Radiotherapy and Oncology 189 (2023) 109910

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Stereotactic arrhythmia radioablation: A multicenter pre-post intervention safety evaluation of the implantable cardioverter-defibrillator function

Martijn H. van der Ree [a,b,c], Wiert F. Hoeksema [a], Adrian Luca [c], Jorrit Visser [d], Brian V. Balgobind [d], Michiel Zumbrink [a], Raymond Spier [a], Claudia Herrera-Siklody [c], Justin Lee [e], Matthew Bates [f], Jim Daniel [g], Clive Peedell [g], Judit Boda-Heggemann [h], Boris Rudic [i], Roland Merten [j], Edith M. Dieleman [d], Cristopher A. Rinaldi [k], Shahreen Ahmad [l], John Whitaker [k], Pranav Bhagirath [a,k], Matthew Q. Hatton [m], Stephen Riley [m], Melanie Grehn [n], Luis Schiappacasse [o], Oliver Blanck [n], Stephan Hohmann [p], Etienne Pruvot [c], Pieter G. Postema [a,*]

[a] Amsterdam UMC location University of Amsterdam, Department of Cardiology, Meibergdreef 9, Amsterdam, the Netherlands
[b] Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, the Netherlands
[c] Department of Cardiology, Lausanne University Hospital, Lausanne, Switzerland
[d] Amsterdam UMC location University of Amsterdam, Department of Radiation Oncology, Meibergdreef 9, Amsterdam, The Netherlands
[e] Department of Cardiology, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK
[f] Department of Cardiology, South Tees Hospitals NHS Foundation Trust, Middleborough, UK
[g] Department of Radiation Oncology, South Tees Hospitals NHS Foundation Trust, Middlesborough, UK
[h] Department of Radiation Oncology, University Medical Center Mannheim University of Heidelberg, Mannheim, Germany
[i] Department of Cardiology, University Medical Center Mannheim University of Heidelberg, Mannheim, Germany
[j] Department of Radiation Oncology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
[k] Department of Cardiology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom
[l] Department of Radiation Oncology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom
[m] Department of Clinical Oncology, Weston Park Hospital, Sheffield, UK
[n] Department of Radiation Oncology, University Medical Center Schleswig-Holstein, Kiel, Germany
[o] Department of Radiation Oncology, Lausanne University Hospital, Lausanne, Switzerland
[p] Hannover Heart Rhythm Center, Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

ARTICLE INFO

Keywords:
Cardiac radioablation
stereotactic arrhythmia radiotherapy (STAR)
ventricular tachycardia (VT)
Implantable cardioverter defibrillator (ICD)
Safety

ABSTRACT

Background: Stereotactic arrhythmia radioablation (STAR) appears to be beneficial in selected patients with therapy-refractory ventricular tachycardia (VT). However, high-dose radiotherapy used for STAR-treatment may affect functioning of the patients' implantable cardioverter defibrillator (ICD) by direct effects of radiation on ICD components or cardiac tissue. Currently, the effect of STAR on ICD functioning remains unknown.
Methods: A retrospective pre-post multicenter study evaluating ICD functioning in the 12-month before and after STAR was performed. Patients with (non)ischemic cardiomyopathies with therapy-refractory VT and ICD who underwent STAR were included and the occurrence of ICD-related adverse events was collected. Evaluated ICD parameters included sensing, capture threshold and impedance. A linear mixed-effects model was used to investigate the association between STAR, radiotherapy dose and changes in lead parameters over time.
Results: In total, 43 patients (88% male) were included in this study. All patients had an ICD with an additional right atrial lead in 34 (79%) and a ventricular lead in 17 (40%) patients. Median ICD-generator dose was 0.1 Gy and lead tip dose ranged from 0-32 Gy. In one patient (2%), a reset occurred during treatment, but otherwise, STAR and radiotherapy dose were not associated with clinically relevant alterations in ICD leads parameters.

Abbreviations: CTV, Clinical target volume; ICD, Implantable cardioverter-defibrillator; ITV, Internal target volume; IQR, Interquartile range; LV, Left ventricle; PTV, Planning target volume; RA, Right atrium; RV, Right ventricle; STAR, Stereotactic Arrhythmia Radioablation; VT, Ventricular tachycardia.

* Corresponding author at: Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
E-mail address: p.g.postema@amsterdamumc.nl (P.G. Postema).

https://doi.org/10.1016/j.radonc.2023.109910
Received 13 May 2023; Received in revised form 8 September 2023; Accepted 8 September 2023
Available online 12 September 2023

Conclusions: STAR treatment did not result in major ICD malfunction. Only one radiotherapy related adverse event occurred during the study follow-up without patient harm. No clinically relevant alterations in ICD functioning were observed after STAR in any of the leads. With the reported doses STAR appears to be safe.

