

# Cardiac ablation with radiotherapy

Expert: **Dr David Krug**, Clinic for Radiation Therapy, University Clinic of Schleswig-Holstein (UKSH), Kiel, Germany

Discussant: **Prof Pierfrancesco Franco**, University of Eastern Piedmont, Novara, Italy

## Extract from the e-ESO policy

The website contains presentations aimed at providing new knowledge and competences, and is intended as an informational and educational tool mainly designed for oncology professionals and other physicians interested in oncology.

These materials remain property of the authors or ESO respectively.

ESO is not responsible for any injury and/or damage to persons or property as a matter of a products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material published in these presentations.

Because of the rapid advances in medical sciences, we recommend that independent verification of diagnoses and drugs dosages should be made. Furthermore, patients and the general public visiting the website should always seek professional medical advice.

Finally, please note that ESO does not endorse any opinions expressed in the presentations.



e-Sessions via e-ESO.net

Your free education is just a click away!

©2021 The European School of Oncology

# Cardiac Ablation with Radiotherapy

PD Dr. David Krug

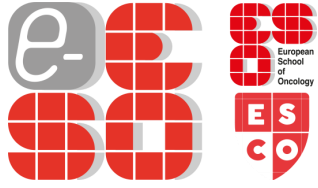
Deputy Director

Department of Radiation Oncology

University Hospital Schleswig-Holstein, Kiel, Germany

Do not duplicate or distribute without permission from the author and ESO

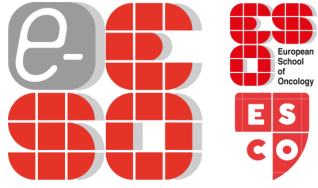




# Conflicts of interest

- Honoraria: Merck Sharp & Dohme, Pfizer
- Research funding: Merck KGaA

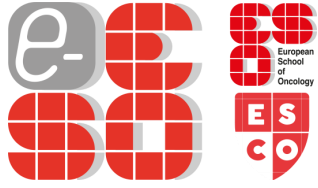
Do not duplicate or distribute without permission from the author and ESO



# Overview

1. Introduction to the topic
2. Clinical results
3. Preclinical experiments
4. Ongoing clinical trials
5. Open questions
6. Conclusions

Do not duplicate or distribute without permission from the author and ESO

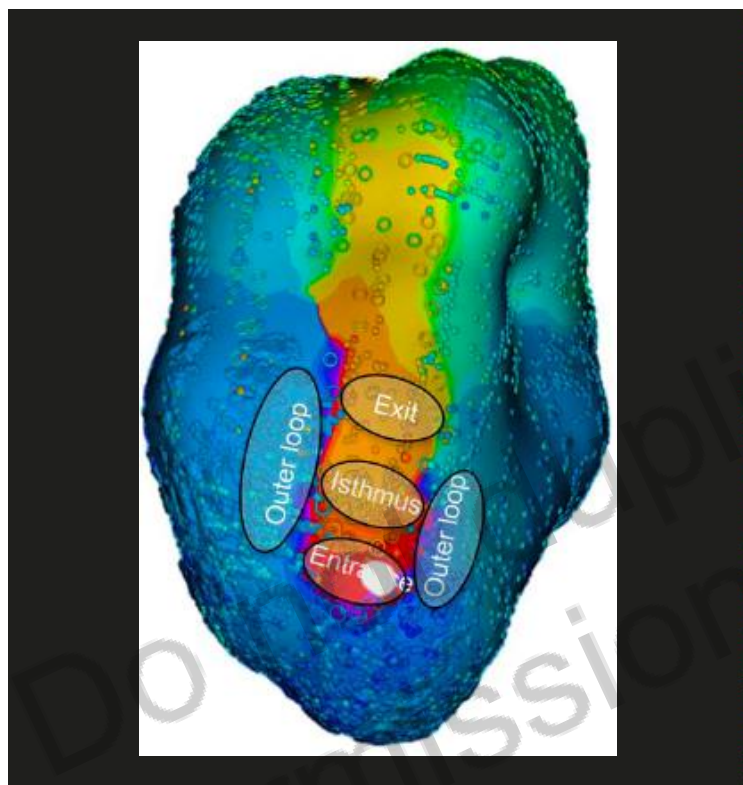


# Ventricular tachycardia

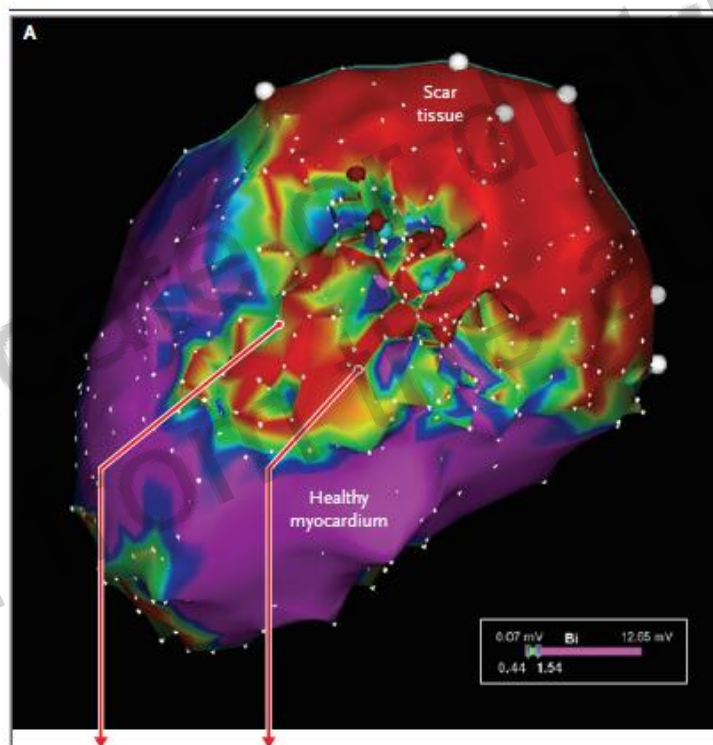
- Arrhythmia arising from the heart chambers
- Risk of sudden cardiac death
- Structurally normal heart
  - Outflow tract, His-Purkinje-System, Papillary muscles, Fascicular VT
- **Structural heart disease**
  - **Ischemic cardiomyopathy**
  - **Dilated cardiomyopathy**
  - Hypertrophic cardiomyopathy
  - Cardiac sarcoidosis, Chagas cardiomyopathy
  - Inherited arrhythmia syndrome - Arrhythmogenic right ventricular cardiomyopathy
  - **Intracardiac tumors (primary or secondary)**
- Management includes antiarrhythmic drugs, placement of implantable cardioverter defibrillator, catheter ablation

