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23 Short title: Recurrences after arrhythmia radioablation

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1 Abstract

Background and Aims. Stereotactic arrhythmia radioablation (STAR) has been recently
introduced for the management of therapy-refractory ventricular tachycardia (VT). VT
recurrences have been reported after STAR but the mechanisms remain largely unknown.
We analyzed recurrences in our patients after STAR.

Methods. From 09.2017 to 01.2020, 20 patients (68±8y, LVEF 37±15%) suffering from
refractory VT were enrolled, 16/20 with a history of at least 1 electrical storm. Before STAR,
an invasive electro-anatomical mapping (Carto3) of the VT substrate was performed. A mean
dose of 23±2Gy was delivered to the planning target volume (PTV).

Results. The median ablation volume was 26 ml (range) 14-115) and involved the 10 interventricular septum in 75% of patients. During the first 6 months after STAR, VT burden 11 decreased by 92% (median value, from 108 to 10 VT/semester). After a median follow-up of 12 13 25 months, 12/20 (60%) developed a recurrence and underwent a redo ablation. VT recurrence was located in proximity of the treated substrate in 9 cases, remote from the PTV 14 in 3 cases and involved a larger substrate over ≥3 LV segments in 2 cases. No recurrences 15 occurred inside the PTV. Voltage measurements showed a significant decrease in both 16 bipolar and unipolar signal amplitude after STAR. 17

Conclusion. STAR is a new tool available for the treatment of VT, allowing for a significant reduction of VT burden. VT recurrences are common during follow-up, but no recurrences were observed inside the PTV. Local efficacy was supported by a significant decrease in both bipolar and unipolar signal amplitude.

22 Keywords

Ventricular tachycardia, stereotactic arrhythmia radioablation, toxicity, electrical storm,
 radiofrequency catheter ablation, arrhythmogenic substrate

25

1 What's New?

2 • This is the largest series of STAR published and provides for the first time data

3 on long-term follow-up.

- STAR lead to a significant reduction in VT burden, including 80% of patients with a
 history of one or more electrical storms.
- STAR also showed a positive safety profile. The interventricular septum was targeted
 in 75% of the patients, but none of them developed a high-degree AV-block at follow up.
- 9 VT recurrences were common after STAR. The analysis of sites of recurrence
- 10 showed that VT did not originate from the treated volume, but often in proximity to or
- 11 remote from the targeted volume.
- 12 Abbreviations
- 13 VT: ventricular tachycardia
- 14 ICD: implantable cardiac defibrillator
- 15 AAD: anti-arrhythmic drugs
- 16 CA: catheter ablation
- 17 STAR: stereotactic arrhythmia radioablation
- 18 AS: arrhythmogenic substrate
- 19 LGE-MRI: magnetic resonance imaging with late gadolinium enhancement
- 20 RV: right ventricle
- 21 LV: left ventricular
- 22 EAM: electroanatomical mapping
- 23 EGM: electrograms

- 1 CT: computed tomography
- 2 OAR: organs at risk
- 3 GTV: gross target volume
- 4 ITV: internal target volume
- 5 PTV: planning target volume
- 6 SBRT: stereotactic body radiation therapy
- 7 RT: radiotherapy
- 8 IVS: interventricular septum
- 9 TAS: arrhythmogenic substrate targeted by STAR

10

1 Introduction

2 Ventricular tachycardia (VT) is a life-threatening event for patients with heart disease, with a 3 significant impact on quality of life(1) and life expectancy(2, 3). Implantable cardioverter 4 defibrillators (ICD) improve prognosis but cannot prevent recurrences of sustained VT. 5 Treatment options to reduce VT burden include antiarrhythmic drugs (AAD) and catheter ablation (CA)(4, 5). AAD are often limited by side effects(6), while catheter ablation results in 6 limited success rates, with recurrences ranging between 40 and 70%(7-10). Limitations of 7 8 CA procedures include, among others, intramyocardial or epicardial circuits not accessible with conventional approaches such as intramural septal VT(11, 12). Stereotactic arrhythmia 9 radioablation (STAR) was first introduced in 2012(13) for the treatment of refractory VT. 10 Several case reports and series have been published worldwide, with good short-term 11 12 results(14-22), but VT recurred frequently(23, 24). Whether VT recurrences occurred within the treated STAR volume or were part of a remote substrate remains unknown to date. The 13 compassionate use of STAR was approved in 2016 in Switzerland in order to offer this 14 new treatment for patients in whom all conventional attempts to control sustained VT 15 recurrences failed. Herein, we report the efficacy and safety of STAR in the Swiss cohort, 16 and the frequency and sites of VT recurrences after STAR. 17

