Recurrences of ventricular tachycardia after stereotactic arrhythmia radioablation arise outside the treated volume: analysis of the swiss cohort

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Short title: Recurrences after arrhythmia radioablation

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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 interventricular septum in 75% of patients. During the first 6 months after STAR, VT burden decreased by 92% (median value, from 108 to 10 VT/semester). After a median follow-up of 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 in 3 cases and involved a larger substrate over ≥3 LV segments in 2 cases. No recurrences occurred inside the PTV. Voltage measurements showed a significant decrease in both bipolar and unipolar signal amplitude after STAR.

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.

Keywords

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

What's New?

- ***This is the largest series of STAR published and provides for the first time data 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.
- VT recurrences were common after STAR. The analysis of sites of recurrence showed that VT did not originate from the treated volume, but often in proximity to or remote from the targeted volume.

Abbreviations

VT: ventricular tachycardia

ICD: implantable cardiac defibrillator

AAD: anti-arrhythmic drugs

CA: catheter ablation

STAR: stereotactic arrhythmia radioablation

AS: arrhythmogenic substrate

LGE-MRI: magnetic resonance imaging with late gadolinium enhancement

RV: right ventricle

LV: left ventricular

EAM: electroanatomical mapping

EGM: electrograms

CT: computed tomography

OAR: organs at risk

GTV: gross target volume

ITV: internal target volume

PTV: planning target volume

SBRT: stereotactic body radiation therapy

RT: radiotherapy

IVS: interventricular septum

TAS: arrhythmogenic substrate targeted by STAR

Introduction

Ventricular tachycardia (VT) is a life-threatening event for patients with heart disease, with a significant impact on quality of life(1) and life expectancy(2, 3). Implantable cardioverter defibrillators (ICD) improve prognosis but cannot prevent recurrences of sustained VT. 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 limited success rates, with recurrences ranging between 40 and 70%(7-10). Limitations of CA procedures include, among others, intramyocardial or epicardial circuits not accessible with conventional approaches such as intramural septal VT(11, 12). Stereotactic arrhythmia radioablation (STAR) was first introduced in 2012(13) for the treatment of refractory VT. Several case reports and series have been published worldwide, with good short-term 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 compassionate use of STAR was approved in 2016 in Switzerland in order to offer this new treatment for patients in whom all conventional attempts to control sustained VT recurrences failed.*** Herein, we report the efficacy and safety of STAR in the Swiss cohort, and the frequency and sites of VT recurrences after STAR.

Methods

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).

VT mapping

The extent and location of the AS were identified on cardiac magnetic resonance imaging **with late gadolimium enhancement (LGE-MRI)** whenever possible. Otherwise, myocardial scars were defined using available cardiac imaging modalities (CT scan or echocardiography). Scar location was described following the 17-segment model of the American Heart Association.(25) Every effort was made to collect 12-lead ECGs of the clinical VT. If feasible, all patients underwent an invasive electrophysiological study before STAR. To define the endpoint of CA, VT induction was attempted using a standard programmed ventricular stimulation protocol from the right ventricle (RV) consisting of 2 basic cycle lengths (S1) up to 3 extrastimuli (S2-S4) down to 200 ms or to the RV effective refractory period. Use of intravenous isoproterenol was left to the discretion of the operator. All induced monomorphic VT were recorded. For clinical VT only recorded by the ICD, monomorphic VT with a cycle ± 20 ms from that of the ICD recording was considered as the clinical VT. A left ventricular (LV) endocardial electroanatomical mapping (EAM) in sinus 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 every septal VT case. To optimize delineation of the AS, the mitral annulus and the coronary 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) or multipolar diagnostic catheters (Pentaray, Biosense Webster, Diamond Bar, CA) and the

Carto3 system (Biosense Webster, Diamond Bar, CA). Areas displaying bipolar electrograms (EGM) voltage ≤1.5 mV were defined as abnormal. EGM suggesting local slow conduction (fragmented or late potentials), either spontaneously or unmasked by delivery of premature beats, were tagged. A substrate-based approach was used to target the AS. Then, re-induction of VT was attempted. If still inducible, every effort was made to characterize the clinical VT isthmus: activation time mapping, pace-mapping, morphology correlation using 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 were verified using entrainment maneuvers whenever possible.

