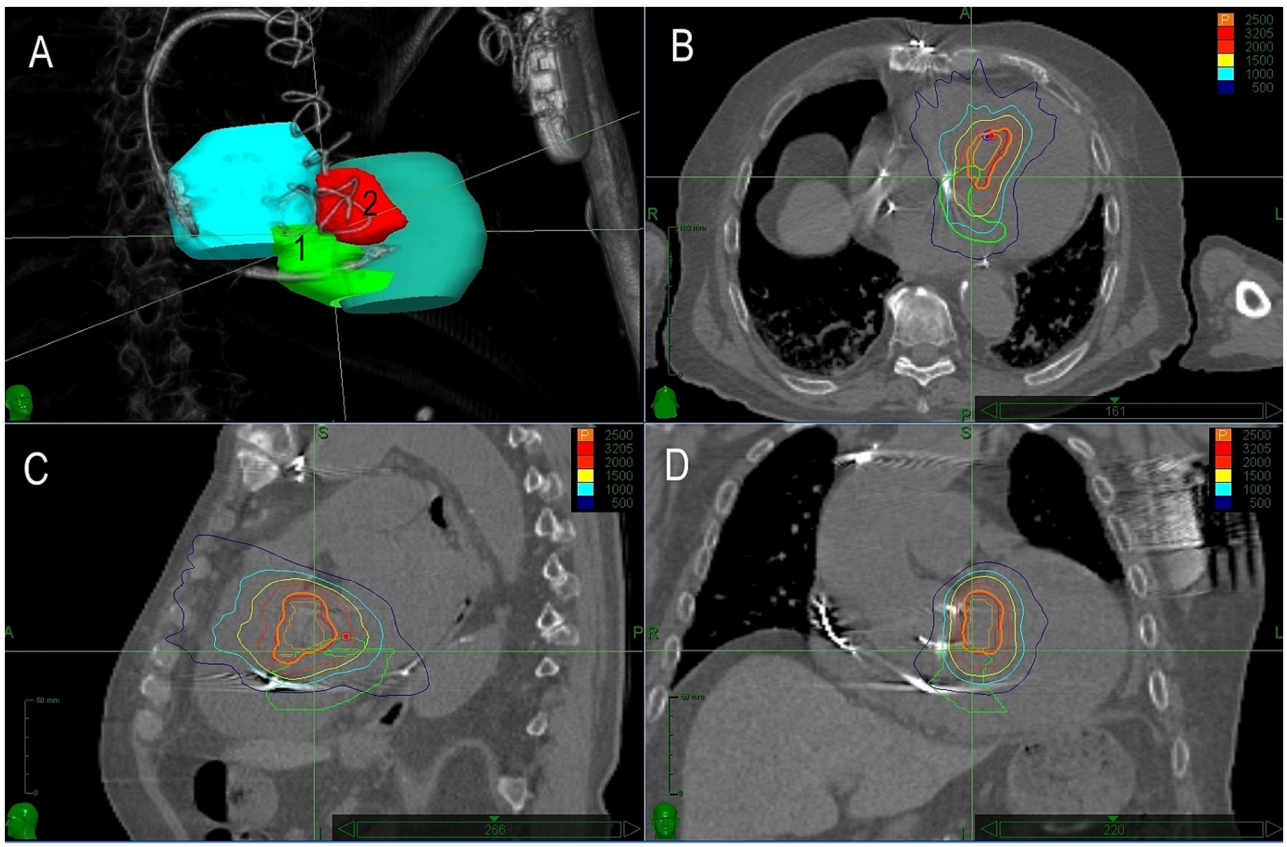

FIGURE 4 | The treatment plan for Case 3. Description of **(A–D)** is identical as in **Figure 1**. In this case, the second planned volume covered extensive substrate within the basal septum.

remained without VTs and did not gain any adverse effects for 22 months.

Case 3

The third patient was a 77-year-old man with a diagnosis of non-ischemic cardiomyopathy and intramural location of fibrosis in the basal region of the left ventricle. The patient presented with ventricular arrhythmias for several years and was implanted with a single chamber ICD. Later, aortic valve replacement with mechanical prosthesis was performed for aortic regurgitation together with a concomitant MAZE procedure. After 3 years, the device was upgraded to cardiac resynchronization therapy-defibrillators (CRT-D). At that time, the patient presented with an electrical storm. They underwent electroanatomical mapping and substrate ablation in the inferoseptal region of the left ventricle two times. For sporadic recurrences of VT, the patient was referred for SBRT 1 month later (**Figure 3**). A 25 Gy dose was applied to the basal inferoseptal region. After temporary improvement, the patient presented with recurrent VTs and underwent 2 months later another electrophysiology study. Three different VTs were induced, all with the exit in the septum above the initially irradiated region. The entire basal septum showed decreased bipolar voltage and catheter ablation covered it all. No VT was inducible at the end of the procedure. The patient was readmitted for decompensated heart failure due to incessant VT with an exit in the upper septum and was indicated to re-do SBRT. The septal region adjacent to the initial PTV was delineated as a new PTV with minimal spatial overlap. The second SBRT was performed 4 months after the first one (**Figure 4**). After SBRT, the patient continued to present with slow VT (CL around 600 ms) which necessitated another catheter ablation from both sides of the interventricular septum. Non-inducibility of VT was achieved. Although the patient was without VT, their overall clinical status gradually deteriorated and then eventually died due to the progression of heart failure 1 month later. No autopsy was performed.

Timelines of treatment for all three patients are listed in **Table 1**. Dose-volume parameters of organs at risk (OAR) and PTVs are enumerated in **Table 2**.

DISCUSSION

This case series is the first of this kind that reports on the feasibility and acute and mid-term safety of re-do SBRT in patients with recurrent VTs. The reason for repeated SBRT was different in all three subjects. One reason was the inaccuracy of targeting when using indirect comparison of electroanatomical

TABLE 1 | Timelines.

Case 1	
Index date	A 66-year-old male with ischemic cardiomyopathy and recurrent VTs requiring therapy from ICD
1,5,11 months	Repeated ineffective catheter ablations due to intramural location of the substrate
18 months	First SBRT with continuing recurrences of VT
34 months	Remapping after the first SBRT
38 months	Second SBRT, after 3 months VT disappeared
69 months	Last follow-up visit, no arrhythmias
Case 2	
Index date	A 34-year-old patient with an intramyocardial fibroma (60 x 40 x 25 mm) in the inferolateral wall of the left ventricle and recurrent VTs of different morphologies
6 months	Empirical circumferential epicardial cryoablation around the tumor, 6 months without recurrences of VT
13 months	Catheter ablation for recurrences of 2 morphologies of VT, one non-inducible, other almost incessant
14 months	First SBRT, within 6 months all arrhythmias gradually disappeared
38 months	v Re-do catheter ablation, without elimination of VT due to intramural substrate located in the opposite side of the tumor
38 months	Second SBRT, within 3 months VT disappeared
60 months	Last follow-up visit, no arrhythmias
Case 3	
Index date	A77-year-old male with non-ischemic cardiomyopathy, aortic valve replacement and fibrosis in basal region of left ventricle and sporadic interventions of ICD
70 months	Repeated catheter ablation for electrical storm
71 months	First SBRT, arrhythmias less frequent
73 months	Re-do catheter ablation for VT recurrences in basal septal region above the previous SBRT, non-inducibility
75 months	Second SBRT for incessant VT, leading to slowing VT to 100 bpm
76 months	Re-do catheter ablation in the basal septum, non-inducibility
77 months	Progression of heart failure and cachexia, death

TABLE 2 | Parameters of organs at risk (OAR) and planning target volume (PTV).

OAR and PTV volume parameter	Case 1	Case 2	Case 3
Heart D15 ml (Gy)	46.3	42.4	42.9
Heart D0,035 ml (Gy)	61.0	51.3	50.0
Heart Dmean (Gy)	4.8	13.5	14.5
Lung Left Dmean (Gy)	1.8	7.7	2.1
Esophagus D5 ml (Gy)	5.9	4.9	13.3
Esophagus D0,035 ml (Gy)	8.6	7.1	21.9
Stomach D10 ml (Gy)	10.4	7.3	6.5
Stomach D5 ml (Gy)	12.2	8.0	8.7
Stomach D0,035 ml (Gy)	18.3	11.6	14.3
PTV (mL)	21.2	23.4	43.4
PTVredo (mL)	18.3	62.2	20.0
PTVxPTVredo (mL)	11.3	0.1	0.4
PTVxPTVredo (%)	61.7	0.2	2.2
PTVxPTVredo Dmax (Gy)	32.1	25.6	25.8
PTVxPTVredo D0,035 ml(Gy)	31.9	24.5	25.6
PTVxPTVredo Dmean (Gy)	28.8	24	25.2

Dose-volume parameters are based on integrated isodose plans calculation from the first and second SBRT sessions. Both CT series from simulation were registered according to the heart region and summation of dose distribution was performed. D—abbreviation for dose; D5 ml, D10 ml, and D15 ml represents the dose to 5, 10, and 15 ml of relevant OAR, respectively. D.035 ml represents near-maximum dose, "x" means the intersection of volumes, redo means second irradiation.

maps with pretreatment CT. The second reason for re-do SBRT was an unusual character of the substrate, wherein there is an inoperable cardiac fibroma associated with several morphologies of VT from different regions of the tumor. The third reason for repeated SBRT was the large intramural basal septal substrate in the setting of dilated cardiomyopathy and advanced heart failure.

Regarding the safety of re-do SBRT, it is important to keep in mind that the risk of cardiovascular complications associated with chest radiotherapy can persist for many years (21, 22). Studies on the relationship between the dose and adverse outcomes show up to 16% relative risk of heart disease and major cardiac events per Gy of the mean heart dose (23, 24). In addition, other studies showed correlations between radiation doses to specific cardiac regions and cardiac morbidity and mortality (21). In the case of repetition of SBRT, the likelihood of severe toxicity may increase. Since no radiation-related adverse events were observed in our patients, we were not able to comment about the relationship between the dose to organs at risk dose and the occurrence of side effects.

Another fear may concern the further worsening of left ventricular ejection fraction after the second SBRT. Importantly, we did not observe a significant change in this parameter nor the significant increase of cardiac troponin after the second SBRT. Additionally, our patients had no clinical symptoms or signs of pericarditis or pneumonitis. The third patient died of terminal heart failure which was not in our opinion in relation to the second SBRT. One explanation for the good tolerability of the repeated SBRT may reflect the fact that our strategy of SBRT uses relatively small PTV, covering the critical region of the substrate (12).

We found only one case of re-do SBRT description in the literature. It was in a series by Lloyd et al. (15) who reported on outcomes of SBRT in 10 patients with advanced heart failure and VTs. One patient in this group who had no response to SBRT underwent a second SBRT ineffective treatment 90 days later. The patient was considered an outlier and ultimately underwent heart transplantation for recurrent VTs despite all therapies. No more details were available.

For a discussion on the indication to re-do SBRT and its safety, it is important to recall that the tissue effect of SBRT for VT in humans remains largely unknown, and also the time window to

clinical effect is highly variable. Most of the experimental studies suggested that electrophysiological effects are rather delayed and that the development of fibrosis is important for clinical effect (25, 26). Our recent report analyzing 3 post-mortem hearts after SBRT is in line with the above experimental data on early apoptosis and delayed fibrosis (27). Furthermore, the clinical effect of SBRT was delayed and a similar pattern was observed also in the current series (28, 29). In the largest published clinical study of Encore VT, the blanking period of 6 weeks was used to avoid counting early recurrences of VT (9). It appeared that in the majority of cases, the clinical effect should be observed after 2–3 months. Later recurrences or incessant VT could be considered either for re-do catheter ablation or repeated SBRT.

However, anecdotal cases described the immediate clinical effect of SBRT resulting in acute termination of an electrical storm (11, 13, 14, 16). Some recent experimental studies suggested that the clinical effect of SBRT is not necessarily related to the development of fibrosis and even deconstruct fibrosis as the main antiarrhythmic mechanism. A study by Zhang DM et al. demonstrated that postmortem heart specimens from four patients, with a substantial reduction of VT after SBRT, did not exhibit transmural fibrosis within the timeframe of VT reduction (30). In an experimental study, electrophysiologic assessment of irradiated murine hearts revealed a persistent supraphysiologic electrical phenotype, mediated by increases in components of the Natrium channel and Cx43. Additionally, increased $Na_V1.5$ expression was also found in the explanted human heart from the said clinical study. The authors offered an alternative explanation of the effect of SBRT—increased cardiac conduction. Interestingly, another experimental study suggested a different mechanism for the early effect of SBRT (31). In the rat model of SBRT, the authors found acute structural changes, such as interstitial and subsarcolemmal edema, widening of intercalated discs, and microvascular inflammatory responses. These acute structural changes resulted in the slowing of intracardiac conduction on ECG, which might be an alternative explanation of the effect of SBRT. These observations may suggest that an even shorter time window than 2–3 months could be employed to consider a failure of SBRT and re-do procedure.

Our first case emphasized the need for using the accurate and reproducible strategy of planned target volume delineation. Using the novel method of co-registration of electroanatomical maps with pretreatment CT, we were able to correct the previous treatment plan and deliver successfully therapy (20). More recently, we showed reproducibility of this strategy (32). The other important issue related to accuracy and safety is how to minimalize the treatment volume with respiratory compensation. We used ICD lead tracking as described above. The other possibility is the use of continuous real-time imaging and tracking of the moving target during treatment with gated irradiation using MR-guided radiotherapy (33). Therefore, with current strategies of accurate targeting of the critical substrate region and motion mitigation, the main reason for considering re-do SBRT should be either extensive substrate or development of a new substrate in a different region of the heart.

CONCLUSION

Our observations suggest that SBRT for VT could be repeated in case of arrhythmia recurrences with good acute and mid-term safety. Long-term safety remains to be further documented. The clinical effect of SBRT appears to be predominantly delayed and re-do procedures should be considered after a 2–3 month period. For earlier indications, there is still limited evidence. With current strategies of accurate targeting of the critical substrate region and precise delivery of SBRT, the main reason for considering re-do SBRT should be either extensive substrate or development of the new substrate in a different region of the heart.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Institute for Clinical and Experimental Medicine, Prague, Czechia. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JH: preparation of the manuscript and organization. PP: catheter ablation, organization, and correction of manuscript. MŠ: development of co-registration strategy and correction of manuscript. JC: radiotherapist and reading manuscript. LK: radiotherapy planning and figure preparation. OJ: catheter ablation. RN: organization, leading part of project, and preparation of manuscript. JK: catheter ablation, leading project, and final corrections to manuscript. All authors contributed to the article and approved the submitted version.

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Radiosurgery in Treatment of Ventricular Tachycardia – Initial Experience Within the Polish SMART-VT Trial

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Background: Stereotactic Arrhythmia Radioablation (STAR) is an emerging treatment modality for patients with sustained ventricular tachycardia (VT) and refractory to treatment with drugs and radiofrequency catheter ablation (RFA). It is believed that up to 12–17% of patients experience recurrence of VT within 1 year of follow-up; thus, novel therapeutic options are needed. The aim of this article is to present initial experience within a novel treatment modality for VT.

Case Summary: Two patients with a medical history of coronary artery disease and heart failure with reduced left ventricle (LV) ejection fraction, after implantation of cardioverter-defibrillator (ICD) and previous unsuccessful RFAs owing to sustained VT were admitted to the cardiology department due to recurrence of sustained VT episodes. With electroanatomical mapping (EAM), the VT substrate in LV has been confirmed and specified. In order to determine the target volume for radioablation, contrast-enhanced computed tomography was performed and the arrhythmia substrate was contoured using EAM data. Using the Volumetric Modulated Arc Therapy technique and three 6 MeV flattening filter-free photon beam fields, a single dose of 25 Gy was delivered to the target volume structure located in the apex and anterior apical segments of LV in the first patient and in the apex, anterolateral and inferior apical segments of the second patient. In both cases, volumes of the target structures were comparable. Interrogation of the implanted ICD at follow-up visits throughout 6 months after the treatment revealed no VT episodes in the first patient and sudden periprocedural increase in VT burden with a subsequent gradual decrease of ventricular arrhythmia to only two non-sustained episodes at the end of the follow-up period in case of the second patient. A significant reduction in premature ventricular contractions burden was observed compared to the pre-treatment period. No noticeable deterioration in

LV function was noted, nor any adverse effects of radiosurgery associated with the implanted device.

Conclusion: The early response to STAR can be unpredictable and probably does not reflect the final outcome of irradiation. Close monitoring of patients, especially in the early period after irradiation is crucial to properly handle potentially harmful early reactions to STAR.

Keywords: radioablation, electrical storm, structural heart disease, arrhythmia-stereotactic body radiotherapy, ventricular tachycardia

INTRODUCTION

Stereotactic Arrhythmia Radioablation (STAR) is an emerging treatment modality for patients with persistent ventricular tachycardia (VT), a potentially life-threatening disorder caused by malfunctioning electrical conduction of the myocardium often associated with structural heart disease (1). The therapeutic options include implantable cardioverter-defibrillator (ICD), antiarrhythmic medications, and percutaneous radiofrequency catheter ablation (RFA) of the arrhythmic substrate (2). The ICD improves survival rate at the expense of a patient's quality of life and increases the possibility of exacerbating the underlying cardiac failure. Although capable of reducing the VT burden, antiarrhythmic medications are often associated with considerable toxicity. Finally, RFA can permanently terminate VTs; however, up to 12–17% of patients experience recurrence as soon as at 1 year of follow-up (3), indicating a pressing need for novel therapeutic options.

To no surprise, the first case reports on STAR (4–6) and encouraging results of the phase I/II study by Robinson et al. (7) have met with avid interest, resulting in multiple centers adopting the method as compassionate treatment and within new prospective clinical trials (8). One of them is the Polish trial SMART-VT (ClinicalTrials.gov Identifier: NCT04642963) (9). It was launched on September 11, 2020, and aims to evaluate treatment safety, as described in detail in the trial protocol (10). Briefly, the inclusion criteria are: structural heart disease and implanted cardioverter-defibrillator (ICD), clinically significant arrhythmia with at least 3 VT episodes per month despite adequate pharmacological treatment, at least one episode of monomorphic VT registered during the electrophysiological study, recurrent VT despite at least one prior catheter ablation and adequate pharmacotherapy or contraindications to catheter ablation and/or pharmacotherapy, ability to understand and will to sign a written informed consent document. Here we present the cases of the first two patients treated in Poland within the SMART-VT trial.

CASE REPORT

Cases Presentation

First Patient

A 69-year-old man with a medical history of coronary artery disease, heart failure with reduced ejection fraction (left ventricle ejection fraction of 22% and New York Heart Association class II), after ICD implantation and previous unsuccessful RFAs was admitted to the cardiology department in December 2020, due to sustained, clinically significant VT. Despite previous conventional RFAs, the VT substrate persisted and led to an electrical storm with recurrent episodes of ventricular tachycardia, which demanded hospitalization approximately a month before the admission to our hospital. The ICD interrogation revealed 14 episodes of VT (7 episodes of non-sustained VT and eight episodes of sustained VT). Sustained episodes were treated successfully with anti-tachycardia pacing (ATP). Furthermore, the device interrogation disclosed 76 episodes of VT with 302 ATPs since device implantation. Considering the limited remaining options of therapy and ineffectiveness of the past RFAs, the patient was enrolled in the SMART-VT trial.

Second Patient

A 72-year-old patient with a history of coronary artery disease and heart failure with reduced ejection fraction (left ventricle ejection fraction of 20% and New York Heart Association class III) was admitted to the cardiology department in December 2020 due to an electrical storm with two adequate, high-voltage interventions. The patient had a history of ICD implantation (with a subsequent upgrade to cardiac resynchronization

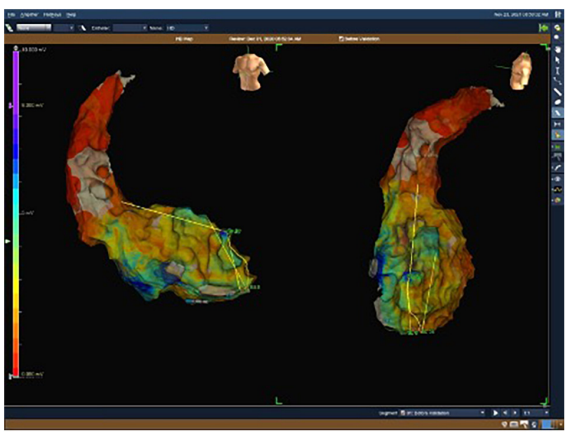

FIGURE 1 | Electroanatomical map with unipolar (UV) voltage of the first patient. UV range from 0.05 mV (red color) to 8.3 mV (purple color).

therapy) and underwent several RFAs procedures in the past. Prior to the STAR procedure, the CRT-D interrogation was performed, confirming five high-voltage interventions. The patient was also enrolled in the SMART-VT trial.

Treatment

After excluding reversible causes of VT, both patients underwent 3D electroanatomic mapping (EAM) using The EnSite Precision^{TM} Cardiac Mapping System by Abbott. Based on the obtained electrophysiological map (**Figures 1**, **2**), data from previous RFAs and computed tomography (CT), the target volume for radioablation was specified and transferred to the Varian ECLIPSE^{TM} treatment planning system. The target volume contouring was performed on the spot, using a remote access workstation, through indirect comparison of EAM data and contrast-enhanced CT fused with Deep Inspiration Breath Hold (DIBH) treatment planning CT. The organs-at-risk (OARs) and derivative structures were prepared according to the study protocol (10). Using Volumetric Modulated Arc Therapy (VMAT) technique, three 6 MeV flattening filter-free photon beam fields, DIBH respiratory motion management, a dose of 25 Gy was delivered to the planning target volume (PTV) (**Figure 3A**). It was localized in the apex and anterior apical segments of LV in the first patient and in the second patient's apex, anterolateral and inferior apical segments. In both cases, volumes of the target structures were similar and equaled 56.37 and 56.72 cm^3, respectively. According to the safety-first paradigm, the dose was reduced to account for OARs such as coronary arteries (**Figure 3B**). Dose constraints for OARs and dose to target are presented in table below (**Table 1**). Most of them are based on values for thoracic stereotactic radiotherapy, however, dose constraints for coronary arteries have been extrapolated form available data with principle of maximum safety (10). Each RT fraction is supervised by a cardiologist. In accordance with national recommendations of the Heart Rhythm Section of the Polish Cardiac Society and the Polish Society of Radiation Oncology several safety procedures are used: continuous audiovisual contact with the patient, ECG monitoring, pulse oximetry, and capillary pulse wave recording. An access to an external defibrillator and also to external stimulation options and portable programmer is provided. During RT, it is recommended to temporarily switch off ventricular tachycardia/ventricular fibrillation detection (11).

The whole radiotherapy session took approximately 35 min, including 13 min of beam-on time, using a C-arm linear accelerator EDGE by Varian. No substantial acute toxicity was observed. Except for mild discomfort associated with the treatment session, both patients remained free of adverse effects until the final discharge from the hospital ward 2 days later.

RESULTS

First Patient Follow-Up

Interrogation of the implanted ICD revealed no VT episodes throughout 6 months of follow-up. A significant reduction in premature ventricular contractions burden was observed compared to the pre-treatment period (**Figure 4**). No noticeable deterioration in LV function was noted, nor any adverse effects of radiosurgery associated with the implanted device. The laboratory tests did not show any myocardial damage both at 3 and 6-months after treatment, and the patient did not report any clinically relevant adverse effects of radiosurgery.

Second Patient Follow-Up

During 6 months of follow-up since the initial procedure, interrogation of the implanted CRT-D was performed multiple times. In the periprocedural period (4 days after irradiation), 67 episodes of VT (7 episodes of non-sustained VT and 60 episodes of sustained VT) were revealed, treated with two high-voltage interventions and 60 ATPs. The patient was immediately admitted to the hospital with considerate hypokalemia and discharged 2 days later with supplementation of electrolytes, intravenous amiodarone administration and alteration of pharmacotherapy. Three weeks after the STAR procedure, the patient was hospitalized again due to reported chest pain and alleged device intervention. During the hospitalization, the CRT-D was interrogated and no high-voltage interventions nor the history of VT were disclosed. No deterioration of LV function was noted nor laboratory tests changes. The patient was discharged from the ward with the diagnosis of intercostal neuralgia 2 days later. Another hospitalization was required 3 months after STAR due to congestive heart failure exacerbation with pulmonary congestion, pleural effusion, and peripheral pulmonary embolism. The patient received inotropic agents (dopamine, levosimendan), and right pleural thoracentesis was made with the evacuation of transudative fluid. LVEF remained unchanged (EF = 20%). Until the end of the 6-months of observation, an additional two non-sustained VT (nsVT) episodes were recorded. However, the number of VT episodes during this observation period decreased considerably compared to the periprocedural period.

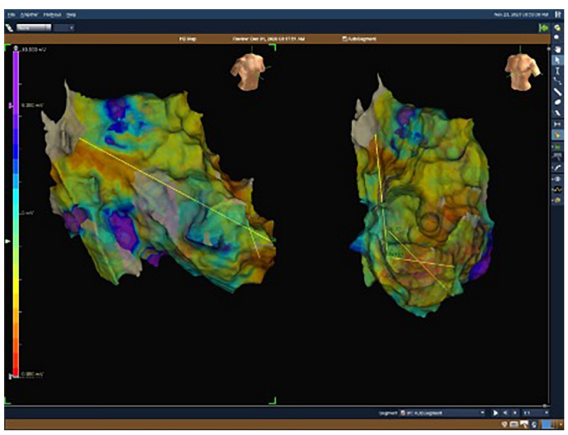

FIGURE 2 | Electroanatomical map with unipolar (UV) voltage of the second patient. UV range from 0.05 mV (red color) to 8.3 mV (purple color).

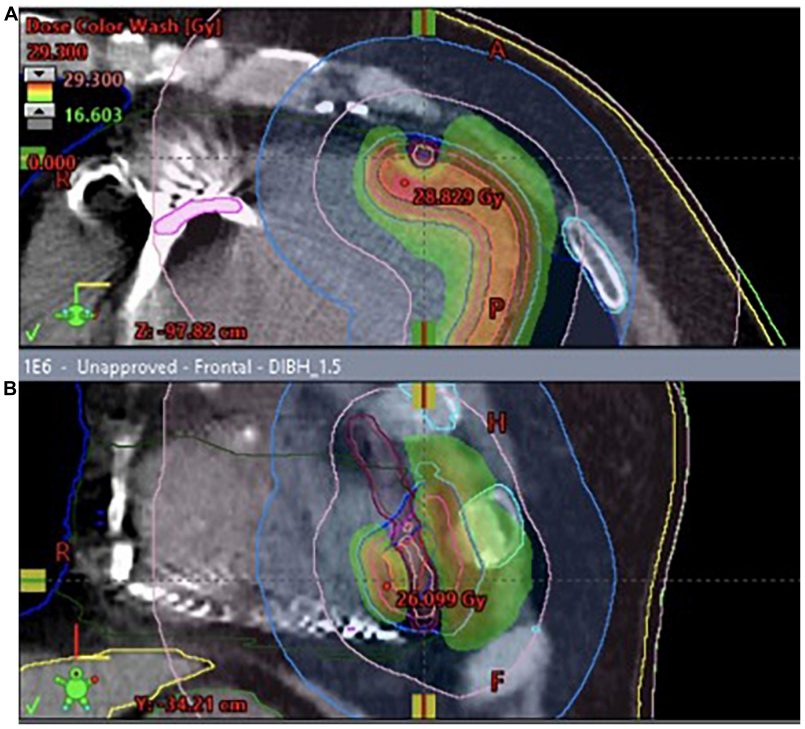

FIGURE 3 | (A) 3D visualization of the treatment plan with three coplanar dynamic arcs (VMAT technique), spatial reconstruction of contoured structures and DRRs (Digitally Reconstructed Radiograms) used for preliminary positioning of the patient. The final adjustment was performed using cone-beam CT (CBCT) superimposed on the planning CT. **(B)** The dose distribution was optimized to cover the planning target volume while accounting for organs-at-risk such as coronary arteries. Red and orange color represent higher dose, green- lower.

DISCUSSION

To the best of our knowledge, this article depicts the first two patients treated with STAR in Poland and demonstrates the possibility of stereotactic radiosurgery application for the treatment of VT in patients with post-RFA recurrence.

Eventually, in both patients treatment success can be announced; however, post-STAR courses differed significantly in each case. The initial concept of the treatment was based on the assumption that the biological mechanism of STAR leads to transmural fibrosis in the region of the arrhythmogenic substrate and subsequent cessation of electric signal propagation. The delivery of 25–35 Gy to the target area induces fibrosis within 6 months of irradiation, as shown on animal models (12). However, clinical studies demonstrated that STAR is capable of inducing immediate treatment effect (13, 14). The first patient treated in our study presented an excellent response to STAR treatment with no ventricular arrhythmia recurrence or LV function deterioration during 6 months of follow-up. The STAR effect was rapid, with an evident reduction in premature ventricular contractions (ICD interrogation, electrocardiography) and improvement in the patient's symptoms (quality of life questionnaire). Such swift response is probably an effect of functional changes in the myocardium after STAR. One of the possible explanations was described by Zhang et al. (13). The authors demonstrated alteration of Notch signaling pathway resulted with upregulation of NaV1.5 and Cx. This may influence the conduction velocity and thus, represent a mechanistic explanation of the observed phenomena. In one patient the manifestation of the physiologic processes was anticipated and expressed by rapid reduction of the VT burden, whereas in the other the severity of arrhythmia surprisingly increased.

This demonstrates the complexity of the myocardial response to irradiation and indicates that the physiological phenomena standing behind the final clinical effect are still largely unknown and require more in-depth evaluation than previously stipulated.

As mentioned above, the treatment course of the second patient was more complex. During the follow-up period, the patient required a few hospitalizations not necessarily related to irradiation, however we cannot exclude congestive heart failure exacerbation, pleural effusion and peripheral pulmonary embolism as adverse events potentially related to STAR (reported according to commonly used terminology criteria for adverse events as Grade 3 in SMART-VT Trial). Nevertheless, the second patient's LV function remained unchanged during the follow-up. A transient ventricular arrhythmia intensification was observed during his periprocedural period with eventually sustained VT absence at 6 months of follow-up. The second patient's response to the treatment theoretically could also be a manifestation of transient post-procedural cardiac tissue damage followed by concurrent electrical and structural changes, so initially expressed by a marked dysregulation of the cardiac function but finally

TABLE 1 | Dose constraints for organs-at-risks (OARs) and dose to target.

OAR	Volume	Volume dose	Point dose*
PTV minus CTV	–	–	31.25 Gy
CTV	<1 cm^3	32.5 Gy	35 Gy
Spinal cord	<0.35 cm^3	10 Gy	14 Gy
	<1.2 cm^3	8 Gy	
Esophagus	<5 cm^3	11.9 Gy	15.4 Gy
Stomach	<5 cm^3	17.4 Gy	22 Gy
Duodenum	<5 cm^3 <10 cm^3	11.2 Gy 9 Gy	17 Gy
Trachea and main bronchi	<4 cm^3	17.4 Gy	20.2 Gy
Lungs (together)	<1500 cm^3	7 Gy	
	<1000 cm^3	7.6 Gy	
	<37%	8 Gy	
Liver	<700 cm^3	11 Gy	
Kidneys (together)	<200 cm^3	9.5 Gy	
Coronary arteries ^	–	–	12 Gy
Ribs	<5 cm^3	28 Gy	33 Gy
Skin	<10 cm^3	25.5 Gy	27.5 Gy

**Defined as point dose in < 0.035 cc. ^ Left coronary artery including anterior intraventricular and circumflex, and right coronary artery including posterior descending artery.*

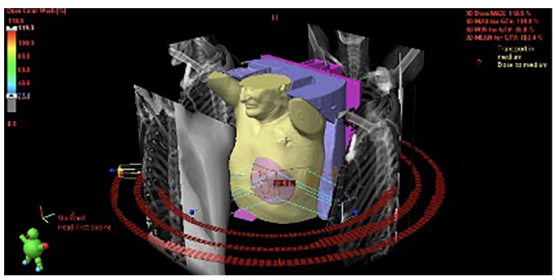

FIGURE 4 | Premature ventricular contractions burden before and after the treatment of the first patient.

leading to the expected clinical result. The post-STAR course differing significantly in each case indicates that an individual approach is required after the procedure and the clinical course of the disease after STAR can be unpredictable.

Stereotactic Arrhythmia Radioablation can be performed using conventional (c-arm) or CyberKnife (CK) accelerators. Both techniques have their advantages and disadvantages. First of all, it is important to be mentioned that the main difference between these two machines is the way in which target volume is irradiated. CK uses multiple small beams (tens-hundreds) to irradiate target volume while Linac accelerator irradiates the whole target volume at the same time. This important technical difference result in significant reduction in the delivery time from 60–70 min for CK to 5–6 min for Linac (without DIBH) (15–18). Both CK and Linac, allow to compensate for the respiratory motion. CK uses the respiratory tracking technique (Synchrony) during the whole respiratory cycle. The accelerator head moves synchronously with the respiratory movement of the body following the correlation curve calculated using the data on spatial position of the internal marker used for target tracking linked with the position of the light markers on the vest used for respiratory motion tracking. It allows for continuous delivery of the beam during the respiratory cycle but still, the target is irradiated part by part with numerous beams which causes the beam-on time to be approximately 35–69 min and total treatment time of 65–99 min according to Wang et al. (17). Conventional linac uses the respiratory gating technique (irradiation during the end-expiratory phase of the breathing cycle, usually between the last 10% of expiration and first 10% of the inspiration phase) or DIBH (irradiation during the deep inspiration breath hold) to manage the respiratory motion. The emission of the beam is interrupted in both cases but the number of beams is small (usually 2–4), the whole target volume is irradiated at the same time and the total treatment times are usually 37–56 min and beam delivery time 5–6 min (17). This numbers are similar with numbers observed in our clinical data.

Comparison of treatment plans created for different techniques by Weidlich et al. have shown larger dose gradients nearby PTV for CK plans, showing its advantage in sparing nearby OAR's comparing to the Linac-based accelerator which is superior in sparing distant OAR's.

CONCLUSION

An individual approach is required after the STAR procedure, and the clinical course of the disease can be unpredictable. Functional changes could appear relatively early, manifested by swift decrease of VT burden, as well as transient exacerbation of the arrhythmia. The SMART-VT study is ongoing, and the clinical course of the two presented cases clearly indicates that the complete toxicity profile of the STAR can be assessed only within a clinical trial.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Komisja Bioetyczna Narodowego Instytutu Onkologii w Gliwicach. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Feasibility of an Automatic Ultrasonographic Image Acquisition System Associated With an Artificial Intelligence Algorithm for Real-Time Monitoring of Cardiac Motion During Cardiac Radio-Ablation

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Background: The management of the cardio-respiratory motion of the target and the reduction of the uncertainties related to patient's positioning are two of the main challenges that stereotactic arrhythmia radio-ablation (STAR) has to overcome. A prototype of a system was developed that can automatically acquire and interpret echocardiographic images using an artificial intelligence (AI) algorithm to calculate cardiac displacement in real-time.

Methods: We conducted a single center study enrolling consecutive patients with a history of ventricular arrhythmias (VA) in order to evaluate the feasibility of this automatic acquisition system. Echocardiographic images were automatically acquired from the parasternal and apical views with a dedicated probe. The system was designed to hold the probe fixed to the chest in the supine position during both free-breathing and short expiratory breath-hold sequences, to simulate STAR treatment. The primary endpoint was the percentage of patients reaching a score $\geq$2 in a multi-parametric assessment evaluating the quality of automatically acquired images. Moreover, we investigated the potential impact of clinical and demographic characteristics on achieving the primary endpoint.

Results: We enrolled 24 patients (63 $\pm$ 14 years, 21% females). All of them had a history of VA and 21 (88%) had an ICD. Eight patients (33%) had coronary artery disease, 12 (50%) had non-ischemic cardiomyopathy, and 3 had idiopathic VA. Parasternal, as well as apical images were obtained from all patients except from one, in whom parasternal view could not be collected due to the patient's inability to maintain the supine position. The primary endpoint was achieved in 23 patients (96%) for the apical view, in 20 patients (87%) for the parasternal view, and in all patients in at least one of the two views. The images' quality was maximal (i.e., score = 4) in at least one of the two windows in 19 patients (79%). Atrial fibrillation arrhythmia was the only clinical characteristics associated

with a poor score outcome in both imaging windows (apical $p = 0.022$, parasternal $p = 0.014$).

Conclusions: These results provide the proof-of-concept for the feasibility of an automatic ultrasonographic image acquisition system associated with an AI algorithm for real-time monitoring of cardiac motion in patients with a history of VA.

Keywords: cardiac radioablation, motion monitoring, ventricular arrhythmia, echocardiography, artificial intelligence

INTRODUCTION

The therapeutic strategies currently available for the prevention of ventricular arrhythmias (VAs), namely antiarrhythmic drugs and invasive catheter ablation, are limited by suboptimal efficacy and a non-negligible incidence of adverse events and procedural complications (1–4). Furthermore, some arrhythmic patients with refractory VAs, are not eligible for traditional invasive ablative approaches due to their frailty and/or the inability to access VAs substrate with catheters (5). With the aim to offer a further therapeutic strategy for these patients, the possibility of treating arrhythmias was devised and developed by delivering high dose of ionizing radiations focused on the tissues critical for the genesis of arrhythmias [i.e., stereotactic arrhythmia radio-ablation (STAR)] (6, 7). The clinical experiences accumulated so far in this field have shown that the management of the cardio-respiratory movements of the target and the reduction of uncertainties related to patient positioning are two critical challenges that STAR has to overcome (8). The need for target's movement management is of the utmost importance particularly in case of respiratory gated delivery for radiotherapy with heavy particles such as protons and carbon ions (9, 10). At present, the strategies applied for cardio-respiratory movements compensation are limited by the need to consistently increase the size of the treated volume (e.g., internal target volume generated by 4D cardiac or respiratory CT or both), extend treatment time (e.g., gated delivery), and globally by the unsolved need to directly monitor cardio-respiratory movements in real-time without the use of fiducial markers (6, 8, 11, 12). A possible solution to this issue could be represented by the use of echocardiography as a fully non-invasive tool for monitoring internal motion. However, the context of radiotherapy treatment offers new challenges even for this versatile tool, such as the need for an immobilization system for the probe and the need for an automatic acquisition system that works in supine position and is able to process the acquired images with extremely short computation times and provide precise information about cardiac movements. A prototype of a system was developed that can automatically acquire and interpret echocardiographic images using an artificial intelligence (AI) algorithm to calculate cardiac displacement in real-time (EBAMed SA, Geneva, Switzerland). The development and the first experiments of this system were carried out on a general cardiology patient database (13) and on healthy volunteers; moreover, the set of images on which the algorithm was trained consisted of echocardiographic sequences mostly acquired in left lateral decubitus. No previous studies have evaluated the feasibility of this system in the context and on the patient population for which it was designed. Therefore, the aim of this study was to evaluate the ability of the automatic echocardiographic imaging system to obtain images of sufficient quality to be correctly interpreted by the AI algorithm in patients with a history of VAs in supine position, as well as to identify any factors limiting acquisition in this specific setting and population.

MATERIALS AND METHODS

We conducted a single center, single arm, feasibility study on patients referred to the Arrhythmia and Electrophysiology Unit of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, with a previous history of VAs. All consecutive patients evaluated in our clinic between May and September 2021 were screened for enrollment. This study received ethical approval from the local institutional review board (approval number 57629/2021) and, after being properly informed, all participants signed a written informed consent.

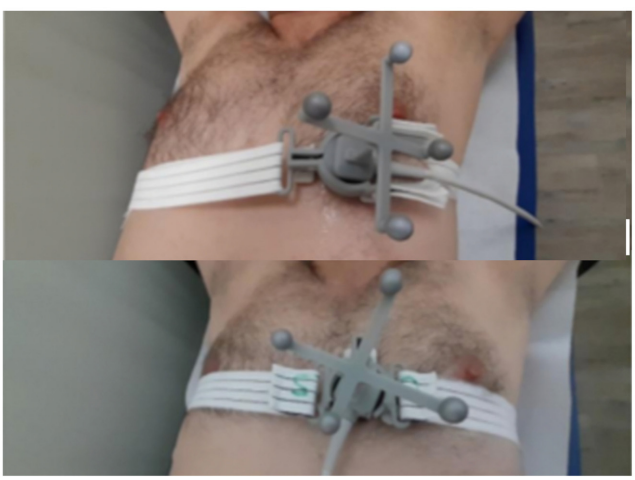

FIGURE 1 | Images of the ultrasound probe housed in the holder containing the markers for optical localization. The probe and the support are kept adherent to the patient's chest by means of an adjustable elastic band. Upper panel apical position; Lower panel parasternal position.

The Acquisition System

The image acquisition system used in the study consisted of a dedicated echocardiographic probe positioned inside a support and held adherent to the patient's chest by means of an adjustable elastic band. Two types of holders were conceived, alternatively used for the acquisitions made from the apical and parasternal windows (**Figure 1**). Each of the two holders housed four spherical references functional to an optical location system of the probe position (Polaris Vega® XT, NDI, Ontario, Canada). Simultaneously with the acquisition of echocardiographic images, the surface electrocardiographic signal (ECG) was recorded through three adhesive electrodes positioned at the root of both upper limbs and at the level of the left antero-superior iliac spine. The R-waves were automatically detected by the AccuSync® 42 trigger (AccuSync Medical Research Corporation, Milford, CT, USA). The acquired echocardiographic and ECG signals were conveyed to the processing module called Demonstrator 2 developed by EBAMed SA (Geneva, Switzerland). Beamforming of echocardiographic signals was performed using a Terason USB3.0 Engine (Teratech Corporation, Boston, MA, USA). The ultrasounds system recorded bidimensional (B-mode) ultrasound images at 40 Hz from two perpendicular plans. Once processed, the data were sent to the workstation which communicated with the Demonstrator

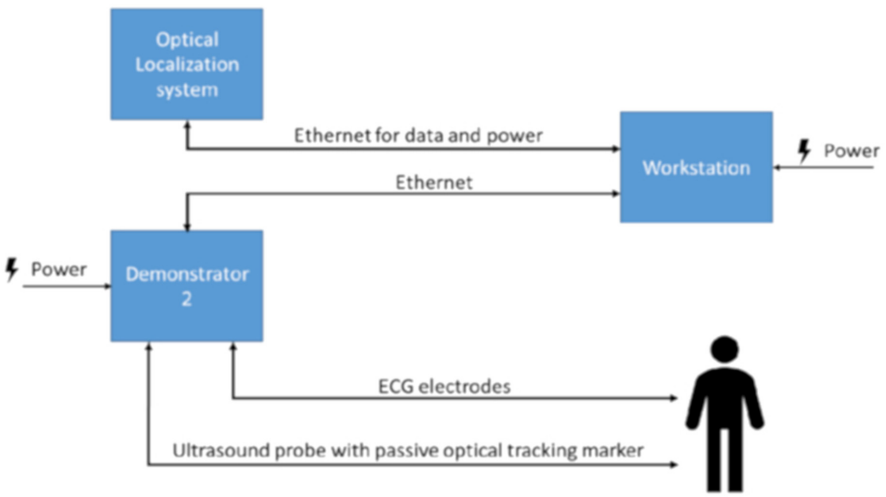

FIGURE 2 | Scheme representing of the acquisition system flow.