18

19 Methods

20 Patient population

This study included the first 20 consecutive patients treated with STAR for sustained VT *refractory to conventional treatment* in Switzerland at the University Hospitals in Lausanne (*Centre hospitalier universitaire Vaudois,* CHUV), in Bern (Inselspital) and in Zürich (*Unisersitätsspital Zürich,* USZ). All patients had been previously implanted with an ICD due to recurrent symptomatic scar-related VT. In all patients, treatment consisting of several AAD and at least one RF CA using an endocardial and/or epicardial approach if feasible (as listed in table 1) had failed. Arterial ethanol infusion targeting septal VT had also been attempted if considered suitable. For patients in whom the critical part of the arrhythmogenic substrate (AS) was deemed inaccessible, STAR was offered as a bailout strategy. *There no exclusion criteria.* Every case was evaluated by a multidisciplinary board including cardiac electrophysiologists and radiation oncologists. The patients, or their legal representatives, gave informed consent before STAR. The study was approved by the local Institutional Review Boards and Ethical Committees (Project-ID 2020-02637).

8 VT mapping

The extent and location of the AS were identified on cardiac magnetic resonance imaging 9 with late gadolimium enhancement (LGE-MRI) whenever possible. Otherwise, myocardial 10 using available cardiac imaging modalities (CT scan 11 scars were defined or echocardiography). Scar location was described following the 17-segment model of the 12 American Heart Association.(25) Every effort was made to collect 12-lead ECGs of the 13 clinical VT. If feasible, all patients underwent an invasive electrophysiological study before 14 STAR. To define the endpoint of CA, VT induction was attempted using a standard 15 programmed ventricular stimulation protocol from the right ventricle (RV) consisting of 2 16 basic cycle lengths (S1) up to 3 extrastimuli (S2-S4) down to 200 ms or to the RV effective 17 refractory period. Use of intravenous isoproterenol was left to the discretion of the operator. 18 All induced monomorphic VT were recorded. For clinical VT only recorded by the ICD, 19 monomorphic VT with a cycle \pm 20 ms from that of the ICD recording was considered as the 20 clinical VT. A left ventricular (LV) endocardial electroanatomical mapping (EAM) in sinus 21 22 rhythm or during RV pacing was performed in all cases using transseptal access, retrograde or both, except in one patient with a cardiac metastasis. The RV was also reconstructed in 23 24 every septal VT case. To optimize delineation of the AS, the mitral annulus and the coronary 25 sinus were also reconstructed when necessary. Voltage maps were created using 3.5-mm irrigated-tip catheters (Navistar or ST-SF Thermocool Biosense Webster, Diamond Bar, CA) 26 or multipolar diagnostic catheters (Pentaray, Biosense Webster, Diamond Bar, CA) and the 27

Carto3 system (Biosense Webster, Diamond Bar, CA). Areas displaying bipolar electrograms 1 (EGM) voltage ≤1.5 mV were defined as abnormal. EGM suggesting local slow conduction 2 3 (fragmented or late potentials), either spontaneously or unmasked by delivery of premature 4 beats, were tagged. A substrate-based approach was used to target the AS. Then, reinduction of VT was attempted. If still inducible, every effort was made to characterize the 5 clinical VT isthmus: activation time mapping, pace-mapping, morphology correlation using 6 7 the PASO algorithm from Carto and stimulation to QRS intervals were analyzed to identify VT exit sites. Finally, the reentrant circuit was mapped during VT and potential isthmuses 8 were verified using entrainment maneuvers whenever possible. 9

10 Treatment simulation

All patients had a set of planning computed tomography (CT) scans: 4D CT-scan and a breath-hold CT-scan with and without intravenous contrast enhancement. LGE-MRI scans were co-registered with the planning CT scan to help for AS delineation. Organs at risk (OAR), including the lungs, esophagus, stomach and coronary arteries were delineated. For patients treated using an MRI-based Linear accelerator (linac), a 0.35T MR-linac simulation without contrast agent was conducted.

