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Original Article

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

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ABSTRACT

Background and purpose: Several studies have suggested stereotactic arrhythmia radioablation (STAR) as a treatment option for patients suffering from therapy-refractory ventricular tachycardia or fibrillation (VT/VF).

Material and methods: We performed a systematic review of human reports of STAR for structural VT/VF to assess its effectivity and safety. All identified publications were assessed for inclusion. This study adheres to the PRISMA guidelines and was registered on PROSPERO (CRD42020183044).

Results: Thirteen studies were included resulting in a population of 57 patients. Median age was 64 (range 34–83), 31 patients (54%) had ischemic cardiomyopathy and 50 patients (88%) had prior catheter ablation (CA) for VT/VF. A mean planned target volume of 64.4 cc (range 3.5–238) with a mean safety margin of 3.3 mm (0–5) was treated with 25 Gy. Immediately following STAR, four patients (7%) experienced an electrical storm. During a mean follow-up duration of 410 days, all patients suffering from sustained VT/VF prior to STAR (n = 55) had a reduction of their sustained VT/VF-burden after STAR, but recurrence occurred in 41 patients (75%) during follow-up. Forty-six patients (81%) had an adverse effect from therapy, but no treatment-related death occurred. Evidence of scar-formation after STAR either by imaging, invasive mapping or histopathology was found in six of nine examined patients (67%).

Conclusion: From the still very limited experience, STAR appears effective and safe in patients with structural heart disease and therapy-refractory sustained VT/VF. It is associated with a significant short-term reduction of sustained VT/VF-burden, but recurrences are common.

Myocardial scar in patients with structural heart disease can lead to ventricular tachycardia (VT) or fibrillation (VF). Current guidelines recommend catheter ablation (CA) for patients with ischemic (ICM) and non-ischemic cardiomyopathy (NICM) suffering from sustained VT/VF episodes or electrical storm (ES) despite optimal medical treatment [1,2]. However, ablation of structural ventricular arrhythmias can be challenging, even if extensive ablation strategies such as scar homogenization are employed [3,4]. Intramural or epicardial lesions, which are the hallmark of NICM, but also anatomically difficult to access locations such as the ventricular septum, papillary muscles or LV summit can be particularly difficult to reach through CA [5].

Stereotactic arrhythmia radioablation (STAR) is a novel non-invasive therapy aiming to reduce arrhythmia burden in patients in whom conventional treatment including CA has failed or is contraindicated to control VT/VF. STAR is an adaptation of stereotactic ablative radiotherapy commonly used in radiation oncology for the treatment of e.g. early stage non-small-cell lung cancer or oligometastatic diseases. In swine, treatment of the myocardium with this form of radiation leads to fibrosis or its precursors [6]. The first human case series of five patients was published in 2017, which showed a marked reduction in sustained VT-burden after therapy [7]. Since then, several case reports and smaller case series have been published, but relevant questions with regard to substrate identification and subsequent delineation on planning computed tomography (CT), optimal dose and long-term outcome including toxicity still remain open.

Therefore, we aimed to investigate the effectivity and safety of STAR for structural sustained VT/VF with a particular emphasis on patient and treatment related factors to derive recommendations for future research.

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Material and methods

The protocol for this study was registered in the international prospective register for systematic reviews (PROSPERO) on April 29 2020 before search execution (CRD42020183044). This manuscript has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for reporting (PRISMA) [8] and in accordance with the principles outlined in the Cochrane Handbook for Systematic Review of Interventions [9].

Literature search

We performed a comprehensive search in several databases from start of the database to May 5 2020: MEDLINE (Ovid), Embase, ISI Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, searches were conducted on clinicaltrials.gov, the EU Clinical Trials register and the WHO International Clinical Trials Registry Platform (ICTRP). The search strategy was created with the assistance of a clinical librarian and consisted of keywords related to STAR and VT/VF (supplementary data section 1).

Two reviewers independently screened titles and abstracts for inclusion criteria and then examined the full text of potentially suitable publications to finalize eligibility. All original studies of all designs reporting on STAR to treat structural VT/VF reporting on outcome and safety data including VT/VF-burden and -recurrence were included. Additional studies were retrieved by checking the bibliography of included studies and relevant reviews. In a consensus among all co-authors the decision was made to include case reports in order to report on any occurrence of adverse effects as well as additional relevant methodological aspects of STAR [9,10]. Reviews, editorials, abstracts of unpublished studies and oral communications were excluded. Disagreement in selection of studies was resolved by consensus or arbitration by a third author. Unpublished but registered clinical trials were reviewed for discussion to account for publication bias. Prior to submission of this manuscript, a last search was performed to assess for any novel publications.

Data extraction and outcome definition

Two investigators independently collected information on the design, number of patients, baseline characteristics and all outcome data. Extracted data was categorized as prior to STAR, planning and execution of STAR and outcome following STAR (including safety) (supplementary data section 2).

The primary effectiveness outcome was defined as *any reduction in sustained VT/VF-burden* and was provided by all included studies. The secondary effectiveness endpoint *time to sustained VT/VF-recurrence* and was reported by all but one study. Early sustained VT/VF-recurrence was defined up to ≤6 months of follow-up, late recurrence after >6 months of follow-up.