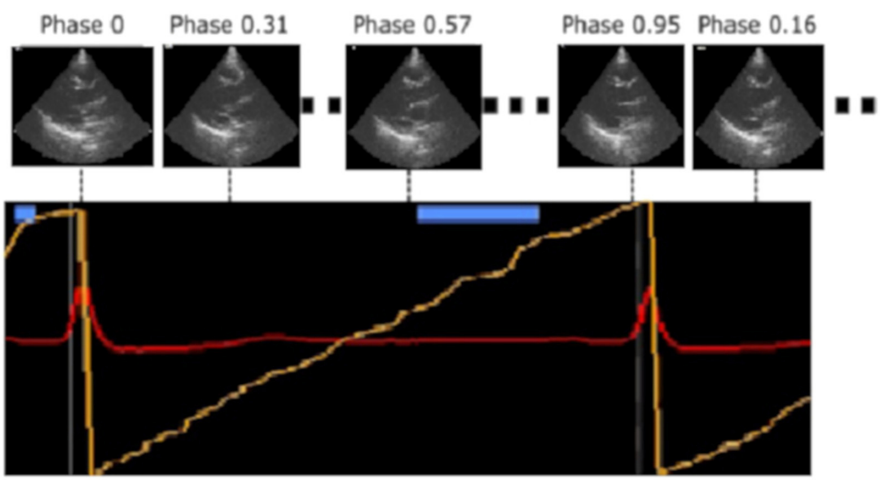

FIGURE 3 | Identification of the cardiac cycle phase performed by the artificial intelligence algorithm through the real-time analysis of the acquired ultrasound images. A linear mapping between 0 and 1 (yellow line) was performed in the R-R peak interval and a cardiac phase was assigned to each ultrasound frame based on its temporal position within this interval.

2 and with the optical localization system of the probe and provided a graphical interface for the operator (**Figure 2**). The interface screen showed in real time the ECG trace and echocardiographic images, as well as information on the position of the probe and any alarms. During the imaging session, the patients were asked to assume the supine position with the head resting on a suitable support and, when tolerated, to keep the arms raised.

Images Interpretation From the AI Algorithm

The data acquired with the described instrumentation were processed by an AI algorithm previously developed by EBAMed SA, (Geneva, Switzerland) capable of identifying the phase of the corresponding cardiac cycle for each ultrasound image acquired and calculating the extent of the displacement of the image compared to an image acquired in the same phase of a reference cardiac cycle. To obtain the ground truth cardiac phases, a phase of 0 was assigned to each R-peak in the ECG trace and a linear mapping between 0 (included) and 1 (excluded) of the remaining cardiac phases in the R-R peak interval was performed. A cardiac phase was assigned to each ultrasound frame based on its temporal position within the interval (**Figure 3**).

The AI algorithm used for cardiac phase identification is based on a neural network which consists of two parts. The first part, a multi-stage three-dimensional (3D) causal convolution network, is responsible for the extraction of spatial and short-term temporal features from the ultrasound sequence. The second part, a single dimension (1D) temporal convolution neural network, extracts long term temporal features. The network takes an ultrasound sequence of an arbitrary length as input, and it outputs one cardiac phase for each ultrasound image in the sequence. A publicly available database which contains US sequences and ECG traces of 500 cardiac patients (14) was used for the network training and evaluation using 5-fold cross validation. Once the cardiac phase is determined, a separate and additional neural network, previously developed by EBAMed SA, is used to measure the heart displacement in three dimensions (see **Figure 4**). This neural network is inspired by work of de Vos et al. (15) and it determines the heart displacement using rigid registration between the real-time ultrasound image and the reference ultrasound image (for the same cardiac phase). After inputting the real-time and reference ultrasound images, they are concatenated and subsequently passed through several convolution blocks followed by feature map averaging. Subsequently, three paths of fully-connected layers output a rotation angle, as well as a translation in two directions for each perpendicular ultrasound plane. As the location of each (heart) pixel inside the images is known in 3D space thanks to the optical localization system, the output of the network can be used to provide the displacement of the heart in 3D space.

The Acquisition Protocol

During the acquisition of the images, the patients were asked to remain with the chest completely uncovered and to assume the supine position on the acquisition table, with the head resting on a special support and, when tolerated, keeping their arms raised.

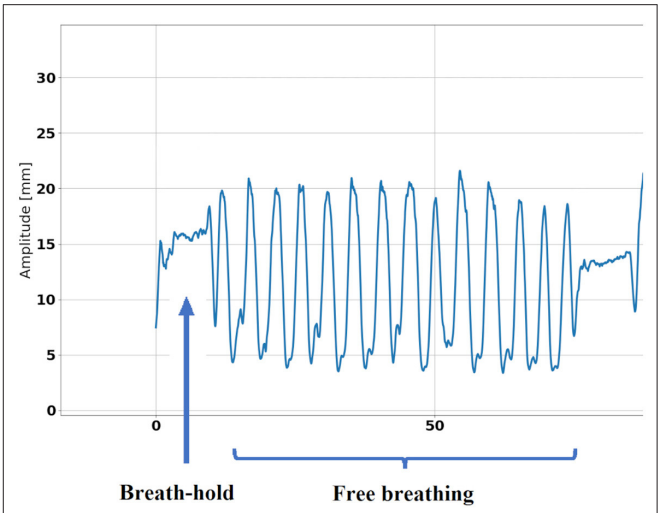

FIGURE 4 | Example of heart displacement measured by ultrasound during respiratory exercise.

The ECG cables were positioned as described above and, after applying the gel, the ultrasound probe was positioned and fixed using the appropriate holder and an elastic tape, at the level of the apical echocardiographic acquisition window. The position of the probe on the chest was noted on the case report form (CRF) and the relative position was monitored through the optical tracking system. Once the positioning of the patient and the initialization of the computer systems were completed, the monitoring of the heart position began. In the first 5 min of acquisition, the patients were asked to relax and breathe normally (*free breathing*); over the next 5 min they were encouraged to take a deep exhalation and hold their breath for 10 s every min, 5 times (*respiratory exercise*). At the end of this phase the probe was removed and repositioned at the level of the parasternal window. The position of the probe in the chest was noted in the CRF and the acquisition procedure was repeated. At the end of the acquisition phase, the probe was removed, and the patients were allowed to clean themselves of the gel left on the chest. Subsequently, before leaving, patients were asked to report any discomfort experienced during the procedure. The described acquisition protocol was conducted by a team of clinicians from the IRCCS San Matteo of Pavia with experience in the field of echocardiography and technicians from the EBAMed SA company.

Population

Screened patients were eligible for the enrollment if they had a history of VAs, were at least 18 years old, were able to maintain the supine position for the time of acquisition, did not have an ongoing VAs, and agreed to be enrolled in this study.

Outcomes

The primary endpoint was defined as the percentage of patients able to obtain a positive result in a multi parametric score of image quality, consisting of:

A– Image quality in terms of allowing a correct identification of the phase of the cardiac cycle by the prototype software:

Score = 1: average phase error per patient, defined as the difference between the phase of the cardiac cycle identified by the algorithm and the one evaluated by the ECG reference <0.1.

Score = 0: average phase error per patient ≥0.1.

B– Image quality in terms of allowing a correct measurement of the heart displacement (mainly due to respiratory motion) by the prototype software:

Score = 1: maximum excursion calculated by the algorithm < 30 mm with a total 3D error in the calculation of the displacement <3 mm.

Score = 0: either maximum excursion calculated by the algorithm ≥30 mm or total 3D error in the calculation of the displacement ≥3 mm (or both).

C– Image quality in terms of the ability to distinguish typical cardiac structures, as assessed visually by the clinical operator:

Score = 1: ability to identify visually by an experienced operator in the acquired image at least one of the following structures: left ventricular free wall, interventricular septum, mitral valve, or aortic valve.

Score = 0: inability to identify at least one of these structures.

D– Image quality in terms of the stability of the image throughout the respiration cycle, as assessed visually by the clinical operator:

Score = 1: persistence of cardiac structures within the echocardiographic image during respiratory motion.

Score = 0: disappearance of cardiac structures from the echocardiographic image during respiratory motion.

For each patient, scoring was done for each imaging view (i.e., parasternal and apical). If the score was 2 (at least 1 point in A or B and 1 point in C or D) or greater for at least one of the imaging views, the outcome was considered as positive. The final result is the proportion of patients (in %) with a positive outcome, defined as the number of patients with a positive evaluation divided by the total number of patients x 100.

The secondary endpoints of the study were the percentage of patients able to obtain a positive result in each of the items of the primary endpoint and the percentage of patients with maximum image quality for algorithm operation, defined as those patients who scored a 4 on the multi-parametric assessment.

Scores A, C, and D were evaluated on *free-breathing* sequences while score B was evaluated during *respiratory exercise*. The reference for calculating the phase error of the cardiac cycle was the ECG signal acquired simultaneously with the ultrasonographic images. The magnitude of the maximum accepted error was set to 0.1 consistent with the performance obtained by the algorithm on the validation dataset. Prior to assignment of score A and B, ECG traces acquired with their associated automatic R-wave markers were reviewed by an experienced operator and any inconsistencies between the automatic marker and the operator's opinion were recorded in a special log. Markers referable to ventricular and supraventricular premature complexes were also identified. Images acquired during extrasystolic cycles or during those in which the automatic markers were not consistent with the operator's opinion were excluded from scores A and B analyses. Regarding the tracking of heart displacement, the maximum acceptable threshold in the displacement calculated by the algorithm was conservatively set at 30 mm, in order to exclude that the magnitude of this excursion was not consistent with the maximum displacement of a cardiac tissue reported in the literature. The total geometric error in 3D space in the calculation of position was taken as the relevant metric. The threshold value of 3 mm was calculated as 10% of the

TABLE 1 | Characteristics of the enrolled population.

	Number of patients enrolled	**24**
Clinical and demographics characteristics	Age (years)	63 ± 14
	Female gender	5 (21%)
	Height (cm)	173 ± 7
	Weight (kg)	82 ± 16
	BMI (kg/m^2)	26 (24–30)
	Left ventricular ejection fraction (%)	52.5 (36.5–60)
	History of smoking	17 (71%)
	COPD or other significant pneumopathy	6 (25%)
History of arrhythmias	History of VT	23 (96%)
	History of VF	4 (17%)
	History of atrial arrhythmias	8 (33%)
	Previous VT ablation	9 (38%)
Type of heart disease	Ischemic heart disease	8 (33.3%)
	Non-ischemic cardiomyopathy	12 (50%)
	Dilated cardiomyopathy	4 (16.6%)
	Hypertrophic cardiomyopathy	4 (16.6%)
	Arrhythmogenic cardiomyopathy	1 (4.2%)
	Other cardiomyopathies	3 (12.5%)
	Corrected congenital heart disease	1 (4.2%)
	Absence of structural heart disease	3 (12.5%)
Devices	ICD	21 (87.5%)
	Single-chamber ICD	7 (29%)
	Dual-chamber ICD	4 (17%)
	Biventricular ICD	7 (29%)
	Subcutaneous ICD	3 (12.5%)
	Loop recorder	3 (12.5%)
Mechanical Valve		1 (4%)

Data are presented as number (%), mean ± standard deviation or median (interquartile range); BMI, body mass index, COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 2 | Multi-parametric score results and primary outcome.

Scores	Apical view	Parasternal view	
A-average cardiac phase error <0.1	20 out of 24 (83%, CI 95% 62–95%)	18 out of 21 (86%, CI 95% 64–97%)	
B-maximum excursion < 30 mm and total displacement error < 3 mm	22 out of 23 (96%, CI 95% 79–100%)	20 out of 21 (95%, CI 95% 76–100%)	
C-ability to visually identify cardiac structures	23 out of 24 (96%, CI 95% 79–100%)	20 out of 23 (87%, CI 95% 66–97%)	
D-persistence of cardiac structures in the image during breathing	22 out of 24 (92%, CI 95% 73–99%)	18 out of 23 (78%, CI 95% 56-92%)	**At least one view**
Primary outcome (score ≥2 with at least 1 within A and B and at least 1 within C and D)	**23 out of 24 (96%, CI 95% 79–100%)**	**20 out of 23 (87%, CI 95% 66–97%)**	**24 out of 24 (100%, CI 95% 86–100%)**

CI, confidence interval.

maximum accepted excursion, consistent with the performance obtained by the algorithm on the validation dataset.

Statistics

Sample Size

As this is a feasibility study at an early stage of research, an enrollment of 24 patients was planned. With the goal of obtaining 90% positive patients at the primary endpoint (success in 22 out of 24 patients), enrollment of this number of patients would ensure a 95% confidence interval between 71 and 98%.

Data Analysis and Presentation

Outcomes were reported as the number of patients who achieved the outcome with the relative percentage and 95% confidence interval (CI). The impact of clinical and demographic characteristics of the enrolled patients on the quality of the acquired images was also assessed. The descriptive variables collected were presented as number and relative percentage for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous variables, as appropriate based on the normality of the distribution of the variable in question verified by Shapiro-Wilk test. Comparisons between means were performed with the *t*-test or the Welch-test, based on the result of the F-test previously performed to compare the variances between groups. Comparisons between medians were made with the Mann-Whitney test and categorical variables were compared with the Chi^2 test or Fisher's exact test, as appropriate. Patients who experienced significant protocol violations were excluded from the analysis, as detailed in the next sections.

RESULTS

Population Characteristics

During the period from May 2021 to September 2021, 24 patients were enrolled in the study. Five were female (21%). The mean age of the patients was 63 ± 14 years. All patients had a history of at least one episode of VA: in 23 patients (96%) at least one ventricular tachycardia (VT) had been recorded and 4 patients (17%) had at least one episode of ventricular fibrillation (VF). Most of the enrolled patients had an ICD (87.5%) and 3 patients were monitored with a loop-recorder (12.5%). The etiology of the arrhythmia was ischemic in 8 patients (33%), 12 patients (50%) had non-ischemic cardiomyopathy, and 3 patients had a history of idiopathic VT/VF. Further details on the characteristics of the enrolled population are presented in **Table 1**.

Acquisitions

The mean heart rate (HR) during acquisitions was 63 ± 8 bpm for the apical window and 62 ± 8 bpm for the parasternal window. Two patients (8%) had an irregular rhythm due to atrial fibrillation throughout the acquisition, and 6 (25%) patients had an extrasystolic burden, defined as the percentage of extrasystolic atrial or ventricular complexes on total complexes, >10%.

Deviations

Both imaging views were attempted in all patients except one who, after having performed the respiratory exercise for the apical window acquisition, developed an access of cough that made it impossible to continue the experiment with the acquisition from the parasternal window. This patient was therefore excluded from the score evaluation for the parasternal window. In two patients it was not possible to obtain, despite repeated attempts, a parasternal view adequate for image acquisition. For these two patients it was therefore not possible to calculate the performance of the algorithm for points A and B, and a score of 0 was assigned in points C and D; consequently, it was considered that these patients did not obtain a positive evaluation in the multiparametric score of the primary outcome.

In one case it was not possible to obtain an apical window from which the cardiac structures did not disappear from the ultrasound image during the respiratory exercise. This patient was therefore excluded from the evaluation of score B for the apical window.

Because of a not always optimal quality of the ECG trace during acquisition, at least one oversensing phenomenon of deflections different from R-wave occurred in 9 patients (37.5%) and at least one episode of R-wave undersensing occurred in 7 (29%) patients. Images acquired during extrasystolic cycles and during those for which the ECG trace was subject to undersensing or oversensing errors, thus not being able to be used as a reference

TABLE 3 | Additional detailed results for scores A and B.

		Apical	Parasternal
A	Average phase error [threshold value used in score A is 0.1]	0.05 ± 0.04	0.06 ± 0.06
B	Respiratory motion amplitude (mm) [threshold value used in score B is 30 mm]	17 ± 7	16 ± 8
	3D Error in calculation of displacement (mm) [threshold value used in score B is 3 mm]	1.1 ± 0.2	1.1 ± 0.4

Data are presented as mean ± standard deviation.

of the cardiac cycle phase, were excluded from the analyses of score A and B.

Outcomes

The primary outcome was achieved in 23 patients (96%, CI 95% 79–100%) for the apical window, in 20 patients (87%, CI 95% 66–97%) for the parasternal window, and in all patients (100%, CI 95% 86–100%) in at least one of the two windows (**Table 2**).

A mean phase error in the correct identification of the cardiac cycle phase <0.1 was found in 20 patients (83%, CI 95% 62–95%) for images acquired from the apical window and in 18 patients (86%, CI 95% 64–97%) for the parasternal one. The average phase error was 0.05 ± 0.04 and 0.06 ± 0.06, respectively for the apical and parasternal windows (**Table 3**).

A cardiac displacement >30 mm was measured for one patient in apical view (31 mm) and another patient in parasternal view (31 mm). On average, recorded displacements were 17 ± 7 mm in apical view and 16 ± 8 mm in parasternal view, with an average 3D error of 1.1 ± 0.2 mm and 1.1 ± 0.4 mm, respectively.

In 23 patients (96%, CI 95% 79–100%) for the apical window and in 20 for the parasternal one (87%, CI 95% 66–97%) it was possible to identify by an experienced operator at least one among the free wall of the left ventricle, the interventricular septum, or a valvular structure. For two patients it was not possible to obtain, despite repeated attempts, a parasternal window sufficient for the identification of these structures.

In 2 patients for the apical view (8%, CI 95% 1–27%) and in 5 for the parasternal window (22%, CI 95% 8–44%) cardiac structures transiently disappeared from the echocardiographic image during the quiet breathing movement.

The image quality scores were maximal (with a multiparametric score of 4), in 16 patients for both apical and parasternal (70%, CI 95% 48–87%) views, and in 19 patients (79%, CI 95% 56–93%) in at least one of the two windows.

During the procedures related to the experimental protocol, no significant adverse events occurred to the patients. Only one patient, with advanced chronic heart failure and smoke-induced chronic obstructive pulmonary disease, had to stop the experiment due to a coughing access following the effort made to perform the respiratory exercise during the acquisition of the apical window.

Influence of Parameters on Results

When analyzing the clinical characteristics of patients, the only parameters found to be statistically correlated with the achievement of images of maximal quality were the heart rate and heart rhythm stability during acquisition (**Tables 4**, **5**). Irregular heart rhythm due to atrial fibrillation resulted in higher median errors for the cardiac cycle phase identification (0.13 vs. 0.03, $p = 0.0215$ for the apical view, and 0.11 vs. 0.03, $p = 0.0381$ for the parasternal view). Excluding patients with atrial fibrillation arrhythmia from the analysis, no statistically significant differences were observed between the heart rate of the patients who obtained a positive evaluation on score A compared to those who did not (62 ± 7 vs. 63 ± 4, $p =$ 0,83). Notably, as previously mentioned, images acquired during extrasystolic cycles were excluded from scores A and B analyses. Accordingly, no differences were found based on extrasystolic burden (**Table 4**).

DISCUSSION

The results of our study provide the proof-of-concept for the feasibility of an automatic ultrasound image acquisition system associated with an AI algorithm for real-time monitoring of heart movement in patients with a history of VAs.

As previously mentioned in the introduction, the need for target's movement management is of the utmost importance during arrhythmia radio-ablation and the strategies currently available for this task have several limitations. A possible solution could be the use of a relatively simple and cheap imaging system such as echocardiography. The additional advantages of an ultrasound-based motion management over current techniques are that the solution is fully non-invasive and enables real-time monitoring of the internal motion (as opposed to the use of external surrogates). The recently reported use of nuclear magnetic resonance imaging for this purpose is limited by the fact that a direct tracking of the heart as well as the heart's substructures was not possible (16). The context of radiotherapy treatment offers new challenges even for echocardiography. Obvious radiation protection requirements prevent a human operator from acquiring the ultrasound images during the delivery of therapy and force to develop automatic acquisition systems. The supine position assumed by the patient on the therapy table, not being for anatomical reasons the most suitable for the acquisition of echocardiographic images, makes this task even more difficult. Moreover, to be useful in the real-time guidance of treatment, the acquired images must be processed with extremely short computation times and provide precise information about cardiac movements. To try to meet these challenges, a prototype of a system for automatic acquisition of echocardiographic images was designed and developed (EBAMed SA, Geneva, Switzerland). The images thus acquired are then processed and interpreted by an AI algorithm to calculate the cardiac displacement in real time. The possibility to carry out this task, extremely complex for the common *rule-based* systems, is facilitated by the use of a technology based on *machine-learning* algorithms (17). The

TABLE 4 | Comparison of the clinical demographic characteristics of patients with maximal image quality versus those with lower image quality.

	Patients with maximal image quality in at least one ultrasound window ***N = 19 (79%, CI 95% 56–93%)***	**Patients with suboptimal image quality in both ultrasound windows** ***N = 5 (21%, IC 95% 7–42%)***	***P*-value**
Age (years)	62 ± 15	68 ± 6	0.38
Female gender	5 (26.3%)	0 (0%)	0.54
Height (cm)	172 ± 7	174 ± 8	0.55
Weight (kg)	80 ± 13	89 ± 25	0.27
BMI (kg/m^2)	26 (24–29)	25 (23–35)	0.97
LV ejection fraction (%)	55 (36–60)	46 (37–59)	0.72
History of smoking	13 (68.4%)	4 (80%)	1
COPD	5 (26.3%)	1 (20%)	1
History of VT	19 (100%)	4 (80%)	0.21
History of VF	2 (10.5%)	2 (40%)	0.18
History of atrial arrhythmias	4 (21.1%)	4 (80%)	**0.03**
Previous VT ablation	5 (26.3%)	4 (80%)	0.05
Ischemic heart disease	7 (36.8%)	1 (20%)	0.63
Non-ischemic cardiomyopathy	9 (47.4%)	3 (60%)	1
Absence of structural heart disease	3 (15.8%)	0 (0%)	1
Single-chamber ICD	4 (21.1%)	3 (60%)	0,13
Dual-chamber ICD	3 (15.8%)	1 (20%)	1
Biventricular ICD	6 (31.6%)	1 (20%)	1
Subcutaneous ICD	3 (15.8%)	0 (0%)	1
Loop recorder	3 (15.8%)	0 (0%)	1
Mean HR (bpm)	61 ± 7	69 ± 7	**0.04**
Atrial fibrillation arrhythmia	0 (0%)	2 (40%)	**0.036**
Extrasystolic burden > 10%	5 (26.3%)	1 (20%)	1

Data are presented as number (%), mean ± standard deviation or median (interquartile range); BMI, body mass index; bpm, beats per minute; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, heart rate; ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 5 | Evaluation of the impact of heart rate and heart rhythm stability on the ability of the algorithm to correctly identify the phase of the cardiac cycle.

		Apical score			**Parasternal score**		
		1	***0***	***P***	***1***	***0***	***P***
A	Mean HR during acquisition (bpm)	62 ± 7	71 ± 10	**0.048**	61 ± 8	69 ± 8	0.107
	Atrial fibrillation arrhythmia during acquisition	0 out of 20 (0%)	2 out of 4 (50%)	**0.022**	0 out of 18 (0%)	2 out of 3 (100%)	**0.014**

Data are presented as mean ± standard deviation.

development and the first usages of this system were carried out on a general cardiology patient database (13) and on healthy volunteers, and the set of images on which the algorithm was trained consisted of echocardiographic sequences mostly acquired in left lateral decubitus. It is therefore necessary to test the feasibility of using this system in the context and on the patient population for which it was designed and which, as has been mentioned, proposes specific challenges. Accordingly, the main aim of the present study was to evaluate whether the automatic echocardiographic image acquisition system under study could obtain adequate images to ensure the functioning of the AI algorithm in real patients with a history of VAs and to identify any limiting factors for acquisition in this specific population. On the other hand, it was beyond the scope of this study to evaluate the functioning and reliability of the algorithm in tracking cardiac movements.

Some considerations can be made about the representativeness of the enrolled population compared to the population potentially eligible for radio-ablation treatment. The average age of the patients enrolled, as well as the percentage of females and the spectrum of underlying cardiac disorders, are globally in line with that of the types of patients who could benefit from STAR (6, 11, 18). All body sizes were coved, as well as all ranges of left ventricle ejection fraction, including patients with a markedly depressed left ventricle systolic function, that are at present the main candidates for STAR (6). Previous clinical studies on STAR did not systematically report on cardiac rhythm stability during

treatment, however it appears plausible, even considering the percentage of patients with dual-chamber ICD and CRT (18), that the population included in our study, even in this respect, was representative of the cohort of patients eligible for STAR.

The primary endpoint of the study was achieved in all patients for at least one of the two windows. The attempt to acquire the parasternal window failed in 2 out of 23 patients, but in those patients in whom the window was obtained, there were no significant differences in terms of the quality of the images obtained compared with the apical window. The difficulty in acquiring the parasternal window can be partially explained by the supine position of the patient and the need to apply strong pressure of the probe on the thorax to obtain an image. However, considering that in a possible treatment phase the best of the two probe positions studied could be used, our results are reassuring.

The evaluation of the adequacy of the images provided by the automatic acquisition system for the definition of the phase of the cardiac cycle showed a good performance of the system in 83 and 86% of patients for the apical and parasternal windows respectively. The good quality of the acquired images is confirmed by the low average phase errors calculated, that are globally consistent with that showed by the algorithm on the validation set, thus confirming a good performance of the algorithm on real patients in the treatment position. For this score, as opposed to score B, the study conducted allows us to evaluate not only the quality of the images acquired but also the actual operation of the algorithm. Having available a known reference of the measured quantity (i.e., the phase of the cardiac cycle provided by the ECG hardware) the calculated average phase error can be considered as a real error. Pre-requisite for this to be feasible is the correctness of the R-wave markers on the ECG trace. As shown in the Results section this assumption did not always prove to be correct and, in order to compensate the effect of this phenomenon, the images acquired in those cycles in which a certain reference to determine the phase error was missing, were excluded from the analysis. Despite this correction, in 4 patients for the apical view and in 3 for the parasternal view the mean phase error exceeded the threshold of 0.1. As evidenced by our analysis, one possible explanation for this difficulty may lie in cardiac rhythm instability. In these conditions, the constant variability of the RR interval deprives the algorithm of a unique reference for its functioning in this task. The same difficulty would also appear at treatment planning when a cardiac 4D-CT has to be acquired. If the heart rhythm is not stabilized, it will not be possible to obtain adequate CT images for treatment planning. In order to overcome this limitation, one could, in particular in patients with a device, enhance the negative dromotropic therapy and/or increase the pacing rate to try to regularize the frequency. The *rate smoothing* algorithms could also be useful for this purpose (19). Moreover, once the image acquisition and the algorithm operation are optimized, it will not be strictly necessary to have a high-quality ECG trace with correct R-wave markers, because the algorithm operation is independent from the ECG trace, which is used for the purposes of the study to have a reference in the calculation of the phase error, and not for the intrinsic operation of the system.

For the evaluation of score B (magnitude of maximum displacement and error on the calculation of displacement) the quality of the acquired images allowed a positive scoring in most of the patients. In contrast to what was reported for the evaluation of score A, there was no statistically significant influence on the performance of the algorithm by R-R cycle instability. This being said, due to the small number of patients enrolled in this feasibility study, strong conclusions cannot be drawn. In contrast to the evaluation of score A, it should be mentioned that there was no reference (ground-truth) of the true cardiac displacement in the study that would allow to evaluate the error in the actual performance of the algorithm. The quality of the acquired images was adequate for most of the patients, as demonstrated by the fact that the magnitude of the calculated maximum displacements was plausible and the calculated error on the displacement was in line with what observed on the validation set. In order to plan a future clinical application of the system studied, it will be necessary to evaluate the accuracy of the amount of displacement calculated by the algorithm with respect to the actual cardiac displacement monitored using a reference method. Further studies are planned to answer this question.

A further consideration to be made concerns the visual assessment of the quality of the images (score C). Compared to the images normally used for clinical purposes, the quality of the images automatically acquired by the system in our study is on average significantly lower. This is because the data displayed in the prototype user interface are the raw images and none of the usual visualization post-processing techniques (e.g., frame averaging or speckle reduction) have been implemented. Future versions of the prototype will instead include these visualization tools. This being said, the purpose of the acquisition is not to obtain images of diagnostic quality, but adequate to be interpreted automatically by the algorithm and to ensure that the operator can check that the heart is visible in the picture. This is the reason why in the evaluation of score C, a less restrictive criterion was used, accepting as sufficient even the visualization of a single cardiac structure. Since the visualization of a specific cardiac structure is not necessary for the functioning of the algorithm, thanks to the machine-learning approach, even images which are not perfectly interpretable by the human eye are acceptable, extending the audience of patients in which this method can be applied also to patients with a non-optimal acoustic window if evaluated with standard criteria. Also, in view of this, it is not surprising that the ablative target itself does not necessarily need to be identified by ultrasound. Being a cardiac target, monitoring of the organ itself should theoretically ensure sufficient accuracy.

Assuming that the evaluation of the displacement is accurate, for the system to be able to guide a radiotherapy treatment it will have to be able to recognize precisely the phase of the cardiac cycle in which each image is acquired, calculate accurately the displacement comparing images acquired in similar phases of different cardiac cycles and, to do this, at least one cardiac structure will have to be always visible and the heart should not disappear with respiration. Based on this consideration, we have defined as maximal that image

quality that satisfies all 4 points of the multi-parametric score. No significant differences were found in the clinical and demographic characteristics of patients with maximal image quality compared to those with lower quality, except for those factors that limit the regularity of the cardiac cycle, as previously discussed. None of the patient's physical characteristics were found to be significantly associated with lower image quality, although the limited sample size does not allow any definite conclusion in this matter. Based on our results it is likely that an echocardiographic system could be of clinical utility to guide radiotherapy treatment in most patients (i.e., about 80%).

A possible limitation of the use of this system during the delivery of therapy could be represented by the interaction between the probe positioned on the chest and the radiant beam. Future studies have already been planned to verify this risk.

If further studies will confirm the functioning of this system, it can be hypothesized that its clinical application could lead to significant advantages for STAR. With a real-time system for heart monitoring available, the need to increase the target volume to compensate for cardio-respiratory movements could be limited. In addition, a precise gating or tracking could be done without the need and limitations of a fiducial marker. This could further reduce the safety margins to be applied and perhaps reduce treatment times, particularly in case of respiratory gated delivery for radiotherapy with heavy particles such as protons and carbon ions (9, 10, 12, 20). A further usefulness of this system could consist in increasing the safety in the treatment phase, by controlling in real time the cardiac cycle and heart movements and allowing to interrupt the delivery of the radiant beam in case of anomalies on each of these two factors with extremely short reaction times. For the purposes of clinical applicability, it will also be important to develop and optimize the communication and integration between the ultrasound system and the systems commonly used for treatment planning and radiation beam delivery. Finally, further studies on a larger population will be needed to confirm the feasibility of this system and to optimize its operation on the widest possible spectrum of patients with different physical and clinical characteristics.

CONCLUSIONS

The results of the present study provide the proof-of-concept for the feasibility of an automatic ultrasonographic image acquisition system associated with an AI algorithm for real-time monitoring of cardiac motion in patients with a history of VAs. Although further studies are needed before this system can be applied to clinical practice, the possibility of real-time, non-invasive monitoring of cardiac position would lead to a significant improvement in the quality and safety of stereotactic radiotherapy treatment for patients with VAs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG, SC, JG, and TB designed and developed the prototype used for the acquisitions and the AI algorithm. MC, VD, AG, SC, and JG carried out the acquisitions. MC, AG, and JG performed the analyses on the acquired data. MC wrote the draft of this manuscript. All authors discussed the results and approved the final version of the manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Long Term Follow-Up of Stereotactic Body Radiation Therapy for Refractory Ventricular Tachycardia in Advanced Heart Failure Patients

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Background: Initial studies of stereotactic body radiation therapy (SBRT) for refractory ventricular tachycardia (VT) have demonstrated impressive efficacy. Follow-up analyses have found mixed results and the role of SBRT for refractory VT remains unclear. We performed palliative, cardiac radio ablation in patients with ventricular tachycardia refractory to ablation and medical management.

Methods: Arrhythmogenic regions were targeted by combining computed tomography imaging with electrophysiologic mapping with collaboration from a radiation oncologist, electrophysiologist and cardiac imaging specialist. Patients were treated with a single fraction 25 Gy. Total durations of VT, the quantity of antitachycardia pacing (ATP) and shocks before and after treatment as recorded by implantable cardioverter-defibrillators (ICDs) were analyzed. Follow-up extended until most recent device interrogation unless transplant, death or repeat ablation occurred sooner.

Results: Fourteen patients (age 50–78, four females) were treated and had an average of two prior ablations. Nine had ACC/AHA Stage D heart failure and three had left ventricular assist devices (LVAD). Two patients died shortly after SBRT, one received a prompt heart transplant and another had significant VT durations in the following months that were inaccurately recorded by their device. Ten of the 14 patients remained with adequate data post SBRT for analysis with an average follow-up duration of 216 days. Seven of those 10 patients had a decrease in VT post SBRT. Comparing the 90 days before treatment to cumulative follow-up, patients had a 59% reduction in VT, 39% reduction in ATP and a 60% reduction in shocks. Four patients received repeat ablation following SBRT. Pneumonitis was the only complication, occurring in four of the fourteen patients.

Conclusion: SBRT may have value in advanced heart failure patients with refractory VT acutely but the utility over long-term follow-up appears modest. Prospective randomized data is needed to better clarify the role of SBRT in managing refractory VT.

Keywords: stereotactic body radiation therapy, refractory ventricular tachycardia, advanced heart failure, ventricular tachycardia ablation, ventricular tachycardia storm

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INTRODUCTION

SBRT (stereotactic body radiation therapy) has emerged as an experimental treatment for refractory ventricular tachycardia (VT) in recent years. Conventional ablations, while effective, have high rates of long term recurrence of VT and are unable to easily access deeper swaths of myocardium that frequently contribute to ablation failure (1–3). SBRT holds the potential advantage of reaching those deeper, larger portions of myocardium and is non-invasive (4).

Initial cases, case series and a prospective analysis have shown very impressive durable success in treating previously refractory VT with SBRT (5–7). Follow-up studies have been mixed but notably, the methods are quite heterogeneous and the role of SBRT in refractory VT treatment remains under investigation (7–12). Most prior studies have excluded advanced heart failure patients who make up an important subset of patients who have high burdens of VT/VF and have high mortality (13). Our prior case series of 10 initial patients treated with palliative SBRT for refractory VT demonstrated reasonable effectiveness in acutely reducing burdens of refractory VT/VF (8).

Here we report our cumulative experience with all follow-up to date with palliative SBRT treatment of advanced heart failure patients with refractory VT.

MATERIALS AND METHODS

Patients reported in this retrospective analysis received treatment under the compassionate use mechanism under the direction and approval of the Emory University Institutional Review Board. Methods were the same as reported in our prior retrospective analysis (8). All Patients considered for SBRT were required to have failed antiarrhythmic drugs, failed at least one RF ablation (or be inappropriate for RF ablation), or failed one adjunctive therapy such as mechanical support or sympathetic blockade, with failure defined as recurrent VT after intervention. Patients were required to provide consult with a radiation oncologist.

Wearable multielectrode vest technology with computed tomography (CT) registration (Cardio insight, Medtronic Corp., Minneapolis, MN) was not used in this cohort due to logistical constraints of this system applied to critically ill patients. All patients underwent at least one 3-dimensional imaging study and one electrophysiology study with electroanatomic mapping to identify the treatment target. Antiarrhythmic drug regimens were not altered after SBRT treatment, except for conversion to oral therapy.

The details of ablation modalities used and the general characteristics of ventricular arrhythmias of our cohort before SBRT are listed in **Table 1**.

All but one patient had previously undergone extensive ablation procedures. Endocardial and epicardial voltage maps were obtained, with published designations of "scar" (0.5 mV bipolar), "transition zone" (0.5–1.5 mV bipolar), and "healthy" (>1.5 mV) being used. Epicardial voltage maps and use of unipolar mapping varied. Treatment strategies for each patient focused on scar homogenization, with use of entrainment for clinically tolerated VTs and pace-mapping as adjuncts. Powers ranged from 35 to 50 W using irrigated RF systems. Two types of mapping systems were used (EnSite Precision, Abbott, Abbott Park, IL; or CARTO, Biosense Webster, Diamond Bar, CA). Ablation catheters, mapping catheters, and intracardiac ultrasound systems included current-generation systems available in the United States. Definitions of inducibility and non-inducibility were determined by programmed ventricular stimulation that was performed before ablation and at end of the procedure using up to 3 extrastimuli to refractoriness or a coupling interval $\geq$ 200 ms.

Target zones for SBRT were chosen by 3-dimensional imaging and electroanatomically derived substrate, in addition to the recurrent VT morphology and comparison to remaining inducible VTs postablation. Of note, target planning for those patients with LVAD were performed in a manner similar to those without, and no clinically actionable changes were observed in LVAD pump speed, flow, pulsatility index, or power.

Radiation Treatment

Before SBRT treatment, all patients underwent CT simulation. Rigid immobilization was used in a fashion consistent with SBRT treatment for lung cancers. All patients were simulated with administration of intravenous contrast if the estimated glomerular filtration rate was in the appropriate range. Axial images (1-mm slices) were obtained. A 4-dimensional CT was also obtained to assess target motion. For patients requiring intensive care unit care, continuous cardiac monitoring with telemetry was performed throughout radiation planning and treatment procedures.

For cardiac SBRT, structures at risk include the skin, spinal cord, lung, esophagus, rib, airway, and gastrointestinal organs, including the stomach and small bowel (particularly for targets located in the apex of the heart). Dose constraints for single-fraction SBRT for these normal organs were adopted from the TG101, a task force consensus statement regarding dose constraints and technical specifications for SBRT treatment constraints, with maximum point dose (MPD) for skin, 26 Gy; rib, 30 Gy; main bronchus, 20 Gy; spinal cord, 14 Gy; stomach, 12.4 Gy; duodenum, 12.4 Gy; esophagus, 15.4 Gy; and lungs at least 1,500 cc, < 7 Gy (14).

Planning target volumes (PTVs) were designed for all patients in collaboration with a team of specialists. Myocardial scar was identified on imaging studies and pretreatment electroanatomic mapping. Based on consensus, treatment areas were chosen as regions of scar identified as the source of the exit site of clinical VTs. The clinical target volume varied according to patient characteristics: in those with numerous exist sites, planned targets as determined in collaborative planning meetings encompassed all or most of identified substrate, while those with a single exit site, or those with very large scar burdens, had targets restricted to areas felt to be critical to arrhythmogenesis as determined by the details of prior electroanatomic mapping and EP study.

The region of myocardial scar was contoured in Eclipse treatment planning software (Varian, Palo Alto, CA), and PTV was created by expanding this region of scar by 1–5 mm. In

TABLE 1 | Characteristics of 14 patients undergoing SBRT.

Patient	Age	Gender	Diagnosis	Prior Ablations	Endo and/or epi	AAD Before	AAD After	Adjuncts	Stage D HF
1	53	F	NICM	1	Endo only	Amio 0.5 mg/min Sotalol 80 mg BID	Lido 0.5 mg/min	LVAD	Yes
2	55	M	ICM	4	Endo only	Carvedilol 25 mg BID, Amio 400 mg QD	Carvedilol 25 mg BID, Amio 400 mg QD, Mex 150 mg TID		Yes
3	65	M	NICM	2	Endo only	Sotalol 80 mg BID, metoprolol 50 mg QD	Sotalol 80 mg BID, metoprolol 50 mg QD		No
4	51	M	NICM	3	Endo/epi	Amio 400 mg QD, mex 150 mg BID, Phenytoin 200 mg BID	Amio 400 mg BID, mex 150 mg TID, Carvedilol 50 mg BID	Symp, LVAD	Yes
5	50	F	ICM	1	Endo only	Amio 400 mg BID, lido 1 mg/min.	Amio 400 mg BID	Symp	Yes
6	58	F	NICM, sarcoid	2	Endo/epi	Sotalol 120 mg BID, carvedilol 12.5 mg BID	Sotalol 120 mg BID, carvedilol 12.5 mg BID		No
7	78	M	ICM	1	Endo only	Amio 400 mg QD, Carvedilol 6.25 mg BID	Amiodarone 200 mg QD, Carvedilol 6.25 mg BID		No
8	70	M	ICM	1	Endo only	Metoprolol 12.5 mg QD, mex 250 mg Q8hr	Mex 250 mg Q8hr	IABP	Yes
9	57	M	NICM, myocarditis	5	Endo/epi	Sotalol 120 mg BID, Metoprolol 75 mg BID Lido 0.5 mg/min	Dofetilide 500 mg BID, Metoprolol 75 mg BID Mexilitine 150 mg Q8hr		No
10	61	M	ICM	2	Endo only	Amio 400 mg BID, Metoprolol 25 mg BID, mex 150 mg Q8hr	Amio 400 mg BID, Metoprolol 50 mg BID, mex 150 mg Q8hr	Symp	Yes
11	67	M	NICM	1	Endo only	Amio 400 mg QD, mex 150 mg TID	Amio 400 mg QD, mex 150 mg TID	LVAD	Yes
12	60	F	NICM	1	Endo only	Amio 1 mg/min, lido 1 mg/min	Amio 1 mg/min, lido 1 mg/min		Yes
13	66	M	NICM	1	Endo/epi	Amio 200 mg BID, Carvedilol 6.25 mg BID	Amio 200 mg BID, Carvedilol 6.25 mg BID		No
14	59	M	NICM, Sarcoid	0		Amio 400 mg QD, mex 150 mg TID	Amio 400 mg QD, mex 150 mg TID, Metoprolol 12.5 mg QD		Yes
Net	*61 + /7*	*10/14 M*	*5/14 ICM 9/14 NICM*	*1.8 ± 1.1*		*2.2 ± 0.4*	*2.1 ± 0.7*	*6/14*	*9/14*

AAD, antiarrhythmic drug; AA, after at 1 month following SBRT or closest other follow up. Amio, amiodarone; IABP, intra-aortic balloon pump; ICM, ischemic cardiomyopathy; Immunorx, immunotherapy; LVAD, left ventricular assist device; Lido, lidocaine; Mex, mexiletine; NICM, non-ischemic cardiomyopathy; Symp, sympathectomy or sympathetic blockade; Endo, endocardial; epi, epicardial.

order to ensure accuracy is maintained during transfer of the target into the CT space, an experienced operator who was both a clinician and software engineer created a MATLAB application that read the relevant information and plotted it in 3D for visualization and to compare it with medical reports. In a process similar to prior studies, this format was then manually validated using an interface in MATLAB to manually align the electroanatomic mapping output to the planning CT space (15, 16). Once the alignment was confirmed, a code converted this spatial information into a binary mask that could then be imported into a clinical viewing system where it was reviewed, again, visually to be in relation to the plan and other structures by this experienced operator. Of note, our team compared this approach with an automated registration for our cases, however after trying different approaches it was concluded than an expert review and frequent visual validation of the results was more practical than an automated registration. For automated registration to work, it has to match some anatomy or voxel values that are common in both images to be aligned, which was difficult to accomplish in our cases since the information from the electroanatomic mapping systems did not necessarily have an anatomic equivalent on the CT. The prescribed dose was 25 Gy in a single fraction. Volumetric modulated arc treatment was used for every patient. Radiation dosimetry mandated that 95% of the PTV received the prescription dose of 25 Gy, and heterogeneity of dose within the PTV ranged from 110 to 140% of the prescription dose. SBRT treatment was delivered on Varian Trubeam linear accelerators. To ensure accurate target localization, KV images were taken of the patient in the treatment position and adjustments made from bony anatomic landmarks. A cone beam CT was then obtained and matched to bony anatomy. Further refinements were then made by the treating physician. At times, ICD leads were helpful landmarks located in the vicinity of the target and could aid in target localization.