17 Target delineation

18 The targeted AS (TAS) was defined primarily aiming the clinical VT, using the electrical information of the 12-lead ECG of the clinical VTs and data derived from invasive EAM, 19 combined with the morphological information from previous substrate imaging. The 20 gross target volume (GTV), corresponding to the TAS, was drawn by both the 21 electrophysiologists and the radiation oncologists. Additional margins around the GTV, called 22 23 internal target volume (ITV), were added to account for internal motion of the GTV caused by breathing and cardiac motion as assessed by reviewing the 4D-CT and/or MRI. For cases 24 treated with Cyberknife, 4D-CT was used to ensure that there was a rigid relation between 25 26 the movement of fiducials (ICD lead) and GTV. Finally, an additional safety margin of 2-5 mm (according to internal guidelines of each center) was added to the ITV for treatment planning
to create a planning target volume (PTV), which accounts for any residual uncertainties in
patient setup, motion and delivery. The images of the final treatment planning were analyzed
by the electrophysiologists and radiation oncologists in order to determine which LV
segments were included in the PTV. A third expert was involved in case of disagreement.

6 STAR planning and delivery

7 Inverse planning was used to spare OAR by applying the standard dose constraints dedicated to stereotactic body radiation therapy (SBRT) treatments as suggested by the 8 9 report of the American Association of Physicists in Medicine(26). No guidelines were 10 available for maximal doses on intracardiac structures, but special care was taken to limit the dose delivered to coronary arteries (<12 Gy) and all patients were informed about 11 the risk of iatrogenic AV block. The prescribed dose was 20-25 Gy in a single fraction 12 based on center preference. For patients treated in Bern and Lausanne, STAR treatments 13 were delivered using robotic SBRT with the Cyberknife system (Accuray, Sunnyvale, CA, 14 USA) with real-time tracking. For patients treated in Zurich, two radiotherapy (RT) devices 15 were available: an image-guided radiotherapy-equipped (IGRT) linac (TrueBeam, Varian 16 Medical Systems) that uses cone-beam CT and, alternatively, the MRIdian® Linac system 17 (ViewRay Inc., Oakwood Village, OH) with an onboard MRI(27). 18

19 STAR efficacy assessment

After STAR, patients were followed according to our standard of care after VT ablation. Patients were seen in the outpatient clinic at least twice a year with ICD interrogations at each visit. ICD programming was left to the discretion of the physician. *The efficacy of the treatment was assessed by quantifying VT burden (number of sustained VT episodes) at every follow-up and comparing it to all available data on VT burden before STAR.* Appropriate ICD antitachycardia pacing (ATP) and shocks, and untreated sustained VT in the monitoring zone were considered as recurrent VT episodes. The treating electrophysiologists
 adjudicated all ICD interrogations.

3 Radiation-related toxicity

Possible toxicities related to STAR were reported according to the Common Terminology
Criteria for Adverse Events (CTCAE, version 4.0). Serious adverse events were defined as
any grade 3 toxicity requiring hospitalization or any grade 4 to 5 toxicity.

7 VT recurrence after STAR

8 Sustained VT recurrences after STAR were managed with AAD whenever possible. 9 Otherwise, a new CA procedure was attempted. The site of VT recurrence was defined 10 following standard criteria as mentioned in the "VT-mapping" paragraph. Some patients 11 presented recurrences from distinctive sites, which were separately analyzed. In order to 12 determine the dose at the site of VT recurrence, EAM maps and STAR plans were reviewed 13 side-by-side by the electrophysiologists and radiation oncologists, then the delivered dose 14 was estimated based on the STAR plan.

15 Voltage measurements at sites of STAR during redo procedure

To **estimate** the effects of STAR on cardiac tissue, bipolar and unipolar voltage EGMs before and after STAR were retrospectively compared using the EAM data whenever available. Only data collected with a contact force sensing catheter were used for this analysis. All available points evenly distributed in the PTV were selected with a contact force $\geq 3g$, and compared to points collected from the same area during the last CA before STAR.

21 Statistical analysis

22 Continuous data are reported as mean (±standard deviation) or median (range) for non-23 normal distributions. Paired t-test or non-parametric Wilcoxon paired tests were used to 24 compare values before and after treatment at the 5% level of significance.

25 Results

1 Characteristics of the study population

2 From September 2017 to January 2020, 20 patients (15 males and 5 females) with recurrent refractory sustained VT were treated with STAR because of an intramural or inaccessible 3 AS, representing 5.3% of all CA for VT in patients with structural heart disease in the 4 participating centers. Table 1 shows the clinical characteristics of the study population, 5 whose median age was 68 years old and median LV ejection fraction 31%. 70% of the cases 6 7 were non ischemic. All patients had been implanted with an ICD, except the case with the 8 septal metastasis in whom a double chamber pacemaker had been implanted because of an estimated high risk of AV-block following STAR(28). All patients (except the case with a 9 cardiac metastasis) had a large AS with myocardial scarring distributed over a median of 5.5 10 segments (range 4-11). Eighteen patients (90%) had undergone several unsuccessful 11 attempts including AAD, endocardial and epicardial CA and ethanol infusion to control their 12 VT (Table 1). In one patient with a history of CABG and an uncontrollable electrical storm 13 (ES), STAR was performed as a primary treatment because of an LV thrombus. The patient 14 with the cardiac metastasis did not undergo a CA procedure. 15

