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Refining Treatment Planning in STereotactic Arrhythmia Radioablation (STAR): Benchmark Results and Consensus Statement from the STOPSTORM.eu Consortium

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Highlights

- STOPSTORM aims to standardize treatment planning for STereotactic Arrhythmia Radioablation (STAR).
- 20 centers generated 67 treatment plans for 3 STAR cases demonstrating current clinical practice in Europe.
- Treatment planning showed agreement on dose prescription methods and trade-offs and no agreement on dose inhomogeneity and cardiac substructure dose limits.
- Consensus statements for STAR treatment planning were issued for future harmonization.

Refining Treatment Planning in STereotactic Arrhythmia Radioablation (STAR): Benchmark Results and Consensus Statement from the STOPSTORM.eu Consortium

STAR Treatment Planning Benchmark

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Author Statement

VT, MG, MI and OB designed and coordinated the treatment planning benchmark study and drafted the paper. VT, AB, MG, MB, BvA, JDA, LD, CD, SE, EFV, JF, DGC, DH, AK, LK, SL, AM, VR, GS, VV and EW created the treatment plans for their center. VT, AB and MG analyzed the data and AS created the review software for the AIFM. MG, VT, DS, BB, JBH, MM, OE, NA, DK, MF, WVE and OB developed the treatment planning guidelines and all participating centers voted on the final guideline. OB is the PI and JV, EP and MF are the Co-PIs of the STOPSTORM consortium. All authors read and approved the final manuscript.

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Data Availability

Detailed treatment planning data is available upon reasonable request to the lead authors.

Conflict of Interests

JBH received personal fees from EBAMed SA, Switzerland, speaker honoraria from AstraZeneca and a research grant from Elekta AB, outside the submitted work. OE received honoraria for participation on advisory board meetings from Merck Serono, MSD, and AstraZeneca concerning oncologic treatments, and received project funding for clinical trials from non-profit organizations, all outside of the submitted work. DK has received honoraria from Merck Sharp & Dome, Med Update, Onkowissen, Best Practice Onkologie, ESO, ESMO, Gilead and Pfizer as well as research funding from Merck KGaA, all outside of the submitted work. All other authors declare no conflict of interests.

Keywords: STOPSTORM consortium, STereotactic Arrhythmia Radioablation (STAR), Stereotactic Body Radiotherapy (SBRT), ventricular tachycardia (VT), treatment planning, benchmark, guidelines

Abstract

Background and purpose

STereotactic Arrhythmia Radioablation (STAR) showed promising results in patients with refractory ventricular tachycardia (VT). However, clinical data is scarce and heterogeneous. The STOPSTORM.eu consortium was established to investigate and harmonize STAR in Europe. The primary goal of this benchmark study was to investigate current treatment planning practice within the STOPSTORM project as a baseline for future harmonization.

Methods

Planning target volumes (PTV) overlapping extra-cardiac organs-at-risk and/or cardiac substructures were generated for three STAR cases. Participating centers were asked to create single fraction treatment plans with 25 Gy dose prescription based on in-house clinical practice. All treatment plans were reviewed by an expert panel and quantitative crowd knowledge-based analysis was performed with independent software using descriptive statistics for ICRU report 91 relevant parameters and crowd dose-volume-histograms. Thereafter, treatment planning consensus statements were established using a dual-stage voting process.

Results

Twenty centers submitted 67 treatment plans for this study. In most plans (75%) Intensity Modulated Arc Therapy (IMAT) with 6 MV flattening-filter-free beams was used. Dose prescription was mainly based on PTV $D_{95\%}$ (49%) or $D_{96\text{-}100\%}$ (19%). Many participants preferred to spare close extra-cardiac organs-at-risk (75%) and cardiac substructures (50%) by PTV coverage reduction. PTV $D_{0.035cm3}$ ranged 25.5-34.6 Gy, demonstrating a large variety of dose inhomogeneity. Estimated treatment times without motion compensation or setup ranged 2-80 minutes. For the consensus statements, strong agreement was reached for beam technique planning, dose calculation, prescription methods and trade-offs between target and extra-cardiac critical structures. No agreement was reached on cardiac substructure dose limitations and on desired dose inhomogeneity in the target.

Conclusion

This STOPSTORM multi-center treatment planning benchmark study showed strong agreement on several aspects of STAR treatment planning, but also revealed disagreement on others. To standardize and harmonize STAR in the future, consensus statements were established, however clinical data is urgently needed for actionable guidelines for treatment planning.

Keywords: STOPSTORM consortium, STereotactic Arrhythmia Radioablation (STAR), Stereotactic Body Radiotherapy (SBRT), ventricular tachycardia (VT), treatment planning, benchmark, consensus statements

Introduction

Ventricular tachycardia (VT), potentially leading to sudden cardiac death, is a severe arrhythmia arising mainly from structural heart disease [1]. Patients are prescribed antiarrhythmic and cardio-protective drugs and often receive an implantable cardioverter defibrillator (ICD) to detect and terminate VT by means of anti-tachycardia pacing (ATP) or defibrillation shocks [1, 2]. For patients with refractory VT, catheter ablation is performed to localize and disrupt the underlying arrhythmogenic substrate. While antiarrhythmic drugs and catheter ablation can control VT episodes long term, they also come with significant risks of complications and VT recurrences in 20-50% leading to repeat interventional procedures [3]. Still, some patients continue to have recurrent VTs despite all treatments [1-3].

STereotactic Arrhythmia Radioablation (STAR) recently showed promising results for patients with refractory VT and limited treatment options [4-6]. In a systematic review, STAR showed > 85% reductions in VT episodes with promising safety profiles in more than 40 patients [4] and many more STAR procedures have been performed since [7]. For STAR, a single fraction radiotherapy dose of 25 Gy is applied to the arrhythmogenic substrate using stereotactic body radiotherapy (SBRT) techniques that are routinely utilized for cancer treatment [8, 9]. However, reported outcomes for STAR are based on heterogeneous cohorts with different inclusion criteria, target definitions and dose distributions in the target and treatment techniques [7, 10]. STAR requires high quality standards for optimal treatment due to the complexity of STAR with respect to arrhythmogenic substrate identification by electroanatomic mapping (EAM) and scar imaging [11], target volume delineation [12, 13], beam-delivery technique planning [14], cardiac and respiratory motion management [10] and the application of high single fraction doses.

Since STAR is an emerging treatment, the EU funded a Standardised Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary (STOPSTORM) consortium (EU-Horizon-2020 GA No. 945119) to create a unified database to evaluate the safety and efficacy of this novel therapy and eventually optimize and harmonize STAR [7]. One work package of STOPSTORM focuses on comprehensive quality assurance (QA) of the procedure which includes various benchmark studies for STAR. Herein, we report on the results of the treatment planning benchmark study for which the participation was part of the accreditation process for the consortium member institutions [7]. Besides accreditation, the primary goal of this study was to evaluate current treatment planning approaches of STAR. Furthermore, the benchmark results were used to provide treatment planning consensus statements by the participating center to refine and standardize future clinical (trial) protocols.

Materials and methods

Detailed project descriptions and background of the STOPSTORM.eu consortium have been reported previously [7]. Benchmark establishment for critical structure contouring and treatment planning was intended per protocol and covered by the approval of the institutional ethics committee of the lead institution for the quality assurance work package (XXX). For the treatment planning benchmark, an interdisciplinary expert panel was formed based on clinical experience on STAR and on multicenter treatment planning benchmarks [15]. The expert panel consisted of four medical physicists, four radiation oncologists and one cardiologist and the whole benchmark process was monitored by the STOPSTORM credentialing and audit committee [7].

