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
INTRODUCTION
Since its first application in October 2012, radiotherapy in the
treatment of ventricular tachycardia (VT) has proven its effec-
tiveness 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. Radio-
frequency 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 ab-
lation [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 be-
tween radiation oncologists, cardiologists and electrophysi-
ologists, 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 contraindcations
to catheter ablation, will be treated with single-fraction
radiotherapy 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 up-
take 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 – Ra-
diosurgery in Treatment of Ventricular Tachycardia (SMART-VT)
and received clinical trial identifier NCT04642963.

TRIAL FUNDING
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towice, Poland. The authors and investigators receive no remu-
neration for the participation in this trial.

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 produc-
ning fibrotic lesions, similar to those induced by catheter ablation
[3, 4]. Despite an ongoing dispute regarding the actual mecha-
nism of action of ionizing radiation on the ventricular myocardi-
um, 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], includ-
ing results of two prospective clinical trials. The first study, pub-
lished by Robinson et al. [12], demonstrated both safety and ef-
fectiveness 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 epi-
dodes 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 in-
consistent results of the recent clinical trial [13] and retrospective
never yet been performed in Poland and treatment techniques
are significantly different between institutions and authors, a pi-
lot 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 radiothera-
py. The sample size planning is based on the assumption that ob-
served safety of < 50% (null hypothesis) will lead to the rejection
of the alternative hypothesis of a safety of > 90% (H1). 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% (β = 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.

WORK-UP AND TREATMENT DELIVERY
The procedural workflow is briefly presented on figure 2.

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 induced VT during electrophysiological study.
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>
<thead>
<tr>
<th>OAR</th>
<th>Volume</th>
<th>Volume dose</th>
<th>Point dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV minus CTV</td>
<td></td>
<td>-</td>
<td>31.25 Gy</td>
</tr>
<tr>
<td>CTV</td>
<td>&lt; 1 cm³</td>
<td>32.5 Gy</td>
<td>35 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>&lt; 0.35 cm³</td>
<td>10 Gy</td>
<td>14 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.2 cm³</td>
<td>8 Gy</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>&lt; 5 cm³</td>
<td>11.9 Gy</td>
<td>15.4 Gy</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt; 5 cm³</td>
<td>17.4 Gy</td>
<td>22 Gy</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt; 5 cm³</td>
<td>11.2 Gy</td>
<td>17 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 cm³</td>
<td>9 Gy</td>
<td></td>
</tr>
<tr>
<td>Trachea and main bronchi</td>
<td>&lt; 4 cm³</td>
<td>17.4 Gy</td>
<td>20.2 Gy</td>
</tr>
<tr>
<td>Lungs (together)</td>
<td>&lt; 1500 cm³</td>
<td>7 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 1000 cm³</td>
<td>7.6 Gy</td>
<td></td>
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<td></td>
<td>&lt; 37%</td>
<td>8 Gy</td>
<td></td>
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<tr>
<td>Liver</td>
<td>&lt; 700 cm³</td>
<td>11 Gy</td>
<td></td>
</tr>
<tr>
<td>Kidneys (together)</td>
<td>&lt; 200 cm³</td>
<td>9.5 Gy</td>
<td></td>
</tr>
<tr>
<td>Coronary arteries^</td>
<td></td>
<td>-</td>
<td>12 Gy</td>
</tr>
<tr>
<td>Ribs</td>
<td>&lt; 5 cm³</td>
<td>28 Gy</td>
<td>33 Gy</td>
</tr>
<tr>
<td>Skin</td>
<td>&lt; 10 cm³</td>
<td>25.5 Gy</td>
<td>27.5 Gy</td>
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</table>

* 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.

<table>
<thead>
<tr>
<th></th>
<th>pre-RT</th>
<th>post-RT</th>
<th>1 wk</th>
<th>6 wk</th>
<th>3 m</th>
<th>6 m</th>
<th>9 m</th>
<th>12 m</th>
<th>18 m</th>
<th>24 m</th>
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<tr>
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<td>X</td>
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<tr>
<td>ECG</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Holter ECG</td>
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<tr>
<td>Echocardiography</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>AE – CTCAE v5.0</td>
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<td>Drug uptake assessment</td>
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<tr>
<td>NYHA, EuroQol EQ-SD</td>
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<tr>
<td>CT</td>
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<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>MRI</td>
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<td>O</td>
<td>O</td>
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</tbody>
</table>

O – optional.
References

Stereotactic management of arrhythmia – radiosurgery in treatment of ventricular tachycardia (SMART-VT) – clinical trial protocol and study rationale
Authors' contributions:
Marcin Miszczyk: study design, literature search, review and analysis, manuscript and figure preparation and review;
Tomasz Jadczyk: study design, literature search, manuscript and figure preparation;
Bartłomiej Tomasik: study design, development of study statistical rationale;
Tomasz Latusek: study design, literature search, manuscript preparation;
Jacek Bednarek: study design, manuscript preparation;
Tomasz Latusek: literature search and manuscript preparation;
Radosław Kurzelowski: literature search and manuscript preparation;
Krzysztof Gołba: manuscript review and supervision;
Wojciech Wojakowski: study design, manuscript review and supervision;
Krystian Wita: manuscript review and supervision;
Łukasz Dolla: study design – irradiation technique and quality assurance, manuscript preparation;
Aleksandra Grządziel: study design – irradiation technique and quality assurance, manuscript preparation;
Slawomir Blamek: study design, manuscript preparation, review and supervision.

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