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PHYSICS CONTRIBUTION

Refining Treatment Planning in STereotactic Arrhythmia Radioablation: Benchmark Results and Consensus Statement From the STOPSTORM.eu Consortium

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Purpose: STereotactic Arrhythmia Radioablation (STAR) showed promising results in patients with refractory ventricular tachycardia. However, clinical data are 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 and Materials: Planning target volumes (PTVs) overlapping extracardiac organs-at-risk and/or cardiac substructures were generated for 3 STAR cases. Participating centers were asked to create single-fraction treatment plans with 25 Gy dose prescriptions 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 International Commission on Radiation Units and Measurements 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 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 extracardiac organs-at-risk (75%) and cardiac substructures (50%) by PTV coverage reduction. PTV $D_{0.035cm3}$ ranged from 25.5 to 34.6 Gy, demonstrating a large variety of dose inhomogeneity. Estimated treatment times without motion compensation or setup ranged from 2 to 80 minutes. For the consensus statements, a strong agreement was reached for beam technique planning, dose calculation, prescription methods, and trade-offs between target and extracardiac critical structures. No agreement was reached on cardiac substructure dose limitations and on desired dose inhomogeneity in the target.

Conclusions: This STOPSTORM multicenter treatment planning benchmark study not only 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 are urgently needed for actionable guidelines for treatment planning.

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 cardioprotective drugs and often receive an implantable cardioverter defibrillator (ICD) to detect and terminate VT by means of antitachycardia pacing or defibrillation shocks.[1,2] For patients with refractory VT, catheter ablation is performed to localize and disrupt the underlying arrhythmogenic substrate. Although antiarrhythmic drugs and catheter ablation can control VT episodes in the long term, they also come with significant risks of complications and VT recurrences in 20% to 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 >40 patients,[4] and many more STAR procedures have been performed since.[7] For STAR, a single-fraction radiation therapy dose of 25 Gy is applied to the arrhythmogenic substrate using stereotactic body radiation therapy (SBRT) techniques that are routinely used 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 because of the complexity of STAR with respect to arrhythmogenic substrate identification by electroanatomic mapping and scar imaging,[11] target volume (TV) delineation,[12,13] beam-delivery technique planning,[14] cardiac and respiratory motion management,[10] and the application of high single-fraction doses.

Because 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. Here, 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.

Methods and Materials

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 QA work package (UKSH Kiel, D483/21)). 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 4 medical physicists (DS, WVE, MI, OB), 4 radiation oncologists (BB, JB, MM, DK), and 1 cardiologist (EP), 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[12,14,17] were selected by the expert panel for this treatment planning benchmark. In brief, the patients who had sustained VT were treated with STAR as previously described[18-20] 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 (eg, 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 (1 mm × 1 mm × 1.5-2.0 mm) in head-first supine were deformably coregistered with contrast-enhanced, ECG-triggered cardiac CT.[10]

The TV definition was based on the original clinical cases[18-20] refined by an expert panel consensus of a target delineation benchmark study,[12] which was guided for this study by a recently developed QA tool for STAR.[13] Respiratory motion management for treatment planning was implemented using an internal target volume (ITV) approach based on 4-dimensional computed tomography (CT) (case 1[18]), a robotic real-time tracking approach based on an ICD lead tip (case 2[19]), and a beam gating approach based on real-time MR-guidance (case 3[20]). 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] TVs for cases 1, 2, and 3 were 10.3 cm^3, 14.1 cm^3, and 14.9 cm^3 and PTVs were 97.3 cm^3, 62.2 cm^3, and 83.1 cm^3, respectively.

Delineation of extracardiac and intracardiac organs-at-risk (OAR) was based on the consensus of the critical structure contouring benchmark for all 3 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). A graphical case presentation can be found in Supplement E1 (Figure E1). The anonymized planning and cardiac CT and the contours of the 3 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.[18-20] From July until November 2021, each participating institution was required to create one clinically acceptable treatment plan for each of the 3 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 of 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 <25 Gy in and outside the PTV (eg, because of close critical structures) were up to the individual institution. Extracardiac 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[17,28-32] were provided.