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.

Target delineation

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, ***combined with the morphological information from previous substrate imaging***. The gross target volume (GTV), corresponding to the TAS, was drawn by both the electrophysiologists and the radiation oncologists. Additional margins around the GTV, called 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 treated with Cyberknife, 4D-CT was used to ensure that there was a rigid relation between 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.

STAR planning and delivery

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 report of the American Association of Physicists in Medicine(26). ***No guidelines were 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 the risk of iatrogenic AV block.*** The prescribed dose was 20-25 Gy in a single fraction based on center preference. For patients treated in Bern and Lausanne, STAR treatments were delivered using robotic SBRT with the Cyberknife system (Accuray, Sunnyvale, CA, USA) with real-time tracking. For patients treated in Zurich, two radiotherapy (RT) devices were available: an image-guided radiotherapy-equipped (IGRT) linac (TrueBeam, Varian Medical Systems) that uses cone-beam CT and, alternatively, the MRIdian® Linac system (ViewRay Inc., Oakwood Village, OH) with an onboard MRI(27).

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.

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.

VT recurrence after STAR

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

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 ≥3g, and compared to points collected from the same area during the last CA before STAR.

Statistical analysis

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

Results

Characteristics of the study population

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 AS, representing 5.3% of all CA for VT in patients with structural heart disease in the participating centers. Table 1 shows the clinical characteristics of the study population, whose median age was 68 years old and median LV ejection fraction 31%. 70% of the cases were non ischemic. All patients had been implanted with an ICD, except the case with the 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 cardiac metastasis) had a large AS with myocardial scarring distributed over a median of 5.5 segments (range 4-11). Eighteen patients (90%) had undergone several unsuccessful attempts including AAD, endocardial and epicardial CA and ethanol infusion to control their VT (Table 1). In one patient with a history of CABG and an uncontrollable electrical storm (ES), STAR was performed as a primary treatment because of an LV thrombus. The patient with the cardiac metastasis did not undergo a CA procedure.

STAR procedure

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

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.

Efficacy and Safety of STAR

Overall, STAR was followed by an important VT burden reduction from a median of 108 (3-5502) episodes six months before to a median of 10 (0-150) events six months after STAR ($p<0.005$). 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 implantation of a left-ventricular assist device and discharge from the hospital 3 months later. 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 treated by STAR, an important VT burden reduction (88.1% reduction, $p<0.005$) was observed in 9 (82%) patients as shown in Figure 2, with a drop in sustained VT episodes from 108 (3-5502) six months before to 6 (0-150) events (median values) six months after STAR. Two patients had continuous VT episodes despite STAR, but the tachycardia changed from previously fast VT to incessant slow VT (Figure 2). In one patient, VT resolved spontaneously, and in the other patient successful CA was performed. STAR allowed tapering of the prescribed dose of amiodarone in four (36%) out of these 11 patients.

Table 3 reports the complication rates of the three antiarrhythmic approaches including prescription of AAD, CA procedures and STAR. One patient showed an immediate increase 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 reaction(27). Three (15%) patients developed ≥1 complication likely related to STAR: one case of grade 2 nausea lasting 3 weeks after targeting the infero-basal LV, who developed later on a fibrotic pericardial reaction preventing epicardial needle access (grade 1); one case developing a spontaneous rib fracture (grade 2) spontaneously resolving within 3 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.

VT recurrence after STAR

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

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.

Dose evaluation at site of recurrence

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

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.

Efficacy and safety of STAR

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

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 case with VT recurrence after STAR related to an inaccurate delineation of the TAS(34). ***Qian et al. also reported a recurrence arising from the area close to the PTV(35).*** 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 recurrences, a possible strategy would be targeting a larger volume, encompassing as 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 scarce. We therefore intently minimized PTV by targeting the VT exit site. ***On the other hand,*** enlarging the PTV might also increase the risk of collateral damage and toxicities(15, 17, 23). The choice of the treatment facility (linear accelerator versus radiosurgery system) has also an impact on the size of the target volume and dose distribution, and must be taken into account when planning the PTV and potential toxicities. We also showed that VT recurrences can occur at sites remote from the PTV, from an evolving arrhythmogenic substrate that might be addressed by CA. Hence, VT recurrence after STAR might not be systematically considered as a failed procedure.

