

Stereotactic ablative radiotherapy in patients with refractory ventricular tachyarrhythmia

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Stereotactic ablative body radiotherapy (SABR) is an innovative therapeutic approach in patients (pts) with a diagnosis of refractory ventricular tachyarrhythmia (VT) after the use of drugs, radiofrequency catheter ablation, and/or defibrillator (ICD) implant. The current efficacy data of SABR are limited and several prospective clinical studies are ongoing to support the use of ablative radiation dose to control VT. The aim of the current prospective pilot study is to report the efficacy and tolerability of SABR in ICD implanted pts with refractory VT in our centre. Non-invasive electroanatomical mapping (EAM), cardiac computed tomography (CT), and ¹⁸F-fluorodeoxyglucose positron emission (FDG-PET)-CT scan were used and combined with a radiation CT scan. A dose prescription of 25 Gy in a single dose was delivered by volumetric modulated arc therapy (VMAT) Linac-based. The primary endpoint was efficacy, defined as a reduction in ICD shocks after SABR treatment, while the secondary endpoint was safety. Six consecutive pts (five males and one female) implanted with an ICD and with three or more VT were enrolled. One pts died after 1 month, due to end-stage heart failure. Two pts experienced ICD shocks in VT 2 and 5 months after treatment. Three pts experienced no more ICD shocks on VT after therapy. Our data suggest the efficacy and safety of SABR treatment in pts with VT. Larger dataset of pts and longer follow-up are otherwise required to validate the impact of SABR as a standardized treatment in these pts.

Introduction

Ventricular tachycardia (VT) is a hazardous arrhythmia potentially leading to sudden death (SD); this has an estimated incidence range from 4% to 16% in over 60s cardiopaths. The leading cause of this arrhythmia in the presence of re-entrant electric circuits activation located in the ventricular myocardium, usually scar related.

The management of VT is based on anti-arrhythmic drugs, radiofrequency catheter ablation (RFCA), and/or cardioverter-defibrillator (ICD) device implant.¹ The implant of an ICD, despite being very effective in reducing the incidence of SD, does not modify the causes of the arrhythmias, with many studies otherwise reporting a significant detrimental impact on patients' quality of life too.^{2,3}

Therefore, recurrences of VT after drug failure or in the case of unfitness for RFCA remain a matter of concern. In this scenario, stereotactic ablative body radiotherapy (SABR) is arising as an attractive non-invasive alternative for the treatment of ventricular arrhythmias, with some preliminary studies reporting very promising results in

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terms of safety and efficacy, especially for pts with refractory arrhythmias who have experienced both drug and ablation failures.⁴⁻⁶

Stereotactic ablative body radiotherapy principles are based on the possibility to deliver, with high accuracy, ablative doses to very small volumes of tissue, also by means of tracking or gating systems that take into account the target motion.⁷

Unlike cryoablation or radiofrequencies, which rely on thermal stress, SABR provides biological damage to the arrhythmogenic focus resulting in an ischaemic and pro-apoptotic effect with consequent fibrosis and termination of the abnormal electrical activity.⁸

A recent review of the literature by van der Ree *et al.*⁹ has collected the currently available evidence concerning the use of SABR for cardiac arrhythmias, reporting promising preliminary results in terms of short-term efficacy and safety. Further prospective studies are ongoing with the aim of providing larger data and higher quality evidence in support of this therapeutic option.¹⁰

In this study, we report the initial results of the first six patients (pts) treated at our centre with SABR for refractory ventricular tachyarrhythmia (VT).

Methods

The present experience reports the outcomes of the first six pts (five males and one female) enrolled in a prospective mono-institutional pilot study with the aim to assess the safety and feasibility of SABR for ventricular arrhythmias. Inclusion criteria for the study were:

- age >18 years;
- ICD implanted from at least 6 months with a complete record of the activity of the device;
- Three or more recent episodes of VT with ICD activation; and
- Unfitness, or previous failure, for RFCA or drug-resistant arrhythmia.

