Stereotactische radiotherapie voor de behandeling van ventriculaire tachycardie

Ines Joye

Voorjaarssymposium KARVA 02/03/2024

- AZ Klina
- AZ Monica
- AZ Rivierenland
- AZ Voorkempen
- GZA Ziekenhuizen
- UZA
- Vitaz
- ZNA

Normale conductie

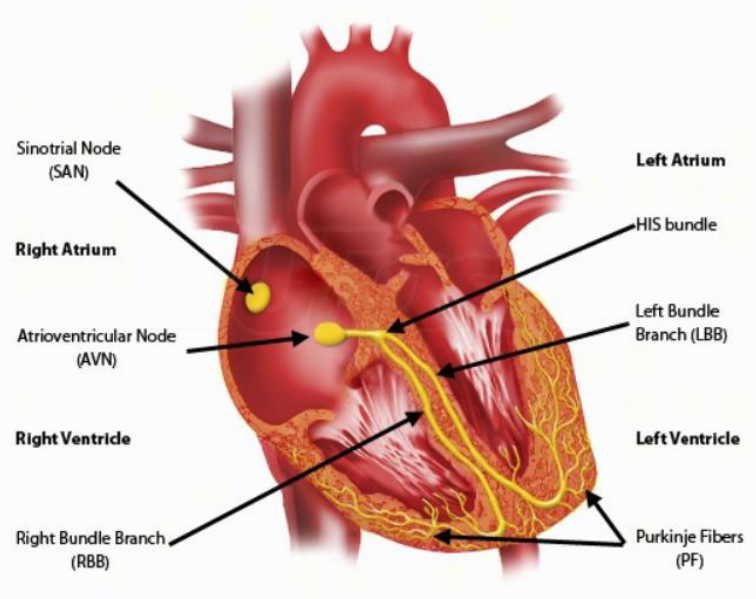
Sinoatriale knoop

AV knoop

Bundel van His

Li/re bundeltak

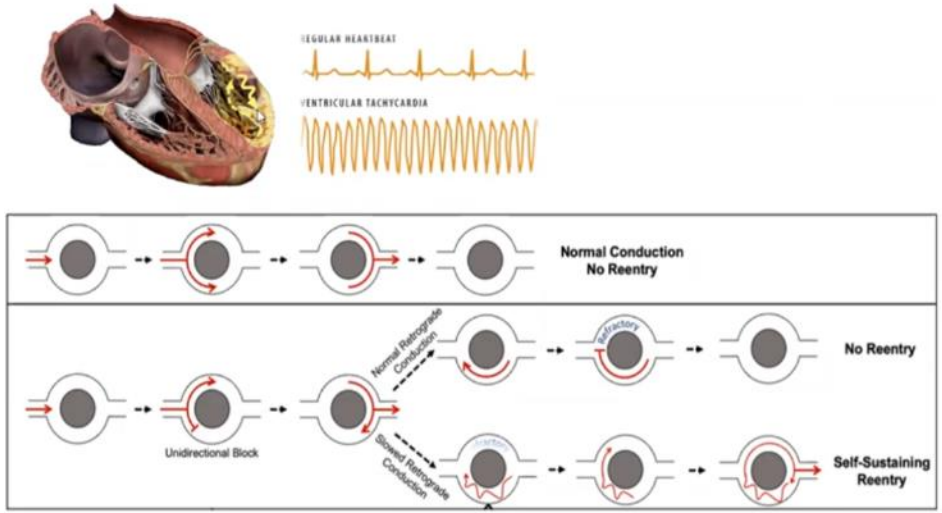
Purkinje vezels



Socratic.org

Ventriculaire tachycardie

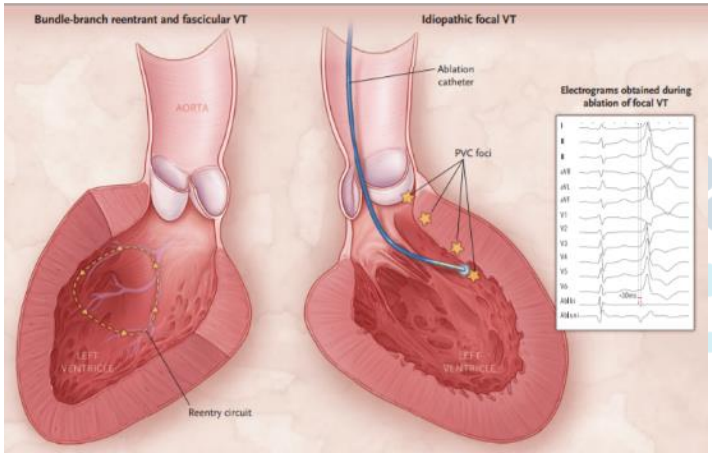
Levensbedreigend
- duizeligheid
- thoracale pijn
- dyspnee
- flauwvallen
- lichthoofdigheid



- Implanted cardioverter defibrillator (ICD)
- Medicatie (amiodarone)
- Catheter ablatie

Ablatie

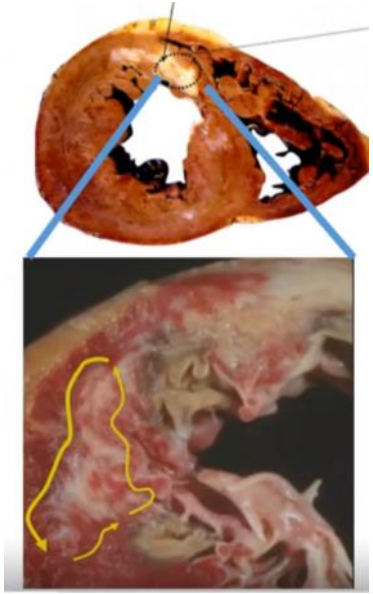
- RFA: sinds 1990, in geval medicatie/ICD niet effectief zijn of geen optie zijn
- **Invasieve** procedure, electrofysiologische mapping en ablatie (RF of cryo) van de VT target area
- Noodzaak tot invasieve catheters om kritische zones van VT te bereiken binnen de verlittekende zones van het myocard.
- **Meer complex** voor VT tov SVT
- **Effectief in 50-70%** van de patiënten



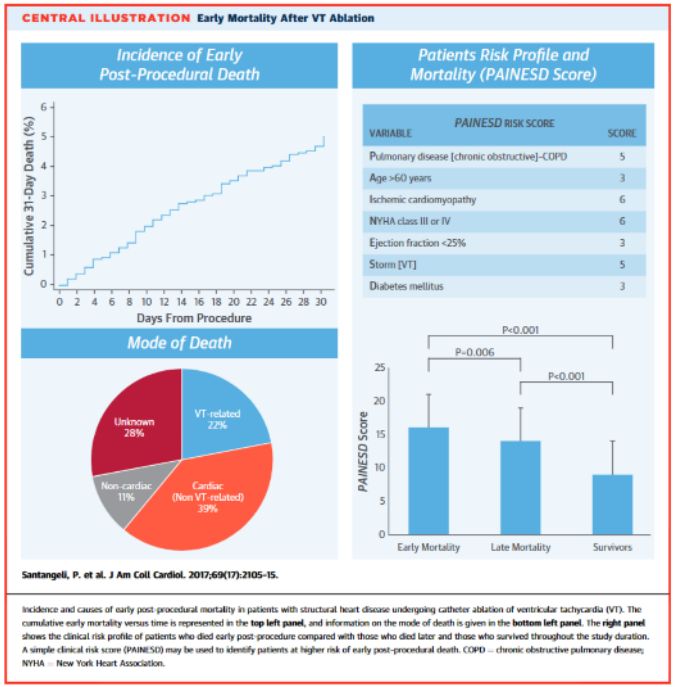
Shivkumar NEJM 2019

Catheter ablatie challenges

Anatomische restricties



Veiligheid voor high-risk patiënten



Nood aan veilig en effectief alternatief

Santangeli et al. J Am Coll Cardiol 2017

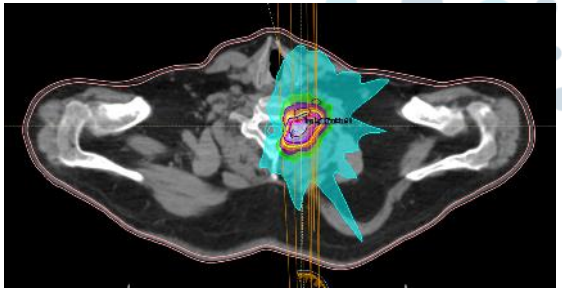
Stereotactic body RadioTherapy

Externe bestraling waarbij zeer precies een hoge bestralingsdosis toegediend wordt in één of meerdere fracties en dit op een extracranieel doelvolume.