Statistical Analysis

Data analysis was stopped as of September 2021. At that time transplant, death or repeat ablation had occurred in the entire cohort. ICD detections and therapies were held constant pretreatment and posttreatment. Patients from our prior analysis were included and followed through their complete course after SRBT (8). The total seconds of detected VT or VF, total ICD shocks, and total antitachycardia pacing (ATP) sequences were tabulated for up to 3 months pretreatment and compared to posttreatment follow-up which extended until death, transplant or repeat ablation.

In order to normalize data due to the variable times of follow-up, the total VT seconds, ATP therapies, and ICD shocks were normalized to frequency per month per patient. Total ventricular arrhythmia burden was defined as VT seconds/30 days, ATP sequences/30 days, and ICD shocks/30 days.

Data regarding follow-up changes in VT/VF/NSVT, ATP and ICD shocks was included only from patients with useable ICD interrogations following SBRT. Patients were followed through the duration of their charted follow-up to assess for adverse events even after an outcome such as that of transplant or repeat ablation occurred.

RESULTS

As shown in **Table 1**, of the 14 patients undergoing SBRT, 10 were male, nine carried a diagnosis of non-ischemic cardiomyopathy (NICM), and nine had ACC/AHA Stage D heart failure. Patients had an average of 1.8 prior ablations and were on an average of 2 AEDs before SBRT. Notably, 3 patients had left ventricular assist devices (LVADs) and 1 patient had an intra-aortic balloon pump (IABP) at the time of treatment. One patient (patient 4) received repeat SBRT. ICD data for that patient extended until repeat SBRT and there were no repeat interrogations following their second SBRT as the patient received transplant shortly thereafter. The individual SBRT treatment details and outcomes are listed in **Table 2**. Three patients did not have a follow-up device interrogation after SBRT. Another patient (patient 3) had very significant VT burden following SBRT but which was not accurately recorded by their device and consequently was not included in the cumulative percent change data. Of the 10 patients with ICD interrogation data after SBRT, follow-up extended an average of 216 days.

The collective data for the cohort of 14 patients is described in **Table 3**. Overall, on follow-up, there was a 59% reduction in VT/VF/NSVT, 39% reduction in ATP and 60% reduction in shocks over follow-up compared with the 3 months before SBRT. The change in VT/VF/NSVT per patient per month is shown in **Figure 1**. There was a substantial decrease in arrhythmia immediately following treatment though as described in other reports, the reduction VT/VF/NSVT was more pronounced after an initial washout period (6). Only six patients were still alive without transplant or repeat ablation after 5 months. Five of the original cohort of 14 patients went on to receive transplant.

Of the nine patients not receiving transplant, only three survived longer than 1 year after SBRT treatment, and all of those patients had eventual recurrent VT requiring repeat ablation. There were four patients in total who received repeat ablation following SBRT. Patient 3 had recurrent VT due to the same region near the LV summit and ultimately received additional ablations of the same area with alcohol, and a combined surgical/endovascular approach. Patient 4 had very significant burdens of recurrent VT following SBRT initially of the RV free wall and ultimately received repeat SBRT of the septum 3 months later before transplant. Patient 6 received repeat ablation after 2 months of effectively the same region over the basal septum and anterior wall. Patient 13 also had recurrent VT arising from a bordering region and received endovascular ablation over the lateral LV extending slightly anteriorly and posteriorly. All four of these patients who received repeat ablation had NICM. The mean time to repeat ablation was 10.2 months. Nine of the 11 patients with follow up ICD data after SBRT demonstrated recurrences in treated VT/VF with ATP or shocks with a mean time to first treated episode of 2.6 months.

The only adverse event related to SBRT occurring though the duration of charted follow-up was pneumonitis which likely occurred in four of the 14 patients. The details of each case of possible pneumonitis are described below.

Four months after SBRT treatment patient 1 presented to the hospital with cough and shortness of breath and was found to have opacities in the left lung. The patient was admitted due to her high-risk status with her recent transplant and immunosuppression but did not require supplemental oxygen. At the time, she was treated with 7 days of antibiotics for community acquired pneumonia but on review it was felt that there was a high likelihood this was radiation related pneumonitis.

Approximately 6 weeks following patient 4 receiving his first SBRT treatment, he was hospitalized for 1 week of cough without hypoxia with mild opacities on chest x ray which was treated with antibiotics, inhalers and a prednisone taper. He improved with these measures which on review was felt to likely represent radiation pneumonitis.

Patient 8 had a complicated course following SBRT, and 1 month later suffered a ground level fall and subdural hematoma which was managed conservatively. The patient had a history of both COPD and lung disease related to amiodarone toxicity with baseline 2–4L O2 requirements. 5 months after SBRT the patient presented initially with symptoms of heart failure but was found to have hypoxia requiring high flow nasal cannula which did not improve with diuresis. A CT chest demonstrated pneumonitis and after consultation from pulmonology, the patient with given intravenous methylprednisolone with improvement in his oxygenation to baseline over a few days. To complete treatment for possible pneumonitis, the patient was prescribed a 4-week taper of prednisone. That hospitalization was also complicated by worsening dysphagia and the patient transitioned to hospice care on discharge after many discussions with palliative care in line with his wishes.

Approximately 7 months following patient 11 receiving SBRT, while the patient was recovering from OHT in the intensive care unit he was noted to have a lingering oxygen requirement of 4L which did not improve with diuresis and a chest x ray showing bibasilar infiltrates. The ICU team was concerned for

TABLE 2 | SBRT treatment and outcomes.

Patient	Target location	Margins (mm)	Follow-up months	Decrease in VT/VF	Months to first treated episode	Outcome	Adverse events
1	LV	1	0.5	Unknown	NA	Transplant	Pneumonitis
2	Lateral Apical LV	3	1.6	No	1.5	Transplant, died after	
3	LV summit	2	10.7	No	4.2	Repeat ablation ×3 (endo, surgical, alcohol)	
4	RV freewall	1	3.9	No	2.1	Repeat SBRT, Transplant	Pneumonitis
5	LV apex septum	1	0.2	Unknown	NA	Hospice	
6	Basal septum, LV anteroapex	2	2.0	Yes	0.1	Repeat ablation	
7	Apex	1	9.1	Yes	No recurrence	Hospice	
8	Posterolateral LV	3	9.6	No	0.1	Hospice	Pneumonitis
9	Anterobasal	5	6.7	Yes	0.4	Transplant	
10	LV apex	1	5.8	Yes	3.5	Hospice	
11	Pericannula	2	7.0	Yes	2.6	Transplant	Possible Pneumonitis
12	Inferolateral LV	1	0.1	Unknown	NA	Died shortly after SBRT	
13	Inferolateral LV	2	24.0	Yes	8.6	Repeat ablation	
14	Anteroseptal, anterolateral LV	1	2.0	Yes	No recurrences	Hospice, fungal pneumonia	
Net		*1.9 ± 1.1*	*5.9*	*64% (7/11)*	*9 with treated recurrences avg 2.6 months after 2 without recurrence 3 without follow up data*	*5 transplant (1 later died), 7 hospice/death 3 repeat catheter ablation 1 repeat SBRT, (later transplanted)*	*29% (4/14) Pneumonitis*

possible aspiration pneumonitis or pneumonia and treated the patient with 7 days of ceftriaxone. The patient was already on prednisone 10 mg daily for immunosuppression in relation to recent OHT but did not receive additional steroids at the time. His hypoxia improved over that 7-day treatment course with ceftriaxone, continued daily prednisone and oral diuretics.

Five of the 14 patients who underwent SBRT eventually received OHT. A description of the events leading to their transplant are overviewed below.

Patient 1 received OHT shortly after SBRT. She was listed for worsening heart failure symptoms despite LVAD, a chronic drive line infection and for recurrent VT. Her heart failure related symptoms included dyspnea on exertion, dizziness and generally did not correlate with her episodes of NSVT which were observed while the patient was hospitalized. The patient had a follow up trans thoracic echocardiogram completed shortly before her transplant which showed an ejection fraction of 10–15% which was unchanged from her prior before SBRT. The patient has done well following transplant.

TABLE 3 | Cumulative follow-up data.

Cumulative follow-up data	
Reduction in VT, NSVT, VF*	59%
Reduction in ATP*	39%
Reduction in shocks*	60%
Mean time to first treated VT**	2.6 months
Transplants	5/14
Repeat ablations	4/14
Alive at 6 months	8/14
Alive at 12 months	7/14
Alive without transplant	3/14
Repeat ablations in patients alive without transplant	3/3
Complications (Pneumonitis)	4/14

**Only 10 of the original 14 patients had sufficient and valid follow-up ICD data to calculate percent changes in VT, ATP and shocks.*
***Nine of 11 with follow up ICD data showing treated episodes.*

Patient 2 received a OHT at an outside institution and presented to our institution specifically for consideration of SBRT. The patient received transplant due to a long history of significant ICM and VT. The patient died due to primary graft failure and several complications post-transplant. Due to his following for further treatment at an outside institution, we do not have access to the full details of his care after SBRT and OHT.

Patient 4 had a long-standing history of Stage D heart failure requiring LVAD. Two months after his initial SBRT he was admitted for symptoms of heart failure and later developed recurrent VT storm and received repeat SBRT. He was listed as 1A for heart transplant due to recurrent VT in the setting of prior LVAD implantation. The patient's ejection fraction and left ventricular end systolic volume just prior to the first SBRT was 10% and 6.4 cm and shortly after the second SBRT 3 months later were effectively unchanged at 10% and 6.3 cm, respectively. The patient is doing well and following in transplant clinic.

Patient 9 initially improved after SBRT but had recurrent VT storm 6 months after treatment requiring CCU admission and intravenous lidocaine. In the context of his recurrent arrhythmia the patient also had progression of his heart failure and a

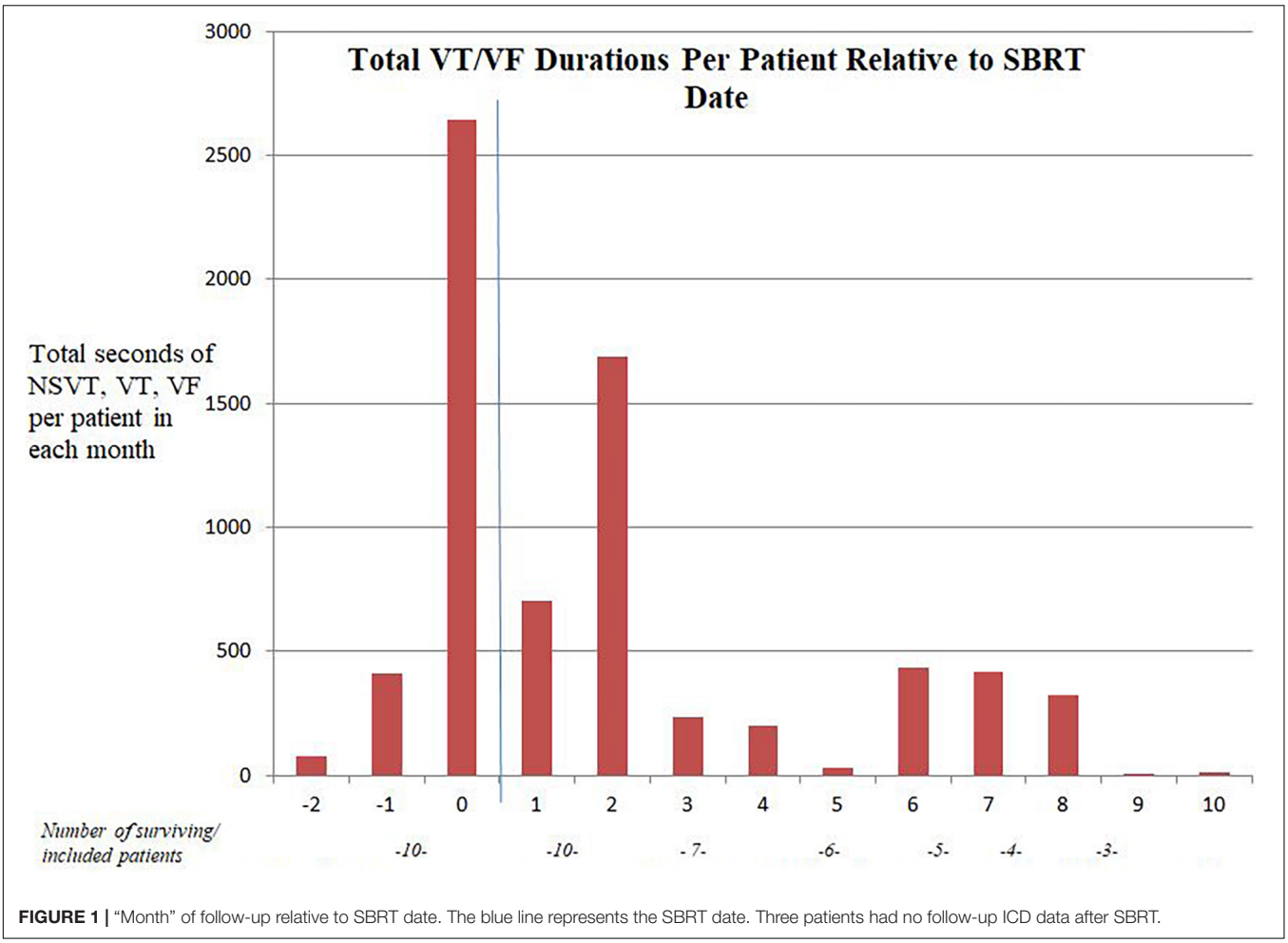

FIGURE 1 | "Month" of follow-up relative to SBRT date. The blue line represents the SBRT date. Three patients had no follow-up ICD data after SBRT.

significant reduction in ejection fraction. From just prior to SBRT his EF and left ventricular end systolic volume were 40% and 4.9 cm, respectively and 6 months following SBRT they were 20% and 5.9 cm, respectively. It is not possible to completely exclude SBRT as related to worsening of the patient's heart failure, but his arrhythmia burden was felt to be the most likely causative factor. The patient has done well since transplant.

Patient 11 had an extensive history of NICM requiring LVAD prior to SBRT. Following SBRT, the patient initially had improvements in VT burdens but after 2 months began having VT episodes requiring ATP. Six months after SBRT the patient had increased burdens of VT and episodes of VF requiring shocks and the patient was placed on an amiodarone infusion and was upgraded to UNOS status 2 after which a suitable donor was identified approximately 1 week later. Just prior to SBRT, the patient's ejection fraction was 10% with a left ventricular end systolic diameter of 6.0 cm with an LVAD in place. Six months later, the echocardiogram was effectively unchanged with an ejection fraction of 10% and a left ventricular end systolic diameter of 5.9 cm with the LVAD. Their post-operative course was complicated by pneumothorax requiring chest tube placement. The patient is now doing well and following in transplant clinic.

All patients in the cohort eventually reached an endpoint where they received transplant, died or received repeat ablation.

DISCUSSION

Our retrospective cohort of critically ill advanced heart failure patients was notable for a few findings. Our cohort of advanced heart failure patients which includes 8 ACC/AHA Class D patients, 3 patients with LVADs, and 1 with an IAPB is apparently more critically ill than any other published cohort to our knowledge. Our results again demonstrate that there is an immediate reduction in VT burden following treatment showing the potential utility of SBRT in the management of refractory VT even in critically ill advanced heart failure patients. This acute reduction in VT burden importantly helped bridge five patients to transplant.

While there was a significant acute reduction in VT burden, there were late recurrences requiring ablation in all patients surviving patients without transplant. Our total net reduction

in VT is lower than reported in most other cohorts and clinical trials and there are a few differences in patients and methodology which could account for the discrepancy (6, 7, 9, 10). As noted previously, due to practical constraints and the critically ill state of many of these patients, wearable multielectrode vest technology was not used which could have better localized the arrhythmogenic origin. Of the four patients who received repeat ablation, one had VT mapped and ablated at different localization (the septum vs. the RV wall) for which initial use of the wearable multielectrode vest may have been important. This cohort was also more critically ill than others as previously mentioned and with more patients with NICM which also could account for some of the differences. Also of note, patient 12, died shortly after SBRT. Acute toxicity, when reported in prior series, with SBRT is generally mild, however, severe complications can occur. This particular patient had continued electrical storm and progressive hemodynamic collapse which we believe was the cause of death, but we cannot entirely exclude an adverse reaction to SBRT. Patient 9 had a significant decline in their EF following SBRT and ultimately required transplantation, and while this was more likely directly related to the significant burdens of VT, a direct radiation related toxicity cannot completely be excluded. Four other patient had clinical syndromes following SBRT possibly consistent with pneumonitis. Patient 11's symptoms were slightly outside the expected timeframe for pneumonitis and had alternative explanations including possible aspiration but we did include this patient as a possible case of pneumonitis. The other patients fit well into the expected time frames and symptoms and were overall quite consistent with radiation pneumonitis (17).

Our study is additionally limited due to its small size and retrospective cohort design. Further in depth sub-group statistical analysis cannot reasonably be performed due to these limitations. Given the relatively short average follow-up duration we additionally cannot accurately assess the long term safety of this experimental therapy.

CONCLUSION

SBRT may have value in advanced heart failure patients with refractory VT acutely and to aid bridging to transplant, but its utility over long-term follow-up appears modest. Prospective randomized data is needed to better clarify the role of SBRT in managing refractory VT.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Emory University IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW: data acquisition and manuscript writing. ASc and TB: data acquisition. AZ: editing and data presentation. NB, SK, ASh, SW, and KH: clinical care. ML: clinical care and editing. All authors contributed substantially to this work.

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METHODS
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Stereotactic Ablative Radiotherapy of Ventricular Tachycardia Using Tracking: Optimized Target Definition Workflow

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Background and Purpose: Stereotactic arrhythmia radioablation (STAR) has been suggested as a promising therapeutic alternative in cases of failed catheter ablation for recurrent ventricular tachycardias in patients with structural heart disease. Cyberknife® robotic radiosurgery system utilizing target tracking technology is one of the available STAR treatment platforms. Tracking using implantable cardioverter-defibrillator lead tip as target surrogate marker is affected by the deformation of marker–target geometry. A simple method to account for the deformation in the target definition process is proposed.

Methods: Radiotherapy planning CT series include scans at expiration and inspiration breath hold, and three free-breathing scans. All secondary series are triple registered to the primary CT: 6D/spine + 3D translation/marker + 3D translation/target surrogate—a heterogeneous structure around the left main coronary artery. The 3D translation difference between the last two registrations reflects the deformation between the marker and the target (surrogate) for the respective respiratory phase. Maximum translation differences in each direction form an anisotropic geometry deformation margin (GDM) to expand the initial single-phase clinical target volume (CTV) to create an internal target volume (ITV) in the dynamic coordinates of the marker. Alternative GDM-based target volumes were created for seven recent STAR patients and compared to the original treated planning target volumes (PTVs) as well as to analogical volumes created using deformable image registration (DIR) by MIM® and Velocity® software. Intra- and inter-observer variabilities of the triple registration process were tested as components of the final ITV to PTV margin.

Results: A margin of 2 mm has been found to cover the image registration observer variability. GDM-based target volumes are larger and shifted toward the inspiration phase relative to the original clinical volumes based on a 3-mm isotropic margin without deformation consideration. GDM-based targets are similar (mean DICE similarity coefficient range 0.80–0.87) to their equivalents based on the DIR of the primary target volume delineated by dedicated software.

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Conclusion: The proposed GDM method is a simple way to account for marker–target deformation-related uncertainty for tracking with Cyberknife® and better control of the risk of target underdose. The principle applies to general radiotherapy as well.

Keywords: stereotactic, radiotherapy, target definition, motion management, tracking, deformation, Cyberknife

INTRODUCTION

Stereotactic arrhythmia radioablation (STAR) has been suggested as a promising therapeutic alternative in cases of failed catheter ablation for recurrent ventricular tachycardias (VTs) in patients with structural heart disease (1–4). Various radiotherapy treatment modalities are available for STAR. Each modality is associated with a technology and workflow-specific target definition process (2, 5, 6) with consequences to treatment efficacy and toxicity. STAR-specific combinations of cardiac and respiratory motions present challenging conditions for safe and accurate treatment.

The general principles of radiotherapy apply also to STAR. This includes acquiring a 3D planning CT scan of a patient comfortably placed and/or immobilized in the treatment position and allowing free access of radiation beams to deliver the treatment dose. The planning CT scan is then used as a 3D patient's model to define target volume(s) and critical organs in the vicinity of the target by computerized delineation and, after applying dose prescription and constraints, to optimize and calculate the final deliverable dose distribution. This procedure is known as radiation treatment planning and is carried out using dedicated computers and software known as *Treatment Planning Systems* (TPS). As the 3D patient's model in principle represents only a snapshot in time, i.e., excluding information about variations of anatomy during treatment delivery, various *motion management* approaches apply. These approaches differ in complexity, accuracy, technological demand, and, mostly, in the definitive treated volume to cover the whole range of assumed target motion. Simplified target volume concepts are as follows: the *clinical target volume* (CTV) indicates the 3D volume to treat, the *internal target volume* (ITV) is the CTV expanded by a known or estimated range of internal motion due to physiological processes such as respiration, and *planning target volume* (PTV) is the final volume to cover all remaining geometrical uncertainties to avoid missing (underdosing) any part of the CTV.

Cyberknife® (Accuray Inc, Sunyvale, CA, USA) is a stereotactic radiotherapy dedicated treatment platform based on a 6MV X-ray medical linear accelerator mounted on an industrial robotic arm, a 4D or 6D robotic treatment couch as patient support during treatment, and two X-ray imaging systems for target localization before and during treatment. The prescribed treatment dose is delivered to the patient *via* dozens (typically 50–150) of radiation beams directed in a patient in a generally non-coplanar non-isocentric geometry. Collimator systems define the aperture of a group of radiation beams representing a key technological feature to conform the dose distribution to the target while minimizing the dose to the surrounding healthy tissue particularly the more sensitive structures known as organs at risk (OARs). One of the key features of the system is the ability to track. The tracking mode relevant to STAR is Synchrony using "fiducials." Based on a target surrogate (in the case of STAR a selected *implantable cardioverter-defibrillator* (ICD) lead tip ideally close to the target), a correlation respiratory motion model is created before the treatment based on the ICD lead's 3D locations extracted from a series of X-ray image pairs and corresponding respiratory phase signal from LED markers placed on the patient's chest. The created model is used during dose delivery to control the radiation source position and orientation to move in synchrony with the target (surrogate) while the beam is on. During treatment, the correlation model is updated with every subsequently acquired new pair of X-ray images. By making use of three or more non-colinear markers, the system has the capability of tracking in 6D (3D translational + 3D rotational axes). In the case of STAR applications with a single marker, tracking is limited to 3D translations. In principle, this technology requires minimum target volume expansion for covering respiratory motion-related target position variation during breathing. Therefore, in theory, it is relatively more effective in sparing normal tissue from dose than standard clinical applications. On the other hand, there is a principle inconsistency between radiation treatment planning and treatment delivery. A treatment plan is created on a static single selected phase (typically expiration breath hold) CT model while treatment itself is performed at free breathing. There are two associated uncertainties: (a) the dose calculation and resulting optimized dose distribution are based on a limited CT model neglecting potential changes due to different tissue distribution at complementary breathing phases, and (b) the potential variation of mutual geometry between the target surrogate ("visible" by the system) and the target itself. The first aspect, that is the variation of dose distribution, is generally considered insignificant especially for a large number of treatment beams, range of beam directions, long beam delivery times compared to the breathing period and the resulting compensations of minor under- and over-doses. However, the second aspect represents a potential failure of the critical indirect tracking condition, i.e., the assumed fixed geometry bound between the tracked target surrogate and the target itself. In this work, we focus on investigating the magnitude of target surrogate (marker)–target geometry deformation and proposing a simple method using the Cyberknife® system default equipment to compensate for associated uncertainty in target coverage through individual asymmetric margins to create ITV (in dynamic coordinates of tracked ICD lead tip) and final PTV for dose distribution optimization. This is the key aspect of the proposed target definition workflow improvement.

MATERIALS AND METHODS

Original Workflow

Our treatment planning and delivery procedure have been described in detail previously (4, 7–9). After initial development, the original target definition workflow was established as follows:

- primary planning CT series (CT model for dose optimization and calculation): expiration breath hold CT (*CTebh*), full range for treatment planning.
- secondary CT image series acquired during one CT exam (CT study).
  - IV contrast expiration (shorter range) CT for electro-anatomical mapping and CTV definition (*CTebh-ivc*).
  - (natural) inspiration (shorter range) CT to sample cardiac and respiratory motion (*CTibh*).

Target definition is based on the 3D maps from the electroanatomic mapping system (CARTO, Biosense-Webster, Israel) (8, 10–12). Either endocardial or epicardial mapping points are acquired during the ablation process. Points are acquired in systole and expiration breathing phase controlled by respiratory phase monitor, so that the resulting 3D surface for registration with the reference radiotherapy target definition *CTebh-ivc* involves minimum uncertainty in position produced by breathing and cardiac motion. Sometimes, specific points that indicate scar region are identified by a cardiologist during the ablation process. In such cases, 3D image registration is driven also by points ("markup to points"). The "Rigid body" registration process is made in 3D Slicer software (13) and involves heart segmentation on the reference *CTebh-ivc*. Transferred points-voxels are "burned" in the reference *CTebh-ivc* image by associating with a high intensity (voxels with high Hounsfield units). This modified secondary CT image series is imported back in the TPS and registered with the primary planning *CTebh* series to form the base for the CTV. The radiation oncologist working concurrently with the cardiologist may change or correct the volume based on a detailed assessment of the anatomy and any complementary information. An additional isotropic 3-mm CTV-PTV margin is added to account for mainly LED signal—marker position correlation uncertainty, marker position—target position fixed bound uncertainty, and residual motion and technological uncertainty. The secondary image series are used to assess OAR relative to the target position at extreme respiratory phases and to provide contrast for indicating ventricle volume for CARTO-based target definition.

The dose distribution is optimized and calculated using Multiplan® TPS (Accuray, Inc., Sunnyvale, CA, USA). The required coverage is for $\geq$ 95% of the PTV to receive 25 Gy, with the prescribed dose as close as possible to the 80% (of the global dose maximum) isodose line. The end of the right ventricular septal ICD lead is used as the surrogate marker and is continuously tracked with the target locating system of the Cyberknife®. Live images are acquired every 60 s (minimum) during treatment, and the correlation model is continuously updated. As the Synchrony system does not allow compensating rotations during treatment when only a single marker is being used, rotations of the body are eliminated during an initial patient setup based on an additional dummy spine-align treatment plan where spine in the target region is aligned to within 1°/1 mm from the CT model using the Xsight Spine tracking mode. This, however, does not compensate for target internal rotations which are an additional possible source of uncertainty and must be accounted for by the PTV margin. After spine alignment, the patient is moved to the treatment center with a robotic couch. The first pair of live images are acquired in the same breathing phase as in the digitally reconstructed radiographs (DRRs) generated from the planning CT scan. Patient alignment at the treatment center is verified using visible structures in the image, e.g., ICD lead, chest wall, diaphragm, stainless steel wires in the patient's chest, and spine structures.

Improved Target Definition Workflow Description

The proposed target definition workflow improvement consists in addressing deformation of mutual geometry between the marker, i.e., ICD lead tip, and target volume during dose delivery at free breathing. One of the key attributes of the suggested method is its simplicity. The new target definition workflow is described as follows:

- primary planning CT series (CT model for dose optimization and calculation): expiration breath hold CT (*CTebh*), full range for treatment planning.
- secondary CT image series acquired during one CT exam.
  - IV contrast at expiration (shorter range) CT for electro-anatomical mapping and CTV definition (*CTebh-ivc*).
  - (natural) inspiration (shorter range) CT to sample cardiac and respiratory motion (*CTibh*).
  - 3x native free-breathing CT (shorter range) to sample cardiac and respiratory motion (*CTfb1-3*).

The purpose and parameters of the primary planning *CTebh* and also the first secondary *CTebh-ivc* remain the same. Notwithstanding the fact that both *CTebh* and *CTebh-ivc* are acquired at the same respiratory phase and the use of respiratory monitor to control reproducibility, there may be some misregistrations between the two image series. As previously mentioned, *CTebh-ivc* is used for primary CTV definition using CARTO mapping. Transferring this volume to the primary planning CT model (*CTebh*) without introducing uncertainty requires a registration check of the secondary image based on the cardiac anatomy particularly in and around the target region. The remaining four secondary CT series (*CTibh, CTfb1-3*) are used for both cardiac and respiratory motion assessment with respect to the variability of relevant anatomy relative to the marker tracked by the system during treatment delivery at free breathing. This means that after importing all image series in the TPS all but the *CTebh-ivc* are first 6D registered to the spine as motion intact anatomy used for the patient's initial pretreatment setup mainly to eliminate rotations not accounted for during single marker tracking. Subsequently, these are registered 2nd time to the marker. Since the marker

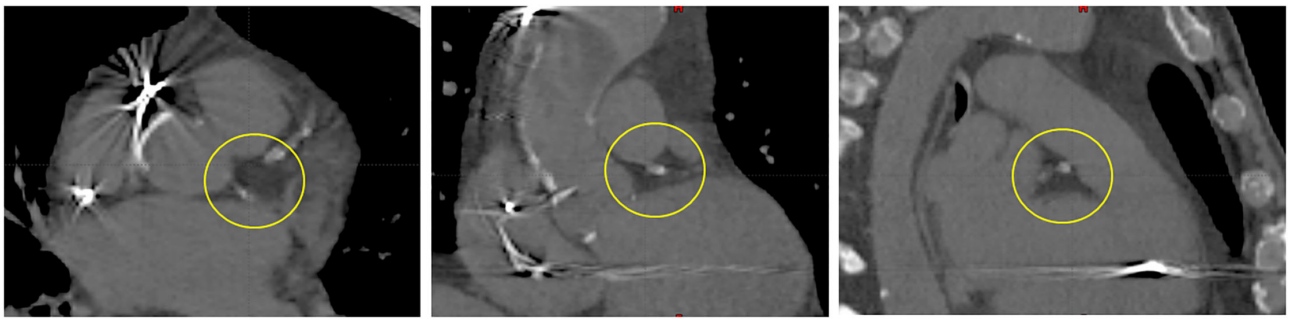

FIGURE 1 | LMCA region (circled)—a visible heterogeneity used as the primary target surrogate inside a heart (RefSTRUCT). From left to right: transverse, coronal, and sagittal view.

is tracked by the system, visible variations of anatomy on the secondary images now represent parasite motion (rotations and deformations) which would need to be accounted for by appropriate target expansion—ITV (in dynamic coordinates of the tracked marker). Since the anatomy landmarks in the target region are difficult to distinguish on a CT image, it would be possible to expand the original CTV simply by contouring. We developed a simple procedure using a clear heterogeneous structure inside the heart as a target surrogate in terms of marker–target geometry. This reference structure *RefSTRUCT*, shown in **Figure 1**, is the area around the *left main coronary artery* (LMCA).

To quantify motion for the needed compensation, we record 3D translation coordinates stored by the TPS in the image registration transform matrix after initial 6D/spine + 3D/marker registrations. In the next step, we perform the 3rd registration—3D translation to the *RefSTRUCT* for each secondary image used for motion assessment (3D/*RefSTRUCT*). Then, we record the changed 3D translation coordinates from the transform matrix. The difference in each direction represents the associated change of marker–target (surrogate) geometry to be used to expand the original CTV for eliminating the known risk of target underdose during free-breathing treatment delivery. For the final ITV definition, the maximum detected difference from all four motion assessment CT image series in six major anatomical directions (anterior, posterior, right, left, superior, and inferior) is used to expand the original CTV by this generally anisotropic margin—*geometry deformation margin* (GDM).

For final PTV, an additional isotropic margin of 2 mm is added to compensate mainly LED signal—marker position correlation uncertainty, intra- and inter-observer variabilities as the major sources of uncertainty of the GDM method, and residual motion and technological uncertainty.

Treatment planning data of a total of seven recent patients (2019–2021, 5 men, 2 women, various ages, and conditions) treated with STAR at our institution were analyzed retrospectively to create an alternative target volume (ITV_{GDM} and PTV_{GDM}) following the proposed improved target definition workflow. For all patients, the clinically applied, i.e., treated, PTV was created using the original workflow described in the previous section. However, as a part of the planning CT acquisition, all patients underwent additional CT imaging (2 or 3 shorter range free-breathing CT series) to sample cardiac and respiratory motion making the data coverage equivalent to the improved target definition workflow. Retrospectively, created ITV_{GDM} and PTV_{GDM} volumes were imported in Eclipse® TPS (version 13.6, Varian Medical Systems Inc., Palo Alto, CA, USA) for analysis with respect to the objectives of this study.

Improved Workflow Verification

Although the principle of the suggested target definition workflow, based on the semi-automated (6D/spine) and individual manual rigid registration (3D/marker + 3D/*RefSTRUCT*) of secondary image series often with significant metal image and motion artifacts is clear, the outcomes are dependent on intra- and inter-observer variabilities. Within the described workflow, the estimated intra- and inter-observer variabilities of the subjected manual image registration should form the basis for the residual motion uncertainty component of the PTV margin.

In principle, the investigated motion aspect is the deformation of the mutual marker–target geometry during free breathing. With the primary CTV based on CARTO mapping on CT at expiration, it is logical to consider the primary CTV expansion through an application of deformable image registration (DIR) of underlying CT images acquired at complementary respiratory phases (*CTibh*, *CTfb1-3*) to cover fully the sampled range of motion at free breathing. The merging of the primary CTV structure deformed on the background of all four complementary CT images forms a technique equivalent to an ITV constructed using GDM as described above. A number of two dedicated state-of-the-art software products, MIM (MIM® software Inc., Beachwood, OH, USA) and Velocity® (version 4, Varian Medical Systems Inc., Palo Alto, CA, USA), were used to compare ITVs obtained using the proposed simple method based on GDM (ITV_{GDM}) with ITV equivalents ITV_{VELO} and ITV_{MIM} obtained using DIR.

Intra- and Inter-Observer Variabilities

All available secondary CT series acquired for motion management purposes (i.e., *CTibh*, *CTfb1-2* or *CTfb1-3*) underwent a full sequence of manual image registrations

(6D/spine + 3D/marker + 3D/*RefSTRUCT*). Relevant parameter values from the image registration transform matrix for five recent patients—a subgroup of seven used for ITV_{GDM} testing—were recorded. Each image registration was repeated 3 times (not consecutive runs) by each of the two observers. A total of two metrics were chosen for the comparisons:

- DICE similarity coefficient representing the similarity of two 3D volumes (14), in this case, $_{i-j}ITV_{GDM}$ where $i = 1,2$ (observers performing registrations), $j = 1,2,3$ (number of tests performed).
- Hausdorff average distance (H-AVE) indicating mean distance between each point of one compared structure to the closest point in the other structure (15). The reason for using also H-AVE is mainly because it is closely related to a size of margin in mm to cover observed uncertainty—major expected outcome from intra- and inter-observer variation tests.

For intra-observer variability investigation, each patient, and each of two observers, altogether, three mutual comparisons were made, i.e., $_{1-j}ITV_{GDM}$ and $_{2-j}ITV_{GDM}$, respectively ($j = 1,2,3$), giving 6 measurements per patient in total.

For inter-observer variability investigation, each patient, each secondary image series, and each of 3 tests by observer 1, comparisons with results of equivalent tests by observer 2 were made, i.e., $_{i-j}ITV_{GDM}$ and $_{i-j}ITV_{GDM}$, respectively ($i = 1,2$, $j = 1,2,3$), giving 9 measurements per patient in total.

DIR Using MIM®

All relevant secondary CT series (*CTibh*, *CTfb1-2* or *CTfb1-3*) registered (6D/spine + 3D/marker) previously in Multiplan® TPS together with original primary planning CT series (*CTebh*) and associated original structure set (RS) selection including original CTV were imported in MIM® software for each patient. Using standard *AdaptiveRecontour–Deform* workflow, we DIR-registered the planning *CTebh* + RS to each of 3 or 4 secondary CT series. During the workflow run, the initial rigid registration was reset to maintain the original registration on the marker. The registration products, i.e., deformed planning *CTebh* and deformed RS were saved. In the following step, the deformed *CTebh* was opened together with the original DIR target image (*CTibh*, *CTfb1-2,* or *CTfb1-3*), and using the image fusion mode and tools, the quality of DIR was checked focussing on the area of the marker and *RefSTRUCT*. Finally, depending on a patient, three or four deformed primary CTV structures together with deformed *CTebh* images were exported from MIM® and imported in Eclipse® TPS as components of ITV_{MIM} volume and for further analysis.

DIR Using Velocity®

Deformable registrations carried out in Velocity® used the same inputs as MIM®. The images were then initially manually registered according to the marker using a rigid transformation. Following this, a DIR was performed inside a region of interest which was set with a 1-cm margin around the heart. The employed DIR uses a modified B-spline deformable algorithm with mutual information metric for the evaluation of similarity between registered images (16). Other available algorithms were either not suitable for given CT series or produced significant image artifacts. As with MIM®, DIR products and, depending on the patient, three or four deformed primary CTV structures together with the deformed *CTebh* images were exported from Velocity® and imported in Eclipse® as the components of ITV_{VELO} volume and for further analysis.

For both MIM® and Velocity® registration products, sometimes, the DIR process moved the marker within the CT series, so the marker centered registration had to be slightly adjusted.

Mutual Comparisons

For each patient, the final sets of structures for data analysis in Eclipse® contain the original CTV, original PTV, volumes created by methods described above, ITV_{GDM}, ITV_{VELO}, $ITV_{MIM,}$ and the derived PTV volumes obtained by the isotropic expansion of the respective ITV volume by 2 mm (PTV_{GDM}, $PTV_{VELO,}$ and PTV_{MIM}, respectively). In addition, an extra $ITV_{GDM-SUM}$ volume was created as an alternative to the GDM method (based on the maximum translational difference of all secondary images in each of the six major cardinal directions) by merging all secondary image registration-related subvolumes, i.e., an analogous method as applied for the ITV_{MIM} and ITV_{VELO} (refer to **Figure 2** for an example of the difference.) For a subgroup of five patients, an additional reference structure, *RefSTRUCT+*, was used as a target surrogate in the last 3D translational registration to determine GDM components. The reason was that this anatomy (less clear but still well identifiable) was significantly closer to the target. Therefore, two versions of ITV and resulting PTVs were included for this subgroup. Definitive sets of structures for mutual comparisons are PTV, $_1PTV_{GDM}$, $_1PTV_{GDM-SUM}$, PTV_{MIM}, PTV_{VELO} (for all patients), and $_2PTV_{GDM}$ and $_2PTV_{GDM-SUM}$ (for the subgroup of 5 patients).

With regard to mutual comparisons of created structures, four objectives were defined:

1. What is the difference between the original treated PTV volume and the alternative PTV_{GDM}? if volumes are comparable, there is a question whether the more laborious workflow is justified. If a GDM volume is larger, there is the question of the relative increase in potential toxicity of treatment (assuming the same target coverage).
2. is PTV_{GDM} (or rather $PTV_{GDM-SUM}$) similar to volumes obtained using DIR (PTV_{MIM} and/or PTV_{VELO})? if it is then this can be interpreted as mutual validation of the GDM principle, i.e., a simple GDM method is validated by a clinical standard DIR software product(s).
3. What is the difference between PTV_{GDM} based on *RefSTRUCT* and *RefSTRUCT+* target surrogates for situations where distance between marker and target is larger? if the difference is small, then marker–target geometry deformation is more likely to be described by the default universal *RefSTRUCT* even for larger marker–target distances.
4. What is the difference between PTV_{GDM} and $PTV_{GDM-SUM}$ to compare approaches based on the maximum observed translation (GDM) and based on the merge of 3D translational

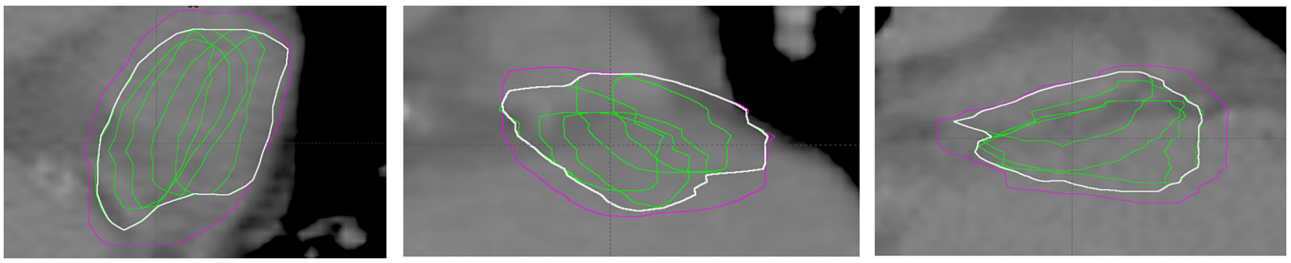

FIGURE 2 | Example of ITV_{GDM} based on maximum detected translation (magenta) vs. $ITV_{GDM-SUM}$ (white) based on merging motion sampling subvolumes (green). From left to right: transverse, coronal, and sagittal view.

difference subvolumes? If the difference exists, then the GDM approach is preferred because it has the principal advantage of not missing parts of target due to (continuous respiratory) motion undersampling.

A number of two metrics were selected for mutual comparisons of volumes:

- absolute volumes in cm^3.
- DICE similarity coefficient for each subjected pair of volumes compared.

The statistics were calculated using the software STATISTICA 13 (TIBCO Software Inc., Palo Alto, CA, USA). All quantitative data were expressed as mean±SD. Paired *t*-tests were used to distinguish between two paired sets of measurements. All tests were performed at the 5% level of significance.

RESULTS

Intra- and Inter-Observer Variabilities

Intra-observer variability results for reproducibility of triple image registration (GDM method) in terms of both DICE coefficient and H-AVE are presented in **Table 1**. Inter-observer analogy is summarized in **Table 2**.