16 STAR procedure

STAR was performed for the following indications (Table 2): 8 (40%) cases presented an 17 uncontrollable ES despite multiple AAD, of whom 4 (20%) were in the intensive care unit due 18 to incessant VT; 9 (45%) cases with recurrent VT required multiple ICD therapies; 2 (10%) 19 patients with multiple highly symptomatic non-sustained VT and 1 case after an ES triggered 20 21 by a cardiac metastasis. STAR was performed with the Cyberknife system in 16 (80%) 22 cases, with an MR-linac in 2 (10%) patients and with an IGRT-linac in the remaining 2 (10%) cases. A median dose of 24 (20-25) Gy was administered. The median GTV was 16 (4-74) 23 ml and the median PTV was 26 (14-115) ml. The smallest volume was observed with the 24 Cyberknife (PTV range 14-36 ml), followed by the IGRT-linac (PTV range 55-72 ml) and 25 finally the MR-linac (PTV range 66 to 115 ml). Table 2 and Figure 1 detail the AS targeted by 26 STAR: the interventricular septum (IVS) in 15 (75%) cases with an extension to the antero-27

basal LV in 6 and to the infero-basal LV in 3; in the remaining 5 (25%) cases, STAR was
delivered to non-IVS sites including the antero-lateral LV in 2 cases, the lateral LV in 1 case,
the inferior LV in 1 case and the antero-basal LV in 1 case.

4 Efficacy and Safety of STAR

Overall, STAR was followed by an important VT burden reduction from a median of 108 (3-5 5502) episodes six months before to a median of 10 (0-150) events six months after STAR 6 7 (p<0.005). In the 9 patients with an ES, 8 (89%) were successfully controlled by STAR. In one patient with terminal heart failure, the successful control of the ES by STAR allowed the 8 9 implantation of a left-ventricular assist device and discharge from the hospital 3 months later. 10 In the remaining patient with an ES (11%), STAR failed to suppress the incessant VT, resulting in the patient's death four days later. In the remaining 11 patients with recurrent VT 11 treated by STAR, an important VT burden reduction (88.1% reduction, p<0.005) was 12 observed in 9 (82%) patients as shown in Figure 2, with a drop in sustained VT episodes 13 from 108 (3-5502) six months before to 6 (0-150) events (median values) six months after 14 STAR. Two patients had continuous VT episodes despite STAR, but the tachycardia 15 changed from previously fast VT to incessant slow VT (Figure 2). In one patient, VT resolved 16 spontaneously, and in the other patient successful CA was performed. STAR allowed 17 tapering of the prescribed dose of amiodarone in four (36%) out of these 11 patients. 18

Table 3 reports the complication rates of the three antiarrhythmic approaches including 19 prescription of AAD, CA procedures and STAR. One patient showed an immediate increase 20 21 of VT episodes and developed a grade 4 ES following STAR (PTV 115 ml), which lasted 2 days and was treated with high-dose dexamethasone, presumably due to an inflammatory 22 reaction(27). Three (15%) patients developed ≥ 1 complication likely related to STAR: one 23 case of grade 2 nausea lasting 3 weeks after targeting the infero-basal LV, who developed 24 25 later on a fibrotic pericardial reaction preventing epicardial needle access (grade 1); one 26 case developing a spontaneous rib fracture (grade 2) spontaneously resolving within 3 27 months after STAR targeting the LV apex; one case of a rapid progression of a previously moderate and stable aortic stenosis to severe aortic stenosis requiring percutaneous aortic
valve replacement 16 months after STAR delivery at the anterior base of the LV (grade 4). *No ICD dysfunctions were observed.* Out of the 20 patients, seven (35%) died at a median
follow-up of 25 (0.1-47.6) months: four patients at 3, 12, 14 and 15 months after STAR
because of terminal heart failure and two due to recurrent ES 4 days and 7 months after
STAR. The last deceased patient decided to switch off his LVAD at 25 months due to
extreme psychological stress.

