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Original Article

Stereotactic management of arrhythmia - radiosurgery in treatment of ventricular tachycardia (SMART-VT). Results of a prospective safety trial

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ABSTRACT

Background and purpose: Despite its increasing popularity, there are limited prospective data on stereotactic arrhythmia radioablation (STAR). In this trial, we assessed the safety and efficacy of STAR in patients with ventricular tachycardia (VT), focusing on early treatment-related grade $\geq$ 3 adverse events (AE).

Materials and methods: This prospective trial was designed for adults with VT recurrence following catheter ablation (CA) despite adequate pharmacotherapy, or contraindications to CA. A single dose of 25 Gy was delivered to the arrhythmia substrate defined on electro-anatomic mapping and cardiac-gated CT. The primary endpoint was safety, defined as two or fewer treatment-related grade $\geq$ 3 AEs during the first three months in 11 patients. Additional endpoints included treatment efficacy, clinical and biological markers of cardiac injury, and quality of life.

Results: Eleven patients with a median age of 67 years, structural heart disease, and a clinically significant recurrence of VT despite adequate pharmacotherapy and 1–4 previous CAs were enrolled between 2020/09 and 2022/10. Following the treatment, one patient developed a possibly treatment-related grade $\geq$ 3 AE, a grade 4 heart failure exacerbation at 87 days, which resolved after conservative treatment. There was a total 84.3% reduction in VT burden in 10 evaluable patients; however, VT recurrence was eventually observed in eight, and three patients required additional CAs. Three deaths due to unrelated causes were recorded.

Conclusions: STAR appears to be safe and efficient. It is a promising treatment for selected patients; however, long-term outcomes remain to be evaluated, and controlled trials comparing STAR with standards of care are missing.

Ventricular tachycardia (VT) is a life-threatening arrhythmia that affects the heart's lower chambers and can cause rapid, abnormal heartbeats. VTs are a major cause of sudden cardiac death [1] and a significant clinical challenge in situations when conventional therapies, including antiarrhythmic drugs (AADs), implantable cardiac defibrillators (ICD), and invasive catheter ablations (CA) fail to provide effective results [1,2]. Subepicardial and deep-intramural localizations of the arrhythmogenic substrate, as well as the vicinity of critical structures, increase the risk of CA failure, resulting in up to 20–50% of recurrences [3,4]. In such cases, STereotactic Arrhythmia Radioablation (STAR), also referred to as cardiac stereotactic body radiotherapy (cardiac SBRT), holds promise for a ground-breaking solution.

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This minimally invasive technique uses high-precision radiotherapy (RT) to deliver a high single dose to the arrhythmia substrate. The case series by Cuculich et al. [5] followed by the trial by Robinson et al. [6] ignited worldwide interest, but the clinical data is still sparse [7]. So far, only three prospective trials have published their results [6,8,9]. In this article, we describe primary outcomes of the SMART-VT trial (NCT04642963). The study was conducted in collaboration with the Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary (STOPSTORM) consortium (https://www.stopstorm.eu/), and supported by the European Union's Horizon 2020 grant (No 945119). The basic information on the structure and function of the consortium can be found in the article published by Grehn at al. [10].

Material and methods

The SMART-VT trial was a prospective single-arm safety trial conducted at two cooperating centres, including Maria Sklodowska-Curie National Research Institute of Oncology in Gliwice responsible for STAR delivery, and Leszek Giec Upper-Silesian Medical Centre of the Medical University of Silesia in Katowice, responsible for the cardiologic aspects of the treatment. The study was approved by the Bioethical Committee of Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland, on 2020/07/10 (KB/430–45/20), and amended on 2021/07/21 to adhere to the requirements of the STOPSTORM consortium.

A detailed trial protocol description has been previously published [11]. Eligible patients were aged 18 years or older with structural heart disease and an ICD. The patients had clinically significant monomorphic VT recurrence despite adequate pharmacotherapy and at least one prior CA, or contraindication to CA. The exclusion criteria were heart failure (HF) requiring inotropic treatment or mechanical assistance, channelopathy-related arrhythmia, reversible aetiology of VT, New York Heart Association (NYHA) class IV, and myocardial infarction or cardiac surgery within three months prior to enrolment. Patients with a life expectancy of less than six months or pregnant were not eligible for the trial.