# Mapping of ventricular tachycardia

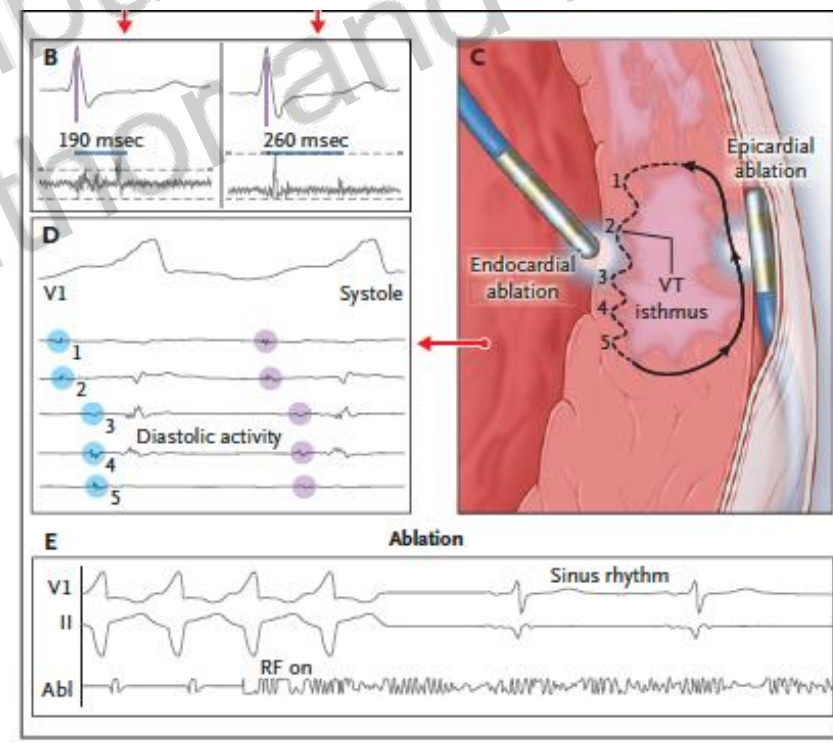
VT mapping



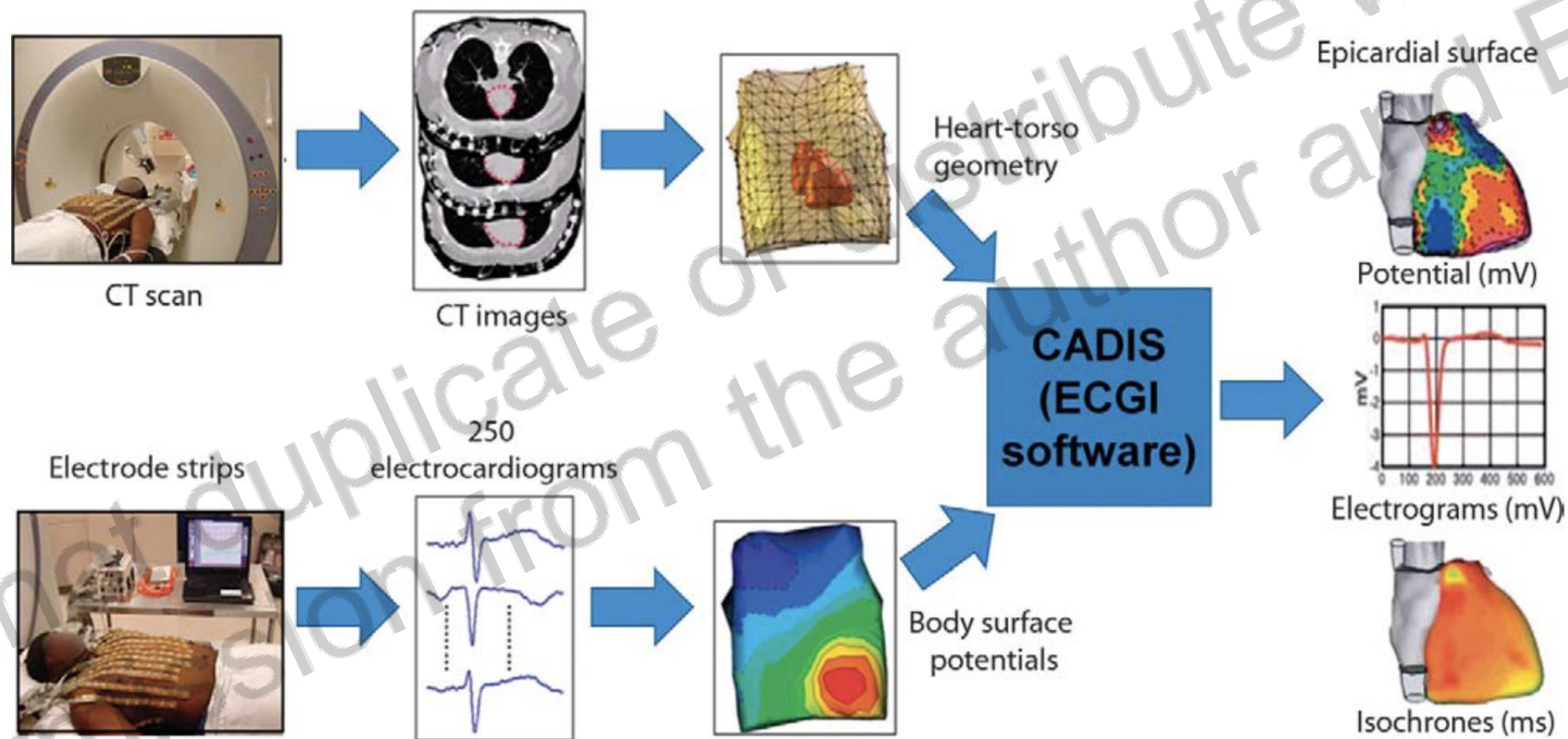
Voltage mapping



Catheter ablation



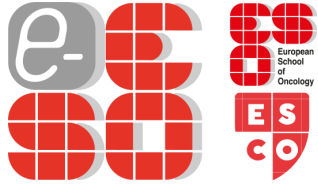
# Non-invasive mapping of ventricular tachycardia



# Catheter ablation for VT

**Table 2. Selected Clinical Trials of VT Ablation.\***

Trial	Design	Study Population (Comparison)	No. of Patients	Months of Follow-up†	Outcome
SMASH VT, <sup>49</sup> 2007	RCT	Patients with ICM (ICD plus VT ablation vs. ICD alone)	128	22.5±5.5	Ablation superior (incidence of ICD therapy, 12% in ablation group vs. 33% in control group at 2 yr)
VTACH, <sup>50</sup> 2010	RCT	Patients with ICM (ICD plus VT ablation vs. ICD alone for stable VT)	107	22.5±9.0	Ablation superior (median time to recurrence of VT or VF, 18.6 mo in ablation group vs. 5.9 mo in control group)
VANISH, <sup>48</sup> 2016	RCT	Patients with ICM (VT ablation vs. escalation of antiarrhythmic-drug therapy for drug-refractory VT)	259	27.9±17.1	Ablation superior (primary composite end point of death, VT storm, or appropriate ICD shock, 59.1% in ablation group vs. 68.5% in control group)
Multicenter Thermocool VT Ablation Trial, <sup>26</sup> 2008	Observational	Patients with ICM	231	12	Catheter ablation of VT is a reasonable option for clinical management (freedom from recurrent VT, 53% at 6 mo)
IVTCC, <sup>47</sup> 2015	Retrospective	Patients with ICM or NICM	2061	12	Freedom from VT recurrence, 70% at 1 yr; transplantation-free survival, 90% for patients without recurrence vs. 71% for those with recurrence



# Stereotactic body radiotherapy (SBRT)

Generally, stereotactic radiotherapy is defined as

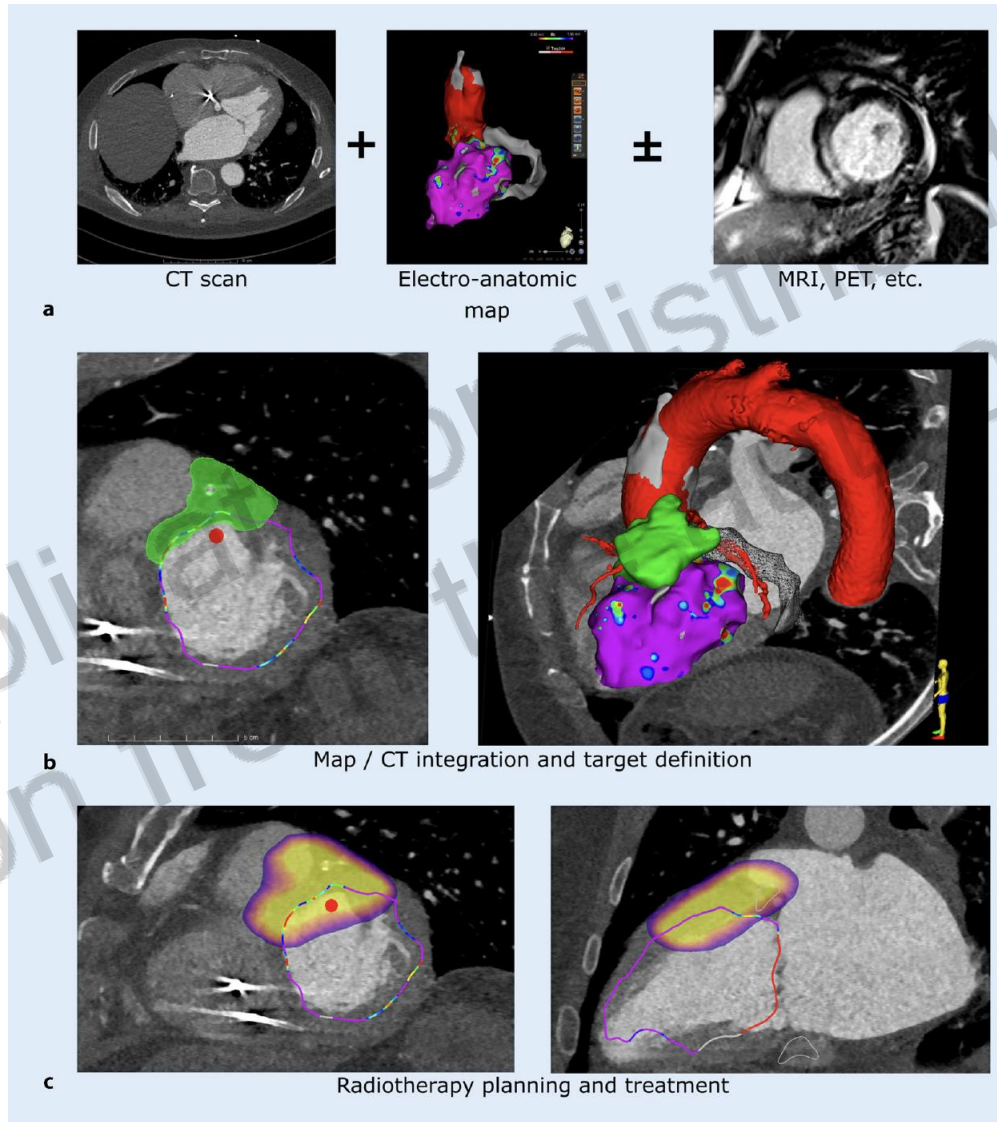
1. a method of percutaneous external beam radiotherapy, in which
2. a clearly defined target volume
3. is treated with high precision and accuracy
4. with a biologically high radiation dose
5. in one single or a few fractions
6. with locally curative intent.