The differential histogram of DICE coefficients for both intra- and inter-observer variabilities is shown in **Figure 3**. The two histograms present variation of volume-comparison metrics with identical input, i.e., with an identical outcome expected. All tests showed DICE over 0.75; 95% (71/75) of tests showed DICE value over 0.8.

Integral histogram of H-AVE values of both intra- and inter-observer tests is shown in **Figure 4**. In both categories of tests, 2 mm of margin covers observed volume variability in terms of image registration and selected volume-comparison metrics. This is an important estimate of image registration-related component of GDM method uncertainty that should be compensated for by additional margin to ITV_{GDM} to avoid target underdose.

Mutual Comparisons

Table 3 shows absolute volumes of all relevant structures to demonstrate the differences across the given volume categories. The original (treated) volumes are always smaller than any alternative (GDM- and DIR-based) volumes. This demonstrates that deformation of marker–target geometry during free breathing is present and, based on the presented values, is not small. General increase in target volume is technically associated with the relative increase in treatment toxicity. To what extent this is relevant to STAR is the subject of the Discussion.

Volumes, constructed by merging subvolumes that are based on sampling location during motion, are generally smaller (GDM-SUM, MIM, and VELO) than volumes based on the original GDM method with maximum detected range of motion in six anatomical directions followed by appropriate volume expansion. This is in agreement with the expected undersampling of the volume location during motion (for demonstration refer to **Figure 2**). The same mechanism makes GDM-SUM volumes closer to DIR-based (MIM and VELO) volumes confirming it is this volume construction method that should be used for GDM vs DIR comparison purpose.

$_2PTV_{GDM}$ volumes do not appear larger than $_1PTV_{GDM}$ volumes generated by image registration to *RefSTRUCT* and *RefSTRUCT+*, respectively. This would be expected if there is a relative increase of deformation with increasing distance from the marker. This finding would support using primary *RefSTRUCT* as a possible universal target surrogate.

Results of the comparison of respective volumes in terms of DICE coefficient are presented in **Table 4**. There is a significant difference ($p = 0.025$) between DICE values for 1PTVGDM vs PTV (0.73 ± 0.08) and all other DICE values from **Table 4** not related to comparisons with PTV (0.84 ± 0.05). The same applies to $_2PTV_{GDM}$ volumes based on *RefSTRUCT+* with $_2PTV_{GDM}$ vs. PTV (0.74 ± 0.10). This supports the justification of the GDM method for the difference in final location, shape, and volume of target volume, assuming it better addresses motion-related uncertainty.

Mean DICE values (range 0.80–0.87) for comparisons between $PTV_{GDM-SUM}$ volumes and DIR-based, i.e., PTV_{MIM} and PTV_{VELO} volumes are relatively larger, comparable to mean DICE values for intra- (0.88) and inter-observer (0.89) variabilities where the "only" source of difference is reproducing work instruction for image registration and also to the guidelines recommended 0.8–0.9 to test DIR quality (17). The range of DICE values for individual patients and both $_1PTV_{GDM-SUM}$ and $_2PTV_{GDM-SUM}$ is 0.71–0.91 with 4 of 24 values below

TABLE 1 | Intra-observer variability results (DICE and H-AVE) of mutual comparisons of ITV_{GDM} volumes after triple image registration made by 2 observers (3 tests for each of 5 patients).

Vol. 1	vs. Vol. 2	DICE					H-AVE [mm]				
		1	2	3	4	5	1	2	3	4	5
$_{1-j}ITV_{GDM,j=1,2,3}$	$_{1-j}ITV_{GDM,j=1,2,3}$	0.83	0.84	0.91	0.92	0.86	1.6	2.1	0.7	0.8	1.2
		0.84	0.87	0.91	0.87	0.88	1.6	1.6	0.8	1.5	1.1
		0.88	0.92	0.90	0.87	0.91	1.1	1.0	0.8	1.4	0.8
$_{2-j}ITV_{GDM,j=1,2,3}$	$_{2-j}ITV_{GDM,j=1,2,3}$	0.91	0.97	0.90	0.76	0.95	0.9	0.4	0.9	2.3	0.5
		0.94	0.91	0.98	0.69	0.92	0.7	1.3	0.2	3.1	0.7
		0.92	0.90	0.89	0.87	0.97	0.8	1.4	1.0	1.6	0.2
	mean =			0.89					1.1		

TABLE 2 | Inter-observer variability results (DICE and H-AVE) of mutual comparisons of ITV_{GDM} volumes after triple image registration made by 2 observers (3 tests for each of 5 patients).

Vol. 1	vs. Vol. 2	DICE					H-AVE [mm]				
		1	2	3	4	5	1	2	3	4	5
$_{1-1}ITV_{GDM}$	$_{2-j}ITV_{GDM,j=1,2,3}$	0.86	0.87	0.92	0.82	0.88	1.4	1.4	0.6	1.7	1.1
		0.87	0.94	0.87	0.83	0.95	1.2	0.8	1.1	1.7	0.4
		0.85	0.89	0.91	0.88	0.90	1.5	1.4	0.8	1.3	0.9
$_{1-2}ITV_{GDM}$	$_{2-j}ITV_{GDM,j=1,2,3}$	0.83	0.88	0.85	0.84	0.90	1.7	1.5	1.3	1.6	0.9
		0.86	0.90	0.90	0.78	0.88	1.5	1.3	0.8	2.1	1.1
		0.84	0.93	0.95	0.75	0.91	1.6	0.9	0.3	2.3	0.8
$_{1-3}ITV_{GDM}$	$_{2-j}ITV_{GDM,j=1,2,3}$	0.87	0.86	0.98	0.80	0.98	1.3	1.9	0.2	1.9	0.2
		0.82	0.98	0.92	0.77	0.90	1.7	0.2	0.7	2.2	1.0
		0.89	0.97	0.91	0.91	0.93	1.1	0.4	0.8	2.1	0.7
	mean =			0.88					1.2		

0.8 for patients 1 and 2 and DIR based on MIM®. Minimum DICE value for DIR-based volumes using Velocity® is 0.8. These results support the similarity between GDM-SUM and DIR-based volumes.

Mean DICE values for comparisons between $_1PTV_{GDM}$ and $_2PTV_{GDM}$ volumes are large (0.89, range 0.86–0.94) supporting the hypothesis that dominant deformation of marker–target surrogate geometry occurs mainly in the area between the marker and *RefSTRUCT,* making possible this main reference structure applicable even for targets more distant from the marker. This is also supported by the significant difference ($p < 0.001$) between DICE values for $_1PTV_{GDM}$ vs. $_2PTV_{GDM}$ (0.89 ± 0.04) and all other DICE values from **Table 4** not related to comparisons with PTV (0.83 ± 0.05).

$PTV_{GDM-SUM}$ volumes compared with PTV_{MIM} and PTV_{VELO} volumes show slightly larger (mean) DICE values compared to corresponding values for original PTV_{GDM} volumes; however, none of all relevant comparisons {($_{1,2}PTV_{GDM}$ vs. $PTV_{MIM,VELO}$) vs. ($_{1,2}PTV_{GDM-SUM}$ vs. $PTV_{MIM,VELO}$)} showed any statistically significant difference, so the expected better agreement with GDM-SUM volumes is not statistically confirmed.

Figure 5 shows an example of the subjected target volumes for one patient. The expected shift toward inspiration phase CT data, larger volume, and better similarity among GDM and DIR-based targets (PTV_{GDM}, $PTV_{GDM-SUM}$, $PTV_{MIM,}$ and PTV_{VELO}) compared to the original target (PTV) can be seen.

DISCUSSION

The main motivation for this study was to improve target definition workflow for STAR using Cyberknife® target tracking technology by explicit consideration of deformation of the marker–target geometry present during treatment delivery as a result of cardiac and respiratory motion. To be applicable clinically, the workflow must not only be effective but also simple and robust to ensure efficiency while ideally relying on minimum extra resources. The proposed approach requires only essential equipment. In principle, the problem is solved using a "4D planning" approach (18). However, although 4D planning module on Accuray system has been available in the past, it is not offered as a feature in newer versions of TPS (Precision®, version 3.+) anymore, mainly because it was very rarely used in the clinical practice (19). The application of additional DIR capable software in the way applied to MIM® and Velocity® in this study would be a natural alternative to the proposed GDM method, which is associated with the

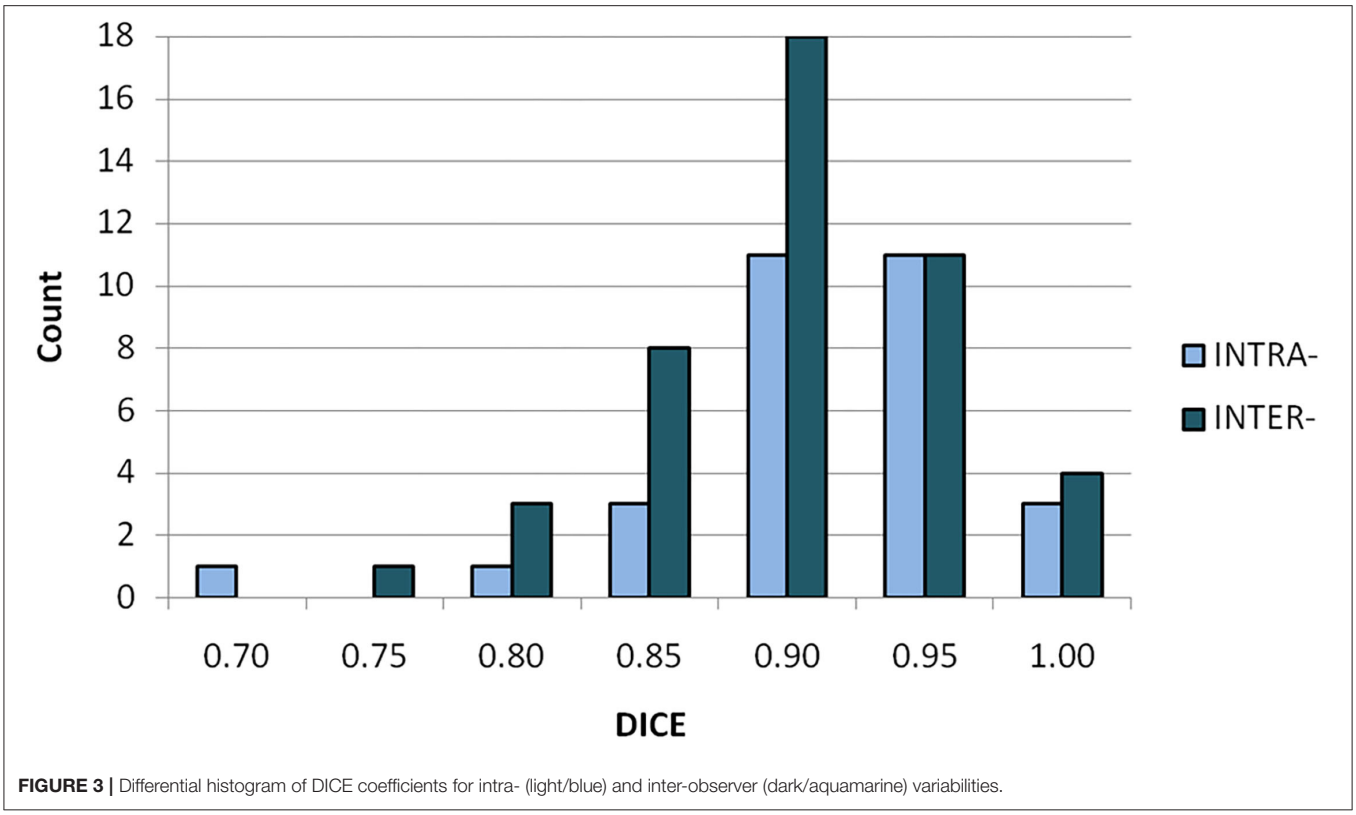

FIGURE 3 | Differential histogram of DICE coefficients for intra- (light/blue) and inter-observer (dark/aquamarine) variabilities.

need for additional resources and data transfers. Using DIR dedicated software to deform the initial CTV and merge would require uncertainty of DIR product assessment to replace the registration observer variability margin component applied in the PTV_{GDM}. In general, DIR dedicated software may produce good results with time-saving but considering the complexity of the specific input data, i.e., CT series with motion and metal artifacts, this may not be a simple task as shown for example in Speight et al. (20) and Tong et al. (21). In addition, when using repeated free-breathing CT series to sample respiratory motion with consequent merging subvolumes, there is a risk of the total volume being smaller than adequate for risk of motion range undersampling as demonstrated, e.g., in **Figure 2** or at GDM-SUM vs. GDM comparisons in this study. This represents an additional consideration for DIR-capable software alternative to the GDM method.

Considering these factors, the GDM method seems to be a simple and, based on this study, acceptable approximation of "4D planning" (in terms of geometry, not dosimetry) with the potentially important advantage of direct user control of the output.

Study Limitations

The presented GDM method has several essential considerations. The first is a question of the representativeness of multiple CT image series to sample combined respiratory and cardiac motion. In particular, *CTibh* tends to be exaggerated when the patient is instructed or respiratory phase monitoring is suboptimal, so careful respiratory management of data acquisition and assessment is important. Although 4DCT is certainly an option, it is not currently available in our department and even with 4DCT, there is a question of representativeness and image quality including residual motion and metal artifacts. Nevertheless, the presented GDM is applicable to 4DCT as well.

The next principal question is the relevance of using LMCA area (and other contrast anatomy in heart) as yet another target surrogate. Nevertheless, based on the relatively large deformation observed (demonstrated also by the larger resulting PTV_{GDM} vs. PTV volumes) and the relatively small difference between volumes based on *RefSTRUCT* and *RefSTRUCT+*, the method can be justified as an adequate approximation bringing with it the benefit of considering deformation for target definition. For 5 of 7 patients, in addition to the LMCA (*RefSTRUCT*), we used an additional reference anatomical structure *RefSTRUCT+*, which was significantly closer to the target area. This anatomical landmark varied based on the target position within the heart and also based on regional image quality in all relevant sample CT series. Final products in terms of GDM method, i.e., $_1PTV_{GDM}$ (*RefSTRUCT*) and $_2PTV_{GDM}$ (*RefSTRUCT+*) target volumes, show the largest similarity parameter of all mutual comparisons performed as seen in **Table 4**-line 3 (DICE: mean 0.89, range 0.86–0.94). This is one reason why we believe that using the LMCA is reasonably justified for the estimation of the deformation between the marker and target volume because using *RefSTRUCT+*, which is closer to the target compared with *RefSTRUCT*, did not lead to a significantly different target

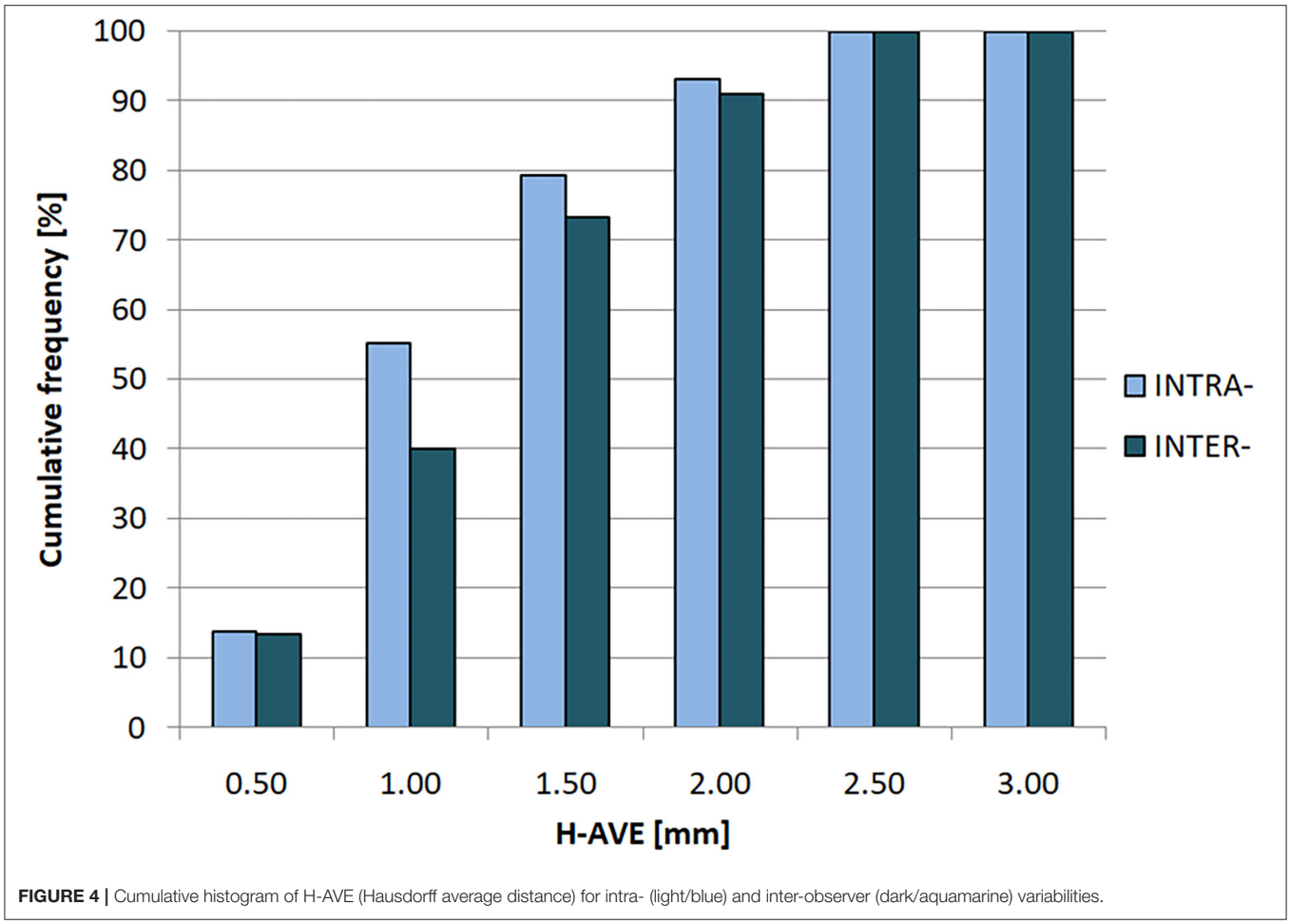

FIGURE 4 | Cumulative histogram of H-AVE (Hausdorff average distance) for intra- (light/blue) and inter-observer (dark/aquamarine) variabilities.

volume. In addition, a good similarity between DIR-based (PTV_{MIM} and particularly PTV_{VELO}) and ${}_1PTV_{GDM}$ (DICE range 0.80–0.92, **Table 4**-line 8) and particularly ${}_1PTV_{GDM-SUM}$ (DICE range 0.85–0.91, **Table 4**-line 9) volumes supports interpretation of the GDM method as a reasonably justified approximation since automated DIR software always considered the entire heart volume as a minimum, i.e., not only the LMCA (*RefSTRUCT*) or an alternative manually selected anatomical surrogate (*RefSTRUCT+*). This means that using the GDM method based on the LMCA surrogate, we obtained similar final outcomes (target volumes) as using a DIR software taking into account at least (deformation of) the entire heart. Nevertheless, before using the GDM method based on the LMCA, we recommend the assessment of its target representativeness on an individual basis and, in case of doubt, consider an alternative anatomical landmark in closer proximity to the target.

Regarding intra- and inter-observer variabilities, the 2-mm resulting isotropic ITV-PTV margin is considered also to cover residual geometry uncertainty aspects. For our technology, it is, namely, LED marker correlation uncertainty. However, since in GDM-based volume, cardiac motion should be included, the same factor causing the increase in the correlation uncertainty (7) should not be included again. Again, for this reason, we decided to use a 2-mm isotropic margin overall. Very similar results between intra- (mean DICE 0.88) and inter-observer variabilities (mean DICE 0.89) demonstrated a good implementation of related work instruction. It is also expected that with time and increasing experience, the variability may decrease with possible margin reduction.

Regarding mutual volume comparisons, using the DICE similarity coefficient is associated with a question of what ranges of values represent "rather similar" and how much "rather different". The AAPM guidelines (17) contain recommended values that are used to test DIR performance are 0.8–0.9. Also, based on the results of observer reproducibility tests, we consider 0.80 as the minimum for "rather similar" and 0.70 as maximum for "rather different."

As seen in **Table 3**, the absolute volumes of the GDM (and DIR) based volumes are larger than the original PTVs built using generic a 3-mm isotropic margin. Direct comparison is not 100% fair owing to individual doctor's intervention at the end of the original target definition process. Where applicable, this may include removing vessels from the target and other volume reduction related to toxicity control. Alternative GDM (and DIR)-based volumes presented in this study did not involve any of such volume reductions so, in many cases, the real

difference may be smaller. At the same time, having relatively larger volumes justified by individual motion management leads to higher confidence in the final target volume reductions for mentioned toxicity control reasons. Nevertheless, the relative increase in clinically applied target volumes must be investigated in terms of the potential increase of toxicity and is subjected to ongoing study.

The next relevant aspect is that in this study, we assumed a priory that the general principle of radiation oncology which is that "each part of target must receive the prescription dose" applies to STAR. This normally requires minimum of 95–98% PTV coverage. However, as STAR is not oncology and the biological objective of irradiation is different, this requirement may not be as essential. If it shows that partial coverage of a precisely defined target volume is sufficient, the situation is different. Nevertheless, target volumes considering individual patient deformation due to cardiac and respiratory motion are still more valid compared to volumes based on a generic isotropic margin, especially considering an initial CTV defined at the extreme respiratory phase (*CTebh*).

TABLE 3 | Absolute volumes indicated by TPS for each constructed structure for 7 patients.

Volume [cm^3]	Patient No						
	1	2	3	4	5	6	7
PTV	28.3	45.0	12.5	19.8	25.9	69.3	39.2
$_1PTV_{GDM}$	69.7	79.5	21.6	35.8	36.6	94.5	67.3
$_2PTV_{GDM}$	65.7	68.5	NA		42.7	87.4	73.4
$_1PTV_{GDM-SUM}$	50.4	63.5	17.5	30.1	34.0	86.3	53.0
$_2PTV_{GDM-SUM}$	45.8	58.6	NA		38.1	83.1	60.5
PTV_{MIM}	44.1	102.7	17.5	24.7	41.2	97.9	62.6
PTV_{VELO}	47.8	63.3	20.9	26.5	33.3	86.7	50.3

TABLE 4 | Results of relevant volumes mutual comparison in terms of DICE coefficient for 7 patients.

Vol. 1	vs Vol. 2	Patient No							Mean	StDev
		1	2	3	4	5	6	7		
$_1PTV_{GDM}$	PTV	0.58	0.72	0.73	0.71	0.82	0.83	0.73	0.73	0.083
$_2PTV_{GDM}$	PTV	0.59	0.78	NA		0.75	0.87	0.70	0.74	0.103
$_1PTV_{GDM}$	$_2PTV_{GDM}$	0.86	0.87			0.92	0.94	0.87	0.89	0.036
$_1PTV_{GDM}$	PTV_{MIM}	0.71	0.75	0.83	0.81	0.86	0.90	0.84	0.81	0.065
$_1PTV_{GDM-SUM}$	PTV_{MIM}	0.77	0.71	0.89	0.85	0.84	0.90	0.85	0.83	0.068
$_2PTV_{GDM}$	PTV_{MIM}	0.71	0.76	NA		0.85	0.88	0.77	0.79	0.069
$_2PTV_{GDM-SUM}$	PTV_{MIM}	0.79	0.72			0.84	0.88	0.78	0.80	0.061
$_1PTV_{GDM}$	PTV_{VELO}	0.80	0.84	0.84	0.84	0.90	0.92	0.80	0.85	0.046
$_1PTV_{GDM-SUM}$	PTV_{VELO}	0.85	0.88	0.83	0.87	0.91	0.91	0.86	0.87	0.030
$_2PTV_{GDM}$	PTV_{VELO}	0.77	0.86	NA		0.85	0.91	0.80	0.84	0.054
$_2PTV_{GDM-SUM}$	PTV_{VELO}	0.80	0.86			0.87	0.90	0.86	0.86	0.036
PTV_{MIM}	PTV_{VELO}	0.85	0.73	0.90	0.92	0.84	0.87	0.81	0.85	0.063

PTV = original treated volume, $_1PTV_{GDM}$ = based on GDM (maximum detected translation) and RefSTRUCT, $_1PTV_{GDM-SUM}$ = based on merging motion sampling subvolumes, PTV_{MIM} and PTV_{VELO} = based on merging motion sampling subvolumes from DIR by MIM/Velocity, and $_2PTV_{GDM-SUM}$, and $_2PTV_{GDM}$, analogically for RefSTRUCT+.

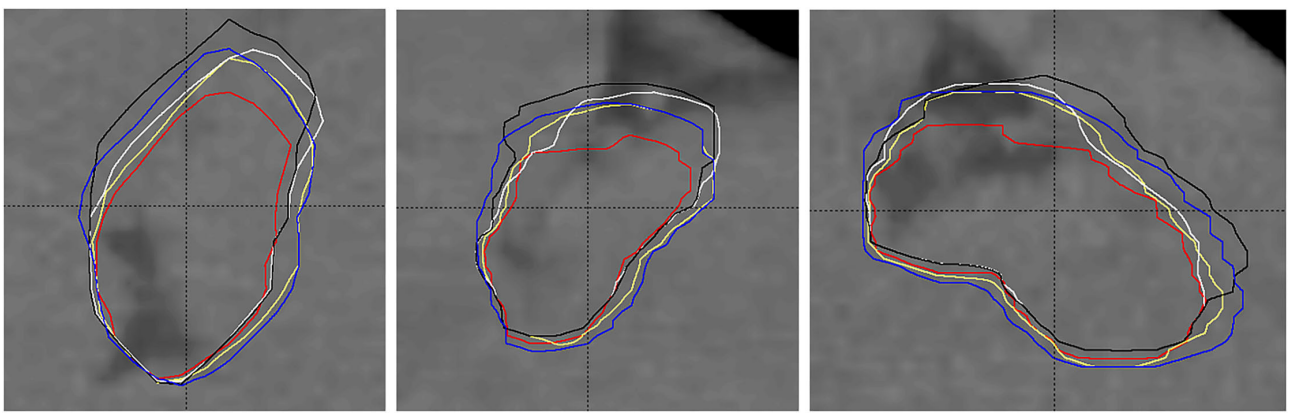

FIGURE 5 | Example of planning target volumes: original treated PTV (red, smallest), PTV_{GDM} (blue), $PTV_{GDM-SUM}$ (yellow), PTV_{MIM} (white), and PTV_{VELO} (black). 1) RefSTRUCT (LMCA) on background CT image used as target surrogate, 2) anisotropic extension of the original target toward inspiration, 3) lesser differences among GDM- and DIR-based volumes than their difference to the original PTV.

Overall, the relative increase of absolute target volume does not necessarily mean a final increase in treatment toxicity. The GDM-based volume reflects the center of target location better. This is certainly an advantage even for approaches where partial target coverage would be considered sufficient.

Comparisons between GDM-SUM and DIR-based volumes show similarity supporting expected mutual confirmation of "deformation considered" target volumes. Results from Velocity® show generally larger DICE values compared to results from MIM®; however, this should not be interpreted as a result of comparing the two commercial platforms as the purpose and test design were aimed at presenting examples of constructing target volume equivalent in principle with GDM-based volumes using standard clinical software. DIR workflows were neither optimized nor controlled to a degree sufficient for comparing quality of DIR products. User experience and chosen workflow may have an impact on the values obtained.

Possible Alternatives

Regarding possible alternative approaches, another logical approach when considering deformation for target definition is applying an initial CTV definition process (based on CARTO physiological mapping) to all secondary CT image series, followed again, by merging resulting subvolumes (including the aspect of potential undersampling). However, based on the publications, the method seems not to be sufficiently developed yet for, e.g., relatively large reported inter-observer variability (22) and likely deformation between CARTO surfaces and segmented CT anatomy to match. Repeating the whole target definition process for all motion sampling CT series using the current state of the process would be probably too laborious and affected by observer variations. In addition, IV contrast importance for CARTO transfer would probably need to be revised.

Taking into account the treatment modalities not based on target tracking technology, beam gating technology and even abdominal press limiting respiratory motion range without beam control during treatment also belong to STAR treatment platforms currently in use (4, 5). Comparing relative advantages and disadvantages among treatment platforms is and will be subjected to ongoing studies and further research.

The proposed GDM method is a simple way to account for marker–target deformation-related uncertainty for tracking with Cyberknife® and better control of risk of target underdose. The principle would equally apply to general radiotherapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB University Hospital Ostrava. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PD designed the GDM workflow and methods of its validation, participated in data collection including image registrations including MIM software, data transfers, data analysis, and presenting results. LK participated in the study design and methods, data collection including registrations for intra- and inter-observer variabilities, data analysis, and presenting results. DD performed deformable image registrations using velocity. PB participated in data collection, data transfers, and analysis. JC participated in the study design, data collection, and carried out a critical review of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW
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Stereotactic Radiotherapy Ablation and Atrial Fibrillation: Technical Issues and Clinical Expectations Derived From a Systematic Review

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Aim: The purpose of this study is to collect available evidence on the feasibility and efficacy of stereotactic arrhythmia radio ablation (STAR), including both photon radiotherapy (XRT) and particle beam therapy (PBT), in the treatment of atrial fibrillation (AF), and to provide cardiologists and radiation oncologists with a practical overview on this topic.

Methods: Three hundred and thirty-five articles were identified up to November 2021 according to preferred reporting items for systematic reviews and meta-analyses criteria; preclinical and clinical studies were included without data restrictions or language limitations. Selected works were analyzed for comparing target selection, treatment plan details, and the accelerator employed, addressing workup modalities, acute and long-term side-effects, and efficacy, defined either by the presence of scar or by the absence of AF recurrence.

Results: Twenty-one works published between 2010 and 2021 were included. Seventeen studies concerned XRT, three PBT, and one involved both. Nine studies (1 *in silico* and 8 *in vivo*; doses ranging from 15 to 40 Gy) comprised a total of 59 animals, 12 (8 *in silico*, 4 *in vivo*; doses ranging from 16 to 50 Gy) focused on humans, with 9 patients undergoing STAR: average follow-up duration was 5 and 6 months, respectively. Data analysis supported efficacy of the treatment in the preclinical setting, whereas in the context of clinical studies the main favorable finding consisted in the detection of electrical scar in 4/4 patients undergoing specific evaluation; the minimum dose for efficacy was 25 Gy in both humans and animals. No acute complication was recorded; severe side-effects related to the long-term were observed only for very high STAR doses in 2 animals. Significant variability was evidenced among studies in

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the definition of target volume and doses, and in the management of respiratory and cardiac target motion.

Conclusion: STAR is an innovative non-invasive procedure already applied for experimental treatment of ventricular arrhythmias. Particular attention must be paid to safety, rather than efficacy of STAR, given the benign nature of AF. Uncertainties persist, mainly regarding the definition of the treatment plan and the role of the target motion. In this setting, more information about the toxicity profile of this new approach is compulsory before applying STAR to AF in clinical practice.

Keywords: systematic review, stereotactic arrhythmia radio ablation (STAR), atrial fibrillation, arrhythmias, stereotactic body radiotherapy (SBRT), particle beam radiotherapy, target motion

INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, with an estimated number 8.8 million of affected subjects in Europe. As the prevalence of AF increases with age, it is expected to affect approximately 18 million in the European Union by 2060 (1) and more than 8 million people in the United States by 2050 (2). In addition, the incidence of AF increases in patients with cancer having an incidence of 3.7 per 1,000 person year, also due to medical oncology treatments (3).

Despite being benign in nature, AF represents a well-recognized independent risk factor for stroke (4) and has been associated with potentially severe medical conditions including heart disease (5) and chronic kidney disease (6). Moreover, a substantial proportion of eligible patients are undertreated with medical therapy (7) and 74.6% of the patients (5) are symptomatic despite ongoing medical therapy. Drugs can also have significant side effects such as an increased risk of bleeding; all these features determine a worsened quality of life in patients with AF (8). Based on the presentation, duration, and spontaneous termination of AF episodes, five types of AF can be distinguished: first diagnosed, paroxysmal (self-terminating, in most cases within 48 h), persistent, long-standing persistent (continuous AF lasting for $\geq$1 year), and permanent AF (AF that is accepted by the patient and physician) (9). As AF frequently originates from an electric trigger located in the pulmonary veins, this site is the main therapeutic target of an ablation procedure defined as "pulmonary veins isolation" (PVI) (10). Based on further empirical evidence, the left-posterior atrial wall has been added to this target (11). A wide variety of approaches for PVI, including point-by-point radiofrequency ablation or cryoballoon ablation (9), has been described. Recently, pulsed-field ablation has been introduced as an innovative technique for the ablation of AF. It is based on the induction of cell death by the electric field (electroporation), has shown good preliminary results in terms of safety and efficacy (12, 13). Overall, the efficacy of these procedures reaches 70% in patients with paroxysmal AF and 50% in those with persistent AF (14), while the percentage of severe related complications approximates 3.5% (15). In addition, a significant proportion of patients require more than one procedure to achieve the permanent restoration of sinus rhythm (SR) (16).

While alternative techniques are available, including ethanol, needle, and bipolar ablation, they are not without disadvantages or side effects, including the uncertainty of properly and completely damaging the target (17), cardiac perforation and tamponade (18), or the inability to appropriately hit deep and large substrates (19).

Other than the well-known applications in cancer, radiation therapy has been used for the treatment of benign medical conditions, showing both satisfactory efficacy and a good safety profile (20–22).

In the last 5 years, multiple studies have investigated the potential of stereotactic arrhythmia radio ablation (STAR): most of the literature is about the treatment of recurrent ventricular tachycardia (VT) and involves both conventional linear accelerator (CLA) (23, 24) and radiosurgery Cyberknife® (CK, Accuray, Sunnyvale, CA, United States) accelerator (25–27). The safety and efficacy of this new therapeutic opportunity seem to be good in both cases. Moreover, some preclinical studies (28, 29) have used particle beam therapy (PBT) for cardiac ablation: being able to selectively spare the most critical structures is a clear advantage and might arguably open up to the future possibility of re-irradiations.

An increasing body of literature has focused on intracardiac malignancies undergoing stereotactic radiosurgery, and on its possible related side effects (30–32). Similarly, dosimetric studies on heart irradiation have been published in the last years (33, 34). A significant issue of cardiac radiosurgery may be the long-term effects of radiation on myocardial, conduction, valvular, and other cardiac tissues. These concerns can be at least partially addressed by the study of long-term toxicity in lymphoma (35) and centrally located lung treatment (36).

Abbreviations: 4DCT, four-dimensional computed tomography; AF, atrial fibrillation; BED, biological effective dose; CK, Cyberknife; CLA, conventional linear accelerator; IMPT, intensity-modulated proton therapy; LPW, left posterior wall; MOSFET, metal oxide semiconductor field effect transistor; MRI, magnetic resonance imaging; MRI-Linac, MRI-linear accelerator; PBT, particle beam therapy; PET, positron emission tomography; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PVA, pulmonary vein antra; PVI, pulmonary vein isolation; RBE, relative biological effectiveness; RSPV-LAJ, right superior pulmonary vein-left atrial junction; SR, sinus rhythm; STAR, stereotactic arrhythmia radio ablation; TV, target volume; VMAT, volumetric modulated arc therapy; VT, ventricular tachycardia; WACA, wide-area circumferential ablation; XRT, photon radiotherapy.

Although photons are the most known form of energy in radiation therapy, PBT (both heavy ions and protons) are an emerging alternative to conventional treatments. Advantages of this form of radiotherapy are the favorable physical characteristics and the major relative biological effectiveness (RBE), especially when referring to carbon ion radiotherapy (37). As a consequence, studies favoring the role of stereotactic PBT have been developed (38) over the last couple of years.

Given the lack of comparable works, this article aims to review the current evidence on the feasibility and efficacy of external beam radiotherapy for AF and to provide radiation oncologists and cardiologists with a practical overview of this theme.

MATERIALS AND METHODS

In compliance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (39, 40), literature research was performed in November 2021.

Articles were researched in multiple database sources: NCBI PubMed, EMBASE, PMID, and Scopus. The strings of research employed and the PRISMA's checklist are available in **Supplementary Material 1**. The PRISMA flow diagram for article selection is illustrated in **Figure 1**.

Both preclinical and clinical studies were considered; no data restrictions or language limitations were applied. The inclusion of gray literature was allowed. Studies whose focus were other forms of arrhythmias (i.e., ventricular and nodal) were considered out of the scope of this work and were therefore excluded.

An independent re-assessment was performed by a second reviewer; in case of any disagreement, a third reviewer was engaged. Selected works were independently screened by two reviewers; whenever disagreement occurred regarding the inclusion criteria, a third reviewer was called to resolve the discrepancy.

Summary and definition of the radiation oncology-related terms are available in **Supplementary Material 2**.

RESULTS

Following reviewing and duplicate removal, a total of 21 articles presented from 2010 to 2021 was included in the analysis.

They consisted of one and 8 preclinical studies on treatment plans for animals and humans treatments, respectively, 8 preclinical studies on animal models, and 4 clinical studies on human subjects. Here follows an overview of selected articles, categorized according to the above-mentioned criteria.

Preclinical Studies

Animals Subjects

The first study on the *in vivo* cardio ablation for AF was performed in 2010 by Sharma et al. (41). Overall, preclinical studies were conducted on healthy animals subjects, with 26 mini-pigs; in only 3 studies also canines were considered (42–44), for a total number of 27 cases (**Table 1**). Average or median doses could not be calculated for preclinical works due to a lack of information in some of the included studies.

In most cases, animals underwent general anesthesia and received ablation in a single fraction delivered by CK. For treatments delivered by CK, fiducials (both gold seeds and catheter tips) were necessary to evaluate target motion. A CLA was used in 3 cases (44–46). In almost all the articles, both cardiac and respiratory motions were considered, except for Chang et al. (44) who acquired four-dimensional computed tomography (4DCT) only in case of the large respiratory amplitude of the animal, a single phase scan was considered and performed in others. The same authors tried to use masks in 2 dogs and had to change immobilization systems to a vacuum cushion during simulation CT.

The target of the procedure was different across the studies: some works evaluated either left pulmonary veins alone (41) or the right pulmonary veins (43, 45, 46), while 3 studies considered both targets (42, 47). Zei et al. considered only the right superior pulmonary vein as a target because of the excessive respiratory motion of the left superior pulmonary vein in the canine model (43). The follow-up ranged between 1 and 6 months. Efficacy of radiotherapy ablation was generally confirmed at doses up to about 25–30 Gy; side effects (i.e., bronchial-mediastinal fistula with pneumonia and sepsis) were observed in one mini-swine 1 month after irradiation when the delivered dose exceeded 37.5 Gy (46). Moreover, one animal experienced a myocardial infection following fiducial marker placement (43) and another pericardial effusion (44). Mild side effects were mitral valve regurgitation after the procedure in one case (42), one mild reduction of ejection fraction (43), and electrocardiographic, self-limiting abnormalities on T wave after anesthesia (4 animals) (43). On the other hand, one animal died due to pericarditis after electrophysiological study (45). Findings in animal studies were usually evaluated by means of electroanatomic mapping, MRI (46), or anatomopathological study after sacrificing the subjects.

A different approach was chosen by Gardner et al. (42), where the implantable metal oxide semiconductor field-effect transistor (MOSFET) dose verification system and the thermoluminescent dosimetry in pulmonary vein antra (PVA) isolation through CK technology were compared. The authors observed that the implantation method adopted for the MOSFET system shows a better concordance than thermoluminescent dosimetry since it appears not to be affected by body fluids. However, the difference between the measured and the predicted doses in the MOSFET system still accounts for almost 10% when the acceptance threshold has been set at 5% by previous studies (48, 49). The authors hypothesized that a degree of uncertainty might derive from the impossibility to track the dose verification system during treatment delivery.

Dosimetric Studies

In the category of dosimetric studies, a total of 122 treatment plans on both photon radiotherapy (XRT) and PBT were considered, with a median dose of 25 Gy (**Table 2**).

A dosimetric study is a preclinical work in which subjects undergo simulation CT without experiencing radiation treatment or in which the treatment plan is delivered to a phantom. These

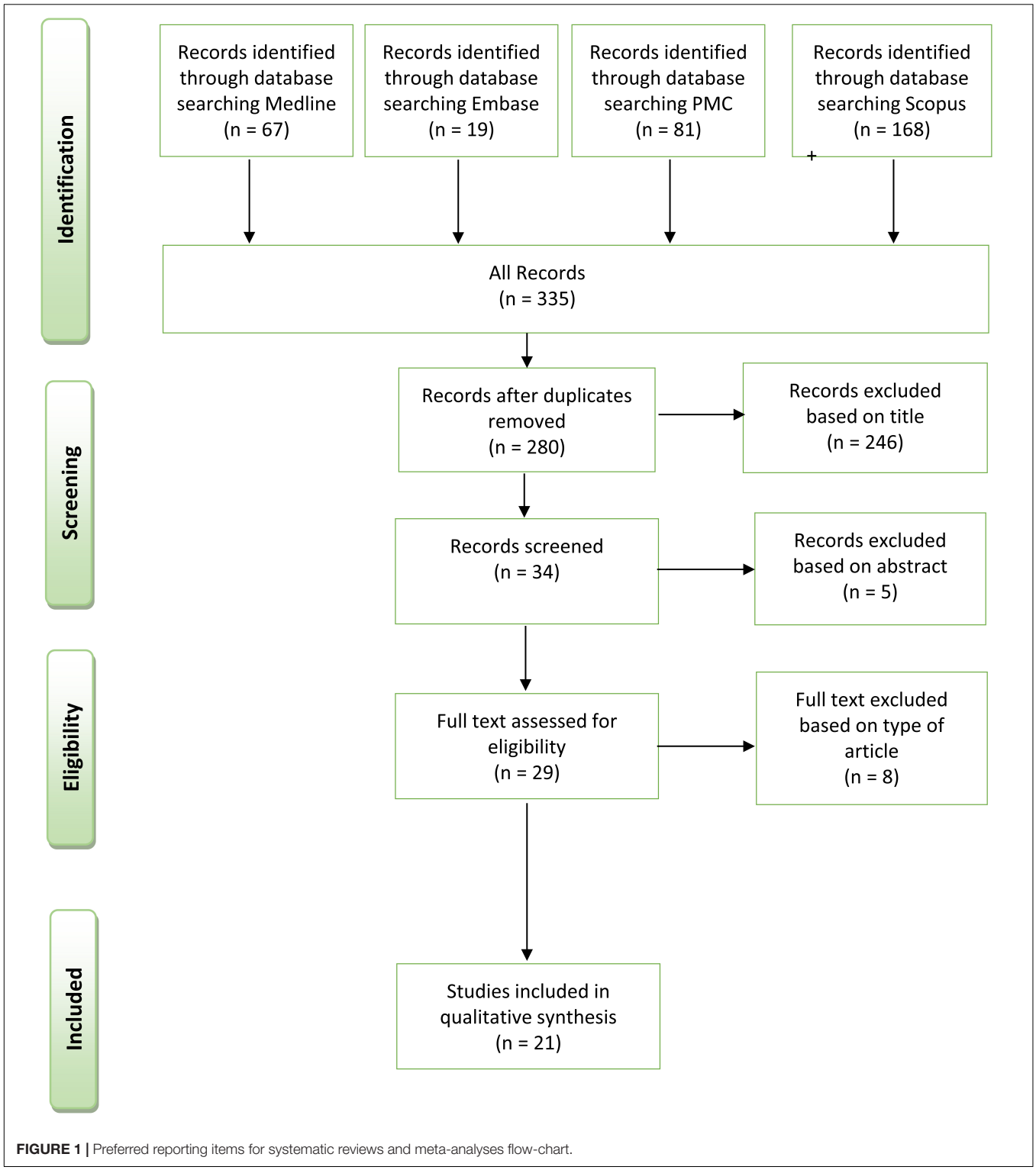

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses flow-chart.

permit the evaluation of dosimetry in the target region and organs at risk, avoiding any toxicity.