The target volume definition was based on a synthesis of available electrophysiological and medical data, including a catheter-based electro-anatomical study (EAM) performed on the EnSite Precision intracardiac system, 12-lead electrocardiography (ECG), ICD memory readouts, records from previous CAs, and cardiac-gated contrast-enhanced computed tomography (CT). Healthy, diseased, and fibrotic myocardium were defined as presenting a bipolar voltage of > 1.5 mV, 1.5–0.5 mV, and < 0.5 mV on the 3D colour-coded voltage map. The target definition was aided by the American Heart Association (AHA) heart segment model [12] and the built-in EnSite Precision CT-integration feature. The Slicer3D-aided workflow developed by Hohmann et al. [13] and the heart segmentation guide described by Brownstein et al. [14] were adopted as additional supportive tools. The data was post hoc reviewed using CARDIO-RT software [15]. Following the definition by a multidisciplinary team, the target volume was transferred to the treatment planning CT.

The internal target volume (ITV) was expanded by 3 mm to produce a planning target volume (PTV). A single dose of 25 Gy was delivered to the PTV using volumetric modulated arc therapy (VMAT), typically consisting of 3–4 arcs, delivered on a Varian EDGE^{TM} linear accelerator (Fig. 1). The OAR dose constraints were described previously [11]. Adherence to organs at risk (OAR) dose constraints had priority over PTV coverage, including coronary artery sparing (Fig. 2). The respiratory movement was managed using deep inspiration breath hold (preferred) or free-breathing respiratory gating. Image-guided RT included 2D kV-kV imaging, respiratory-gated cone beam CT, and continuous surface-guided RT. ICDs were checked both before and after STAR using dedicated programmers. During RT, the arrhythmia detection was turned off,

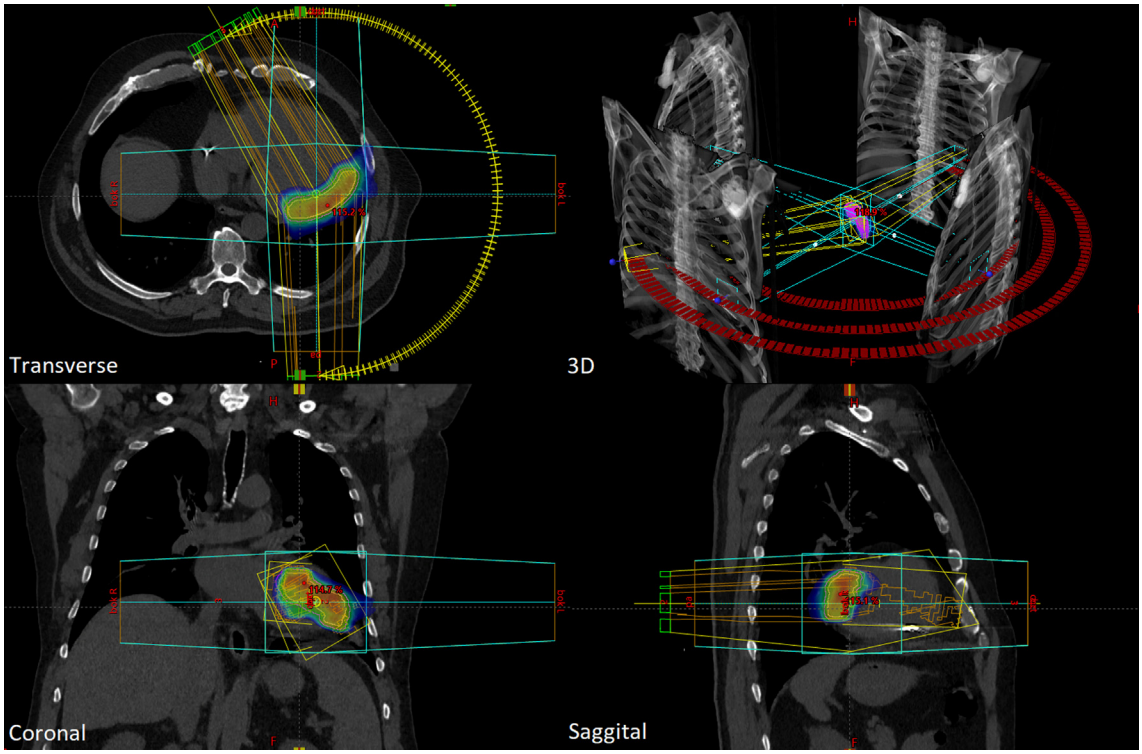

Fig. 1. An example of VMAT RT delivery plan used in the SMART-VT trial. The yellow and purple structures represent the ITV and PTV, respectively.