SBRT is a guideline-recommended treatment for early stage lung cancer, prostate cancer, hepatocellular carcinoma, bone/lung/liver metastases.

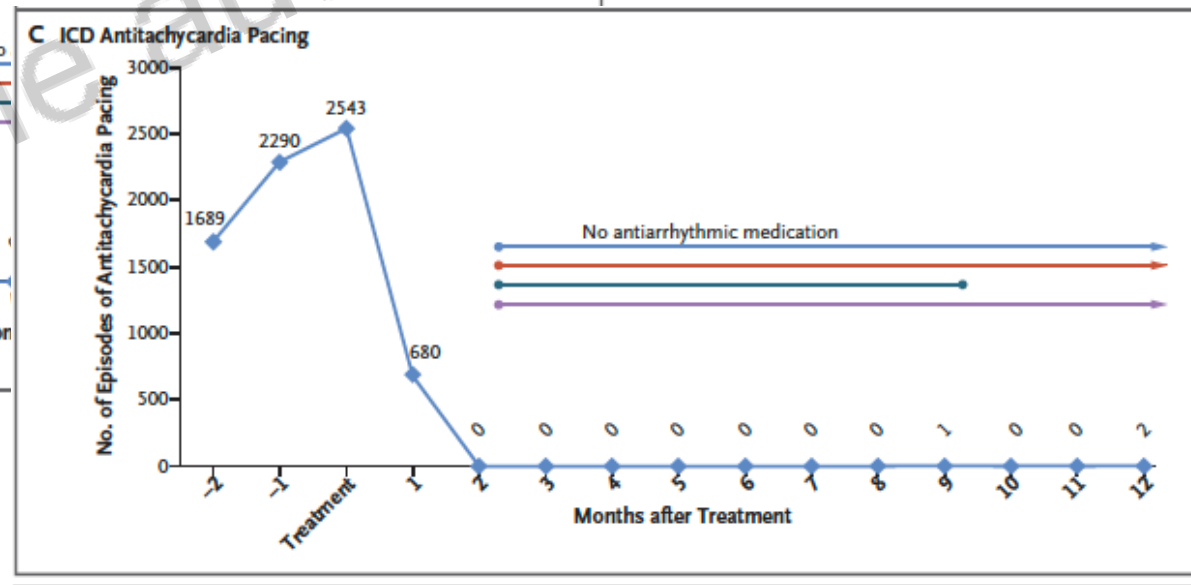
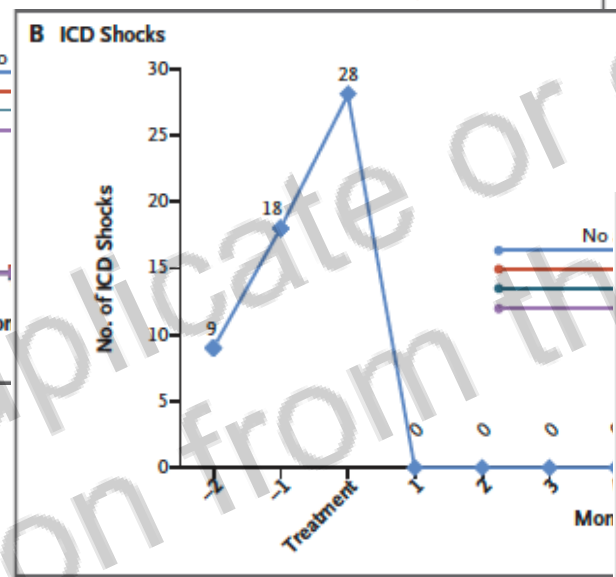
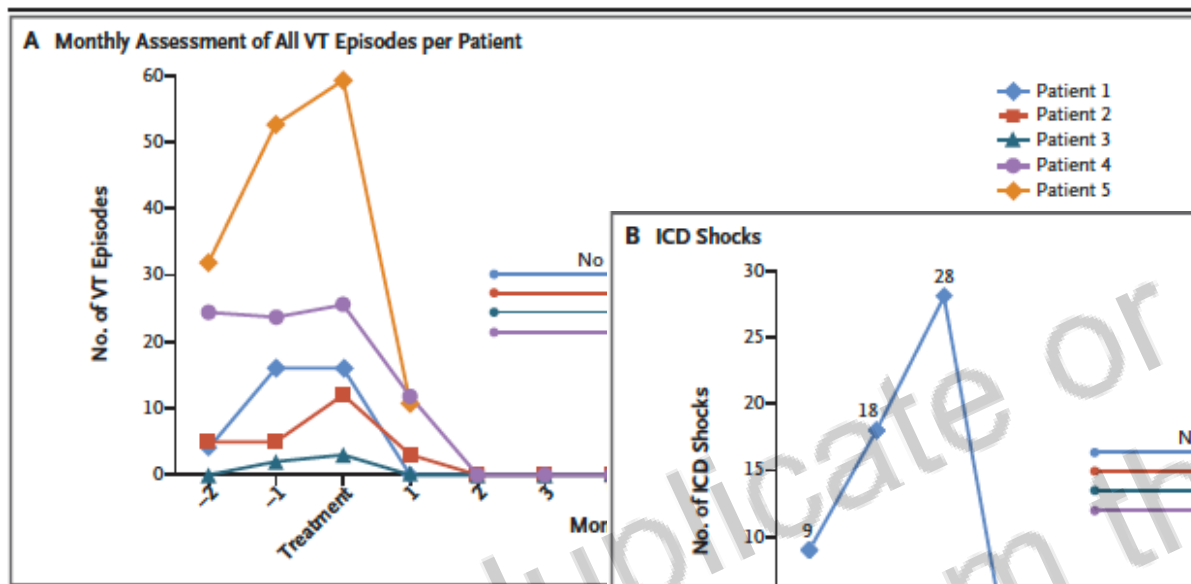
# SBRT for intracardiac tumors

Author/ Institution	Bonomo 2015	Corradini 2021	Gabani 2019	Soltys 2008	Jumeau 2020
Number of patients	3	4	1	1	1
Follow up	8 months	4 months	6 months	2.5 months	9 months
Histology	Primary and secondary	Primary	Primary	Primary	Secondary
Radiotherapy dose and fractionation	3 x 8 Gy (80%) 5 x 6 Gy (80%)	5 x 6-7 Gy	5 x 6 Gy (with Paclitaxel)	3 x 11 Gy (79%)	1 x 20 Gy (88%)
Cardiac toxicity	None	Chest pain G1 Dyspnea G1-2	None	None	None