Meanly treatment plans consisted of one single fraction and were delivered with CK in 2 cases (50, 51). Conversely, in the other studies, a greater dose was planned with a CLA: 50 Gy in 5 fractions (10 Gy/fraction), according to the biological effective dose (BED) (52, 53). According to Xia et al. (52), a radiobiological modeling study (54) was used for BED calculation with an alpha/beta ratio of 3 Gy; in the second study, Lydiard et al. (53) did not explain how BED was evaluated and which

TABLE 1 | Main characteristics of the preclinical studies on animals included in the analysis.

Study	Energy	N° subjects	Subjects	Total dose (Gy)	N° of fractions	Target	Fiducials	Accelerator	Respiratory motion control	Cardiac motion control	Delivered plan	Follow-up (months)	Efficacy	Toxicity
Blanck et al. (45)	XRT	9	Mini-pigs	15–35	1	RSPV	N/A	CLA	Yes	Yes	Yes	6	Dose ≥32.5 Gy	No
Bode et al. (46)	XRT	8	Mini-pigs	23–40	1	RSPV	No	CLA	Yes	Yes	Yes	6	Dose ≥30 Gy	Dose ≥37.5 Gy
Chang et al. (44)	XRT	7	Canines	33	1	WACA	N/A	CLA	Partially	No	Yes	2–4	50%	Pericardial effusion
Gardner et al. (42)	XRT	4	Canines, mini-pigs	20–35	1	PVA	Yes	CK	Yes	Yes	Yes	5	N/A	No
Maguire et al. (47)	XRT	2	Mini-pigs	25–35	1	PVA	Yes	CK	Yes	Yes	Yes	6	Yes	Trace MVR
Sharma et al. (41)	XRT	4	Mini-pigs	38–40	1	LPV	Yes	CK	Yes	Yes	Yes	1–6	Yes	No
Zei et al. (43)	XRT	19	Canines, mini-pigs	15–35	1	RSPV	Yes	CK	Yes	Yes	Yes	3–6	Dose ≥25 Gy	Min. reduction EF

CLA, conventional linear accelerator; CK, Cyberknife; EF, ejection fraction; LPV, left pulmonary vein; MVR, mitral valve regurgitation; N/A, not available; PVA, pulmonary vein antra; RSPV, right superior pulmonary vein; WACA, wide area circumferential ablation; XRT, photon radiotherapy.

TABLE 2 | Main characteristics of the dosimetric photon and particle beam-based studies included in the analysis.

Study	Energy	N° subjects	Subjects	Total dose (Gy)	N° of fractions	Target	Fiducials	Accelerator	Respiratory motion control	Cardiac motion control	Delivered plan	Follow-up (months)	Efficacy	Toxicity
Blanck et al. (50)	XRT	46	Humans	25	1	PVA	Yes	CK	Yes	Yes	No	N/A	N/A	N/A
Constantinescu et al. (58)	PBT	14	Humans	25–40	1	WACA	No	AA	Yes	Yes	No	N/A	N/A	N/A
Gardner et al. (51)	XRT	4	Humans	16–25	1	PVA ± LPW	No	CK	N/A	N/A	No	N/A	N/A	N/A
Ipsen et al. (55)	XRT	6	Humans	30	1	PVA	No	MRIL	Yes	Yes	No	N/A	N/A	N/A
Lehmann et al. (60)	PBT	3	Pigs	30–40	1	RSPV-LAJ	Yes	AA	Yes	Yes	Yes	6	Yes	No
Lydiard et al. (53)	XRT	15	Humans	50	5	PVA	No	CLA	Partially	Partially	Dynamic phantom	N/A	N/A	N/A
Ren et al. (61)	XRT/PBT	11	Humans	25	1	WACA	No	AA/CLA	Yes	Yes	No	N/A	N/A	N/A
Richter et al. (59)	PBT	3	Pigs	30–40	1	RSPV-LAJ	Yes	AA	Yes	Yes	No	N/A	N/A	N/A
Xia et al. (52)	XRT	20	Humans	50	5	PVA	No	CLA	No	No	No	N/A	N/A	N/A

AA, adron accelerator; CLA, conventional linear accelerator; CK, Cyberknife; EF, ejection fraction; LPV, left pulmonary veins; LPW, left posterior wall; MRI, magnetic resonance imaging; MRIL, MRI-Linac, MRI-linear accelerator; MVR, mitral valve regurgitation; N/A, not available; PBT, particle beam therapy; PVA, pulmonary vein antra; RSPV, right superior pulmonary vein; RSPV-LAJ, right superior pulmonary vein-left atrial junction; WACA, wide area circumferential ablation; XRT, photon radiotherapy.

alpha/beta ratio considered. The prescription dose was delivered to a dynamic phantom only in the study by Lydiard et al. (53). Specifically, the authors registered the respiratory profiles of 3 healthy patients and subsequently associated the recorded profiles to the phantom to deliver plans differing in complexity. The first was created using a dynamic conformal arc and a 3 mm target volume (TV) margin expansion, one using volumetric modulated arc therapy (VMAT) plan, a restricted number of monitor unit and a 3-mm TV margin expansion, the other VMAT plans with TV margin expansions of 0, 3, and 5 mm, respectively. All dynamic plans were compared with the static ones, and the superiority of multileaf collimator (MLC) tracking over tracking without MLC was demonstrated, with a minor failure percentage appreciated through a gamma failure rate, and a better TV dose coverage.

Only Ipsen et al. (55) involved MRI-linear accelerator (MRI-Linac) in their work: they evaluated the role of real-time MRI target localization and efforted the treatment planning for cardiac radiosurgery with MRI-Linac on 6 male volunteers.

The above-described preclinical studies considered PVA as the only target of irradiation. Only Gardner et al. (51) compared 2 different target extensions: PVA and PVA plus left posterior wall (LPW); the last one was optimized to spare mitral valve annulus, right coronary, and circumflex arteries. Better compliance with radiation therapy oncology group limits was observed in the second target set, with the purpose to reduce the dose to the ventricles where most cardiac adverse events after radiation therapy would originate (56).

Overall, fiducials were implanted only by Blanck et al. (50); in this work, the authors compared a spectrum of different tracking systems: the partially invasive one, such as a catheter in the right atrial septum (temporary fiducials), CK marker-less tracking system for lung tumors (XSight® Lung, Accuray) or ultrasound tracking (50). In the same article, Blanck et al. (50) described a prevalidation, contouring study comprising a series of 133 patients' CT scans: esophagus segmentation revealed that in 50% of the cases the organ is directly in contact with the target, similarly to transcatheter ablation (57).

Particle Beam Therapy

Four studies focused on PBT, and carbon ions were used in all cases: 2 works were dosimetric (58, 59) and one reported on *in vivo* dosimetry on animals (60). The last one (61) compared intensity-modulated proton therapy with XRT delivered through VMAT and helical tomotherapy.

Constantinescu et al. (58) evaluated 9 and 5 CT scans of complete respiratory and cardiac cycles, respectively: they planned 25–40 Gy single fraction carbon ion treatments involving intensity-modulated particle therapy (IMPT). Authors defined the importance of respiratory and heartbeat motions with a lesion displacement of, respectively, $\leq$2 cm and <6 mm; in this last case a worsening in dose coverage (V95 < 90%) was registered. Carbon ion beam rescanning was used to improve dose coverage.

The same rescanning technique was employed also by Lehmann et al. (60) to reduce the interference between the scanning motion of the beam and the target motion, the so-called "interplay." In their work, carbon ion irradiation in different TV was evaluated: a 30–40 Gy single fraction treatment was delivered on the right superior pulmonary vein-left atrial junction (RSPV-LAJ) of 3 pigs; one of the 3 animals was irradiated with a lower dose of 30 Gy to spare esophagus (due to specifical anatomy of the animal), the others with 40 Gy. All the treatments were delivered with in-beam positron emission tomography (PET) to verify the correct deposition of carbon ions during irradiation. In the end, they evaluated apoptotic markers employing the Western blot technique with anti-caspase-3, antitubuline, and horseradish peroxidase-conjugated secondary antibodies. As a result, they found that an increase of these markers occurred 3 months after the irradiation, but 6 months after the treatment all the markers turned negative. With the same dataset, Richter et al. (59) evaluated 17 treatment plans (3 on RSPV-LA, 14 on other targets) with ECG-based-4D-dose reconstruction, showing higher safety with respect to cardiac structures and efficient dose verification.

The most recent article included on PBT, Ren et al. (61), evaluated dosimetric properties of intensity-modulated proton therapy in comparison with VMAT and tomotherapy treatment planning; the prescription dose was 25 Gy in all plans. The proton-based technique resulted in a significantly reduce dose in surrounding tissues, compared to photon-based ones, in patients with AF.

Clinical Studies

Three of the selected studies considered human subjects, with a total number of 6 patients (**Table 3**). The first clinical work is a case report by Monroy et al. (62) on a 59-year-old man with symptomatic AF suffering from adverse effects caused by antiarrhythmic drugs and an ischemic stroke in oral anticoagulant therapy. The need of performing catheter manipulation within the left atrium, which is required by classical PVI, was judged as a contraindication to a catheter-based procedure. Therefore, a radio ablation was proposed by the cardiologist, and the patient underwent radiosurgery, delivered by CK in a single fraction, with a prescription dose to pulmonary veins of 25 Gy to the 71% isodose line. Details on the use of fiducials were not reported, and the details of cardiac motion control. Respiratory motion was compensated by synchrony image guidance during the whole course of treatment delivery. Six months after the procedure the patient developed a permanent AF requiring him to restart the medical therapy. An MRI was performed 1 year the after procedure and a late enhancement was recorded at the radio-ablated structure, which may correspond to the development of a scar.

A second study [Qian et al. (63)] involved 2 patients with symptomatic AF who had refused a catheter procedure and had agreed to an experimental non-invasive ablation. Both had undergone a fiducial placement and a subsequent simulation contrast-enhanced CT scan. A prescription dose of 25 Gy was delivered through a CK accelerator in both cases. Patients were followed for 24 months (patient 1) and 48 months (patient 2), showing the absence of any significant treatment-related side effects. Six months after irradiation, patient 1 developed persistent AF, leading to permanent medical therapy. Conversely, the second patient had no AF recurrences during the entire

TABLE 3 | Main characteristics of the clinical studies included in the analysis.

Study	Energy	N° subjects	Total dose (Gy)	N° of fractions	Target	Fiducials	Accelerator	Respiratory motion control	Cardiac motion control	Delivered plan	Follow-up (months)	Efficacy	Toxicity
Monroy et al. (62)	XRT	1	25	1	PVA	N/A	CK	Yes	N/A	Yes	12	No	No
Qian et al. (63)	XRT	2	25–35	1	WACA	Yes	CK	Yes	Yes	Yes	48	50%	No
Shoji et al. (64)	XRT	3	22–30	1	WACA	Yes	CK	Yes	Yes	Yes	24	No	No

CK, Cyberknife; LPV, left pulmonary veins; N/A, not available; PVA, pulmonary vein antra; WACA, wide area circumferential ablation; XRT, photon radiotherapy.

follow-up. Only the second patient performed a pre- and post-ablation MRI, showing evidence of a scar at the radiosurgery site after 1 year.

The most recent article in the clinical area has been published by Shoji et al. (64): 3 oncologic patients with refractory AF were treated with a target dose of 25–30 Gy in a single fraction delivered by CK. The TV was represented by a "box" lesion set including a circumferential wide-area ablation (WACA) set around pulmonary veins and the maximum follow-up was 24 months. One patient died 4 days after the procedure due to oncologic disease. The autopsy revealed evidence of fibroblasts and fibrogenesis in the region of radio-ablated tissues. On the other two patients, who remained in AF, clear evidence of clinical efficacy cannot be found: authors encountered some limitations as a consequence of the second patient's refusal to undergo electrograms of LPW recorded from the esophagus. However, the third patient underwent this exam and no atrial potentials were seen from the esophageal electrogram recordings after radio ablation. This evidence suggests an electrical block, which is the clinical goal of the procedure. No acute or late effects were registered during follow-up.

Gray Literature

Two of all the articles selected were gray literature: the first was the preclinical study of Rahimian et al. (65) which included 3 patients' treatment plans for a 25 Gy single fraction therapy. The most recent study, Gregucci et al. (66) is currently enrolling patients, and results are not yet available. All the studies considered PVA as TV. No information about efficacy or toxicity is now available from all this literature but it suggests the increasing interest in this particular topic.

DISCUSSION

Main Evidence

Results from our work show the application of STAR for AF. A prescription dose of at least 25 Gy in a single fraction is necessary to have good efficacy despite an acceptable toxicity profile.

The major cause of failure of traditional catheter ablation of AF is incomplete circumferential vein isolation (9). It is worth considering that, according to the existing literature on catheter ablation, the choice of the target (11) and the circumferential scar (67) is essential to obtain an effective procedure. Target selection appears to have the same importance in non-invasive cardio-ablation procedures, as confirmed by target heterogeneity among considered studies (see section "Results").

Target motion control, involving fiducials or other simulation strategies (4DCT and cardio-CT or electroanatomic mapping) is deemed necessary to improve the accuracy of the procedure.

It is worth saying that, despite the interest in the topic, a limited number of humans has currently undergone STAR for AF and only 2 articles including more than one patient have been published (63, 64). In the study of Quian et al. (63), efficacy was observed in one of 2 treated patients, but no detail on treatment plan features was provided by the authors; moreover, 2 different

pathways of preprocedural and follow-up exams were applied, which cannot be considered as being completely comparable. The absence of toxicity was the only shared feature between the patients included. In the study of Shoji et al. (64), no acute or late effects were observed; nevertheless, the choice to select oncologic patients makes it more difficult to evaluate the endpoint of efficacy. Even if clinical efficacy on human subjects is difficult to be defined in a limited sample, fibrosis (63, 64), or electrical block (64) was observed in the radio-ablated area in both studies. A similar finding, obtained by an MRI exam, was recorded in the case report (62). All the above-mentioned evidence may be interpreted as the confirmation of the radio-ablation lesion.

In conclusion, available evidence reports acceptable tolerability of the cardio-ablation treatment on humans; further analyses, together with the newest results coming from the current "gray literature," however, are deemed necessary to reach the highest level of efficacy.

Validation of Stereotactic Arrhythmia Radio Ablation With Regard to Different Experimental Settings

We observed a prevalence of preclinical studies, the majority of which involved mini pigs. This choice can be explained by their relative growth stability and the consequent capability of weight maintenance during follow-up. Three of the analyzed studies also considered a canine model (42–44). However, regardless of the chosen animal models (68), transferability concerns for clinical applications in humans exist. Significant examples may be the incomplete pericardium of dogs (47) or the different cardiac chambers anatomy and number of pulmonary veins in humans and canines (44). Specifically, these anatomical peculiarities could affect respiratory and cardiac target motions, which are essential parameters in treatment planning.

When evaluating the preclinical studies on animals it has been shown that the efficacy is higher when mini pigs (41, 47) are treated as compared with canines (44) or mixed samples (42).

Total prescription doses in the considered works ranged from 15 to 50 Gy/fraction and the minimum dose threshold for efficacy was 25 Gy. Most of the studies encompassed stereotactic radiosurgery delivered in a single fraction except for few articles describing 5-fraction treatments with a dose of 10 Gy/fraction (total dose: 50 Gy). This comparability is based on the BED which was calculated by the authors (52) using a radiobiological model to avoid the overestimation of the total dose resulting from the linear-quadratic BED calculation when the dose is greater than 8–10 Gy (69). Of note, even if BEDs were considered comparable, the heart tissue is a late responder and its alpha/beta ratio is about 3 Gy (31, 52) with the consequence that the effect may be superior with higher doses delivered in a single fraction than with lower fractionated doses.

A discrete number of studies based on the treatment plan evaluation or delivery of the treatment on a dynamic phantom can be found in the literature: even if they appear to be more acceptable from the ethical standpoint, someone may question if the evidence acquired from these studies are comparable, in terms of efficacy and safety, with those acquired from the clinical setting; in some cases (53), authors started from a study of cardiac and respiratory montions on healthy patients, raising the question whether the respiratory and cardiac motions are really comparable in healthy patients with AF, as discussed below.

Role of the Target Motion

The role of the target motion was furthermore discussed in almost all studies. This topic gains importance since the natural motion of the organs influences not only the myocardial or the conduction tissue around the target but also the other organs at risk, the most important one appearing to be the esophagus. The problem of organ motion was solved by some authors (50, 59, 60) by adopting different fiducials such as seeds or catheters, whereas other ones did not (46, 51–53). The presence of fiducials makes the tracking useful in the positioning of the patient and in the reduction of the margin of error due to cardiac and respiratory motion, but it implies the use of tools that are against the peculiar nature of the procedure in terms of non-invasiveness.

Grimm et al. (70) and Abelson et al. (71) faced the problem of organs at risk doses by reviewing literature and patients' data, respectively, and elaborated dosimetric tables as references for the colleagues' work.

In the end, it is important to remember how it is possible that a dilated heart with AF appears to have less movement than a healthy one (61, 72): so, it is also possible that all dosimetric studies on healthy subjects are not completely suitable for the patients with real-AF and more investigations could be necessary.

At last, it is worth noticing the interesting application of MRI to approach the problem of target motion (55, 73): on the one hand, by quantifying target motion ranges on MRI, on the other hand by analyzing the dosimetric benefits of margin reduction assuming the application of real-time motion compensation.

Supporting this hypothesis, a recent article by Lydiard et al. (74), not included in the selection, investigated the feasibility of non-invasive MRI-guided tracking of cardiac-induced target motion in AF cardiac radio ablation by comparing a direct tracking method and 2 indirect tracking methods (tracking indirect left atrial or other targets). They suggested the applicability of non-invasive MRI-guided tracking, showing a potential improvement in treatment efficacy.

Particle Beam Therapy: Pros and Prospectives

Both XRT and PBT involve ionizing radiations, but the second one can deliver its maximum dose at a specific depth (Bragg peak, **Figure 2**) to the TV while no dose in the surrounding tissues (75).

Carbon ion should be particularly indicated for the aim of cardio ablation because of the favorable RBE (three times as much as the photons' one) and the possibility of smaller beam foci and less lateral scattering.

In the included articles, pencil beams were used to better modulate the beam on the TV; the limit of these thin rays is a major sensibility to motion and setup errors, then the correct position of the beam's distal edge remains unknown (75). Ren et al. (61) decided to study this phenomenon in their work using a cardiac motion scan from a patient case. Nevertheless, beam

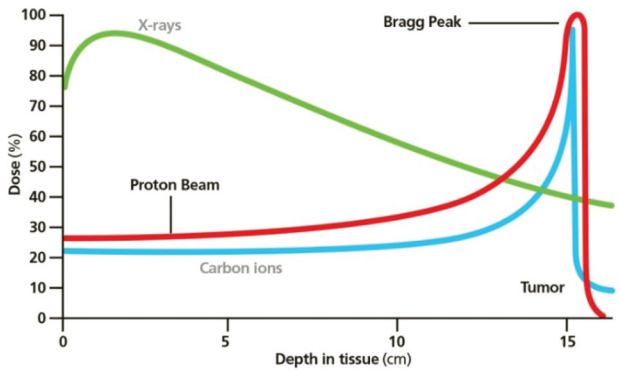

FIGURE 2 | Bragg peak in PBT. Reprinted from Mustapha et al. (81) with the permission of AIP Publishing.

rescanning and 4D dose calculation (58) or the use of in-beam PET can reduce the problem (60).

An interesting biological hypothesis about the effectiveness of carbon ions in arrhythmia ablation was formulated by Amino et al. (76): they studied the role of the upregulation of connexin-43, a protein expressed during myocardial remodeling in myocardial infarction or cardiac hypertrophy. This remodeling effect on gap junctions may reduce the conduction of the arrhythmia through myocardial tissue.

Although photons and carbon ions are so different, according to the articles selected, the time to detect a scar in an anatomopathological analysis is similar and it spans from weeks to months. As further evidence, the process of fibrosis and scar creation starts after the activation of the apoptotic cascade (77, 78), according to Lehmann et al.'s results (60).

Use of Stereotactic Arrhythmia Radio Ablation in Atrial Fibrillation Versus Ventricular Tachycardia

During the evaluation of the efficacy and safety of STAR in AF, some considerations about the comparison between AF and VT are necessary. First, it is worth underlying that specific peculiarities characterize the anatomical and structural substrate for AF as for VT, which reflect in different treatment approaches and need to safeguard surrounding healthy structures. For these reasons, some assumptions that have been preliminarily validated in the field of VT may not be true for AF. Ventricular arrhythmias, that may deserve STAR, are usually life-threatening; patients present with recurrent and/or refractory VTs and are not eligible for conventional approaches or these have proven ineffective. In this clinical setting, STAR represents a promising option, thus more risks, even unknown ones, are allowed. To the best of our knowledge, in literature few severe adverse events, definitely correlated to STAR, are reported. In particular, one patient died of esophagopericardial fistula after 9 months from STAR: of note, the patient had previous bypass surgery with a gastroepiploic artery that might have contributed to this severe adverse event (79); few clinically relevant or symptomatic radiation-induced pericarditis and pericardial effusion and a gastropericardial fistula 2 years after STAR were recorded (80).

Being AF a benign arrhythmia, more attention to the safety rather than the efficacy of STAR is mandatory.

In this setting, more information about the toxicity profile of this new approach is compulsory before applying STAR to AF in clinical practice; this is also the reason why not many clinical articles are available in the literature so far.

Strengths and Limitations

All the above-mentioned works and other already published reviews discuss every type of tachydysrhythmias without a specific focus on AF. The strength of this review is the specificity of the topic treated: stereotactic radio ablation of AF through both XRT and PBT. In this regard, we would like to underline once again that these considerations do not necessarily apply to other patients' conditions (e.g., non-oncological patients).

The main limitations of this work are the relative paucity of works, which is in line with the novelty of the field, and the low evidence of available literature. Moreover, given the nature of our work (qualitative rather than quantitative synthesis), and the relative paucity of studies, it was not possible to fully estimate publication bias—if any—through a funnel plot. To at least account for such potential weakness, gray literature was also included. As a matter of fact, while these works are not peer-reviewed, good-quality gray literature is a source of up-to-date information on ongoing clinical efforts.

CONCLUSION

Stereotactic radio ablation is an innovative non-invasive procedure already in use for ventricular cardiac arrhythmias. Radio ablation of AF, with a prescription dose at least of 25 Gy, might be considered among the future therapeutic option for AF, especially when an interventional ablation procedure is contraindicated or proved ineffective.

Carbon ions are a highly promising radiation technique due to their TV coverage and, at the same time, their greater capability to spare organs at risk; this may be a strong point to achieve an effective safer alternative application for the heart.

Essential issues, such as:

- duration of AF before treatment,
- target definition and motion, and
- doses delivered to the target and organs at risk,

deserve further evaluation to define proper indications and modalities to benefit the most from the use of STAR in patients with AF.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JF contributed to conception of the study and wrote the first draft of the manuscript. SV wrote the first draft of the manuscript and was the third reviewer of the literature. VC performed the literature research and contributed to write the first draft of the manuscript. CP was the first reviewer of the literature. EC, GP, and FC contributed to write sections of the manuscript. MP designed and prepared the tables. AMC was the second reviewer of the literature. DA and CT critically revised the final version. BAJ-F contributed to conception of the study and critically revised the final version. CC designed the study and contributed to wrote the first draft of the manuscript and the final revision. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Case Report: Treatment Planning Study to Demonstrate Feasibility of Transthoracic Ultrasound Guidance to Facilitate Ventricular Tachycardia Ablation With Protons

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Background: Cardiac arrhythmias, such as ventricular tachycardia, are disruptions in the normal cardiac function that originate from problems in the electrical conduction of signals inside the heart. Recently, a non-invasive treatment option based on external photon or proton beam irradiation has been used to ablate the arrhythmogenic structures. Especially in proton therapy, based on its steep dose gradient, it is crucial to monitor the motion of the heart in order to ensure that the radiation dose is delivered to the correct location. Transthoracic ultrasound imaging has the potential to provide guidance during this treatment delivery. However, it has to be noted that the presence of an ultrasound probe on the chest of the patient introduces constraints on usable beam angles for both protons and photon treatments. This case report investigates the possibility to generate a clinically acceptable proton treatment plan while the ultrasound probe is present on the chest of the patient.

Case: A treatment plan study was performed based on a 4D cardiac-gated computed tomography scan of a 55 year-old male patient suffering from refractory ventricular tachycardia who underwent cardiac radioablation. A proton therapy treatment plan was generated for the actual treatment target in presence of an ultrasound probe on the chest of this patient. The clinical acceptability of the generated plan was confirmed by evaluating standard target dose-volume metrics, dose to organs-at-risk and target dose conformity and homogeneity.

Conclusion: The generation of a clinically acceptable proton therapy treatment plan for cardiac radioablation of ventricular tachycardia could be performed in the presence of an ultrasound probe on the chest of the patient. These results establish a basis and justification for continued research and product development for ultrasound-guided cardiac radioablation.

Keywords: ultrasound, ventricular tachycardia, protons, stereotactic radioablation, cardiac motion monitoring

INTRODUCTION

Treatment of cardiac arrhythmias using a non-invasive treatment technique based on external beam radiation has recently shown promising results (1–6). This technique involves delivery of photon or proton beams in a single out-patient session with the aim to stop the electrical conduction in the arrhythmogenic substrate. The surrounding tissues, typically referred to as organs-at-risk (OARs), should be spared from radiotoxic effects as much as possible. This might be achieved, for example, by choosing protons beams over photons beams, as proton therapy has to ability to precisely deliver a radiation dose via the Bragg peak phenomenon (7).

In addition to beam choice, it is of critical importance to take cardiac motion into account during treatment planning and treatment beam delivery. Several solutions have been proposed to handle the cardiac motion during treatment including enlargement of the treatment targets with margins (3, 8) or inferring the cardiac motion based on ECG signals (9–11), electrical impedance signals or X-ray imaging of implanted leads (3, 12). The limitations of these solutions are, among others, the requirement to implant fiducial markers, additional ionizing radiation dose deposition to the patient and the need for a motion surrogate (13).

Transthoracic ultrasound (US) imaging allows for real-time cardiac motion monitoring during the treatment. This image modality has been used for radiation therapy guidance for oncological targets before (14–16) and it overcomes some limitations associated with the currently available motion monitoring solutions. The usage of US imaging, however, requires placing an US probe on the chest of the patient. The presence of the US probe in the path of the radiation beam during the treatment can potentially cause dose delivery errors, which may influence the treatment outcome of the patient.

In literature several options to deal with the presence of an US probe during photon radiation treatment of oncological targets have been described (12, 17–19). To the best of our knowledge, none of the published works focused on dealing with a US probe during the irradiation of cardiac targets with protons. For this reason, this work presents a case report of a patient with ventricular tachycardia (VT) for whom a proton treatment planning study was performed. The aim of this treatment planning study was to design a clinically acceptable cardiac radioablation proton treatment plan for a real VT target.

CASE DESCRIPTION

For this proof-of-concept study the 4D cardiac-gated CT scan from a 55 year-old male patient suffering from VT was used. The CT data of this VT patient has been previously used for other purposes in a work published by Gianni et al. (20). The treatment target for this patient had a size of 45 cm^3 and it was located on the left ventricular free wall. This clinical target volume (CTV) was determined by electrophysiological mapping and contoured prior to the treatment by a medical doctor from the Texas Heart Arrhythmia Institute in Austin, USA. The left anterior descending coronary artery, the circumflex coronary arteries and the non-involved left ventricle were OARs near the target.

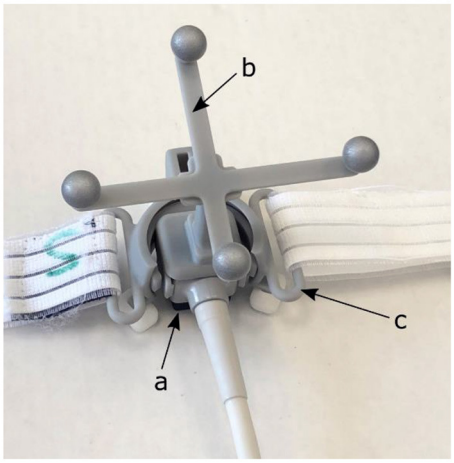

FIGURE 1 | Prototype version of the EBAMed proprietary US probe system (a) equipped with an optical localization marker (b) and a probe holder with strap (c) that allows for fixation to the patient's chest.

First, the 4D CT scan of the VT patient was loaded into the Raysearch® Raystation treatment planning system (version 10B, Raysearch Laboratories AB, Stockholm, Sweden). Subsequently, a virtual representation of the prototype version of the proprietary US probe system of EBAMed (Geneva, Switzerland) was manually inserted as volume of interest (VOI) in two locations representing the estimated position of the apical and parasternal US viewing windows. A separate study has already verified that these US viewing windows provide US images of sufficient quality for VT patients in supine position (21). The US probe was simulated as a cube of $2 \times 2 \times 2$ cm. It is equipped with infrared markers such that the probe can be localized by an optical camera (see **Figure 1**) and it is attached to a holder such that it can be fixed on the chest of the patient allowing for hands-free imaging during the treatment. To account for uncertainties in repositioning of the US probe during the treatment, including probe position uncertainties due to respiration and breath-hold differences, an isotropic safety margin of 10 mm has been added to the union of the US probe, holder, and optical marker.

The parasternal US probe position allowed entrance of the treatment beams from optimal directions with respect to dosimetry for this particular patient. After selection of this virtual US probe position, a pencil-beam scanned proton therapy treatment plan was generated with the treatment planning system using the CNAO (Pavia, Italy) synchrotron proton beam model adapted to the Hitachi PROBEAT gantry system with 360° range of beam angles (22). During planning, the solid angle was restricted to take into account the US probe, the probe holder and the localization marker. Two fields were applied both with a gantry angle of 25° and a couch rotation of 0° and 90° for beam 1 and 2, respectively. The treatment volume was planned with an internal target volume (ITV) approach in order to compensate for shape and position changes of the target due to

TABLE 1 | Evaluation metrics for a clinically acceptable plan (all constraints must be satisfied for a plan to be considered clinically acceptable).

Structure	Dose-volume metric	Dose-volume limit	Source dose-volume limit
Target volume	D95%	100% dose (25.0 CGyE) to 95% volume	Prescription isodose (100%)
Target volume	D2% (near max dose)	120% dose (30 CGyE) to 2% volume	Hot spot allowable in target volume up to 120% of prescription dose for stereotactic body RT (23)
Target volume	D98% (near min dose)	95% dose (23.75 CGyE) to 98% volume	Cold spot allowable at 95% prescription isodose
Spinal cord	D (max)	7 CGyE	(23)
Coronary arteries	D (max)	14 CGyE	(24)
Skin	V (23Gy)	10 cm^3	(23)
ICD	D (0.03cc)	2 CGyE	(25)
Aorta	D (max)	20 CGyE	(24)

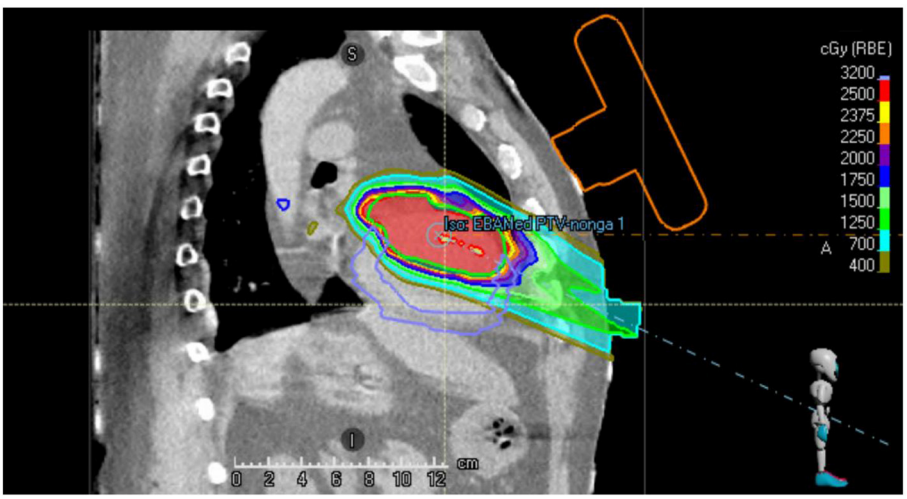

FIGURE 2 | Sagittal slice of the single beam proton plan generated for the VT patient. The location of the virtual US probe with localization marker on the chest of the patient is shown in orange.

the heartbeat. It was assumed that the motion of the heart due to respiration would be mitigated using a breath-hold technique or respiratory gating. The envisioned role of the US imaging during this treatment was real-time cardiac motion monitoring and sending an alert to the operator in case the measured motion was outside of predefined limits.

For the generation of the ITV, the heartbeat motion envelope was extracted from the 4D CT scan by deformable registration of each phase of the 4D CT scan to the planning CT scan. The resulting ITV is the union of the CTVs at all phases of the 4D CT. Finally, the planning target volume (PTV) was generated by adding a 5 mm margin to the ITV based on typical patient set-up errors which are expected when no image guidance tool like US imaging is used.

Dose constraints on dose-volume tolerances (**Table 1**) in agreement with prior investigators were set as planning objectives. All doses are reported in Cobalt Gray Equivalent Dose (CGyE). The plan required the ITV to be covered by the 25 CGyE isodose, which is a dose level used in prior clinical studies to achieve safe, efficacious radioablation. To achieve this, the plan was normalized so that PTV D92% = 25 CGyE. Also, in order to arrive at a satisfactory treatment plan (26, 27), robust optimization with 2 mm set-up error in all directions and 2% range uncertainty was used during planning.

To verify the clinical acceptability of the generated plan, evaluation of standard target dose-volume metrics D98, D95 D50 and D2 was performed. In addition, the dose to OARs and the target dose conformity and homogeneity were evaluated.

DISCUSSION

Figure 2 shows a sagittal slice of the proton treatment plan that has been generated for the patient studied in this case report. It can be observed that the beams do not intersect the orange contour of the virtual US probe.

TABLE 2 | Proton treatment plan characteristics.

Dosimetric parameter	Value
ITV -> PTV margin	5 mm
D95 (ITV)	25.1 CGyE
D98 (ITV)	21.8 CGyE
D2 (ITV)	30.2 CGyE
D50 (ITV)	26.6 CGyE
Homogeneity Index (ITV)	0.32
Conformity Index to PTV	1.02
Minimum beam energy	81.0 MeV
Maximum beam energy	160.5 MeV
Dose to Nearby OARs	
• Non-involved left ventricle (V20Gy)	9.82 cm^3
• Non-involved left ventricle (Dmean)	4.53 CGyE
• Left anterior descending coronary artery (D0.03cc)	10.7 CGyE
• Circumflex coronary arteries (D0.03cc)	9.42 CGyE

Table 2 details the proton treatment plan characteristics. Target coverage and dose conformity as well as sparing of OARs, were found to be acceptable. The D98 was less than the value required in **Table 1**, due to the coronary arteries abutting the PTV in the superior extent of the target. Limiting the dose received by these structures was prioritized over target coverage in this region of the target.

This case report describing a treatment planning study for a VT patient has shown that the use of an US probe in parasternal viewing position during treatment delivery will not prevent a clinically acceptable treatment with proton radiation for this particular patient. These findings establish a basis and justification for the continued research and product development to arrive at an integrated solution for ultrasound-guided cardiac radioablation. The usage of US imaging during the treatment will potentially allow for ITV margin reductions. However, before final conclusions can be drawn, more extensive treatment planning studies are necessary in which actual US probe positions (both parasternal and apical US viewing windows) instead of estimated probe positions are considered. In addition, future research efforts are planned to focus on improved OAR sparing, which can be achieved by more precise targeting. This can, for example, be accomplished by cardiac phase gating with a careful definition of the gate range, instead of only monitoring the cardiac motion as considered in this work.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RP, AG, and MF-V design of work. RP and PM: data collection and drafting the article. RP, AM, ER, CD, VV, and PM: data analysis and interpretation. GW, PM, and SB: critical revision of article. AG, RP, PM, and MC: final approval of version to be published. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: PM is founder and owner of MedDevicePharma LLC. GW is founder and owner of National Medical Physics and Dosimetry Company. PM and GW are consultants to EBAMed SA. RP was previously employed and AG is still employed by EBAMed SA.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Histopathological Examination of an Explanted Heart in a Long-Term Responder to Cardiac Stereotactic Body Radiotherapy (STereotactic Arrhythmia Radioablation)

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Cardiac stereotactic body radiotherapy is an emerging treatment method for recurrent ventricular tachycardia refractory to invasive treatment methods. The single-fraction delivery of 25 Gy was assumed to produce fibrosis, similar to a post-radiofrequency ablation scar. However, the dynamics of clinical response and recent preclinical findings suggest a possible different mechanism. The data on histopathological presentation of post-radiotherapy hearts is scarce, and the authors provide significantly different conclusions. In this article, we present unique data on histopathological examination of a heart explanted from a patient who had a persistent anti-arrhythmic response that lasted almost a year, until a heart failure exacerbation caused a necessity of a heart transplant. Despite a complete treatment response, there was no homogenous transmural fibrosis in the irradiated region, and the overall presentation of the heart was similar to other transplanted hearts of patients with advanced heart failure. In conclusion, our findings support the theorem of functional changes as a source of the anti-arrhythmic mechanism of radiotherapy and show that durable treatment response can be achieved in absence of transmural fibrosis of the irradiated myocardium.

Keywords: ventricular tachycardia, structural heart disease, STAR, radioablation, stereotactic body radiotherapy (SBRT)

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INTRODUCTION

Despite a decade of increasing clinical experience, and a growing interest in the application of STereotactic Arrhythmia Radioablation (STAR) (1), also known as Cardiac Stereotactic Body Radiotherapy (Cardiac SBRT), the underlying anti-arrhythmic mechanisms are still a subject of scientific debate. Preclinical animal studies postulated that radiosurgery induces scar homogenization through transmural fibrosis, mirroring radiofrequency catheter ablation (RFA) (2). It was never clear, however, whether 25 Gy is capable of inducing such significant structural changes in the human heart (3). The *in vivo* dynamics of treatment response (4) suggested that the anti-arrhythmic effect precedes clinically significant fibrosis. Finally, a recent study by Zhang et al. found that the clinical effects of STAR might be solely associated with functional electrical conduction changes in the myocardium (5).

Kiani et al. were the first to report on human heart pathology changes after STAR and found that even with relatively long follow-up, despite signs of cell death and injury, there is limited fibrosis (6). In a later study by Kautzner et al., the authors supported the pre-clinical theorem of myocardial apoptosis (up to three months post-STAR) followed by a creation of fibrotic lesion (six to nine months post-STAR) in the irradiated region (7). Zhang et al. suggested that the visible fibrosis is likely a consequence of primary heart disease, previously received treatments and that the intensity of fibrosis is not significantly different from what would be observed pre-treatment (5).

Significant differences in the description of post-STAR organ pathology (5–7), but most important clinically relevant differences in efficacy described by the authors (1) could be associated with individual radiosensitivity. The irradiated regions of the myocardium are initially subjected to cardiomyopathies of ischemic and non-ischemic origin and invasive treatment methods (i.e., RFA, ventricular assist device). There is limited data on human healthy myocardium response to radiation, let alone that of the injured heart muscle. It is possible that the initial condition of the tissue determines the sensitivity to radiation, and thus, the rate and durability of clinical response to STAR. In this article, we present the results of a histopathological examination of an explanted heart in a patient with a durable anti-arrhythmic response to irradiation despite a lack of homogenous scar formation, supporting the theorem of non-fibrotic anti-arrhythmic mechanism of STAR.

MATERIALS AND METHODS

Medical History of the Patient

The patient was a 51-year-old overweight male with a medical history of coronary artery disease, heart failure with reduced ejection fraction, recurrent sustained VT, psoriasis, and hyperthyroidism. He underwent coronary artery bypass graft surgery (LIMA-LAD, Ao-Cx), mitral valve replacement in 2012, and was provided with an ICD in secondary prevention of sudden cardiac death in 2013. The patient underwent five percutaneous coronary interventions (PCI) with implantation of stents within the circumflex branch of the left coronary artery thrice and right coronary artery twice between 2013 and 2020. The patient's medical history is presented in **Figure 1**.

After the ICD implant, the patient experienced eight hospitalizations due to VTs in total, with different VT morphologies recorded during the patient's history. Four hospitalizations were associated with acute coronary syndromes with subsequent PCI's, two episodes happened due to sub-optimal treatment. On two occasions, recurrence of VT happened despite optimal pharmacotherapy and revascularisation. The first such recurrence (01.2019) was followed by a single endocardial RFA of the arrhythmic substrate – the ablated late potentials (LP) were located in the low-voltage zone in the lateral and posterior-septal walls of the left ventricle. The second recurrence (12.2020) developed despite previously introduced oral amiodarone treatment, which led to enrollment in the SMART-VT trial (01.2021). The last episode was not documented on the 12-lead ECG, as the patient received 97 anti-tachycardia pacing bursts and six electrical shocks. In effect, sinus rhythm was present on admission. The electrical storm was caused by a monomorphic VT at 170 bpm (353 ms interval, as per ICD memory). The trial is ongoing and registered under the ClinicalTrials.gov identifier of NCT04642963. A thorough description of the trial protocol can be found in a previously published article (8).

On enrollment, left ventricle ejection fraction (LVEF) was 25% and remained stable at three months after RT. Cardiac ischemia markers remained stable after irradiation and during follow-up. There were no further episodes of sustained VT after STAR. At eight months, the patient was hospitalized due to myocardial infarction with non-obstructive coronary arteries (MINOCA), and subsequent heart failure (HF) exacerbation (LVEF = 10%), which resolved after conservative treatment. Finally, the patient was admitted to the Internal Medicine department nine months after STAR due to a hepatic failure and HF exacerbation. The patient was placed on the heart transplant list, which was performed 11 months post-STAR. The patient died as a result of acute graft failure due to rejection two days after the procedure.