Exclusion criteria were:

- life expectancy <12 months;
- pregnancy at the time of the treatment;
- active collagenopathy or immunosuppressive therapy assumed at the time of the treatment; and
- inability for informed consent.

The primary endpoint of the study is to assess the efficacy of the treatment, based on the arrhythmia records of the ICD, with an expected significant reduction in the arrhythmic burden after the SABR treatment.

Secondary endpoints of the study are safety assessment with the acute and late toxicity evaluation, the all-cause, and cause-specific mortality.

Every single pts was fully informed about the treatment proposed; was completely aware of the risks and that RFCA was the gold standard therapy for his/her case; after a fully and complete information every pts was proposed to the local ethics committee for approval and every single case proposed for radiation treatment obtained approvation; and finally, every pts provided written consent to the treatment. Only after ethic committee approval and written

consent to the treatment was released by the pts we started the procedural workflow with the study and treatment plan.

Electroanatomical mapping

The electroanatomical mapping (EAM) identification of the electro-anatomical target was based on three-dimensional (3D) non-invasive intracavitary mapping (CardioInsight™—Medtronic, Minneapolis, MN, USA); this system collects chest Electrocardiogram (ECG) signals using 252 electrodes and combines these signals with computed tomography (CT) scan heart data to produce simultaneous 3D cardiac maps. In every pts, EAM has been performed during simultaneous programmed ventricular stimulation by ICD with the goal of inducing monomorphic VT and assessing the VT exit site. The exit site has been defined as the first 10 ms of the induced VT (*Figure 1*). The EAM imaging, in post-processing, has been even combined with a ¹⁸F-fluorodeoxyglucose positron emission (FDG-PET)-CT scan; the choice of FDG-PET was in order to increase the accuracy for scar identification. Cardiac magnetic resonance imaging (MRI) is not feasible in these pts with ICD.

Radiotherapy procedures

In all cases, target volumes were identified and contoured by using a combination of electro-anatomical mapping and radiological images. For treatment planning purposes, a 3-mm slice thickness 4D-CT scan was acquired with the pts in a supine position, with the arms above the head and a customized abdominal thermo-plastic mask. Target volume delineation was performed in collaboration with the cardiology team, outlining the gross target volume (GTV) as the hypometabolic area detected by PET-CT. Subsequently, a 5-mm isotropic margin was added to generate the planning target volume (PTV). As organs at risk (OARs), the following structures were contoured: lungs, oesophagus, chest wall, spinal canal, ICD device, trachea, and proximal bronchial tree. Treatment planning was performed by Eclipse v. 16.1.4.4 for a total dose of 25 Gy delivered in a single session (*Figure 2*).

All treatments were delivered using image-guided-volumetric modulated arc therapy (VMAT-IGRT) by means of a TrueBeam Linac (Varian Medical Systems, Palo Alto, CA, USA).

Follow-up and data collection

For the first year, follow-up visits (in presence of remote) were scheduled every 3 months from the SABR treatment.

Toxicity was prospectively collected and assessed according to Common Terminology Criteria for Adverse Events (CTCAE v5.0), assuming as acute any event occurring within 90 days from the end of treatment, and late any event occurring at least after 90 days from the end of treatment.

Results

From March 2020 to July 2021, six pts with a diagnosis of refractory VT were enrolled in SABR treatment. We have summarized the clinical history of all the pts treated.