- Hoge dosis/fractie: **effectieve celdood** door hoge radiobiologische effectiviteit (direct effect, vasculatuur, antitumor immuniteit)
- Scherpe dosis gradiënten: **maximaal sparen OARs**
- **non-invasief**

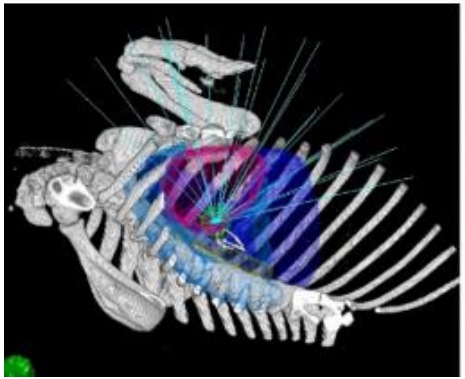
- Origineel toegepast voor hersenletsels (SRS)
- Standaard behandeling voor kleine long- en hersenletsels

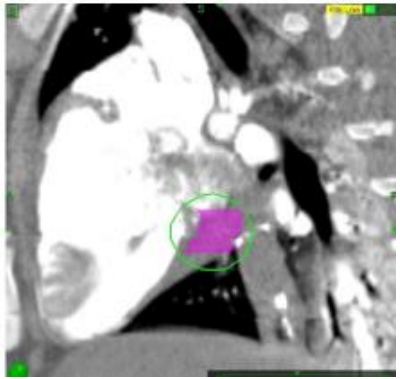
- Meer recent ook gebruikt voor primaire prostaat- en pancreastumoren alsook voor klier-, bot- en levermetastasen

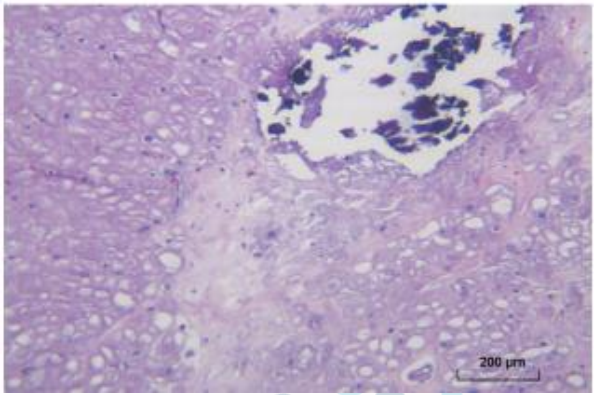


Eerste dierenstudies met CyberKnife

Initiële studies minipigs toonden dat single fraction doses van 25 Gy kunnen leiden tot fibrotische letsels in het hart en blockage van elektrische signalen



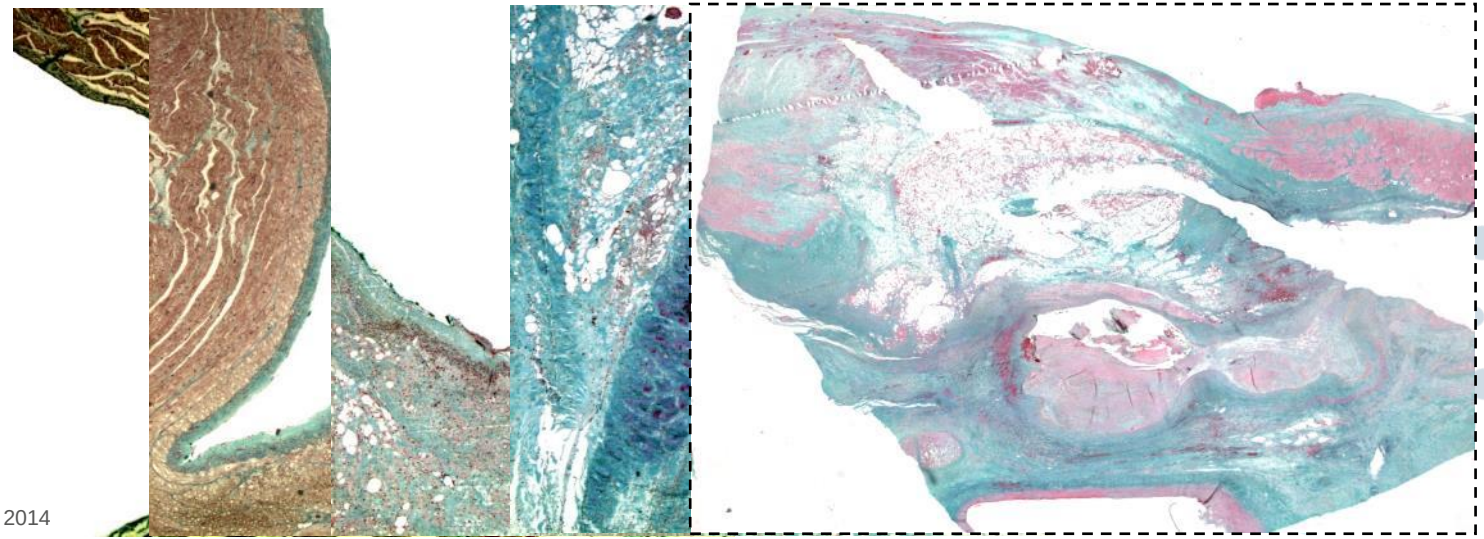




Sharma et al, Heart Rhythm 2010

Dosis-respons relatie

- Regelmatige pulmonale vene structuur in controle
- Milde fibrosis met intermediaire dosis (25Gy)
- Matige fibrosis met intermediaire tot hoge dosis (30Gy)
- Confluerende fibrose met hoge dosis (32.5Gy)
- Transmurale, circumferentiële fibrose met stenose (40Gy)



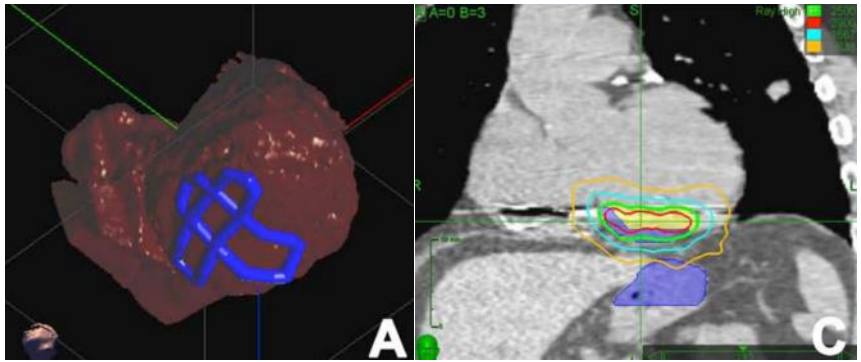
Blanck et al, IJROBP 2014

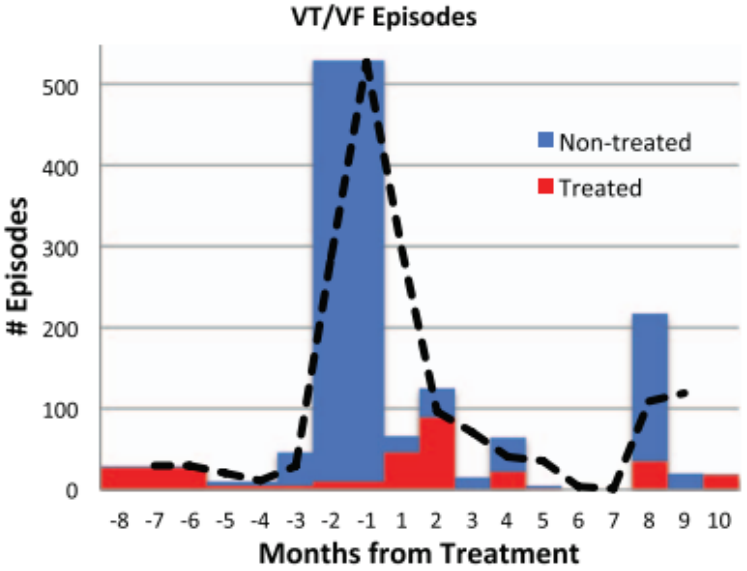
First in human

Man, 71 jaar
Unsustained monomorfische VT
ICD, refractair aan medicatie; catheter ablatie relatief gecontraindiceerd

25 Gy in 90´ (Cyberknife®), dmax 33 Gy

Reductie gemiddeld aantal VT episodes/maand >500 pre SBRT
naar 50 post SBRT
Transiënt effect