Effect of STAR on tissue characteristics

The efficacy of CA relies on scar homogenization using various ablation techniques in order to prevent reentry(38). Early animal studies have shown occurrence of fibrosis in irradiated myocardial tissue, but with only a small number of dense or transmural scars(39-43). Attempts to achieve bidirectional block within the atria appeared difficult with a success as 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 findings. We found a mild decrease in local voltage within the PTV after STAR, particularly in 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 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 contrast, Kautzner et al. and Kiani et al. recently reported seven autopsy cases after the delivery of 25 Gy to the VT substrate showing the appearance of fibrosis and central 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 recurrence within the PTV. It is well established that scar formation starts at best 4 weeks 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 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 alive from the hospital. Until recently, whether STAR displayed some acute antiarrhythmic properties remained debated. Kiani et al. recently reported hemorrhage and degenerative changes in myocytes 12 days after STAR(49). Cha et al. have also shown early widening of intercalated disks, and intercellular and intracellular edema after irradiation in rat hearts, 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 cellular membrane and of intracellular organelles (e.g. damaged mitochondria) evolved over time. The same group also found acute electrophysiological changes in human induced stem-cell derived cardiomyocytes appearing as soon as within 1 hour after radiation(52).

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.***

Conclusion

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

Funding

The project is part of the STOPSTORM.eu consortium and has partially received funding from the European Union's horizon 2020 research and innovation program under grant agreement No 945119.

Disclosures

- CHS received educational grants through her institution from Biosense Webster, Microport and Abbott; and speaker fees from Daiichi-Sankyo

- TR has received research grants from the Swiss National Science Foundation, the Swiss Heart Foundation and the sitem insel support fund, all for work outside the submitted study. Dr. Reichlin has received research support for investigator initiated projects from Biosense-Webster, Biotronik, Boston Scientific and Medtronic, all for work outside the submitted study. He has received speaker/consulting honoraria or travel support from Abbott/SJM, Bayer, Biosense-Webster, Biotronik, Boston-Scientific, Daiichi Sankyo, Farapulse, Medtronic and Pfizer-BMS, all for work outside the submitted study. He has received support for his institution's fellowship program from Abbott/SJM, Biosense-Webster, Biotronik, Boston-Scientific and Medtronic for work outside the submitted study
- BK received educational support from Medtronic, Abbott and Biotronik
- AMS received educational grants through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, BMS/Pfizer, and Medtronic; and speaker /advisory board /consulting fees from Abbott, Bayer Healthcare, Daiichi-Sankyo, Medtronic, Novartis and Pfizer.
- EP received Educational Grants through his institution from Medtronic, and research grants from the Swiss National Science Foundation and from the European Community (H2020)
- All remaining authors have declared no conflicts of interest.

Data availability statement

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

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Supplemental Material

- Table S1.
- Figures S1 and S2.

1 **Table 1.** Patient characteristics.

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)
Device, % (n)	
CRT-D	45 (9)
Double chamber ICD	35 (7)
Single chamber ICD	15 (3)
Double chamber PM	5 (1)
Drug therapy, % (n)	
BB	100 (20)
ACEI or ARBB	80 (16)
Failed AAD, % (n)	
Amiodarone	85 (17)
Sotalol	15 (3)
Flecainide	20 (4)
Propafenone	5 (1)
Lidocaine	10 (2)
Mexiletine	15 (3)
History of electrical storm, % (n)	80 (16)

Failed catheter ablation, median (range)	2 (0-6)
Epicardial procedure, % (n)	25 (5)
Ablation attempt from the CS, % (n)	25 (5)
Double unipolar ablation, % (n)	10 (2)
Arterial septal ethanol infusion, % (n)	10 (2)
Factors precluding catheter ablation	
Endocavitary thrombus, % (n)	10 (2)
History of CABG, % (n)	5 (1)
Number of segments displaying scarring in imaging, median (range)	5.5 (4-11)

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)
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)

Table 3. Complications of VT treatment

Complications of AADs		
Amiodarone-induced hyperthyroidism	4 (20%)	
Amiodarone-induced hepatotoxicity	2 (10%)	
Complications of RFCA		
Iatrogenic AVB	2 (10%)	
Periprocedural stroke	1 (5%)	
Complications of STAR		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

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.