Benchmark Data

Three STAR cases previously used for a critical structure contouring benchmark [16] and for a national clinical trial as described in detail elsewhere [12, 14, 20] were selected by the expert panel for this treatment planning benchmark. In brief, the patients had sustained VT were treated with STAR as previously described [17-19] and represent a meaningful variety of commonly treated STAR

cases in terms of location, dimension and used techniques [7] while at the same time provide challenges for treatment planning for this novel treatment (e.g., overlap with the stomach or the coronary arteries and strong artifacts). For STAR treatment of these cases, national and consensus guidelines on SBRT and STAR were followed [8, 9, 21] and thin-slice planning CTs (1mm x 1mm x 1.5–2.0 mm) in head-first-supine were deformably co-registered with contrast-enhanced, ECG-triggered cardiac CT [10].

The target volume (TV) definition was based on the original clinical cases [17-19] refined by an expert panel consensus of a target delineation benchmark study [12] which was guided for this study by a recently developed quality assurance tool for STAR [13]. Respiratory motion management for treatment planning was implemented using an internal target volume (ITV) approach based on 4D CT (case 1 [17]), a robotic real-time tracking (RTT) approach based on an ICD lead tip (case 2 [18]) and a beam gating (BG) approach based on real-time MR-guidance (case 3 [19]) [10]. Cardiac motion management for treatment planning was implemented using an ITV approach based on cardiac CT in end systole and end diastole [10]. These motion management techniques are routinely used for STAR, cover a broad range of case scenarios, and could be implemented with all common treatment systems used for thoracic SBRT. An isotropic margin of 5 mm to cover treatment delivery uncertainties was used to create the planning target volume (PTV) [8, 9]. TV and PTV for case 1, 2 and 3 were 10.3 cm^3, 14.1 cm^3 and 14.9 cm^3 and 97.3 cm^3, 62.2 cm^3 and 83.1 cm^3, respectively.

Delineation of extra and intra cardiac organs at risk (OAR) was based on the consensus of the critical structure contouring benchmark for all three cases as reported previously [16]. For case 1, the PTV overlapped partly with the stomach and the left anterior descending coronary artery (LAD). For case 2, the PTV overlapped with a left ventricle assist device (LVAD) and minimally with the LAD. For case 3, the PTV overlapped with several cardiac substructures (aorta, mitral and aortic valve, LAD and left circumflex artery (LCX)). A graphical case presentation can be found in Supplement 1 (Figure S1). The anonymized planning and cardiac CT and the contours of the three cases were sent to the radiation oncology departments participating in the STOPSTORM.eu consortium [7].

Treatment Planning

For all cases, the prescribed dose to the surrounding PTV was to be reported according to the International Commission on Radiation Units and Measurements (ICRU) report 91 [22] and was required to be 25 Gy in 1 fraction in line with the literature on STAR [4-6] and the actual treated cases [17-19]. From July until November 2021, each participating institution was required to create one clinically acceptable treatment plan for each of the three benchmark cases as determined by the interdisciplinary team on site for each treatment system in use for STAR.

Further strict requirements for treatment planning were not provided to obtain an unbiased view on current clinical STAR practice. Beam-delivery technique planning strategies such as beam energy, direction, orientation, and modulation selection as well as dose homogeneity within the TV, ITV and PTV and dose-fall below 25 Gy in and outside the PTV (e.g., due to close critical structures) were up to the individual institution. Extra-cardiac OAR and cardiac substructure dose limitations were explicitly not specified, however, references for relevant dose constraints based on international guidelines [22-27] and clinical trials for STAR [20, 28-32] were provided as reference.

The participants had to provide the treatment plan data and radiotherapy dose files and fill out a detailed questionnaire about their planning approach and trade-offs made between target coverage and OAR sparing.

Data Analysis

The treatment plan data was imported into an independent custom-made community-driven software designed for crowd knowledge-based evaluation of multi-center planning studies as previously presented [33, 34]. Dose distributions of PTV and relevant extra-cardiac OAR and cardiac substructures were analyzed using (1) descriptive statistics for ICRU report 91 relevant parameters

(e.g., PTV/GTV $D_{98\%}$, $D_{50\%}$ and $D_{0.035cm3}$ and OAR $D_{0.035cm3}$) [22] and (2) multi-data dose-volume-histograms (DVH), both correlated with institutional experience on STAR and planning approaches from the questionnaires. A quantitative plan quality score was not calculated due to lack of actionable guidelines and clinical data on best practice approaches for STAR.

Treatment Planning Consensus Statements

Based on the results of the benchmark study and discussions during a dedicated workshop, the expert panel drafted treatment planning statements for STAR on requirements, prescription dose, trade-offs and documentation, dose inhomogeneity, dose limitations for cardiac substructures, beam technique planning, dose calculation, and treatment times. In a two-step process, all participating centers voted and commented on the draft statements in the first step. After further refinements by the expert panel based on the results of the first step, all participating centers voted on the final statements in the second step based on a 5-point Likert scale (5 - strongly agree to 1 - strongly disagree). Finally, consensus with agreement as strongly agree or agree (strong agreement ≥80%, moderate agreement ≥66%, no agreement <66%) and interquartile ranges (IQR; small IQR [≤ 1] = harmonized opinion, larger IQR [> 1] = polarized opinions) for each statement was calculated with Microsoft Excel (Version 2308, Microsoft Corporation, Redmond, USA).

Results

For this benchmark, the participating centers submitted 22, 23 and 22 treatment plans for case 1, 2 and 3, respectively. Most of the plans (67%) were generated for c-arm-based linear accelerators using Intensity Modulated Arc Therapy (IMAT) while 22%, 6% and 5% of the plans were generated for robotic-based linear accelerators, MRI-based linear accelerators and synchrotron-based (Intensity Modulated Particle Therapy) accelerators, respectively. For IMAT, 73% and 27% of the plans utilized 6 and 10 mega volt (MV) flattening filter free (FFF) beams. All well-established treatment planning systems (TPS) were used and technical details of the treatment plans can be found in the Supplement 1 Table S1. Since TPS-specific beam technique planning manuals have been published previously for SBRT [36] and STAR [14], we omitted those details in this manuscript.

Planning Target Volume und Prescription Isodose

In accordance with local prescription protocols and employed techniques, prescription criteria varied among the institutions. Almost half of the total plans (49%) were normalized with 100% prescription dose to 95% of the PTV (PTV $D_{95\%}$), 19% prescribed to a PTV volume ranging from 96% to 100% (PTV $D_{96\text{-}100\%}$), 5% normalized to 100% of the TV, while the other 27% used other prescription volumes (see Supplement 1 Table S1). As a result, maximum doses varied from 25.5 Gy to 34.6 Gy (median, 29.9-30.5 Gy for the 3 cases).

Organs-At-Risk and Dose Trade-Offs

Since specific dose limits were not provided, we asked the participants which protocol and guidelines their chosen dose constraints were based on. 85% of the planners based their OAR limits on the provided references of SBRT and STAR clinical trial protocols and guidelines [20, 24-27] while 30% had an internal (clinical trial) STAR protocol already established.

For case 1, the submitted cases compromised the prescription dose coverage in favor of dose sparing to stomach (32%), to A_LAD (32%) or both (18%). PTV $D_{98\%}$ and $D_{0.035cm3}$ range was 6.4-25.0 Gy and 25.5-34.6 Gy, respectively. Stomach and left anterior descending artery (LAD) $D_{0.035cm3}$ range was 6.5-27.0 Gy and 11.2-31.4 Gy, respectively. For case 2, PTV $D_{98\%}$ and $D_{0.035cm}$ range was 21.4-25.6 Gy and 25.7-34.6 Gy, respectively. LAD $D_{0.035cm3}$ range was 10.1-27.2 Gy. For case 3, 46% of the submitted plans compromised prescription dose coverage in favor of OAR dose sparing. PTV $D_{98\%}$ and $D_{0.035cm3}$ range was 6.7-25.2 Gy and 25.9-34.5 Gy, respectively. LCX and LAD $D_{0.035cm3}$ range was 10.7-33.8 Gy

and 11.5-32.2 Gy, respectively. Details of key dosimetric parameters including mean values are presented in Table 1.