8 VT recurrence after STAR

Despite an important reduction in VT burden, 18 (95%) of the 19 patients alive one week 9 after STAR presented a recurrence as sustained VT at a median follow-up of 25 (3-48) 10 months. Four (20%) patients developed a slow VT, including two incessant ones, not seen 11 before STAR. Twelve (67%) of the 18 patients with VT recurrence underwent a redo CA 12 procedure. A median of 1 (1-5) redo CA were performed, the first one at a median of 9 13 months after STAR: 5 for ES, 1 for incessant slow VT and 6 for recurrent fast VT. Figure 3 14 summarizes the localization of 14 VT recurrences occurring in 12 patients according to the 15 PTV. Two patients presented two different VT morphologies originating from distinct AS 16 involving separate myocardial segments. Both cases had a combined AS involving idiopathic 17 IVS fibrosis and an ischemic scar involving the lateral LV. The ischemic VT was successfully 18 treated by CA. The IVS fibrosis required a second STAR procedure targeting an area 19 adjacent to the first PTV delivered 16 and 25 months after the first STAR (Figure 6)(29). 20 There were no VT recurrences within the PTV among patients who underwent a redo CA. 21 22 Mapping of VT recurrences showed an exit site remote from the PTV in 3 (21%) (Figure 4), in proximity of the PTV (defined as in the same or the directly adjacent segment to the 23 **PTV)** in 9 (64%) (Figure 5) and involving a large AS (\geq 3 LV segments) in 2 (14%). 24 25 Supplemental Figure 1 details the EAM before and after STAR, the STAR plan and the bulleye views with PTV and VT recurrence sites for the 14 VT recurrences occurring in 12 26 27 patients.

1 Voltage measurements at sites of STAR in redo procedures

Among the 12 patients who underwent a redo CA after STAR, 9 had exploitable voltage data
of the irradiated region. Seven to eleven points per patient were used for comparison.
Compared to voltage measurements before STAR, a significant decrease in the EGM
amplitude was observed after STAR (1.79±1.23 vs 1.12±1.24 mV, Δ 0.67 mV and 4.37±2.04
vs 3.38±2.33 mV, Δ 0.99 mV, for bipolar and unipolar signals respectively, p=0.02 and 0.01.
Figure 2 supplemental data), with the biggest difference for unipolar EGM.

8 Dose evaluation at site of recurrence

9 The dose delivered by STAR was evaluated at 14 sites of VT recurrence in 12 patients 10 (Figure 7 and supplemental Table 1). In 3 (21%) VTs, redo CA after STAR targeted an AS 11 remote from the PTV. The mean dose delivered at these sites was 1.95±2.92 Gy (range 12 0.12-14.31). In 9 (64%) VTs, the recurrence was at the proximity of the PTV. The mean dose 13 delivered at these sites was 11.31±7.47 Gy (range 0.50-28.37). In the remaining 2 (14%) 14 cases, several VTs involving a much larger AS were found. The mean dose delivered at 15 these sites was 12.46±16.33 Gy (range 0.11-26.16).

16 Discussion

In this highly selected population of patients with refractory VT because of intramural or inaccessible AS, STAR was effective and safe, allowing for stabilization and discharge of 95% of the patients. VT recurrence, however, remained common during follow-up, with two thirds of the patients requiring additional treatments. Importantly, our series shows that most VT recurrences originated from areas outside or in the proximity but not within the PTV, confirming the efficacy of this new treatment modality. Voltage measurements at STAR area showed a significant decrease in both bipolar and unipolar signals amplitude.

24 Efficacy and safety of STAR

STAR is a new treatment modality introduced for refractory VT(13, 30). Currently, it is used 1 as a bailout procedure after failed ablation and antiarrhythmic prescription. In our population 2 3 with intramural or inaccessible AS, STAR resulted in a 92% VT-burden reduction in 17 out of 4 20 patients. This is in line with previously published series, showing a decrease in VT burden of 80-99%(14-16, 18, 21, 23). Compared to former series, our population includes the largest 5 number of non-ischemic and inflammatory cardiomyopathies, and of IVS irradiation, a 6 7 location that is particularly challenging for CA(11). Herein, the safety profile of STAR appeared favorable. Over a median follow-up of more than 2 years, only three cases 8 (15%) developed some radiation-related toxicity, with only one patient requiring intervention 9 due to worsening of an already known aortic stenosis after STAR delivery at the anterobasal 10 LV, close to the aortic root. Our low toxicity rate might be related to low PTV values (median 11 26 ml) thanks to the use of the Cyberknife device in 80% of the cases. Toxicities were 12 previously reported using LINAC-based devices involving rather high PTV values (up to 300 13 ml)(15, 17, 23, 31). Irradiation pneumonitis, one of the most commonly reported 14 complications, typically occurred after delivery of STAR at the LV free wall in close contact of 15 the left lung. Of note, 25% of our patients had already experienced adverse events related to 16 AAD and/or CA, a value higher than that reported after STAR(31). Our series also found a 17 20% death rate due to progression of heart failure after successful VT treatment, which is in 18 line with the published literature (14-16, 19, 32, 33). STAR targeted the IVS in 75% of our 19 20 cases, without any patient developing AV block during follow-up.