Radiotherapy Planning and Delivery

The target volume for STAR was defined based on invasive electroanatomic mapping (EAM) and cardiac-gated contrast-enhanced computed tomography (CT) of the heart. The CT was fused with a 1.5 mm treatment planning CT scan. The imaging for treatment planning and the radiotherapy itself were performed using Deep Inspiration Breath Hold (DIBH) technique to account for respiratory motion, and the Iterative Metal Artifact Reduction algorithm to reduce right ventricle ICD lead interferences. The EAM was indirectly compared with CT, and for scientific purposes, directly registered through the aid of the Slicer3D-based software (9), which is presented on the last page of the **Supplementary Material**.

The Clinical Target Volume (CTV) measured 42.8 cc and included the whole thickness of the myocardial wall in the region of interest located in the anterolateral part of the left ventricle. The irradiated region was marked by late electrical potentials localized in the akinetic, post-ischemic part of the

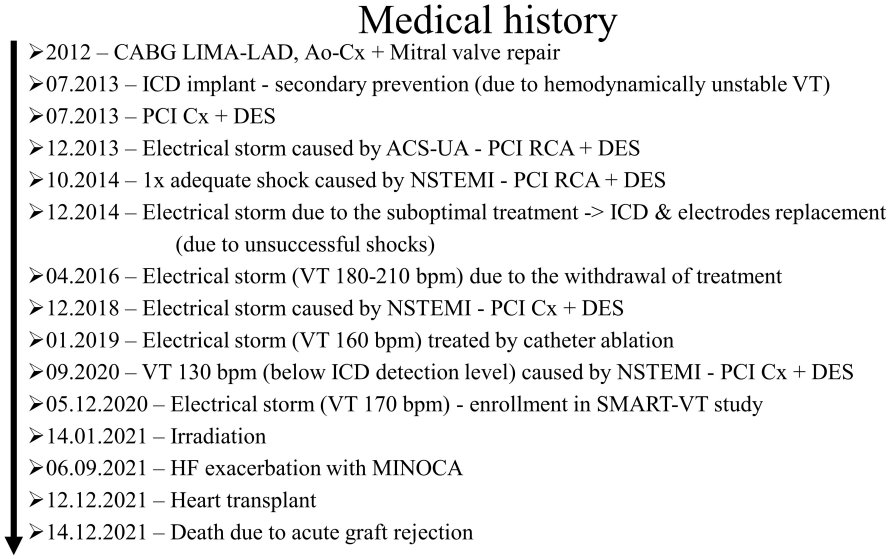

FIGURE 1 | Medical history of the patient treated with STereotactic Arrhythmia Radioablation (STAR). CABG, coronary artery bypass graft surgery; LIMA-LAD, left internal mammary artery – left anterior descending coronary artery; Ao, aortic root; Cx, circumflex branch of the left coronary artery; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; PCI, percutaneous coronary intervention; ACS-UA, acute coronary syndrome – unstable angina; DES, drug eluting stent; RCA – right coronary artery; NSTEMI, non-ST-elevation myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries.

anterolateral wall of the left ventricle, likely caused by a terminal occlusion of the left anterior descending artery due to advanced atherosclerosis (**Figure 2**). No prior RFA was performed in the irradiated region. The CTV was expanded by a uniform margin of three mm to account for residual organ motion and positioning uncertainties, resulting in an 88.7 cc Planning Target Volume (PTV).

The PTV was irradiated up to a total dose of 25 Gy in one fraction. Sparing of organs at risk had higher priority over delivering a homogenous dose to the whole volume of PTV (**Figure 3**). The radiotherapy plan was prepared using the Volumetric Modulated Arc Therapy technique and consisted of three arcs. The radiotherapy delivery was performed on a Varian EDGE linear accelerator. The patient positioning verification was performed with DIBH Cone Beam CT (CBCT). The whole treatment session performed with the DIBH technique took 33 min including 18 min for the initial positioning.

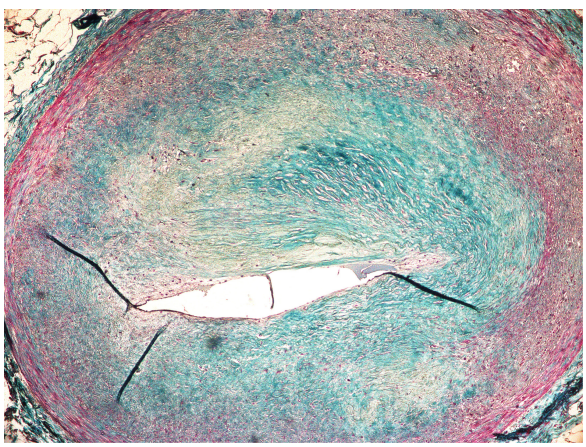

FIGURE 2 | Occluded, atherosclerotic left anterior descending artery with fibrous cap and a lipid core plaque.

Methodology of the Histopathological Examination

The patient's heart was acquired after the heart transplantation was performed due to advanced heart failure. The organ was fixed in buffered neutral 4% formalin solution, sectioned, measured, and described (**Figure 4**). Excised myocardial fragments were dehydrated through graded alcohol and xylene, and embedded in paraffin.

A series of four routine samples from both ventricles and 17 further samples from regions of interest were taken by the pathologist (JN). The acquisition of the samples was directed by the attending radiation oncologist (MM) and two cardiologists (MS and MC) with the aid of pre-treatment cardiac CT fused with radiotherapy-planning structures, adjusted to match the geometry of the following slices through the specimen (**Figure 5**).

The specimens were sectioned into four μm slices and processed using Hematoxylin & Eosin (H&Es), and Masson's trichrome (MTs) staining. The H&Es were used to examine for the presence of necrosis, inflammation, and vascular changes, while MT was primarily used to demonstrate fibrosis. The histopathological findings were provided with matching microscopic images. All of the available specimens were later scanned to produce panoramic images. The authors are willing to share this data, as described in the **Supplementary Material**.

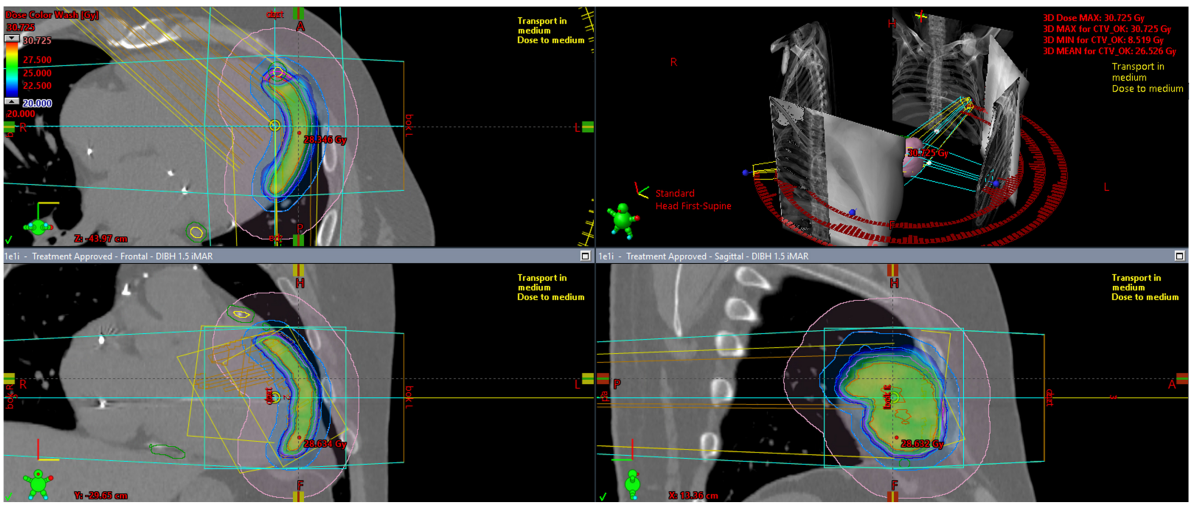

FIGURE 3 | Color-wash representation of the dose distribution within the irradiated heart, ranging from 20 Gy (blue) up to a maximum dose of 30.7 Gy (red). The coronary artery sparing is well-visible in the upper part of the upper-left sagittal projection.

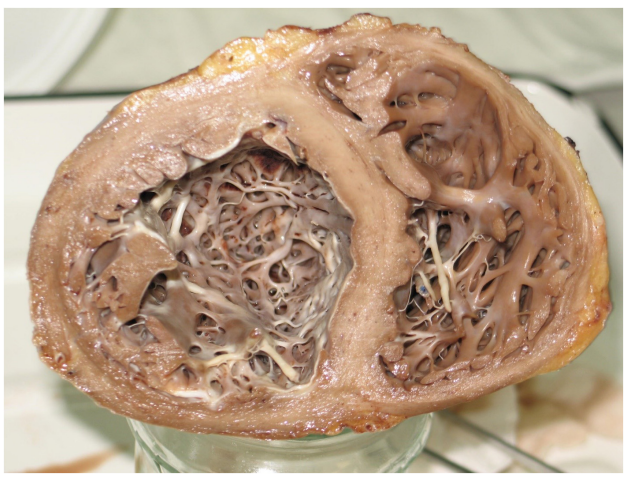

FIGURE 4 | Explanted heart of a patient with early and durable response to STereotactic Arrhythmia Radioablation.

RESULTS

Electrophysiological Examination

There were no significant changes to QRS duration and morphology over the course of follow-up. The QRS length was initially 140.7 ms, followed by 141 and 138 ms at three and six months, respectively. The patient remained VT-free until the end of the follow-up, and the post-mortem ICD interrogation confirmed that the patient did not experience any non-sustained or sustained VT episodes since STAR up to the heart transplant.

Gross Examination

The heart was grossly enlarged, measuring approximately 10 × 14 × 9 cm. The epicardial surface was covered by thin opaque fibrin. The site of irradiation macroscopically corresponded with focally thickened fibrosing endocardium and small parietal thrombi inside the left ventricle. The endocardial layer was thick and fibrous. Mean right ventricular thickness varied between five and six mm, whereas dilated left ventricular thickness never exceeded 10 mm.

Histopathological Examination

The myocardium within the irradiated region (**Figures 6A1–A3,B**) presented with multifocal, mosaic-like fibrosis, and neovascularization of intramuscular connective tissue scars. There were no visible signs of active inflammatory infiltration. The non-homogenous fibrosis was slightly more pronounced sub-endocardial, but there was no transmural scar. The pathological features of the irradiated myocardium were significantly different from the expected sequelae observed after RFA.

Considering that the irradiation was performed in the previously ischemic part of the myocardium, the fibrosis could have been associated with pre-existing ischemic damage to the heart. Moreover, a different etiology of the fibrosis is also suggested by the fact that some of the non-irradiated or marginally irradiated regions presented a similar pattern of fibrosis, albeit subjectively less intense, compared to fully irradiated regions (**Figure 6C**).

The small arteries within the region irradiated with 25 Gy presented with sub-intimal fibrosis, and symptoms of intimal changes such as endothelial cell enlargement and the presence of scattered lymphocytes inside thickened intima. The endothelial layer remained intact, and the lumen was preserved (**Figure 7**).

Summary of the Pathology Review

Compared to other explanted hearts, the pathological image of the specimen closely resembled those of

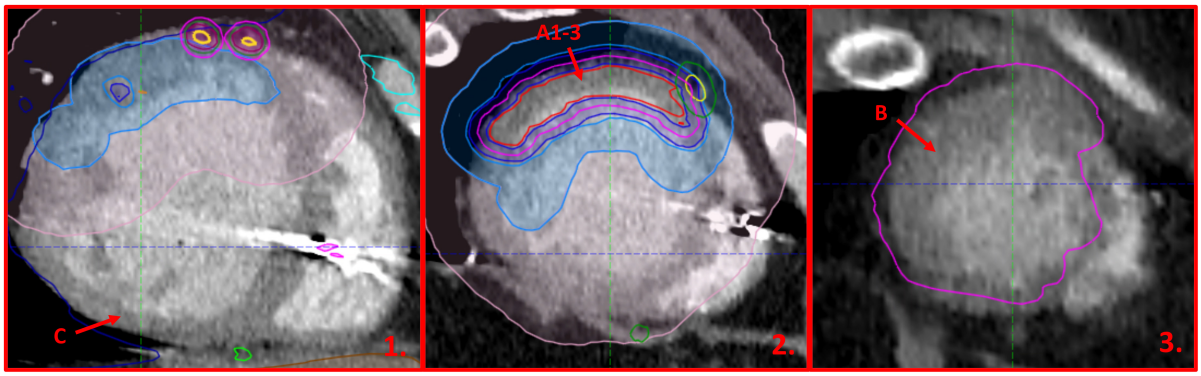

FIGURE 5 | Cardiac-CT images adjusted to the slices performed during the autopsy of the explanted heart. Blue outline (1-2) marks the region irradiated with approximately 7.5 Gy, while violet outline (2-3) shows the planning target volume to which 25 Gy was prescribed. The arrows and letters indicate the approximate localization of the pathology specimens referenced in the article.

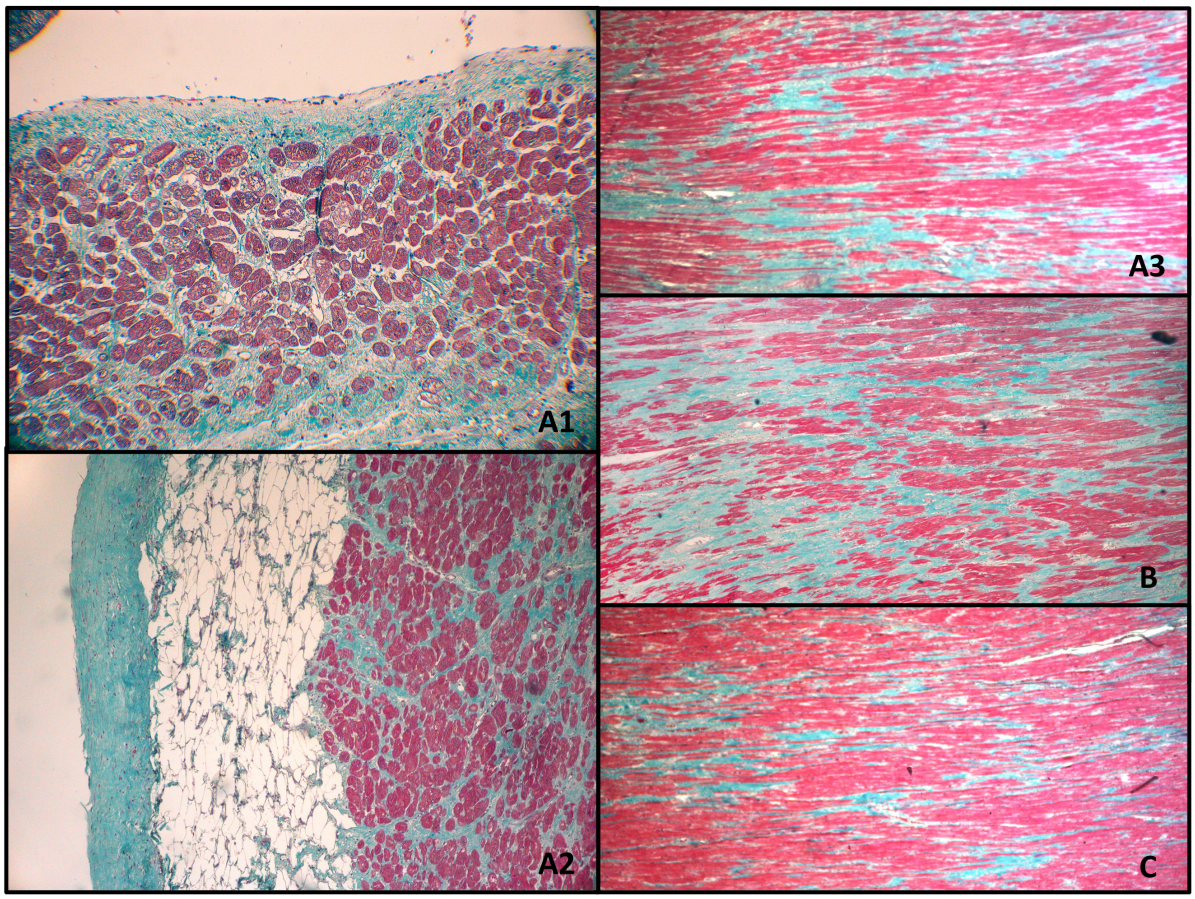

FIGURE 6 | Myocardium 12 months after transmural irradiation with a single dose of 25 Gy. The letters indicate the localization of the specimens as shown in **Figure 4**. Figures **(A1–A3,B)** were located within the PTV and received approximately 25 Gy, while **(C)** was taken from a non-irradiated region. **(A1)** Endocardium; **(A2)** epicardium; **(A3)** middle part of the myocardium; **(B)** middle part of the myocardium; **(C)** middle part of the myocardium (non-irradiated region).

ischemic cardiomyopathy, and it would not be feasible to determine that this patient had undergone STAR based on pathology examination alone. There was no aneurysm, transmural fibrosis, or resorption of necrosis. The post-STAR region was significantly different from the pre-existing post-RFA scar.

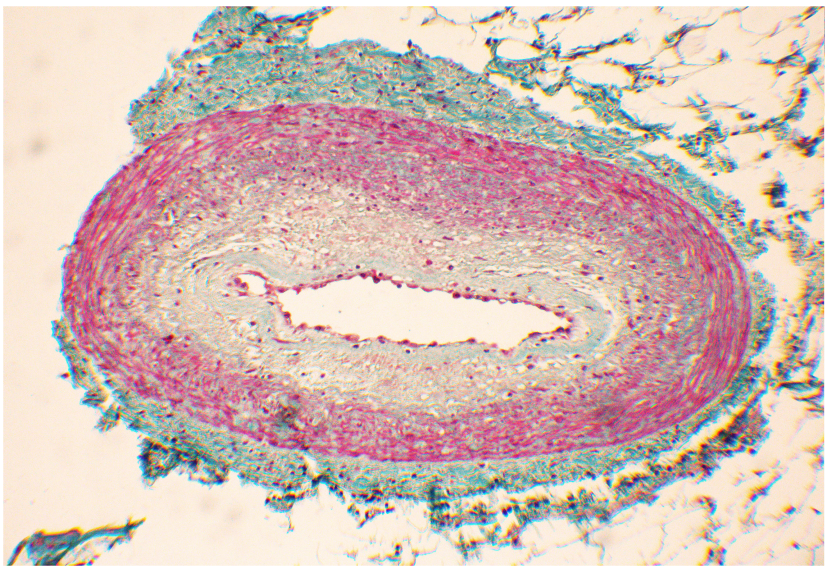

FIGURE 7 | Subendothelial fibrosis of epicardial coronary artery found within the irradiated region.

DISCUSSION

The STAR should not be considered a competitive option for catheter ablation which remains a gold standard in the invasive management of ventricular tachycardia (10). However, considering that several pivotal limitations of RFA do not apply to STAR, the introduction of stereotactic radiotherapy to cardiology and electrophysiology could lead to a substantial improvement in the care of VT patients, and possibly other types of arrhythmias such as atrial fibrillation (11). For example, intramural and epicardial arrhythmic substrate locations, which account for the majority of acute failures in catheter ablation (12), are easily accessible with STAR as the treatment is transmural. Similarly, STAR might be capable of safely ablating volumes adjacent to the critical structures, such as coronary arteries. More data is necessary, but if proven to be correct, this could help to overcome the problem of complex anatomy limiting the application of epicardial ablations.

The initial concept assumed that the biological mechanism of STAR would be similar to RFA through the development of transmural fibrosis in the region of the arrhythmic substrate, and subsequent cessation of electric signal propagation. The clinical experience, however, indicates that STAR induces clinical effects significantly earlier. For example, there are reports of successful electrical storm cessation after STAR (13, 14). Moreover, Kiani et al. found significantly less fibrosis than expected based on the pre-clinical assumptions, despite up to 250 days of follow-up in a total of four explanted hearts (6). As mentioned earlier, a possible game-changing finding was recently published by Zhang et al. (5), suggesting functional changes as a primary mechanism of STAR. If proven to be durable, a significantly different mechanism of treatment could help overcome RFA recurrences. Most importantly this implies a possibility of multimodality treatment, as the irradiated cardiac tissue remains functional and likely sensitive to complementary treatments. This puts into question the use of the word "ablation" when referring to cardiac radiosurgery. As more evidence emerges, it might be more accurate to use the aforementioned "Cardiac SBRT" term, which does not imply bluntly destroying the tissue, but merely associates stereotactic radiotherapy with heart-focused treatment. Another reason to abstain from the "ablation" term would be the effect on small coronary arteries. Despite the expected anti-vascular effect in radiotherapy with fraction doses exceeding 15 Gy (15), we have found that the smaller vessels within the 25 Gy volume remained functional (**Figure 7**). Although the histopathological examination has shown clear signs of degenerative changes, it is difficult to differentiate between radiation-induced and pre-existing changes, as the patient was suffering from ischemic cardiomyopathy.

The patient described in our study was not considered for epicardial ablation due to anatomical constraints, nor received a left ventricle assist device, both of which can lead to significant scarring, hemorrhage, and edema (16, 17) reported by previous authors (6, 7). The lack of visible necrosis could also be associated with the modality of heart rhythm cessation. The patient underwent cardioplegia with isotonic and osmotic solution, which lowers the metabolism and prevents degenerative changes and cell death in cardiomyocytes. Cardiopulmonary resuscitation and postmortem period in hearts explanted from deceased patients can induce previously described necrosis and cardiomyocyte vacuolization (6, 7).

STereotactic Arrhythmia Radioablation is challenged by significant conceptual variability between centers. The target delineation can be based on non-invasive cardiac mapping (4), invasive EAM (8), or even primarily on 12-lead ECG and medical imaging (18). The transfer process of the EAM data to radiotherapy planning systems ranges from indirect comparison to software-based transformations (9), and the

median volume of the final structures varies almost sevenfold between centers (1). Moreover, several different platforms have been used to perform STAR, including C-arm linear accelerators, CyberKnife, and proton beams. To account for the lack of standardization, a European consortium and prospective registry called STOPSTORM was established (19). The registry is funded by a European grant from the Horizon 2020 Framework Programme for Research and Innovation and aims to learn from every case treated in Europe, ultimately resulting in standardized treatment guidelines for STAR.

We acknowledge the limitations of the study, including the case-report nature of the publication and the lack of a control group. It has to be pointed out that theoretically, the patient could have been VT-free without intervention, as there were VT-free periods earlier in the medical history (**Figure 1**). This would not change the pathological description presented in this article but could affect its clinical implications and conclusions. Considering that STAR is an emerging treatment modality, and heart transplants in such patients are exceptionally rare, we believe that our study provides important data, which might be significant for the development of an accurate biological model of the in-human antiarrhythmic effect of STAR.

CONCLUSION

Our findings support the theorem that the anti-arrhythmic effect can occur and be persistent over time despite the lack of RFA-like scar formation. Moreover, the microscopic analysis revealed that up to 12 months after RT, there was no significant occlusion of the small vessels within the high irradiation dose region of the patient's heart, suggesting that coronary artery sparing might be of less importance than previously assumed by some of the authors.

DATA AVAILABILITY STATEMENT

The authors are willing to share the raw data supporting the conclusions of this article upon reasonable request, as described in the **Supplementary Material**.

ETHICS STATEMENT

This study describing a post-mortem histopathological analysis involved human participants, and was a part of the SMART-VT study reviewed and approved by the Bioethics Committee of Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch (KB/430-45/20). The patient provided their written informed consent to participate in the SMART-VT study, and at the time of the treatment provided a separate written informed consent for the pathological examination of the heart in case of heart transplant or death, such as the one described in the article.

AUTHOR CONTRIBUTIONS

MM, MS, KG, and SB contributed to the conception and design of the study. JN performed the pathology examination with the aid of MM and MC. MM, MS, JN, and MC organized the database. MM and MS performed the image editing and wrote the first draft of the manuscript. JN and SB wrote sections of the manuscript. MM, MS, MC, JB, TJ, TL, RK, ŁD, WW, ADr, AG, AB, KG, and SB participated in the described treatment of the patient. ADy and MZ contributed to the heart transplant. KK and AK assisted with the data collection and preparation. All authors contributed to the manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.919823/full#supplementary-material

Supplementary Material 1 | Visual presentation of the location of directed samples, description of the possibility of sharing panoramic images and example of direct EAM to CT registration.

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Successful ventricular tachycardia radioablation in a patient with previous chemical pleurodesis: A case report

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Introduction: Stereotactic arrhythmia radioablation (STAR) is a novel technique for the ablation of ventricular tachycardia in patients with contraindications to standard procedures, i.e., radiofrequency ablation.

Case presentation: We report the case of a 73-year-old man with non-ischemic dilated cardiomyopathy and recurrent VT episodes. Electroanatomic mapping showed VT prevalently of epicardial origin, but direct epicardial access through subxyphoid puncture could not be performed due to pleuropericardial adhesions from a past history of chemical pleurodesis. STAR was performed, with no VT recurrence at 6 months follow-up.

Conclusions: Previous experiences with STAR have demonstrated its importance in the management of patients with refractory VT in whom other ablation strategies were not successful. Our case report highlights the use of STAR as a second choice in a patient with an unfavorable VT anatomical location and technical limitations to an optimal radiofrequency ablation. Moreover, it confirms STAR's effectiveness in the ablation of complex transmural lesions, which are more often associated with non-ischemic structural heart disease.

KEYWORDS

ventricular tachycardia, stereotactic arrhythmia radioablation, chemical pleurodesis, case report, epicardial ventricular tachycardia ablation

Introduction

Stereotactic arrhythmia radioablation (STAR) is a technique in which a single high dose of focused stereotactic radiation is employed for the ablation of cardiac arrhythmias (1). So far, STAR's main field of application has been in the ablation of recurrent monomorphic ventricular tachycardia (VT) (2).

The current gold standard for recurrent VT management is represented by percutaneous radiofrequency ablation (RFA) (3). The conventional procedure involves VT mapping and ablation through an endocardial approach. However, the electroanatomical substrate responsible for VT formation is not always located endocardially, so an epicardial approach is sometimes necessary in order to effectively ablate the arrhythmia.

Since a first case study published by Cuculich et al. in 2017 (4), STAR has been proposed as an alternative to percutaneous RFA in those who cannot undergo such procedure due to patient contraindications or limitations to the procedure itself.

We present the case of effective VT ablation through STAR in a 73 year-old man with recurrent VT of epicardial origin in whom a direct epicardial ablation could not be performed because of a past history of chemical pleurodesis.

Case presentation

A 73-year-old man suffering from non-ischemic dilated cardiomyopathy in NYHA class I was admitted to our hospital because of recurrent VT episodes. Figure 1 summarizes the patient's clinical history.

Cardiovascular risk factors included: former smoking habit, dyslipidemia and a long-term history of systemic arterial hypertension. Noteworthy comorbidities included chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome (OSAS) treated with long-term oxygen therapy and nocturnal continuous positive airway pressure (CPAP). In July 2020 he suffered an episode of spontaneous pneumothorax (PNX), which was successfully treated with blebectomy and chemical pleurodesis.

The underlying cause of the patient's cardiomyopathy had been studied throughout the years by performing multiple coronary angiographies, which showed no evidence of significant coronary artery stenoses. In 2012 he was implanted with a single-chamber implantable cardioverter-defibrillator (ICD) in primary prevention. He also underwent successful atrial fibrillation catheter ablation and atrial flutter catheter ablation.

About 1 year before hospitalization, the patient started experiencing frequent ICD shocks (often during the night), which severely impacted his quality of life. In May 2020, device interrogation showed recurrent VT episodes, either sustained or interrupted by antitachycardia pacing (ATP) or direct-current (DC) shock, therefore optimized anti-arrhythmic therapy with Amiodarone 200 mg twice daily and Mexiletine 200 mg three times a day was started. In April 2021, an electrophysiological study (EPs) showed induction of multiple VTs of different morphologies. All induced VTs caused hemodynamic instability.

The patient was admitted to our Cardiology department in November 2021 to undergo VT ablation. During the 2 months before admission, device interrogation showed that the patient experienced 4 episodes of VT recurrence, all ended by DC shock.

A baseline echocardiogram showed left ventricle (LV) hypertrophy (IVS: 17 mm) and dilation (LVEDVi 76 ml/mq) and a moderately reduced ejection fraction (50%), with inferior basal wall hypokinesia. Cardiac Magnetic Resonance imaging (MRI) was not performed due to the presence of a non MRI-conditional device.

3D Electroanatomic mapping (EAM) of the left ventricle was carried out with the Abbott EnSite system by retroaortic approach. The bipolar map showed low voltage areas (bipolar voltage 0.5–1.5 mV) in the inferior mid LV (total area: 1.4 cm^2), while the unipolar map showed a more extended low voltage area (unipolar voltage 5.5–8 mV) in the inferolateral LV (total area: 2.8 cm^2). Two VTs were induced: the first one (VT1) showed a RBBB morphology, with a cycle length (CL) of 345 s (174 bpm); the second (VT2) showed a CL of 322 s (186 bpm). Figures 2A,B respectively show Bipolar and Unipolar EAMs of the patient's left ventricle.

Since the arrhythmia was not hemodynamically tolerated, endocardial substrate mapping was attempted but turned out to be unsuccessful because of VT2's persistent inducibility at programmed ventricular stimulation. Moreover, various ECG features pointed toward VT of epicardial origin (MDI 0.55) (5). Epicardial approach through percutaneous subxyphoid puncture was therefore attempted. Three attempts from three different electrophysiologists were made, all failing due to the impossibility to advance the guidewire in the pericardial space. Considering the patient's past history of chemical pleurodesis and the related pleuro-pericarditic reaction, no further direct epicardial access attempts were made. STAR was therefore proposed to the patient and informed consent was given.

STAR: Planning and delivery

Treatment simulation

The patient was positioned in the supine position with arms raised above the head. The patient was immobilized with vac-lok cushions (CIVCO Vac-LokTM Cushions). Planning CT (GE, Optima CT580 W, HiSpeed DX/I Spiral) without contrast agent was acquired. Multiple CT acquisition has been performed for simulation: (i) Free breathing CT; (ii) Four dimensional (4D)CT; (iii) Deep inspiration Breath hold CT (DIBH). That enabled respiratory gated delivery approach.

Target definition and delineation

Average CT scan, computed by the 4DCT, was selected for target (in term of Internal Target Volume -ITV-) and Organ at

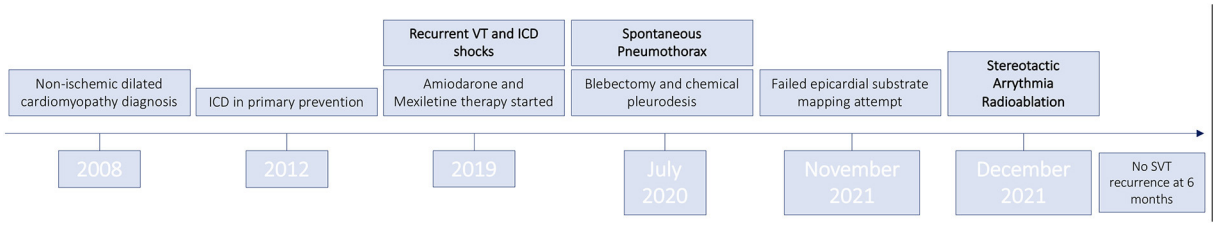

FIGURE 1
Patient clinical history timeline.

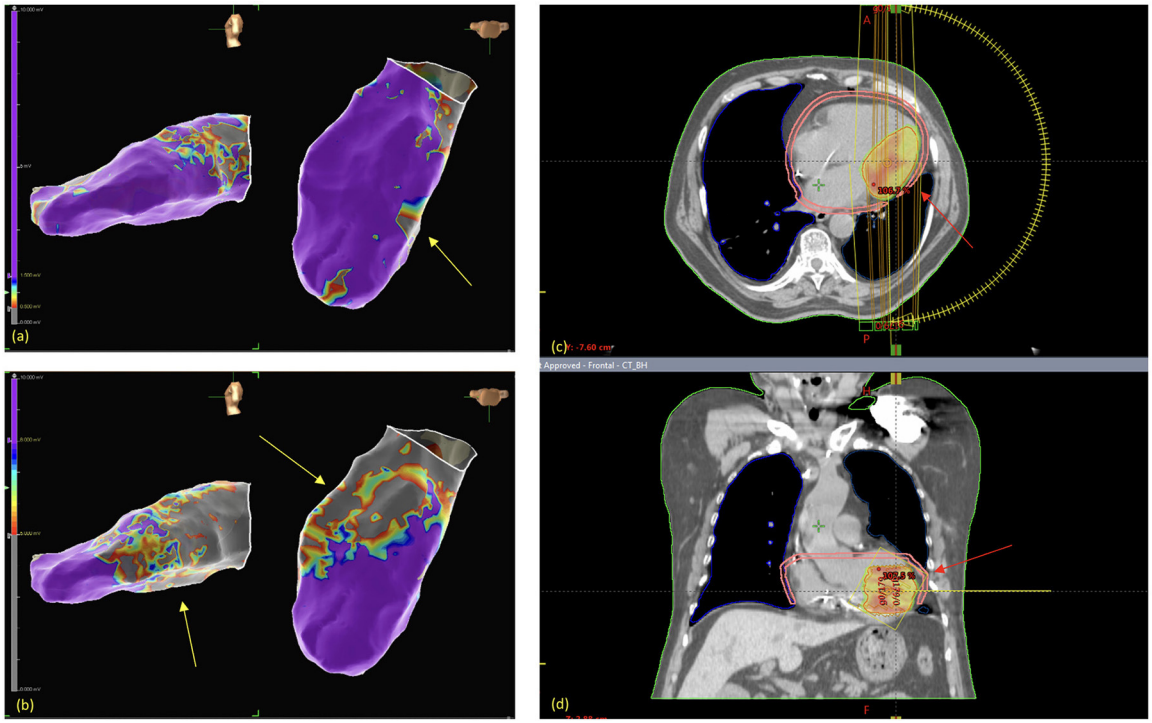

FIGURE 2
Left ventricular (LV) electroanatomic mappings (EAM) show normal voltage areas (in purple), as opposed to low voltage areas (in grey and other colors, representing LV scar area). Bipolar EAM **(a)** shows inferior-mid LV low voltage areas (yellow arrows), while unipolar EAM **(b)** shows a larger scar area on the inferior-lateral LV. STAR treatment planning shows the planning target volume (red arrows) in the axial **(c)** and coronal **(d)** planes.

Risk (OAR) delineation, with a slice thickness of 2.5 mm. Target area (TA) delineation was obtained by merging electroanatomic mapping images with the planning CT scan; merging was applied through a screen-to screen qualitative approach, the anatomical areas of the CT simulation corresponding to the EAM were independently outlined by the radiation oncologist and eventually double-checked by the radiation oncologist with one of the electrophysiologists having performed the EAM. A margin of 3 mm was added to obtain Planning Target Volume (PTV).

Treatment planning

STAR was planned in one fraction using the TrueBeam Edge Linac. The prescribed dose was 25 Gy to the 80% isodose. We used the TrueBeam Edge Linac (Varian Medical Systems, Palo Alto, CA) with 6MV flattening filter free photons and dose calculation algorithm Acuros (Eclipse Version 15.6.04 Varian Medical Systems, Palo Alto, CA). Volumetric Modulated Arc Therapy (VMAT) technique was used with three partial arcs. We did apply the consraints indicated by the AAPM TG101

report (6). All constraints were within the tolerance based on the AAPM TG101 report, except for the pericardia that has been optimized, decreasing the dose as low as reasonably achievable, without compromising target coverage.

Treatment delivery

The patient was treated without the use of either sedation or anesthesia. Image guidance was performed by both volumetric imaging (by Cone Beam CT -CBCT-) before each PA delivery for positioning verification and correction, and by optical surface monitor system (OSMS) for continuous positioning intrafraction tracking and delivery triggering.

The patient was aligned at the isocenter, and 3-dimensional volumetric image guidance through CBCT was acquired. Three-dimensional alignment was performed progressively matching for alignment against the reference images of the treatment plan: bone structures, then organs (e.g., lungs), whole heart, then finally the Clinical Target Volume (CTV). For OSMS: reference image was firstly acquired, defining the tracking Region of Interest (ROI).

Once OSMS was set-up, the first PA was delivered. A CBCT was acquired before each PA. OSMS recorded patient positioning and triggered the beam delivery whenever out of tolerance during the entire delivery procedure. A total dose of 25 Gy in single fraction was delivered. Pre-treatment patient setup was performed in 15 min, including the acquisition of the OSMS reference imaging.

No interruption due to patient related factors was necessary, in particular no ventricular arrhythmia occurred during the intervention. Implantable Cardioverter Defibrillator (ICD) function was normal and cardiac enzymes remained stable after the radiation treatment. Figures 2C,D show radiation therapy treatment planning.

Clinical outcomes

Following the procedure, the patient presented no VT recurrence or acute complications during hospital stay. Post-procedural echocardiography documented the presence of a mild circumferential pericardial effusion (maximum 5 mm) with no hemodynamic impact. The patient was discharged 3 days after the procedure with optimized antiarrhythmic therapy, as described above.

At 3 months follow up, the patient presented no recurring VT episodes on device interrogation. He also reported a significant improvement in quality of life. In light of such findings, Amiodarone dosage was reduced to 200 mg once daily. Follow up echocardiography showed no significant ejection fraction reduction (the patient remained in moderately reduced ejection fraction heart failure, EF: 45%) and complete resolution of the pericardial effusion. 5 months following the procedure, the patient experienced an episode of palpitations. Device interrogation showed a single non-sustained VT, in the absence of other ventricular arrhythmias. On echocardiographic reevaluation, the ejection fraction remained stable (FE: 47%).

No STAR-related side effects were recorded, according to the CTCAE classification v 6.0 (7).

Discussion

Patients with structural heart disease (e.g., ischemic and non-ischemic dilated cardiomyopathy) often suffer from recurrent VT, which greatly affects their prognosis and quality of life, and is generally managed through medical therapy (Class III antiarrhythmic drugs), RFA (the gold standard) and ICD implantation (8).

The use of RFA can be limited by intrinsic technical aspects of the intervention, such as difficult myocardial scar anatomical location, intraprocedural complications, and patient contraindications to the procedure. First and foremost, the invasive nature of percutaneous RFA may limit its use in frail subjects, therefore a completely non-invasive ablation strategy could be a life-saving alternative in this population.

Myocardial scars responsible for reentry mechanisms behind VT recurrence can sometimes be difficult to reach through standard ablation procedures. An example is represented by transmural scars mainly localized on the epicardial surface, which are more commonly reported in patients with non-ischemic dilated cardiomyopathy (9). In such cases, standard endocardial ablation can be complemented by the use of epicardial mapping and ablation through surrounding anatomical structures (e.g., coronary veins, coronary cusps) or through percutaneous subxyphoid pericardial puncture, which allows direct access to the epicardium (10). This procedure carries a series of risks and complications, which include RV puncture and pericardial bleeding, damage to coronary arteries and injury to surrounding structures (11). In addition, patients may present preexisting conditions that make the direct epicardial access unfeasible. Examples include tissue adhesions due to previous chest surgery or an anatomically unfavorable conformation of the thorax.

Chemical pleurodesis involves the administration of sclerosing agents to prevent pneumothorax recurrence. These chemical irritants induce a cytokine-induced inflammatory reaction and consequent fibroblast proliferation, which result in pleural space obliteration (12). In our case report, direct epicardial access through subxyphoid pericardial puncture was hindered by pleurodesis-induced fibrosis, therefore complete transmural VT ablation could not be performed. Following

STAR treatment, our patient experienced an immediate significant reduction in VT burden. At 6 months follow up, there were no sustained VT recurrences nor STAR-related side effects, with a patient-reported significant improvement in quality of life.

According to the literature, an acute reduction in ventricular arrhythmia burden is seen in most patients within few days or weeks from STAR treatment. However, sustained VT/VF recurrence was reported in 75% of the studied population, mostly within the first 6 months (13). In our case report, no sustained VT episodes were registered in the first 6 months following treatment. Longer term durability of the effects of STAR in our patient are unknown.

Few mechanisms underlying the effects of radiation in VT ablation have been proposed. Preclinical studies showed inflammatory cell infiltration and fibrin deposition in radiation-exposed myocardial areas (14). Accordingly, a study by Kiani et al. (15) demonstrated the presence of subendocardial fibrosis and signs of acute myocardial injury in explanted hearts from patients who received orthoptic heart transplantation. Nonetheless, radiation-induced fibrosis is typically seen after a blanking period of a few weeks and cannot explain the reduction in VT burden seen in our patient immediately following the procedure.

Anticipated STAR effects may be explained by a preclinical study by Zhang et al. (16) that showed how radiotherapy also induces myocardial electrical conduction reprogramming through increased expression of sodium channels (Nav1.5), upregulation of Connexin 43 (involved in gap junction coupling) and Notch signaling activation. Their findings also elucidate a possible reason behind STAR's effectiveness on transmural scars despite the fact that the standard 25 Gy radiation dose doesn't create transmural myocardial lesions in animal models (17).

This case report highlights the importance STAR is gaining in every day's clinical practice. STAR is mainly regarded as the last option when all other possibilities (pharmacological and interventional) fail. Notably, its main field of application has been in, but not limited to, elderly end-stage heart failure patients unable to tolerate a long and complex VT ablation procedure. Our patient was a 73 years old man, in NYHA class I and with a moderately reduced ejection fraction and recurrent episodes of VT. After STAR, the subject experienced no more VT episodes and went back to his normal, active life. Our case report therefore confirms previous findings that STAR is not only a last resort treatment option in advanced structural heart disease patients, but that it can be a safe and effective alternative for the management of lower NYHA class patients whose quality of life is greatly affected by VT recurrence.

To the best of our knowledge this is the first case of STAR of a VT in a patient with difficulty in obtaining epicardial access due to previous chemical pleurodesis.

In the next future, thanks to the continuous refinement of the technique and with the expansion of its availability, STAR has the possibility to become one of the weapons in electrophysiologist's arsenal rather than a last resort tool.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Safety and Efficacy of Stereotactic Arrhythmia Radioablation for the Treatment of Ventricular Tachycardia: A Systematic Review

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Catheter ablation (CA) is a fundamental therapeutic option for the treatment of recurrent ventricular arrhythmias. Notwithstanding the tremendous improvements in the available technology and the increasing amount of evidence in support of CA, in some patients the procedure fails, or is absolutely contraindicated due to technical or clinical issues. In these cases, the clinical management of patients is highly challenging, and mainly involves antiarrhythmic drugs escalation. Over the last 5 years, stereotactic arrhythmia radioablation (STAR) has been introduced into clinical practice, with several small studies reporting favorable arrhythmia-free outcomes, without severe side effects at a short to mid-term follow-up. In the present systematic review, we provide an overview of the available studies on stereotactic arrhythmia radioablation, by describing the potential indications and technical aspects of this promising therapy.

