Original article

Stereotactic management of arrhythmia – radiosurgery in treatment of ventricular tachycardia (SMART-VT) – clinical trial protocol and study rationale

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ABSTRACT

Patients with ventricular tachycardia are usually treated with antiarrhythmic drugs and ablation if the arrhythmia substrate is available for invasive treatment. Despite high efficiency of this treatment there is a significant group of patients who do not benefit from available treatment methods, either because they cannot be applied or do not allow for durable control of the disease. For that reason a novel treatment method, STereotactic Arrhythmia Radioablation (STAR) has been proposed and its safety and efficiency is extensively studied throughout the world. The method is based on irradiation of the arrhythmia substrate identified with electrophysiological examination with high-precision image-guided radiosurgical methods usually used for ablation of malignant tumors. Here we present the protocol of the first Polish study on STAR in patients with intractable ventricular tachycardia (STAR-VT, NCT04642963), designed to test the safety of the method. Secondary endpoints include measures of the treatment efficiency.

Key words: ventricular tachycardia, ablation, radiosurgery, STAR, arrhythmia

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INTRODUCTION

Since its first application in October 2012, radiotherapy in the treatment of ventricular tachycardia (VT) has proven its effectiveness through case reports, clinical series and prospective trials [1]. The rapid development of STereotactic Arrhythmia Radioablation (STAR) was driven by a relatively large subset of patients with unmet medical needs at that time. Radiofrequency catheter ablation is a standard treatment strategy for VT being associated with up to 50% recurrence rate at 6 months and decreasing efficacy with every subsequent ablation [2]. In such patients, STAR can be effective despite prior treatment failures, providing alternative clinical solution. The first Polish prospective clinical trial presented in this article aims to confirm the safety of STAR, establish cooperation between radiation oncologists, cardiologists and electrophysiologists, and provide framework for future studies.

TRIAL METHODOLOGY

This is a prospective, two-center, single-arm study. Patients with a medical history of sustained or recurrent VT despite previous catheter ablation procedures, or presenting with contraindications to catheter ablation, will be treated with single-fraction radiosurgery of 25 Gy to the arrhythmia substrate located with electrophysiological mapping. The trial aims to demonstrate the safety of the treatment method defined as 3-month observation without grade 3 or higher adverse events (CTCAE v5.0) in at least 6 out of 7 patients in the 1st stage of the study, and in total in at least 9 out of 11 patients (2nd stage) with an interim safety analysis of primary outcome data in 7 consecutively enrolled patients. After the initial period, the patients will be monitored every 3 months until 12th month, and every 6 months thereafter. Secondary aims include assessment of clinical efficacy (reduction of VT burden and improvement in patient reported outcomes), changes in the uptake of antiarrhythmic medications, dynamics of myocardial injury biomarkers, and overall survival and cause-specific survival.

TRIAL REGISTRATION

The study is registered in the ClinicalTrials.gov database of the National Institute of Health – U.S. National Library of Medicine, under the name Stereotactic Management of Arrhythmia – Radiosurgery in Treatment of Ventricular Tachycardia (SMART-VT) and received clinical trial identifier NCT04642963.

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BRIEF HISTORY OF STAR

The cardiac ablation radiosurgery was set in motion a decade ago by pre-clinical studies conducted within the CyberHeart™ project which determined that a dose of 25–35 Gy is capable of producing fibrotic lesions, similar to those induced by catheter ablation [3, 4]. Despite an ongoing dispute regarding the actual mechanism of action of ionizing radiation on the ventricular myocardium, the findings were soon translated into clinic through the first-in-human applications in 2012 in the US by Loo et al. [5], followed shortly by Cvek et al. [6] in Europe. Up to date, a number of clinical applications have been described in the literature [5–21], including results of two prospective clinical trials. The first study, published by Robinson et al. [12], demonstrated both safety and effectiveness of this method. The authors reported no serious acute adverse effects, and treatment related grade ≥3 toxicity developed in only 2 out of 19 patients. The 50% and 95% reduction in VT episodes were achieved in 94% and 61% of the patients, respectively. On the other hand, in the study by Gianni et al. [13], despite the favourable safety profile, the efficacy was suboptimal and long-term arrhythmia control was not achieved, similarly to the recently published retrospective case series by Chin et al. [11].

STUDY RATIONALE

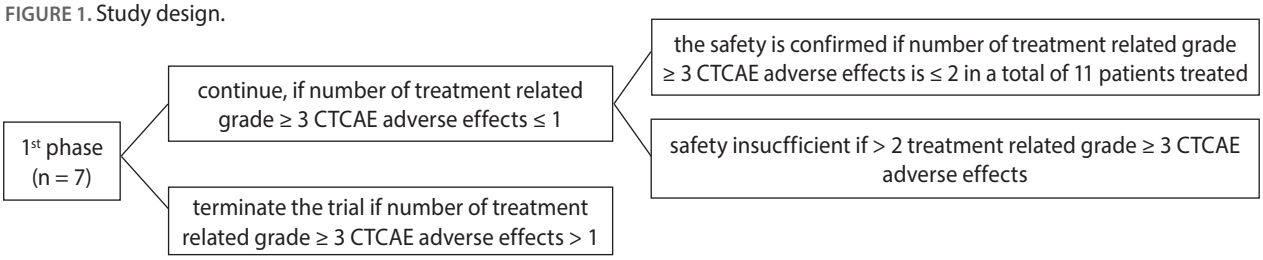
Although majority of literature data is in favour of STAR, the inconsistent results of the recent clinical trial [13] and retrospective report [11] warrant further investigation. Considering STAR has never yet been performed in Poland and treatment techniques are significantly different between institutions and authors, a pilot trial focused on treatment safety was chosen to be the most appropriate.