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 corresponding 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 third of the basal IVS. **B.** 3-D reconstruction of the irradiation plan with the PTV in red. **C.** Bull's eye plot displaying the location of the PTV in the 17-segment AHA-model (in red). **D.** Bull's eye plot displaying the location of the VT recurrence in the 17-segment AHA-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 scar, at the basal part of the lateral wall.

Figure 5. An example of VT recurrence in proximity of the PTV. A. LV EAM corresponding 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 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 eye's plot displaying the location of the VT recurrence in the 17-segment AHA-model (in red). 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 superior third of the basal IVS (white star).

Figure 6. Overview of the radiotherapy treatments in the 2 patients with redo STAR 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-model (in 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). B. Patient #9. 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-model (in 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)

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 (≥3 LV segments) are on the right.

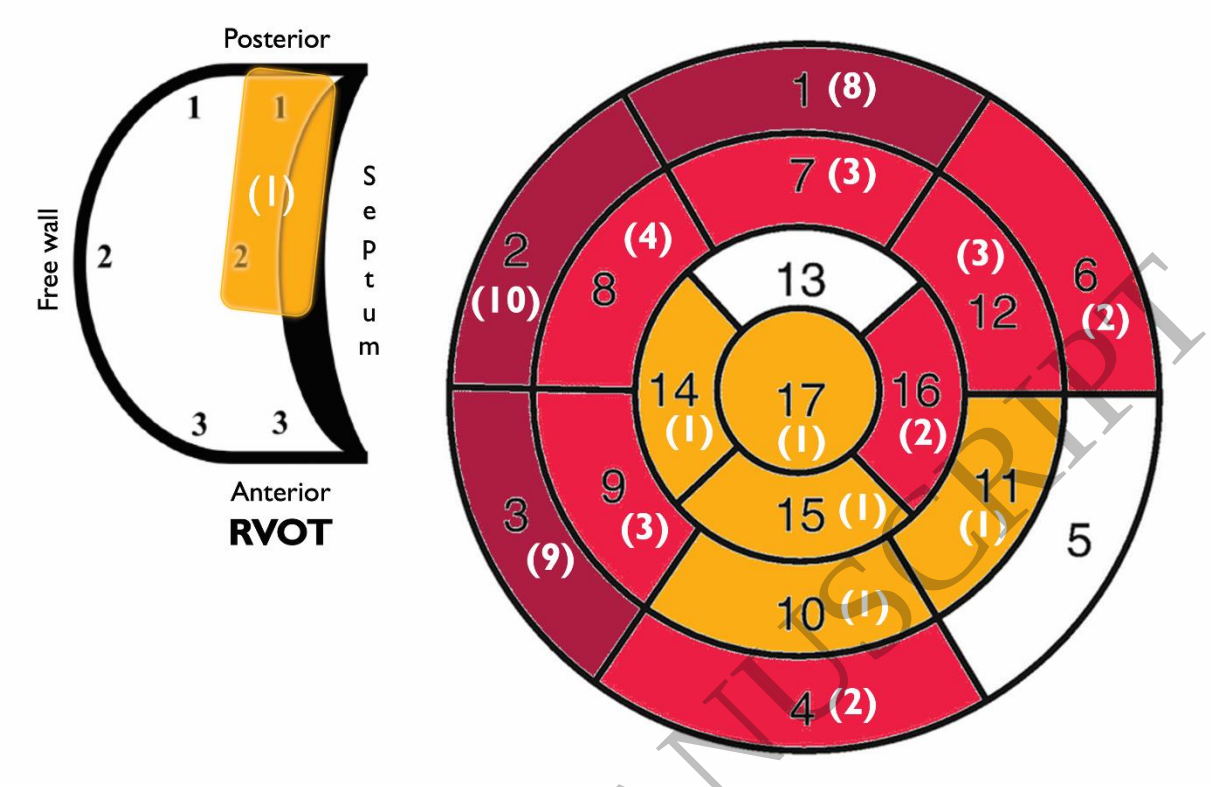

Figure 1
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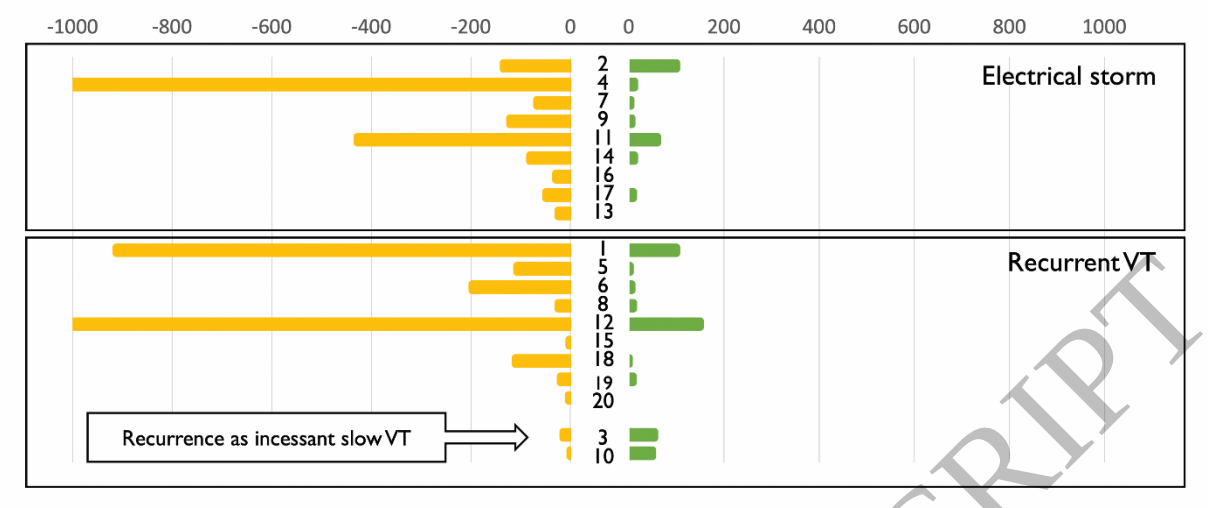

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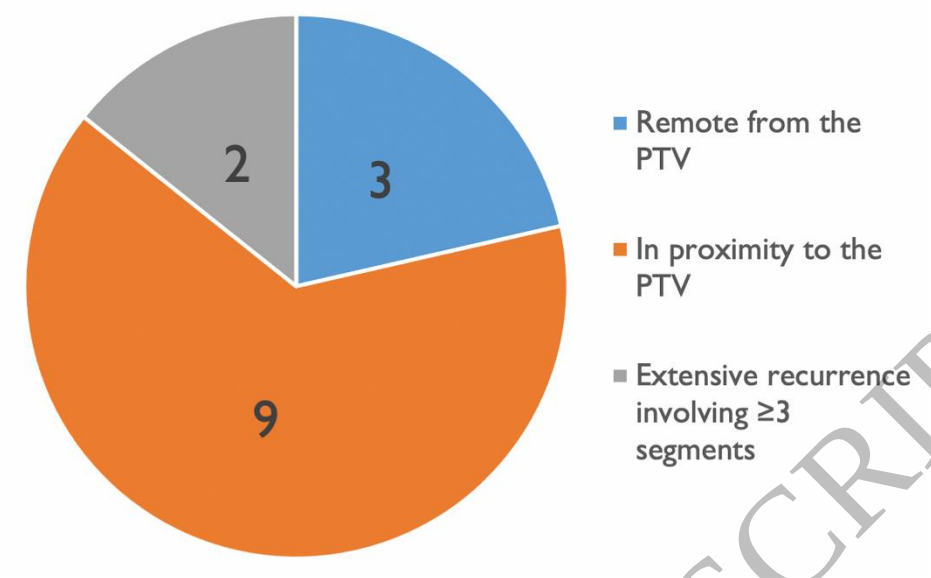