Safety was assessed by collecting data on reported *short-, mid- and long-term adverse events (defined as <3 months, 3–12 months and >12 months*, respectively) as commonly done in investigations of radio-oncologic treatments and coded according to the Common Terminology Criteria for Adverse Effects (CTCAE) 4.0 [11].

When the predefined endpoint was not reported in a study, the equivalent reported endpoint was used.

Internal validity and quality assessment

Two reviewers independently adjudicated study quality and carried out the risk-of-bias assessment of eligible publications using the ROBINS-I tool for non-randomized clinical trials [12]. Case reports and case series were evaluated using a modified form of the Newcastle Ottawa Scale for the assessment developed specifically for case reports [13] (supplementary data section 3).

One inherent bias for all included studies was the use of patients as their own reference after the intervention, which although is a frequently encountered method in VT-ablation studies, has its challenges as changes in ICD programming, drug therapy and the natural history of the disease can influence results [1]. These confounders were assessed and taken into account in each included study.

Data analysis, synthesis and statistics

Due to the heterogeneity of studies and endpoints, the reported data was not suitable for a meta-analysis. Further, the majority of the studies did not report a p value for the primary outcome. Therefore, we chose vote-counting based on the direction of effect to assess the primary endpoint [9,14,15]. Any reduction of sustained VT/-VF-burden was counted as a benefit, and no reduction or increase in sustained VT/VF-burden was counted as no benefit. Safety was qualitatively assessed and reported.

Categorical variables are reported as numbers (%), continuous variables as means, medians and range, as appropriate. The included studies were grouped according to the study population (case reports (n = 1), case series ($n \geq 2$) or prospective clinical trials), their methodological quality, and relevant clinical parameters.

Results

Eight case reports [16–23], three retrospective case series [7,24,25] and two prospective non-randomized clinical trials [26,27] were ultimately included in our systematic review (Fig. 1, supplementary data section 3–5). The quality of included studies is shown in the supplementary data section 3.

The total number of patients included was 57, with individual study populations ranging from 1-19. Baseline characteristics of the patient population is shown in Table 1. The LVEF ranged from 15 to 55% (reported in n = 24, 42% [7,17–24,27]). NYHA classes were I, II, III and IV in 2 (4%), 14 (25%), 15 (26%) and 8 (14%) patients, respectively (reported in n = 39, 68%) [7,24,26,27]. Guideline directed heart failure medication was reported in 25 patients (44%) [7,23,26]. Twelve patients (21%) received cardiac resynchronisation therapy (CRT) [17,19,26,27]. An LVAD was present in five patients (9%) [20,21,25].

Fifty-five out of 57 (96%) suffered from sustained VT or VF, and 54 (95%) had an ICD implanted. The number of previous CA ranged from 0-4. Fifty patients (88%) had ≥1 endocardial ablation, 14 patients (25%) had at least one epicardial ablation (catheter or surgical ablation). Seven patients (12%) had no prior CA due to contraindications [7,18,26] and one due to unfavourable scar-location [17]. The number of AAD at baseline ranged from one to three (reported in 11/13 publications [7,16,27,17–21,23,25,26]), with amiodarone-use reported in 40 patients (70%) and a sodium-channel blocker in 28 patients (49%).

The origin of arrhythmia and the target for STAR is shown in Table 1. The target was defined using invasive electrophysiological study (EPS) in 33 patients (58%), non-invasive mapping (NIPS) in 23 patients (40%) and 12-lead ECG in one patient (2%) (supplementary data section 5). From the available electrophysiologic studies, the critical isthmus was targeted in 11 patients (20%), the VT exit zone alone in 3 patients (5%), the whole scar area in 33 patients (60%) and the total scar area plus the exit zone in 8 patients (15%).

As part of the target definition for radioablation, all patients underwent a computed tomography (CT). Transfer of the defined target into the planning software was performed with a designated