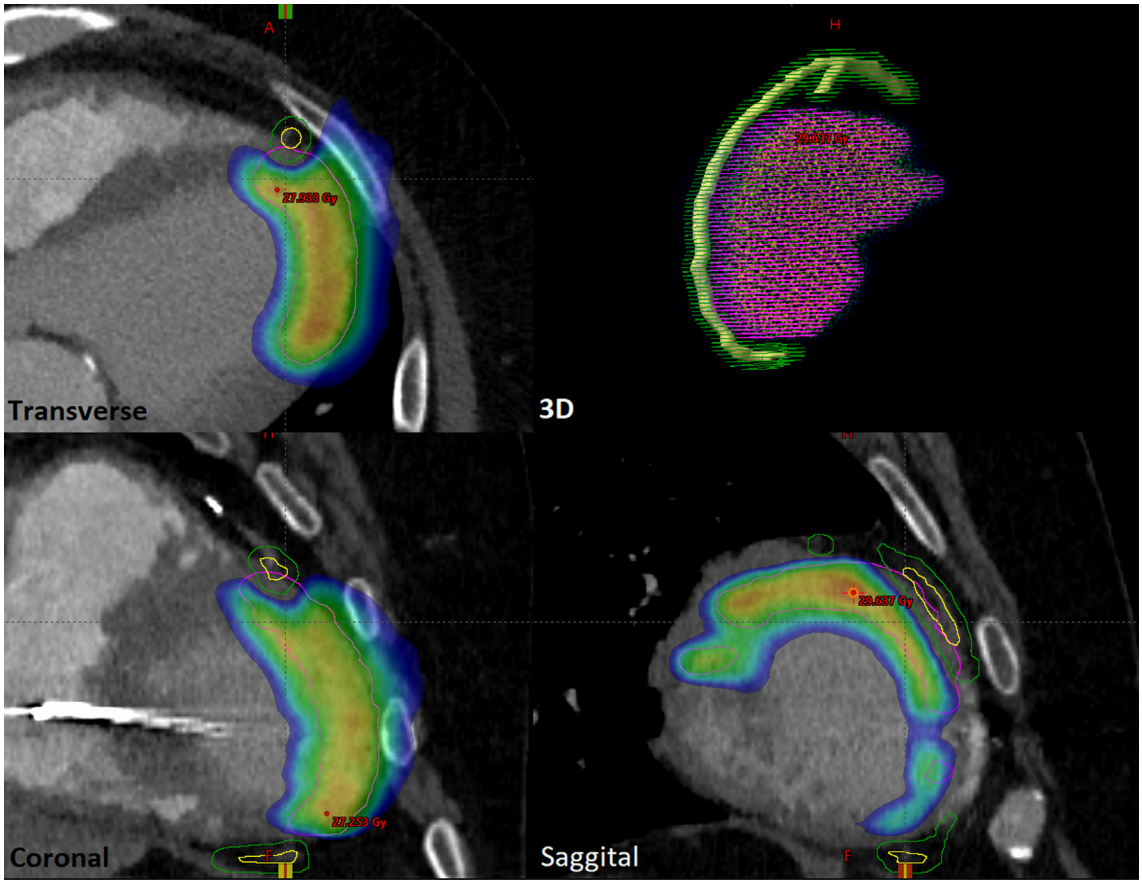

Fig. 2. An example of coronary artery sparing.

and patients were monitored using an external cardiac monitor. The treatments were conducted in line with the available guidelines [16].