Overall, approximately 75% and 50% of the participants of this planning benchmark study preferred to spare close extra-cardiac OAR and cardiac substructures, respectively, over achieving high PTV coverage. This center preference was noted in the treatment plan by simultaneous low PTV $D_{98\%}$ and low $D_{0.035cm3}$ for the closest OAR and was independent of treatment planning system or beam technique planning and not correlated to institutional experience on STAR. Example dose distributions for different planning approaches showing significant underdosing of the PTV on one hand and high OAR doses on the other are presented in Figure 1. The crowd DVH for PTV and relevant OAR for the three cases is shown in Figure 2.

Dose Calculation and Artefact Handling

Dose calculation algorithms [9, 22] were type-a (20%), type-b (25%) and type-c (55%) where type-A algorithms only model the primary particle transport correctly (e.g., Ray Trace, Pencil Beam), type-B algorithms include more sophisticated models for the management of secondary particles (e.g., Collapsed Cone, Convolution/Superposition), and type-C algorithms explicitly consider the lateral particle transport (e.g., MonteCarlo, Boltzmann Solver) [9, 22]. Grid sizes for dose calculation were 1.0-2.5 mm with 26% based on CT slice thickness (2-2.5 mm) and 61% based on higher resolution interpolation (1.0-1.5 mm) while the rest did not provide any information (13%). To manage the LVAD artifacts for case 2, 74% of the participants decided to override the artifacts' density with water or air (depending on whether they were inside or outside the body) and the rest did not employ any artifact management strategy (13%) or did not provide any information (13%) (see Supplement 1 Table S2).

Estimated Beam-On Times

Estimated beam-on times without motion compensation and setup times were for c-arm based system 2.7-10 min, 2.6-10 min and 2.4-10 min and for robotic based systems with and without MLC 21-66 min, 32-71 min and 33-80 min for case 1, 2 and 3 respectively. For intensity modulated treatments with c-arm based systems, a mean modulation factor (total MU/2500) of 3.0 (range, 2.2-4.1), 3.8 (range, 2.2-7.5) and 3.4 (range, 2.0-6.1) was calculated for case 1, 2 and 3, respectively.

STOPSTORM Project Accreditation

As the participation in this Benchmark study was a mandatory part of the accreditation process within the STOPSTORM project [7], the expert panel provided detailed feedback for each participant in reference to the crowd DVH to improve the overall quality of STAR treatment planning within the consortium. A dedicated, mandatory workshop with group discussions on approaches and trade-offs thereafter resulted in the draft of consensus statements and the part-accreditation of the participating centers for this subpart of the STAR treatment chain.

Treatment Planning Consensus Statements

Twenty-seven statements and six cardiac substructure dose limitation scenarios were created after the two-staged treatment planning statement establishment process. Twenty centers voted on the final statements (Table 2 and Supplement 2) and dose limitation scenarios (Table 3). Strong agreement was achieved for STAR requirements, prescription dose, trade-offs and documentation, dose calculation, treatment times, and general approaches for cardiac substructure dose limitations, albeit not for specific dose values. Strong or moderate agreement was also achieved on two thirds of the beam technique planning sub points while no agreement was reached on specific required beam energies, dose to ICD electrodes, and plan complexity. Also, no agreement was reached for the use of doses over 30 Gy, albeit strong agreement was reached that if higher doses are used, they should be

confined to the target volume. Detailed information with score frequency, median agreement and IQR are shown in Supplement 2.

Rating Score

Recently, Radiotherapy Treatment plannINg study Guidelines (RATING) were published along with a scoring metric to assess the quality of treatment planning studies [35]. Based on self-assessment of our study we achieved a RATING score of 179 out of 200 points (90%, Supplement 3), which was validated by two independent reviewers.

Discussion

This is the first large-scale multi-center treatment planning benchmark study for Stereotactic Arrhythmia Radioablation (STAR) representing current treatment approaches on diverse treatment settings from experienced centers in Europe [7]. In contrast to other benchmark studies [14, 33, 34, 36, 37], we provided limited constraints and objectives for this novel treatment to investigate different approaches on STAR treatment planning in current clinical practice. As expected from previous experience with multi-center planning studies [38, 39], providing only a sparse set of objectives and constraints resulted in very divergent treatment plans with different methods of dose prescription and prioritization of PTV coverage and extra-cardiac OAR and cardiac substructure dose sparing. Due to the novelty of this treatment and lack clinical results on larger cohorts, there is currently no consensus on best practice approaches for treatment planning, which is why a plan score metric [14, 36, 38, 39] was not used to evaluate overall plan quality. Instead, we used a crowd DVH-based data presentation where for detailed feedback we were able to show individual plan DVH in relation to the average and range of all treatment plans submitted this study. With such data presentation, individual plans can be discussed in comparison to other plan and the overall average for potential quality improvement as demonstrated in other planning studies. Furthermore, this benchmark may serve as a basis for creating meaningful score metrics in the future for more qualitive and conclusive plan comparisons.

One of the current controversies in STAR concerns the actual biological mechanisms of high single fraction radiation dose in the heart. While for solid tumors (e.g., early-stage non-small cell lung cancer) dose-response relationships are clinically accepted for several dose parameters (i.e., PTV $D_{98\%}$, GTV $D_{50\%}$ and PTV $D_{2\%}$) [40], clinical data for STAR are still sparse and inconclusive [4-7]. In preclinical experiments, two main mechanisms were identified for higher doses: fibrosis and necrosis after doses exceeding 30 Gy [41, 42], and increased conduction velocity with protein changes due to notch activation with doses between 20-25 Gy [43, 44]. Clinical investigations, however, may yield contrasting results [45, 46], highlighting complex interactions and variable effects in VT patients following high-dose left ventricle radiation. These controversies will lead to different concepts of dose inhomogeneity and dose conformity to the target, which resulted in large variances in this benchmark study and in no agreement on the consensus statements. These questions may be answered in the future by the STOPSTORM project and its associated clinical trials (e.g., NCT05594368), but, as a prerequisite, moderate agreement was reached to consequently prescribe, record and report STAR treatments according to the ICRU report 91 standards [22]. However, since the ICRU report 91 was written for photon beams, discussions on how to harmonize proton and photon beam therapy in the context of SBRT and STAR are still ongoing. Indeed, protons were also used in this Benchmark and a first patient treatment has already been reported [47], but it remains unclear if the conduction modulating effects of median doses in the heart are comparable to photons. Furthermore, it remains unclear if the reduction of low doses in the heart with protons (e.g., 5 Gy) are desired as new studies suggested ventricular function improvement after low doses for cardiomyopathy patients [48].

Strong agreement was reached for extra-cardiac OAR dose limits, which are well known for thoracic SBRT for solid tumors [49-52]. However, the actual treatment plans submitted showed that not in all cases the extra-cardiac OAR dose limits were strictly kept. For case 1, the PTV overlapped with the stomach due to the utilized ITV approach. While 75% of the planners favored extra-cardiac OAR dose sparing over PTV coverage in favor of, 50% of the treatment plans still showed higher maximum doses over 19 Gy exceeding clinically accepted dose limitations [49-52]. Esophageal and stomach fistulas have already been reported in some rare cases after STAR [30, 53] and keeping well below known limits while scarifying dose coverage in the PTV, which still may lead to therapeutic effects [43, 54], must be considered in those cases. Another possibility to increase the safety for target locations close to the stomach and/or esophagus could be strict fasting protocols and/or to use gating or tracking techniques if technically and clinically feasible [10]. No agreement on the other hand was found for cardiac substructure dose limitations, mainly due to inconclusive clinical data and practice at this time and depending on overlap, 20-50% of the plans reduced PTV coverage to spare cardiac substructures. However, strong agreement was reached on basing individual patient-specific dose limitations for coronary arteries and valves on the primary indication for STAR as well as the target volume location, the individual patient anatomy, and the substructure functionality.