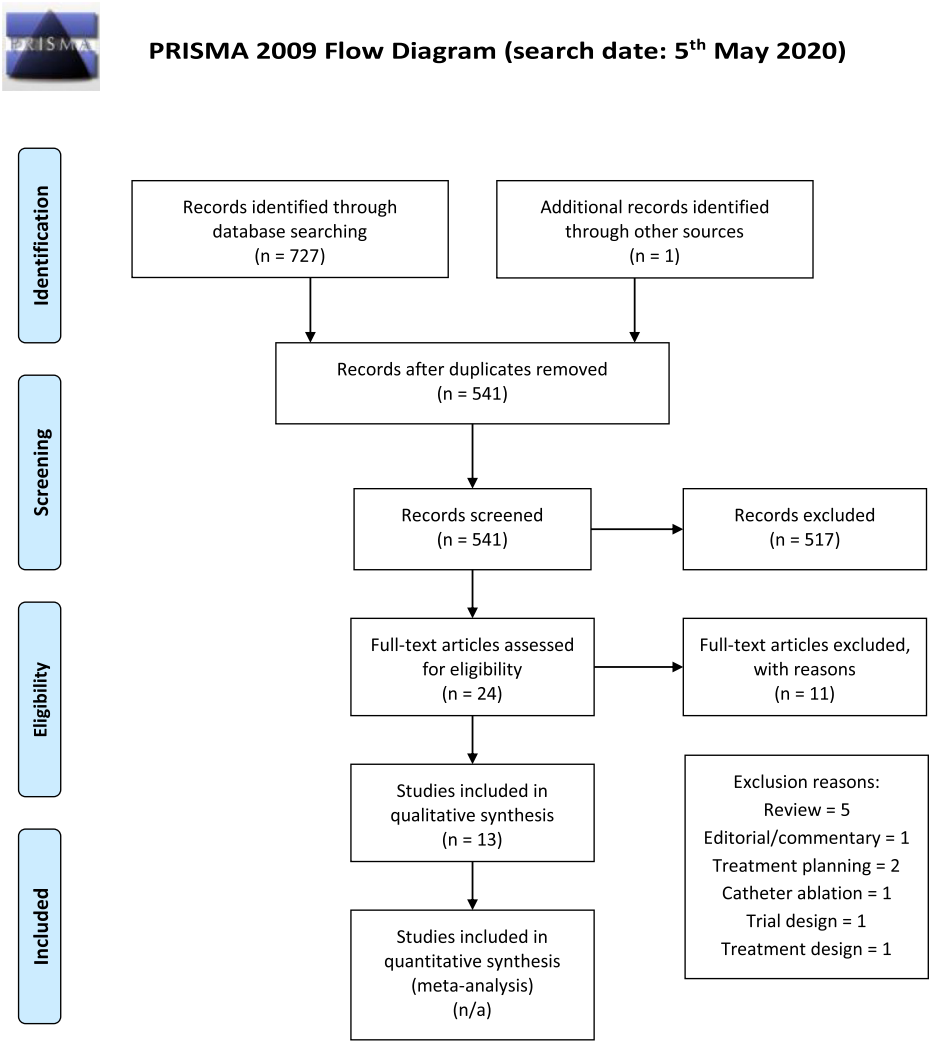

Fig. 1. PRISMA 2009 Flow Diagram (search date 5th of May 2020).

software for cardiac STAR in one case report and one clinical trial (n = 6, 11%) specifically investigating the use of this software [18,27]. In all other cases manual transfer was used. The various cardiac structures were delineated in the Treatment Planning System following interdisciplinary discussions between the involved specialists.

Fifty-six patients were treated with a radiation dose of 25 Gy and one patient was treated with 24 Gy (Tables 1 and 2) [21]. Of note, of all patients treated with Cyberknife (n = 18, 31%) [18,19,22,24,27], five patients from one publication had a PTV generated with the use of a safety margin accounting for the target motion relative to the cardiac cycle [27]. PTV size was reported in 11 of the 13 publications and ranged from 3.5 to 238 cc. Reported prescription isodose lines (n = 34, 79%) [17–21,23–25,27] ranged from 66 to 95%.

The median follow-up duration across the studies was 365 days (range 21–1620; Table 1). The primary outcome assessment included reduction in sustained VT/VF burden defined as a combination of sustained VT episodes, VT seconds and/or appropriate ICD therapies in the individual studies (supplementary data section 6), since this endpoint was assessed in all available publications to allow for comparison between the studies.

All of the included publications reported a reduction of sustained VT/VF-burden after STAR (n = 55, 96% after excluding two patients with PVC [26]), which results in a 0.93 effectivity probability applying Bayes estimate on the 100% positive outcome results. These patients were either complete (no more sustained VT/VF-recurrence during follow-up) or partial responders (reduction of sustained VT/VF-burden after STAR, but recurrence of at least one sustained VT/VF episode during follow-up) after STAR. When assessing individual patient level outcome (n = 38, 67%) [7,16,25,27,17–24], failure to achieve any sustained VT/VF-burden reduction was only reported in one patient (2%), who then received repeat STAR and subsequently underwent heart transplantation [25]. Forty-one patients (75%) [7,16,27,17,18,21–26] experienced at least one recurrent sustained VT/VF episode during follow-up. Early recurrence was reported in 29 patients (53%) [7,16–18,21–23,26,27] and late recurrence in five patients (9%) [7,24]. One publication did not report time to sustained VT/VF-recurrence, where seven patients had recurrences. The recurrence rate < and ≥6 months after STAR is shown in Table 3 [25].

Sustained VT/VF-recurrence was not reported for six patients for varying reasons: one patient passed away from an accident at day 17, and one patient died of sepsis 57 days after STAR, respectively [17,26], two patients were lost to follow-up five days after STAR due to "deceleration of care" [25], one had repeat CA 28 days after intervention [7], and one had repeat STAR 90 days after intervention [25]. Recurrence rate during the entire follow-up period rose to 84% (41/49), when these patients were excluded.

Table 1
Summary of included patient population.