# Workflow



# Initial data from WUSTL

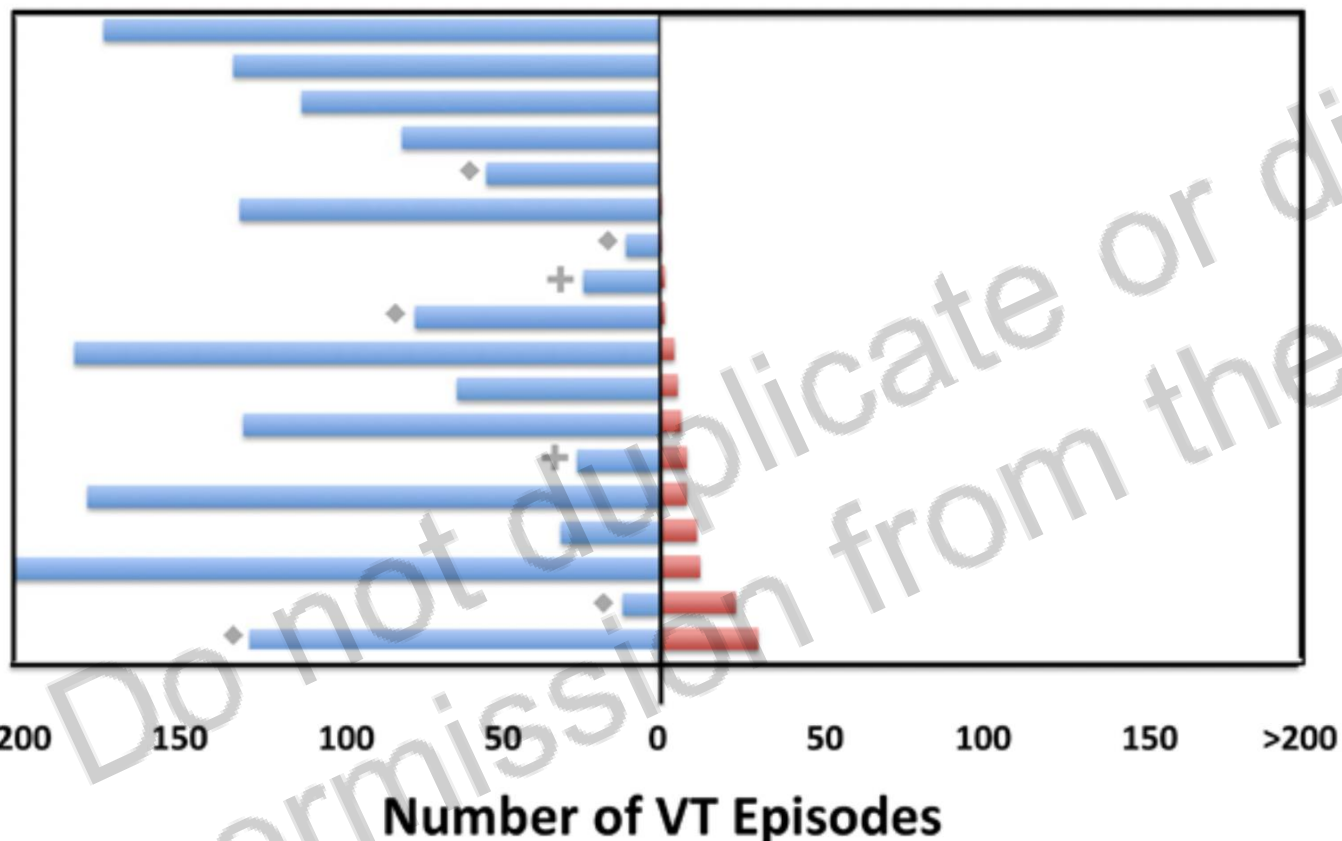




# ENCORE-VT trial

Pre-treatment

Post-treatment



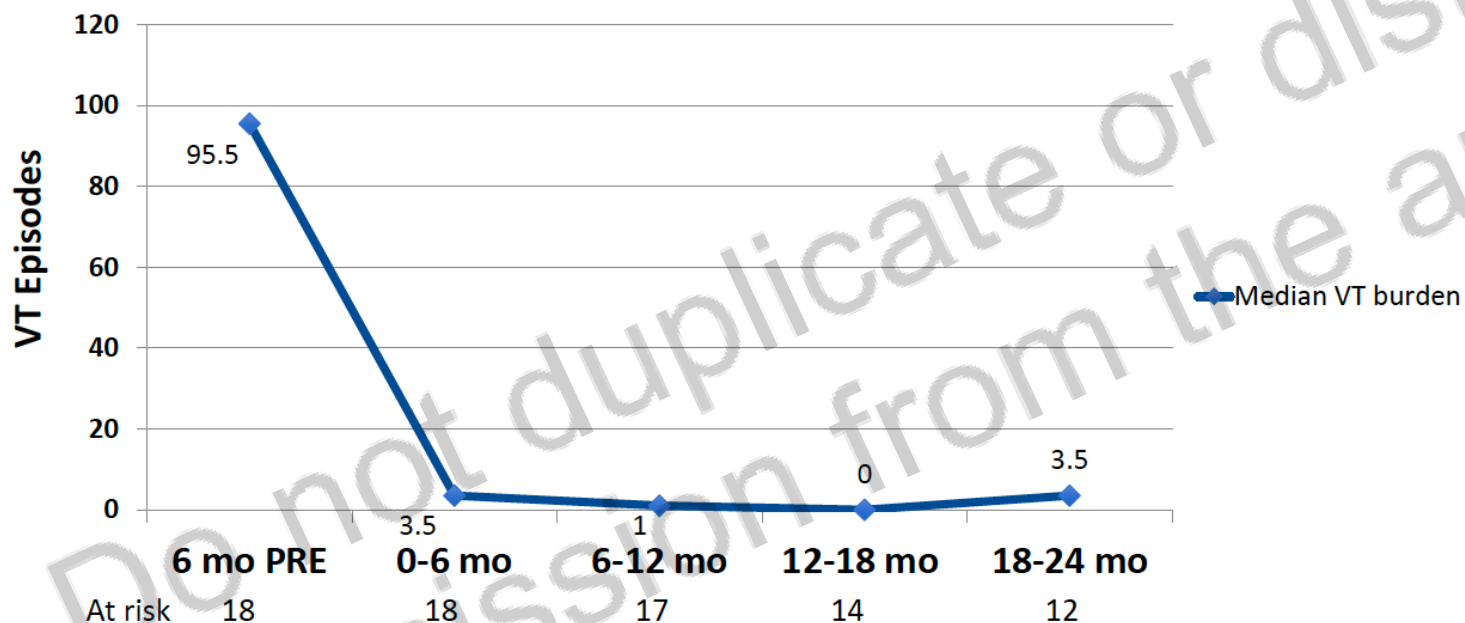
- Stable LV-EF
- Improved quality of life
- Decreased use of antiarrhythmic drugs
- 2 possible or probable acute grade 3-events: heart failure and pericarditis



# Long-term results from ENCORE-VT

## Phase II – Efficacy Over Time

Per-Patient VT Episodes by 6-month time periods



Late treatment-related grade 3-4 toxicity:

- 2 cases of pericarditis
- 1 case of gastropericardial fistula

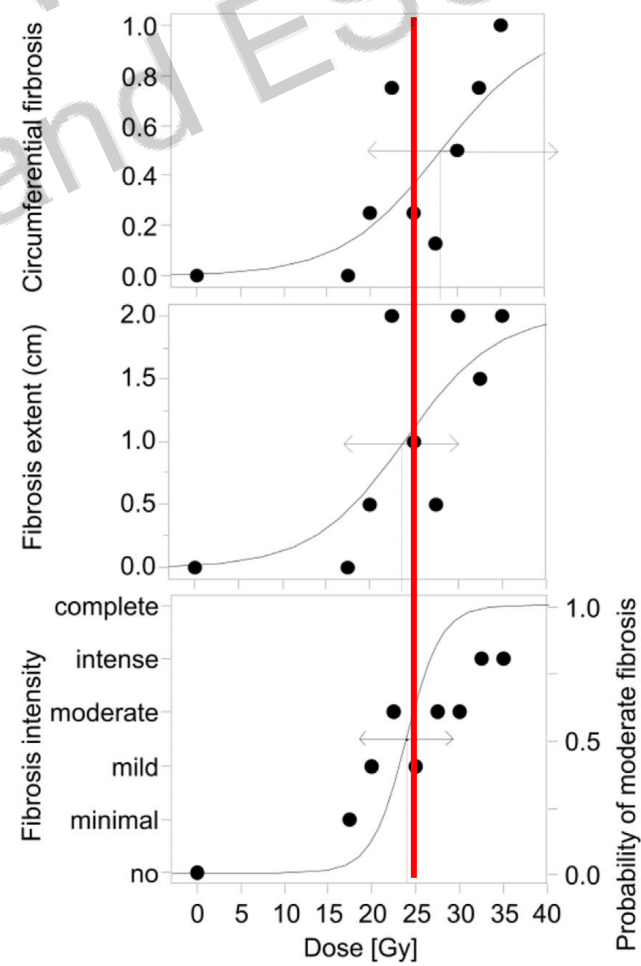
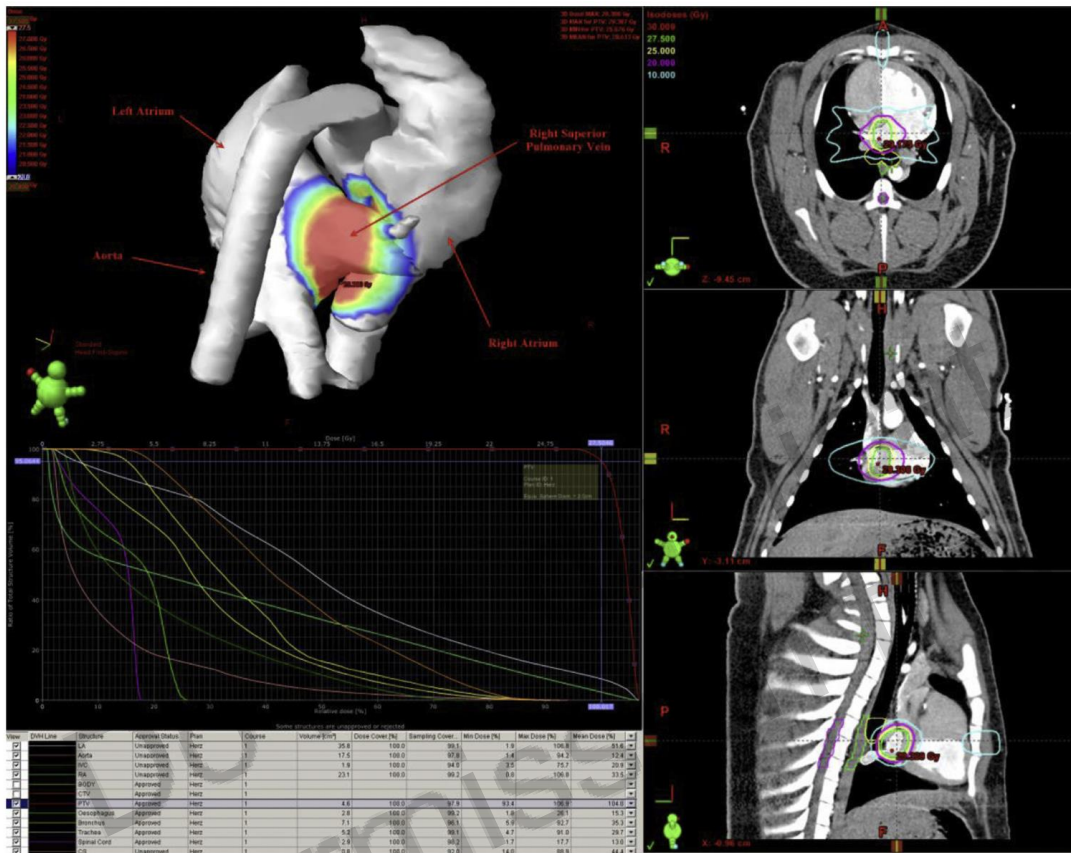
# Summary of clinical case series