Loo et al. Circ EP 2015

Human case series

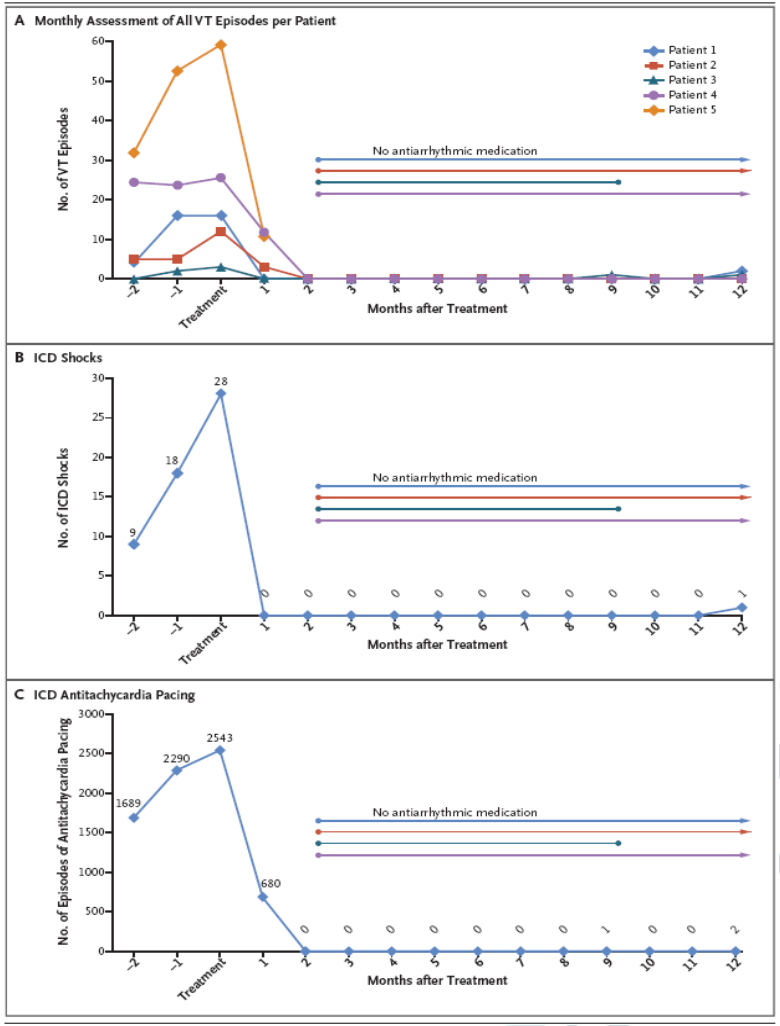
Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia

Phillip S. Cuculich, M.D., Matthew R. Schill, M.D., Rojano Kashani, Ph.D., Sasa Mutic, Ph.D., Adam Lang, M.D., Daniel Cooper, M.D., Mitchell Faddis, M.D., Ph.D., Marye Gleva, M.D., Amit Noheria, M.B., B.S., Timothy W. Smith, M.D., D.Phil., Dennis Hallahan, M.D., Yoram Rudy, Ph.D., and Clifford G. Robinson, M.D.

4/2015-11/2015
5 ptn high risk refractaire VT
1x 25 Gy in 11-18 min

- Tijdens 3 maand pre RT: **6577 VT episodes**
- Tijdens 6 weken post ablatie (blanking period): **680 episodes**
- Na 6 weken **4 VT episodes over 46 ptnmaand**
- **reductie van 99.9%** tov baseline

•Geen verschil in EF



Cuculich et al, NEJM 2017

Human case series

Published in final edited form as:
Circulation. 2019 January 15; 139(3): 313–321. doi:10.1161/CIRCULATIONAHA.118.038261.

Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia

Clifford G. Robinson, MD[1], Pamela P. Samson, MD, MPHS[1], Kaitlin M.S. Moore, BS[2],

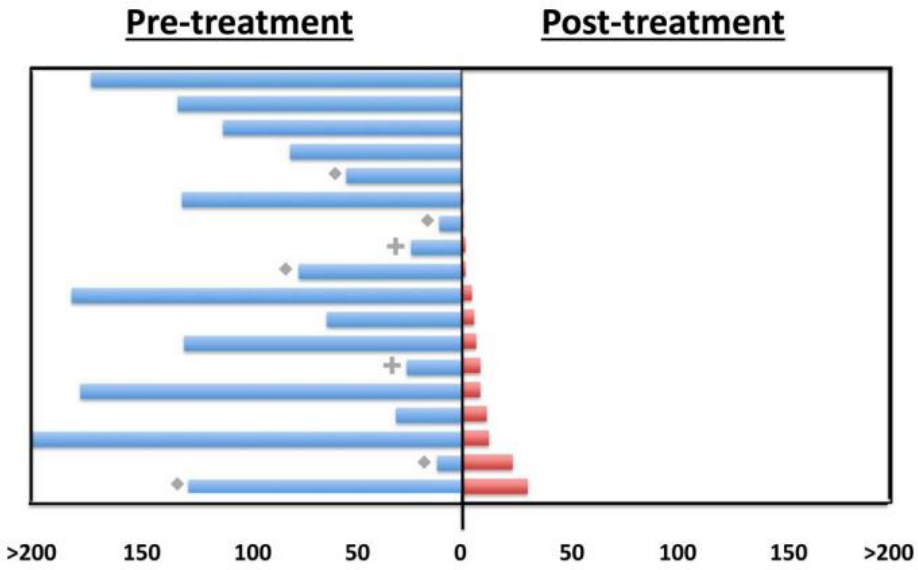
ENCORE-VT
Prospectieve single center fase I/II studie
17 ptn refractaire VT, 2 ptn met cardiomyopathie obv PVC

1x 25 Gy

Safety: aantal SAE <90d post SBRT
G3 met noodzaak tot hospitalisatie, G4-5

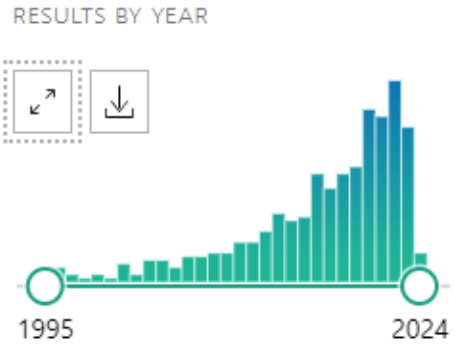
2 G3: HF exacerbatie; pericarditis

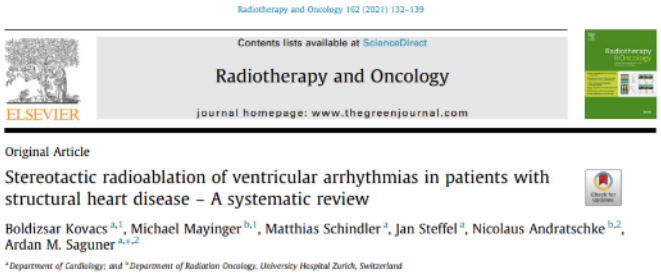
Efficacy: Mediaan 119 6m pre ablatie vs.
3 6m post ablatie (post blanking)



Robinson, Circulation 2019

- Verschillende retrospectieve reports, reeksen
- Single-center prospectieve reeksen
- Veel reviews, opinies




Radiotherapy and Oncology 162 (2021) 132–139

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Stereotactic radioablation of ventricular arrhythmias in patients with structural heart disease – A systematic review

Boldizsar Kovacs [a,1], Michael Mayinger [b,1], Matthias Schindler [a], Jan Steffel [a], Nicolaus Andratschke [b,2], Ardan M. Saguner [a,*,2]

[a] Department of Cardiology; and [b] Department of Radiation Oncology, University Hospital Zurich, Switzerland


HeartRhythm

CONTEMPORARY REVIEW | ARTICLES IN PRESS

Cardiac radioablation—A systematic review

Martijn H. van der Ree, MD • Oliver Blanck, PhD • Jacqueline Limpens, PhD • Charlie H. Lee, BSc • Brian V. Balgobind, MD, PhD • Edith M.T. Dieleman, MD • Arthur A.M. Wilde, MD, PhD • Paul C. Zei, MD, PhD • Joris R. de Groot, MD, PhD • Ben J. Slotman, MD, PhD • Phillip S. Cuculich, MD • Clifford G. Robinson, MD • Pieter G. Postema, MD, PhD • Show less

Heart Rhythm. 2020 Aug;17(8):1381-1392

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Leveraging Radiobiology for Arrhythmia Management: A New Treatment Paradigm?