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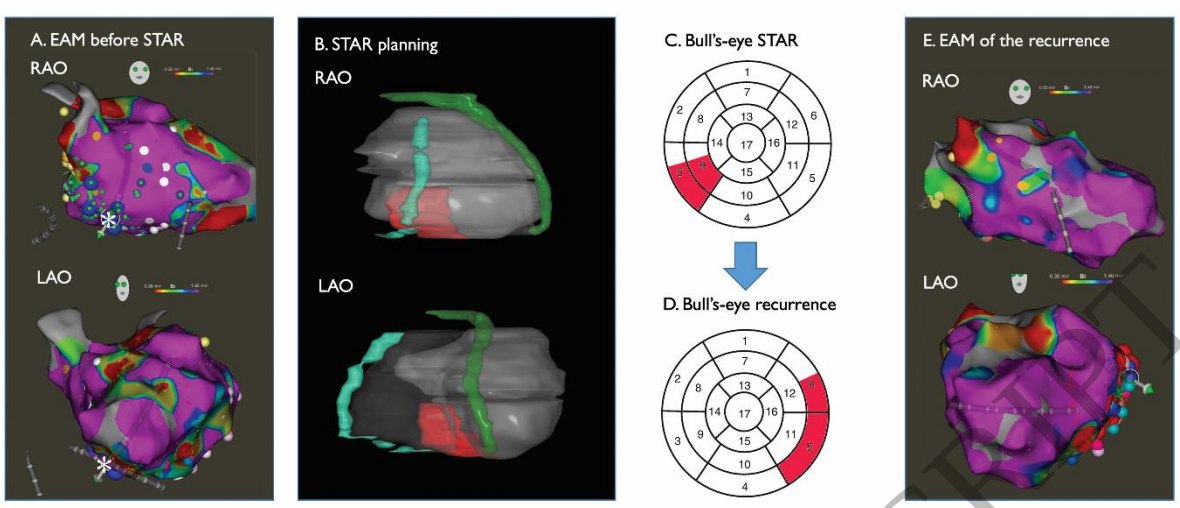

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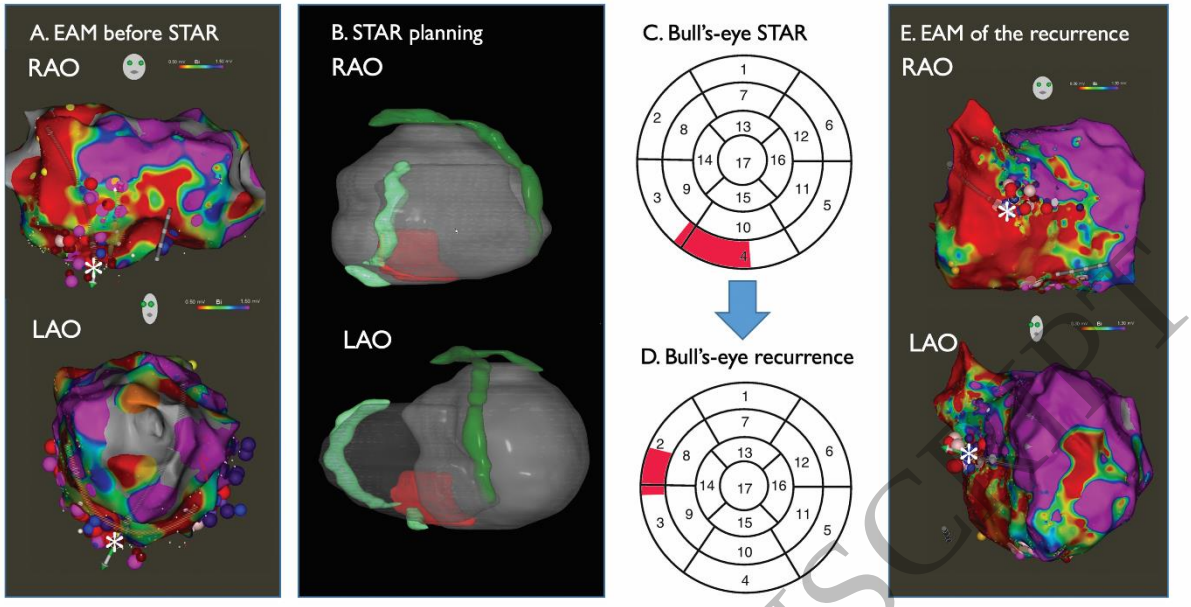

