

CLINICAL INVESTIGATION

Treatment Planning for Cardiac Radioablation: Multicenter Multiplatform Benchmarking for the RADiosurgery for VENtricular TACHycardia (RAVENTA) Trial

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Purpose: Cardiac radioablation is a novel treatment option for patients with refractory ventricular tachycardia unsuitable for catheter ablation. The quality of treatment planning depends on dose specifications, platform capabilities, and experience of the treating staff. To harmonize the treatment planning, benchmarking of this process is necessary for multicenter clinical studies such as the RADiosurgery for VENtricular TACHycardia trial.

Methods and Materials: Planning computed tomography data and consensus structures from 3 patients were sent to 5 academic centers for independent plan development using a variety of platforms and techniques with the RADiosurgery for VENtricular TACHycardia study protocol serving as guideline. Three-dimensional dose distributions and treatment plan details were collected and analyzed. In addition, an objective relative plan quality ranking system for ventricular tachycardia treatments was established.

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Data sharing statement: The data used and generated in this work are available upon reasonable request from the lead institutions on an individual basis, providing that ethical and data protection considerations are met.

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Results: For each case, 3 coplanar volumetric modulated arc (VMAT) plans for C-arm linear accelerators (LINAC) and 3 non-coplanar treatment plans for robotic arm LINAC were generated. All plans were suitable for clinical applications with minor deviations from study guidelines in most centers. Eleven of 18 treatment plans showed maximal one minor deviation each for target and cardiac substructures. However, dose-volume histograms showed substantial differences: in one case, the planning target volume ≥ 30 Gy ranged from 0.0% to 79.9% and the ramus interventricularis anterior $V_{14\text{Gy}}$ ranged from 4.0% to 45.4%. Overall, the VMAT plans had steeper dose gradients in the high-dose region, while the plans for the robotic arm LINAC had smaller low-dose regions. Thereby, VMAT plans required only about half as many monitor units, resulting in shorter delivery times, possibly an important factor in treatment outcome.

Conclusions: Cardiac radioablation is feasible with robotic arm and C-arm LINAC systems with comparable plan quality. Although cross-center training and best practice guidelines have been provided, further recommendations, especially for cardiac substructures, and ranking of dose guidelines will be helpful to optimize cardiac radioablation outcomes. © 2022 Elsevier Inc. All rights reserved.

Introduction

Ventricular tachycardia (VT) is a serious complication of structural heart disease derived from diverse underlying causes and is associated with a poor prognosis and significant mortality.¹

Besides pharmacologic treatment with antiarrhythmic drugs and implantation of automated implantable cardioverter defibrillators (ICD),² catheter ablation (CA) is accepted as an effective treatment in many clinical situations.³ However, CA carries a relevant risk of complications, including access-site vascular injury, thromboembolism, and cardiac perforation. Especially in patients with VTs originating in deep intramural locations or for patients with nonischemic VTs, recurrence rate after CA is $>50\%$ in the first 2 years.⁴

In the past few years, cardiac radioablation (RA) has been developed as a promising new and noninvasive method for treatment of VT after failed CA.⁵⁻⁷ RA uses stereotactic body radiation therapy (SBRT) to target the critical substrate in the ventricular myocardium identified by invasive electroanatomical mapping procedures or alternatively by noninvasive mapping techniques.^{8,9} In the recent years a small number of case series and first clinical studies have evaluated the safety and efficacy of RA.^{5,10-13} Although the efficacy is dependent on myocardial tissue alterations within the myocardial target zone,⁶ safety parameters might be connected to alterations of surrounding tissues.¹⁴

Exact target volume definition by combination of electroanatomical mapping procedures and various imaging techniques and subsequent transformation to the planning computed tomography (CT) is of critical importance for successful RA.^{15,16} In addition, rigorous motion management and highly conformal dose delivery are prerequisites for treatment success and minimization of treatment-related morbidity.¹⁷ So far, patients have been treated with different radiation devices including C-arm linear accelerators (LINAC),⁵ robotic radiosurgery,¹¹ MR-LINAC,¹⁸ and protons.¹⁹ Most studies applied 25 Gy in one fraction with a considerable dose heterogeneity within the target volume.⁹

Several treatment planning studies for RA have evaluated effects of different treatment planning approaches as well as

treatment platforms²⁰⁻²² analyzing prescription modalities, geometric approaches, and dose delivery concepts. These studies show several shortcomings due to monocentric design or limited plan comparison. Other studies have given examples for harmonization of treatment planning approaches for SBRT.²³⁻²⁵

For the German RADiosurgery for VENtricular TACHycardia (RAVENTA) trial,²⁶ we recently described a benchmarking process for clinical target volume generation in a multicentric approach.¹⁶ In the present study, we aimed to compare different treatment planning approaches with the goal to establish a planning benchmark for the multicenter, multiplatform RAVENTA trial. We analyze treatment planning approaches and parameters of plan quality from 5 different academic medical centers for various VT cases formerly treated under compassionate use.

Methods and Materials

Target volume definition and cardiac radiosurgery centers

The detailed background and study protocol of the RAVENTA trial (NCT03687747) have been published before.²⁶ As part of the study rationale and covered by the institutional review board of the primary sponsor site (UKSH Kiel, D476/19), the establishment of benchmarks for the definition of the target volume as well as for the treatment planning according to the study protocol was intended. The first 3 available patients with persistent VT treated with RA in compassionate use at the centers planning to participate in the study were selected for benchmarking. The patients have been treated under SBRT and RA guidelines²⁷⁻²⁹ and detailed patient and treatment characteristics have been described before.^{16,18,30}

For each of these cases, a planning CT (1.5-2.0 mm slices) was coregistered with a contrast-enhanced, ECG-triggered cardiac CT in diastole. A consensus clinical target volume (CTV) was defined during the RAVENTA-benchmark study for target volume definition.¹⁶ To compensate for residual uncertainties the consensus target was expanded by 5 mm to