The primary endpoint was 3-month safety, defined as the rate of treatment-related grade $\geq$ 3 serious adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 in the first 90 days after RT. The sample size was based on a 95% success rate for the primary endpoint ($\leq$5% rate of treatment-related serious AEs), α level of 5%, and a power of 90%. Based on Simon and Fleming's two-stage designs [17,18], an interim analysis was planned after the first seven patients, and the study would be terminated if the primary endpoint occurred in more than one patient. To reject the null hypothesis, no more than two patients would have to experience treatment-related grade $\geq$ 3 events in total. Secondary endpoints included reduction of VT burden (defined as the total number of ICD shocks, VT episodes, and anti-tachycardia pacing [ATP] during each time interval), changes in quality of life (QoL) measured using the EQ-5D questionnaire, estimation of cardiac injury through biochemical markers (including cardiac troponin T [TnT], creatine kinase [CK], and N-terminal prohormone B-type natriuretic peptide [NT-proBNP]), and left ventricular ejection fraction (LVEF), changes in antiarrhythmic drug uptake, late toxicity, and mortality.

The patients were followed up using a previously described schedule [11]. The ICD devices were programmed according to the guidelines [19,20]. The VT burden was calculated as the total number of VT episodes in a given time recorded by an ICD, 12-lead ECG, or Holter ECG. The electrograms of all documented episodes were reviewed to prevent the collection of other tachyarrhythmias. Sustained VT was defined as over 30 seconds long or until properly treated, with no low cut-off value. VTs resulting in ventricular fibrillation were registered as VT episodes. One treatment per episode (ATP, ICD shock, or external cardioversion) was recorded. Electrical storms and incessant VTs were defined according to previously described criteria [21]. VT recurrence was defined as any VT episode occurring after STAR.

Results

The clinical characteristics of the study group are summarised in Table 1. From September 2020 to November 2022, 11 patients with a median age of 67 years (range 45–72) were enrolled. The majority of patients had ischemic cardiomyopathy (81.8%), NYHA score of II (72.7%), and a median LVEF of 27% (range 20–40). All patients were accrued due to a VT recurrence following at least one previous CA (median 1, range 1–4), including an epicardial ablation in one case. The median FU was 22.2 months (range 1.3–28.6).

The list of grade $\geq$ 3 AEs is presented in Table 2. During the first 90 days, one patient experienced a grade $\geq$ 3 treatment-related toxicity, a grade 4 HF exacerbation at 87 days was classified as possibly attributable to the treatment. The AE resolved after conservative treatment (intravenous inotropic agents, diuretics, and levosimendan) without any major lasting effect on the patient's LVEF. Three more non-treatment-related grade $\geq$ 3 AEs occurred during the first 90 days, including a grade 3 drug-related hyperthyroidism with hypokalaemia and subsequent VT at one week, a

Table 1
Clinical characteristics of the SMART-VT trial study group. Nominal variables presented as counts and percentages, continuous variables presented as median and range.

Variable	N = 11
Median age [years]	67 (45–72)
Median follow-up [months]	22.2 (1.3–28.6)
Sex [male]	10 (90.9%)
Median distance from domicile to hospital [km]	125 (12–339)
Type of cardiomyopathy:	
Ischemic	9 (81.8%)
Non-ischemic (peripartum cardiomyopathy)	1 (9.1%)
Non-ischemic (inflammatory dilated cardiomyopathy)	1 (9.1%)
NYHA class	
I	1 (9.1%)
II	8 (72.7%)
III	2 (18.2%)
Median LVEF [%]	27 (20–40)
Number of prior LV catheter ablations	
1	6 (54.5%)
2	1 (9.1%)
3	2 (18.2%)
4	2 (18.2%)
Type of implantable device	
ICD (dual chamber)	5 (45.5%)
ICD (single chamber)	3 (27.3%)
Cardiac resynchronization therapy with defibrillator	3 (27.3%)
Comorbidities (stabilized before enrolment):	
Type 2 diabetes mellitus	5 (45.5%)
Hyperthyroidism	6 (54.5%)
Hypothyroidism	2 (18.2%)
Stage $\geq$ 3 chronic kidney failure	5 (45.5%)
Median BMI	27.2 (23.7–34.7)
Cardiologic medication uptake:	
Amiodarone 200 mg/d	4 (36.4%)
Mexiletine 600 mg/d	4 (36.4%)
β-blockers	11 (100%)
Angiotensin enzyme converting inhibitors	6 (63.7%)
Angiotensin receptor-neprilysin inhibitors	4 (36.4%)
Angiotensin receptor blockers	10 (90.1%)
Diuretics	8 (72.7%)
Radiotherapy technique:	
DIBH, VMAT	10 (90.9%)
FBRG, VMAT	1 (9.1%)
Median VMAT arcs	3 (3–4)
Median number of CBCT per treatment	2 (1–5)
Median planning target volume (PTV) [cc]	73 (18.6–111.3)
Median beam-on time [minutes: seconds]	13:26 (9:25–18:54)
Median treatment session time* [minutes: seconds]	43:54 (31:34–101:47)