Background

Ventricular tachycardia (VT) is a potentially life-threatening arrhythmia associated with a reduced quality of life and increased morbidity and mortality [1]. To prevent sudden cardiac death in patients at risk for VT, an implantable cardioverter-defibrillator (ICD) is recommended [2]. Anti-arrhythmic drugs and (repeated) invasive catheter ablations are used to prevent and manage VT [2]. These conventional therapies are not always successful in preventing VT. The optimal treatment strategy for those therapy-refractory patients is uncertain. Stereotactic arrhythmia radioablation (STAR) appears to be beneficial in selected patients with therapy-refractory VT [3–6]. In STAR, the ventricular arrhythmogenic substrate is noninvasively targeted with high doses of radiotherapy, ranging between 20–25 Gy in a single fraction [3,5–8].

These high doses of radiotherapy used for STAR treatment may, however, affect cardiac implantable electronic devices, as has previously been described for non-cardiac radiotherapy targets [9,10]. Radiation-induced malfunction of the ICD includes software errors related to interactions with ionizing particles and signal interference as a consequence of the electromagnetic field during treatment. This may result in (partial) resets leading to loss of memory, changes in programming, restoration of factory-programmed settings, and transitory oversensing [9].

Furthermore, ICD functioning may be altered by changes in cardiac tissue after STAR. The exact tissue effects and subsequent anti-arrhythmic mechanism(s) of STAR remain to be completely elucidated, however. Based on current evidence, radiation-induced reprogramming of cardiac electrophysiology and myocardial fibrosis formation are likely to play a role [3,11–13]. When alterations in myocardial tissue and cardiac electrophysiology are induced, this may also affect ICD functioning, especially when the site of lead tip insertion is in (proximity to) the target area [14]. Potential problems that may arise as a consequence are loss of capture and changes in intracardiac signals and herewith undersensing issues [10,15–17]. In preclinical work, a reduction of amplitudes and increased capture thresholds have indeed been reported after STAR [18,19].

Currently, the effects of STAR on ICD functioning are unknown. Because of the potential issues associated with radiotherapy and the cardiac remodeling after STAR, effects on ICD functioning are conceivable and should be studied, as proper ICD function is critical for these patients. Therefore, we performed a multicenter pre-post safety evaluation of patients treated with STAR.

Methods

The study data are available from the corresponding author upon reasonable request. The study was approved by the Institutional Committee on Human Research at the Amsterdam UMC.

Study design

This retrospective study was designed as pre-post multicenter study evaluating ICD related adverse events and ICD parameters in the 12 months before and up to 12 months after STAR. The occurrence of radiotherapy- and ICD-related adverse events (e.g. under- or oversensing, partial reset of device) were collected. Evaluated ICD parameters included sensing of the intracardiac signal in millivolt (mV), capture threshold in volts (V) and the impedance in Ohm (Ω) of all inserted leads. All available ICD readouts, both (out)patient clinic visits and home monitoring, within the 12 months before and after treatment were included and collected using Castor EDC [20]. ICDs of all manufacturers were included in this analysis. Efficacy and non ICD-related safety were not investigated.

Patients and STAR treatment

Patients with (non)ischemic cardiomyopathies with therapy-refractory VT who underwent STAR in prospective clinical studies or registries (e.g., within the Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary [STOPSTORM] consortium) [21] or as compassionate use according to expert recommendations [22] treated between 2017 and 2022 were included in this analysis without restrictions on STAR techniques (e.g., radiation dose, target motion management, treatment device [23]). All patients were required to have an ICD implanted prior to STAR. Patients with a device and/or lead change after STAR were excluded. The pro-arrhythmic substrate (i.e. the clinical target volume [CTV]) was delineated based on clinical and electrophysiological information with various methods according to clinical or local protocols [24,25]. The CTV was expanded to account for cardiorespiratory motion based on the selected motion management strategy [23]. The addition of a treatment uncertainty margin resulted in the final planning target volume (PTV) for radiotherapy treatment planning. Dose escalation was allowed according to local treatment protocols. During treatment planning, the ICD generator was considered an avoidance structure in all patients to meet the strict dose limits for radiotherapy [26]. In contrast, the ICD lead tip(s) were not considered during treatment planning and were retrospectively delineated for research purposes according to a study delineation protocol designed as pragmatic and user-friendly approach, prioritizing reproducibility in dose estimation over accuracy and precision to allow for mean dose calculations (Supplementary material).

Statistical analysis

Descriptive analysis was performed with SPSS Statistics (version 28.0, IBM Corporation, Armonk, NY USA). The median value and interquartile range (IQR) were used as summary statistic. The association between STAR and changes in the lead parameters over time was evaluated using linear mixed-effects models with the time of measurements (months) and STAR (0 = before, 1 = after) as fixed effects, and with the time of measurements and subjects as random slope and intercept, respectively, to allow both the rate of change and mean value to vary by subject. For each individual patient, spaghetti plots with all measurements were visually inspected for changes in lead functioning before and after STAR. Linear fixed models for repeated measures were also used to assess the dose effect on lead parameters. The models included the time of measurements, mean lead-tip dose (Gy), lead type (Right atrium [RA] and Right ventricle [RV]) and interaction between them, using two random intercepts to allow for variance between individual leads and between subjects and a random time slope. For this analysis, the RA and RV lead data were pooled and only measurements after STAR were included.