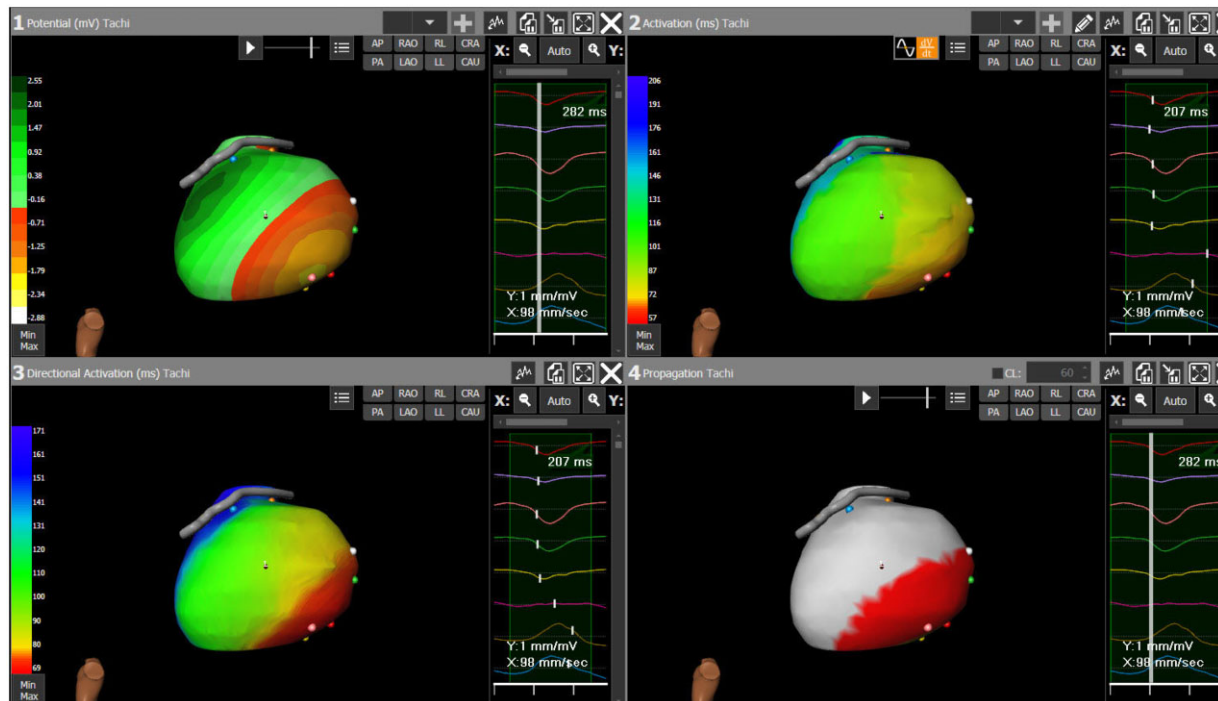


Figure 1 Electroanatomical mapping of left ventricle on 3D non-invasive intracavitary mapping in latero-lateral view; at induction of monomorphic VT, the exit site is visible in Panels 3 and 4.