21

22 VT recurrence after STAR

As described in all previous published series, despite a marked reduction in VT burden, 95% of our population developed VT recurrence requiring a redo CA procedure in 60% of the cases over a mean follow-up of 24 months. In this subset of patients, we found that 64% of the VT occurred in proximity of the PTV, and 36% from a substrate remote from the PTV. To the best of our knowledge, our series is the first to show the high efficacy of this new

modality, where recurrence never occurred within the PTV. Recently, Peichl et al. reported a 1 2 case with VT recurrence after STAR related to an inaccurate delineation of the TAS(34). 3 Qian et al. also reported a recurrence arising from the area close to the PTV(35). 4 Altogether, these data highlight the importance of improving AS delineation and precise transfer to the planning CT to ensure VT control(36, 37). In order to prevent VT 5 recurrences, a possible strategy would be targeting a larger volume, encompassing as 6 7 much arrhythmogenic substrate (i.e. fibrotic tissue) as possible with STAR. Our experience with STAR dated back to 2017, when data on efficacy and toxicity of STAR were 8 scarce. We therefore intently minimized PTV by targeting the VT exit site. On the other 9 hand, enlarging the PTV might also increase the risk of collateral damage and toxicities(15, 10 17, 23). The choice of the treatment facility (linear accelerator versus radiosurgery system) 11 has also an impact on the size of the target volume and dose distribution, and must be taken 12 into account when planning the PTV and potential toxicities. We also showed that VT 13 recurrences can occur at sites remote from the PTV, from an evolving arrhythmogenic 14 15 substrate that might be addressed by CA. Hence, VT recurrence after STAR might not be systematically considered as a failed procedure. 16

17 Effect of STAR on tissue characteristics

The efficacy of CA relies on scar homogenization using various ablation techniques in order 18 to prevent reentry(38). Early animal studies have shown occurrence of fibrosis in irradiated 19 myocardial tissue, but with only a small number of dense or transmural scars(39-43). 20 21 Attempts to achieve bidirectional block within the atria appeared difficult with a success as 22 low as 7%(39) and required doses >40 Gy(43, 44). Most of these studies showed a decrease in local tissue voltage in the range of 83 to 100% (39, 40, 43). Our data are in line with these 23 24 findings. We found a mild decrease in local voltage within the PTV after STAR, particularly in 25 unipolar signals, which is suggestive of a transmural effect. Also in accordance with animal and human data, none of our patients with preserved AV conduction developed 3rd degree 26 27 AV block after STAR over a 2-year follow-up (18, 23, 40, 45, 46). Recently, Zhang et al. did

not observe fibrosis until 42 weeks after the delivery of up to 25 Gy to murine hearts (47). In 1 2 contrast, Kautzner et al. and Kiani et al. recently reported seven autopsy cases after the 3 delivery of 25 Gy to the VT substrate showing the appearance of fibrosis and central 4 hemorrhage(48, 49). Our series includes patients treated with 20 and 25 Gy. This mild difference in dose delivery did not appear to affect STAR efficacy, as shown by the lack of 5 recurrence within the PTV. It is well established that scar formation starts at best 4 weeks 6 7 after irradiation(50). The antiarrhythmic effects in some of our patients were seen much sooner than expected. Four of our patients were in the ICU because of uncontrollable VT 8 9 resistant to therapy. STAR was performed while the patients were intubated for >1 week in 2 cases. Both cases could be extubated within three days and all four could be discharged 10 11 alive from the hospital. Until recently, whether STAR displayed some acute antiarrhythmic properties remained debated. Kiani et al. recently reported hemorrhage and degenerative 12 changes in myocytes 12 days after STAR(49). Cha et al. have also shown early widening of 13 intercalated disks, and intercellular and intracellular edema after irradiation in rat hearts, 14 15 which might explain the early antiarrhythmic effect of STAR(51). Interestingly, the intercellular edema resolved within a week, while alterations of the intercalated disk, of the 16 cellular membrane and of intracellular organelles (e.g. damaged mitochondria) evolved over 17 time. The same group also found acute electrophysiological changes in human induced 18 stem-cell derived cardiomyocytes appearing as soon as within 1 hour after radiation(52). 19