The participants had to provide the treatment plan data and radiation therapy 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 were imported into an independent custom-made community-driven software designed for crowd knowledge-based evaluation of multicenter planning studies as previously presented.[33,34] Dose distributions of PTV and relevant extracardiac OAR and cardiac

substructures were analyzed using the following: (1) descriptive statistics for ICRU report 91 relevant parameters (eg, PTV/gross tumor volume $D_{98\%}$, $D_{50\%}$ and $D_{0.035cm3}$ and OAR $D_{0.035cm3}$)[22] and (2) multidata dose-volume histograms (DVHs), both correlated with institutional experience on STAR and planning approaches from the questionnaires. A quantitative plan quality score was not calculated because of a 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 2-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 the 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).

Results

For this benchmark, the participating centers submitted 22, 23, and 22 treatment plans for cases 1, 2, and 3, respectively. Most of the plans (67%) were generated for c-arm–based linear accelerators using intensity modulated arc therapy whereas 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 intensity modulated arc therapy, 73% and 27% of the plans used 6 and 10 MV flattening filter free beams. All well-established treatment planning systems (TPSs) were used and technical details of the treatment plans can be found in Supplement E1 Table E1. Because TPS–specific beam technique planning manuals have been published previously for SBRT[35] and STAR,[14] we omitted those details in this manuscript.

PTV and 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% ($PTV\ D_{96\%-100\%}$), 5% normalized to 100% of the TV, whereas the other 27% used other prescription volumes (see Supplement E1 Table E1). As a result, maximum doses varied from 25.5 Gy to 34.6 Gy (median, 29.9-30.5 Gy for the 3 cases).

OAR and dose trade-offs

Because specific dose limits were not provided, we asked the participants which protocol and guidelines their chosen dose constraints were based on. Eighty-five percent of the planners based their OAR limits on the provided references of SBRT and STAR clinical trial protocols and guidelines[17,24-27] whereas 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 were 6.4 to 25.0 Gy and 25.5 to 34.6 Gy, respectively. The stomach and LAD $D_{0.035cm3}$ range were 6.5 to 27.0 Gy and 11.2 to 31.4 Gy, respectively. For case 2, PTV $D_{98\%}$ and $D_{0.035cm}$ range were 21.4 to 25.6 Gy and 25.7 to 34.6 Gy, respectively. LAD $D_{0.035cm3}$ range was 10.1 to 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 were 6.7 to 25.2 Gy and 25.9 to 34.5 Gy, respectively. The left circumflex artery and LAD $D_{0.035cm3}$ range were 10.7 to 33.8 Gy and 11.5 to 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 extracardiac 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 the TPS 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 3 cases is shown in Figure 2.

Dose calculation and artifact 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 (eg, ray trace, pencil beam), type-B algorithms include more sophisticated models for the management of secondary particles (eg, collapsed cone and convolution/superposition), and type-C algorithms explicitly consider the lateral particle transport (eg, Monte Carlo, Boltzmann solver).[9,22]

Table 1 Mean and median doses for PTVs and considered OARs for the 3 benchmark cases

	Dose endpoints	Mean	Median	SD	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

Abbreviations: A_LAD: left anterior descending coronary artery; A_LCX = left circumflex coronary artery; A_LM = left main coronary artery; AVN = atrioventricular node; OAR = organs-at-risk; PTV = planning target volume.

Grid sizes for dose calculation were 1.0 to 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) whereas 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 E1 Table E2).

Estimated beam-on times

Estimated beam-on times without motion compensation and setup times were for c-arm–based systems 2.7 to 10 minutes, 2.6 to 10 minutes, and 2.4 to 10 minutes, and for robotic-based systems with and without multi-leaf-collimator 21 to 66 minutes, 32 to 71 minutes, and 33 to 80 minutes for cases 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 cases 1, 2, and 3, respectively.

STOPSTORM project accreditation

Because 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 part-accreditation of the participating centers for this subpart of the STAR treatment chain.