While long-term toxicity data is emerging for cardiac substructures from lung cancer SBRT for patients without cardiac diseases [55-57], short-term toxicity data for single fraction irradiation to specific regions in the heart for patients with significant cardiac diseases continues to be inconclusive [58-60]. While Knutson et al. acknowledged the fact that survival after STAR seems to be correlated with target volume, it remained unclear if the extent of the underlying cardiomyopathy or the dose to the left ventricle was the main correlating factor for survival [58]. On the other hand, van der Ree et al. Krug et al. and Miszczyk et al. showed no reduction in left ventricle ejection fraction after STAR with varying left ventricle mean doses [59-61] and recent studies even suggest ventricular function improvement after STAR [48]. In our benchmark study, the left ventricle mean dose was 26.8 Gy (22.7 - 30.0), 27.5 Gy (24.9 - 30.3) and 9.66 Gy (0.729 - 12.8) for case 1, 2 and 3, respectively with different strategies to spare other regions in the heart (e.g., left atrium or superior vena cava [20, 55]). Near maximum doses to the valves, predominantly to the aortic and mitral valve, however, seem to be of clinical relevance for preserving aortic valve functionality. Van der Ree et al. showed significant differences between 1.5-7.2 Gy and 12.7-19.8 Gy for reduction in valve functionally, however, they also were not able to distinguish between a clear dose effect and progression of the underlying cardiomyopathy close to the valves [59]. In our benchmark study the aortic and mitral valve near maximum dose ranged from 8.6-18.3 Gy and 24.5-30.3 Gy, respectively, as they were close and even overlapping with the PTV in case 3. Special consideration on the primary clinical goal of the treatment and the current VT burden in such cases is strongly advised. In example, if the patient is in uncontrollable VT storm (like case 3), achieving high effective dose coverage in the target area with short treatment times may be preferred over reducing potential toxicity in the valves, but not all planners choose this approach.

Other important close critical cardiac substructures for STAR are the coronary arteries. Data on long-term toxicity in the form of occlusion/stenosis and increased mortality is known from intracoronary brachytherapy [62] and from conventional lung radiotherapy [63]. For STAR, there are no reports of coronary toxicity to date. This may be related to several factors, among them limited long-term follow-up [7, 60], competing mortality from the underlying heart disease, underreporting since cause of death may be difficult to discern and a possibly a higher tolerance of the coronary arteries to SBRT than previously believed. The main coronary artery was going through the PTV in case 3 and 46% of the planners decided to underdose the PTV in favor of sparing the coronary artery. The same discrepancy was noted in the treatment planning statements and again, the VT burden and coronary artery function (e.g., after infarct) in comparison to the potentially manageable late side effects of stenosis (e.g., with stenting) must be considered (e.g., when the patient is in uncontrollable VT storm), but again not all planners choose the approach of high PTV coverage. Dosimetric data on

further cardiac substructures is available for this benchmark study, however, more clinical data on toxicity to those is needed and hence strong agreement was reached for consequently recording and reporting STAR treatments according to the ICRU report 91 standards [22].

Finally, moderate agreement was found for doses to the ICD main electronics, but not for required beam energies, in both the statements and the benchmark study, despite existing recommendations [64-67]. Also, no agreement was found for maximum dose limitations for the ICD leads as clinical data suggests that higher doses may be safely delivered to leads in or near the target area in the left ventricle [68]. Concerning image artifacts, frequently occurring from ICD devices and leads and potentially from LVAD systems [18] (benchmark case 2), discrepancy in dose calculation up to 10% may occur [69, 70] and hence density override of the artifacts after use of metal artifact reduction with appropriate dose calculation algorithms especially when density inhomogeneities are present in the PTV [9] should be standard practice for STAR (strong agreement).

Limitations of this benchmark study are the limited number of cases (n = 3) and that only STOPSTORM.eu consortium centers (n = 22) were able to participate. Current standard practice for multi-center planning studies is the use of 3 cases [15] and we mitigated the risk of selection bias using previous expert panel selection processes [12, 14]. Another limitation may be the predefined motion compensation strategy with the according margins for each of the cases. However, the motion management strategy was selected based on the actual treatment performed [17-19] and studies have shown that all systems currently used for thoracic SBRT can deliver the same treatment accuracy with appropriate techniques (e.g., c-arm based gating and robotic-based tracking [71]). Furthermore, the primary reason for reduced coverage in the PTV in this study was the overlay of close critical structures and not the motion management strategy or the planning technique used. Granted, for case 1 the PTV-stomach overlay could be reduced with an active motion management strategy (e.g., gating), but like in previous studies [36, 38] our aim was to create challenging scenarios often faced in clinical routine. Nevertheless, while different motion management strategies could lead to improved treatment plans for some cases presented in this work, it remains unclear if high accuracy for STAR dose delivery using tracking or gating techniques is required biologically [43, 72], pathologically [72, 73] or even clinically [72]. The latter also comes with the consideration that patients are often in a fragile state [74] and active motion management strategies will prolong treatment times significantly. Furthermore, accreditation for STOPSTORM was based on participation, feedback, and discussion and not on actionable guidelines as clinical results correlation with treatment techniques are lacking at this time. Overall, we tried to minimize the risk of bias as much as possible to allow for generalizability of the results and statements comparable to previous treatment planning benchmarks [33-39]. Not addressed in this work was the re-treatment scenario with STAR and great caution is advised concerning dose limitations in such cases [75]. Re-planning with more specific dose constraints and objectives and plan quality assessment will be addressed in subsequent benchmark studies as well as plan delivery quality assurance for the created treatment plans.

Conclusion

This benchmark study provided a very detailed view on current STAR treatment planning approaches in Europe which will serve as a baseline for future harmonizing of this novel treatment for cardiac arrhythmias. For new centers seeking to start a clinical STAR program, we provided treatment planning consensus statements derived from the results of this study to enhance a safe and effective start. Nevertheless, more information on efficacy and toxicity in larger cohorts is needed to move towards actionable practice guidelines and prescribing, recording, and reporting STAR treatments according to ICRU report 91 standards is mandatory to generate missing data.

References

[1] Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997-4126.

[2] Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;138(13):e272-e391.

[3] Fernandez-Armenta J, Soto-Iglesias D, Silva E, et al. Safety and Outcomes of Ventricular Tachycardia Substrate Ablation During Sinus Rhythm A Prospective Multicenter Registry. Jacc Clin Electrophysiol. 2020;6:1435-1448.

[4] van der Ree MH, Blanck O, Limpens J, et al. Cardiac radioablation-A systematic review. Heart Rhythm. 2020;17(8):1381-92.

[5] Kovacs B, Mayinger M, Schindler M, et al. Stereotactic radioablation of ventricular arrhythmias in patients with structural heart disease - A systematic review. Radiother Oncol. 2021;162:132-9.

[6] Miszczyk M, Jadczyk T, Golba K, et al. Clinical Evidence behind Stereotactic Radiotherapy for the Treatment of Ventricular Tachycardia (STAR) - A Comprehensive Review. J Clin Med. 2021;10(6).

[7] Grehn M, Mandija S, Miszczyk M, et al. Stereotactic Arrhythmia Radioablation (STAR): the Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary consortium (STOPSTORM.eu) and review of current patterns of STAR practice in Europe. Europace. 2023;25(4):1284-1295.