NYHA – New York Hearth Association; LVEF – left ventricle ejection fraction; ICD – implantable cardioverter-defibrillator; CA – catheter ablation; BMI – body mass index; DIBH – deep inspiration breath hold; VMAT – volumetric modulated arc therapy; FBRG – free breathing respiratory gating; CBCT – cone beam computed tomography.
* calculated from the initiation of kV-kV 2D positioning to the completion of delivery of the last field of the treatment plan.

diagnosis of an advanced pelvic tumour that led to the death of one of the patients at 5.5 weeks, and a grade 4 tooth infection with subsequent sepsis and an electrical storm at six weeks. Considering the probable cause associated with systemic infection and the different, previously unrecorded VT cycle length, the electrical storm was designed as a non-treatment-related AE.

Including the aforementioned events, eight out of 11 patients experienced grade $\geq$ 3 AEs, and nine patients (81%) were hospitalized due to HF (n = 8 in five patients at a median of 9.6 months) or VT recurrence (n = 11 in six patients) over the course of FU. One patient experienced myocardial infarction without coronary artery occlusion at 7.6 months. Another patient had percutaneous coronary intervention performed twice at approximately nine and 12 months due to restenosis in the left anterior descending artery outside of the irradiated region. A grade 3 pleural effusion was diagnosed at 10.8 months, attributed to a supraventricular ablation for previously diagnosed grade 3 paroxysmal atrial fibrillation, both of which were regarded as non-treatment related events. The remaining three grade $\geq$ 3 AEs were found to be unequivocally non-attributable to STAR, including COVID-19-related pneumonitis, a complicated urinary tract infection, and a diagnosis of early-stage laryngeal cancer. A complete list of grade $\geq$ 3 AEs is presented in Table 2. The maximum dose to the ICD did not exceed 0.1 Gy in any case, and we did not observe any ICD malfunctions following STAR.

The individual patient data on LVEF, NYHA class, biochemical markers of cardiac injury, and QoL described in this paragraph are presented in Supplementary File 1. We generally did not observe signs of excessive acute cardiac injury following STAR. The median patient had 0% change in LVEF at three months, including four patients with LVEF reduction and four patients with LVEF increase (range −8% to + 24%). At 12 months, the median change was an increase by 4%; five out of seven evaluable patients had increased LVEF, and the remaining two presented a minor decrease (range −3% to + 16%). The NYHA class was stable in most cases; deterioration was observed in one, while improvement was seen in four out of 10 evaluable patients at three months. Two out of seven patients had improved NYHA class at 12 months, and no change was observed in the remaining five. The biochemical markers did not indicate acute cardiac injury. The median change at three months was 0 ng/mL for TnT (range −0.05 to + 0.01), +4 U/L for CK (range −1 to + 7), and −108 pg/mL for NT-proBNP (range −1141 to + 2228). These changes could be considered adequate to the comorbidity burden and matched periodic events of HF and kidney disease exacerbation. We found that QoL measured using the EQ-5D questionnaire improved in five out of eight evaluable patients at three months, five out of seven at six months, and four out of seven at 12 months. However, there was high variability in QoL reporting, and the results should be interpreted with caution.

Three deaths were recorded, none of which were considered treatment-related. In one case, a large pelvic tumour (13.5 × 12.5 × 15.5 cm) suspected of advanced ovarian cancer was diagnosed during hospitalization due to a general health status decline. The patient died shortly after, at 5.5 weeks after STAR, and experienced an electrical storm before passing away. Neither a biopsy of the lesion nor an autopsy were performed. The second patient died at 11 months following an acute heart transplant rejection performed due to a HF exacerbation with severe hepatic insufficiency secondary to right ventricle failure, and disseminated intravascular coagulation. The third patient died at 22.2 months due to HF exacerbation, pneumonia, and sepsis.