Treatment planning consensus statements

Twenty-seven statements and 6 cardiac substructure dose limitation scenarios were created after the 2-staged treatment planning statement establishment process. Twenty centers voted on the final statements (Table 2 and Supplement E2) 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

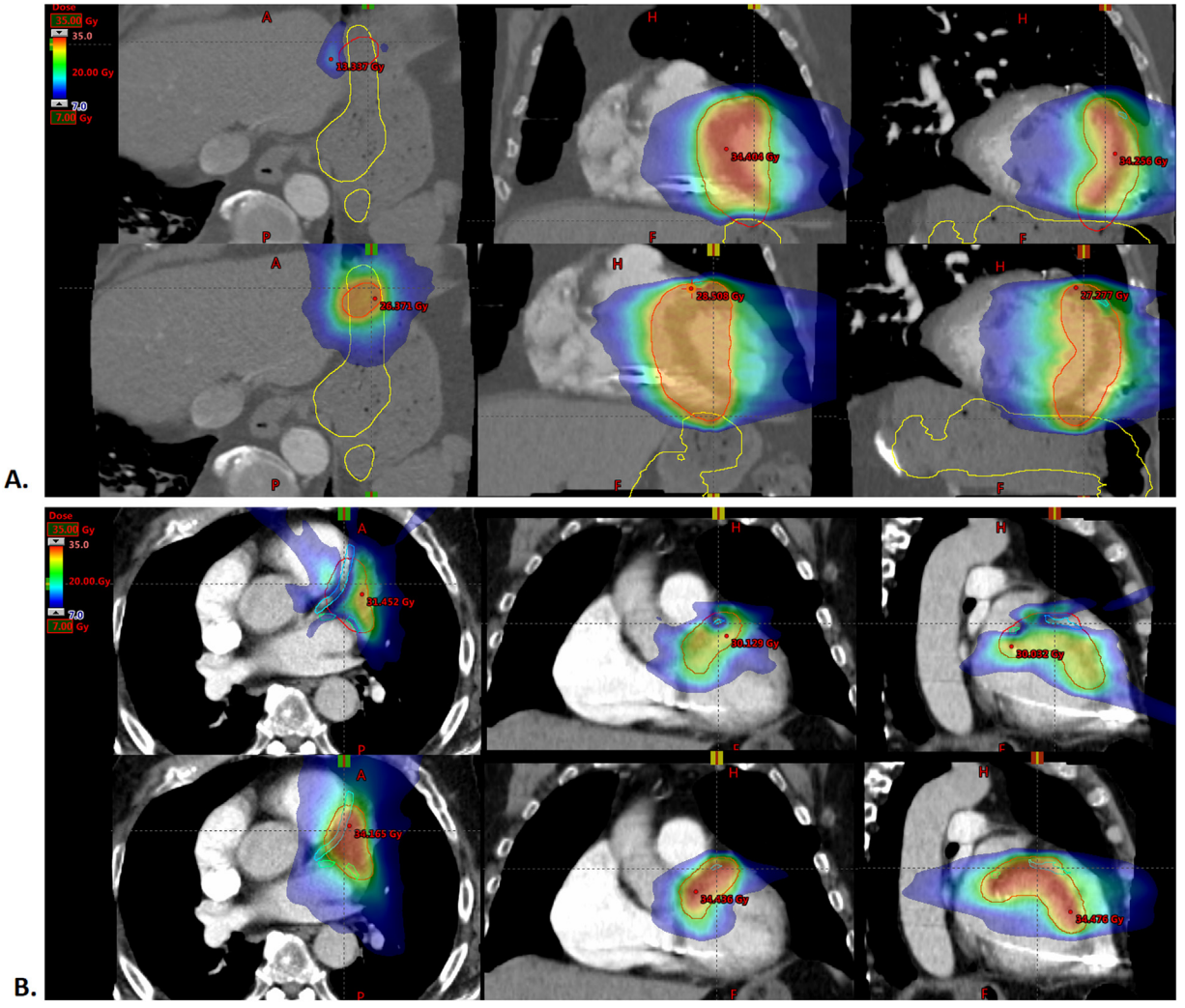

Fig. 1. Three-dimensional dose distribution in axial, sagittal, and coronal views of 2 planning solutions employing an organ-at-risk sparing strategy (top) versus a planning target volume coverage strategy (bottom) for the first (A) and third (B) benchmark cases. The stomach is shown in yellow, left anterior descending coronary artery is shown in light blue, and the planning target volume is shown in red.

substructure dose limitations, albeit not for specific dose values. Strong or moderate agreement was also achieved on two-thirds of the beam technique planning subpoints whereas 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 >30 Gy, albeit strong agreement was reached that if higher doses are used, they should be confined to the TV. Detailed information with score frequency, median agreement, and IQR are shown in Supplement E2.