[8] Guckenberger M, Baus WW, Blanck O, et al. Definition and quality requirements for stereotactic radiotherapy: consensus statement from the DEGRO/DGMP Working Group Stereotactic Radiotherapy and Radiosurgery. Strahlenther Onkol. 2020;196(5):417-20.

[9] Schmitt D, Blanck O, Gauer T, et al. Technological quality requirements for stereotactic radiotherapy: Expert review group consensus from the DGMP Working Group for Physics and Technology in Stereotactic Radiotherapy. Strahlenther Onkol. 2020;196(5):421-43.

[10] Lydiard S, Blanck O, Hugo G, et al. A Review of Cardiac Radioablation (CR) for Arrhythmias: Procedures, Technology, and Future Opportunities. Int J Radiat Oncol Biol Phys. 2021;109(3):783-800.

[11] Abdel-Kafi S, Sramko M, Omara S, et al. Accuracy of electroanatomical mapping-guided cardiac radiotherapy for ventricular tachycardia: pitfalls and solutions. Europace. 2021;23(12):1989-1997.

[12] Boda-Heggemann J, Blanck O, Mehrhof F, et al. Interdisciplinary Clinical Target Volume Generation for Cardiac Radioablation: Multicenter Benchmarking for the RAdiosurgery for VENtricular TAchycardia (RAVENTA) Trial. Int J Radiat Oncol Biol Phys. 2021;110(3):745-56.

[13] Mayinger M, Boda-Heggemann J, Mehrhof F, et al. Quality assurance process within the RAdiosurgery for VENtricular TAchycardia (RAVENTA) trial for the fusion of electroanatomical mapping and radiotherapy planning imaging data in cardiac radioablation. Phys Imaging Radiat Oncol. 2022;25:100406.

[14] Kluge A, Ehrbar S, Grehn M, et al. Treatment Planning for Cardiac Radioablation: Multicenter Multiplatform Benchmarking for the RAdiosurgery for VENtricular TAchycardia (RAVENTA) Trial. Int J Radiat Oncol Biol Phys. 2022;114(2):360-72.

[15] Giglioli FR, Garibaldi C, Blanck O, et al. Dosimetric Multicenter Planning Comparison Studies for Stereotactic Body Radiation Therapy: Methodology and Future Perspectives. Int J Radiat Oncol Biol Phys. 2020;106(2):403-412.

[16] Balgobind B, Visser J, Grehn M, et al. Refining Critical Structure Contouring in STereotactic Arrhythmia Radioablation (STAR): Benchmark Results and Consensus Guidelines from the STOPSTORM.eu Consortium. Radiother Oncol 2023;189:109949

[17] Krug D, Blanck O, Demming T, et al. Stereotactic body radiotherapy for ventricular tachycardia (cardiac radiosurgery): First-in-patient treatment in Germany. Strahlenther Onkol. 2020;196(1):23-30.

[18] Mehrhof F, Bergengruen P, Gerds-Li JH, et al. Cardiac radioablation of incessant ventricular tachycardia in patients with terminal heart failure under permanent left ventricular assist device therapy-description of two cases. Strahlenther Onkol. 2023;199(5):511-519.
[19] Mayinger M, Kovacs B, Tanadini-Lang S, et al. First magnetic resonance imaging-guided cardiac radioablation of sustained ventricular tachycardia. Radiother Oncol. 2020;152:203-207.
[20] Blanck O, Buergy D, Vens M, et al. Radiosurgery for ventricular tachycardia: preclinical and clinical evidence and study design for a German multi-center multiplatform feasibility trial (RAVENTA). Clin Res Cardiol. 2020;109(11):1319-32.
[21] Krug D, Blanck O, Andratschke N, et al. Recommendations regarding cardiac stereotactic body radiotherapy for treatment refractory ventricular tachycardia. Heart Rhythm. 2021;18(12):2137-2145
[22] Seuntjens J, Lartigau EF, Cora S, et al. ICRU report 91. Prescribing, recording, and reporting of stereotactic treatments with small photon beams. J ICRU 2014;14:1–160.
[23] Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw. 2021;19(3):254-266.
[24] Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. Med Phys. 2010,37:4078-4101.
[25] Gerhard SG, Palma DA, Arifin AJ, et al. Organ at Risk Dose Constraints in SABR: A Systematic Review of Active Clinical Trials. Pract Radiat Oncol. 2021;11(4):e355-e365.
[26] Stam B, Peulen H, Guckenberger M, et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I-II NSCLC patients. Radiother Oncol. 2017;123(3):370-375.
[27] Chan ST, Ruan D, Shaverdian N, et al. Effect of Radiation Doses to the Heart on Survival for Stereotactic Ablative Radiotherapy for Early-stage Non-Small-cell Lung Cancer: An Artificial Neural Network Approach. Clin Lung Cancer. 2020;21(2):136-144.e1.
[28] Carbucicchio C, Andreini D, Piperno G, et al. Stereotactic radioablation for the treatment of ventricular tachycardia: preliminary data and insights from the STRA-MI-VT phase Ib/II study. J Interv Card Electrophysiol. 2021;62(2):427-39.
[29] Kurzelowski R, Latusek T, Miszczyk M, et al. Radiosurgery in Treatment of Ventricular Tachycardia - Initial Experience Within the Polish SMART-VT Trial. Front Cardiovasc Med. 2022;9:874661.
[30] Robinson CG, Samson PP, Moore KMS, et al. Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia. Circulation. 2019;139(3):313-21.
[31] Lee J, Bates M, Shepherd E, et al. Cardiac stereotactic ablative radiotherapy for control of refractory ventricular tachycardia: initial UK multicentre experience. Open Heart. 2021;8(2).
[32] van der Ree MH, Dieleman EMT, Visser J, et al. Non-invasive stereotactic arrhythmia radiotherapy for ventricular tachycardia: results of the prospective STARNL-1 trial. 2023;25(3):1015-1024.
[33] Esposito M, Masi L, Zani M, et al. SBRT planning for spinal metastasis: indications from a large multicentric study. Strahlenther Onkol. 2019;195(3):226-235.
[34] Villaggi E, Hernandez V, Fusella M, et al. Plan quality improvement by DVH sharing and planner's experience: Results of a SBRT multicentric planning study on prostate. Phys Med. 2019;62:73-82.
[35] Hansen CR, CrijnsW, Hussein M, et al. Radiotherapy Treatment planning study Guidelines (RATING): A framework for setting up and reporting on scientific treatment planning studies. Radiother Oncol 2020;153:67-78.
[36] Moustakis C, Blanck O, Chan MKH, et al. Planning Benchmark Study for Stereotactic Body Radiation Therapy of Liver Metastases: Results of the DEGRO/DGMP Working Group on Stereotactic Radiation Therapy and Radiosurgery. Int J Radiat Oncol Biol Phys. 2022;113(1):214-227.
[37] Giglioli FR, Clemente S, Esposito M, et al. Frontiers in planning optimization for lung SBRT. Phys Med. 2017;44:163-170.
[38] Moustakis C, Blanck O, Ebrahimi Tazehmahalleh F, et al. Planning benchmark study for SBRT of early stage NSCLC: Results of the DEGRO Working Group Stereotactic Radiotherapy. Strahlenther Onkol. 2017;193(10):780-790.