STATISTICAL ASSUMPTIONS

The primary endpoint is to assess the post-intervention safety defined as no treatment-related serious adverse events (grade ≥ 3 according to CTCAE v5.0) in the first 90 days after radiotherapy. The sample size planning is based on the assumption that observed safety of < 50% (null hypothesis) will lead to the rejection of the alternative hypothesis of a safety of > 90% (H_1). If the safety is in between, the statement will be confined to the confidence interval. We assumed α level of 2.5% (one-sided) and a power of 80% ($\beta = 0.2$).

Based on Simon and Fleming's two-stage designs [22, 23], an interim analysis is performed after the first seven included patients have been assessed for the primary endpoint (fig. 1). The inclusion of additional patients cannot be carried out until at least 90 days after the completion of treatment of the seventh patient. The study will be terminated early if an endpoint occurs in more than one patient in this group. Otherwise, an additional four patients will be enrolled and the total number of patients will be eleven. To reject the null hypothesis, no more than two grade ≥ 3 events can occur.

FIGURE 1. Study design.



INCLUSION AND EXCLUSION CRITERIA

The study includes patients of 18 years or older, which meet the following criteria:

- Patients with structural heart disease and implantable 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 electrophysiological study.
- Recurrent VT despite at least one prior catheter ablation and adequate pharmacotherapy OR contraindications to catheter ablation and/or pharmacotherapy (i.e., patient with medically contraindicated catheter ablation is obliged to undergo only pharmacotherapy prior to study enrolment).
- Patient must be able to understand and be willing to sign a written informed consent document.

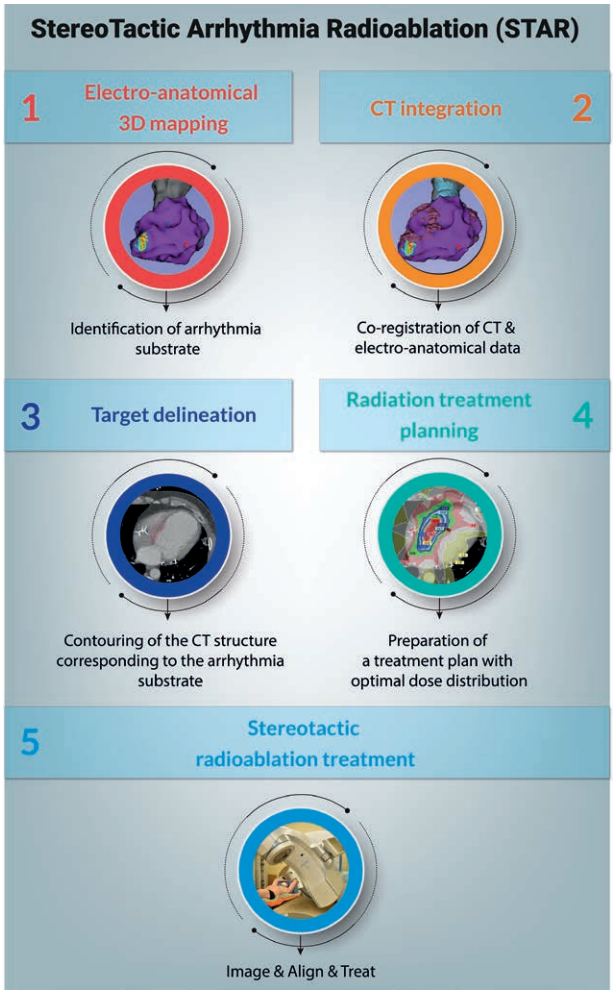
The patient must not meet the following exclusion criteria:

- heart failure requiring inotropic treatment or mechanical assistance
- arrhythmia due to cardiac channelopathy
- reversible source of arrhythmia
- NYHA (New York Heart Association) stage IV heart failure
- myocardial infarction or cardiac surgery within last 3 months
- life expectancy < 6 months
- polymorphic VT
- pregnancy
- prior radiotherapy to the thoracic region (relative contraindication)
- failure to induce VT during electrophysiological study.

WORK-UP AND TREATMENT DELIVERY

The procedural workflow is briefly presented on figure 2.

FIGURE 2.
Procedural workflow.



The radiotherapy planning procedures start with preparation of individual immobilization device (vacuum bag). Then, deep inspiration breath hold (DIBH) or respiratory-gated non-contrast enhanced treatment planning computer tomography (CT) is performed, followed by contrast-enhanced diagnostic thoracic CT.