Rating score

Recently, Radiotherapy Treatment plannINg study Guidelines (RATING) were published along with a scoring metric to assess the quality of treatment planning studies.[36] Based on the self-assessment of our study, we achieved a RATING score of 179 out of 200 points (90%, Supplement E3), which was validated by 2 independent reviewers.

Discussion

To our knowledge, this is the first large-scale multicenter treatment planning benchmark study for STAR representing current treatment approaches in diverse treatment settings from experienced centers in Europe.[7] In contrast to other benchmark studies,[14,33-35,37] we provided limited constraints and objectives for this novel treatment to investigate different approaches to STAR treatment planning in current clinical practice. As expected from previous experience with multicenter 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 extracardiac OAR

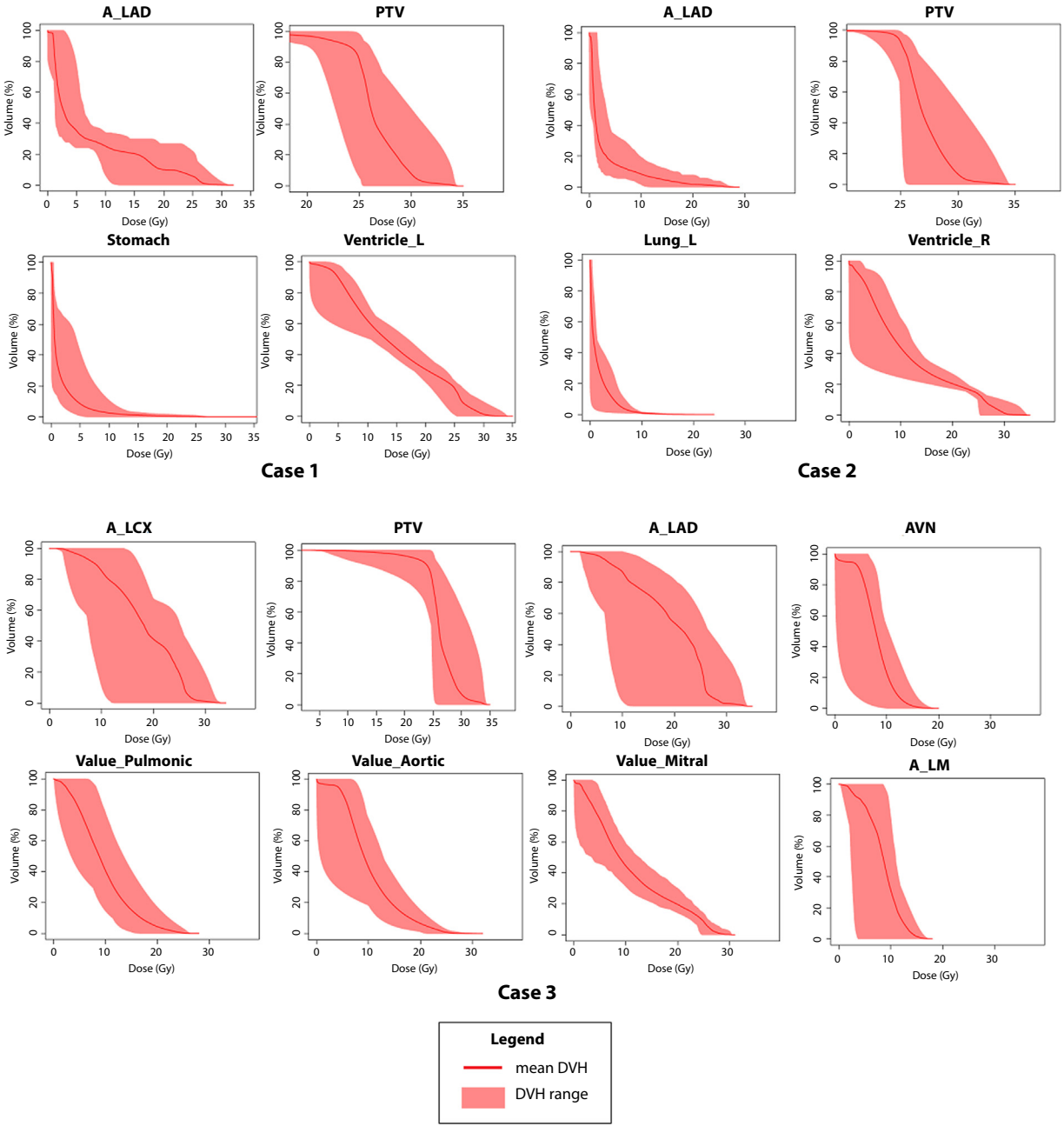

Fig. 2. Dose-volume histograms (DVH) distribution of relevant organs-at-risk and planning target volume (PTV) structures for all 3 benchmark cases. The mean DVH is shown in red while its range is shown in the shaded area. *Abbreviations:* A_LAD = left anterior descending coronary artery; A_LCX = left circumflex artery; A_LM = left coronary artery; AVN = atrioventricular node.

and cardiac substructure dose sparing. Because of the novelty of this treatment and the lack of clinical results on larger cohorts, there is currently no consensus on best practice approaches for treatment planning, which is why a plan score metric[14,35,38,39] 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 in this study. With such data presentation, individual plans can be discussed in comparison to other plans 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 qualitative 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. Although for solid tumors (eg, early-stage non-small cell lung cancer) dose-response relationships are clinically accepted for several dose parameters

Table 2 Final vote on the most important treatment planning statements for STAR. E2

	Agreement in %	Strength of agreement
For well-known single-fraction dose limits of extracardiac OAR,[25,49,50] the dose trade-off in the PTV for STAR must be in favor of OAR sparing to minimize risks of severe and fatal toxicities[52]	100	Strong agreement
For dose limitations on the coronary arteries as defined in Balgobind et al,[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[56,60,61]	100	Strong agreement
For dose limitations on the cardiac valves as defined in Balgobind et al,[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
Because dose limits for cardiac substructures are not well established,[17,26,54-57,60,61] 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 (eg, IMAT and FFF modes and ITV motion management concepts if clinically and technically reasonable) because of 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 extracardiac 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 extracardiac 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[62−65]	65	No agreement