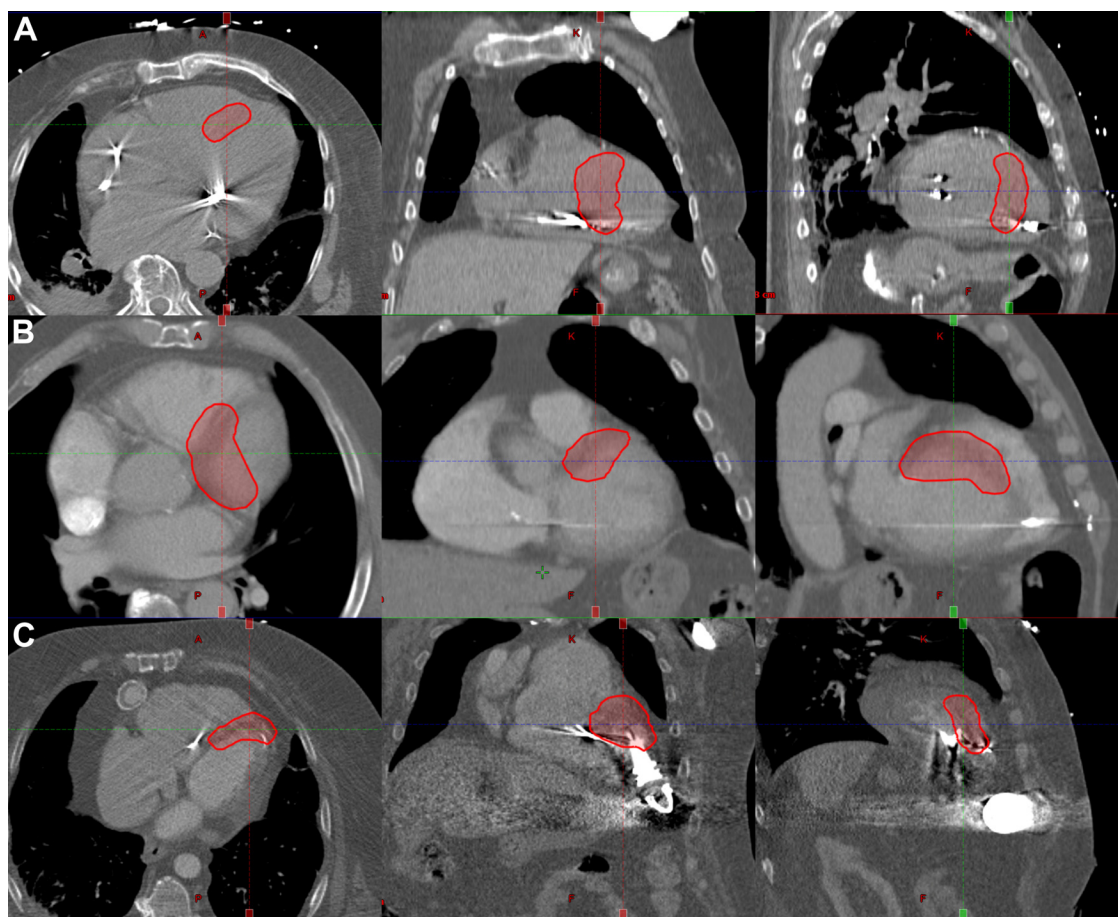


Fig. 1. Target location in axial, coronal, and sagittal slices (left to right) for case 1 (A), 2 (B), and 3 (C). The planning target volume is shown in red.

generate the planning target volume (PTV) assuming an active motion compensation technique during treatment.⁹ The final PTVs (Fig. 1) for this study had volumes of 36.5 cm³ (case 1), 62.4 cm³ (case 2), and 52.8 cm³ (case 3). Planning CT, target structures and relevant organs at risk (OAR) including cardiac substructures based on the RAVENTA protocol²⁶ were anonymized and sent to 5 participating radiation oncology centers for plan generation. Participating centers were free to choose the treatment platform and the related treatment planning system (TPS). Due to general recommendations for treatment of patients with implanted cardiac electrical devices, the treatment energy was restricted to 6 MV and beam delivery through ICD electronic was forbidden.³¹

Dose prescription and organs at risk constraints

Predefined values for dose specification of target volume coverage and dose limitations of adjacent organs and cardiac subcompartments have been described in detail.²⁶ For the RAVENTA protocol a single dose of 25 Gy with a coverage of 95% (PTV $V_{25\text{Gy}} \geq 95\%$) has to be administered to the PTV. The near maximum dose is limited to 32.5 Gy (PTV $D_{2\%} \leq 32.5$ Gy) with recommended peak doses within the

CTV >30 Gy. Minor protocol deviations regarding dose coverage ($90\% \leq \text{PTV } V_{25\text{Gy}} < 95\%$) or maximum dose (PTV $V_{32.5\text{Gy}} \leq 5\%$ or PTV-CTV $D_{2\%} \geq 30$ Gy) are accepted. For certain cardiac substructures like the aorta and left coronary arteries (ramus interventricularis anterior [RIVA] and ramus circumflexus), dose constraints are defined.³²⁻³⁴ For many other cardiac substructures (vena cava superior, left atrium, heart, PTV) dose recommendations are given according to previously published data.^{5,32-35} An outline of target and cardiac OAR constraints is given in Table E1. For noncardiac OAR like esophagus, upper and lower airways, spinal canal, skin and lungs, dose, and volume constraints are specified with definition of minor and major deviations. The stomach should use the same constraints as the esophagus, and for all other potentially nearby organs, the usual constraints for SBRT apply.^{26,32} Per protocol, the RAVENTA trial requires a documented risk analysis and approval for cases with more than one minor deviation.

Data collection and dosimetric comparison

Dose distributions of all treatment plans were imported into Eclipse v15.5 (Varian Medical Systems) TPS for plan comparison. In addition to dose distributions, a questionnaire

regarding treatment and planning parameters, such as beam arrangement and dose calculation algorithm, as well as an estimated treatment time was collected. The treatment time includes beam-on time, device movements, and initial patient positioning and was estimated by each center. All plans underwent and passed internal quality assurance programs and were deemed deliverable.

In accordance with best practice standards for treatment planning studies,²³ a feedback round and potential correction strategies were discussed during the 2nd German Cardiac Radiosurgery Workshop on March 5th 2021.