The smaller numbers of left ventricular (LV) measurements did not allow for evaluating the effect of STAR using linear-mixed-effects model and only descriptive statistics are presented. The implementation of the linear mixed-effects model was conducted using R version 4.2.2 (https://www.r-project.org/). A p-value of < 0.05 was considered statistically significant.

Results

In total, 43 patients (n = 38 males [88%], n = 5 [12%] female) from eight international centers were included in this STAR ICD safety evaluation. Table 1 shows an overview of the baseline characteristics and device information. Median age at time of STAR was 68 (range: 47–84) years and the median left ventricular ejection fraction was 34% (range: 10–64). The majority of STAR treatments were on a compassionate use base (n = 30, 70%). All patients had a transvenous ICD with an additional right atrial lead in 34 (79%) and left ventricular lead in 17 (40%) patients. Table 2 shows an overview of STAR treatment details. All patients were treated using photon beam energies of 6–10 MV (median 6; interquartile range: 6–6). Most of the patients were treated using a c-arm linear accelerator with volumetric-modulated arc therapy (n = 22, 51%) or other techniques (n = 3, 7%) and a robotic-mounted linear accelerator with step-and-shoot technique (n = 18, 42%). The median ICD generator dose was 0.1 Gy (range: 0–2.8) and the median dose received by the lead tips was 3.6 Gy (range: 0.04–32) for all leads (Table 2).

The 12-month follow-up was completed by 30 (70%) patients, 8 (18%) patients died and 5 (12%) patients did not yet complete the full 12-month follow-up (range: 4–9 months in these patients). The median follow-up was 12-months with a total follow-up of 38 patient-years. The median number of ICD readouts was 8 (interquartile range: 4–16) during the study period.

In one (2%) patient, a radiotherapy- and ICD-related adverse event occurred during the study follow-up. In this patient a restoration of factory-programmed settings occurred during treatment. Directly after STAR treatment, the ICD was manually reprogrammed to the pre-STAR settings without any further sequela.

The trend in RV and RA lead parameters over time before and after STAR was evaluated using a linear mixed model. Fig. 1 shows the trend in lead parameters over time for the RV sensing, RV capture, RV lead impedance and shock lead impedance. For the RV sensing amplitude, non-significant regression coefficients for STAR of −0.13 (95% CI: −0.78, 0.50; p = 0.68) and time −0.06 (95% CI: −0.13, 0.09; p = 0.09) were observed. For the RV capture threshold, also non-significant regression coefficients for STAR of 0.10 (95% CI: −0.006, 0.21; p = 0.065) and time of −0.0004 (95% CI: −0.01, 0.01; p = 0.92) were observed. This was also the case for the RV lead impedance (STAR: −8.68 [95% CI: −19.9, 2.48; p = 0.12] and time of −0.41 [95%CI: −1.18, 1.05; p = 0.58]) and for the shock impedance (STAR: −1.05 [95% CI: −3.44, 1.32; p = 0.38] and time of −0.031 [95% CI: −0.27, 0.33; p = 0.84]).

Table 1
Overview of the baseline characteristics and device information.

Baseline characteristics	
Age at STAR	68 (IQR: 62–75)
Sex, n (%)	
Male	38 (88)
Female	5 (12)
Body mass index, kg/m^2	27 (IQR: 24–30)
Left ventricular ejection fraction at baseline	34 (IQR: 25–45)
Treatment type	
Compassionate use, n (%)	30 (70)
Prospective trial, n (%)	13 (30)
Type of cardiomyopathy	
Ischemic, n (%)	23 (54)
Nonischemic, n (%)	20 (46)
Dilated	14 (70)
Inflammatory	4 (20)
Hypertrophic	1 (5)
Idiopathic	1 (5)
Previous catheter ablation, n (%)	37 (86)
Device information	
Type of ICD	
Transvenous, n (%)	43 (100)
ICD manufacturer	
Biotronik, n (%)	4 (9)
Boston Scientific, n (%)	6 (14)
Medtronic, n (%)	18 (42)
Abbott (formerly St. Jude Medical), n (%)	14 (33)
Microport (formerly Sorin), n (%)	1 (2)
Implanted leads	
Right atrial lead, n (%)	34 (79)
Right ventricular lead, n (%)	43 (100)
Left ventricular lead, n (%)	17 (40)

Table 2
Overview of treatment details.