**Table 1** Overview of published case series of stereotactic ablative body radiation (SABR) for ventricular tachycardia (VT) ablation. Numbers given as median (range), unless indicated otherwise

Series	Number of patients	Age [years]	Cardiomyopathy (ischemic/non-ischemic)	LVEF [%]	PTV [ml]	Dose [Gy]	Efficacy	Potential toxicity
Cuculich 2017 [12]	5	62 (60–83)	2/3	22 (15–37)	51.3 (17.3–81.0)	25	<u>99.9% VT burden reduction at 12 months</u> One invasive re-do ablation	One fatal stroke at 3 weeks Inflammatory changes on lung CT at 3 months, resolved at 12 months
Robinson 2019 [35]	19	66 (49–81)	11/8	25 (15–58)	98.9 (60.9–298.8)	25	<u>94% VT burden reduction at 13 months</u>	One heart failure exacerbation One radiation pericarditis Two cases of radiation pneumonitis
Neuwirth 2019 [29]	10	64 (61–78)	8/2	28 (23–33)	22 (14.2–29.6)	25	<u>87.6% VT burden reduction at 28 months</u> <u>VT recurrence in 8/10</u>	Nausea (four patients) One mitral regurgitation worsening at 17 months
Lloyd 2020 [26]	10	61 (50–78)	4/6	N/A	71.5 (29–238)	25	<u>69% VT burden reduction at 5.8 months</u>	Two cases of radiation pneumonitis
Jumeau 2020 [22]	10	66 (47–75)	3/7	37 ± 14 (mean ± SD)	23 (14–35)	20–25	<u>99.4% VT burden reduction at 4 months</u>	Nausea, rib fracture
Gianni 2020 [15]	5	67 (45–76)	4/1	25 (20–55)	<u>173 (80–184)</u>	25	<u>Recurrence in all patients</u> , three patients underwent repeat RFCA Two deaths in 12 months f/u (after 10 and 12 months)	None
Qian 2021 [32]	6	72 (IQR 70–73)	6/0	20 (IQR 16–20)	<u>319.5 (170.5–443.9)</u>	25	<u>Total VT episodes not significantly reduced in 6 months after SABR</u> , but significantly less ICD shocks Three patients died of end-stage heart failure	Pneumonia at 1 month Decompensated heart failure at 3 months
Chin 2021 [10]	8	74 (65–86)	4/4	20 (15–33)	<u>118.7 (21.1–190.7)</u>	25 (15–25)	<u>Mixed response</u> . Significant benefit (VT burden reduction) in 3/8 patients	None

LVEF left ventricular ejection fraction, PTV planned treatment volume, SD standard deviation, IQR interquartile range, N/A not available (not reported), RFCA radiofrequency catheter ablation, ICD implantable cardioverter-defibrillator, f/u follow-up

# Preclinical data from a dose-escalation study



# Insights into biological mechanism of action



ARTICLE



<https://doi.org/10.1038/s41467-021-25730-0>

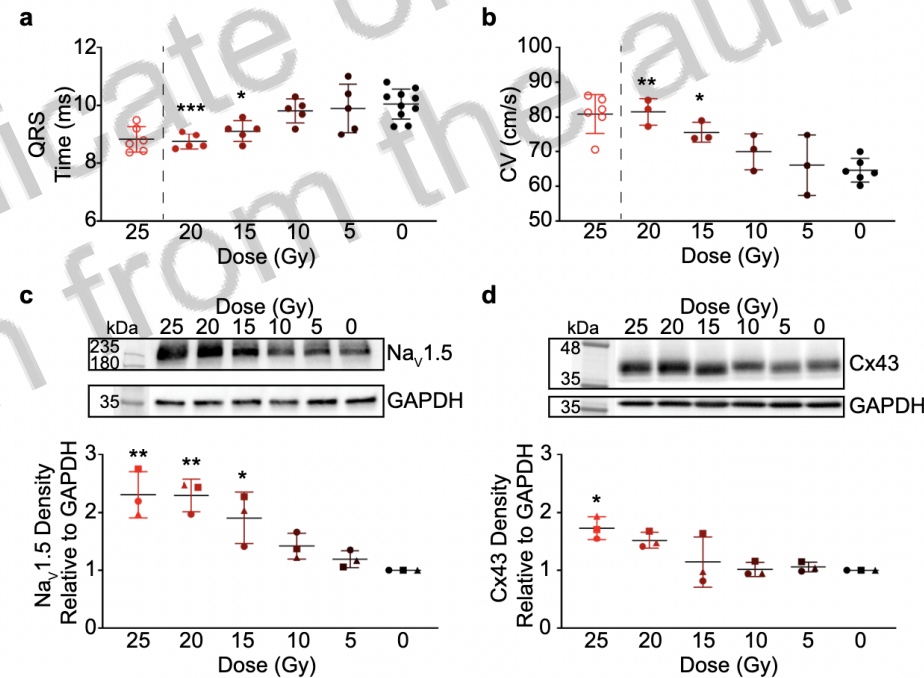
OPEN

## Cardiac radiotherapy induces electrical conduction reprogramming in the absence of transmural fibrosis

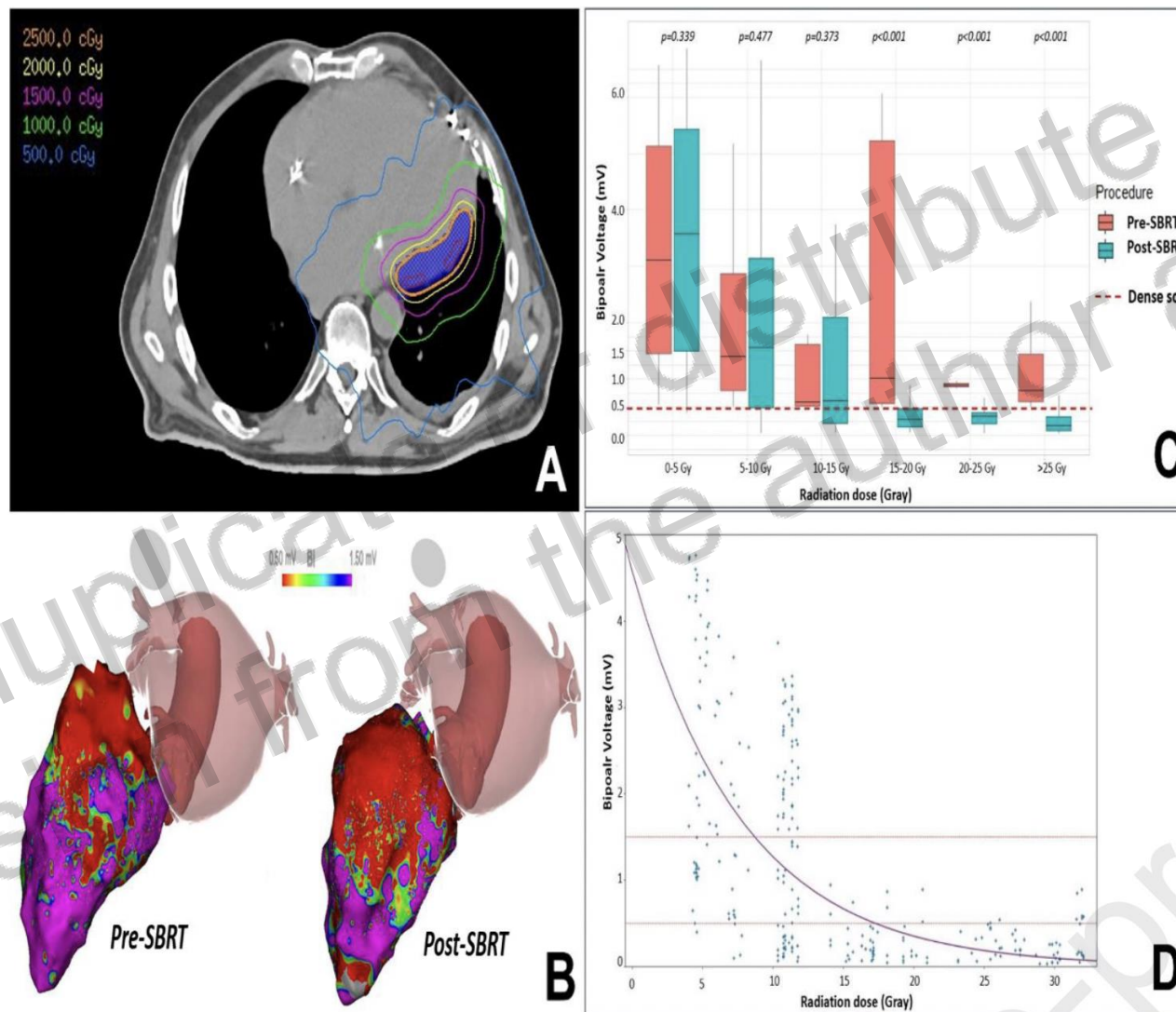
David M. Zhang <sup>1,2</sup>, Rachita Navara <sup>1,2</sup>, Tiankai Yin <sup>2</sup>, Jeffrey Szymanski<sup>3</sup>, Uri Goldsztejn <sup>2,4</sup>, Camryn Kenkel<sup>2,4</sup>, Adam Lang<sup>5</sup>, Cedric Mpoy<sup>3</sup>, Catherine E. Lipovsky<sup>2,6</sup>, Yun Qiao<sup>2,4</sup>, Stephanie Hicks<sup>2</sup>, Gang Li<sup>2,4</sup>, Kaitlin M. S. Moore<sup>1,2</sup>, Carmen Bergom <sup>1,3</sup>, Buck E. Rogers<sup>3</sup>, Clifford G. Robinson<sup>1,2,3</sup>, Phillip S. Cuculich<sup>1,2,3</sup>, Julie K. Schwarz <sup>1,3</sup> & Stacey L. Rentschler <sup>1,2,4,6</sup>✉