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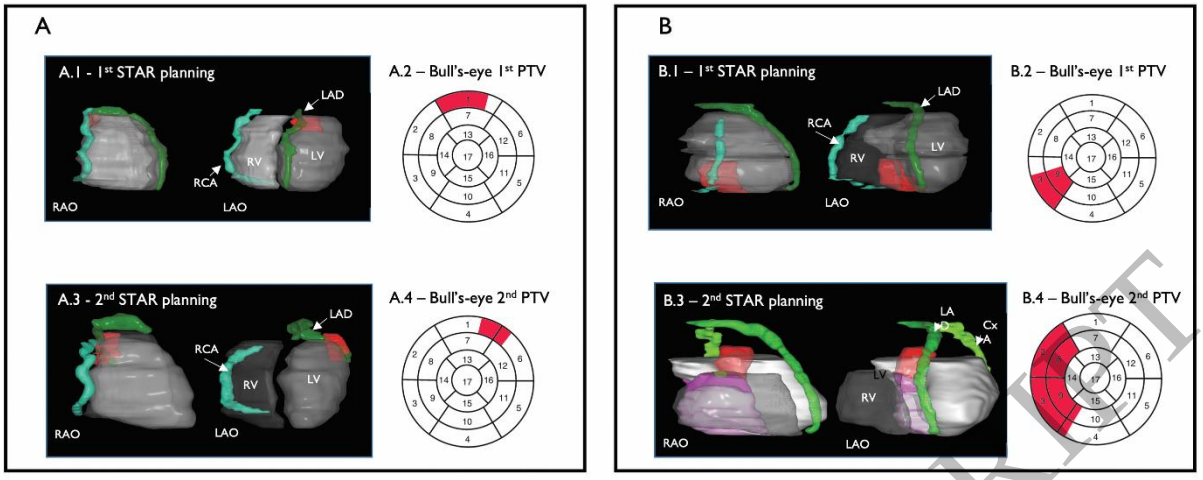

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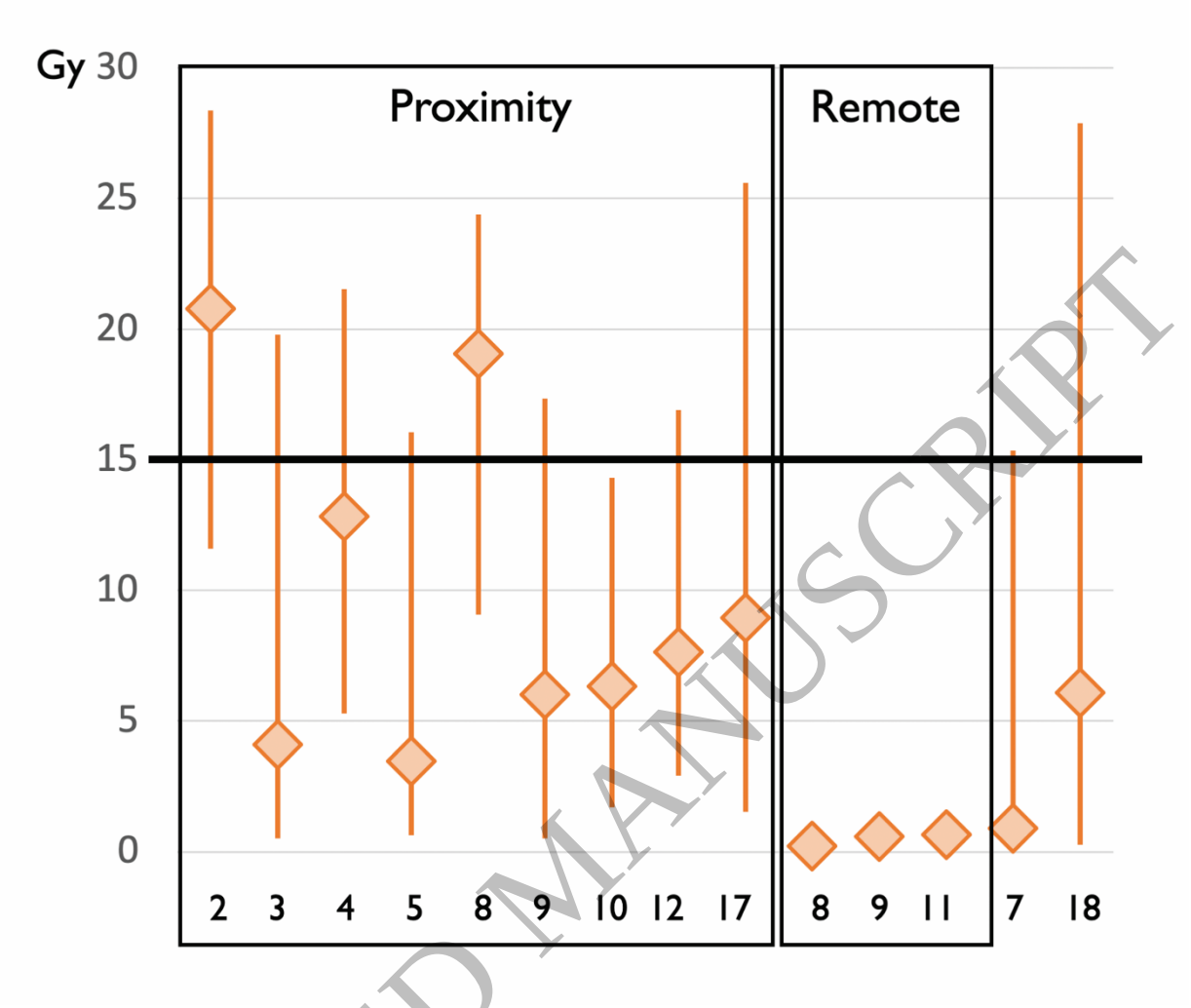