[39] Giglioli FR, Strigari L, Ragona R, et al. Lung stereotactic ablative body radiotherapy: A large scale multi-institutional planning comparison for interpreting results of multi-institutional studies. Phys Med. 2016;32(4):600-6.
[40] Klement RJ, Sonke JJ, Allgäuer M, et al. Correlating Dose Variables with Local Tumor Control in Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer: A Modeling Study on 1500 Individual Treatments. Int J Radiat Oncol Biol Phys. 2020;107(3):579-586.
[41] Blanck O, Bode F, Gebhard M, et al. Dose-escalation study for cardiac radio-surgery in a porcine model. Int J Radiat Oncol Biol Phys. 2014;89(3):590-98.
[42] Kim JS, Choi SW, Park Y, et al. Impact of High-Dose Irradiation on Human iPSC-Derived Cardiomyocytes Using Multi-Electrode Arrays: Implications for the Antiarrhythmic Effects of Cardiac Radioablation. Int J Mol Sci. 2021;23(1):351.
[43] Zhang DM, Navara R, Yin T, et al. Cardiac radiotherapy induces electrical conduction reprogramming in the absence of transmural fibrosis. Nat Commun. 2021;12:5558.
[44] Blanck O, Boda-Heggemann J, Hohmann S, et al. [Cardiac stereotactic radiotherapy induces electrical conduction reprogramming]. Strahlenther Onkol. 2022.198(2):209-11.
[45] Whitaker J, Bredfeldt J, Williams SE, et al. Ventricular Conduction Velocity Following Multimodal Ablation Including Stereotactic Body Radiation Therapy for Refractory Ventricular Tachycardia. JACC Clin Electrophysiol. 2023;9(1):119-121.
[46] Kučera T, Jedličková K, Šramko M, et al. Inflammation and fibrosis characterize different stages of myocardial remodeling in patients after stereotactic body radiotherapy of ventricular myocardium for recurrent ventricular tachycardia. Cardiovasc Pathol. 2023;62:107488.
[47] Dusi V, Vitolo V, Frigerio L, et al. First-in-man case of non-invasive proton radiotherapy for the treatment of refractory ventricular tachycardia in advanced heart failure. Eur J Heart Fail. 2021;23(1):195-196.
[48] Pedersen LN, Valenzuela Ripoll C, Ozcan M, et al. Cardiac radiation improves ventricular function in mice and humans with cardiomyopathy. Med. 2023;4(12):928-943.e5.
[49] Grimm J, LaCouture T, Croce R, et al. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys. 2011;12(2):3368.
[50] Gerhard SG, Palma DA, Arifin AJ, et al. Organ at Risk Dose Constraints in SABR: A Systematic Review of Active Clinical Trials. Pract Radiat Oncol. 2021;11(4):e355-e365.
[51] Timmerman R. A Story of Hypofractionation and the Table on the Wall. Int J Radiat Oncol Biol Phys. 2022;112(1):4-21.
[52] Diez P, Hanna GG, Aitken KL, et al. UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for Oligometastatic, Primary Lung and Hepatocellular Carcinoma Stereotactic Ablative Radiotherapy. Clin Oncol (R Coll Radiol). 2022;34(5):288-300.
[53] Haskova J, Jedlickova K, Cvek J, et al. Oesophagopericardial fistula as a late complication of stereotactic radiotherapy for recurrent ventricular tachycardia. Europace. 2022;24(6):969.
[54] Jumeau R, Ozsahin M, Schwitter J, et al. Stereotactic Radiotherapy for the Management of Refractory Ventricular Tachycardia: Promise and Future Directions. Front Cardiovasc Med. 2020;7:108.
[55] Stam B, Peulen H, Guckenberger M, et al. Dose to heart substructures is associated with noncancer death after SBRT in stage I-II NSCLC patients. Radiother Oncol. 2017;123(3):370-375.
[56] McWilliam A, Khalifa J, Vasquez Osorio E, Banfill K, Abravan A, Faivre-Finn C, et al. Novel Methodology to Investigate the Effect of Radiation Dose to Heart Substructures on Overall Survival. Int J Radiat Oncol Biol Phys. 2020;108(4):1073-81.
[57] van der Ree MH, de Bruin-Bon RHA, Balgobind BV, Hoeksema WF, Visser J, van Laarhoven HWM, et al. Dose-dependent cardiac effects of collateral cardiac irradiation: Echocardiographic strain analysis in patients treated for extracardiac malignancies. Heart Rhythm. 2023;20(1):149-51.
[58] Knutson NC, Samson PP, Hugo GD, et al. Radiation Therapy Workflow and Dosimetric Analysis from a Phase 1/2 Trial of Noninvasive Cardiac Radioablation for Ventricular Tachycardia. Int J Radiat Oncol Biol Phys. 2019;104(5):1114-1123.
[59] van der Ree MH, Luca A, Herrera Siklody C, et al. Effects of stereotactic arrhythmia radioablation on left ventricular ejection fraction and valve function over time. Heart Rhythm. 2023:S1547-5271(23)02252-X.

[60] Krug D, Zaman A, Eidinger L, et al. Radiosurgery for ventricular tachycardia (RAVENTA): interim analysis of a multicenter multiplatform feasibility trial. Strahlenther Onkol. 2023;199(7):621-630.
[61] Miszczyk M, Sajdok M, Bednarek J, et al. Stereotactic management of arrhythmia - radiosurgery in treatment of ventricular tachycardia (SMART-VT). Results of a prospective safety trial. Radiother Oncol. 2023;188:109857.
[62] Grise MA, Massullo V, Jani S, et al. Five-year clinical follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation. 2002;105(23):2737-40.
[63] Atkins KM, Chaunzwa TL, Lamba N, Bitterman DS, Rawal B, Bredfeldt J, et al. Association of Left Anterior Descending Coronary Artery Radiation Dose With Major Adverse Cardiac Events and Mortality in Patients With Non-Small Cell Lung Cancer. JAMA Oncol. 2021;7(2):206-19.
[64] Gauter-Fleckenstein B, Israel CW, Dorenkamp M, et al. DEGRO/DGK guideline for radiotherapy in patients with cardiac implantable electronic devices. Strahlenther Onkol 2015;191:393-404.
[65] Miften M, Mihailidis D, Kry SF, et al. Management of radiotherapy patients with implanted cardiac pacemakers and defibrillators: A Report of the AAPM TG-203. Med Phys. 2019;46(12):e757-e788.
[66] Gauter-Fleckenstein B, Nguyen J, Jahnke L, et al. Interaction between CIEDs and modern radiotherapy techniques: Flattening filter free-VMAT, dose-rate effects, scatter radiation, and neutron-generating energies. Radiother Oncol. 2020;152:196-202.
[67] Gauter-Fleckenstein B, Tülümen E, Rudic B, et al. Local dose rate effects in implantable cardioverter-defibrillators with flattening filter free and flattened photon radiation. Strahlenther Onkol. 2022;198(6):566-572.
[68] van der Ree MH, Hoeksema WF, Luca A, et al. Stereotactic Arrhythmia Radioablation: a multicenter pre-post intervention safety evaluation of the Implantable Cardioverter-Defibrillator function. Radiother Oncol. 2023;189:109910.
[69] Parenica HM, Mavroidis P, Jones W, et al. VMAT Optimization and Dose Calculation in the Presence of Metallic Hip Prostheses. Technol Cancer Res Treat. 2019;18:1533033819892255.
[70] Pawałowski, B., Ryczkowski, A., Panek, R. et al. Accuracy of the doses computed by the Eclipse treatment planning system near and inside metal elements. Sci Rep 12, 5974 (2022).
[71] Boda-Heggemann J, Jahnke A, Chan MKH, et al. In-vivo treatment accuracy analysis of active motion-compensated liver SBRT through registration of plan dose to post-therapeutic MRI-morphologic alterations. Radiother Oncol. 2019;134:158-165.
[72] Fast MF, Lydiard S, Boda-Heggemann J, et al. Precision requirements in stereotactic arrhythmia radioablation for ventricular tachycardia. Phys Imaging Radiat Oncol. 2023;28:100508.
[73] Stevens RRF, Hazelaar C, Fast MF, et al. STereotactic Arrhythmia Radioablation (STAR): Assessment of cardiac and respiratory heart motion in ventricular tachycardia patients - A STOPSTORM.eu consortium review. Radiother Oncol. 2023;188:109844.
[74] Botrugno C, Crico C, Iori M, et al. Patient vulnerability in stereotactic arrhythmia radioablation (STAR): a preliminary ethical appraisal from the STOPSTORM.eu consortium. Strahlenther Onkol. 2024 Apr 23.
[75] Herrera Siklody C, Pruvot E, Pascale P, et al. Refractory ventricular tachycardia treated by a second session of stereotactic arrhythmia radioablation. Clin Transl Radiat Oncol. 2022;37:89-93.