# Key findings

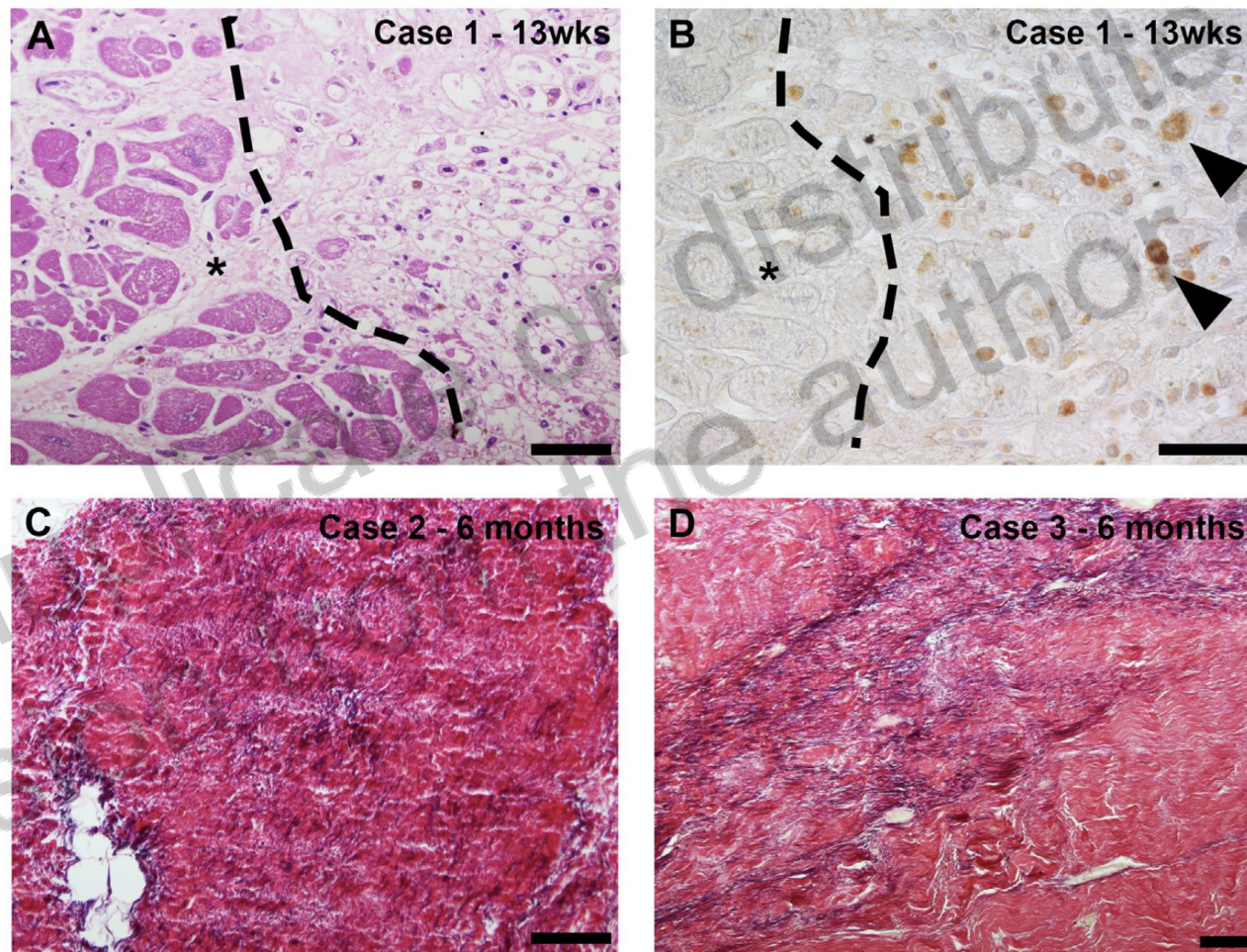
1. SBRT does not lead to significant myocardial fibrosis.
2. SBRT increases cardiac conduction velocity by increasing cardiac conduction protein levels through Notch activation.
3. These effects are observed even at doses of 15-20 Gy, but not at lower doses.