Keywords: radioablation, arrhythmia, electric storm, ventricular tachycardia, systematic review

INTRODUCTION

Currently, catheter ablation (CA) is the treatment of choice for drug-refractory macroreentrant ventricular arrhythmias (1). The aim of CA is the elimination of clinical ventricular tachycardias (VT) and the modification of the myocardial substrate by abolishing areas displaying abnormal fragmented/late electrograms, which highlight the presence of viable slow-conducting myocardial fibers often interspersed with fibrous tissue and potentially responsible for further reentrant circuits (2).

In the last decade, a new form of non-invasive ablation using radiotherapy has been introduced in the field of clinical cardiac electrophysiology. Stereotactic radiosurgery is a form of radiation therapy in which high-dose ionizing radiations affect a localized part of tissue (3). In comparison to conventional radiotherapy (RT) with linear accelerators, stereotactic RT delivers radiation in the target tissue from different trajectories: this technique allows to deliver high dose of ionizing particles in the target zone and to minimize irradiation in the surrounding tissues. The technique was first introduced in the 1950s by the Swedish neurosurgeon Lars Leksell for the treatment of intracranial tumors (4).

The first preclinical studies of stereotactic radiosurgery for the treatment of arrhythmias in guinea pigs dates back to 2010 (5). In the first stereotactic radioablation procedures, lesions were created inside the atrium for blocking the cavotricuspid isthmus, the atrioventricular node and the junction between the pulmonary veins and the left atrium. To obtain an effective ablation it was necessary to perform deliveries with a single high intensity radiation dose, ranging between 40 and 70 Gy. Higher dose of radiation is necessary to create lesion in the conduction system (AV nodal ablation), whereas ventricular and atrial walls are more sensitive to radiation and 30–40 Gy dose seems to be effective. The time window required for maximal clinical efficacy ranged between 35 and 50 days, which are required for the formation of connective tissue.

MATERIALS AND METHODS

Data Sources and Search

We performed a comprehensive search in MEDLINE using keywords related to STAR and VT. The search was update on January 27, 2022, and was limited to human studies in peer reviewed journals in English language. This search was conducted using the terms "(radiosurgery OR radioablation OR STAR OR SBRT) AND (ventricular tachycardia OR ventricular tachyarrhythmia)."

Study Selection

This manuscript has been prepared using Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for reporting (PRISMA) (6).

We identified 103 articles, out of which 30 full-text articles were reviewed for possible inclusion (**Figure 1**).

Two reviewers independently screened titles for inclusion criteria and then examined the full text of potentially suitable publications. All original studies of all designs about STAR to treat VT reporting outcome and safety data were included. Being reports of single cases, 20 studies were excluded from the review. The studies have to fulfill the following criteria to be included in the analysis: enrolling two or more patients, reporting a primary effectiveness outcome (defined as post-procedure sustained VT burden) as well as safety data (defined as adverse events related to the procedure).

Data Extraction and Quality Assessment

Two reviewers independently adjudicated study quality and carried out the risk-of-bias assessment of eligible publications. Data were extracted using standardized protocol and reporting forms.

Data Analysis, Synthesis, and Statistics

The studies included in this review are heterogeneous in terms of outcomes, patient characteristics, and indications for the procedure, so it was not possible to perform a meta-analysis.

The effectiveness of the procedure was related to reduction of VT burden at follow up. Safety was analyzed and qualitatively reported.

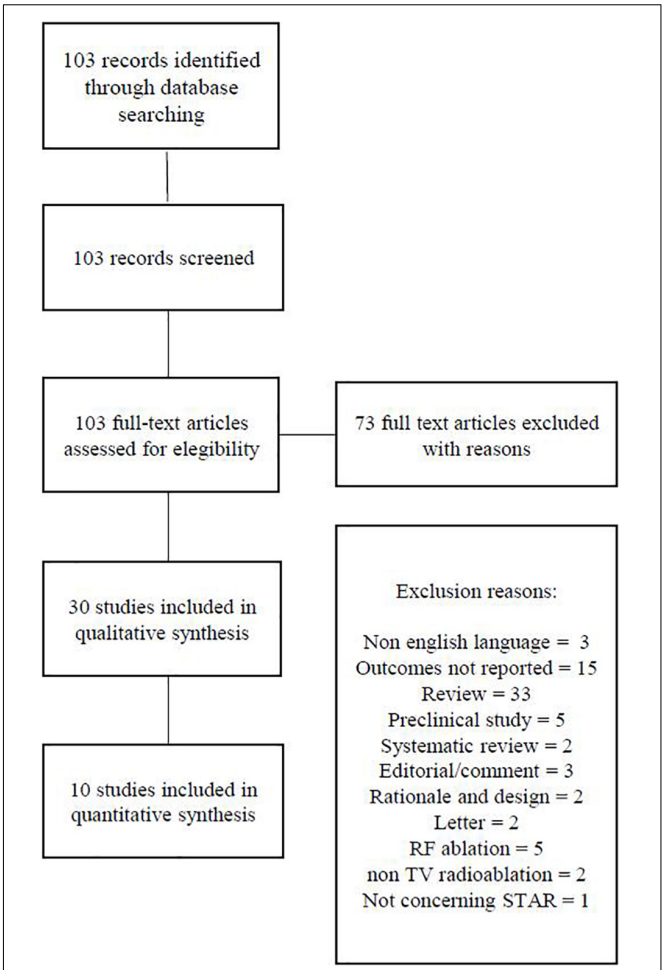

FIGURE 1 | PRISMA flow diagram.

RESULTS

Three retrospective case series (7–9), two retrospective (10, 11), and five prospective studies (12–16) were included in our systematic review. The baseline characteristics of the patients included in the analysis are reported in **Table 1**. Overall, a total of 80 patients were enrolled in 10 studies: the largest study included 19 patients and the smallest included 3 patients. Most of patients were male (86%), LVEF was <35% in most patients, and 58.7% of them had ischemic cardiomyopathy. 90% of patients were treated with a radiation dose of 25 Gy using the Cyberknife system in 18.7% of patients.

Outcomes

Most of the studies reported a blanking period ranging between 2 and 4 months to evaluate the effectiveness of the procedure, to allow time for the formation of fibrosis. However, in a case report by Jumeau et al. (17), STAR immediately controlled an ES in a patient sedated and intubated: this suggest that radioablation may also modulate the arrhythmogenicity of the myocardial substrate with immediate mechanisms, not involving the fibrous

TABLE 1 | Characteristics of the studies included in the analysis.

	Robinson et al.	Cuculich et al.	Gianni et al.	Neuwirth et al.	Lloyd et al.	Carbucicchio et al.	Lee et al.	Qian et al.	Chin et al	Yugo et al.
Study design	Prospective Single-center	Case series Single-center	Prospective 2-centers	Case series Single-center	Retrospective Single-center	Prospective Single-center	Prospective 3-center	Prospective Single-center	Retrospective Single-center	Case series Single-center
No patients	19	5	5	10	10	7	7	6	8	3
Male–no (%)	17 (89.5)	4 (80)	5 (100)	9 (90)	7 (70)	7 (100)	4 (57)	6 (100)	8 (100)	2 (69)
Age	66 (49–81)	66 (60–83)	62	66 (61–78)	61 (51–78)	70 ± 7	60–70s	72 (70–73)	75 ± 7.3	72 (65–83)
Ischemic cardiomyopathy–no (%)	11 (57.9)	2 (40)	4 (80)	8 (80)	4 (40)	3 (43)	5 (71.4)	6 (100)	4 (50)	0
Non-ischemic cardiomyopathy–no (%)	8 (42.1)	3 (60)	1 (20)	2 (20)	6 (60)	4 (57)	2 (28.6)	0	4 (50)	3 (100)
LVEF (%)	25 (15–58)	23 (15–37)	34	26.5 ± 3.2	/	27 ± 11	27	20 (16–25)	21 ± 7	20–59
NYHA cl. (%)					/					
I	5.3		20			29		\		69
II	21.1		80	60		71	42.8	\		33
III	52.6	20		40			42.8	\	62.5	
IV	21.1	80					14.3	\	37.5	
Radiation type	Linac	Linac	Cyberknife	Cyberknife	Linac	Linac	Linac	Linac	Linac	Linac
Dose (Gy)	25	25	25	25	25	25	25	25	22.2 ± 3.6	25
Treatment time (min)	15.3 (5.4–32.3)	14	82 (66–92)	68 (45–80)	/	31 ± 6	38	13.8 (11–15)	18.2 ± 6	/
Mean follow up	6 months	12 months	12 ± 2 months	28 (16–54) months	5.8 (3.9–9.3) months	4 pt complete 6 months FU	6 months	7.7 (7.06–10.37) months	7.8 (4.83–9.97) months	0.5–13.5 months
VT burden reduction	94%	99.9%	No reduction	87.6%	69%	93%	85%	31%	80%	61%
Complication relater to STAR	1 pericarditis 1 heart failure (possible)	1 stroke (non-clearly related)	None	1 nausea 1 progression of mitral regurgitation	2 pneumonitis	1 nausea/ vomiting 1 pulmonary fibrosis	None	1 pneumonitis 1 heart failure 1 moderate pericardial effusion	None	None

substitution of slow conducting myocyte bundles. Most patients had fewer ventricular arrhythmias and ICD shocks after the procedure, mostly after the first month.

The duration of follow-up in these studies ranged from 6 to 54 months. The most common primary outcome was the reduction of sustained VT burden and ICD therapies (ICD shocks and ATPs). In 6 studies, there was a significant reduction (>80%) of VT burden at follow-up. In other studies reduction of VT burden at follow up ranges between 30 and 70% (9, 10, 16), or there was no reduction in one case (13).

In the first 6–12 months after treatment, almost all patients experienced recurrences of VTs or ICD shocks. Robinson et al. reported a 94% reduction in VT burden in 19 patients treated with STAR, with 89% overall survival after at 6 months (12). Cuculich et al. performed STAR on 5 patients, with a 99.9% reduction in VT burden after the first 6 months of follow-up (7).

Adverse Effects

All the studies included reports of adverse events related to radiotherapy. Overall, two patients experienced episodes of nausea and vomiting due to the proximity of the target volume to the stomach; the symptoms were effectively managed with antiemetic therapy (13, 14). Three patients had pneumonia, and two patients developed pericarditis after radiotherapy. There was one case of progression of mitral regurgitation at the end of follow up. One patient experience stroke and two patients an episode of heart failure, but both of them were not clearly related to radiotherapy. No reductions in LVEF neither ICD malfunctions were reported. Carbucicchio et al. reported a case of paramediastinal fibrosis, which was not judged clinically relevant (14). The death of 28 (35%) patients at follow up were attributed to advanced heart failure, or non-cardiac cause rather than being directly related to radioablation treatment.

DISCUSSION

Stereotactic arrhythmia radioablation can be considered for patients with structural heart disease who have recurrent VT or electrical storm despite optimal antiarrhythmic drug therapy and prior CA, or in case of contraindications to CA, such as in case of aortic and mitral mechanical prosthetic valves (**Table 2**).

Recurrences after CA are frequent due to the possible evolution of the substrate over time and to the three-dimensional complexity of the arrhythmia circuitry, which often extends deep inside the myocardial wall and cannot by adequately ablated with neither an endocardial nor an epicardial approach (18). In these cases, novel approaches for intramural ablation, such as needle ablation and coil embolization, can be used (19–21). In addition, bipolar ablation, in which two catheters are positioned on opposite sides of the ventricular wall has also been reported to be successful (22). However, all these techniques are currently investigational, and carry theoretical risks of serious complications. Recently, a new kind of energy

TABLE 2 | Patients characteristic eligible to STAR and possible complications.

Patients characteristic	Complications
- Structural heart disease - Recurrent monomorphic ventricular tachycardia or electrical storm - Optimal antiarrhythmic therapy - Previous attempt of catheter ablation or contraindication	- Pneumonitis - Nausea/vomiting - Heart failure - Pericarditis/pericardial effusion - Stroke

called pulsed field ablation has been introduced: the ablation is non-thermally produced by creating nanoscale pores in cell membranes and has the advantage of being myocardium specific, thus minimizing collateral damage (23). Nonetheless, this energy source has not yet been tested in the ventricular myocardium in human subjects to date. It has to be mentioned that in patients who have both mechanical aortic and mitral prostheses, it is not possible to advance ablation catheters into the left ventricular endocardium with conventional routes: although there are few cases described with trans-right atrial access to the left ventricle (24), these patients are generally considered ineligible for endocardial left ventricular CA. The histological and clinical effects of ionizing radiation in tissues can appear in the weeks, months, or years after treatment (25). In the acute phase, the damage produced by oxygen free radicals causes cell necrosis with consequent tissue edema and triggering of inflammation mechanisms that eventually lead to the deposition of collagen and the formation of fibrous tissue over time. As for the treatment of cardiac arrhythmias, necrosis and consequent fibrosis may lead to the elimination of those areas of slowing of the electrical impulse propagation, which are the substrate of macroreentrant ventricular arrhythmias. Depending on the tissue involved and the replicative cellular activity, radiation energy may have different side effects (25). Clinically relevant effects of radiation on the heart involve coronary arteries, pericardium, conduction system, and valves. Radiation-induced coronary damage is characterized by sclerosis of the vascular wall, which can lead to myocardial infarction, often silent due to concomitant nerve damage. With regard to valve damage, cusps and leaflets undergo fibrotic degeneration and thickening, often associated to calcification. Pericardial damage may manifest as acute pericarditis and pericardial effusion, up to constrictive pericarditis when the resulting fibrosis impedes normal diastolic function. Although uncommon, alterations in cardiac conduction are may lead to symptomatic bradiarrhythmias and require pacemaker implantation (26). Therefore, it is clear that stereotactic radioablation carries a significant risk of clinically relevant collateral damage to the heart. The first stereotactic radioablation in humans was performed by Loo et al. for the treatment of a patient with malignant ventricular arrhythmias unresponsive to CA (27). Cuculich et al. reported the first case series comprising five patients with prior failed CA. The procedure was highly effective, with a 99.9% reduction of the burden of VT after the first 6 weeks after stereotactic radioablation (blanking period) as compared to baseline, and the risk of adverse events was low, with no complication during the index hospitalization and only one patient dying for stroke (7). Robinson et al. (12) published the largest cohort of patients treated with stereotactic arrhythmia radioablation (STAR). Nineteen patients were included in the study, two of whom with premature ventricular complexes-induced cardiomyopathy. The study showed a significant reduction in VT episodes and PVC burden, as well as a reduction of antiarrhythmic drugs (12).

Recent reviews (28, 29) showed that most of the patients treated with STAR had multiple recurrences of VT and one or more previous attempts of CA before treatment. As shown

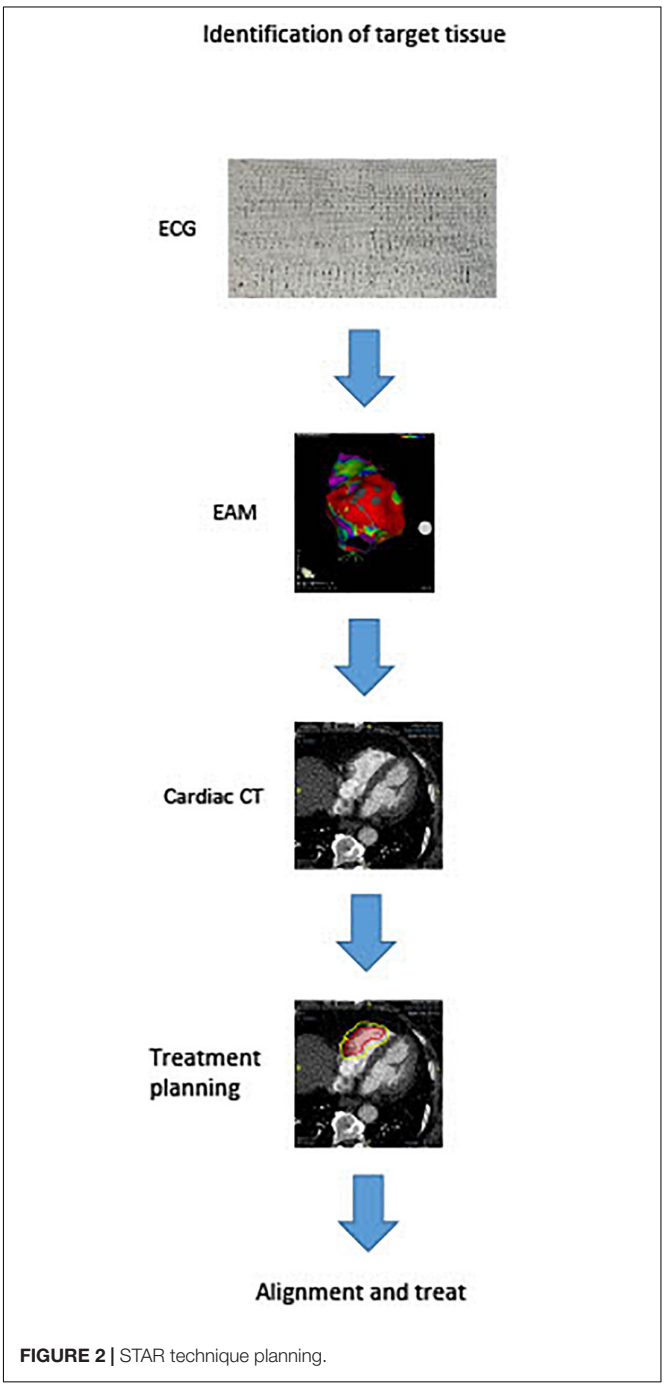

FIGURE 2 | STAR technique planning.

in **Table 1**, most of case series included patients with severe reduction of left ventricular ejection fraction and with III-IV NYHA class. Currently there is variability in patients with indication to STAR: Carbucicchio et al. in STRA-MI-VT study excluded patients in NYHA IV class, whereas Lloyd et al. in a recent case series included patients with advanced heart failure, three patients had left ventricular assist devices, and one patient had intra-aortic balloon pump support at the time of treatment (10, 14). This technique is therefore used as a last line of treatment for patients with malignant ventricular arrhythmias who do not respond to all other treatments as per current guidelines and recommendations (1, 29). Patients treated with STAR generally have advanced heart disease with a short life expectancy, in which STAR is usually considered on an individual case-by-case compassionate use basis (30, 31). Overall all studies have shown that STAR is a safe technique with low risk of serious complications in the short-to-midterm as shown in **Table 2**. However, it should be considered that the patients currently treated with this technique are heterogeneous due to structural heart disease and the localization of the fibrotic tissue on which the treatment is performed is variable. This could explain the variation in terms of clinical response to treatment that is observed in the various studies. Being a new and recently introduced technique, with the few data available it is not possible to correlate the variability of the clinical response to the type of structural heart disease of the patient or to the different myocardial localization of the scar. In term of safety, in the studies present in the literature there are data only in the short-to-midterm and the adverse events observed at follow up are not directly related to the treatment, considering that mainly patients with a short life expectancy being treated.

Procedural Technical Aspect

There are currently numerous non-invasive techniques for identifying scar areas from which ventricular tachycardias are arising. These include cardiac MRI and CT scan. Recently, Soto-Iglesias et al. (32) established the feasibility of VT CA guided by cardiac magnetic resonance (CMR), using pixel signal intensity (PSI) maps derived from late gadolinium enhancement (LGE) CMR sequences. This approach enables a totally non-invasive identification of the target area to be treated, and may soon enter the clinical arena for STAR planning. Actually studies report that the arrhythmogenic target for the ablation can be identified by substrate map using electroanatomic mapping to create a three-dimensional map in order to locate scar tissue and the target of the radioablation. After then the anatomical target for radioablation is defined with cardiac computed tomography (CT) as shown in **Figure 2**. Treatment radiation planning is then created upon this technical information. This anatomical portion of the heart is will be used to center the radiation dose just before treatment. Cooperation between different professionals for the treatment of VTs refractory to drug therapy and catheter ablation is key for STAR. Clinical indication is decided primarily by the cardiac electrophysiologist who identifies patients with structural cadiomiopathy and ventricular arrhythmias that could be eligible for treatment and performs an electroanatomical mapping. The radiologist with experience in cardiac imaging and the radiotherapist will subsequently evaluate the technical possibility of the STAR and its planning. Almost all studies used a single dose of 25 Gy for STAR and treatment time was variable, ranging from few minutes to thousand minutes. This range of treatment duration varies from different types of groups (8, 13, 14, 33). However, this dose was in some cases reduced, when the target volume was localized in the diaphragmatic face of the heart. In these cases, in which the region of interest was located in the inferior wall of the left ventricle, multiple doses with deep inspiration-breath hold to reduce radiation dose to the stomach can be effective (34).

CONCLUSION

Actually, there are few studies in literature, which included small patient populations. The treatment involves various professional figures (cardiologists, electrophysiologists, radiologists, and radiotherapists), and is not yet standardized, varying with the experience of the center. STAR currently appears to be effective in reducing the burden of ventricular arrhythmias and ICD treatments, with no serious adverse effects in the short-to-midterm directly related to STAR. However, more studies involving a larger sample population are necessary to improve the efficacy and safety of treatment. Longer follow up are also needed to assess the safety of the treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

GV, PC, and MC: conceptualization and resources. LCi, QP, YV, LCa, AG, AD, and MC: writing—review and editing. MC and AD: supervision and project administration. All authors contributed to writing—original draft preparation and read and agreed to the published version of the manuscript.

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A case report of long-term successful stereotactic arrhythmia radioablation in a cardiac contractility modulation device carrier with giant left atrium, including a detailed dosimetric analysis

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Introduction: Catheter ablation (CA) is the current standard of care for patients suffering drug-refractory monomorphic ventricular tachycardias (MMVTs). Yet, despite significant technological improvements, recurrences remain common, leading to increased morbidity and mortality. Stereotactic arrhythmia radioablation (STAR) is increasingly being adopted to overcome the limitations of conventional CA, but its safety and efficacy are still under evaluation.

Case presentation: We hereby present the case of a 73-year-old patient implanted with a mitral valve prosthesis, a cardiac resynchronization therapy-defibrillator, and a cardiac contractility modulation device, who was successfully treated with STAR for recurrent drug and CA-resistant MMVT in the setting of advanced heart failure and a giant left atrium. We report a 2-year follow-up and a detailed dosimetric analysis.

Conclusion: Our case report supports the early as well as the long-term efficacy of 25 Gy single-session STAR. Despite the concomitant severe heart failure, with an overall heart minus planned target volume mean dosage below 5 Gy, no major detrimental cardiac side effects were detected. To the best of our knowledge, our dosimetric analysis is the most accurate reported so far in the setting of STAR, particularly for what concerns cardiac substructures and coronary arteries. A shared dosimetric planning among centers performing STAR will be crucial in the next future to fully disclose its safety profile.

KEYWORDS

case report, stereotactic body radiation therapy, ventricular tachycardia, radiotherapy, cardiac contractility modulation

Introduction

Catheter ablation (CA) is the standard of care for patients suffering drug-refractory monomorphic ventricular tachycardias (MMVT) (1). However, despite significant technological advances, arrhythmic recurrences after CA remain common (2, 3). VT recurrences expose the patient to frequent readmission to intensive care units, psychological morbidity, progression of heart failure, and increased mortality (4).

New approaches have been proposed to improve the management of this highly challenging clinical condition, including neuromodulation and noninvasive VT treatment using radiotherapy (RT) (5–8). Stereotactic body radiation therapy (SBRT) applied to the heart, better known as STereotactic Arrhythmia Radioablation (STAR), is based on the precise delivery to a small volume of the heart of a single fraction of a high biologically effective dose of RT and has reported promising results (9, 10). STAR may overcome several limitations of conventional CA, which are strongly associated with VT recurrence, such as accessing regions of the heart chambers that cannot be reached with conventional CA (e.g., intramural scars or subepicardial locations). In addition, being noninvasive, STAR appears to be a safe alternative for most fragile patients (11).

As for conventionally fractionated RT, implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) carriers are eligible for STAR (12), although no firm conclusions can be currently drawn on the effects of thoracic stereotactic treatment on cardiac implantable electrical devices (CIEDs) patients, because of the lack of large prospective studies. A recent retrospective study (13) concluded that thoracic SBRT can be safely delivered when the dose to the CIED is kept below 2 Gy, the device is placed outside of the radiation beam, and the beam energy is $\leq$10 MV, irrespective of the pacing-dependency and of the CIED type (pacemaker or ICD). Therefore, by attending to these indications, CIEDs carriers can be eligible for STAR. No data, instead, are available on STAR in patients with cardiac contractility modulation (CCM), an emergent device for the management of patients with chronic heart failure and reduced ejection fraction (HFrEF) whose usage has become increasingly widespread in recent years (14). CCM aims at improving the strength of the cardiac contraction by generating relatively high-voltage ($\approx$7.5 V), long duration ($\approx$20 milliseconds), nonexcitatory biphasic electrical signals during the absolute myocardial refractory period. The system is constituted by one rechargeable implantable pulse generator and two active fixation leads secured to the right ventricular septum for sensing the ventricular activity and the bipolar delivery of the CCM pulses. The device has already been tested for potential interactions with ICD functioning (14).

We hereby present the case of a patient implanted with a CRT-D and a CCM device, treated with STAR for recurrent drug and transcatheter ablation resistant MMVT in the setting of advanced HFrEF and a giant left atrium, reporting 2-year follow-up and detailed dosimetric analysis.

Clinical report

This case report was prepared following the CARE Guidelines (15); the Timeline is summarized in Supplementary Figure 1.

In April 2019, a 72-year-old Caucasian man was admitted at the Emergency Department with an ongoing MMVT (right bundle block with positive precordial concordance and inferior axis) at 185 beats per minute (bpm). The VT had started after a painful dental surgery including topic administration of adrenaline. Past medical history included permanent atrial fibrillation (AF) since 1968, mitral valvuloplasty due to rheumatic stenosis in the same year, followed by biological first (1986) and then mechanical (1995) valve prosthesis insertion; in 1998, a single lead pacemaker was implanted due to symptomatic slow ventricular response AF. The last cardiac ultrasound (US) performed in March 2019 showed left ventricle (LV) enlargement (188 ml, 66 mm) with a moderately depressed (40%) left ventricular ejection fraction (LVEF), giant left atrium (left atrial volume index, LAVI, of 989 ml/mq), regular mitral valve prosthesis functioning and no signs of pulmonary hypertension (PH). Outpatient functional class was relatively good (New York Heart Association, NYHA Class II) despite the concomitant presence of a severe restrictive respiratory disease requiring nocturnal bilevel positive airway pressure (BiPAP) therapy. The patient also suffered from chronic kidney disease (CKD). The VT was interrupted by electrical cardioversion (ECV) after intravenous amiodarone failure; LVEF in sinus rhythm was 30%, with a mild right ventricle (RV) dysfunction, a moderate tricuspid regurgitation (TR), and a mild PH. Coronary artery disease was excluded through angiography. The patient was discharged after pharmacological HFrEF therapy optimization.

One month later, the same MMVT relapsed at 165 bpm and was treated with ECV. Due to the concomitant respiratory disease, endocardial CA was preferred over chronic amiodarone treatment to prevent recurrences. Electroanatomic (EAM) activation and substrate maps were acquired (CARTO3, Biosense Webster, Irvine, CA, USA) and merged with pre-procedural CT scan (Figure 1). Late and fragmented potentials during sinus rhythm and mesodiastolic potentials during the clinical VT consistently pointed to a relatively restricted area located at a basal inferolateral region of the LV, which was targeted for ablation, leading to acute VT interruption and noninducibility at the end of the procedure. Due to the high percentage of RV pacing and the reduced LVEF, the patient subsequently underwent CRT-D implantation.

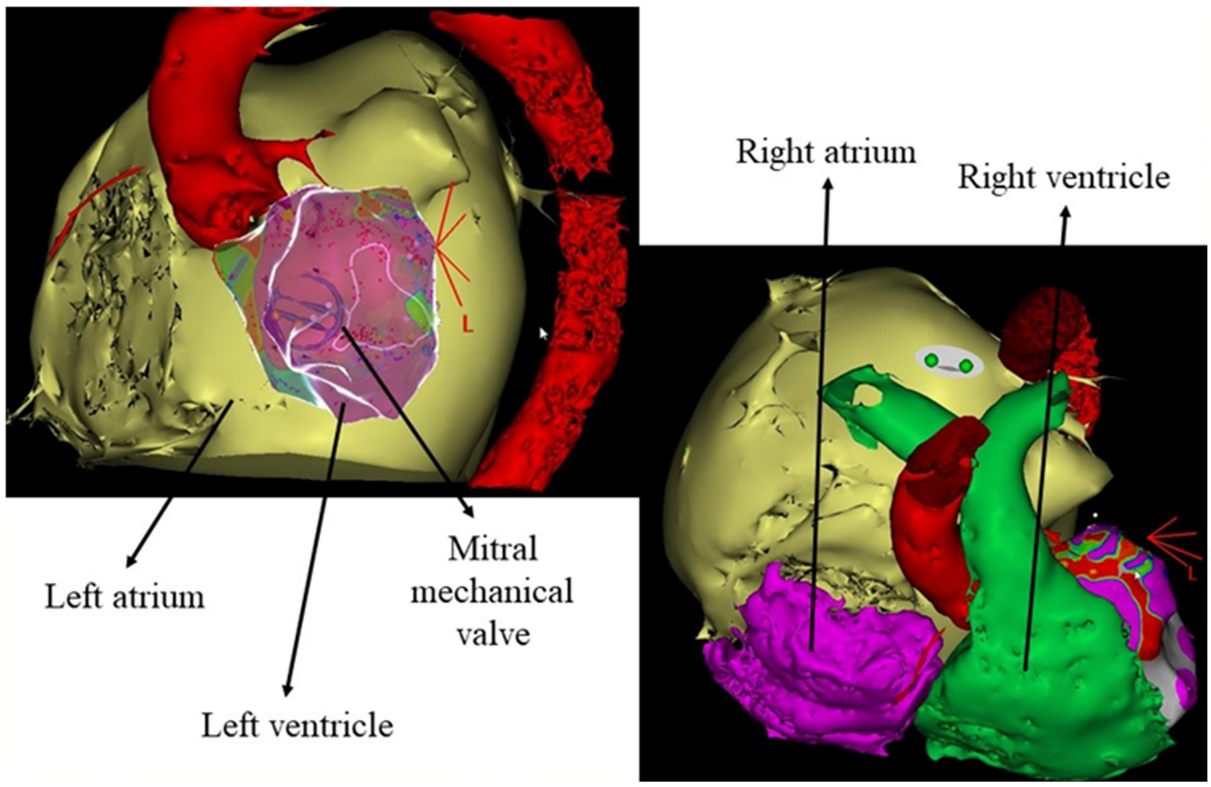

FIGURE 1
Anatomical details reconstructed from the preprocedural cardiac CT scan. Aorta in red, left atrium in yellow, right atrium in purple, and right ventricle in green.

In July 2019, the clinical MMVT recurred, albeit slower (155 bpm) and below ICD detection, and was acutely interrupted during amiodarone infusion after several unsuccessful attempts of overdrive pacing. Despite the challenge related to a retrograde (through the aorta) only approach and navigation of the ablation catheter in the proximity of the mechanical mitral prosthesis annulus, a second endocardial CA procedure was carried out. Activation mapping during the clinical VT confirmed exit from the same spot identified at the first procedure (Figure 2A), which also showed an excellent 97% morphological matching during pacemapping in the site of mesodiastolic potentials; therefore, consolidation of the previous lesions at this spot was performed. Additionally, in an attempt to reduce the risk of recurrences, a subsequent substrate mapping during RV stimulation was performed, which led to the extension of the ablation lesions in the surrounding basal inferolateral area of the LV (white outlined area of Figures 2A,B) and, to a much lesser extent, to the anterolateral mediobasal regions of the LV (not shown in Figure 2). Again, non-inducibility was achieved at the end of the procedure. LVEF at discharge was 35% on nadolol 40 mg/die. In the following months, he was admitted to the hospital several times due to acute HF decompensation; cardiac US showed severe RV dysfunction and severe functional TR (Carpentier 1), not amenable to percutaneous correction. Therefore, in December 2019, he underwent uncomplicated CCM implantation, obtaining a subsequent transient functional improvement from outpatient NYHA class III to IIb.

Unfortunately, in February and March 2020, a total of seven episodes of the clinical MMVT recurred, both as isolated episodes and in form of electrical storms, with a mean heart rate of 140–145 bpm. Antitachycardia pacing (ATP) was not always successful, leading to ICD shocks. The patient was back to NYHA class III. Prophylactic amiodarone (200 mg/die) was started. Last cardiac US showed advanced biventricular dysfunction: LVEF 32%, RV fractional area change (FAC) 29%.

Due to the ineffectiveness of the two previous endocardial CA, the challenging anatomy (giant left atrium and mechanical mitral prosthesis), and the contraindication in approaching the epicardial side of the target area (previous cardiothoracic surgeries) without a new thoracotomy in a very fragile patient, he was referred for STAR. The patient provided informed consent for a compassionate-use protocol for STAR.

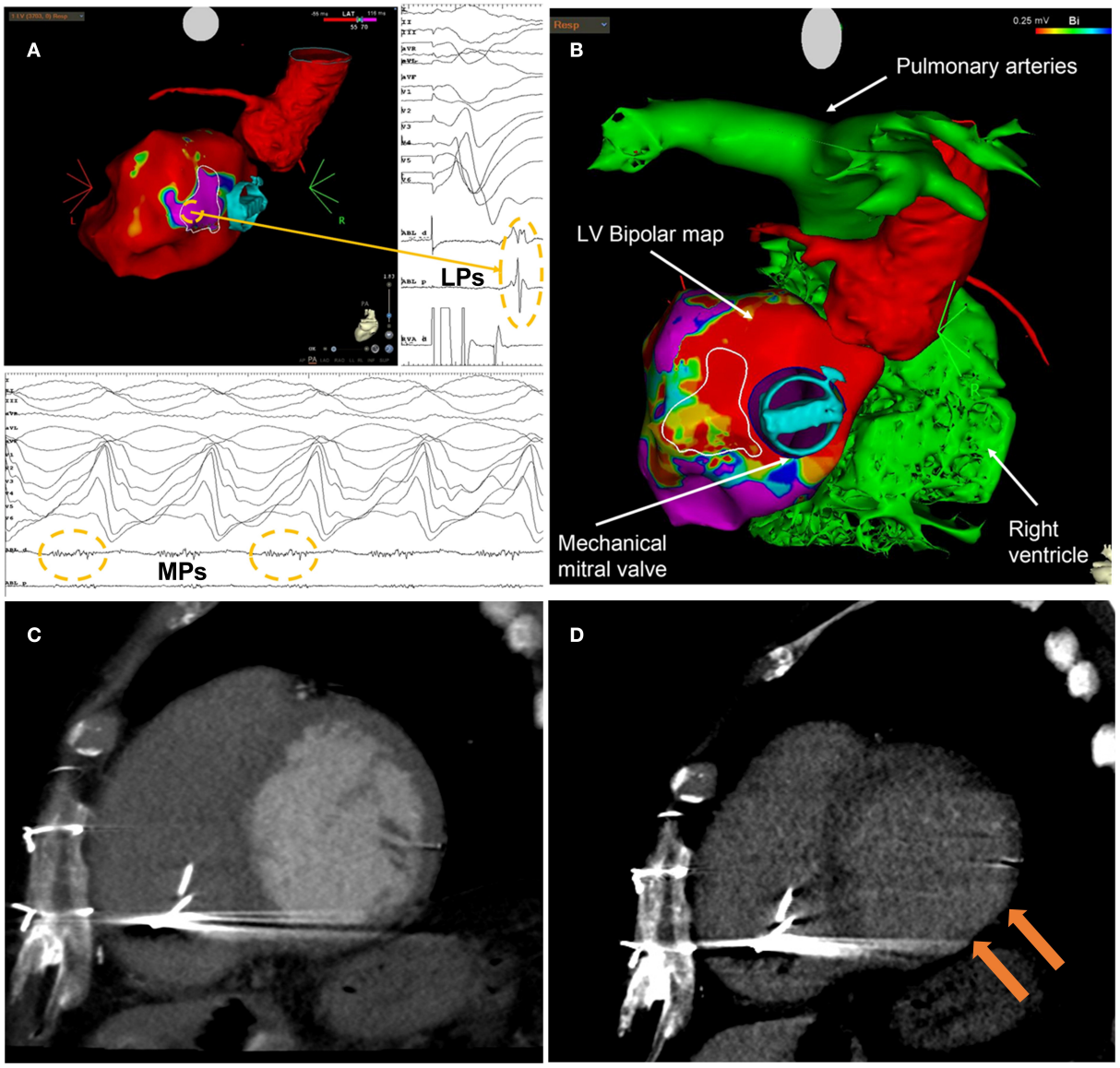

FIGURE 2
(A) Endocardial electroanatomic substrate map (CARTO3, Biosense Webster, Irvine, CA, USA) obtained from the second VT ablation procedure. The map highlights the area of late potentials (LPs) characterized by a local late activation time (LAT) after paced QRS end, located at the basal inferolateral segment of the left ventricle. Mesodiastolic potentials (MPs) recorded during the clinical VT were located at the same spot of the farthest LPs. **(B)** Integration of CT imaging with CARTO imaging data (bipolar voltage map). In both **(A,B)**, the white outlined area is the arrhythmogenic target for STAR identified at EAM mapping. **(C)** LV short axis view of cardiac CT angiographic phase with thinned basal inferolateral myocardium. **(D)** LV short axis view of late cardiac CT phase with hyperdensity on basal inferior-lateral wall that represents transmural fibrosis.

STAR planning and procedure

An ECG-gated contrast-enhanced (CE) cardiac CT including myocardial delayed enhancement (DE) assessment and a CT scan in a supine position, using a dedicated device for immobilization (frameless Bluebag® vacuum pillow), were obtained for planning purposes.

Cardiac CT was performed using a whole heart coverage (16 cm along with z-axis) CT scan (Revolution CT, GE Healthcare, Milwaukee, WI, USA) with the following parameters: slice configuration 256 × 0.625 mm, gantry rotation time 280 ms, and prospective electrocardiography (ECG) triggering. A new generation of iterative reconstruction was used for image reconstruction. The patient received a 1.5 ml/kg bolus of contrast medium (Visipaque 320 mg/ml,

GE Healthcare), divided into two separate boluses of 5 ml/s followed by saline infusion. A first CT scan was obtained at the angiographic phase to have an adequate coronary artery opacification. A second series was acquired 7 min after contrast agent injection for the detection of myocardial DE. Visual evaluation of DE was performed using a narrow window width and level (350 W and 150 L) and a thick average intensity projection (0.5–0.8 cm). The presence of DE was confirmed as hyperdense myocardium with signal intensity >2 standard deviations above remote myocardium. A thinned basal inferolateral myocardium with transmural DE was identified (Figures 2C,D).

Free-breathing four-dimensional CT simulation (4D CT) allowed an assessment of the total cardiac and pulmonary motion. Ten CT phases distributed equally over the different phases of the breathing cycle were reconstructed for the 4D-CT data set. CE cardiac CT images were co-registered with those acquired during the simulation phase.

Definition of the gross tumor volume (GTV) was based on the combination of structural data from CE cardiac CT (wall thickness and DE) and EAM mapping data. Specifically, EAM mapping data from the two previous invasive endocardial CA procedures were combined to build a GTV for cardiac STAR that included the areas of previous ablations and the full myocardial thickness of the associated ventricular scar. Accordingly, the target volume was in the basal inferolateral region of the LV (white outlined area in Figures 2A,B). The contoured volume was strictly limited to regions of abnormal myocardium, either from a structural or an electrical point of view.

The GTV was defined using anatomical reference points such as the mitral valve and the interventricular septum. The LV was divided into basal, mid-cavity, and apex thirds by means of two plans parallel to the plane passing through the mitral valve. A further plan divided the basal third into two equal parts. Seven segments of the LV were identified: basal septal, basal lateral, mid septal, mid-lateral, apical septal, apical lateral, and apex. Additional plans perpendicular to the previous ones were placed to obtain a useful template with more reference points to guide the contouring of the target volume. The 3D reconstruction of the LV and of the contoured GTV, also including the ascending aorta and the prosthetic mitral valve, is shown in Supplementary Figure 2; the figure underlines the relationship between the GTV and the mitral valve. Once the GTV was contoured on a single series (CT 0%) of the 4D-CT, it was then moved to the other series and then adapted based on the LV displacement related to respiratory motion. All GTVs, contoured on the ten scans of the 4D-CT, were then moved to the average scan and summed altogether to generate an internal target volume (ITV) to compensate for the respiratory motion-related displacements of the target. An isotropic margin of 5 mm was added to the ITV to generate the planning target volume (PTV). The volume of GTV, ITV, and PTV were 26, 32, and 89 cc, respectively. With the aid of dedicated atlases (16–18), all organs at risk (OAR) including cardiac substructures were outlined on the average scan to estimate the average and the maximum cumulative radiation dose (Table 1). The enlarged left atrium with its 2,667 cc was contoured first. The co-registration between simulation CT and CE cardiac CT scans was used to contour all coronary arteries. A 3-to-5 mm expansion margin (PRV) was added to each coronary artery (CA-related PRVs) to cover the displacement due to cardiac motion and compensate for their motion, as previously reported (18, 19). Due to its proximity to the GTV, the mechanical mitral valve prosthesis was used as a landmark to identify the target volume and to measure the distance of the surrounding structures.

The prescription dose was 25 Gy in a single fraction. Ninety-five percent of the PTV was encompassed by the 80% prescription isodose. STAR was planned and then delivered with a volumetric modulated arc therapy (VMAT) solution. Ray Station software was used for treatment planning and the Monte Carlo algorithm for dose calculation. Two full arcs were delivered with flattening filter-free beams of 6 MV photons on an Elekta Versa Linear Accelerator (Elekta, Stockholm, Sweden). Figure 3 illustrates the dose distribution achieved with the VMAT plan. Notably, the average dose to the whole heart minus the PTV was well below the conventional 5 Gy safety threshold. Yet, due to the location of the target, the maximum and average dose to the circumflex artery were 32.5 and 18.67 Gy, respectively. The dose constraints of cardiac devices (12, 20) and all organs at risk (Table 1) were respected according to the latest recommendations for lung SBRT (21). Specific dosimetric constraints for CCM in patients undergoing SBRT are nonavailable yet; we thought reasonable using those recommended for pacemakers and ICDs.

Before treatment, image guidance using cone-beam CT (CBCT) was used to localize the target (22, 23). During RT treatment, audio-visual monitoring of the patient allowed intervention in case of necessity. Additionally, an emergency kit with an external defibrillator was available, and the treating cardiologists attended the treatment outside the linear accelerator (LINAC) room. Radiation delivery time was ∼6 min. CRT-D and CCM devices were checked before and after irradiation.

Clinical response and follow-up

STAR therapy was delivered in May 2020. The procedure was well-tolerated without sedation or anesthesia, and no acute complications occurred. The patient was discharged 3 days after, in stable conditions (NYHA class III).

After STAR, the patient was clinically evaluated at 1 month, and then every 3–4 months for the following 2 years. No more

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TABLE 1 Dosimetric parameters for organs at risk (OARs).