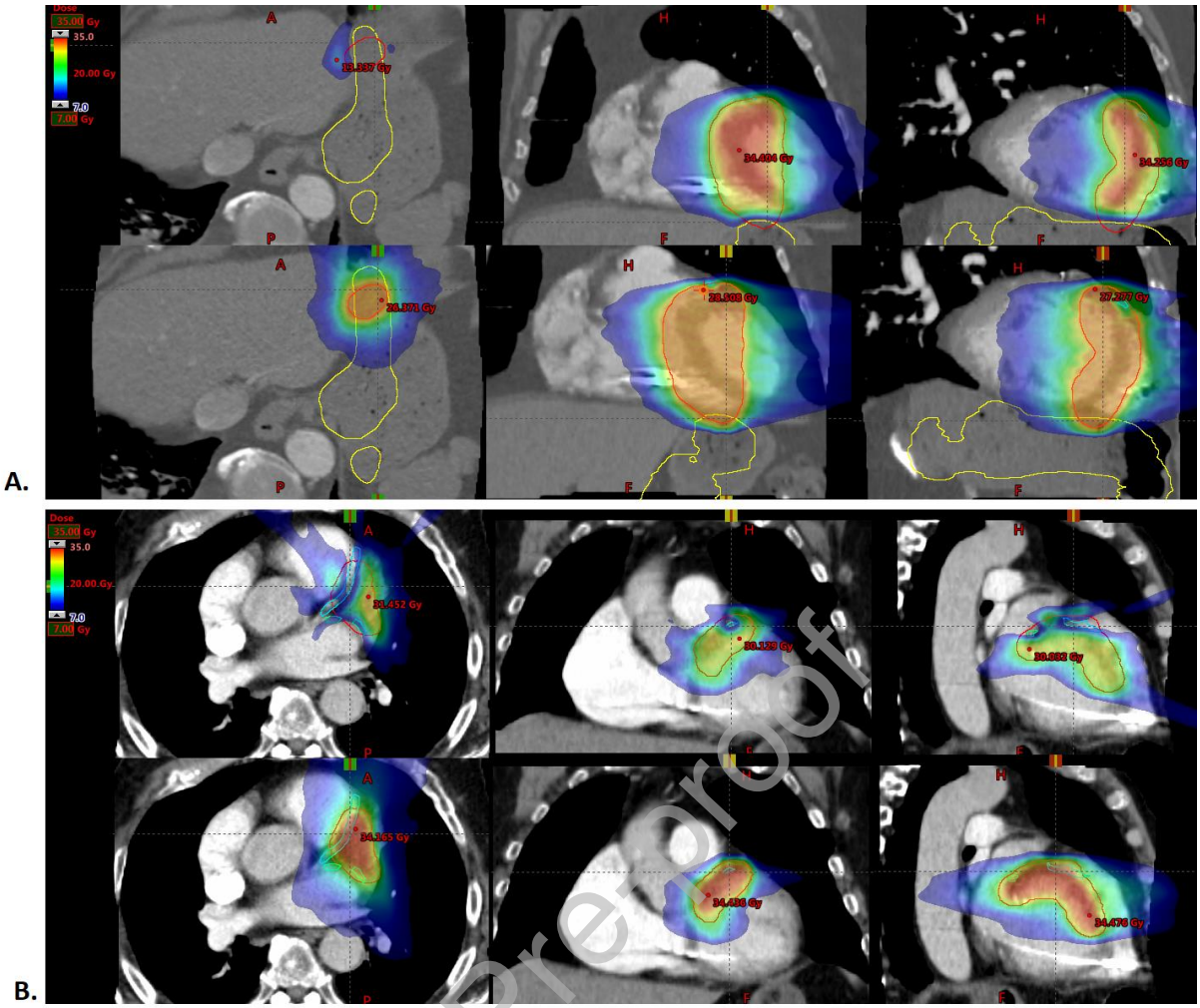

Figure 1: 3D dose distribution in axial, sagittal and coronal views of two planning solutions employing an organ-at-risk sparing strategy (top) versus a PTV coverage strategy (bottom) for the first (A) and third (B) benchmark case. The stomach is shown in yellow, the LAD in light blue and the PTV in red.