For analysis and comparison of different treatment plans, we evaluated compliance to given constraints for targets, OAR and cardiac substructures. Dose parameters $D_{2\%}$, $D_{98\%}$, $D_{50\%}$, and coverage of PTV (PTV_{25Gy}) and CTV (CTV_{30Gy}), as well as the near maximal dose of the marginal region (PTV-CTV), were analyzed based on the International Commission on Radiation Units and Measurements report 91 recommendations.^{36,37} Common plan quality parameters such as normalized conformity (CI),³⁸ gradient (GI), and homogeneity indices (HI) were evaluated according to the following equations:

$$CI = 1 - (PTV_{25Gy}^2 / [PTV \times V_{25Gy}]) \text{ (ideal} = 1.0)$$

$$GI_{high} = V_{18.75Gy} / V_{25Gy}$$

$$GI = V_{12.50Gy} / V_{25Gy} \quad (\text{as low as possible})$$

$$GI_{low} = V_{6.25Gy} / V_{25Gy}$$

$$HI = (D_{PTV2\%} - D_{PTV98\%}) / D_{PTV50\%} \text{ (homogeneous} = 0.0)$$

Necessary volumes like the PTV receiving 25 Gy (PTV_{25Gy}) and the complete volumes described by the isodoses of 6.25 Gy ($V_{6.25Gy}$), 12.5 Gy ($V_{12.50Gy}$), 18.75 Gy ($V_{18.75Gy}$), and 25 Gy ($V_{25.0Gy}$) were extracted with Eclipse. The plan quality parameters were compared for treatment platforms (C-arm LINAC vs robotic arm LINAC) and single treatment plans. Furthermore, monitor units (MU) and estimated treatment time for the 3 cases and all plans were compared and discussed.

Plan quality ranking

To condense and objectify the plan quality classification, plans were ranked on a scale from 1 to 3 (good, average, and below average) based on the distribution of all plans in terms of target coverage, constraint compliance, plan quality indices, and MU. This relative plan ranking method was adapted from previously published works.^{24,39,40} We chose to rank the plans into 3 grades instead of the 4 described in the literature due to the limited number of plans for each case.⁶ All relevant parameters were evaluated by dividing their value range linearly into 3 categories. These subratings of the individual parameters were weighted, summed, and rated again according to the same scheme for the final plan rating. This allows all individual parameters to be considered according to their clinical

significance. To find a representative weighting procedure, 2 ratings were tested. In a first rating all RAVENTA constraints and plan quality indices were weighted equally, and recommendations were weighted half as much. In a second rating, relevant target constraints and OAR in direct proximity (≤ 2 cm) to the target were weighted twice higher than all other parameters, as rather low doses from distant structures were thought to be clinically less relevant for overall plan assessment. In addition, the second weighting allows for more flexible handling of multiple organs in close proximity to the target structure. Both versions were evaluated and compared.

RATING score

Recently, Radiotherapy Treatment plannINg study Guidelines (RATING) were published along with a scoring metric to assess the quality of treatment planning studies.⁴¹ Briefly outlined, various questions relating mainly to methodological aspects of the study are answered in a checklist, weighted, standardized, and summarized into an overall score.

Results

Treatment platform and planning techniques

For each of the 3 patients 6 treatment plans were created with free choice of radiation therapy modalities and TPS (Table 1). One of the 5 centers contributed with both a C-arm LINAC and a CyberKnife (Accuray Incorporated, Sunnyvale, CA) plan. Among the treatment centers, 3 chose the CyberKnife VSI robotic radiosurgery with IRIS-collimation, flattening-filter-free mode, and a maximal dose rate of 1000 MU/min. The TPS was Precision v2.0 for 2 of the 3 centers and MultiPlan v4.6.1 for one center, calculation algorithm was Ray-tracing for all CyberKnife applications. The remaining 3 treatment plans used C-arm platforms with coplanar volumetric modulated arc therapy (VMAT), among these one Varian Clinac DHX, one Varian True-Beam STx (Varian Medical Systems, Palo Alto, CA), both in combination with Eclipse v15.5 TPS and one Elekta Versa HD (Elekta AB, Stockholm, Sweden) with Monaco TPS (Elekta AB, Stockholm, Sweden). Two C-arm systems were planned in a flattening-filter-free mode with dose rates of 1400 MU/min. Only the Varian Clinac DHX-system used the flattening filter mode with 600 MU/min.

Dose calculation was performed using the common algorithms and settings (Table 1) of the centers with a grid size for all plans being less than or equal to 2.5 mm.

Deviations from study guidelines

According to the study protocol of the RAVENTA-trial, plans were judged regarding target volume conformity (n = 3; PTV, PTV-CTV, CTV), constraints (c) and recommendations (r)

Table 1 Technical requirements and treatment planning parameters

	CK1	CK2	CK3	VMAT1	VMAT2	VMAT3
Treatment system/ planning system	CyberKnife VSI Precision v2.0	CyberKnife VSI Multiplan v4.6.1	CyberKnife VSI Precision v2.0	Varian Clinac DHX Eclipse v15.5	Elekta Versa HD Monaco v5.51	Varian TrueBeam STx Eclipse v15.5
Beam arrangement	Noncoplanar	Noncoplanar	Noncoplanar	Coplanar	Coplanar	Coplanar
Collimation	IRIS	IRIS	IRIS	Millennium 120 MLC	Agility MLC	High definition 120 MLC
Mode	FFF	FFF	FFF	FF	FFF	FFF
Maximal dose rate	1000 MU/min	1000 MU/min	1000 MU/min	600 MU/min	1400 MU/min	1400 MU/min
Assumed motion management	Tracking	Tracking	Tracking	Gating	Gating	Gating
Calculation algorithm	Ray Trace	Ray Trace	Ray Trace	AAA	Monte Carlo	Acuros XB
Dose grid resolution	CT resolution* (≤ 2.0 mm)	CT resolution* (≤ 2.0 mm)	CT resolution* (≤ 2.0 mm)	2.5 mm	2.0 mm	1.0 mm
* Case 1: $0.9 \times 0.9 \times 2.0$ mm ³ ; case 2: $1.0 \times 1.0 \times 2.0$ mm ³ ; case 3: 1.5 mm isotropic. Abbreviations: CK = robotic arm LINAC; FF = with flattening filter; FFF = flattening filter free; VMAT = volumetric modulated arc therapy.						