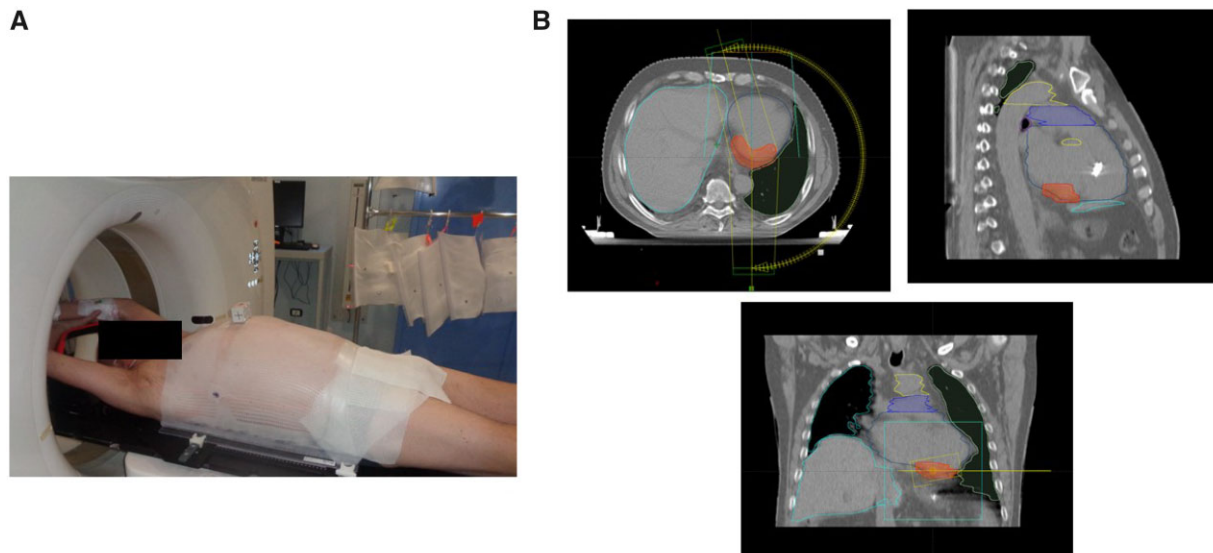


Figure 2 (A) Immobilization device and CT simulation. (B) SABR treatment plan in patient with a VT diagnosis. The outlined areas represented the planning target volume (PTV) in axial, coronal, and sagittal. These areas included the isodoses between 95% and 100% of dose prescription (25 Gy in 1 fraction) in the PTV.

Patient 1

Female, 81 years, persistent atrial fibrillation (AF), amiodarone-induced overt hypothyroidism, and mitral valve replacement with mechanical prosthesis (2005) with perioperative inferior myocardial infarction (MI). Severe left ventricular dysfunction [EF 21%—New York Heart Association (NYHA) Class III] with Cardiac Resynchronization Therapy Defibrillator (CRT-D) implantation. From November 2019 to January 2020, an arrhythmic

storm with 104 VT (*Figure 3*) symptomatic of aborted syncope feeling was always solved by ATP and/or shocks. At 16-month follow-up (FU), SABR was completely reversible with the complete disappearance of VT.

Patient 2

Male, 61 years, Type 2 diabetes and history of MI. Severe left ventricular dysfunction (EF 28%—NYHA Class III) with ICD implantation in primary prevention. In 2018, four

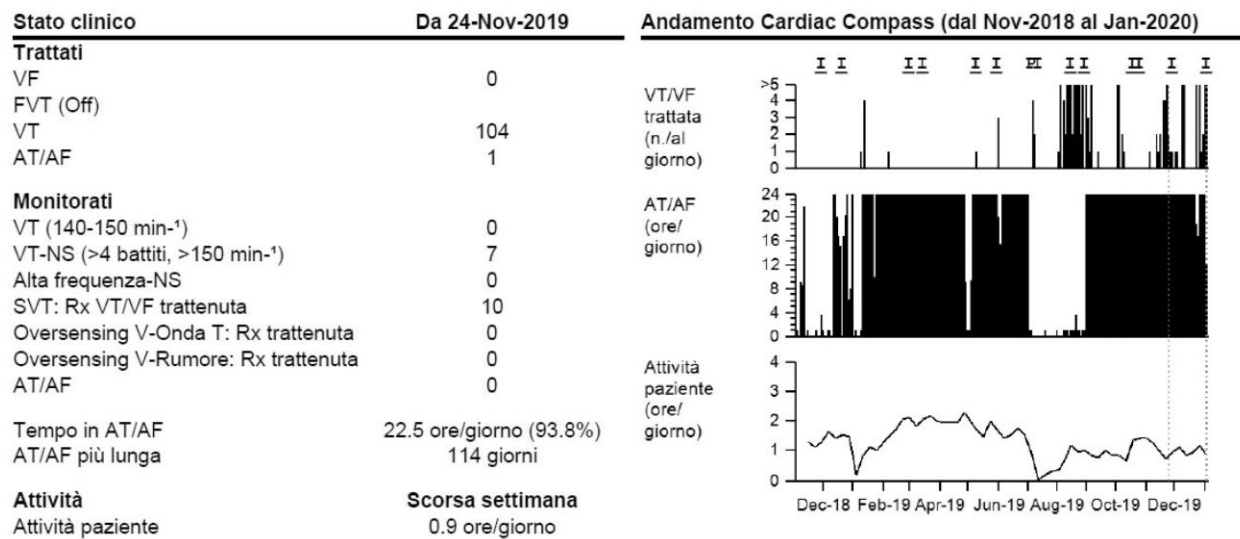


Figure 3 Report of ICD interrogation showing the number of 104 VT treated (ATP and/or DC shock) in the months before SABR of patient no. 1; the increase in the number of VT leads to a significant decrease in patient activity level and consequently in quality of life.