Figure 7
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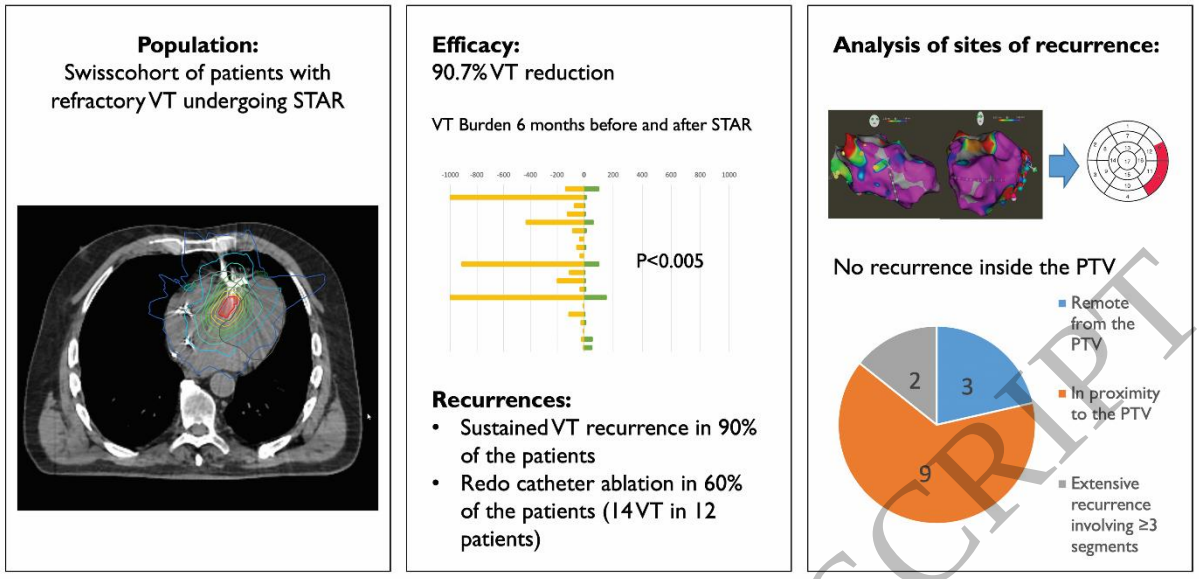

Graphical Abstract