To avoid changes in functionality of the ICD electrodes (eg, 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.[66]	60	No agreement

The full list of statements can be found in Supplement. *Abbreviations:* FFF = flattening filter free; ICD = implantable cardioverter defibrillators; IMAT = intensity modulated arc therapy; ITV = internal target volume; OAR = organs-at-risk; PTV = planning target volume; STAR = STereotactic Arrhythmia Radioablation.

(ie, PTV $D_{98\%}$, gross tumor volume $D_{50\%}$, and PTV $D_{2\%}$),[40] clinical data for STAR are still sparse and inconclusive.[4-7] In preclinical experiments, 2 main mechanisms were identified for higher doses: fibrosis and necrosis after doses exceeding 30 Gy,[41,42] and increased conduction velocity with protein changes because of notch activation with doses between 20 and 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 (eg, NCT05594368), but, as a prerequisite, a moderate agreement was reached to consequently prescribe, record, and report STAR treatments according to the ICRU report 91 standards.[22] However, because 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 (eg, 5 Gy) is desired as new studies suggested ventricular function improvement after low doses for cardiomyopathy patients.[48]

Strong agreement was reached for extracardiac OAR dose limits, which are well-known for thoracic SBRT for solid tumors.[25,49-51] However, the actual treatment plans submitted showed that not in all cases the extracardiac OAR dose limits were strictly kept. For case 1, the PTV overlapped with the stomach because of the used ITV approach. Although 75% of the planners favored extracardiac OAR dose sparing over PTV coverage, 50% of the treatment plans still showed higher maximum doses >19 Gy exceeding clinically accepted dose limitations.[25,49-51] Esophageal and stomach fistulas have already been reported in some rare cases after STAR[30,52] and keeping well below known limits while scarifying dose coverage in the PTV, which still may lead to therapeutic effects,[43,53] must be considered in those cases. Another possibility to increase the safety for target locations

Table 3 Final vote on the dose constraints of cardiac substructures

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,[57-61] given that the coronary arteries as defined in Balgobind et al[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 Balgobind et al[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 Balgobind et al[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,[54,57,58] given that the valves as defined in Balgobind et al[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 Balgobind et al[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 Balgobind et al[16] are located inside the TV, the near maximum dose ($D_{0.035cc}$) should not exceed:	0	0	0	9	5	6

Abbreviations: ALARA = as low as reasonably achievable; PTV = planning target volume; STAR = STereotactic Arrhythmia Radioablation; TV = (clinical) target volume.