ventricular fibrillation (VF) was solved by ICD shocks. In 2019 and 2020, there were arrhythmic storms with several ICD shocks. In May 2020, SABR. In October 2020 and August 2021, VT recurrences with ICD shocks.

Patient 3

Male, 85 years, non-ischemic cardiomyopathy with severe left ventricular dysfunction (EF 20%—NYHA Class IV), CRT-D implantation, amiodarone-induced overt hypothyroidism, previous AV node ablation for relapsing AF; in 2020, an arrhythmic storm with syncope and several hospital admissions. In July 2020, SABR. Patients died in August 2020 of end-stage heart failure.

Patient 4

Male, 80 years, previous MI (1983) with severe left ventricular dysfunction (EF 25%—NYHA Class III), amiodarone-induced overt hypothyroidism, coronary artery bypass grafting (CABG), mitral clips, CRT-D, and several arrhythmic storms from 2009, VT unsuccessful RFCA attempt. In September 2020, SABR. At 12-month FU, asymptomatic and without ventricular arrhythmias.

Patient 5

Male, 65 years, ischaemic cardiomyopathy, AF, amiodarone-induced overt hypothyroidism, severe left ventricular dysfunction (EF 36%—NYHA Class II), CRT-D. From 2012, several VT with shocks. In 2013, VT successful RFCA. In 2019, AF ablation attempt was made with tamponade complications. In 2020, an arrhythmic storm with hospital admission. In April 2021, SABR. At 6-month FU, asymptomatic and without ventricular arrhythmias.

Patient 6

Male, 79 years, non-ischemic cardiomyopathy, permanent AF, and moderate left ventricular dysfunction (EF 42%—NYHA Class II). ICD, in 2021, an arrhythmic storm even if in therapy with Amiodarone and Mexiletine. In July 2021,

SABR. In September, ICD shocks due to high-frequency AF and VT.

Discussion

We report a case series of six pts with ischaemic and non-ischemic cardiomyopathy, arrhythmic ventricular storm, and ICD interventions not controlled by optimal medical treatment with antiarrhythmic drugs that underwent SABR.

In this small group of pts, SABR targeted the VT substrate in the LV myocardium, with no acute or late complications. Our cases confirm the safety and efficacy observed in the previous first five cases reported by Cuculich *et al.*⁴ in which a 99.9% reduction in VT burden was observed after treatment with 25 Gy ionizing radiation. More recently, a prospective Phase I/II trial undertaken by the same authors in 19 pts who either previously failed or were not eligible for catheter radiofrequency ablation reported a 94% reduction in episodes of VT or premature ventricular beats and a 12-month survival rate of 72% in a very compromised population.¹¹ Our data also confirmed earlier single-case reports described in the literature of the potential efficacy of SABR.⁴

Radiofrequency catheter ablation is currently the most effective therapy for most pts with recurrent drug-refractory VT and is considered the ‘gold’ standard treatment for this pathological condition that has a tremendous impact on the patient’s quality of life and mortality. However, despite continued advances in RFCA techniques and our ability to better understand VT mechanisms, RFCA remains ineffective in a lot of pts for several reasons (i.e. the inability to correctly identify the VT substrate, a large substrate not suitable for effective ablation, or an inaccessible arrhythmic substrate with currently available RFCA technologies). Moreover, serious complications of this procedure are still a major concern.¹ Therefore, there is a need to develop safer and more effective therapies.