STAR treatment planning technique	
Robotic-Guided Step-and-Shoot, n (%)	18 (42)
Dynamic Conformal Arcs, n (%)	2 (5)
Intensity-Modulated Step-and-Shoot, n (%)	1 (2)
Volumetric-Modulated Arc Therapy, n (%)	22 (51)
Photon treatment, n (%)	43 (100)
Energy of the beams, MV	6 (IQR: 6–6)
VT- target	
Prescribed dose, Gy	25 (IQR: 20–25)
Clinical target volume, cc	22 (IQR: 12–43)
Planning target volume, cc	73 (IQR: 33–112)
ICD doses	
ICD generator, Gy	0.1 (IQR: 0.03–0.12)
Right atrial lead tip, Gy	2 (IQR: 0.7–3.7)
Right ventricular lead tip, Gy	6.8 (IQR: 3.2–12.4)
Left ventricular lead tip, Gy	6.7 (IQR: 2.2–9.6)

The results for RA analysis showed a modest, but significant, effect on the sensing regression coefficient (-0.21 [95% CI: −0.37, 0.04; p = 0.001]). For the capture threshold and lead impedance no significant effect of STAR was observed (0.02 [95% CI: −0.096; 0.14], p = 0.68 and −6.28 [95% CI: −14.2; 2.5], p = 0.15 respectively). Supplemental Figure 1 shows the detailed results of the RA analysis. For the LV lead parameters, no clinically relevant alterations were observed (Sensing: +7%, capture: 0% and lead impedance −8%) comparing the median values before and after STAR.

For sensing and capture parameters, no significant effect of radiotherapy dose was observed and no interaction between time and lead type was found. For impedance, a significant interaction between time of measurement and radiotherapy dose was found with a regression coefficient of −0.19 (p < 0.001) indicating that during the 12-month follow-up with increasing time and radiotherapy dose there is a minor decrease in the lead impedances. Detailed results of the dose-dependent evaluation are presented in Supplementary Tables S1-S3.

Discussion

This is the first study evaluating the effects of STAR on ICD functioning on a significant number of patients with refractory VT. In only one patient a radiotherapy-related ICD adverse events occurred during the study follow-up. We observed no clinically relevant alterations in the sensing, capture or impedance measurements in any of the implanted leads after STAR in this multi-center and multi-platform study.

Radiotherapy could result in ICD malfunction in two ways. Firstly, as a consequence of electromagnetic field and interaction of the ICD with ionizing particles during treatment and secondly by inducing alterations in myocardial tissue characteristics [9,10].

Importantly, despite the high doses of radiotherapy used for STAR treatment, we observed no under- or oversensing because of electromagnetic field during treatment and only 1 patient (2%) experienced an adverse event potentially induced by an interaction between the ICD and ionizing particles. Despite a relatively low ICD generator dose of 0.02 Gy and a beam energy of 6 MV, a restoration of factory-programmed settings occurred during treatment that resulted in asymptomatic VVI pacing at 70 beats per minute. The dose in this patient was below the median ICD generator dose and the device was blocked from the primary beam. As previously reported, it appears that the dose for the occurrence of such ICD adverse events might not be directly correlated to