D.M. Zhang *, J. Szymanski †, C. Bergom †, P.S. Cuculich *†, C.G. Robinson *†, J.K. Schwarz †, S.L. Rentschler *‡§

Clin Oncol (R Coll Radiol). 2021 Nov;33(11):723-734

https://cardiocradioablation.wustl.edu

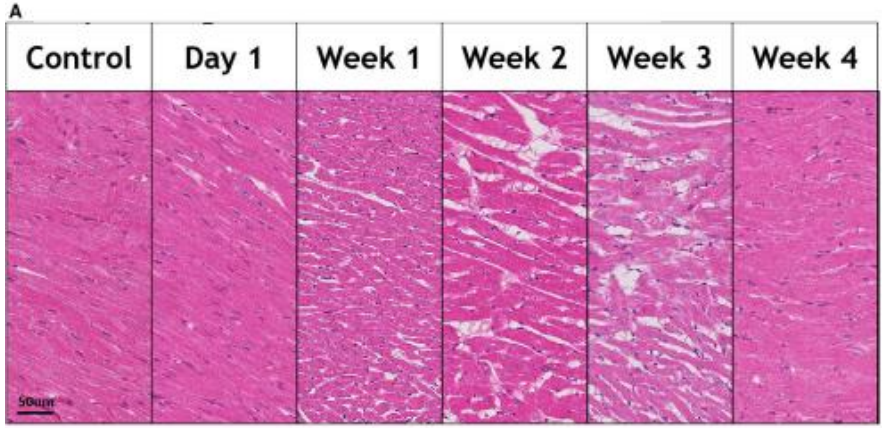
Radiobiologisch effect

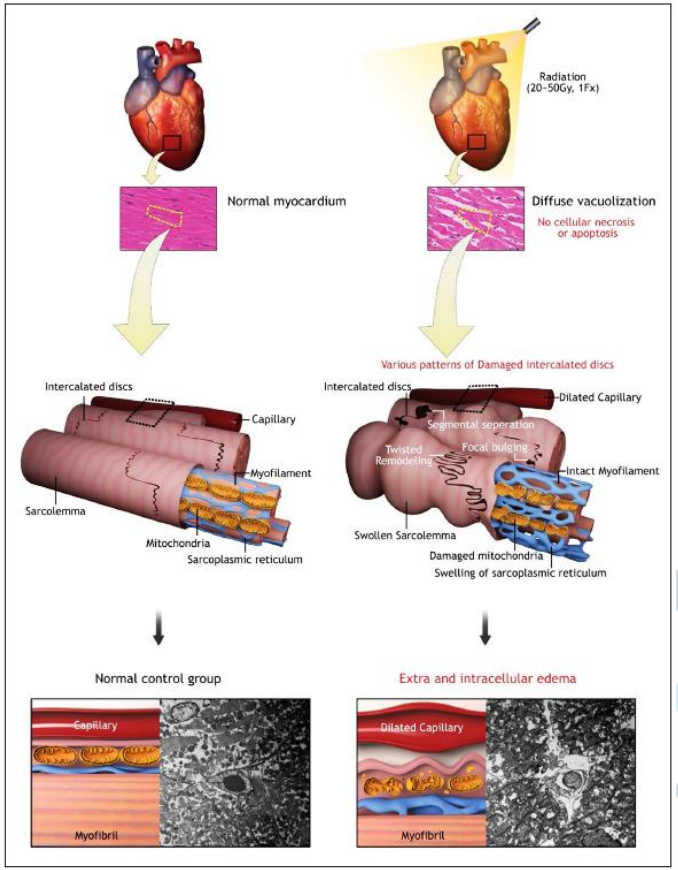
- Eerste 3 weken: extra- en intracellulair oedeem en vacuolisatie: eerder inflammatoir effect

==> vroegtijdig effect eerder door conductie stoornissen en membraan alteraties zonder necrose

- Na 4-6 weken fibrose en celdood bij doses > 30 Gy

LV subendocardiale vacuolisatie





Cha et al, JAHA 2021

nature COMMUNICATIONS

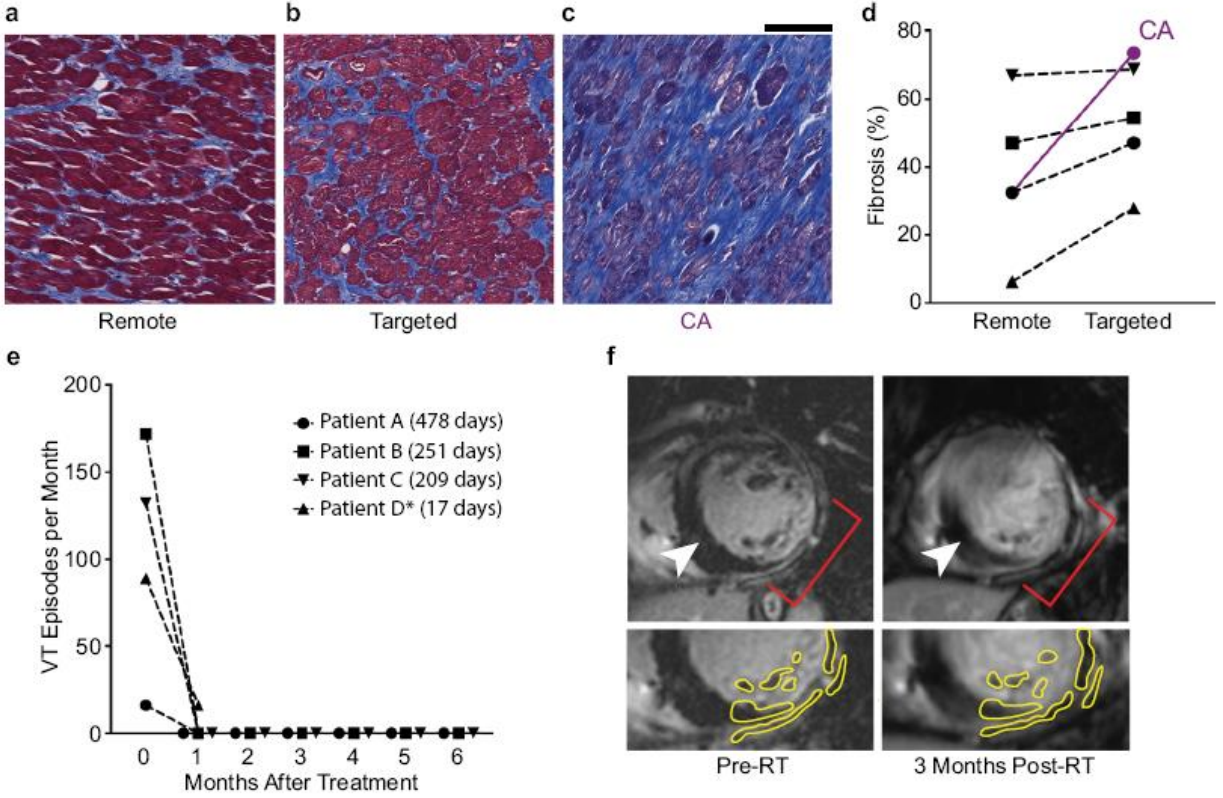
ARTICLE

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

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

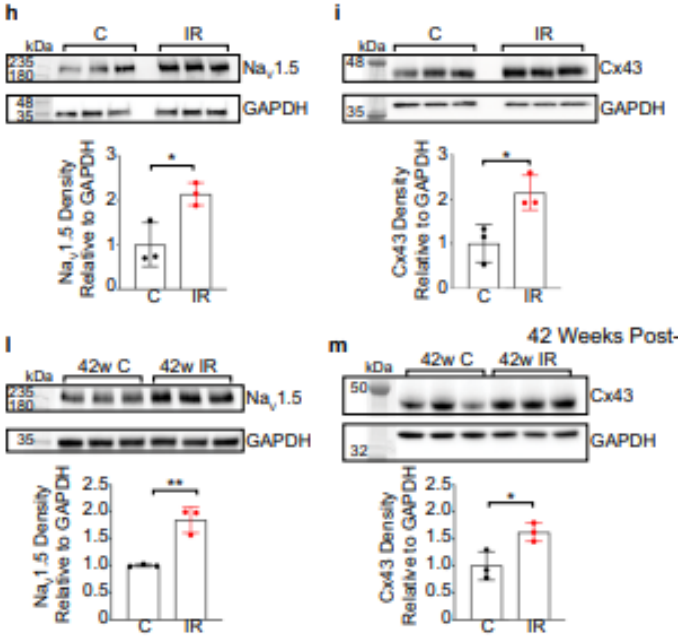
David M. Zhang[1,2], Rachita Navara[1,2], Tiankai Yin[2], Jeffrey Szymanski[3], Uri Goldsztejn[2,4], Camryn Kenkel[2,4], Adam Lang[5], Cedric Mpoy[3], Catherine E. Lipovsky[2,6], Yun Qiao[2,4], Stephanie Hicks[2], Gang Li[2,4], Kaitlin M. S. Moore[1,2], Carmen Bergom[1,3], Buck E. Rogers[3], Clifford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

Masson's trichroom kleuring (collageen)