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 because of inconclusive clinical data and practice at this time, and depending on overlap, 20% to 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 TV location, the individual patient anatomy, and the substructure functionality.

Although long-term toxicity data are emerging for cardiac substructures from lung cancer SBRT for patients without cardiac diseases,[26,54,55] short-term toxicity data for single-fraction irradiation to specific regions in the heart for patients with significant cardiac diseases continue to be inconclusive.[56-58] Although Knutson et al[56] acknowledged the fact that survival after STAR seems to be correlated with TV, it remained unclear if the extent of the underlying cardiomyopathy or the dose to the left ventricle was the main correlating factor for survival. On the other hand, van der Ree et al,[57] Krug et al,[58] and Miszczyk et al[59] showed no reduction in left ventricle ejection fraction after STAR with varying left ventricle mean doses, 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 Gy), 27.5 Gy (24.9-30.3 Gy), and 9.66 Gy (0.729-12.8 Gy) for cases 1, 2 and 3, respectively with different strategies to spare other regions in the heart (eg, left atrium or superior vena cava[17,26]). Near maximum doses to the valves, predominantly to the aortic and mitral valves, however, seem to be of clinical relevance for preserving aortic valve functionality. Van der Ree et al[57] showed significant differences between 1.5 and 7.2 Gy and 12.7 and 19.8 Gy for the 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. In our benchmark study, the aortic and mitral valve near maximum dose ranged from 8.6 to 18.3 Gy and

24.5 to 30.3 Gy, respectively, as they were close and even overlapping with the PTV in case 3. Special consideration of the primary clinical goal of the treatment and the current VT burden in such cases is strongly advised. For example, if the patient is in an uncontrollable VT storm (similar to 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 are known from intracoronary brachytherapy[60] and from conventional lung radiation therapy.[61] 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[7,58] competing mortality from the underlying heart disease, underreporting because the cause of death may be difficult to discern, and possibly 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 (eg, after infarct) in comparison with the potentially manageable late side effects of stenosis (eg, with stenting) must be considered (eg, 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 are available for this benchmark study; however, more clinical data on toxicity to those are 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.[62-65] Also, no agreement was found for maximum dose limitations for the ICD leads as clinical data suggest that higher doses may be safely delivered to leads in or near the target area in the left ventricle.[66] Concerning image artifacts, frequently occurring from ICD devices and leads and potentially from LVAD systems[19] (benchmark case 2), discrepancy in dose calculation up to 10% may occur[67,68] 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 multicenter 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[18-20] and studies have shown that all systems currently used for thoracic SBRT can deliver the same treatment accuracy with appropriate techniques (eg, c-arm–based gating and robotic-based tracking[69]). 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 (eg, gating), but similar to previous studies[35,38] our aim was to create challenging scenarios often faced in clinical routine. Nevertheless, although 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,[43,70] pathologically,[70,71] or even clinically.[70] The latter also comes with the consideration that patients are often in a fragile state[72] 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 because clinical result correlation with treatment techniques is lacking at this time. Overall, we tried to minimize the risk of bias as much as possible to allow for the generalizability of the results and statements comparable with previous treatment planning benchmarks.[33-39] Not addressed in this work was the retreatment scenario with STAR and great caution is advised concerning dose limitations in such cases.[73] Replanning with more specific dose constraints and objectives and plan quality assessment will be addressed in subsequent benchmark studies as well as plan delivery QA for the created treatment plans.

Conclusion

This benchmark study provided a very detailed view on current STAR treatment planning approaches in Europe that 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 toward actionable practice guidelines, and prescribing, recording, and reporting STAR treatments according to ICRU report 91 standards is mandatory to generate missing data.

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