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One-Year Mortality and Causes of Death after Stereotactic Radiation Therapy for Refractory Ventricular Arrhythmias: A Systematic Review and Pooled Analysis

SHORT TITLE: Mortality after Cardiac Stereotactic Radiation Therapy

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ABSTRACT

Patients treated with cardiac stereotactic body radiation therapy (radioablation) for refractory ventricular arrhythmias are patients with advanced structural heart disease and significant comorbidities. However, data regarding 1-year mortality after the procedure are scarce. This systematic review and pooled analysis aimed at determining 1-year mortality after cardiac radioablation for refractory ventricular arrhythmias and investigating leading causes of death in this population.

MEDLINE/EMBASE databases were searched up to January 2023 for studies including patients undergoing cardiac radioablation for the treatment of refractory ventricular arrhythmias. Quality of included trials was assessed using the NIH Tool for Case Series Studies (PROSPERO CRD42022379713).

A total of 1,151 references were retrieved and evaluated for relevance. Data were extracted from 16 studies, with a total of 157 patients undergoing cardiac radioablation for refractory ventricular arrhythmias. Pooled 1-year mortality was 32% (95%CI: 23-41), with almost half of the deaths occurring within three months after treatment. Among the 157 patients, 46 died within the year following cardiac radioablation. Worsening heart failure appeared to be the leading cause of death (52%), although non-cardiac mortality remained substantial (41%) in this population. Age \geq 70yo was associated with a significantly higher 12-month all-cause mortality ($p<0.022$). Neither target volume size nor radiotherapy device appeared to be associated with 1-year mortality ($p=0.465$ and $p=0.199$, respectively).

About one-third of patients undergoing cardiac stereotactic body radiation therapy for refractory ventricular arrhythmias die within the first year after the procedure. Worsening heart failure appears to be the leading cause of death in this population.

Keywords: Arrhythmia; ventricular tachycardia; radiotherapy; radioablation; radiation therapy; mortality; death; heart failure; refractory

ABBREVIATIONS LIST:

CA: Catheter ablation

HF: Heart failure

LVEF: Left ventricular ejection fraction

LVAD: Left ventricular assist device

SBRT: Stereotactic body radiation therapy

VA: Ventricular arrhythmias

VT: Ventricular Tachycardia

INTRODUCTION

In radiation oncology, the historical approach consisting of delivering very low doses of radiation over a large number of sessions has seen the more recent emergence of stereotactic body radiation therapy (SBRT), also known as stereotactic radioablation(1). SBRT is a technique that delivers precise and high doses of radiation to highly defined targets in the body within a limited number of sessions, minimizing exposure to adjacent normal tissue.(2) Developed in the in the 1950s using the Leksell Gamma Knife system (Elekta AB; Stockholm, Sweden), SBRT is now widely used as a standard of care in the treatment of various solid cancers, including prostate, lung, hepatocellular, breast, and metastatic cancers (1,2). Outside of the field of malignant pathologies, SBRT is also used in the treatment of non-tumoral diseases such as arteriovenous malformation, epilepsy or trigeminal neuralgia (3). Recently, cardiac SBRT has emerged as a promising non-invasive alternative for patients with ventricular arrhythmias (VAs) resistant to medication and conventional catheter ablation (CA) approaches(4–6).

After the initial case reports in human in 2014 and 2015, the ENCORE-V and ENCORE-VT trials demonstrated the short-term safety and efficacy of the technique for reducing VA recurrences (more than 90% of patients experiencing significant VA burden reduction (>75%), with a remarkable 99.9% reduction in ICD events from baseline in the whole cohort) (6,7). Although some teams subsequently reported less marked improvements, cardiac SBRT has emerged as a promising ablative therapy with a growing number of case series reporting the effectiveness of the technique in reducing the burden or eliminating VAs refractory to conventional therapies(5,8–10).

While data regarding clinical outcomes associated with the technique are increasing, data regarding the precise effect of cardiac SBRT on cardiac remodeling and the mechanisms supporting its antiarrhythmic effects are scarce. Effect of SBRT on tissue is complex and progressive, combining vascular and immune remodeling, delayed apoptosis and fibrosis creation(10,11). Recently, Zhang et al also reported a possible role of conduction velocities improvement through cellular reprogramming as a contributor to the antiarrhythmic effect of cardiac SBRT(12).