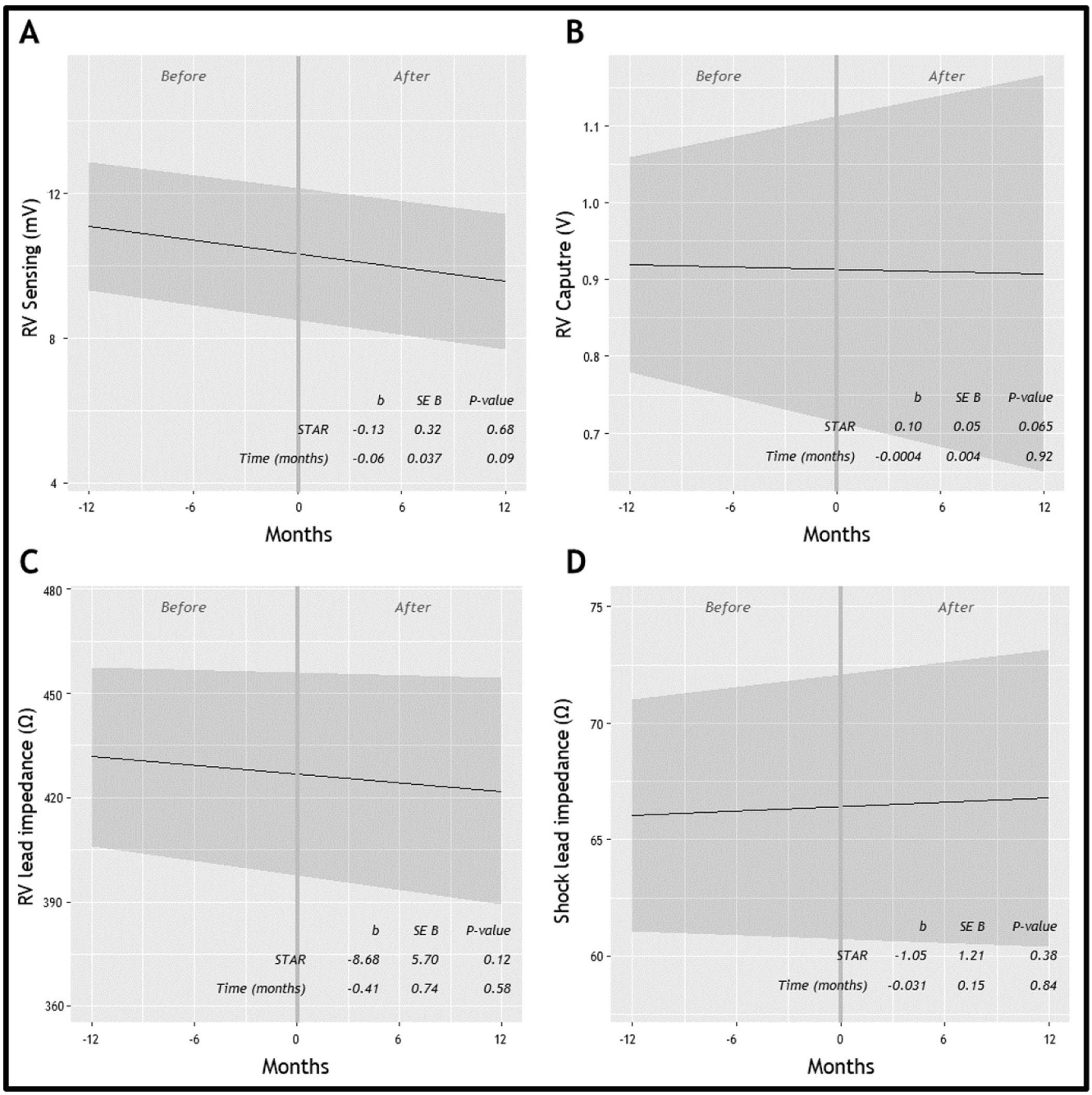

Fig. 1. The trend in lead parameters over time for the RV sensing, RV capture, RV lead impedance and shock lead impedance.
The black line indicates the predicted value for the ICD measurement over time and the grey surface represent the 95% confidence interval. STAR treatment is performed at time point 0 as indicated by the grey line. *b: regression coefficient and SE: standard error of b (regression coefficient).*

radiotherapy dose [10]. From the literature, a prevalence of 2–7% is reported for ICD-related adverse events such as reprogramming, memory loss and (partial) resets [17,27,28]. When such malfunctions do occur, they are usually well tolerated and easily corrected by (re)programming [9]. This was also the case in the patient of our study; after STAR treatment the ICD was reprogrammed to the pre-STAR settings without any further sequela.

The strongest predictor for radiotherapy-induced ICD malfunction is the exposure to neutrons formed during radiotherapy treatment, especially with energies of $>$ 10 MV, but radiotherapy dose rate may also play a role [9,29]. In our study, the energy of the beams ranged between 6–10 MV, which may explain the low prevalence of ICD malfunction. It is also important to acknowledge that our cohort is small when taking the low prevalence of such radiotherapy-related ICD malfunction into account, albeit that deliberate cardiac radiotherapy was certainly not intended in previous literature [17,27,28]. This notwithstanding, the number of patients treated with STAR is low globally and our STAR study cohort is one of the largest reported yet.

STAR could induce alterations in myocardial tissue and cardiac electrophysiology, which, in turn, may affect ICD functioning. Radiation-induced edema, reprogramming of cardiac electrophysiology and myocardial fibrosis formation are thought to play a role [3,11–13,30]. From preclinical work we know that doses of >15 Gy might already be able to induce reprogramming in cardiac electrophysiology and that doses of 30–40 Gy may induce fibrosis from three months onwards [3,11,31]. The RV and LV leads received a dose >15 Gy

in ten and three patients respectively. The effects of such alterations in cardiac electrophysiology of STAR on the intracardiac signal amplitude in the ventricles is currently unknown. Fibrosis induction at the site of the ICD lead tip insertion after STAR could potentially result in lower signal amplitudes, as it has been observed in preclinical work, and higher capture tresholds [16,18,19]. We did observe a mild decrease in signal amplitude, however this was only significantly associated with STAR treatment for the RA lead. Interestingly, this effect was not dependent on radiotherapy dose. A potential explanation why this reduction in RA signal amplitude only has been observed in our study, may be the differences in tissue thickness between the atria and the ventricles. As a consequence of a smaller atrial myocardial tissue mass, the effect of fibrosis after STAR on local signal amplitude could be more pronounced. A trend towards higher capture threshold (positive regression coefficients after STAR) was also observed, but this was not significantly associated with STAR nor radiotherapy dose. Lastly, radiotherapy could in theory also change lead impedances, either by direct damage of the lead (although leads are thought to be radiation resistant) [32] or by changes in the conduction properties of the tissue. There is one report of a patient with rising shock lead impedance after radiotherapy, but whether this increase is caused by actual radiation-induced damage to the leads or by alterations in (local) tissue is undecided [33]. A decrease in lead impedances after radiotherapy, indicative of insulation defects within the lead, has not been reported in literature. Interestingly, although our findings appear inconsistent (decrease in RV and RA lead impedance, but increase in shock lead impedance), we did observe a significant association between time and radiotherapy indicating that a mild decrease in RV and RA lead impedance may occur over time and radiotherapy dose. It remains unknown how STAR could induce such alterations in lead impedances and we feel this finding should be explored in larger cohorts with longer follow-up duration (e.g. within the STOPSTORM consortium).