All studies*			Value	Range over studies	Number of eligible studies (n = 13)
Year published		Median	2019	2015–2020	13
Age at radioablation		Median	64	34–83	13
		Mean	64		
Gender					
	Male	n (%)	48 (84)		13
	Female	n (%)	9 (16)		
Heart disease					
	Ischemic	n (%)	31 (54)		13
	Non-ischemic	n (%)	26 (46)		
LVEF (%)					
		Mean	27	15–55	9[1–9]
		Median	28		
VT origin[&]					
	LV	N	56		13
	RV	N	4		
	Septum	N	13		
Treatment target[&]					
	VT scar	N	43		13
	VT isthmus	N	11		
	VT exit zone	N	11		
Rx-Type					
	Cyberknife	n (%)	18 (31)		13
	CBCT Linac	n (%)	39 (67)		
	MRI-based Linac	n (%)	1 (2)		
Safety margin (mm)					
		Mean	3.3	0–5	10[2–7,9–12]
		Median	5		
PTV (cc)					
		Mean	64.4	3.5–238	10[1,2,4–7,9,11–13]
		Median	46.5		
Isodose (%)					
		Mean	84.8	66–95	9[1–4,6–9,12]
		Median	82		
Follow-up (days)					
		Mean	410	21–1620	10[$][1–6,8,9,11,12]
		Median	365		

Abbreviations: CBCT, cone beam computed tomography; Linac, linear accelerator; LVEF, left ventricular ejection fraction; PTV, planned target volume; PVC, premature ventricular contractions; Rx-Type, linear accelerator type; VT, ventricular tachycardia.
*Including two patients with PVC. & More than one VT origin or target per patient possible resulting in sum > 57. $ Excluding two patients from Lloyd et al. [13] with "deceleration of care" five days after radiotherapy.

Postinterventional use of AAD was reported in 46 patients (81%) [7,16–18,21,23,24,26,27] with a reduction in antiarrhythmic therapy in 17 patients (30%) [7,16,20,21,23,24,27] at the end of follow-up.

Immediately following radiotherapy, an electrical storm was reported in 4 patients (7%) [16,21,23] (Table 3). The presence of further cases cannot be excluded due to the frequent use of a blanking period between six and twelve weeks post STAR (n = 35, 61%) [7,18,24,26]. Arrhythmic events arising during the blanking period were not included in the primary outcome in the reported studies.

Adverse events related to radiotherapy were reported in six publications (n = 46, 81%) [7,16,17,24–26]. Two studies reported the use of a systematic data collection on intervention-related adverse effects using the CTCA 4.0 system (n = 29, 51%) [24,26]. The most frequently reported adverse effects categorized as at least "severe" (requiring hospitalization) were heart failure exacerbations, nausea and vomiting (Table 4). Low-grade adverse effects were specifically reported in one clinical trial (n = 19, 33%) [26] (supplementary data section 7). Follow-up LVEF was reported for 25 patients (44%) [7,17,18,20,22–24,27]; two patients (4%) had transient reduction of LVEF [27], otherwise no reduction in LVEF was reported. No adverse events related to ICD malfunction after radiotherapy were reported.

A total of 15 patients died during follow-up resulting in an overall mortality of 26%. Nine patients (16%) died of cardiovascular causes [7,18,24,26,27] and five of non-cardiac causes (10%) [7,17,24,26] (Table 3). Time to death ranged from 21 to 1620 days (~4.5 years) after the intervention [25].

Histopathological examination of irradiated myocardial tissue was available in 5 patients (9%) [7,17,25]. Of these, three patients showed "mild" fibrosis [25], while no evidence of fibrosis was found in the other two [7,17]. Development of fibrosis was additionally assessed either by MRI [20,23], PET [18] or invasive electroanatomical mapping (EAM) [27] in 4 patients (7%). Of these, three reported new scar formation as compared to before STAR.

Discussion

The key findings of this systematic review of the until now limited evidence with STAR are: (1) STAR reduces sustained VT/VF-burden during the first 6 months of follow-up in the vast majority of patients with structural heart disease and therapy-refractory sustained ventricular arrhythmias; (2) recurrence of sustained ventricular arrhythmias is common in this population and mortality reached 26% during the median follow-up period of 1 year; (3) STAR appears to be a safe option for therapy-refractory sustained VT/VF; but (4) acute post-radiation electrical storm can be observed in at least 7% of patients.

Our findings significantly expand on a previously published systematic review of STAR. The prior publication was of narrative nature and included all preclinical studies including ex-vivo and animal studies and investigated the effect of radiation on any type

Table 2
Stereotactic arrhythmia radioablation procedural characteristics.