The changes in VT burden are presented in Fig. 3. There were 313 VT episodes in the three month period before treatment (median 27; range 2–100) in the 10 evaluable patients, compared to 49 (median 0; range 0–28) in the corresponding 3-month post-blanking period. This translates to a total reduction of VT episodes of 84.3%. The 95%, 75%, and 50% VT burden reductions were achieved in 80%, 80%, and 90% of patients, respectively. In the same time frame, the number of ICD shocks was reduced by 88.3%, from 103 (median 4.5; range 0–30) to 12 (median 0; range 0–9), the number of ATPs was reduced by 85.1%, from 202 (median 10; range 0–70) to 30 (median 0; range 0–22), and the number of electrical storms or incessant VTs was reduced by 80.8%, from 26 (median 2; range 1–6) to five (median 0; range 0–3). During the 3-month blanking period in between, there were a total of 108 VT episodes (median 0; range 0–60), 11 ICD shocks (median 0; range 0–6), 95 ATPs (median 0; range 0–58), and 11 electrical storms or incessant VTs (median 0; range 0–6).

The VT recurrence was observed in eight out of 10 patients at a median of 6.5 months (range 3.5–20.3). In three cases, based on the VT cycle length, it was suspected that the patients experienced

Table 2
Grade 3 or higher AEs following STAR.

Attribution*	G3		G4		G5	
	Non-attributable	Attributable	Non-attributable	Attributable	Non-atributtable	Attributable
≤ 90 days						
Heart Failure				1		
Hyperthyroidism	1					
Tooth infection			1			
Neoplasms benign, malignant and unspecified: Ovarian cancer suspected^					1	
> 90 days						
Heart Failure	2		3		2	
Myocardial infarction	1					
Cardiac disorders:Coronary Artery Disease	2					
Supraventricular Tachycardia	1					
Pneumonitis#			1			
Urinary tract infection	1					
Neoplasms benign, malignant and unspecified: laryngeal cancer	1					
Pleural Effusion&	1					

* Adverse events were scored on a 5-item scale. The event was regarded as attributable if the attribution was ranked as 'definite', 'probable' or 'possible', or as non-attributable if ranked as 'unlikely' or 'unrelated'; ^Large abdominal mass, ovarian cancer suspected. Patient died before histopathology could be performed; #COVID-19 infection; &Complication of supraventricular catheter ablation performed at 9 months.