As we observed no relevant alterations in lead functioning after STAR, it could be that higher radiotherapy doses in proximity to the lead tips are required to induce clinically relevant alterations in ICD functioning, or that effects may develop over a longer follow-up period. It should be noted that the mortality of patients with therapy-refractory VT receiving STAR within these first 12-months is high, ranging from 20-50% in studies [4–6,34–39].

Clinical implications

Based on the current study results, with a median generator dose of 0.1 Gy (range: 0–2.8) and median lead-tip dose of 3.6 Gy (range: 0.04–32), STAR did not result in clinically relevant alterations in ICD functioning. For the ICD generator we suggest following the current available constraints [9,32]. For the ICD lead tips, we propose not to use a dose constraint. Presence of an electrophysiologist and/or ICD technician during STAR should be discussed based on VT burden and risk of recurrence during treatment. The observed results are reassuring also for the use of single fraction high-dose radiation for the treatment of malignancies in proximity to the heart (e.g. lung cancer).

Furthermore, for this study ICD lead tip delineation instructions were designed that allow for future reproducible comparisons of ICD lead-tip dose between centers, previously such delineation instructions were not available. They were designed as pragmatic and user-friendly approach, prioritizing reproducibility in dose estimation over accuracy and precision and should be seen as a starting point. Potential future improvements may include evaluation of the lead tips in all scan phases of the 4D-CT scan instead of using the average.

Conclusion

In this multi-center multi-platform study, the effects of radiotherapy in the context of STAR treatment on ICD functioning was evaluated in the largest STAR study cohort to date. STAR treatment did not result in major ICD malfunction. Only one radiotherapy-related adverse ICD event occurred during the study follow-up and no clinically relevant alterations in ICD parameters including the sensing, capture and impedance were observed after STAR in any of the leads. STAR appears to be safe with regards to ICD function when appropriate measures are taken.

Funding

van der Ree has been supported by the Foundation “De Drie Lichten” in The Netherlands. Dutch Heart Foundation grant 03-003-2021-T061 to dr. Postema. The study participants partly received funding from the EU-Horizon-2020 STOPSTORM consortium project (Grant Agreement Number 945119) for STAR related projects, but this study was not directly funded by the EU-Horizon-2020 grant.

CRediT authorship contribution statement

Martijn H. van der Ree: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration, Funding acquisition. **Wiert F. Hoeksema:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Project administration. **Adrian Luca:** Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Jorrit Visser:** Conceptualization, Writing – original draft. **Brian V. Balgobind:** Conceptualization, Writing – original draft. **Michiel Zumbrink:** Conceptualization, Writing – review & editing. **Raymond Spier:** Conceptualization, Writing – review & editing. **Claudia Herrera-Siklody:** Investigation, Data curation, Writing – review & editing. **Justin Lee:** Investigation, Writing – review & editing. **Matthew Bates:** Investigation, Writing – review & editing. **Jim Daniel:** Investigation, Writing – review & editing. **Clive Peedell:** Investigation, Writing – review & editing. **Judit Boda-Heggemann:** Investigation, Writing – review & editing. **Boris Rudic:** Investigation, Writing – review & editing. **Roland Merten:** Investigation, Writing – review & editing. **Edith M. Dieleman:** Investigation, Writing – review & editing. **Cristopher A. Rinaldi:** Investigation, Writing – review & editing. **Shahreen Ahmad:** Investigation, Writing – review & editing. **John Whitaker:** Investigation, Writing – review & editing. **Pranav Bhagirath:** Investigation, Writing – review & editing. **Matthew Q. Hatton:** Investigation, Writing – review & editing. **Stephen Riley:** Investigation, Writing – review & editing. **Melanie Grehn:** Investigation, Writing – review & editing. **Luis Schiappacasse:** Conceptualization, Writing – original draft, Visualization. **Oliver Blanck:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – original draft, Visualization. **Stephan Hohmann:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Etienne Pruvot:** Conceptualization, Methodology, Formal analysis, Resources, Writing – original draft, Visualization, Supervision. **Pieter G. Postema:** Conceptualization, Methodology, Formal analysis, Resources, Writing – original draft, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [SH reports speaker honoraria from Medtronic (outside the reported work). JBH reports consulting fees from EBAMEd SA (outside the reported work) and a research grant from Elekta (outside the reported work). JL declares a consultancy agreement with Varian Medical Systems (outside the reported work).].