for cardiac substructures ($n = 5$; aorta (c), left coronary artery (c), V. cava superior (r), left atrium (r), heart-PTV (r)), and noncardiac OAR ($n = 7$; esophagus, trachea, bronchus, spinal canal, skin, lungs, ICD) with 1-3 constraints for each organ. Eleven of the 18 proposed treatment plans met the study guidelines with no more than one minor deviation for target and cardiac substructures (Table 2). For case 1, all plans except for one fulfilled study guidelines without deviation. Only one plan had a slightly elevated $D_{2\%}$ for the marginal region (PTV-CTV) of 30.1 Gy (<30.0 Gy). For case 2 all plans bared at least 2 minor deviations for cardiac substructures (aorta and left coronary artery) and additional minor deviations for target volume constraints (PTV coverage and $D_{\max}$ of PTV-CTV) in 3 of 6 plans. One plan presented a major deviation for the $D_{2\%}$ of PTV-CTV-margin contour. In case 3, one plan had a major deviation with respect to PTV coverage ($>90.0\%$) at 89.4%. Regarding cardiac substructures, a relevant number of dose recommendations were exceeded for case 2 (11 of 18) while fewer exceedances to recommended cardiac substructure doses were presented for case 1 (6/18) and case 3 (2/18). The left atrium turned out to be the most critical structure among those having dose recommendations (Table 2). The number of protocol deviations regarding OAR constraints and recommendations for cardiac substructures did not differ substantially between robotic arm LINAC and C-arm LINAC treatment plans (34 for robotic arm and 27 for C-arm LINAC plans).

Dosimetric comparison

Despite detailed prescription guidelines, dose and homogeneity within CTV and PTV varied between treatment

plans (Table 3). Homogeneity was slightly higher for VMAT plans compared with robotic arm LINAC (CK) plans, with a median HI of VMAT-plans of 0.20 (range, 0.16-0.25) and for robotic arm LINAC plans of 0.28 (range, 0.22-0.34), respectively. A higher homogeneity did not correlate with low V_{30Gy} of CTV, which was higher for case 1 in the VMAT plans and for cases 2 and 3 in the robotic arm LINAC plans. V_{30Gy} ranged between 0.8% and 72.2% (case 1), 0.0% and 79.9% (case 2), and 0.0% and 50.4% (case 3).

Dose conformity and dose falloff outside the PTV was comparable for all plans when looking at the International Commission on Radiation Units and Measurements conformity ($CI_{CK} = 0.79$; range, 0.76-0.85; $CI_{VMAT} = 0.87$; range, 0.71-0.94) and gradient index ($GI_{CK} = 4.5$; range, 3.4-5.5; $GI_{VMAT} = 4.0$; range, 3.4-5.0). Due to the different type of beam delivery, the dose is distributed more axially in VMAT plans and more spherically in robotic arm LINAC plans (Fig. 2). Although VMAT plans demonstrate a steeper gradient for higher doses ($GI_{CK-high} = 2.2$; range, 1.9-2.5; $GI_{VMAT-high} = 1.9$; range, 1.7-2.3), robotic arm LINAC plans had slightly smaller low-dose regions ($GI_{CK-low} = 13.5$; range, 9.3-18.2; $GI_{VMAT-low} = 17.6$; range, 14.9-20.4). For all 3 cases, VMAT-planning of one participating center (VMAT3) yielded best results regarding CI and GI in the high dose range; yet another center (CK2) reached best GI values in terms of low-dose volume.

Dose-volume histograms of OAR near the heart and of heart substructures show considerable variation (Fig. 3) without major deviations of given constraints. V_{14Gy} of the RIVA for example ranged between 0.1% and 30.6% for case 1, between 4.0% and 45.4% for case 2, and between 0.0% and 6.3% for case 3, and no major deviations ($D_{\max} > 20$ Gy) were noted. For the left and right ventricle, dose-volume

Case 1	CK1	CK2	CK3	VMAT1	VMAT2	VMAT3
PTV V _{25Gy} in %	95.2	95.5	95.4	95.0	97.2	98.7
PTV-CTV D _{max} in Gy	30.4*	30.4*	29.3	30.3*	30.4*	29.5
PTV-CTV D _{2%} in Gy	29.7	30.1 [†]	28.7	29.9	30.0	29.2
Aorta D _{max} in Gy	9.1	5.0	6.3	7.6	7.6	4.8
RIVA D _{max} in Gy	18.7*	14.9*	13.1	17.8*	19.4*	18.4*
RCX D _{max} in Gy	-	-	-	-	-	-
Vena cava superior D _{50%} in Gy [‡]	0.2	0.1	0.4	0.6	0.3	0.1
Left atrium D _{max} in Gy [†]	7.2*	5.0*	4.7*	6.0*	6.8*	3.9
Heart-PTV D _{50%} in Gy [†]	3.0	3.2	3.4	4.3	5.3*	2.7
No. of exceeded recommendations	1	1	1	1	2	0
No. of minor deviations	2	2	0	2	2	1
No. of major deviations	0	1	0	0	0	0
Case 2						
PTV V _{25Gy} in %	90.8*	96.0	94.6*	95.9	94.8*	97.4
PTV-CTV D _{max} in Gy	29.7	30.6*	31.0*	29.0	30.5*	30.6*
PTV-CTV D _{2%} in Gy	29.2	30.0	30.2 [†]	28.3	29.7	29.4
Aorta D _{max} in Gy	22.3*	23.7*	24.4*	24.0*	22.0*	16.9
RIVA D _{max} in Gy	16.1*	19.1*	14.8*	15.5*	17.1*	16.7*
RCX D _{max} in Gy	15.6*	18.4*	16.8*	14.7*	12.1	15.4*
Vena cava superior D _{50%} in Gy [†]	1.1*	0.7*	0.8*	3.3*	1.8*	0.6
Left atrium D _{max} in Gy [†]	27.4*	28.8*	28.3*	27.8*	28.9*	29.2*
Heart-PTV D _{50%} in Gy [†]	3.9	4.2	3.5	3.8	3.3	1.7
No. of exceeded recommendations	2	2	2	2	2	1
No. of minor deviations	4	4	5	3	4	3
No. of major deviations	0	0	1	0	0	0
Case 3						
PTV V _{25Gy} in %	97.8	89.4 [†]	97.2	97.5	95.2	94.8*
PTV-CTV D _{max} in Gy	30.7*	30.1*	29.7	29.3	29.0	29.5
PTV-CTV D _{2%} in Gy	29.9	29.5	29.3	28.9	28.6	28.6
Aorta D _{max} in Gy	0.4	0.3	1.7	0.3	0.4	0.3
RIVA D _{max} in Gy	15.0*	17.6*	11.0	13.0	17.0*	18.2*
RCX D _{max} in Gy	3.3	2.4	2.1	2.3	2.1	2.4
Vena cava superior D _{50%} in Gy [†]	0.1	0.1	0.1	0.1	0.1	0.1
Left atrium D _{max} in Gy [†]	5.4*	4.2	4.2	4.3	5.2*	4.1
Heart-PTV D _{50%} in Gy [†]	2.7	1.8	2.5	2.0	2.2	1.7
No. of exceeded recommendations	1	0	0	0	1	0
No. of minor deviations	2	2	0	0	1	2
No. of major deviations	0	1	0	0	0	0
<i>Abbreviations:</i> CTV = clinical target volume; PTV = planning target volume; RCX = ramus circumflexus; RIVA = ramus interventricularis anterior; VMAT = volumetric modulated arc therapy. * minor deviation; [†] major deviation. [‡] Recommendations are marked to distinguish them from the stricter constraints						