Next, the patient is admitted to the cardiology ward for catheter-based electro-anatomical study of the left ventricle (LV) and/or right ventricle (RV) using EnSite Precision intracardiac system. Three-dimensional (3D) reconstruction of LV/RV combined with high-density endocardial map allows for precise identification of the healthy and diseased myocardium as well as fibrotic tissue characterized by bipolar voltage of > 1.5 mV, 1.5–0.5 mV and < 0.5 mV, respectively. Selection of arrhythmogenic areas is based on 3D color-coded voltage map delineating diseased/scar tissue border. Additionally, programmed ventricular stimulation is used to confirm inducibility of sustained monomorphic VT.

The location of the arrhythmia substrate is transferred to the contrast-enhanced CT through the mutual effort of electrophysiologist, cardiologists and radiation oncologist involved in the treatment. The precise delineation of the treatment volume is crucial. The process is aided by defining the involved heart segment as described previously [24]. The location of the target volume for radiotherapy can be additionally compared to the results of fusion of the EP data and CT images performed with Slicer 3D software run with an extension developed by Hohmann et al. as a double-check procedure for target delineation [25].

The radiotherapy planning is carried out using Varian ECLIPSE™ treatment planning system (TPS) and VMAT (volumetric modulated arc therapy) technology with either DIBH or respiratory gating, using dose constraints presented in table 1. Most of these values are adopted from thoracic stereotactic radiotherapy (i.e. targeted at primary and metastatic lesions in lungs or skeleton), with the exception of coronary arteries. The dose constraint for coronary arteries was chosen through extrapolation of available data using the principle of maximum safety, and is prone to change when additional data on safety is available. The choice of the treatment technique depends on the patient's ability to hold breath for time required to deliver the dose. If breath-hold technique cannot be applied, the dose is delivered during free breathing and the operation of the linear accelerator is gated with patient's breath. The treatment can be performed either with Varian EDGE™ machine allowing for short treatment time and offering gated CBCT image verification prior to treatment, or with the Accuray CyberKnife™ platform. The latter can also produce excellent STAR radiotherapy plans [26] and, although is not capable of CBCT imaging, it can track the position of the ICD lead during irradiation which in fact becomes a fiducial marker for radiotherapy. Along with the Synchrony® automatic real-time motion synchronization and tracking system it allows for effective respiratory motion management without the need of gated radiation delivery.

TABLE 1.
Dose constraints.

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	< 5cm^3	28 Gy	33 Gy
Skin	< 10 cm^3	25.5 Gy	27.5 Gy

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

The treatment is performed in the assistance of the responsible cardiologist, with appropriate ICD management and continuous cardiac monitoring during radiotherapy delivery [27]. The patient is admitted to the cardiology ward a day prior, and transported back to the hospital after the procedure.

FOLLOW-UP

The follow-up schedule is presented in table 2. The ICD readouts serve as a measure to assess the VT burden along with the electrocardiography examination (ECG). Holter ECG monitoring performed after RT provides additional information regarding immediate anti-arrhythmic effect of the treatment. As the VT burden decreases, the attending physician is encouraged to decrease the anti-arrhythmic drugs therapy, and the current dose is recorded at every visit.

Due to the fact that majority of the patients present with heart failure with reduced ejection fraction (HFrEF), often with left ventricle ejection fraction (LVEF) of 20–30%, echocardiography is crucial for monitoring of the treatment toxicity along with the assessment of adverse effects using CTCAE v5.0 scale. Moreover, the heart failure severity is assessed with NYHA scale, and patient reported outcomes are measured through EuroQol EQ-5D questionnaire. Laboratory tests – creatine kinase, cardiac T troponin, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) serve as an additional index of myocardial injury.

The optional examination includes follow-up CT and MRI. Generally, due to significant comorbidities presented by the patients, often including renal failure, we leave the choice to the attending physician discretion.

OTHER CONSIDERATIONS

The cooperation between radiotherapy and cardiology departments extending far beyond the usual safety or treatment side effects management issues brings a multitude of new challenges and difficulties. Despite proper theoretical work-up and practical training in centers experienced in cardiac radiosurgery, our team has found dozens of unexpected obstacles, and it took us many mock cases to overcome those. A number of issues starting from proper imaging, through integration of electrophysiological data, appropriate patient setup and target tracking during treatment had to be worked out and solved. We encourage physicians who consider using STAR to contact the corresponding author for further information. We have started enrolment and the first patient was treated in December 2020.

TABLE 2.
Follow-up schedule.

	pre-RT	post-RT	1 wk	6 wk	3 m	6 m	9 m	12 m	18 m	24 m
Clinical examination	X	X	X	X	X	X	X	X	X	X
ECG	X			X	X	X	X	X	X	X
Holter ECG		X								
Echocardiography	X				X			X		X
ICD readout	X			X	X	X	X	X	X	X
AE – CTCAE v5.0	X	X	X	X	X	X				X
Drug uptake assessment	X	X	X	X	X	X	X	X	X	X
NYHA, EuroQol EQ-5D	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X		X	X	X			X		X
CT	X				O			O		O
MRI	O				O			O		O

O – optional.

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