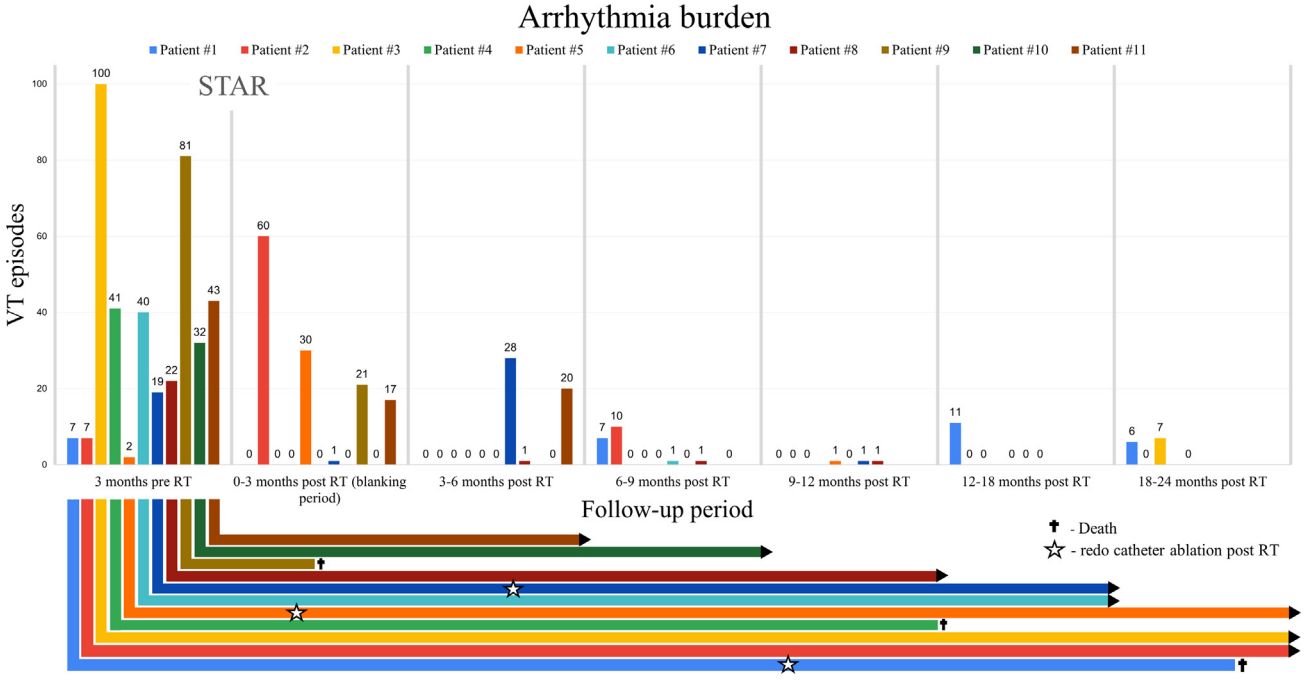

Fig. 3. The changes in VT burden over time following STAR.

recurrences of previously treated arrhythmias; similar morphology was confirmed by ECG in one case. Another two patients presented with slower VT of significantly different morphology on ECG. In the remaining three cases, the patients experienced a recurrence of a slower VT despite comparable oral medication uptake, but ECG record was not available. Three patients received additional CA due to incessant VT at 1.7 months or recurrent VT at 3.6 and 17 months.

Discussion

We present the results of the first Polish study on the use of RT in treating VT, and the largest prospective European trial on STAR to report its primary endpoints so far. We found that STAR was associated with acceptable short-term toxicity and no major concerns for acute cardiac toxicity. VT recurrences were noted, but the VT burden was significantly reduced. Late AEs remain to be evaluated.

Similarly to previously published studies, we found that the rate of grade ≥ 3 AEs associated with STAR is low. There was only one grade ≥ 3 AE, an HF exacerbation at approximately three months. There were two grade 3 treatment-related AEs during the first three months of FU in the ENCORE-VT trial, including an HF exacerbation and pericarditis [6]. No patients experienced treatment-related grade ≥ 3 AEs during the first three months of the STARNL-1 trial [9], among the first five patients treated in the RAVENTA trial [22], or in the first seven patients treated in the STRA MI VT trial [23]. However, the AE attribution seems highly

subjective. For example, we observed a total of eight instances of grade $\geq$ 3 HF exacerbations in 11 patients, seven of which were designated as non-treatment-related, while Robinson et al. reported nine instances of grade $\geq$ 3 HF in 19 patients, eight of which were marked as "possibly" related to STAR [6]. It indicates a possible reporting bias and the necessity for prospective controlled trials to account for spontaneously occurring AEs (e.g. cardiovascular hospitalisations occur 0.47 times per year in HF patients on average) [24].

Recent studies suggest that evaluating outcomes of VT treatment as a reduction of VT burden rather than dichotomous "recurrence" is more clinically relevant [25,26]. We found that STAR reduces the VT burden by 84.3%, comparable to previously reported rates of 87 – 94% [6,8,9]. Consistent with other authors, we also observed that most of patients experience clinical recurrence; however, as suggested earlier, the clinical implications differed. Only half of the evaluable patients required VT-related hospitalization, including three repeated ablation. Among the non-hospitalized patients, two experienced a singular VT with adequate ICD treatment, one had VT induced by an exacerbation of ischemic heart disease, and two remained VT-free. That said, there was general agreement to continue the previously most effective drug, and treatment modification was preferred over the attempt to discontinue AADs.