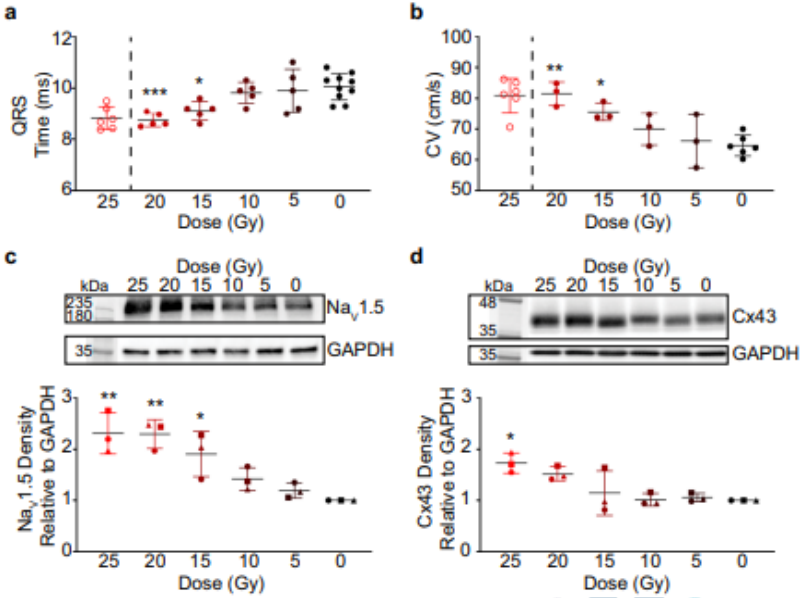


- Verhoging Nav1.5 en Cx43
- Gene sequencing: Notch signalling

Reprogramming cardiale conductie

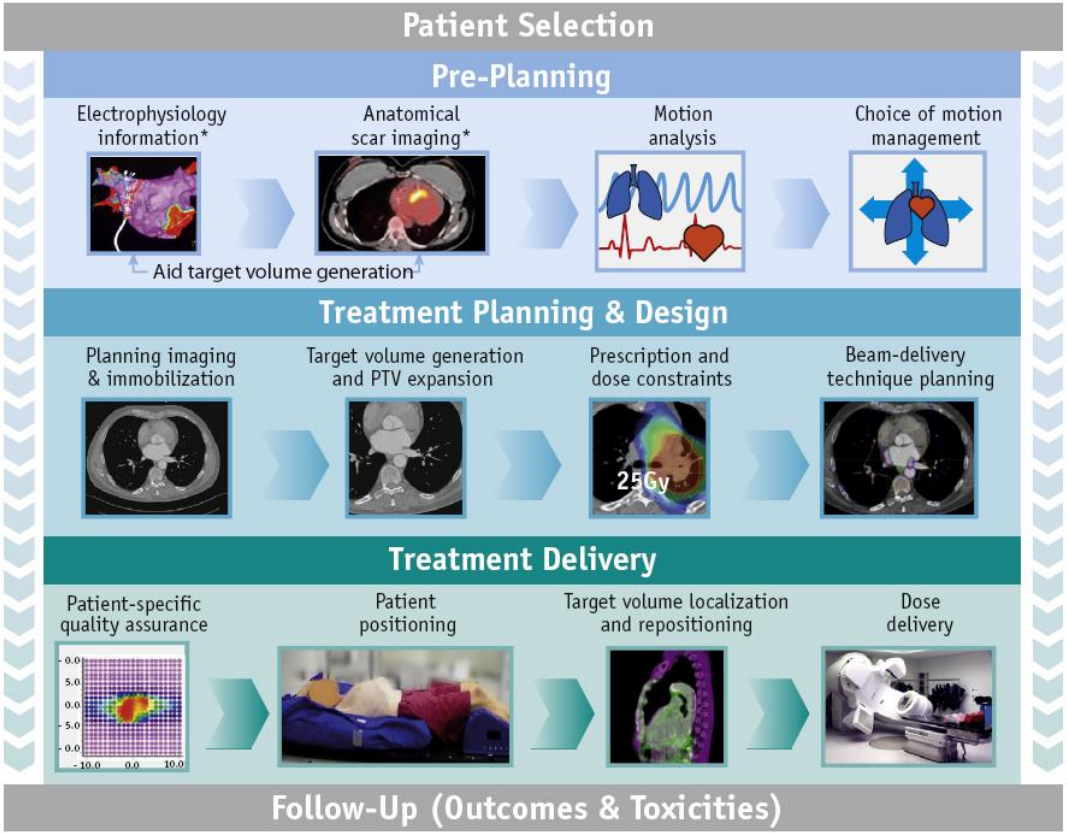


- Verhoging Nav1.5 en Cx43 ook bij lagere doses



Zhang et al, Nature Comm 2021

SBRT procedure

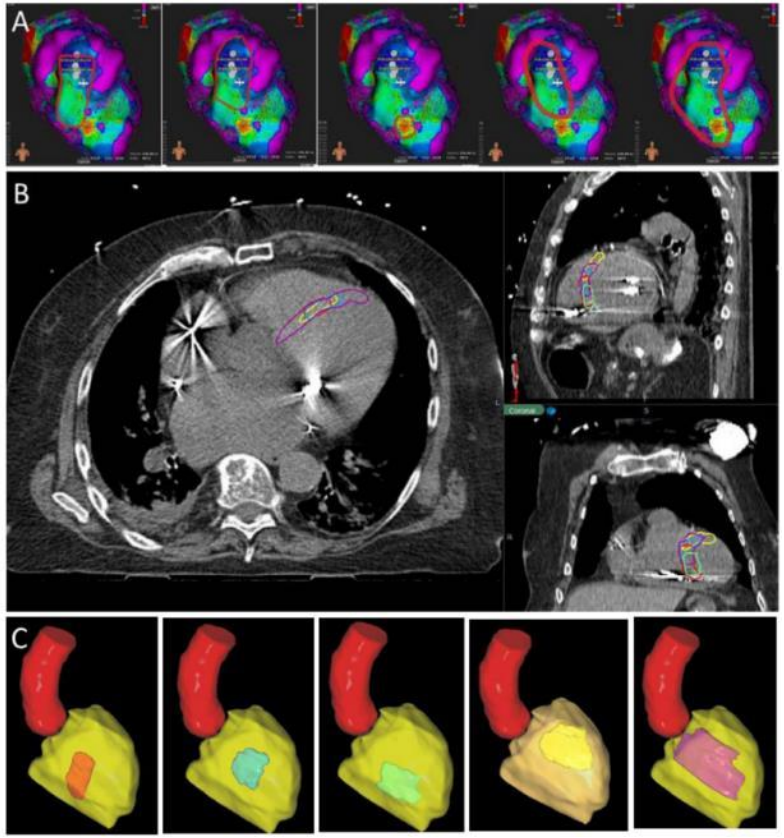


Critical Review

A Review of Cardiac Radioablation (CR) for Arrhythmias: Procedures, Technology, and Future Opportunities

Suzanne Lydiard, PGDip,*,† Oliver Blanck, PhD,† Geoffrey Hugo, PhD,‡ Ricky O'Brien, PhD,* and Paul Keall, PhD*

Target definitie



Clinical Investigation

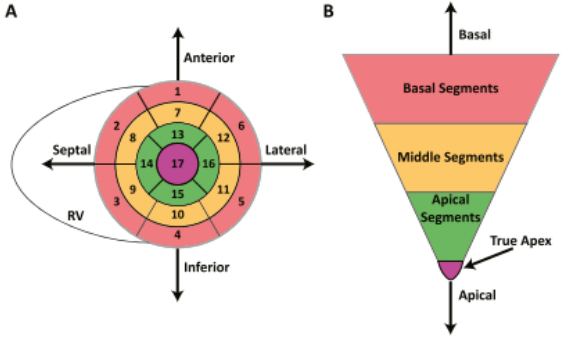
Interdisciplinary Clinical Target Volume Generation for Cardiac Radioablation: Multicenter Benchmarking for the RAdiosurgery for VENtricular TAchycardia (RAVENTA) Trial

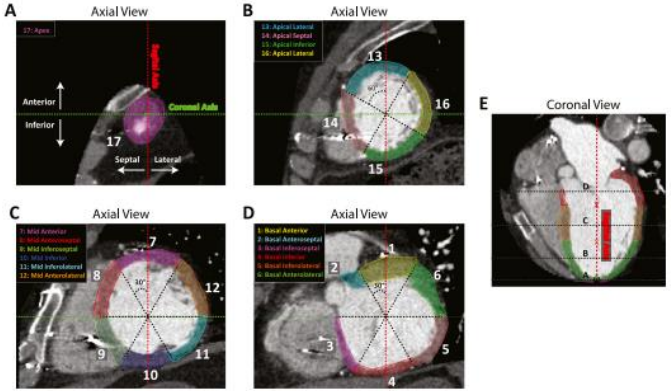
Judit Boda-Heggemann, MD, PhD,* Oliver Blanck, PhD,† Felix Mehrhof, MD,† Floris Ernst, PhD,† Daniel Buergy, MD,* Jens Fleckenstein, PhD,* Erol Tülümen, MD,† David Krug, MD,† Frank-Andre Siebert, PhD,† Adrian Zaman, MD,¶ Anne K. Kluge, PhD,‡ Abdul Shokor Parwani, MD,# Nicolaus Andratschke, MD,** Michael C. Mayinger, MD,** Stefanie Ehrbar, PhD,** Ardan M. Saguner, MD,†† Eren Celik, MD,‡‡ Wolfgang W. Baus, PhD,‡‡ Annina Stauber, MD,§§ Lena Vogel, MD,* Achim Schweikard, PhD,§ Volker Budach, MD,‖ Jürgen Dunst, MD,† Leif-Hendrik Boldt, MD,# Hendrik Bonnemeier, MD,¶ and Boris Rudic, MD¶¶