Publication (*n*)	Radiation dose (Gy)	Prescription isodose (%)	Fiducial marker	Safety margin (mm)	PTV[&] (ml)	GTV (ml)	Treatment duration (min)
Cyberknife*							
Cvek (1)	25	82	CRT CS-lead	0	NR	NR	114
Loo (1)	25	75	Temporary pacing wire	NR	NR	NR	90
Jumeau (1)	25	NR	ICD RV-lead	0	21	21	45
Neuwirth (10)	25	80 (66–84)	ICD RV-lead	0	22.2 (14.2–29.6)	22.2 (14.2–29.6)	65 (48–80)
Gianni (5)	25	77 (74–80)	Transjugular temporary active fixation pacing lead	3	142 (80–184)	NR	82 (66–92)
CBCT based linac							
Bhaskaran (1)	25	NR	n/a	5	52	NR	5
Krug (1)	25	83	n/a	5	42.2	8.1	15
Martí-Almor (1)	25	95	n/a	3	3.5	NR	4
Scholz (1)	24	80	n/a	2	82.4	55.8	10
Cuculich (5)	25	NR	n/a	5	49 (17–81)	NR	14 (11–18)$
Robinson (19)	25	NR	n/a	5	98.9£ (60.9–298.8)	25.4£ (6.4–88.6)	15.3£ (5.4–32.3)#
Lloyd (10)	25	95	n/a	1–5	81.4 (29–238)	NR	<30@
MRI based linac[%]							
Mayinger (1)	25	85	n/a[ç]	2–3	115.1	73.6	46

Abbreviations: CBCT ,cone beam computed tomography; CRT cardiac resynchronisation therapy; CS, coronary sinus; GTV, gross target volume; ITV, internal target volume; PTV, planned target volume; RV, right ventricle. Continuous variables are reported in means (range) unless indicated otherwise.
*Tracking during irradiation was performed in all studies reporting the use of Cyberknife. Otherwise ITV-free-breathing was reported. & When no safety margin was used, PTV = CTV.$ On table treatment time. # beam-on time. @ "total time in radiation oncology suite". Ç respiratory gating. % Respiratory expiration breath-hold gating based irradiation.

Table 3
Patient outcomes in individual publications.

Study	Mean follow-up duration in days (range)	Sustained VT/VF recurrence < 6 months	Sustained VT/VF recurrence ≥ 6 months	Acute VT-storm post-STAR	Cardiovascular death	Noncardiac death
Cuculich	296 (21–365)[£]	3/5 (60)	2/5 (40)	0/5 (0)	1/5 (20)	0/5 (0)
Robinson*	390[&]	11/17 (65)	NR	NR	3/17 (18)	3/17 (18)
Neuwirth	705 (180–1410)	4/10 (40)	3/10 (30)	1/10 (10)	2/10 (20)	1/10 (10)
Lloyd	176 (118–273)[$]	NR	NR	NR	0/8 (0)	0/8 (0)
Gianni	365 (300–420)	5/5 (100)	5/5 (100)	0/5 (0)	2/5 (40)	0/5 (0)
Case report						
Cvek	120	0	0	0	0	0
Jumeau	120	1	0	0	0	0
Bhaskaran	60	1	NA	1	0	0
Krug	57	1	NA	0	0	1
Martí-Almor	120	0	0	0	0	0
Mayinger	90	1	NA	1	0	0
Loo	270	1	0	0	1	0
Scholz	60	1	NA	1	0	0

Abbreviations: NR, not reported; PVC, premature ventricular contraction; STAR, stereotactic arrhythmia radioablation; VT, ventricular tachycardia. Ratios are reported (percentage).
* Two patients treated for PVC were excluded from this table. & median reported. $ Two patients were excluded whose care was decelerated after five days. £ One patient passed away after three weeks follow-up.

of cardiac radiotherapy [28]. Our systematic review only focuses on the effectivity and safety of STAR for the treatment of sustained ventricular arrhythmias in humans with structural heart disease. We provide a comprehensive comparison of the available studies and included a larger number of patients. The critical assessment of effectivity and safety in this context has not been performed in such a systematic fashion to date: (1) We report on rate of treatment failure (recurrence of sustained VT/VF) and median duration of treatment effect and (2) provide a dedicated report on safety including the newly observed *post-radiation electrical storm*.

Reduction of sustained VT/VF burden

In patients with structural heart disease treated with STAR for therapy-refractory sustained VT/VF, a reduction in the number of sustained VT/VF episodes appeared within days to weeks after STAR in 98% of reported patients [7,16,25–27,17–24]. The only patient without any reduction in sustained VT/VF-burden ultimately underwent heart transplantation [25]. Disease stage however did not seem to be associated with treatment failure. In fact, several publications reporting on "rescue treatment" of patients with advanced heart disease and electrical storm reported acute

Table 4
Stereotactic arrhythmia radioablation related serious adverse events reported.

Intervention related adverse events (n = 57)*	Acute (within 48 hours of intervention)	Short-term (2 days to 90 days)*	Medium- term (90 days to 12 months)£2	Long-term (>12 months)#
Cardiovascular	• **1** slow-VT occurring during intervention[1]	• **1** pericarditis[2] • **1** heart failure exacerbation[2] • **2** pulmonary embolisms [3,4] • **1** stroke[&5]	• **1** pericardial effusion • **7** heart failure exacerbations • **4** Chest pain • **1** hypotension • **1** presyncope	• **1** progression of mitral regurgitation[6]
Pulmonary	–	• **2** pneumonitis[1]	• **1** hypoxia • **1** pneumonia • **1** pulmonary edema	–
Gastrointestinal	• **5** nausea and vomiting[$2,4,6]	–	–	–
Other	–	–	• **1** dehydration • **1** shoulder pain	–