Table 3 Target doses ($D_{98\%}$, $D_{50\%}$, $D_{2\%}$), coverage (V_{25Gy}), and dose indices

			CK1	CK2	CK3	VMAT1	VMAT2	VMAT3
Case 1	PTV	V_{25Gy} in %	95.2	95.5	95.4	95.0	97.2	98.7*
		$D_{98\%}$ in Gy	23.8	22.3	22.4	24.0	24.5	25.4*
		$D_{50\%}$ in Gy	28.3	28.8	27.4	28.5	28.5	28.4
		$D_{2\%}$ in Gy	31.0	31.1	29.5	31.3	31.1	30.6
		CI	0.77	0.76	0.83	0.90	0.87	0.92*
		GI	5.48	4.26	4.65	4.63	3.82*	4.04
		HI	0.25	0.31	0.26	0.25	0.23	0.18
	PTV-CTV	$D_{2\%}$ in Gy	29.7	30.1	28.7	29.9	30.0	29.2
	CTV	V_{30Gy} in %	38.8	58.3	0.7	68.0	72.2	39.6
Case 2	PTV	V_{25Gy} in %	90.8	96.0	94.6	95.9	94.8	97.4*
		$D_{98\%}$ in Gy	21.9	23.7	22.3	23.5	23.1	24.8*
		$D_{50\%}$ in Gy	28.0	29.0	28.8	27.6	27.5	28.4
		$D_{2\%}$ in Gy	31.3	32.2	31.8	28.5	29.8	30.8
		CI	0.85	0.84	0.76	0.82	0.73	0.94*
		GI	4.54	3.40*	4.50	4.96	4.79	3.40*
		HI	0.34	0.30	0.33	0.18	0.25	0.21
	PTV-CTV	$D_{2\%}$ in Gy	29.2	30.0	30.2	28.3	29.7	29.4
	CTV	V_{30Gy} in %	46.5	79.9	66.4	0.0	1.8	31.0
Case 3	PTV	V_{25Gy} in %	97.8*	89.4	97.2	97.5	95.2	94.8
		$D_{98\%}$ in Gy	24.9*	23.1	23.4	24.5	24.3	24.3
		$D_{50\%}$ in Gy	28.5	27.9	28.0	28.1	27.1	27.6
		$D_{2\%}$ in Gy	31.0	31.0	30.0	29.4	28.6	29.7
		CI	0.76	0.85	0.79	0.71	0.83	0.87*
		GI	4.56	3.88	5.45	3.93	4.95	3.73*
		HI	0.22	0.28	0.24	0.17	0.16	0.20
	PTV-CTV	$D_{2\%}$ in Gy	29.9	29.5	29.3	28.9	28.6	28.6
	CTV	V_{30Gy} in %	50.4	45.5	7.1	0.2	0.0	1.7
Abbreviations: CI = conformity index; CTV = clinical target volume; GI = gradient index; HI = homogeneity index; PTV = planning target volume; VMAT = volumetric modulated arc therapy.								
* Best result.								

histograms from the different centers show a high degree of agreement (Fig. 3).

Treatment plan complexity

Suggested plans for robotic arm LINAC and C-arm platforms differed considerably regarding the treatment complexity enunciated by the amount of monitor units and the estimated treatment time. Treatment plans for the robotic arm LINAC resulted in an average of 17,898 MU (range, 14,355-28,686 MU) and an estimated average treatment time of 43 minutes (range, 35-88 min). For the C-arm platforms, the amount of MU and the resulting

estimated treatment time were considerably lower with 7712 MU (range, 5882-16,329 MU) and 10 minutes treatment time (range, 4-17 min). In addition, a workflow-dependent setup time for patient positioning and respiratory compensation of 15 to 30 minutes was specified by the centers for all treatments, regardless of treatment platform.

Plan quality ranking

Use of a sophisticated plan quality ranking system for all 3 treatment cases resulted in a quality order for each case. This order is based on a relative ranking