METHOD AND ATLAS TO ENABLE TARGETING FOR CARDIAC RADIOABLATION EMPLOYING THE AMERICAN HEART ASSOCIATION SEGMENTED MODEL

Running Title: Cardiac Radioablation Contouring Atlas

Jeremy Brownstein, MD[1], Muhammad Afzal, MD, FACC[2], Toshimasa Okabe MD[2], Thura T. Harfi, MD, MPH[3], Matthew S Tong, DO[2], Evan Thomas MD, PhD[3], Geoffrey Hugo, PhD[4], Phillip Cuculich, MD[1,5], Cliff Robinson, MD[1,5]*, Terence Williams, MD, PhD[1,*]



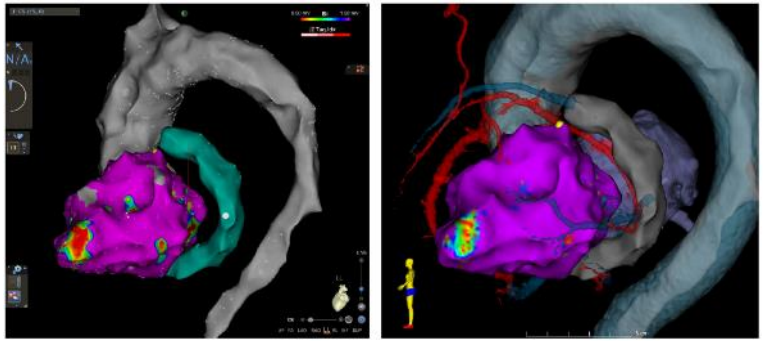


A novel open-source software-based high-precision workflow for target definition in cardiac radioablation

Stephan Hohmann MD[1] | Christoph Henkenberens MD[2] | Christos Zormpas MD[1] | Hans Christiansen MD[2] | Johann Bauersachs MD[1] | David Duncker MD[1] | Christian Veltmann MD[1]

Novel Workflow for Conversion of Catheter-Based Electroanatomic Mapping to DICOM Imaging for Noninvasive Radioablation of Ventricular Tachycardia

Christopher L. Brett, MD,[a,*] Jason A. Cook, MD,[b] Asad A. Aboud, MD,[b] Rashed Karim, PhD,[c] Eric T. Shinohara, MD,[a] and William G. Stevenson, MD, FHRS[b]



Kritische structuren

Organs at risk	Dose recommendations/dose limitations
Aorta	Dose limitations: $D_{max} \leq 20.0$ Gy Minor protocol deviation: 20 Gy $< D_{max} \leq 25$ Gy Major protocol violation: $D_{max} > 25$ Gy
Left coronary arteries	Dose limitations: $D_{max} \leq 14.0$ Gy Minor protocol deviation: 14 Gy $< D_{max} \leq 20$ Gy Major protocol violation: $D_{max} > 20$ Gy
Superior vena cava	Dose recommendations: $D_{50\%} \leq 0.6$ Gy
Left atrium	Dose recommendations: $D_{max} \leq 4.4$ Gy
Whole heart minus PTV	Dose recommendations: $D_{50\%} \leq 5$ Gy
Esophagus	Dose limitations: $D_{max} \leq 14.5$ Gy and $V_{9Gy} \leq 1$ ccm Minor protocol deviation: $D_{max} \leq 19$ Gy, $D_{1ccm} \leq 14.5$ Gy and $V_{9\,Gy} \leq 4$ ccm Major protocol violation: $D_{max} > 19$ Gy ‖ $D_{1ccm} > 14.5$ Gy ‖ $V_{9\,Gy} > 4$ ccm
Trachea	Dose limitations: $D_{max} \leq 15$ Gy and $V_{10\,Gy} \leq 1$ ccm Minor protocol deviation: $D_{max} \leq 20$ Gy, $D_{1\,ccm} \leq 15$ Gy and $V_{10\,Gy} \leq 4$ ccm Major protocol violation: $D_{max} > 20$ Gy ‖ $D_{1\,ccm} > 15$ Gy ‖ $V_{9\,Gy} > 4$ ccm
Bronchial tree	Dose limitations: $D_{max} \leq 15$ Gy and $V_{10Gy} \leq 1$ ccm Minor protocol deviation: $D_{max} \leq 20$ Gy, $D_{1\,ccm} \leq 15$ Gy and $V_{10\,Gy} \leq 4$ ccm Major protocol violation: $D_{max} > 20$ Gy ‖ $D_{1\,ccm} > 15$ Gy ‖ $V_{9\,Gy} > 4$ ccm
Spinal canal	Dose limitations: $D_{max} \leq 7$ Gy and $V_{6\,Gy} \leq 0.1$ ccm Minor protocol deviation: $D_{max} \leq 8$ Gy, $V_{6\,Gy} \leq 1$ ccm Major protocol violation: $D_{max} > 8$ Gy ‖ $V_{6\,Gy} > 1$ ccm
Skin	Dose limitations: $D_{max} \leq 14.4$ Gy and $V_{10\,Gy} \leq 10$ ccm Minor protocol deviation: $D_{max} \leq 16$ Gy, $V_{14.4\,Gy} \leq 10$ ccm Major protocol violation: $D_{max} > 16$ Gy ‖ $V_{14.4\,Gy} > 10$ ccm
Whole lungs	Dose limitations: $V_{100\%} - V_{7Gy} \geq 1500$ ccm ($V_{7\,Gy}$ remaining volume > 1500 ccm) and $D_{5\%} \leq 20$ Gy and $D_{50\%} \leq 3.5$ Gy Minor protocol deviation: $V_{100\%} - V_{7Gy} \geq 1000$ ccm ($V_{7\,Gy}$ remaining volume > 1000 ccm), $D_{6.5\%} \leq 20$ Gy and $D_{50\%} \leq 5$ Gy Major protocol violation: $V_{100\%} - V_{7\,Gy} < 1000$ ccm ($V_{7\,Gy}$ remaining volume < 1000 ccm), $D_{6.5\%} > 20$ Gy and $D_{50\%} > 5$ Gy
ICD (major electronics)	Dose limitations: $D_{max} \leq 0.5$ Gy and blocked from primary beam irradiation Minor protocol deviation: 0.5 Gy $< D_{max} \leq 1.0$ Gy Major protocol violation: $D_{max} > 1.0$ Gy

Clinical Research in Cardiology
https://doi.org/10.1007/s00392-020-01650-9

TRIAL DESIGN

Radiosurgery for ventricular tachycardia: preclinical and clinical evidence and study design for a German multi-center multi-platform feasibility trial (RAVENTA)

Oliver Blanck[1] · Daniel Buergy[2] · Maren Vens[3,4] · Lina Eidinger[1,5] · Adrian Zaman[5] · David Krug[1] · Boris Rudic[6] · Judit Boda-Heggemann[2] · Frank A. Giordano[2] · Leif-Hendrik Boldt[7] · Felix Mehrhof[8] · Volker Budach[8] · Achim Schweikard[9] · Denise Olbrich[3] · Inke R. König[4] · Frank-Andre Siebert[1] · Reinhard Vonthein[4] · Jürgen Dunst[1] · Hendrik Bonnemeier[5]

Radiotherapy Workflow and Dosimetric Analysis from a Phase I/II Trial of Noninvasive Cardiac Radioablation for Ventricular Tachycardia

Nels C. Knutson, PhD[1*], Pamela Samson, MD, MPHS[1*], Geoffrey Hugo, PhD[1], S. Murty Goddu, PhD[1], Francisco Reynoso, PhD[1], James Kavanaugh, MS[1], Sasa Mutic, PhD[1], Kaitlin Moore, BS[2], Jessica Hilliard, MS, CMD[1], Phillip Cuculich, MD[2], & Clifford Robinson, MD[1]

[1] Department of Radiation Oncology, Washington University School of Medicine, Saint Louis, MO
[2] Division of Cardiology, Department of Medicine, Washington University School of Medicine, Saint Louis, MO

Management of Radiotherapy Patients with Implanted Cardiac Pacemakers and Defibrillators: *A Report of the AAPM TG-203**

Moyed Miften**
Co-Chair, Task Group 203, Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado 80045

Dimitris Mihailidis**
Co-Chair, Task Group 203, University of Pennsylvania, Perelman Center for Advanced Medicine, Philadelphia, PA 19104

Stephen F. Kry
Department of Radiation Physics, UT MD Anderson Cancer Center, Houston, Texas 77030