Abbreviations: VT, ventricular tachycardia. *Robinson et al and Neuwirth et al used the CTCAE v4.0 reporting system. Grade 3 or higher and at least possible adverse effects were included in this table. Other publications did not use a specific reporting system. & occurred 3 weeks after intervention in a patient with known atrial fibrillation with contraindication for anticoagulation. $ Radiotherapy of inferior wall of the LV in 4/5 cases. £ Time to diagnosis after intervention in selected cases from the ENCORE-VT study population possibly after 12 months due to the median follow-up of 390 days and lack of specification of the time of adverse event occurrence beyond before or after 90 days post-intervention. # Median follow-up length for included publications 365 days (range 18–1410; excluding 2 patients with hospice care within 5 days of intervention from Lloyd et al).

reductions in VT/VF-burden [21,22,29]. Furthermore, since mean LVEF was 27%, and 88% of patients had at least one prior CA, this indicates a difficult to treat population.

Although an impressive early effect of STAR could be demonstrated, its underlying mechanisms are unclear. Radiation-induced fibrosis has been shown to lead to functional changes in myocardial tissue, but this does not explain the high rate of early VT/VF-burden reduction we observed [6]. Formation of fibrosis is expected to occur as a late effect of radiation at the earliest of 3–6 months post-irradiation [30,31], thus development of homogenous scar cannot explain this early efficacy. Alternate explanations are hypothetical and include an acute inflammatory reaction, edema formation, and upregulation of connexin-43 [32].

VT/VF-recurrences during the long-term

Despite the reported acute reduction in sustained VT/VF-burden, our systematic review shows that 75% of treated patients had recurrence of sustained VT/VF [7,16,27,17,18,21–26], in 53% of patients even within 6 months after STAR [7,16–18,21–23,26,27]. The lack of homogenous scar formation possibly explains this high rate of recurrences. By high-dose irradiation transmural homogenisation of myocardial scar tissue should be achieved leading to reduced arrhythmogenic properties of the treated substrate and consequently a reduction in VT/VF-burden [3,4]. While several preclinical animal studies investigated the electrophysiological effects of STAR, the majority of these studies report on the irradiation of pulmonary veins or the atrioventricular junction [28]. Furthermore, only one porcine study included in a previous systematic review investigated the change in conduction within the ventricular myocardium [28,33]. Importantly, only radiation doses above 30 Gy consistently lead to a transmural scar formation in a dose-escalation model in porcine pulmonary veins [34].

All published patients included in our systematic review were treated with lower doses, i.e. with a prescription dose of 25 Gy. Although in most cases an inhomogeneous dose prescription (66–95%) was used, the highest maximum dose achieved was 33.3 Gy. Thus, the currently prescribed doses may potentially be considered insufficient for homogenous transmural scar formation. Development of fibrosis was still found in 67% of patients either by histopathology, imaging or EPS [7,17,18,20,23,25,27]. Of note, differentiation of newly induced fibrosis from pre-existing scar tissue, natural progression of fibrosis due to the underlying condition, or the presence of local edema mimicking fibrosis cannot be made without a designated protocol. Systematic assessment of post-radiation myocardial fibrosis is thus lacking.

Besides radiation dose, treated volumes may play a role in recurrence rates of ventricular arrhythmias. PTV depends on the electrophysiologic target, use of a free-breathing technique and ITV, and the linac used. In our systematic review, recurrences rates were high independent of the linac used. Neuwirth et al and Gianni et al used a Cyberknife based approach with recurrence rates of 70 and 100%, respectively [24,27]. Robinson et al used a CBCT based approach with a 65% recurrence rate [26] (Tables 2 and 3).

Treatment related adverse effects

Severe adverse effects due to STAR were infrequently reported, with the most common cardiac ones being related to heart failure exacerbation and chest pain [26], and most common non-cardiac adverse effects being nausea and vomiting [17,24,26]. Importantly, clinically relevant or symptomatic radiation-induced pericarditis (2%) and pericardial effusion (2%) were infrequent during medium-term follow-up and were managed medically, however during long-term follow-up of the ENCORE-VT more cases emerged [26,35]. Long-term results are only available from conference papers for the study population of ENCORE-VT [35] and the case series from Neuwirth et al. [36]. The most severe complication reported was development of a gastropericardial fistula two years after treatment [35].

Of note, systematic assessment of treatment-related adverse events using the established CTCAE questionnaire was scarce and would likely increase the documented rate of adverse events [11]. Especially when looking at the mild and moderate adverse effects in addition to the more severe adverse effects reported in the ENCORE-VT, the total number of adverse effects increased from 23 to 88 for the total population [26]. Therefore, it is important to emphasize that mild to moderate adverse events associated with STAR are common, and this should be taken into account during the patient selection- and informed consent process.