Initial studies done on swine suggested that STAR induces transmural CA-like fibrosis [27]. However, the porcine models do not necessarily reflect a structurally damaged, fibrotic human heart. Kautzner et al. reported fibrosis sharply transitioning to viable myocardium in the irradiated volumes [28], while Kiani et al. found necrotic central areas surrounded by a rim of fibrosis, markedly different from the regions of previous CA [29]. Some degree of fibrosis is expected, as the location of pre-existing structural heart damage usually corresponds to the targeted arrhythmia substrate. Zhang et al. found only a minor difference between targeted and non-targeted regions. The authors proposed an alternative theory of electrical conduction reprogramming, mediated by increases in cardiac sodium channel $Na_V1.5$ and connexin 43, explaining the rapid effect of STAR [30]. Following a heart transplant in a patient who had a sustained 1-year response to STAR, we found no signs of transmural fibrosis in the irradiated region [31]. More data is necessary to determine whether higher, fibrosis-inducing doses are necessary or lower doses are sufficient for the reduction of VT burden through the functional remodelling of the myocardium. Currently, there are ongoing trials investigating both dose escalation (NCT05594368) and de-escalation (NCT05258422).

The majority of the authors reference the publications of Robinson et al. [6] and Cuculich et al. [5] as evidence supporting the clinical use of STAR, but few authors implemented the described workflow. For example, in the review of current practices of STAR in Europe by Grehn et al., as few as 13% of the centres reported using non-invasive electrophysiological mapping, and only one used the 17-segment heart model for target definition. In comparison, 71% of the participating sites performed dedicated EAM before STAR [10]. The indirect data transfer introduces interobserver variability. In a benchmarking study by Boda-Heggemann et al., five university centres generated target volumes based on three datasets, resulting in conformity indices as low as 0.02 in worst cases [32]. Abdel-Kafi et al. found significant differences in interobserver target volume definitions, with the lowest overlap (35%) for lateral wall targets [33]. Additional steps, such as mapping at least three heart chambers [33] or the aortic arch [13] should be taken to reduce the risk of error.

Our study has several limitations, including a single-arm design, a modest study group, and limited long-term FU. The strict selection criteria and differences in STAR methodology between centres limit the generalization of the results. The 90-day safety endpoint does not provide information on the risk of late AEs. Due to the lack of a control group, the survival and AE rates are difficult to interpret. Considering the shifting paradigm of mechanisms of action, it is possible that the optimal STAR dose is significantly different from the currently used 25 Gy. High-volume analyses and randomized controlled trials are necessary. We intend to continue our research work in STAR through a subsequent efficacy trial (NCT05913375), and continue contribution to the STOPSTORM consortium [10], which can help to overcome several of the aforementioned limitations.

Conclusions

STAR appears to be a safe and effective treatment modality. The short-term safety profile is favourable, and no clinically relevant cardiac injury was noted; however, non-treatment related grade $\geq$ 3 AEs are common, likely reflecting the significant disease burden of the target population.

Despite common VT recurrences, the treatment results in a significant reduction of the VT burden. STAR remains a promising treatment option for selected patients with structural heart disease and clinically relevant VT recurrence following catheter ablation. Long-term outcomes and prospective studies comparing STAR to standards of care are necessary to draw final conclusions.

CRediT authorship contribution statement

Marcin Miszczyk: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Mateusz Sajdok:** Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Jacek Bednarek:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Tomasz Latusek:** Conceptualization, Investigation, Writing – review & editing. **Wojciech Wojakowski:** Writing – review & editing. **Bartłomiej Tomasik:** Conceptualization, Formal analysis, Investigation, Writing – review & editing. **Krystian Wita:** Writing – review & editing. **Tomasz Jadczyk:** Conceptualization, Investigation, Writing – review & editing. **Radosław Kurzelowski:** Investigation, Writing – review & editing. **Anna Drzewiecka:** Investigation, Writing – review & editing. **Magdalena Cybulska:** Investigation, Writing – review & editing. **Rafał Gardas:** Investigation, Writing – review & editing. **Grzegorz Jarosiński:** Investigation, Writing – review & editing. **Łukasz Dolla:** Methodology, Investigation, Data curation, Writing – review & editing. **Aleksandra Grządziel:** Validation, Investigation, Writing – review & editing. **Kamil Zub:** Methodology, Investigation, Writing – review & editing. **Adam Bekman:** Validation, Investigation, Writing – review & editing. **Konrad Kaminiów:** Resources, Writing – review & editing. **Anna Kozub:** Resources, Writing – review & editing. **Krzysztof S. Gołba:** Methodology, Investigation, Writing – review & editing. **Sławomir Blamek:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109857.

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