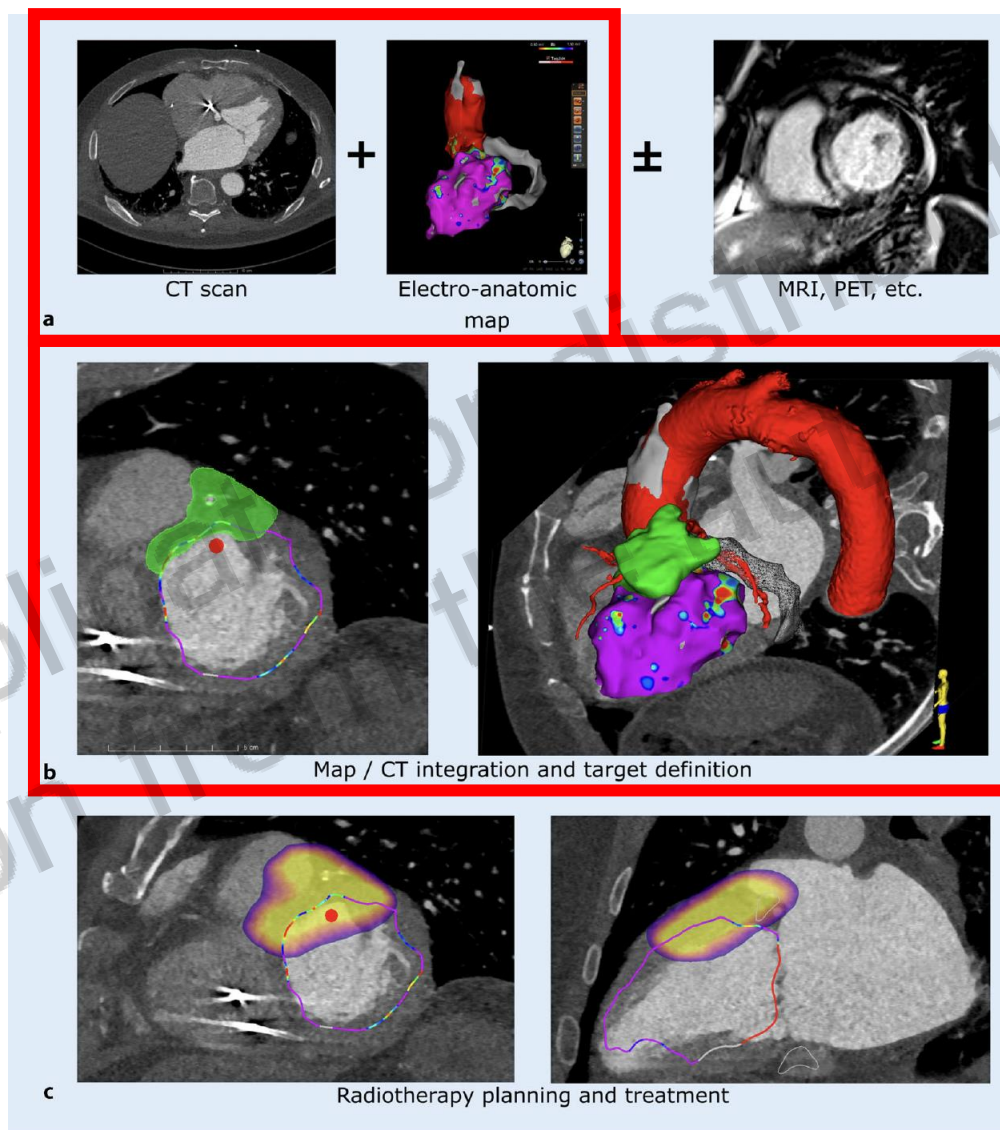
# Clinical evidence for dose-dependency

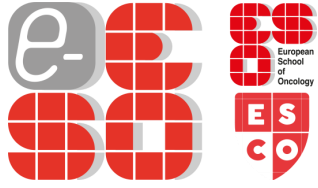


But: Effect may not be uniform and may depend on treatment parameters



# Workflow

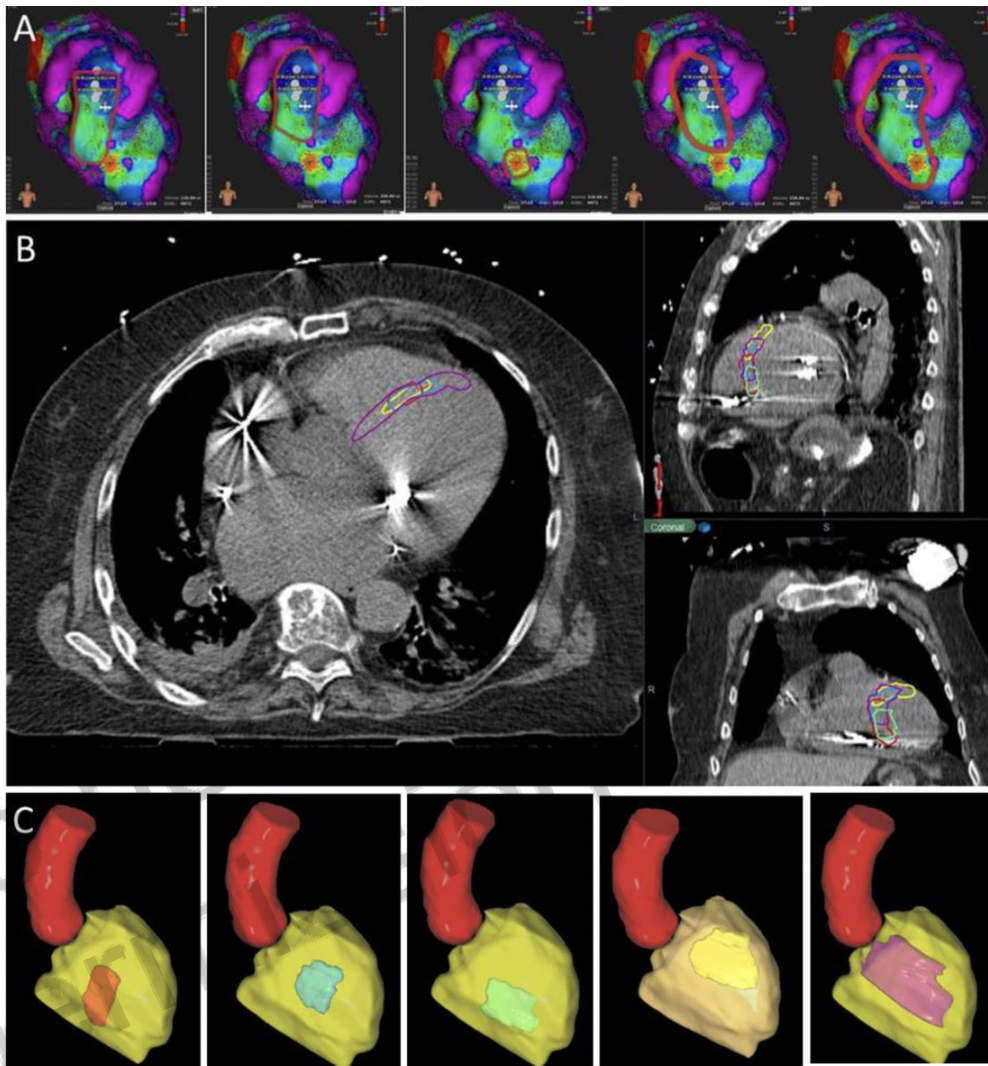




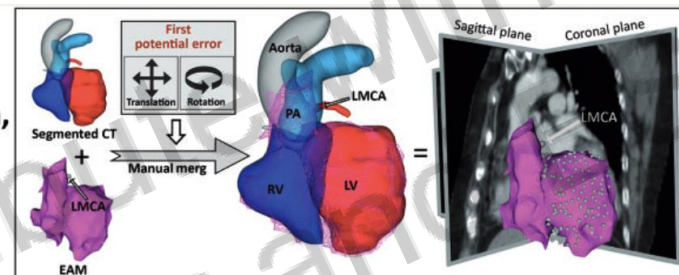
# Target volume definition

- Electroanatomical mapping
  - VT mapping → VT exit site, VT isthmus
  - Voltage mapping → scar
  - Invasive vs. non-invasive
  - Transfer to the treatment planning system (manual vs. automated)
- Planning-CT
  - Account for respiratory motion → respiratory gating or 4D-CT
  - Account for cardiac motion → ECG-triggered CT with contrast
  - Potential for detection of wall thinning?
- Additional imaging
  - Cardiac MRT: late enhancement
  - FDG-PET/CT or myocardial scintigraphy to detect areas of scarring

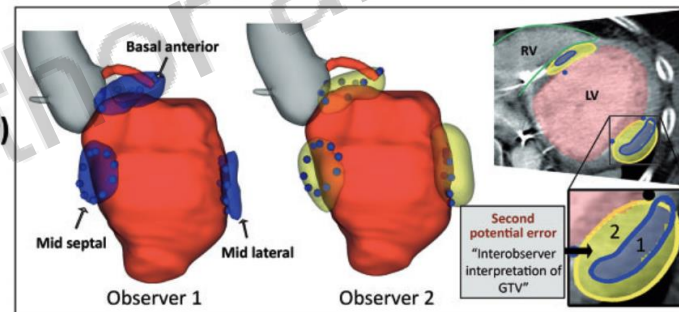
# Limitations of TV-definition and transfer



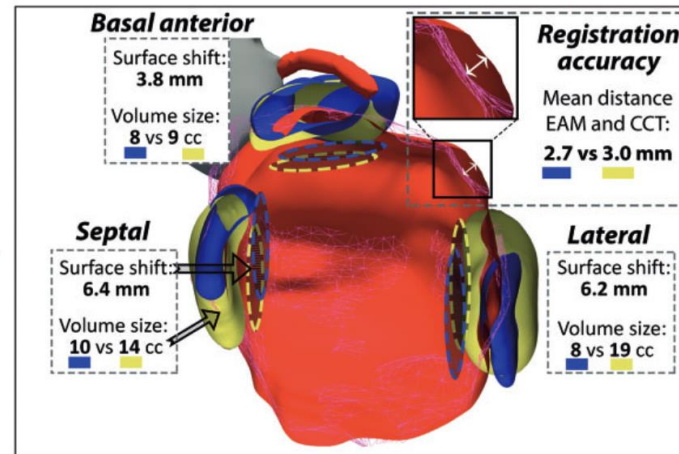
■  
Data collection,  
segmentation  
and merge