20 Limitations

Some technical limitations must be considered. First, the EAM obtained from Carto could not be exported to perform a fusion with the DICOM images for radiotherapy planning and therefore the definition of the TAS *and the segment allocation were* done by integrating all available information side-by-side, a technique subject to large variability (36). Second, there are inaccuracies inherent to radiotherapy, particularly when using techniques without the possibility of target tracking. Even in cases treated with the CyberKnife system (and therefore using real-time tracking), the distance between the target volume and fiducials (ICD lead) was variable from one patient to another. Similarly, the estimation of the dose received at sites of recurrence, as well as voltage measurements based on EAM before and after STAR, were also performed by estimating the correct site by comparing the images side-by-side. Third, it is not possible to determine whether the occurrence of new AS is a pro-arrhythmic effect of low-dose irradiation within the heart, although experimental data did not report cellular changes below 15 Gy(47, 51). *Finally, not all VT recurrences underwent a redo CA, so that recurrences inside the PTV in those patients cannot be excluded.*

8

9 Conclusion

Stereotactic radiotherapy for therapy-refractory VT is a precious new tool available for the 10 treatment of these very ill patients, allowing for a significant reduction of VT burden. VT 11 recurrences are common during follow-up, but in our series none were observed inside the 12 PTV. Local efficacy was supported by a significant decrease in in both bipolar and unipolar 13 signal amplitude. A global approach targeting the whole AS, either with STAR alone or 14 combined with CA, as well as technical improvements allowing for a better integration of all 15 available information into the PTV definition, might improve the results. Bigger series of 16 patients will be necessary in order to confirm our findings and improve the STAR 17 strategy(53). 18

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20 Data availability statement

- 21 The data underlying this article cannot be shared publicly due to the privacy of study
- 22 participants. The data will be shared on reasonable request to the corresponding author.

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6 Supplemental Material

- 7 Table S1.
- Figures S1 and S2.
- 9

10

Table 1. Patient characteristics.

Ī	Age, year (median, range)	68 (47-80)
·	Gender, % (n)	
	Females	25 (5)
	Males	75 (15)
•	Structural heart disease, % (n)	
	Non ischemic cardiomyopathy	45 (9)
	Ischemic cardiomyopathy	30 (6)
	Inflammatory cardiomyopathy	20 (4)
	Cardiac metastasis	5 (1)
	LVEF (median, range), %	31 (20-72)
Ī	Device, % (n)	
	CRT-D	45 (9)
	Double chamber ICD	35 (7)
	Single chamber ICD	15 (3)
	Double chamber PM	5 (1)
	Drug therapy, % (n)	
	ВВ	100 (20)
	ACEI or ARBB	80 (16)
-	Failed AAD, % (n)	
	Amiodarone	85 (17)
7	Sotalol	15 (3)
	Flecainide	20 (4)
	Propafenone	5 (1)
	Lidocaine	10 (2)
	Mexiletine	15 (3)
-	History of electrical storm, % (n)	80 (16)

2 (0-6)
25 (5)
25 (5)
10 (2)
10 (2)
10 (2)
5 (1)
5.5 (4-11)

1 Table 2. STAR characteristics

	STAR facilities, % (n)	
	Cyberknife	80 (16)
	CT linac	10 (2)
	MR linac	10 (2)
	STAR indication, % (n)	
	Uncontrollable ES	45 (9)
	Recurrent sustained VT	45 (9)
	Multiple highly symptomatic NSVT	10 (2)
	GTV, ml (min-max)	
	Cyberknife	16 (4-27)
	CT linac	20 (15-26)
	MR linac	57 (40-74)
	PTV, ml (min-max)	
	Cyberknife	23 (14-36)
	CT linac	63 (55-72)
	MR linac	91 (66-115)
	Median dose, Gy (mean ± SD)	24 (22.70 ± 2.5)
	Targeted segments, n (%)	
	Septal LV segments: 2, 3, 8, 9 and 14	15 (75)
7	Anterior LV segments: 1,7 and 13	9 (45)
	Inferior LV segments: 4, 10 and 15	3 (15)
	Lateral LV segments: 5, 6, 11, 12 and 16	4 (20)
	LV apex: segment 17	1 (5)
	RVOT	1 (5)
·	Number of segments/patient, median (range)	2 (1-6)
	Median dose, Gy (mean ± SD) Targeted segments, n (%)	24 (22.70 ± 2.5)
	Septal LV segments: 2, 3, 8, 9 and 14	15 (75)
7	Anterior LV segments: 1,7 and 13	9 (45)
	Inferior LV segments: 4, 10 and 15	3 (15)
	Inferior LV segments: 4, 10 and 15	3 (15)
	Lateral LV segments: 5, 6, 11, 12 and 16	4 (20)
	LV apex: segment 17	1 (5)
	RVOT	1 (5)
	Number of segments/patient, median (range)	2 (1-6)