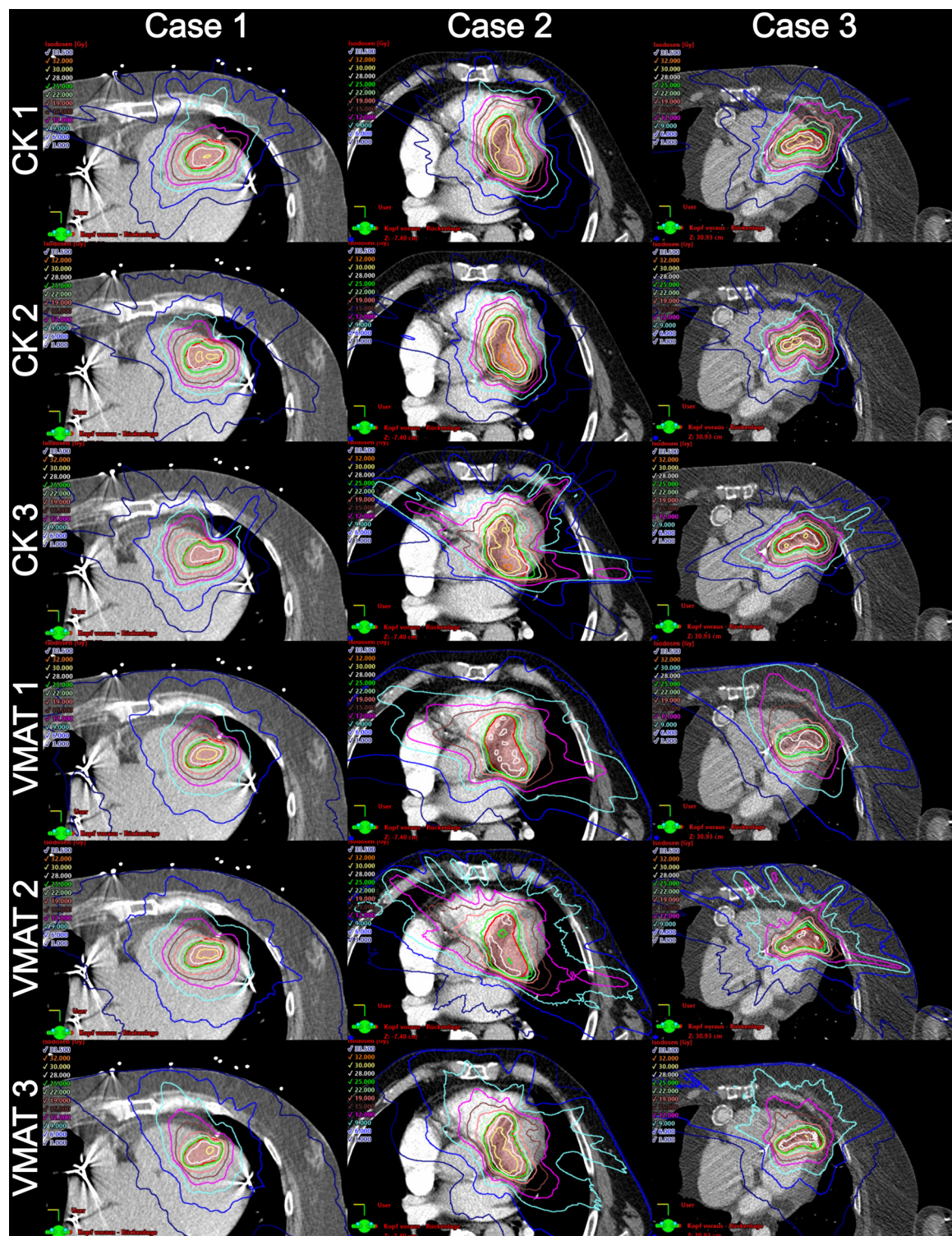


Fig. 2. Dose distributions in axial slices for all plans (top to bottom) of case 1, 2, and 3. The target region is shown in red. Isodose lines ranging from orange (32 Gy) to green (25 Gy) to dark blue (3 Gy).

procedure, ie, one plan must, by definition, be the best and another one the worst. The highest rankings in all 3 cases were achieved by plans from the same institution and platform (VMAT3) regardless of which weighting method was chosen. The second highest rankings

were achieved in plans CK2 or VMAT1 depending on the weighting procedure (Table 4). The main difference here is in the weighting of treatment time, which is significantly longer for the robotic arm LINAC plans, thus worsening the ranking of plan CK2 compared

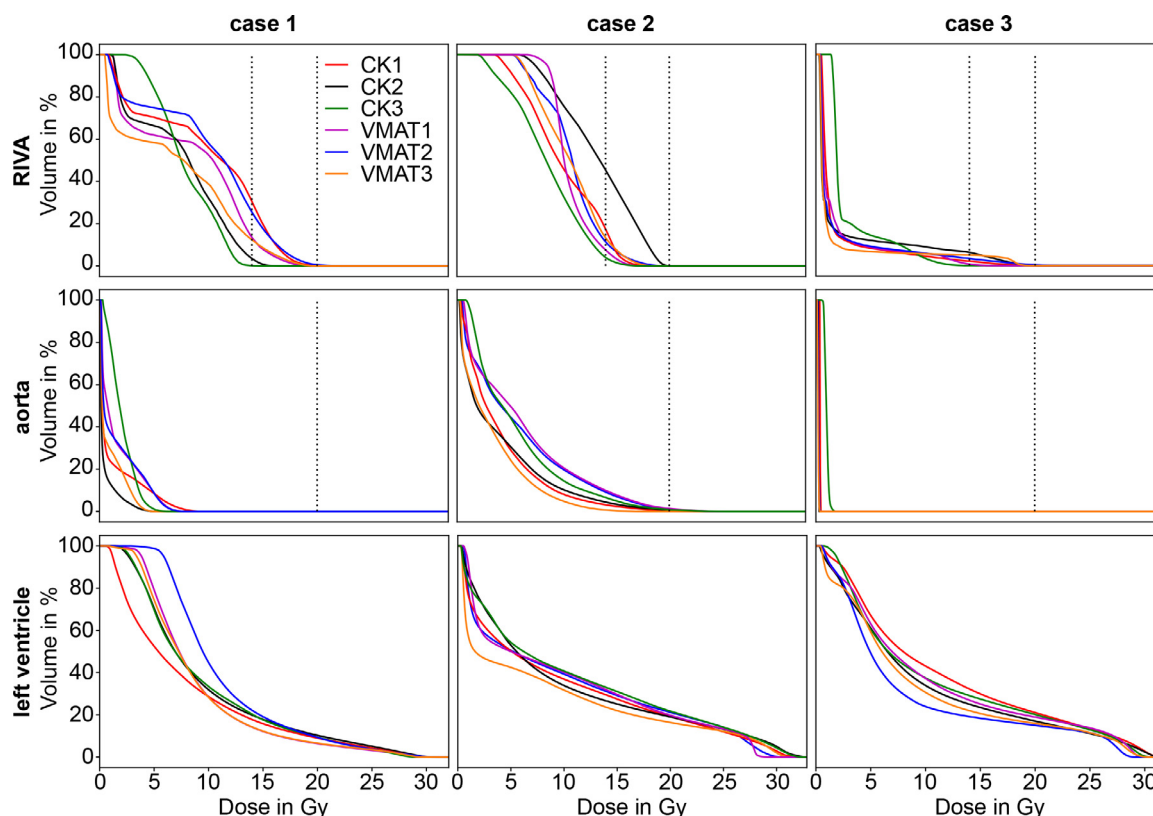


Fig. 3. Dose-volume histograms of ramus interventricularis anterior (RIVA), aorta, and left ventricle. The 3 patient cases and all 6 proposed treatment plans (CK1-3: robotic arm LINAC plans, VMAT1-3: C-arm LINAC plans) are shown. Dotted lines represent constraints for minor and major deviations.

with VMAT1. All other plans achieved comparable scores. The score depends on the number of considered parameters and thus is not comparable between the 2 weightings.

RATING score

Based on self-assessment of our study we achieved a RATING score of 183 out of 203 points (90%, Table E2), which was validated by 2 independent reviewers.