Acknowledgements

We would like to acknowledge Denis Graf (Cardiologist, HFR Fribourg), Chan-Il Park (Cardiologist, Hospital de la Tour) for their

contribution to this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109910.

References

[1] Viles-Gonzalez JF, Arora S, Deshmukh A, Atti V, Agnihotri K, Patel N, et al. Outcomes of patients admitted with ventricular arrhythmias and sudden cardiac death in the United States. Heart Rhythm 2019;16:358–66.

[2] Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022.

[3] van der Ree MH, Blanck O, Limpens J, Lee CH, Balgobind BV, Dieleman EMT, et al. Cardiac radioablation—A systematic review. Heart Rhythm 2020;17:1381–92.

[4] van der Ree MH, Dieleman EMT, Visser J, Planken RN, Boekholdt SM, de Bruin-Bon RHA, et al. Non-invasive stereotactic arrhythmia radiotherapy for ventricular tachycardia: results of the prospective STARNL-1 trial. Europace 2023.

[5] Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, et al. Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia. N Engl J Med 2017;377:2325–36.

[6] Robinson CG, Samson PP, Moore KMS, Hugo GD, Knutson N, Mutic S, et al. Phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation for ventricular tachycardia. Circulation 2019;139:313–21.

[7] Herrera Siklody C, Jumeau R, Reichlin T, Saguner AM, Andratschke N, Elicin O, et al. Recurrences of ventricular tachycardia after stereotactic arrhythmia radioablation arise outside the treated volume: analysis of the Swiss Cohort. Circulation: Arrhythmia Electrophysiol 2023.

[8] Neuwirth R, Cvek J, Knybel L, Jiravsky O, Molenda L, Kodaj M, et al. Stereotactic radiosurgery for ablation of ventricular tachycardia. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2019;21:1088–95.

[9] Indik JH, Gimbel JR, Abe H, Alkmim-Teixeira R, Birgersdotter-Green U, Clarke GD, et al. 2017 HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices. Heart Rhythm 2017;14:e97–153.

[10] Zaremba T, Jakobsen AR, Søgaard M, Thøgersen AM, Riahi S. Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators: a literature review. Europace 2016;18:479–91.

[11] Zhang DM, Navara R, Yin T, Szymanski J, Goldsztejn U, Kenkel C, et al. Cardiac radiotherapy induces electrical conduction reprogramming in the absence of transmural fibrosis. Nat Commun 2021;12:5558.

[12] van der Ree MH, Dieleman EMT, Visser J, Adam JA, de Bruin-Bon RHA, de Jong R, et al. Direct clinical effects of cardiac radioablation in the treatment of a patient with therapy-refractory ventricular tachycardia storm. Adv Radiat Oncol 2022;7:100992.

[13] Hohmann S, Deisher AJ, Suzuki A, Konishi H, Rettmann ME, Merrell KW, et al. Left ventricular function after noninvasive cardiac ablation using proton beam therapy in a porcine model. Heart Rhythm 2019;16:1710–9.

[14] Safavi-Naeini P, Saeed M. Pacemaker troubleshooting: common clinical scenarios. Tex Heart Inst J 2016;43:415–8.

[15] Hayes DL, Vlietstra RE. Pacemaker malfunction. Ann Intern Med 1993;119:828–35.

[16] Sabbagh E, Abdelfattah T, Karim MM, Farah A, Grubb B, Karim S. Causes of failure to capture in pacemakers and implantable cardioverter-defibrillators. J Innov Card Rhythm Manag 2020;11:4013–7.

[17] Zaremba T, Jakobsen AR, Søgaard M, Thøgersen AM, Johansen MB, Madsen LB, et al. Risk of device malfunction in cancer patients with implantable cardiac device undergoing radiotherapy: a population-based cohort study. Pacing Clin Electrophysiol 2015;38:343–56.

[18] Zei PC, Wong D, Gardner E, Fogarty T, Maguire P. Safety and efficacy of stereotactic radioablation targeting pulmonary vein tissues in an experimental model. Heart Rhythm 2018;15:1420–7.

[19] Whitaker J, Zei PC, Ahmad S, Niederer S, O'Neill M, Rinaldi CA. The effect of ionizing radiation through cardiac stereotactic body radiation therapy on myocardial tissue for refractory ventricular arrhythmias: a review. Front Cardiovasc Med 2022;9:989886.

[20] Castor EDC. Castor Electronic Data Capture. https://castoredc.com (August 28, 2019 last accessed).

[21] Grehn M, Mandija S, Miszczyk M, Krug D, Tomasik B, Stickney KE, et al. STereotactic Arrhythmia Radioablation (STAR): the standardized treatment and outcome platform for stereotactic therapy of re-entrant tachycardia by a Multidisciplinary consortium (STOPSTORM.eu) and review of current patterns of STAR practice in Europe. Europace 2023.