2 Table 3. Complications of VT treatment

Complications of AADs		
Amiodarone-induced hyperthyroidism	4 (20%)	
Amiodarone-induced hepatotoxicity	2 (10%)	
Complications of RFCA		
latrogenic AVB	2 (10%)	
Periprocedural stroke	1 (5%)	
Complications of STAR	1	Grade CTCAE
Electrical storm	1 (5%)	4
Nausea	1 (5%)	2
Pericardial fibrosis	1 (5%)	1
Rib fracture	1 (5%)	2
Fast progression to severe aortic stenosis	1 (5%)	4

1 Figures

Figure 1. Arrhythmogenic substrate targeted by STAR. Displayed in white are the number of
patients treated with STAR on each segment of the AHA 17-segment LV model. One patient
was treated with STAR on the posteroseptal RVOT.

Figure 2. VT burden reduction after STAR. The number of sustained VT six months before
STAR is shown in yellow and six months after STAR in green. For cases #3 and #10, the
number of VTs increased due to the appearance of slow VT after STAR.

8 Figure 3. Distribution of VT recurrence according to the PTV.

Figure 4. An illustrative example of VT recurrence remote from the PTV. A. LV EAM 9 10 corresponding to the last CA before STAR: bipolar voltage maps in RAO and LAO views, 11 with the tip of the ablation catheter (white star) located at the best endocardial pacemap spot at the inferior third of the basal IVS. B. 3-D reconstruction of the irradiation plan with the PTV 12 in red. C. Bull's eye plot displaying the location of the PTV in the 17-segment AHA-model (in 13 14 red). D. Bull's eye plot displaying the location of the VT recurrence in the 17-segment AHA-15 model (in red). E. LV EAM corresponding to the CA after STAR: bipolar voltage maps in RAO and LAO views. Mapping showed that the VT recurrence arose from within the ischemic 16 scar, at the basal part of the lateral wall. 17

18 Figure 5. An example of VT recurrence in proximity of the PTV. A. LV EAM corresponding 19 to the last CA before STAR: bipolar voltage maps in RAO and LAO views, with the tip of the ablation catheter (white star) located at the best endocardial pacemap spot at the inferior 20 21 third of the basal IVS. B. 3-D reconstruction of the irradiation plan with the PTV in red. C. Bull eye's plot displaying the location of the PTV in the 17-segment AHA-model (in red). D. Bull 22 eye's plot displaying the location of the VT recurrence in the 17-segment AHA-model (in red). 23 24 E. LV EAM corresponding to the CA after STAR: bipolar voltage maps in RAO and LAO views. The best endocardial pacemap spot had moved to the intersection of the middle and 25 26 superior third of the basal IVS (white star).

Figure 6. Overview of the radiotherapy treatments in the 2 patients with redo STAR 1 2 procedures. A. Patients #8. A.1 RAO and LAO views of the 1st STAR plan with the PTV in red. A.2 Bull eye's plot displaying the location of the 1st PTV based on the 17-segment AHA-3 model (in red). A.3 RAO and LAO views of the 2nd STAR plan with the PTV in red. A.4 Bull 4 eye's plot displaying the location of the 2nd PTV based on the 17-segment AHA-model (in 5 red). B. Patient #9. A.1 RAO and LAO views of the 1st STAR plan with the PTV in red. A.2 6 7 Bull eye's plot displaying the location of the 1st PTV based on the 17-segment AHA-model (in 8 red). A.3 RAO and LAO views of the 2nd STAR plan with the PTV in red. A.4 Bull eye's plot displaying the location of the 2nd PTV based on the 17-segment AHA-model (in red) 9

Figure 7. Radiation dose at sites of recurrence: for each VT recurrence, the graphic displays the initially delivered full dose (in blue) and the estimated dose at the site of recurrence (in orange). The recurrence in proximity of the PTV are displayed on the left, the ones remote from the PTV in the center, and the recurrence involving a large AS (\geq 3 LV segments) are on the right.

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