Charles Reft
Department of Radiation Oncology, University of Chicago, Chicago, Illinois 60637

Carlos Eugenio
Department of Radiation Oncology, UT Health Sciences Center, San Antonio, Texas 78229

Jonathan Farr
Division of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee 38105

David Followill
Department of Radiation Physics, UT MD Anderson Cancer Center, Houston, Texas 77030

Coen Hurkmans
Department of Radiotherapy, Catharina Hospital, Eindhoven, The Netherlands

Arthur Liu
Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado 80045

Olivier Gayou
Department of Radiation Oncology, Allegheny General Hospital, Pittsburg, Pennsylvania 15212

Michael Gossman
Department of Radiation Oncology, Tri-State Regional Cancer Center, Ashland, Kentucky 41101

Malandrappa Mahesh
Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287

Treatment Planning

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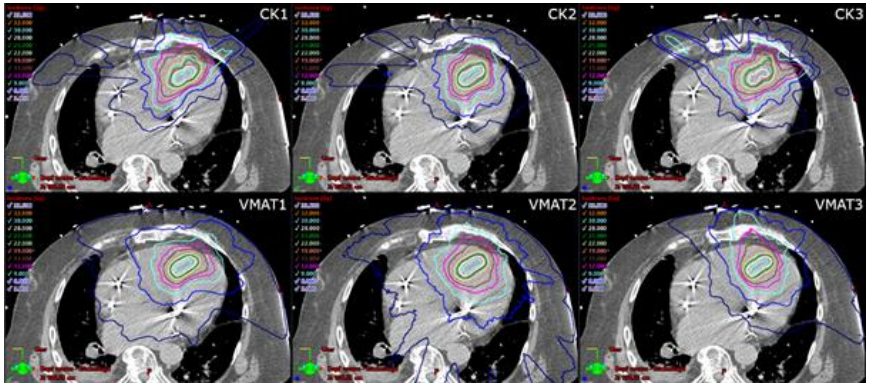
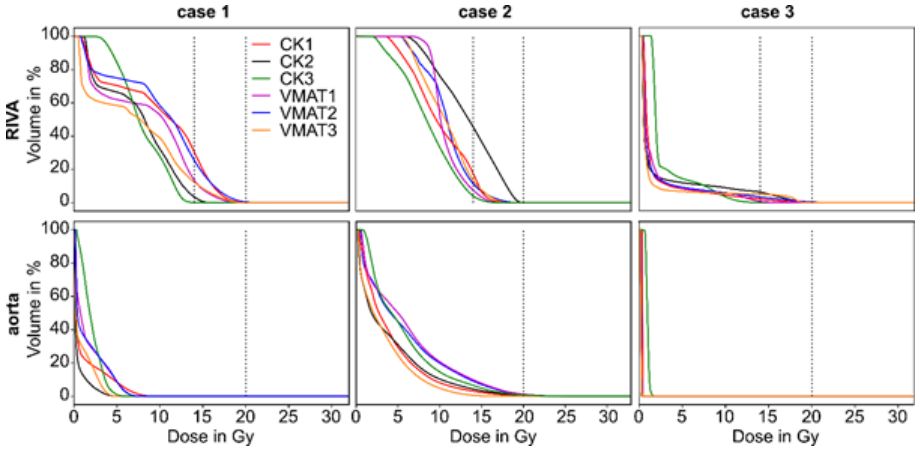
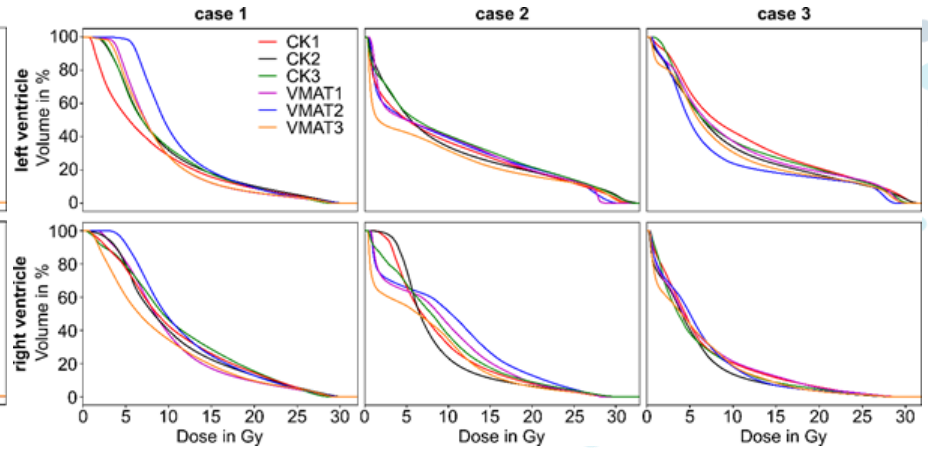
PHYSICS CONTRIBUTION

Treatment Planning for Cardiac Radioablation: Multicenter Multiplatform Benchmarking for the RAdiosurgery for VENtricular TAchycardia (RAVENTA) Trial

Anne Kluge, PhD,* Stefanie Ehrbar, PhD,† Melanie Grehn, MSc,‡ Jens Fleckenstein, PhD,† Wolfgang W. Baus, PhD,‖ Frank-Andre Siebert, PhD,‡ Achim Schweikard, PhD,¶ Nicolaus Andratschke, MD,‡ Michael C. Mayinger, MD,† Judit Boda-Heggemann, MD, PhD,‡ Daniel Buergy, MD,† Eren Celik, MD,‖ David Krug, MD,‡ Boldizsar Kovacs, MD,# Ardan M. Saguner, MD,# Boris Rudic, MD,** Paula Bergengruen, MD,* Leif-Hendrik Boldt, MD,†† Annina Stauber, MD,†† Adrian Zaman, MD,‡‡ Hendrik Bonnemeier, MD,‡‡ Jürgen Dunst, MD,‡ Volker Budach, MD,* Oliver Blanck, PhD,‡ and Felix Mehrhof, MD*







First in Human

First magnetic resonance imaging-guided cardiac radioablation of sustained ventricular tachycardia

Michael Mayinger [a,1], Boldizsar Kovacs [b,1], Stephanie Tanadini-Lang [a], Stefanie Ehrbar [a], Lotte Wilke [a], Madalyne Chamberlain [a], Amanda Moreira [a], Nienke Weitkamp [a], Corinna Brunckhorst [b], Firat Duru [b], Jan Steffel [b], Alexander Breitenstein [b], Hatem Alkadhi [c], Helena I. Garcia Schueler [a], Robert Manka [b,c], Frank Ruschitzka [b], Matthias Guckenberger [a], Ardan M. Saguner [b,2], Nicolaus Andratschke [a,2]

[a] Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Switzerland; [b] University Heart Center Zurich, University Hospital Zurich, University of Zurich, Switzerland and [c] Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, University of Zurich, Switzerland

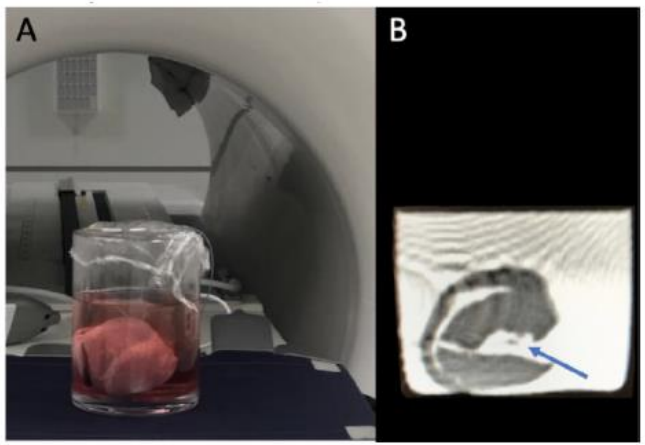
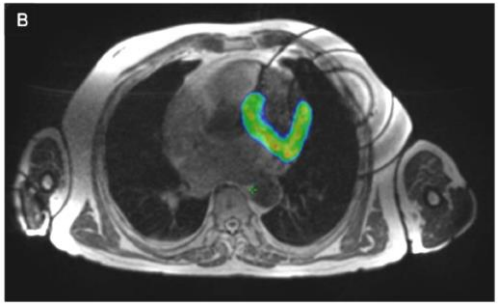


Fig. 1. Pacemaker safety testing using the porcine model. A = setup, B = MR image (Blue arrow = pacemaker electrodes).