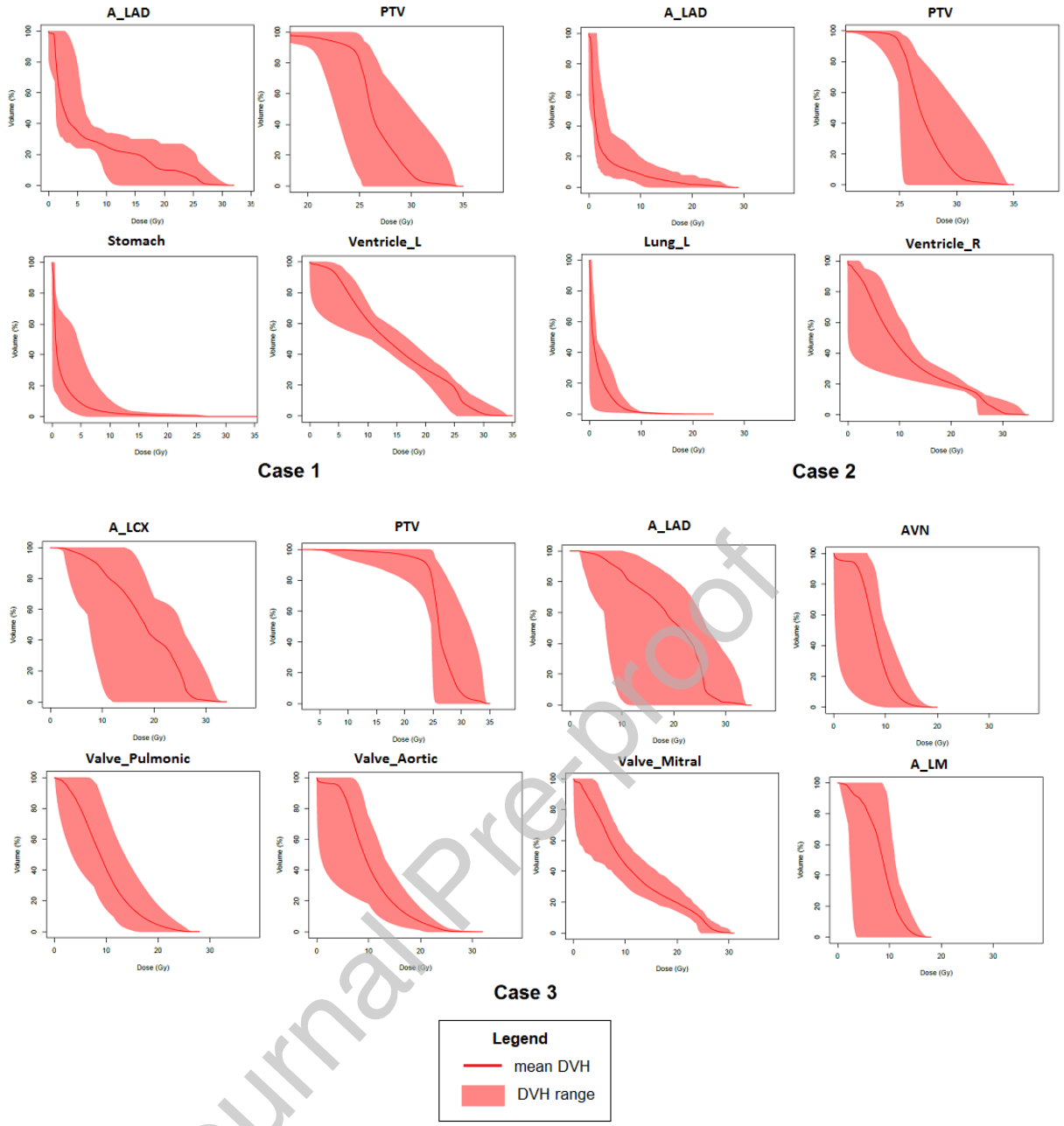

Figure 2: DVH distribution of relevant OARs and PTV structures for all three benchmark cases. The mean DVH is shown in red while its range is shown in the shaded area. PTV = Planning Target Volume, A_LAD = left anterior descending artery, A_LCX = left circumflex artery, AVN = atrioventricular node, A_LM = left coronary artery.

Tables

	Dose endpoints	Mean	Median	STD	Min	Max
Case 1	PTV $D_{98\%}$	16.7	15.4	5.0	6.4	25.0
	PTV $D_{0.035cm3}$	29.9	30.5	2.0	25.5	34.6
	Stomach $D_{0.035cm3}$	18.1	18.5	6.0	6.5	27.0
	A_LAD $D_{0.035cm3}$	29.7	30.2	3.0	25.5	34.3
	Right Ventricle $D_{0.035cm3}$	22.1	21.5	6.0	11.2	31.4
	Left Ventricle D_{mean}	26.9	26.8	1.7	22.7	30.0
Case 2	PTV $D_{98\%}$	24.2	24.4	0.9	21.4	25.6
	PTV $D_{0.035cm3}$	30.4	30.4	2.0	25.7	34.6
	A_LAD $D_{0.035cm3}$	19.9	19.6	6.0	10.1	27.2
	Left Lung $D_{0.035cm3}$	19.4	19.5	1.6	16.8	22.5
	Left Ventricle_D_{mean}	27.3	27.5	1.3	24.9	30.3
Case 3	PTV $D_{98\%}$	20.6	23.4	5.0	6.7	25.2
	PTV $D_{0.035cm3}$	30.3	30.3	2.0	25.9	34.5
	A_LAD $D_{0.035cm3}$	24.0	25.0	6.0	11.5	32.2
	A_LCX $D_{0.035cm3}$	24.6	26.0	6.0	10.7	33.8
	AVN $D_{0.035cm3}$	23.3	24.1	3.0	16.0	26.6
	Valve_Pulmonic $D_{0.035cm3}$	12.5	13.2	3.0	3.3	16.0
	Valve_Aortic $D_{0.035cm3}$	13.4	13.1	3.0	8.6	18.3
	Valve_Mitral $D_{0.035cm3}$	27.4	27.5	1.5	24.5	30.3
	A_LM $D_{0.035cm3}$	25.3	25.1	2.0	20.9	29.3
	Left Ventricle D_{mean}	9.2	9.7	3.0	0.7	12.8

Table 1. Mean and median doses for PTVs and considered OARs for the 3 benchmark cases. Abbreviations: PTV = Planning Target Volume, A_LAD: left anterior descending coronary artery, A_LCX: left circumflex coronary artery, A_LM = left main coronary artery, AVN = atrioventricular node, STD = standard deviation

Table 2: Final vote on the most important treatment planning statements for STAR. The full list of statements can be found in Supplement 2. Abbreviations: SBRT = Stereotactic Body Radiotherapy, STAR = Stereotactic Arrhythmia Radioablation, GTV = Gross Tumor Volume, TV = (Clinical) Target Volume, ITV = Internal Target Volume, PTV = Planning Target Volume, OAR = Organs at Risk, ICD = Implantable Cardioverter Defibrillators, ICRU = International Commission on Radiation Units and Measurements

	Agreement in %	**Strength of agreement**
For well-known single fraction dose limits of extra-cardiac OAR [25, 49, 52], the dose trade-off in the PTV for STAR must be in favor of OAR sparing to minimize risks of severe and fatal toxicities [53]	100	Strong agreement
For dose limitations on the coronary arteries as defined in [16], the individual patient anatomy and coronary function, indication for STAR as well as the location of the target volume must be considered for STAR [58, 9, 62, 63]	100	Strong agreement
For dose limitations on the cardiac valves as defined in [16], the individual patient anatomy and the valves functionality, the indication for STAR as well as the location of the target volume must be considered for STAR	100	Strong agreement
Since dose limits for cardiac substructures are not well established [20, 26, 56-59, 62, 63], the dose trade-off in the PTV for STAR should be based on the clinical situation of the patient	95	Strong agreement
Treatment delivery times for STAR should be kept as short as possible considering all technical options (e.g., VMAT and FFF modes and ITV motion management concepts if clinically and technically reasonable) due to radiation biology considerations and possibly poor patient conditions [7]	95	Strong agreement
The prescription dose and the dose inhomogeneity in the PTV should be based on the clinical situation of the patient, the desired treatment effect, and the target location with its surrounding extra-cardiac and cardiac OARs [7, NCT05258422]	90	Strong agreement
If higher doses over 30 Gy are considered for STAR, these doses should be confined to the target volume and not placed in the PTV margin zone (PTV minus ITV) or in PTV overlapping extra-cardiac OAR or cardiac substructures [14]	90	Strong agreement
For STAR with photon beams, energies ≤ 6 MV should generally be used to avoid malfunction of ICD [62, 63]	65	No agreement
To avoid changes in functionality of the ICD electrodes (e.g., from electrical or from tissue changes), the dose to the ICD electrodes should be reduced to below 15 Gy if the PTV coverage is not affected by this reduction. [68]	60	No agreement

Table 3: Final vote on the dose constraints of cardiac substructures. Abbreviation: STAR = Stereotactic Arrhythmia Radioablation, TV = (Clinical) Target Volume, PTV = Planning Target Volume, ALARA: As Low As Reasonably Achievable

Coronary arteries	16 Gy	20 Gy	25 Gy	30 Gy	We have no limit and optimize to ALARA	We cannot answer the question at this time
To avoid long-term complications for STAR [59-63], given that the coronary arteries as defined in [16] are located outside the PTV, the near maximum dose ($D_{0.035cc}$) must not exceed:	3	3	2	0	8	4
If treatment efficacy is clinically prioritized for STAR and the coronary arteries as defined in [16] are located inside the PTV, but outside the target volume, the near maximum dose ($D_{0.035cc}$) must not exceed:	1	4	7	0	8	3
If treatment efficacy is clinically prioritized for STAR and the coronary arteries as defined in [16] are located inside the target volume, the near maximum dose ($D_{0.035cc}$) should not exceed:	0	1	8	2	8	4
Valves	10 Gy	15 Gy	20 Gy	25 Gy	We have no limit and optimize to ALARA	We cannot answer the question at this time
To avoid long-term complications for STAR [56, 59, 60], given that the valves as defined in [16] are located outside the PTV, the near maximum dose ($D_{0.035cc}$) must not exceed:	0	2	2	3	9	4

If treatment efficacy is clinically prioritized for STAR and the valves as defined in [16] are located inside the PTV, but outside the TV, the near maximum dose ($D_{0.035cc}$) must not exceed:	0	0	4	7	6	3
If treatment efficacy is clinically prioritized for STAR and the valves as defined in [16] are located inside the TV, the near maximum dose ($D_{0.035cc}$) should not exceed:	0	0	0	9	5	6