Post-radiation electrical storm

Another previously under-recognized finding of our systematic review is the occurrence of acute post-radiation ES, which was reported in at least three patients [16,21,23]. This includes patients with a sudden increase in sustained VT/VF episodes acutely following STAR and is important for the post-procedural management

and monitoring of these patients. We postulate an acute inflammatory reaction as the underlying pathomechanism based on the known effects of ionizing radiation and the rapid treatment response to high dose glucocorticoids [23,37]. Currently, it is unknown whether this is a rare condition without further clinical relevance or whether it is underreported, as it occurred within the frequently used blanking period. This hypothesis however remains to be confirmed and future investigations are needed to understand the incidence and impact of such episodes, and the utility of having a blanking period.

Opportunities for future research

Appropriate delineation of the electrophysiologic target and ideal dose prescription remains unclear. While scar homogenization seems to be superior to other techniques for CA of VT [3,4], this has yet to be proven for STAR. Only 25% of patients received selective radiation of the critical VT isthmus or exit [7,17,22,24], which may have an important effect on PTV size and accordingly on efficacy and safety. Furthermore, the method by which target definition is done may be of relevance.

Regardless of the defined target, transfer from EAM to axial planning CT for radiotherapy is a crucial step. A designated transfer software was only used for 11% of patients in one clinical trial and one case report [18,27]. However, despite the use of a transfer software designed for the purpose of STAR by Gianni et al, sustained VT/VF recurrence occurred in all patients, and arrhythmia burden reduction did not approximate other reports indicating that automated target transfer may not be sufficient to overcome the current limitations of STAR [18,27].

A further procedural aspect likely to influence fibrosis development and outcomes is dose distribution in treated myocardium. While dose prescriptions were similar throughout the included studies, a large inhomogeneity with regard to the prescription isodose line and dose distribution existed [38]. This could entail differing biological doses that affect the overall outcome. Future studies investigating the influence of varying dose distributions are necessary.

Strengths and limitations

The strength of this systematic review is the selective assessment of STAR for the treatment of structural ventricular arrhythmias, which currently is its primary indication in cardiac electrophysiology. Furthermore, by the inclusion of case reports the assessed patient population is expanded. The large heterogeneity of included studies rendering a meta-analysis unfeasible is on the other hand a limitation. Heterogenous reporting of individual outcomes in VT-trials has, however, been previously recognized [1,39]. With regard to this, one publication did not report on time to sustained VT/VF recurrence. From a clinical point of view, reduction of overall sustained VT/VF-burden seems to be more important as compared to time to first sustained VT/VF-recurrence. In our study, 96% of patients experienced a reduction of sustained VT/VF-burden, whereas only 25% did not experience any sustained VT/VF-recurrence during follow-up. The latter, however, does not mean that only 25% of patients benefited from STAR. A reduction of sustained VT/VF-burden implies a clinical benefit for 96% of patients, even if 75% had a recurrence of at least one sustained VT/VF episode during follow-up. Moreover, not all arrhythmia episodes have the same impact on patient well-being. E.g., a single episode of anti-tachycardia pacing (ATP) for sustained VT during follow-up means a recurrence, but has less clinical impact as compared to an ICD shock or electrical storm. However, the primary publications did not clearly differentiate between these different endpoints, which impaired a systematic sub-analysis of these endpoints. Finally, overall patient number remains low at present.

Conclusions

STAR appears as an effective and safe treatment option to reduce sustained VT/VF-burden in patients with structural therapy-refractory sustained ventricular arrhythmias. However, experience is still limited and recurrences after STAR are common suggesting that current STAR strategies need further improvement.

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Appendix A. Supplementary data

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References

[1] Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, et al. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. EP Eur 2019;21:1143–4.

[2] Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europe. Eur Heart J 2015;36:2793–867.

[3] Di BL, Burkhardt JD, Lakkireddy D, Carbucicchio C, Mohanty S, Mohanty P, et al. Ablation of stable VTs versus substrate ablation in ischemic cardiomyopathy. J Am Coll Cardiol 2015;66:2872–82.

[4] Tanawuttiwat T, Nazarian S, Calkins H. The role of catheter ablation in the management of ventricular tachycardia. Eur Heart J 2016;37:594–609.

[5] Bhaskaran A, Tung R, Stevenson WG, Kumar S. Catheter ablation of VT in non-ischaemic cardiomyopathies: endocardial, epicardial and intramural approaches. Hear Lung Circ Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) and the Cardiac Society of Australia and New Zealand (CSANZ); 2019;28:84–101.

[6] Rapp F, Simoniello P, Wiedemann J, Bahrami K, Grünebaum V, Ktitareva S, et al. Biological cardiac tissue effects of high-energy heavy ions – investigation for myocardial ablation. Sci Rep 2019;9:5000.

[7] 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.