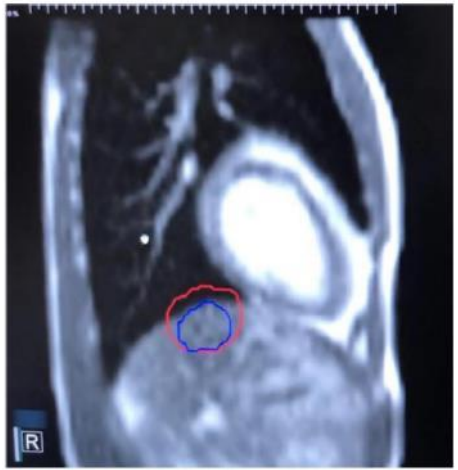
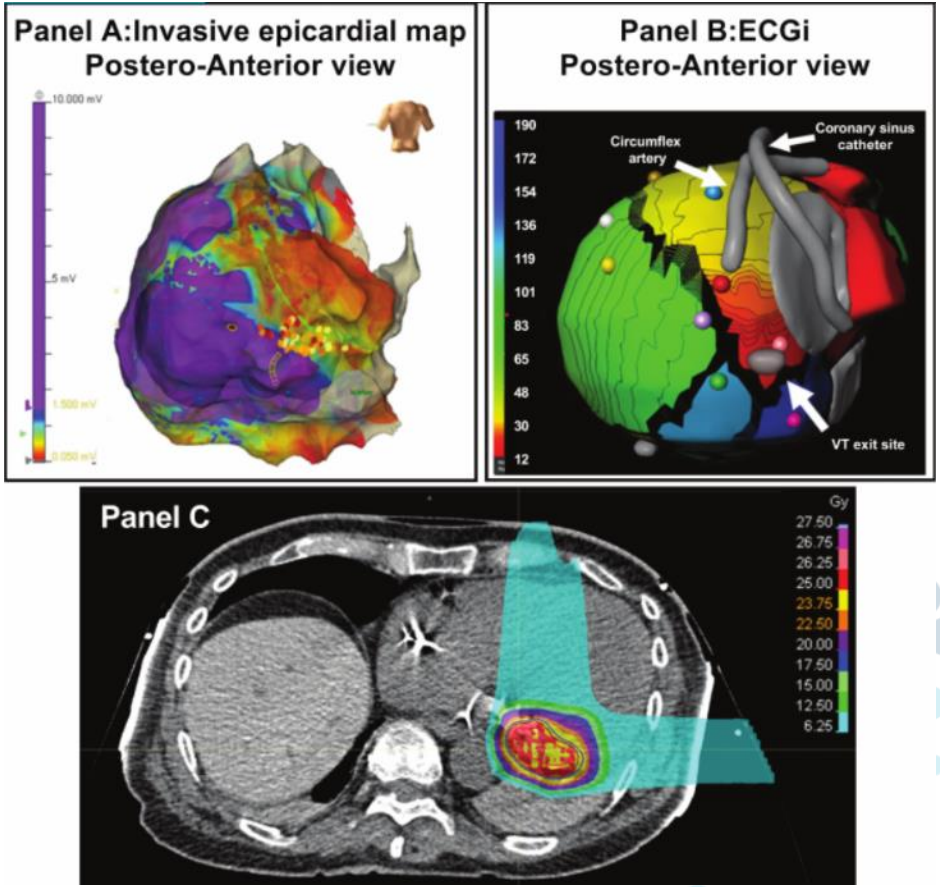


Fig. 3. Successful real-time-tracking of extracardiac structures (e.g. the diaphragm dome, liver).

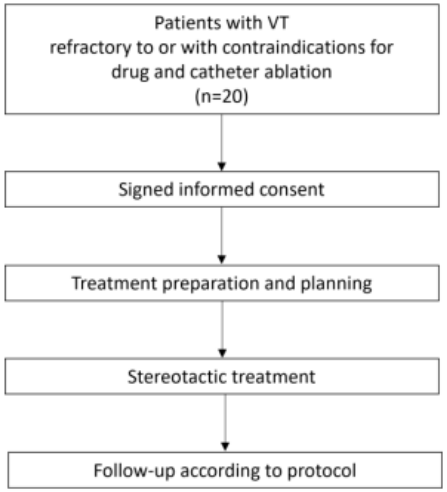
First-in-man case of non-invasive proton radiotherapy for the treatment of refractory ventricular tachycardia in advanced heart failure

Veronica Dusi [1 2], Viviana Vitolo [3], Laura Frigerio [1 4], Rossana Totaro [1 4], Adele Valentini [5], Amelia Barcellini [3], Alfredo Mirandola [3], Giovanni B Perego [6], Michela Coccia [2], Alessandra Greco [4], Stefano Ghio [4], Francesca Valvo [3], Gaetano M De Ferrari [7], Massimiliano Gnecchi [1 2], Luigi Oltrona Visconti [4], Roberto Rordorf [1 4]



CArdiac STereotactic radiation treatment for Ablation o ventRicular tachycardia

CASTAR



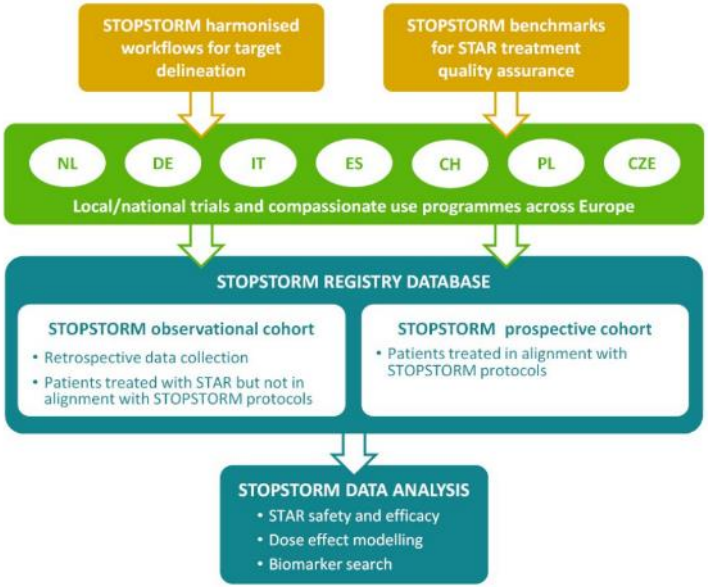
Primaire eindpunten	
Feasibility	Succesvolle implementatie SBRT
Safety	Toxiciteit obv CTCAE v5.0 binnen 31d post SBRT
Secundaire eindpunten	
Efficiëntie	VT burden (blanking period 6w) Tijd tot eerste VT episode, eerste VT storm, sustained VT/ICD shock Reductie in ATP, ICD shocks Nood anti-aritmica OS en nood aan hartTx Cardiale sterfte (non/aritmogeen)
Toxiciteit	CTCAE v5.0 voor acute (30-90d post SBRT) en late toxiciteit (>90d) troponines, CK
QoL	EQ-5D-5L en SF-36 vragenlijsten

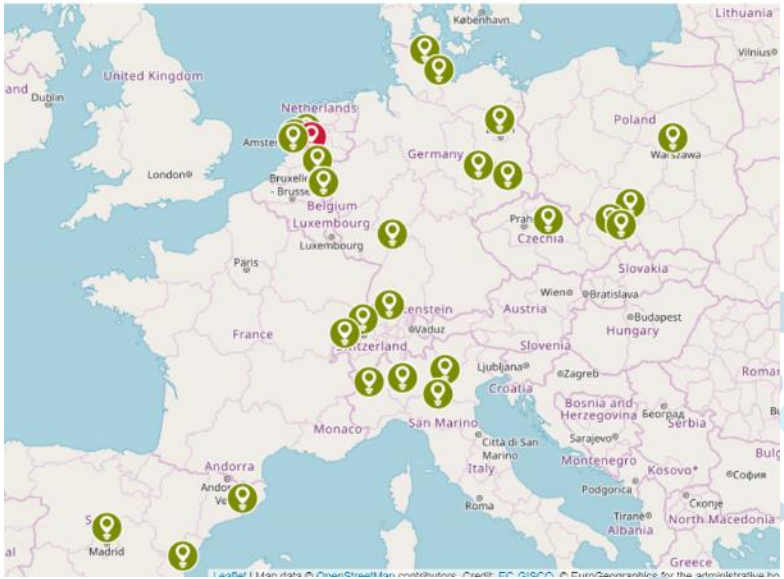
ines.joye@gza.be

HORIZON 2020

A PROSPECTIVE EUROPEAN VALIDATION COHORT FOR STEREOTACTIC THERAPY OF RE-ENTRANT TACHYCARDIA

STOPSTORM





Conclusies

- SBRT is een **veilige, non-invasieve techniek** voor VT patiënten refractair aan of met contraindicatie voor medicatie, ICD en CA.
- SBRT **vermindert aantal VT episodes tijdens de eerste 6 maand** in merendeel van patiënten met structureel hartlijden en therapie-refractair VT.
- Vroegtijdig effect eerder door **verschuiving in conductie** (opregulatie van Cx43), nadien eerder **fibrose.**
- Identificatie van VT **substraat** op planning CT, optimale **dosis** en **laattijdige outcome** incl toxiciteit zijn verder te exploreren.