	Dmax (Gy)	Average (Gy)	$D_{2\%}$	$D_{50\%}$
Heart	29.21	3.15	24.00	1.35
Heart—PTV	19.77	2.69	15.53	1.30
Left ventricle	32.37	8.83	31.88	5.50
Right ventricle	5.98	1.56	5.57	0.68
Left atrium	16.78	2.41	13.05	1.25
Right atrium	2.92	1.06	2.70	1.01
Septum—Left ventricle	9.09	2.71	8.49	2.20
Free wall—Left ventricle	32.99	18.49	32.80	19.75
Aortic valve	0.83	0.47	0.79	0.44
Pulmonic valve	0.39	0.26	0.38	0.25
Mitral valve	27.69	13.23	27.10	11.90
Tricuspid valve	4.32	1.56	4.07	1.32
LMT	0.47	0.41	0.47	0.41
LAD	9.31	2.78	9.12	0.90
CFLX	32.50	18.67	32.43	29.34
RCA	1.28	0.34	1.16	0.28
Aorta arch	0.09	0.05	0.09	0.05
Aorta ascendent	0.36	0.16	0.34	0.15
Aorta descendent	2.96	0.62	2.82	0.22
Superior vena cava	0.23	0.19	0.22	0.18
Chest wall	13.71	2.60	12.87	0.67
Lungs	19.66	1.48	16.01	0.16
Left lung	23.54	2.40	19.43	0.24
Right lung	2.69	0.47	2.49	0.10
Trachea bronchus	0.37	0.08	0.35	0.03
Esophagus	5.86	1.49	5.65	0.48
ICD	0.04	0.02	0.03	0.02
CCM	0.01	0	0.01	0.00
Spinal cord	1.11	0.25	1.08	0.02

CCM, Cardiac contractility modulation; CFLX, Circumflex Coronary; D2%, dose received by 2% of the volume; D50%, dose received by 50% of the volume; Dmax, maximum RT dose; ICD, Implantable Cardioverter-Defibrillator; LAD, Left Anterior Descending Coronary; LMT, Left Main Trunk; PTV, planned target volume; RCA, Right Coronary Artery.

sustained, treated, or even not sustained ventricular arrhythmia episodes were documented with unchanged antitachycardia ICD programming as compared to before STAR. In September 2020, he was hospitalized for a few days due to acute decompensated HF and treated with diuretics, vasodilators, and levosimendan. At cardiac US, LVEF was stable (30%), but a mild further reduction in the already compromised RV function was noted (FAC 20 vs. 29%), accompanied by moderate PH (PAPs 40–45 mmHg compared to 20 mmHg). Nadolol was decreased from 40 to 20 mg/die and amiodarone from 1,400 to 1,200 mg/week. Also, CCM daily stimulation hours were increased from 9 to 14. A further amiodarone dose reduction has not been attempted yet due to the very fragile condition of the patient as well as the presence of polymorphic premature ventricular beats leading to a suboptimal (but stable on amiodarone) biventricular pacing percentage (94–95%) and potential CCM sub efficacy without amiodarone. No further HF decompensation episodes requiring hospitalization occurred thereafter. Cardiac US performed 23 months after STAR confirmed advanced but stable biventricular dysfunction (LVEF 28%, RV FAC 23%) with regular mitral valve prosthesis functioning, severe TR, and mild PH (PAPs 36 mmHg). No signs of leads or devices interference/damage/malfunction, as well as no clinical or radiological signs of late radiation-related complications, were observed (the patient underwent a chest CT scan in May 2022).

Discussion

Our case report shows a complete and long-term VT suppression induced by STAR, applied on a compassionate use

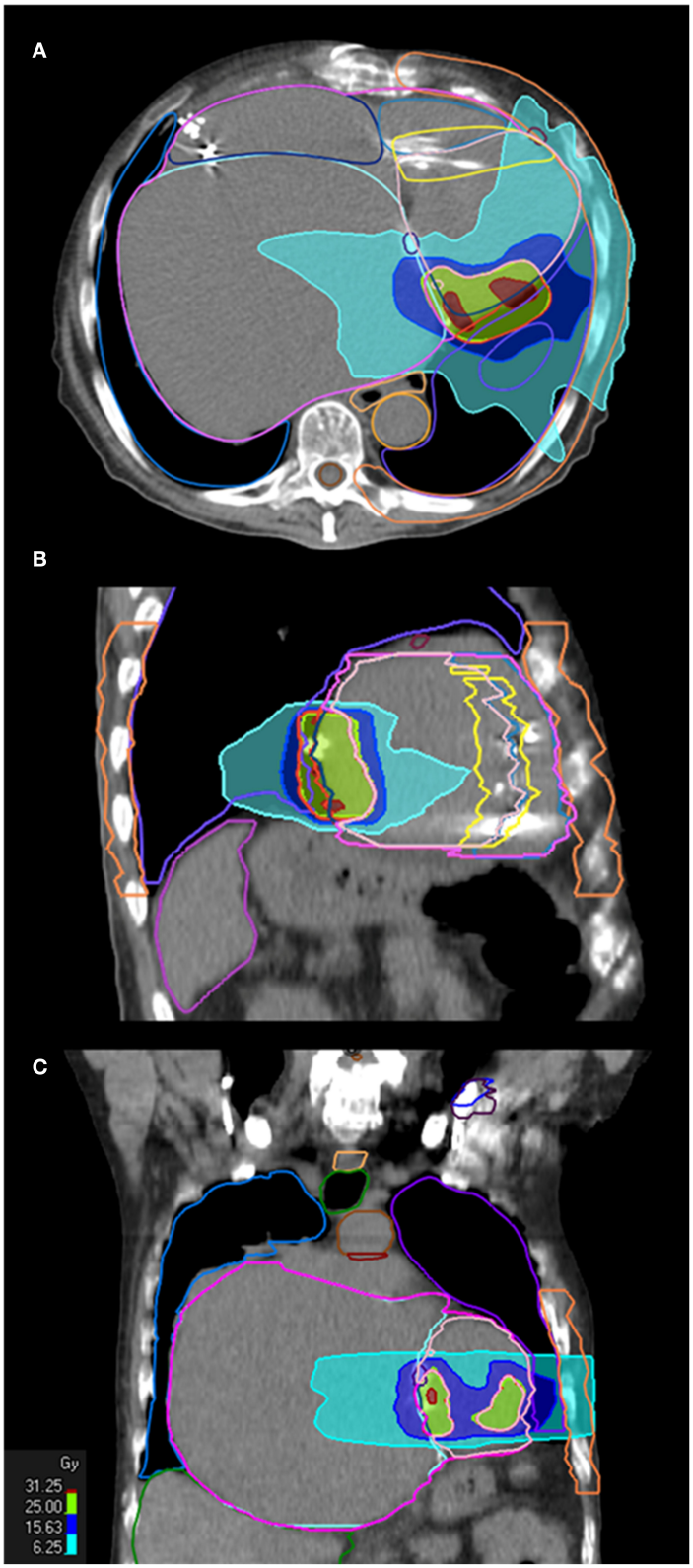

FIGURE 3
STAR treatment plan. Treatment plan in axial **(A)**, sagittal **(B)**, and coronal **(C)** orientation are shown, with dose volume histogram (25 Gy is prescribed on 80% isodose).

basis, in a very fragile patient with advanced HFrEF, giant left atrium, and a challenging VT substrate, implanted with a CRT-D and a CCM device, with no major safety concern. At the time we planned and performed the procedure, only a very small number of patients had been treated with STAR under experimental/compassionate protocols (24), with promising results but still several unsolved methodological and clinical issues. At present, only a minimum set of recommendations based on experts' opinion has been provided, which covers STAR indications and contraindications and monitoring during and after the procedure (25). Yet, optimizing the accuracy of each step from target definition to PTV generation, despite still far from being standardized, is critical to optimize treatment efficacy and safety. Accordingly, when looking at the largest case series of STAR published so far, most of the serious adverse events were clustered among the US-treated patients (9, 10, 26), who underwent STAR treatment on a significantly larger PTV [median PTV 98.9 cc, range, 60.9–298.8 for the 19 patients in the ENCORE-VT trial (10, 26)] than their European counterparts (27, 28) [mean PTV 34 ± 17 cc, range 12.8–62.1 cc, for the 18 patients described by Cvek et al. (28)].

Advanced arrhythmia source mapping for STAR has been performed based upon the results of invasive EAM mapping, electrocardiographic imaging (ECGi) with different systems (9, 26, 29–31), or even computational ECG mapping algorithms based on vectorcardiographic data analysis (32); to identify the GTV, electroanatomical data were then combined with anatomical and/or viability data obtained using different imaging techniques such as cardiac magnetic resonance imaging (9, 10, 33, 34), cardiac single-photon emission CT (9, 10), or CE cardiac CT (27, 30, 31, 33–35). Recent data suggest that enlarging the GTV to the entire potential arrhythmogenic substrates as identified by EAM substrate mapping may not provide further benefits compared to only targeting the critical isthmus of the clinical VT, while increasing side effects (36).

Concerning GTV contouring, manual transfer of the target volume to the RT treatment planning system by visual matching, as we did for our patient, is still the most used method. Yet, the use of a combination of manual transport and software-aided data review tools including semi-automated angulation and segmentation of the heart (37), or of in-house or open-source 3D data matching software (38) only, yield great potential for improvement.

Concerning the optimal compensation for cardiorespiratory movements of the thoracic targets and the reduction of the uncertainties related to patients' positioning, different methods have been proposed, including indirect cardiorespiratory tracking using fiducial markers such as the ICD lead (27, 28), optical surface monitoring system for continuous intrafraction positioning tracking (39), respiratory gating (29, 32) and even MRI-based cardiac gating (40). Considering the small number of patients treated with STAR and the heterogeneity of the local delivery platform and facilities, the benefit and the feasibility of each method are under evaluation. The last frontier in the real-time monitoring of cardiac motion during STAR is represented by an automatic cardiac US image acquisition system associated with an artificial intelligence algorithm (41).

The choice of the dose (25 Gy) was based on the preclinical and clinical data available at the time (24), suggesting a significant potential for myocardial fibrosis starting from 25 Gy and requiring at least 2–3 months to start to develop, with an acceptable safety profile. Notably, recent preclinical data (42) suggest an additional anti-arrhythmic mechanism for RT doses between 15 and 25 Gy, represented by electrical reprogramming leading to an increased conduction velocity, mostly due to an increased expression of NaV1.5 channels and the gap-junctional protein Cx43. This functional effect was observed in animals early after a single RT treatment, but there are no data concerning its long-term durability in the control of ventricular arrhythmias. Accordingly, in several cases (24, 29, 34, 35) including the present one, the anti-arrhythmic effects of STAR were observed immediately after the procedure, with no blanking period. Our dosimetric analysis is the most accurate reported in the setting of STAR, particularly for what concerns cardiac substructures and coronary arteries (18, 19). Notably, the 2010 Task Group report on dose constraints for SBRT treatments (43) does not contain any limitation for cardiac substructure, due to the lack of significant correlations to treatment-related side effects in the available literature. For some of these substructures (not including cardiac valves), the ongoing RAVENTA trial (44), a clinical trial for STAR treatments, suggests specific dose limits, in particular a maximum dosage to the left arteries of 20 Gy, that was not attended in our patient. All the other suggested constraints were respected. A detailed and shared dosimetric planning among centers performing cardiac SBRT will be crucial in the next future to fully disclose its safety profile.

In conclusion, our case report supports the early as well as long-term efficacy of 25 Gy single-session STAR. Despite the concomitant severe HFrEF, with an overall heart-PTV mean dosage below 5 Gy, no major detrimental cardiac effect within 2 years was registered. Yet, it must be acknowledged that basal, perivalvular targets irradiation may lead to late native valve toxicity or coronary damage. In addition, despite encouraging preliminary results of STAR, a significant number of treated patients all over the world were reported to suffer VT recurrences. Whether this is due to inaccurate VT substrate delineation (incorrect target), inaccurate transfer to the treatment planning system or inaccurate or insufficient radiation delivery remains to be elucidated. Translational research, prospective clinical trials, and International consortiums such as the ongoing STOPSTORM,[1] founded by a Horizon 2020 grant,

1 https://www.stopstorm.eu/

will be crucial in the next future to fully unravel the dose–response issue of cardiac SBRT and to standardize treatment planning and delivery as well as patient's selection and data collection, to fill the actual gaps in knowledge and optimize the efficacy and safety of the procedure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the participant/s for the publication of this case report. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML, VD, MM, MC, EG, AD, FF, GD, UR, and MA contributed in different ways to patient's management, STAR planning and/or delivery. ML, VD, and MM wrote the first draft of this manuscript. All authors discussed the results, contributed to improved draft versions, and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.934686/full#supplementary-material

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Ventricular tachycardia ablation through radiation therapy (VT-ART) consortium: Concept description of an observational multicentric trial *via* matched pair analysis

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Introduction: Monomorphic ventricular tachycardia (VT) is a life-threatening condition often observed in patients with structural heart disease. Ventricular tachycardia ablation through radiation therapy (VT-ART) for sustained monomorphic ventricular tachycardia seems promising, effective, and safe. VT-ART delivers focused, high-dose radiation, usually in a single fraction of 25 Gy, allowing ablation of VT by inducing myocardial scars. The procedure is fully non-invasive; therefore, it can be easily performed in patients with contraindications to invasive ablation procedures. Definitive data are lacking, and no direct comparison with standard procedures is available.

Discussion: The aim of this multicenter observational study is to evaluate the efficacy and safety of VT-ART, comparing the clinical outcome of patients undergone to VT-ART to patients not having received such a procedure. The two groups will not be collected by direct, prospective accrual to avoid randomization among the innovative and traditional arm: A retrospective selection through matched pair analysis will collect patients presenting features similar to the ones undergone VT-ART within the consortium (in each center independently). Our trial will enroll patients with optimized medical therapy in whom endocardial and/or epicardial radiofrequency ablation (RFA), the gold standard for VT ablation, is either unfeasible or fails to control VT recurrence. Our primary outcome is investigating the difference in overall cardiovascular survival among the group undergoing VT-ART and the one not exposed to the innovative procedure. The secondary outcome is evaluating the difference in ventricular event-free survival after the last procedure (i.e., last RFA vs. VT-ART) between the two groups. An additional secondary aim is to

evaluate the reduction in the number of VT episodes comparing the 3 months before the procedure to the ones recorded at 6 months (from the 4th to 6th month) following VT-ART and RFA, respectively. Other secondary objectives include identifying the benefits of VT-ART on cardiac function, as evaluated through an electrocardiogram, echocardiographic, biochemical variables, and on patient quality of life. We calculated the sample size (in a 2:1 ratio) upon enrolling 149 patients: 100 in the non-exposed control group and 49 in the VT-ART group. Progressively, on a multicentric basis supervised by the promoting center in the VT-ART consortium, for each VT-ART patient enrollment, a matched pair patient profile according to the predefined features will be shared with the consortium to enroll a patient that has not undergone VT-ART.

Conclusion: Our trial will provide insight into the efficacy and safety of VT-ART through a matched pair analysis, *via* an observational, multicentric study of two groups of patients with or without VT-ART in the multicentric consortium (with subgroup stratification into dynamic cohorts).

KEYWORDS

radiotherapy, ventricular tachycardia, stereotactic arrhythmia radioablation (STAR), stereotactic body radiation therapy (SBRT), radioablation, clinical trial, matched pair analysis

Background

Monomorphic ventricular tachycardia (VT) is a life-threatening condition often observed in patients with structural heart disease. Recurrence poses a serious threat to both patient survival and quality of life (QoL). The most common cause of recurrent monomorphic VT is the presence of an ischemic scar that induces arrhythmias through re-entry mechanisms. Endocardial and/or epicardial radiofrequency ablation (RFA) represents the gold standard for VT ablation, along with medical therapy.

Stereotactic arrhythmia radioablation (STAR) uses stereotactic body radiation therapy (SBRT) for the ablation of cardiac arrhythmias, which is technically related to any arrhythmia. The present study focuses on ventricular tachycardia ablation through radiation therapy (VT-ART), applying STAR particularly focused on sustained monomorphic ventricular tachycardia.

Stereotactic body radiation therapy using VT-ART delivers focused high-dose radiation in a single fraction of 25 Gy, allowing the ablation of VT by inducing myocardial scars. The procedure is fully non-invasive; therefore, it can be easily performed in patients with contraindications to invasive ablation procedures.

Owing to the highly experimental profile of an innovative procedure such as VT-ART, too little is known to draw definitive conclusions about its efficacy, safety, and long-term results.

Aims

Our trial aims to assess the benefits of VT-ART for the ablation of VT in patients with optimized medical therapy in whom traditional techniques, namely, RFA, have either failed to control VT recurrence or cannot be performed.

The importance of our trial relies on the identification of new management options for patients who have not responded to traditional ablation techniques or have contraindications to invasive procedures. The efficacy of VT-ART will be indirectly compared through matched pair analysis with a population of patients not treated with VT-ART, thus avoiding setting a randomized controlled trial that is considerable technically demanding and possibly premature in this research field.

Protocol overview

With current knowledge, it is difficult to set a randomized trial between a population undergoing VT-ART (e.g., in the compassionate setting often applied for patients proposed for such an innovative procedure) and a population not undergone to that. Randomizing a patient's accrual to VT-ART instead of the conventional option implies that some patients would skip a conventional procedure in favor of a procedure still considerate at least still non-standard, although promising. Multiple, reliable phase I and phase II trials are not available, although case series and at least one phase I/II trial have investigated VT-ART efficacy (1).

Finally, it would be difficult to define two balanced treatment arms that are suitable for a clinical randomized comparison, since patients undergoing VT-ART would have either already received RFA or are unable to receive it, and they have already undergone other standard treatments. On the other hand, setting a single-arm trial would test less efficiently the clinical of VT-ART and could imply the adoption of VT-ART only for worse clinical case presentations.

This multicenter observational study will evaluate the efficacy and safety of VT-ART. Our trial will enroll patients with optimized medical therapy, in whom endocardial and/or epicardial RFA is either unfeasible or fails to control VT recurrence. The trial is

set as observational since it indirectly comparing VT-ART with a conventional procedure (i.e., RFA).

Each patient recruited for VT-ART will be profiled according to a predefined list of characteristics that will be circulated within the centers participating to the consortium to collect other patients with a similar profile, not having undergone VT-ART, for final analysis.

The peculiar setting of our trial will avoid precluding VT-ART to patients possibly taking advantage of such a therapeutic option; moreover, it will compare VT-ART with retrospective series not having receive VT-ART anyway. Furthermore, this approach will retrieve otherwise sporadic data about single or limiter case series of each center joining the consortium. This trial is not strictly investigational but can add notable scientific information to the current scenario.

The multicenter setting of this study will allow for faster recruitment of the sample size.

Multicenter recruitment will allow for a more precise assessment of the effects of VT-ART, with the aim of demonstrating that implementing such a procedure is both feasible and safe among centers. Moreover, it will increase the chances to recruit patients with profiles matching the ones in the arm undergone VT-ART.

A standardized data collection has been defined for data regarding both VT-ART and RFA.

The trial will thus both collect prospective and retrospective data about VT-ART (following the predefined standardized data collection). Prospective data collection will be applied within the consortium for the patients referred to VT-ART after the beginning of the trial; retrospective data collection will be allowed for the VT-ART procedure delivered before the formal start of the trial if the data required by the predefined standardized data collection are available for defining the primary and secondary endpoint (see following sections). Similarly, prospective and retrospective data collection will be allowed for data about conventional treatment (i.e., RFA).

Populations

Our aim is to enroll patients with structural heart disease, in whom the presence of a myocardial scar induces refractory monomorphic VT or ventricular fibrillation (VF), as documented by either implantable cardioverter defibrillator (ICD) appropriate shocks or anti-tachycardia pacing (ATP) at ICD interrogation. We will enroll patients with recurrent VT/VF episodes despite optimal medical therapy (i.e., class III antiarrhythmic drugs) and at least one previous attempt of RFA or patients in whom ablation is not feasible, because of contraindications to the procedure or of patient intolerance. Previous percutaneous stellate ganglion blockade is neither a requirement for inclusion criteria nor exclusive criteria that will be collected in the standardized data collection for potential subgroup analysis.

Eligibility criteria are summarized in **Table 1**.

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	1. Patients with structural heart disease and monomorphic VT refractory to optimal medical therapy and previous RFA attempts (minimum of one attempt RFA)
	2. Patients with contraindications to conventional ablation or not suitable for any non-interventional approach, refusing any surgical ablative attempt; or patients who have already undergone RFA with arrhythmogenic focus refractory to previous ablation procedures
	3. Age >18 years
	4. Candidates not suitable for heart transplantation
	5. LVEF >20%
	6. ICD implant
	7. Signed informed consent
	8. Life expectation >1 year in absence of VT
Exclusion criteria	9. ICD interrogation demonstrating polymorphic VT
	10. Patients with INTERMACS class >4
	11. Patients with LVADs
	12. Patients with ongoing neoplastic disease
	13. Previous thoracic RT with cardiac involvement
	14. Active myocardial ischemia
	15. Cardiac revascularization <120 days
	16. NYHA IV
	17. Pregnant women

Methods/design

Our trial will investigate the effects of administering a single fraction of external beam radiation delivered through SBRT techniques at a dose of 25 Gy on patients with recurrent episodes of VT and in whom optimal medical therapy and previous RFA attempts have failed to provide benefit from VT burden control. We will perform matched pair analysis with dynamic cohorts. We will compare two groups of patients: One that has been treated by all the standard approaches but has not undergone VT-ART and a second group that has also received VT-ART. The entire enrolled group (by multicentric recruitment) will be stratified according to some predefined characteristics and analyzed by matched pair analysis, based on the characteristics of patients treated with VT-ART. Once a patient is enrolled to undergo VT-ART within the multicentric consortium, the search for two patients with similar feature profiles not undergoing VT-ART will be shared.

Matching factors taken into account are summarized in **Table 2**.

Figure 1 depicts the design of the VT-ART study.

Radiotherapy

Ventricular tachycardia ablation through radiation therapy will be administered through image-guided radiotherapy (IGRT) by a linear accelerator (Linac) (e.g., TrueBeam–Varian Medical Systems, Palo Alto, CA), an SBRT-dedicated Linac, including a dedicated Linac with gating delivery (e.g., TrueBeam Edge Linac, Varian Medical Systems, Palo Alto, CA) with 6 MV flattening filter-free photons and dose calculation algorithm Acuros (Eclipse Version 15.6.04 Varian Medical Systems, Palo Alto, CA), or a MR-guided Linac (i.e., ViewRay MRIdian). Selection of a specific Linac type for each patient will be addressed based on the best personalization achievable, after

TABLE 2 Applied matching factors.

Parameter type	Subgroup options
Etiology of cardiomyopathy*	ICM
	NICM
	ACM
Age*	
Gender*	
BMI	
LVEF*	
NYHA group*	
Ventricular arrhythmia presentations*	Sustained ventricular tachycardia incessant sustained ventricular tachycardia electrical storm
Arrhythmogenic focus anatomical intracardiac location	Based on VE exit by ECG and by the activation map of VT
Diagnostic tools used for scar definition	CT
	MR
	EAM
	ECG
TA volume*	Endocardial electroanatomic substrate mapping area/volume in all cases; epicardial mapping area/volume in the case of 3D epicardial electroanatomic substrate mapping
Heart volume	cc range
Heart-to-TA volume	cc range
Previous use of amiodaron	Y/N
Number of previous RFA attempts*	
Type of previous RFA attempts	endocardial
	epicardial
Unfeasibility to repeat RFA	Y/N
Local recurrence of TA (same area of last RFA)	Y/N
Previous percutaneous stellate ganglion blockade	Y/N

TA, target area by electroanatomical mapping; BMI, body mass index; RFA, radiofrequency ablation; LVEF, left ventricle ejecting fraction; *mandatory matching factor.

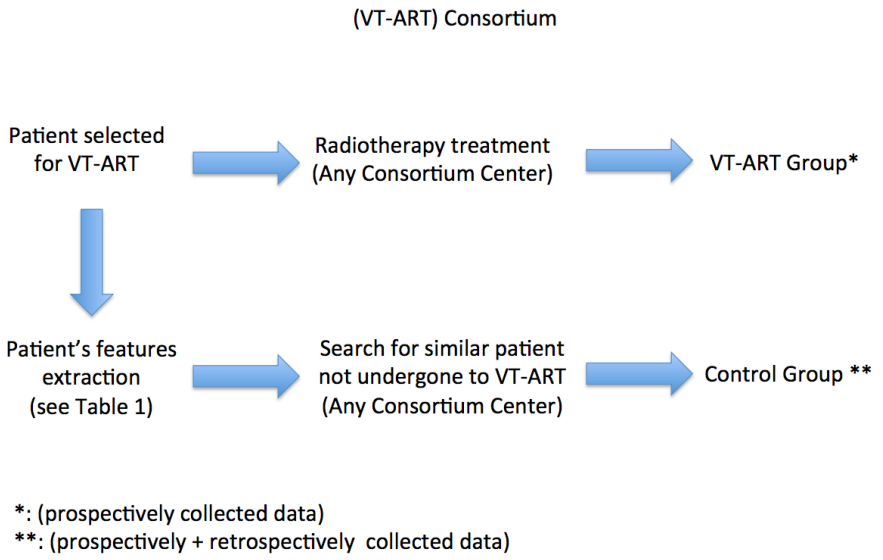

FIGURE 1
Overview of the VT-ART study.

a multidisciplinary discussion of the patient-specific clinical background, needs, compliance, and technical possibilities. The target area (TA), in terms of the clinical target volume (CTV), set-up margin (SM), and internal target volume (ITV), will be determined for each patient on a 3D computer tomography reconstruction based on CT scan or MRI (not performed if the patient has no MRI-conditional ICD), 12-lead ECG data, and electroanatomical mapping (EAM).

Three-dimensional EAM will be performed by three different systems on the basis of availability of the three workstations [Carto 3 system, Biosense Webster Inc. (Diamond Bar, CA, USA), Ensite Precision Cardiac Mapping Navx, Abbott (North Plymouth, MN, USA), and RHYTHMIA HDx^{TM} Mapping System, Boston Scientific, Copyright IBM Corporation (Marlborough, MA, USA)]. Electrical information from the EAM and information from imaging will be combined to build a volumetric target for VT-ART (2).

Electroanatomical mapping data will be fused with CT-reconstructed 3D models applying the previously described approach for non-invasive EAM, through a series of electrode strips (worn by the patient) containing 256 electrodes (BioSemi, Netherlands), with small radiopaque markers attached at the location of the electrodes, to assist with visualization on cardiac imaging. A gated chest CT scan with 3 mm axial resolution was obtained to provide patient-specific heart-torso geometry and the location of the body surface electrodes relative to the heart (1–3). Since there is still no unique, standardized approach for TA delineation for those clinical scenarios, after the anatomical definition of the cardiac areas to be irradiated by EAM, an indirect TA definition by manual delineation of the EAM on a four-dimensional gated simulation CT scan, independently double-checked by two different radiation oncologists and cardiologists referring to the same EAM, will also be allowed.

A 2–5-mm margin will be provided to the TA to determine the planning target volume (PTV). The prescribed dose will be 25 Gy in a single fraction to 80% isodose. A 4D-CT will be applied to account for respiratory motion and either cone-beam computed tomography (CBCT)-based or MR-guided Linac positioning with the addition of either breath hold (BH) or free-breathing respiratory gating, depending on the patient's compliance. If BH could be applied, deep inspiration breath hold (DIBH) should be preferred, but mid inspiration breath hold (MIBH), mid expiration breath hold (MEBH), and deep expiration breath hold (DEBH) are allowed if more suitable for planning.

Volumetric modulated arc therapy (VMAT) will be applied by multiple partial arcs (PA) depending on the arrhythmogenic scar volume and morphology to cover the TA. If an MR-guided Linac is used, static intensity-modulated radiotherapy (IMRT) will be applied.

Dose constraints for organs-at-risks and dose to target will follow the indications from the AAPM report Task Group 101 for single-fraction SBRT (4).

Our trial will combine two IGRT procedures to increase safety: intra-fractional and inter-fractional motion management devices and procedures are mandatory to be used. Volumetric imaging (CBCT- or MR-guided) scans before delivering each PA with regard to inter-fractional monitoring. Intra-fraction monitoring through the gating system is also mandatory. Continuous intra-fraction monitoring through an optical surface monitor system (OSMS) will be applied if available (e.g., TrueBeam Edge Linac, Varian Medical Systems, Palo Alto, CA, USA). Online adaptive procedures will be applied for the MR-guided Linac.

Outcome measures

The primary outcome is investigating the difference in overall cardiovascular survival among the group undergoing VT-ART and the one not exposed to the innovative procedure.

The primary efficacy endpoint is a statistically significant difference in overall cardiovascular survival between the group undergoing VT-ART and the one not exposed to the innovative procedure; this will be defined in months and calculated from the time of the last procedure (represented by the last RFA for the control group and VT-ART for the innovative one, respectively).

The secondary outcome is evaluating the difference in ventricular event-free (referred to VT/VF, appropriate shock or ATP as recorded by the ICD) survival after the last procedure between the two groups (i.e., the single or last RFA in the control group and VT-ART in the innovative group). The respective endpoint is a statistically significant difference in ventricular event-free survival (in months) after the last procedure between the two groups.

An additional secondary aim is to evaluate the reduction in the number of VT episodes compared to the pre-treatment period between the two dynamic cohorts that will be investigated.

Ventricular tachycardia recurrence will be defined as evidence of monomorphic VT at ICD interrogation (either self-limiting or terminated by appropriate shock therapy or ATP). The number of VT episodes, defined as VT burden, in the 3 months before and after the procedure will then be compared.

The respective secondary endpoint will be evaluated facing 3 months before the last procedure (i.e., either RFA or VT-ART) and 3 months after.

We did set a blanking period after VT-ART before evaluate the effect on VT burden; in a recent study by Kautzner et al., the authors supported the pre-clinical theorem of myocardial apoptosis (up to 3 months post-stereotactic ablation) followed by a creation of fibrotic lesion (6–9 months post-stereotactic ablation) in the irradiated region (5). Consequently, we propose a 3-month-blanking period after the procedure.

Since a blanking period of 3 months after the procedure will be applied, the secondary endpoint will evaluate the number of VT episodes interval accounted for the last 3 months before the procedure and of the 3–6 months after it.

Other secondary objectives include identifying the benefits of VT-ART on cardiac function, as evaluated through an electrocardiogram, echocardiographic, biochemical variables, and patient's quality of life.

In particular, we will evaluate the reduction or suspension of antiarrhythmic drug use compared to the baseline and the improvement of cardiac parameters (such as LVEF, left ventricular end-diastolic volume/diameter, ventricular strain, end-systolic volume/diameter, RVEF, and TAPSE for right ventricular function).

Analyzed biochemical variables will include heart failure biomarkers, such as NT-proB-type natriuretic peptide (NTproBNP), troponin (hs-TnI), and inflammation markers, such as polymerase chain reaction (PCR), tumor necrosis factor-alpha (TNF-alpha), and interleukin 6 (IL-6).

Improvement in the patient's quality of life will be assessed compared to the pre-treatment period using the SF36 scale.

The patient's QoL will be assessed before and after VT-ART using the SF36 scale (6); the post-treatment score will be compared to the pre-treatment period's one to assess potential improvement. The post-treatment QoL evaluation will be performed at 3, 6, and

12 months after VT-ART. Once centers join the consortium, the SF36 QoL scale will be offered (although not mandatory) to all patients undergoing RFA: Before and at 6 months after conventional therapy.

Secondary outcome analyses will investigate the improvement of QoL scores after VT-ART and how QoL scores change the comparison between VT-ART and RFA.

Further secondary outcome analyses will be developed through imaging: Contrast infusion MRI and CT scan will be performed as required but not mandatory (if not contraindicated due to ICD) in the experimental arm.

Statistical considerations and sample size for matched pair analysis

A descriptive analysis will summarize the total number and stratification of patients with RFA and VT-ART.

We will perform a comparative analysis between RFA and VT-ART in patients with structural heart disease and refractory VT. Each patient who will be treated by VT-ART will be compared with two patients in the control group treated with RFA and best standard care but without VT-ART, on the basis of the following matching factors: Etiology of cardiomiopathy (ICM, NICM, and ACM), ventricular arrhythmia presentations (sustained ventricular tachycardia; incessant sustained ventricular tachycardia; and electrical storm), diagnostic tools used for scar definition (CT, MR, EAM, and ECG), arrhythmogenic focus anatomical intracardiac location (on the basis of VE exit by ECG and by activation map of VT), TA volume (endocardial electroanatomic substrate mapping area/volume in all cases; and epicardial mapping area/volume in case of 3D epicardial electroanatomic substrate mapping), heart volume, heart-to-TA volume, rate number of previous RFA attempts, type of previous RFA attempts (endocardial and epicardial), time (in days) between the first RFA attempt and VT-ART, time (in days) between the last RFA attempt and VT-ART, previous percutaneous stellate ganglion blockade, time (in days) between the percutaneous stellate ganglion blockade and VT-ART previous use of amiodaron, NYHA group, LVEF, BMI, age, and gender.

As mentioned, applied matching factors are summarized in **Table 2**.

Continuous data will be expressed as mean ± standard deviation, as appropriate, for all variables collected from the entire population or specific subgroups. A comparative analysis for subsequent levels of qualitative variables through the chi-square test and quantitative variables (scores on quality of life) with the *T*-test will be performed.

Non-parametric tests will be provided where the population distribution does not have a known form (normal Gaussian).

The differences in baseline and follow-ups between the same group will be analyzed with repeated measures approach: using the Friedman test and MANOVA for continuous variables and McNemar or Cochran's *Q*-tests for categorical ones.

The significance of the tests is fixed with $p < 0.05$.

Sample size

The calculation of the sample size considered followed assumptions:

- A total of 95% confidence level;
- The drop-out rate of 10%;
- Expected difference between the two treatments for 3-month and 6-month VT burden in terms of overall response rates: 20% higher in arm including VT-ART compared to the control group;
- Power of 80%.

To improve clinically adequate balancing, we will enroll two matching paired patients in the group not undergoing VT-ART for each patient who undergoes VT-ART in a 2:1 ratio, favoring a larger proportion of patients not undergoing the innovative procedure (i.e., VT-ART).

Under these hypotheses, to detect a 20% improvement in the VT burden control rate in the VT-ART group vs. the control group, we calculated the sample size (in a 2:1 ratio) upon enrolling 149 patients: 100 in the non-exposed control group and 49 in the VT-ART group. Progressively, on a multicentric basis supervised by the promoting center in the VT-ART consortium, for each VT-ART patient enrollment, a matched pair patient profile according to the predefined features will be shared with the consortium to enroll two similar patients who have not undergone VT-ART. For enrollment into the control group, recruitment of clinical cases from retrospective case series within the multicentric consortium will also be allowed, with the only condition to be not earlier than 5 years from the enrollment of the matched pair patient in the VT-ART group (to avoid the possible influence of a too early approach for standard procedures).

All statistical analyses will be performed using SPSS® version 25.0 software (©Copyright IBM Corporation 1994, 2017).

Due to the potential difficulty of enrolling the patients through the complete match of all matching factors, a protocol rule will be applied through patient's collection.

Once the planned number of the innovative procedure will be collected, the trial will put a 6-month observation time. If after that, 60% of the planned conventional arm patients will be collected (by all matching factors and in a 2:1 ratio), a further 3 months will be provided to reach the planned accrual. If that would have not been the case, then the patient's enrollment will be allowed by mandatory matching factors only (only beyond that point). The detail of "mandatory matching factors" is reported in **Table 2**. The final analysis will be performed by the whole group and subgroup analyses, discriminating patients collected through "all matching factors" and by "mandatory-only."

The final analysis will not be performed at all if less than a 1:1 ratio (conventional: Innovative group) of patient's enrollment will be collected, and the study will be closed.

The final analysis will be performed specifying that the planned accrual is not met if at least a 1:1 ratio (conventional: Innovative group) enrollment will be accomplished; results will be explored and cautiously evaluated.

Toxicity evaluation

Radiotherapy-related toxicity will be defined using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All adverse events, regardless of the toxicity grade and all-cause mortality, will be reported in the final study. Patients will be re-evaluated at 2 years of follow-up for late-onset toxic effects.

The secondary safety endpoints for VT-ART include the evaluation of all adverse events, which are classified as follows:

- Acute, during the patient's hospital stay;
- Subacute, in the first 90 days from discharge;
- Chronic, 6–12 months following discharge.

Follow-up

Follow-up will be conducted for 36 months after treatment administration.

Patients prospectively enrolled within the consortium and treated by VT-ART will undergo ICD interrogations for up to 36 months after enrollment.

After a blanking period of 3 months, regular ICD interrogations [with intracardiac electrogram (EGM) storage of VT/VF or appropriate shock or ATP] will be prospectively collected for patients treated by VT-ART at 6, 9, 12, 18, 24, 30, and 36 months after the VT-ART procedure.

The ICD interrogation will collect the events along the last 3 months ahead of each follow-up evaluation.

Patients prospectively enrolled within the consortium and treated by RFA will undergo the same follow-up schedule if possible according to the clinical patient's need and compliance.

Patient data retrospectively collected within the consortium and treated by either RFA or VT-ART will be retrospectively extracted at the same time points of prospective follow-up.

The final analysis will be performed only for patients with available data for the mentioned time points, either retrospectively or prospectively collected.

Quality of life will be assessed before the procedure (for prospectively enrolled patients candidate to VT-ART and RFA) and at 3, 6, and 12 months after therapy. Improvement in the patient's quality of life will be assessed compared to the pre-treatment period using the SF36 scale.

Patient follow-up will thus, briefly, include:

- ICD interrogation (with EGM storage of VT/VF) at 6, 9, 12, 18, 24, 30, and 36 months from treatment.
- A total of 12-lead ECG at 3, 6, and 12 months.
- Echocardiography at 3, 6, and 12 months.
- QoL assessment using the SF36 scale (7) will be performed at 3, 6, and 12 months for patients undergoing VT-ART.
- QoL assessment using the SF36 scale will be performed at 6 months for patients undergoing RFA.

Registration

The trial is promoted by Fondazione Policlinico A. Gemelli IRCCS, Rome (Italy). The clinical and investigational procedures will be based on approval from the local ethics committee. Each interested center will submit the protocol to its ethics committee for approval before accrual. After approval, the center will receive a dedicated electronic case report form (CRF). Eligible participants who provide consent and meet the inclusion criteria are anonymously registered in the CRF by assigning a numerical code. Final stratification of the enrolled patients will be performed globally to enhance the homogeneity and balance of the final dataset.

Ethics considerations

The trial will be conducted in compliance with the approved protocol, Declaration of Helsinki 2008, principles of Good Clinical Practice (GCP), and Italian National Normative for clinical experimentation. Upon signing the protocol, every investigator will provide consent for the procedure and instructions in the protocol and run the study according to the GCP, Declaration of Helsinki, and National Normative. Every amendment to the study will be registered and submitted to the ethics committee. Our trial protocol and its attached material have been approved by the Ethics Commission of Fondazione Policlinico Gemelli IRCCS (Rome, Italy). Every participant center must submit our protocol to their respective ethics commission before enrolling patients.

Discussion and final considerations

Sustained monomorphic VT is a potentially life-threatening condition that often affects patients with structural heart diseases. VT recurrence poses a severe threat to health and quality of life. Long-term management of recurring VT relies mainly on ICDs, pharmacological control (i.e., class III antiarrhythmic), and RFA of the pathological arrhythmogenic substrate.

New long-term solutions are currently being sought for patients in whom VT is refractory to conventional treatment strategies or in whom it cannot be performed. In patients with structural heart disease, the rate of VT recurrence after RFA has been reported to be between 25 and 50% (8). Intrinsic technical aspects of the procedure (e.g., difficult anatomical location of the arrhythmic substrate) as well as patient-related factors (e.g., patient frailty) may limit RFA feasibility in a portion of the population. Patients with structural heart disease are often fragile and have a varying number of comorbidities. Therefore, procedure invasiveness could be a limiting factor in the choice of the best treatment strategy (9).

Cuculich et al. first investigated the efficacy and safety of stereotactic radiation for the ablation of VT in a five-patient case series, which was later followed by the publication of a phase I/II prospective study by the same authors, including 19 patients (1, 2). Both studies reported a statistically significant reduction (99.9 and 94%, respectively) in VT episodes after a blanking period of 4 weeks. Subacute and chronic treatment-related side effects ranged from asymptomatic pericardial effusion to radiation-induced pericarditis and pneumonitis and were successfully treated with corticosteroids. Since then, a growing number of scientific articles have been published on this matter.

Overall, VT-ART has been proven to be an effective and adequately safe intervention in other studies (10, 11). Its non-invasive nature makes it a safe alternative for patients who are not suitable for percutaneous RFA (9). Nevertheless, despite the promising results detected by sporadic reports, limited case series, and systematic

reviews (12), we still do not know if and at what level VT-ART (and STAR in general) could significantly and effectively improve the clinical scenario of such complex malignancies.

Conclusion

Our trial will provide insight into the efficacy and safety of VT-ART through a matched pair analysis, by an observational, multicentric study (with prospective and retrospective data collection) *via* subgroup stratification into dynamic cohorts of two groups of patients with or without VT-ART in a multicentric consortium.

Ethics statement

This study was reviewed and approved by the Ethics Commission of Fondazione Policlinico Gemelli IRCCS (Rome, Italy). Written informed consent will be obtained from all participants for their participation in this study and every participant center must submit our protocol to their respective ethics commission before enrolling patients.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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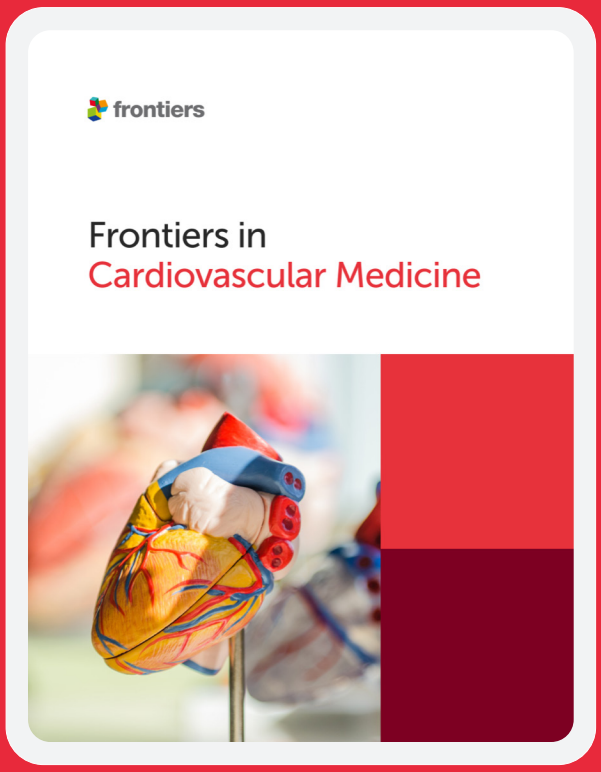

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