Discussion

Based on the protocol of the German RAVENTA trial, we present a treatment planning benchmark study involving 5 different academic treatment centers. Three cases treated with cardiac radioablation for sustained ventricular arrhythmias were included in the study.

Previous analyses^{20,22} evaluating different treatment planning approaches in RA focused on dose conformity at target volume, exposure of near and far OAR, and treatment efficacy, and thus on parameters comparable to our study. Other studies and case series¹⁰⁻¹² were based on outcome analysis with specific treatment platforms. In contrast to these previously

published reports on single treatment platforms/single centers or single cases, we present an academic multicenter plan comparison study that evaluated different treatment cases and different treatment platforms. Our results demonstrate the feasibility of RA with a variety of treatment platforms in the context of the RAVENTA trial protocol.

Other single-center studies have concluded that both C-arm LINAC and robotic arm LINAC based treatments are feasible for treating cardiac targets.^{9,11,20-22,42} A case report by Weidlich and colleagues²⁰ reported a superiority of VMAT plans over CyberKnife plans for distant OAR and the integral dose due to lower leakage dose from fewer MU delivered. In contrast, further sparing of OAR in close proximity to the PTV could be achieved with the CyberKnife, possibly due to the lack of a PTV-margin. In our multicenter study, dose fall-off in high-dose regions (25.00 Gy to 18.75 Gy) was found to be better in the VMAT plans compared with robotic arm LINAC plans while the volume of the 6 Gy isodose was smaller for the robotic arm LINAC plans. Our findings suggest a high conformity, especially for VMAT plans with median CI of 0.87 (range, 0.71-0.94), but also for robotic arm LINAC plans (0.79; range, 0.76-0.85). These findings are consistent with the reported CI by Wang et al,²² whereby Neuwirth et al¹¹ reported slightly higher conformity indices (V_{25Gy}/V_{PTV}) for robotic arm LINAC plans compared with C-arm LINAC plans.

Table 4 Relative plan quality ranking scores for 2 weighting methods: weighting focused on study constraints only and weighting considering nearby structures more strongly

		CK1	CK2	CK3	VMAT1	VMAT2	VMAT3
Case 1	Weighted by study constraints	75	55	65	70	68	42
	Weighted by nearby structures	65	53	47	56	57	37
Case 2	Weighted by study constraints	67	64	74	72	83	60
	Weighted by nearby structures	60	65	68	59	70	46
Case 3	Weighted by study constraints	70	57	63	56	52	47
	Weighted by nearby structures	57	50	55	44	45	40
Sum	Weighted by study constraints	212	176	202	198	203	149
	Weighted by nearby structures	182	168	170	159	172	123

Abbreviations: CK = robotic arm LINAC; VMAT = volumetric modulated arc therapy.
The best results were achieved in plan VMAT3. The lower the score, the better the ranking, as individual parameters were rated from 1 (good) to 3 (worst).

Probably the major advantage of VMAT plans compared with robotic arm LINAC plans is time efficiency. Similar conclusions were drawn by Weidlich and colleagues²⁰ and Wang and colleagues.²² The biological relevance of short treatment times has already been described in Fowler et al⁴³ and was transferred to RA by Blanck et al,³⁵ who demonstrated that shorter dose delivery to cardiac tissue might be an important aspect for treatment outcome in RA. A case report describing the use of an MR-LINAC for RA procedures¹⁸ claims higher treatment accuracy at the cost of even longer treatment times (148 min). It has to be stated that the ideal treatment time of 20 min as postulated in the protocol of the RAVENTA trial can only be achieved with C-arm LINAC at present.

There are several relevant differences between all studies regarding dose prescription guidelines and OAR constraints. The ENCORE-VT trial¹⁰ recommended a coverage goal for at least 95% of the PTV to reach 95% of the prescribed 25 Gy, with an accepted dose escalation up to 35 Gy within ITV and GTV. In the RAVENTA trial in comparison, a maximal dose escalation up to 32.5 Gy is tolerated within the CTV. In the presented plan comparison, the most challenging parameter was the maximum dose to the PTV-CTV ring of 30 Gy, not fulfilled by 10 of 18 plans. In the study of Neuwirth et al¹¹ dose specification was limited to a surrounding isodose of 25 Gy for the PTV. The isodose line covering the prescribed radiation dose was 80%, ranging from 66% ($D_{\max} = 37.9$ Gy) to 84% ($D_{\max} = 29.8$ Gy), compared with a median of 78% (range, 76%-82%) for robotic arm LINAC plans or 80% (range, 79%-85%) for VMAT plans. The study of Lloyd et al¹² mandates more detailed dosimetry specifications with dose heterogeneity within the PTV between 110% ($D_{\max} = 27.5$ Gy) and 140% ($D_{\max} = 35.0$ Gy) of the prescription dose, again prescribing a single dose of 25 Gy. Animal studies aiming on atrial fibrillation treatments have shown that doses >25 Gy are required for transmural fibrosis and electrical block at the pulmonary vein antrum. Therefore, the clinical successes cannot yet be fully explained and might be dependent on

dose inhomogeneities and allowed maxima in the VT target.^{26,44} Lately, data from explanted irradiated hearts and from a mouse model indicates irradiation-induced modulation of conduction-relevant protein levels as a potential mechanism of cardiac radiosurgery apart from radiation induced tissue fibrosis.⁴⁵ For noncardiac OAR (spinal cord, esophagus, stomach, lung, and liver) common dose constraints for SBRT are summarized in the task force consensus statement from the TG101,⁴⁶ facilitating different study results (ENCORE-VT,⁴² Lloyd et al,¹² and also the RAVENTA-protocol²⁶).