[22] Krug D, Blanck O, Andratschke N, Guckenberger M, Jumeau R, Mehrhof F, et al. Recommendations regarding cardiac stereotactic body radiotherapy for treatment refractory ventricular tachycardia. Heart Rhythm 2021;18:2137–45.

[23] Lydiard PS, Blanck O, Hugo G, O'Brien R, Keall P. A review of Cardiac Radioablation (CR) for arrhythmias: procedures, technology, and future opportunities. Int J Radiat Oncol Biol Phys 2021;109:783–800.

[24] Hohmann S, Hillmann HAK, Müller-Leisse J, Eiringhaus J, Zormpas C, Merten R, et al. Stereotactic radioablation for ventricular tachycardia. Herzschrittmachertherapie Elektrophysiol 2022;33:49–54.

[25] Cuculich P, Cooper DH, Anderson C, Robinson C. Myocardial function after noninvasive VT ablation with stereotactic body radiotherapy. Heart Rhythm 2017;14:S480–1.

[26] Miften M, Mihailidis D, Kry SF, Reft C, Esquivel C, Farr J, et al. Management of radiotherapy patients with implanted cardiac pacemakers and defibrillators: a report of the AAPM TG-203(†). Med Phys 2019;46:e757–88.

[27] Brambatti M, Mathew R, Strang B, Dean J, Goyal A, Hayward JE, et al. Management of patients with implantable cardioverter-defibrillators and pacemakers who require radiation therapy. Heart Rhythm 2015;12:2148–54.

[28] Grant JD, Jensen GL, Tang C, Pollard JM, Kry SF, Krishnan S, et al. Radiotherapy-Induced malfunction in contemporary cardiovascular implantable electronic devices: clinical incidence and predictors. JAMA Oncol 2015;1:624–32.

[29] Gauter-Fleckenstein B, Tülümen E, Rudic B, Borggrefe M, Polednik M, Fleckenstein J. Local dose rate effects in implantable cardioverter-defibrillators with flattening filter free and flattened photon radiation. Strahlenther Onkol 2022;198:566–72.

[30] Cha MJ, Seo JW, Kim HJ, Kim MK, Yoon HS, Jo SW, et al. Early changes in rat heart after high-dose irradiation: implications for antiarrhythmic effects of cardiac radioablation. J Am Heart Assoc 2021;10:e019072.

[31] Hohmann S, Deisher AJ, Konishi H, Rettmann ME, Suzuki A, Merrell KW, et al. Catheter-free ablation of infarct scar through proton beam therapy: tissue effects in a porcine model. Heart Rhythm 2020;17:2190–9.

[32] Hurkmans CW, Knegjens JL, Oei BS, Maas AJ, Uiterwaal GJ, van der Borden AJ, et al. Management of radiation oncology patients with a pacemaker or ICD: a new comprehensive practical guideline in The NetherlandsDutch Society of Radiotherapy and Oncology (NVRO). Radiat Oncol 2012;7:198.

[33] John J, Kaye GC. Shock coil failure secondary to external irradiation in a patient with implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2004;27:690–1.

[34] Carbucicchio C, Andreini D, Piperno G, Catto V, Conte E, Cattani F, et al. Stereotactic radioablation for the treatment of ventricular tachycardia: preliminary data and insights from the STRA-MI-VT phase Ib/II study. J Interv Card Electrophysiol 2021;62:427–39.

[35] Gianni C, Rivera D, Burkhardt JD, Pollard B, Gardner E, Maguire P, et al. Stereotactic arrhythmia radioablation for refractory scar-related ventricular tachycardia. Heart Rhythm 2020;17:1241–8.

[36] Ho G, Atwood TF, Bruggeman AR, Moore KL, McVeigh E, Villongco CT, et al. Computational ECG mapping and respiratory gating to optimize stereotactic ablative radiotherapy workflow for refractory ventricular tachycardia. Heart Rhythm 2021;O2:511–20.

[37] Lloyd MS, Wight J, Schneider F, Hoskins M, Attia T, Escott C, et al. Clinical experience of stereotactic body radiation for refractory ventricular tachycardia in advanced heart failure patients. Heart Rhythm 2020;17:415–22.

[38] Qian PC, Quadros K, Aguilar M, Wei C, Boeck M, Bredfeldt J, et al. Substrate modification using stereotactic radioablation to treat refractory ventricular tachycardia in patients with ischemic cardiomyopathy. JACC Clin Electrophysiol 2022;8:49–58.

[39] Lee J, Bates M, Shepherd E, Riley S, Henshaw M, Metherall P, et al. Cardiac stereotactic ablative radiotherapy for control of refractory ventricular tachycardia: initial UK multicentre experience. Open Heart 2021:8.