Stereotactic ablative body radiotherapy is a highly focused radiation therapy used by radiation oncologists to target solid tumours with high accuracy and precision in which a rapid dose fall-off minimizes toxicity to surrounding tissues and seems promising in terms of efficacy and safety in arrhythmic treatment. Unlike thermal ablation that causes immediate coagulative necrosis and subsequent scarring, ablative radiation leads to a complex cascade of acute and chronic tissue effects, leading to fibrosis and modulation of the electrical properties of the myocardium.¹¹

In pre-clinical studies, doses between 5 and 160 Gy have been used to investigate the pathological and electrophysiological effects of radioablation.⁹ Importantly, no radioablative treatment-related complications were seen both with clinical and pathologic/histologic evaluation in treatments up to 35 Gy.⁹ Based on these data and with delivered therapies in the oncology literature and experience, 25 Gy delivered as a single dose has been used in nearly all clinical treatments described.⁹ Of note, recently an electrical conduction reprogramming in mice in the absence of transmural fibrosis and scar was observed with SABR. Zang *et al.*¹¹ showed that radiation-induced electrical reprogramming can occur at lower doses in the range of 15–25 Gy in mice suggesting that also in humans reduced radiation doses might be effective in minimizing side effects. Moreover, they demonstrate that the functional and molecular effects of RT are persistent and expected to directly translate into the long-term durability of therapy. This complex tissue injury mechanism may also account for the observed time course of clinical response and subsequent recurrence in earlier studies.

In this study, three pts showed no VT burden for a median of 13 months after a single RT treatment, whereas two pts had recurrent TV at 2 and 5 months after SABR. In this study, we used a dosage of 25 Gy to minimize the cardiotoxic effects of radiation, and it was well tolerated without evident clinical side effects. However, it has to be recognized that, although this current dose is proven to be safe and effective, there have been reported rare cases of pericarditis, pericardial effusion, radiation pneumonitis, cardioembolism,¹⁰ a single adverse event of gastro-pericardial fistula that occurred 2 years after treatment was also described.¹² In our case series, no acute heart failure exacerbations occurred in the immediate period after treatment; however, a patient died 30 days after SABR for end-stage heart failure, and we cannot completely exclude a possible relationship with the procedure. Likewise, to us also Robinson *et al.*¹⁰ reported in their prospective trial that one patient was hospitalized 65 days after treatment with heart failure exacerbation and this was considered possibly related to SABR. Of note, we did not observe any interference between SABR and ICD.

Limitations

This case series has clearly many limitations, being a single-centre study with limited FU and a very small number of selected pts, which does not allow generalization to larger populations. However, we believe that it supports and expands the findings of previous case reports and smaller prospective studies on the potential efficacy and

safety of SABR in pts with structural cardiomyopathy, ICD recipients, and ventricular arrhythmic storms not responsive to optimal medical treatment and not eligible for radiofrequency catheter ablation. As with any new therapy, these data are surely not enough to demonstrate with confidence the safety and efficacy of this pioneering therapeutic approach. Many unmet questions and unknowns remain unanswered. We are expecting an important contribution from the STOPSTORM Consortium (www.stopstorm.eu), in which we participate; it brings together several European Centers in order to collect a large dataset of pts to verify the results of SABR; this project is funded by European Union HORIZON2020 programme and will contribute to adding other pieces of information to this new field.

Conclusions

The outcome of the SABR observed in our cohort of pts is satisfying, in the absence of major adverse events over the mid-term. What makes this procedure really innovative and interesting is the possibility to use a non-invasive diagnostic mapping system and a non-invasive ablative treatment. Further investigation in larger dataset of pts with structural heart disease not suitable for conventional treatments will help in clarifying the role of SABR, with the attractive possibility of treating arrhythmia substrates, currently with difficult eligibility for conventional approaches, in a safe and non-invasive manner.

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Conflict of interest: none declared.

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