[8] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[9] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.0.2. The Cochrane collaboration, 2011. http://www.cochrane-handbook.org/.
[10] Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004;329:44–7.
[11] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol 1995;31:1341–6.
[12] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i1919.
[13] Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evidence-Based Med 2018;23:60–3.
[14] Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ 2020;368.
[15] Melendez-Torres GJ, Thomas J, Richardson M, Felix L, Lorenc T, Thomas S, et al. Lessons from comparing narrative synthesis and meta-analysis in a systematic review. Lancet Elsevier Ltd 2015;386:S9.
[16] Bhaskaran A, Downar E, Chauhan VS, Lindsay P, Nair K, Ha A, et al. Electroanatomical mapping-guided stereotactic radiotherapy for right ventricular tachycardia storm. Hear Case Rep 2019;5:590–2.
[17] Krug D, Blanck O, Demming T, Dottermusch M, Koch K, Hirt M, et al. Stereotactic body radiotherapy for ventricular tachycardia (cardiac radiosurgery): first-in-patient treatment in Germany. Strahlentherapie und Onkol 2020;196:23–30.
[18] Loo BW, Soltys SG, Wang L, Lo A, Fahimian BP, Iagaru A, et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. Circ Arrhythmia Electrophysiol 2015;8:748–50.
[19] Cvek J, Neuwirth R, Knybel L, Molenda L, Otahal B, Pindor J, et al. Cardiac radiosurgery for malignant ventricular tachycardia. Cureus 2014;6.
[20] Martí-Almor J, Jiménez-López J, Rodríguez de Dios N, Tizón H, Vallés E, Algara M. Noninvasive ablation of ventricular tachycardia with stereotactic radiotherapy in a patient with arrhythmogenic right ventricular cardiomyopathy. Rev Española Cardiol (English Ed) 2020;73:97–9.
[21] Scholz EP, Seidensaal K, Naumann P, André F, Katus HA, Debus J. Risen from the dead: cardiac stereotactic ablative radiotherapy as last rescue in a patient with refractory ventricular fibrillation storm. Hear Case Rep 2019;5:329–32.
[22] Jumeau R, Ozsahin M, Schwitter J, Vallet V, Duclos F, Zeverino M, et al. Rescue procedure for an electrical storm using robotic non-invasive cardiac radioablation. Radiother Oncol 2018;128:189–91.
[23] Mayinger M, Kovacs B, Tanadini-Lang S, Ehrbar S, Wilke L, Chamberlain M, et al. First magnetic resonance imaging-guided cardiac radioablation of sustained ventricular tachycardia. Radiother Oncol Elsevier B.V. 2020:1–5.
[24] Neuwirth R, Cvek J, Knybel L, Jiravsky O, Molenda L, Kodaj M, et al. Stereotactic radiosurgery for ablation of ventricular tachycardia. EP Eur 2019;21:1088–95.
[25] 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. Hear Rhythm Elsevier Inc.; 2020;17:415–422.
[26] 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.
[27] Gianni C, Rivera D, Burkhardt JD, Pollard B, Gardner E, Maguire P, et al. Stereotactic arrhythmia radioablation for refractory scar-related ventricular tachycardia. Hear Rhythm 2020.
[28] van der Ree MH, Blanck O, Limpens J, Lee CH, Balgobind BV, Dieleman EMT, et al. Cardiac radioablation—A systematic review. Hear Rhythm Heart Rhythm Society 2020;17:1381–92.
[29] Jumeau R, Ozsahin M, Schwitter J, Elicin O, Reichlin T, Roten L, et al. Stereotactic radiotherapy for the management of refractory ventricular tachycardia: promise and future directions. Front Cardiovasc Med 2020;7. https://doi.org/10.3389/fcvm.2020.00108.
[30] Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol 2007;67:10–8.
[31] Marks LB, Yu X, Prosnitz RG, Zhou S-M, Hardenbergh PH, Blazing M, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol 2005;63:214–23.
[32] Amino M, Yoshioka K, Kamada T, Furusawa Y. The potential application of heavy ion beams in the treatment of arrhythmia: the role of radiation-induced modulation of connexin43 and the sympathetic nervous system. Int J Part Ther 2018;5:140–50.
[33] Lehmann HI, Gra C, Simoniello P, Constantinescu A, Takami M, Lugenbiel P, et al. Feasibility study on cardiac arrhythmia ablation using high- energy heavy ion beams. 2016;1–13.
[34] Blanck O, Bode F, Gebhard M, Hunold P, Brandt S, Bruder R, et al. Dose-escalation study for cardiac radiosurgery in a porcine model. Int J Radiat Oncol Elsevier Inc.; 2014;89:590–98.
[35] Phillip Cuculich, Pamela Samson, Kaitlin Moore, Geoff Hugo, Nels Knutson, Sasa Mutic, et al. Longer term results from a phase I/II study of ep-guided noninvasive cardiac radioablation for treatment of ventricular tachycardia (ENCORE-VT). HRS Sci Sess 2020.
[36] Cvek J, Knybel L, Neuwirth R, Jiravsky O, Sramko M, Peichel P, et al. Long-term safety of stereotactic body radiotherapy for ablation of ventricular tachycardia: a multicentric study. Eur Heart J 2019;40:3256.
[37] Graeff C, Bert C. Noninvasive cardiac arrhythmia ablation with particle beams. Med Phys 2018;45:e1024–35.
[38] Report 91. J Int Comm Radiat Units Meas 2014;14:1–160.
[39] Martinez BK, Baker WL, Konopka A, Giannelli D, Coleman CI, Kluger J, et al. Systematic review and meta-analysis of catheter ablation of ventricular tachycardia in ischemic heart disease. Hear Rhythm Elsevier Inc.; 2020;17:e206–e219.