As no generally accepted dose constraints are known for cardiac subvolumes yet, the RAVENTA-protocol gives only recommendations for a few structures (left atrium, vena cava superior, whole heart minus PTV). Depending on the localization of the target region, dose constraints and recommendations extrapolated from SBRT to lung tumors might prove to be impossible to meet as with RA the heart is specifically targeted while in thoracic SBRT the heart is generally avoided. The ENCORE-VT study protocol does not specify dose constraints for cardiac substructures. However, Knutson and colleagues⁴² reported achieved median doses for several heart substructures and explain that side effects will be followed up. Despite comparatively tight specifications in the current study, the dose varies widely within these cardiac substructures. Within dose recommendations, volumes achieving relevant doses varied by up to 41% for aorta and left coronary arteries. In previous planning benchmark studies, more strict specifications on planning goals homogenized planning even more.²³ In the RAVENTA trial, specifications for the ventricles, right atrium and right coronary arteries are not included. This resulted in maximal doses of up to 9.0 Gy, 15.6 Gy, and 9.9 Gy for the right atrium in case 1, 2, and 3, respectively. For the left and right ventricles median doses of all plans and cases were 6.4 Gy (interquartile range [IQR], 5.3 Gy) and 6.7 Gy (IQR, 4.9 Gy), respectively. For patients treated in the ENCORE-VT trial⁴² median doses of left and right ventricle were reported with 11.3 Gy (IQR, 5.9 Gy) and 8.3 Gy (IQR, 4.8 Gy), respectively. Even if the left ventricle is the target region and the

constraints given by Gardner et al⁴⁷ cannot be adhered to, it is the most noted cardiac OAR and therefore an attempt should be made to reduce the average dose for the remaining part outside the PTV. Another study reported that the maximum dose to the right atrium, right coronary artery, and ascending aorta was most relevant to tumor patient survival.⁴⁸ In the present study, the aorta was spared as much as possible. However, the maximum dose allowed in the RAVENTA trial is much higher (20 Gy) than the recommended dose of 8.61 Gy (EQD₂ of 23 Gy) in McWilliam et al⁴⁸ but clearly below the most common constraint for great vessels of 37 Gy.⁴⁹ Although these critical substructures of the right heart are relatively distant from typical VT targets, recommendations would help to further reduce and homogenize their doses.

Even though the 3 presented treatment cases differed substantially regarding localization and size of target volume, 61% of the suggested treatment plans met the quality criteria of the RAVENTA protocol, whereas 39% would have required study investigator approval. However, the 3 major PTV deviations were only marginal (discrepancy of 0.1-0.2 Gy and 0.6%, respectively). Partly, small differences could be due to the recalculation of the DVH in Eclipse (TPS) as well as dose grid, rounding and interpolation differences of the initial treatment planning systems.²³ According to the Radiation therapy Treatment planning study Guidelines (RATING) by Hansen et al⁴¹ this problem can be circumvented by renormalizing the treatment plans in a separate software. Concerning OAR, only case 2 would have required study investigator approval because both, aorta and coronary arteries had minor deviations. This was due to the proximity of the aorta and coronary arteries to the PTV. In this case, balancing the importance between PTV coverage and meeting the OAR constraints would be beneficial for future treatment planning. In general, trade-offs made between coverage, conformity, OAR sparing and treatment time varied from plan to plan. For example, plan CK2 showed highest GI of robotic arm LINAC plans and the best dose fall off regarding the low-dose (6.0 Gy) region, having the longest estimated treatment times. Plan CK3 spared the RIVA best, but only partially achieved a desirable dose >30 Gy within the CTV for case 1, had hot spots in the marginal region (PTV-CTV) >30 Gy for case 2 and had the worst GI for case 3. Plan CK1 had shortest estimated treatment times of robotic arm LINAC plans, at the expense of poorer dose gradients. This underlines that priority ranking of multiple conflicting constraints and optimization goals are essential.⁴¹ However, it is not yet possible to say exactly what trade-off should be made, as it strongly depends on the clinical situation.

Besides the described differences of robotic arm LINAC and VMAT techniques, differences in dose distribution are most probably dependent on individual planners.^{39,40,50} Esposito and colleagues⁵¹ recommended stricter constraints or crowd knowledge-based learning to homogenize and standardize treatment planning. Therefore, a best-practice planning guideline for the highest-ranked plans in this study was added to this manuscript to further harmonize and optimize the plan quality for RA (Appendix E1). For objective treatment plan comparison in contrast to focusing on single

parameters and constraints, in our study all plans underwent a plan scoring algorithm described previously. In a first evaluation of this plan quality rating system by Blanck et al⁴⁰ the accordance of the mathematical ranking with the human observer rating was 90%. In the present study the highest rankings (low scores) were achieved with VMAT3 plans. Of the 2 different weightings, the one that also considers treatment time and the distance between OAR and target seems to be a better benchmark for overall plan quality rating.

All plans are largely consistent with DEGRO/DGMP requirements for SBRT.²⁷ Neither computational algorithm nor dose grid resolution are specified in the RAVENTA trial. Only one plan (VMAT1) was calculated with 2.5 mm dose grid resolution, exceeding the DEGRO/DGMP requirements of ≤2 mm. Overall, however, all devices are suitable for SBRT featuring MLCs of <10 mm leaf width over the entire target area or using conic collimators.²⁷ Nevertheless, a default for dose grid resolution and calculation algorithms could homogenize results.

The major limitation of our study is the small number of included cases, although a number of 3 cases is widely accepted in multicenter multiplatform studies. However, the cases may not fully represent the complete spectrum of RA patients, although target dimensions and locations in this benchmark study reflect a significant proportion of the reported literature.⁶ The number of participating centers and platforms used in this benchmark is also limited but RA is still considered to be in its early stages of development, we included the major platforms currently being used for this treatment and all centers have pioneering experience in RA. Nevertheless, the number of plans per case is not high enough to allow for any statistical analysis at the moment. Furthermore, many parameters were freely chosen by the centers and different dose grid resolutions (0.9-2.5 mm), algorithms (Ray Trace to Monte Carlo), and structural representations could lead to slightly different results. Depending on target volume location, type B algorithms may be more appropriate for VT irradiations but should have little effect on the overall outcome in the cases shown. Lastly, this was only a treatment plan comparison without considering the effect of different modulation techniques and degrees and actual treatment times and dosimetric accuracy were tested only partly during patient-specific quality assurance (Table E3). However, all plans were considered deliverable based on national and internal guidelines and protocols for SBRT and RA.^{26,27}

In the future, larger multicenter comparison including more cases and centers, exploration of trade-offs between target coverage and intracardiac critical structure sparing and deliverability of the plans with and without realistic target motion will be the focus of our research.

Conclusions

Treatment plan quality of robotic arm LINAC and C-arm LINAC for cardiac radioablation within the RAVENTA trial is comparable indicating that this treatment is feasible using

both techniques. Cross-center training and best-practice guidelines were provided to harmonize the planning process and allow for optimized treatment plans. More recommendations, especially for cardiac substructures, importance ranking of dose constraints and target goals, and defined dose calculation algorithm parameters would be helpful to further optimize the outcome of cardiac RA.

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