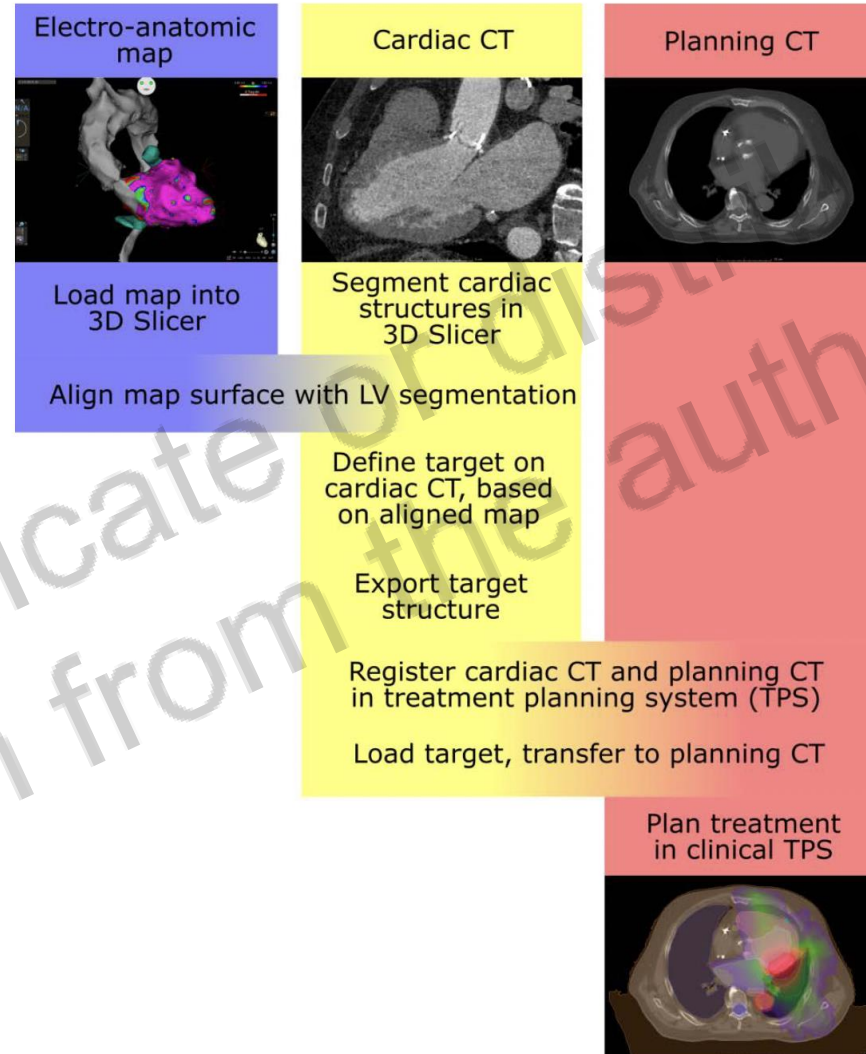
■  
(Interobserver)  
analysis



Results



# TV transfer using an Open Source tool





# Delphi Consensus for cardiac SBRT

- Participating institutions: Charité Berlin, Universitätsklinikum Heidelberg, UKSH – Campus Kiel, CHUV Lausanne, Universitätsmedizin Mannheim, Universitätsspital Zürich
- Areas of lacking consensus:
  - Use of SBRT in patients with NYHA IV, life expectancy < 6 months, prior chest irradiation
  - Use of SBRT in polymorphic VT and/or ventricular fibrillation
  - Use of particle therapy
  - Role of cardiac MRI and myocardial scintigraphy for TV-delineation

# Ongoing or planned clinical trials

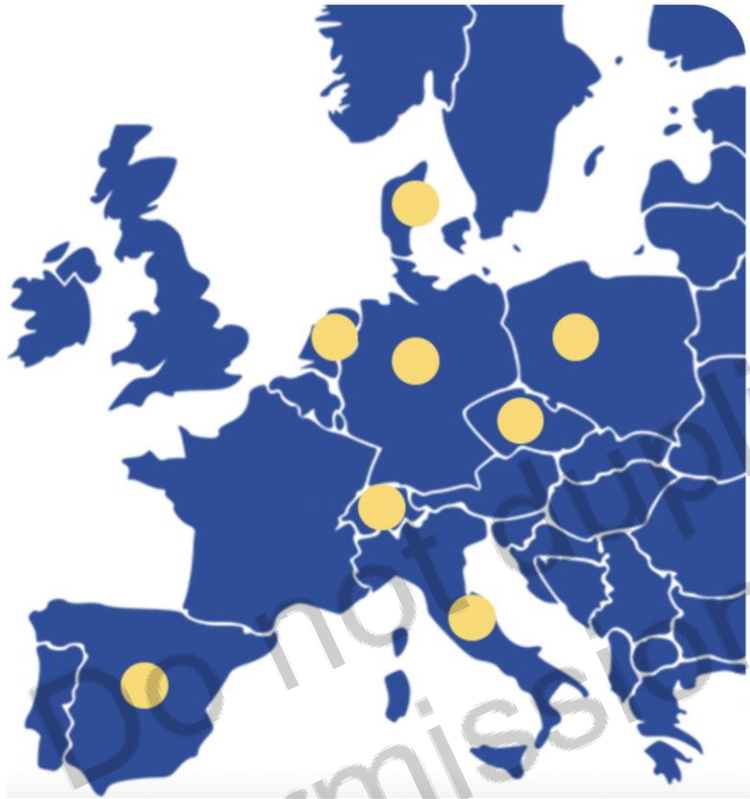
**Table 1** Ongoing or planned clinical trials of STAR for the treatment of VT

N (%)	Randomized	Non-randomized	Total
Number of trials	2 (12.5)	14 (87.5)	16
Number of patients	344 (55.9)	271 (44.1)	615
Intervention: radioablation	2 (12.5)	14 (87.5)	16
Control: catheter ablation	2 (100)	n/a	2
<b>Location</b>	—	—	—
North America	1 (11)	8 (99)	9
Europe	1 (16.7)	5 (83.7)	6
South America	0 (0)	1 (100)	1

Systematic search of clinicaltrials.gov on 1 June 2022 using variations of the terms 'ventricular tachycardia' and 'radioablation', excluding trials listed as completed or withdrawn. The outcome measures were a heterogenous combination of efficacy (VT burden reduction) and safety.

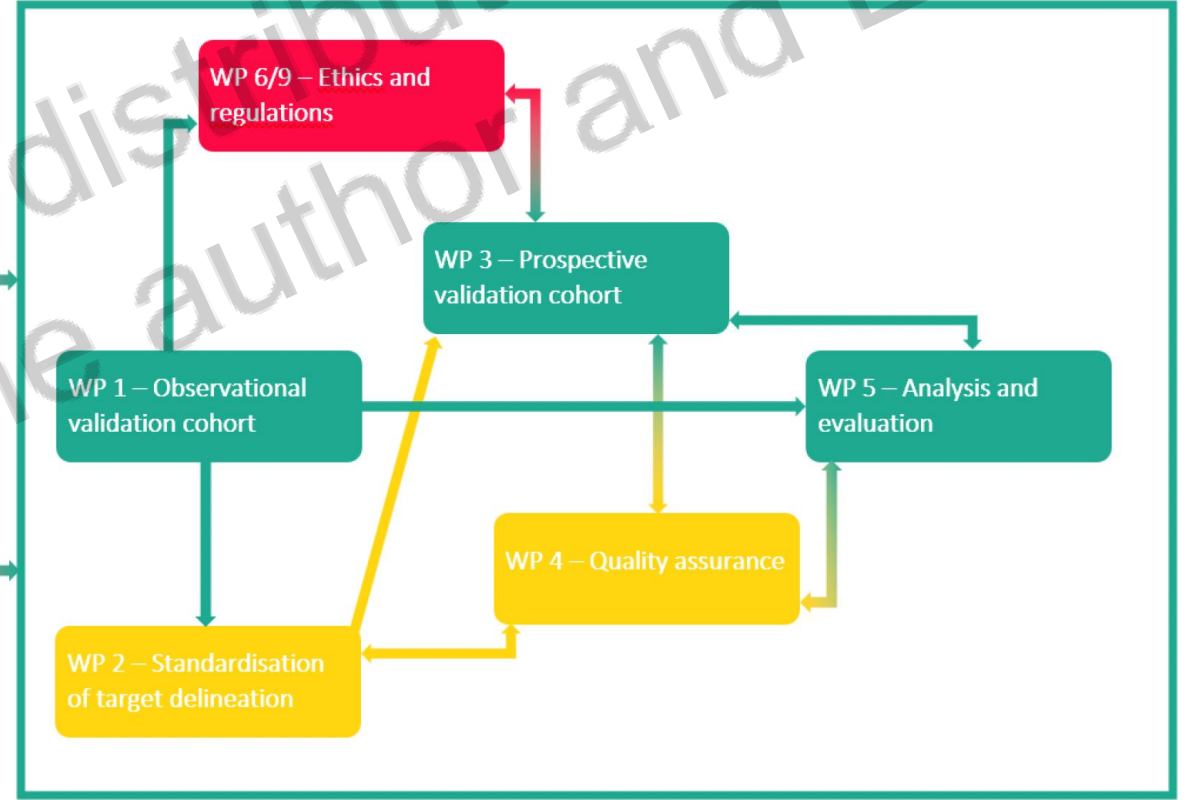


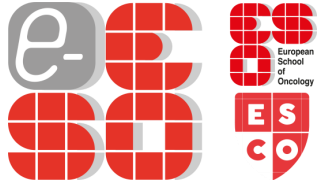
# STOP STORM



WP 7 – Dissemination and communication

WP 8 – Project management





# Open questions

- What are optimal patient selection criteria?
- May SBRT be used earlier in the disease course?
  - Comparison against catheter ablation in eligible patients in prospective trials
- What is the optimal target volume?
  - VT vs. voltage mapping, invasive vs. non-invasive, role of additional imaging
- How should the target volume be transferred to the treatment planning system?
- Is 25 Gy the optimal dose?
  - Dose de-escalation? Role of doses >25-30 Gy for long-term efficacy?
- What is the optimal treatment technique?
  - Compensation of respiratory and cardiac motion
  - Image guidance
- What about long-term safety of high-dose radiotherapy to the heart?
  - Longer follow-up urgently needed
  - Is there a role for particle therapy?



## Conclusions

- SBRT is highly effective as a salvage strategy in patients with refractory VT after catheter ablation, although many patients do ultimately recur
- Short-term safety is promising, however follow-up is very limited
- Treatment requires strong interdisciplinary collaboration between radiation oncology and electrophysiology experts
- Many factors remain unknown
- Prospective trials and registries are urgently needed

Do not duplicate or distribute without permission from the author and ESO



## Thanks to

- ... the audience for your attention
- ... e-ESO and Pierfrancesco Franco for the invitation
- ... the interdisciplinary team in Kiel for the excellent support
- ... the RAVENTA-trial sites for the great collaboration
- ... our patients for their trust in this experimental technique

Do not duplicate or distribute without permission from the author and ESO