On the other hand, VAs are well known to be associated with increased mortality in patients with structural heart disease (SHD)(13). Patients with VAs in the context of SHD usually have complex underlying substrates, concomitant heart failure (HF), and a high

burden of associated comorbidities; all these factors contribute to significant morbidity and mortality in this population(14,15). Patients treated with cardiac SBRT are among the most vulnerable patients, with refractory VA in therapeutic impasse, late-stage HF and severe comorbidities sometimes precluding invasive ablation procedures.

While the one-year mortality after CA for ventricular tachycardia (VT) in patients with SHD is well described, data regarding the one-year mortality after cardiac SBRT for refractory VAs are scarce(16,17). Better understanding of mortality rates and causes of death after cardiac SBRT is critical for clinical decision-making in this tenuous patient population.

The purpose of this systematic review and pooled analysis was to estimate the 1-year mortality after cardiac SBRT for refractory VAs and to investigate the leading causes of death in this specific population.

METHODS

Data Sources and Search

Literature search was performed in PubMed/MEDLINE and EMBASE databases until February 15, 2023, to identify all relevant studies describing patient outcomes after a procedure of cardiac SBRT for the treatment of refractory VAs. Independent searches were performed by two investigators (K.B. and R.M.) using the following Medical Subjects Headings: “tachycardia”, “arrhythmia”, “electrical storm”, “ventricular”, “radioablation”, “radiotherapy”, “stereotactic”, “radiation therapy” and “cardiac radioablation”. This was supplemented by hand-searching bibliographies of retrieved articles as well as relevant review articles (PROSPERO CRD42022379713). Cochrane Collaboration guidelines were followed, and our results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (*Supplemental Data*).

Study Selection

Titles and abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two investigators (K.B. and R.M.) to identify studies that potentially meet the inclusion criteria: (1) studies including patients undergoing a cardiac SBRT procedure for refractory VAs; (2) with at least ≥ 3 patients treated (to exclude case reports and reduce heterogeneity in relation to the novelty of the technique) and (3) reporting mortality after the SBRT procedure. Editorials, reviews, and expert opinions

were not included in the analysis.

Non-English language studies, animal studies and studies including cardiac SBRT for the treatment of atrial arrhythmias were excluded. The full text of the potentially eligible studies was retrieved and independently assessed for eligibility by the two investigators (K.B. and R.M.). Any disagreement between the two reviewers over the eligibility of particular studies were resolved through discussion with a third investigator (A.D.C.).

Data collection and Quality assessment

A structured data collection form was used for the extraction of the baseline characteristics of the study populations and outcomes of interest. Two investigators (K.B. and R.M.) independently extracted data from studies meeting inclusion criteria, and any disagreements were resolved by a third investigator (A.D.C.).

Clinical data were collected including: Age, gender, type of cardiomyopathy and left ventricular ejection fraction (LVEF). SBRT procedural data were also collected, including: the type of radiotherapy device used for SBRT (Cyberknife system or Linear accelerator), the radiation dose prescribed and the planning target volume. This “planning target volume” represents the spatial region that will be targeted during the SBRT procedure. In cardiac SBRT, it incorporates the initial target volume defined by the cardiologist (arrhythmogenic area to be treated), with surrounding volume to account for cardio-respiratory motion of the target, and additional margins (1-3mm) applied to account for the overall uncertainties related to the treatment delivery (e.g. patient positioning)(18,19). Finally, data regarding outcomes after the procedure were extracted: occurrence of death within one year after the procedure, time to death after the SBRT procedure, cause of death, and the likelihood that death was related to the SBRT procedure according to the authors. Assessment of study quality and risk of bias was conducted according to the National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies (K.B.).

Outcome Measures

The primary outcome was the pooled all-cause mortality at 1-year after the SBRT procedure. Secondary outcomes included the 3 and 6-month all-cause mortality, the 1-year HF-related mortality and the 1-year noncardiac mortality.

All causes of death were extracted and classified by the two investigators in charge of data collection (K.B. and R.M.). Any discrepancies between the two observers regarding the cause of death were adjudicated by a third investigator (A.D.C.)

Statistical Analysis

To account for heterogeneity between studies, a meta-analysis of prevalence using a random-effects model was performed to estimate the pooled all-cause mortality at 1 year. For each study, the percentage of patients who died within 3 months, 6 months and 1 year after the SBRT procedure were first transformed using the Freeman-Tukey arcsin transformation. Random-effects models (DerSimonian and Laird method) were applied to pool the transformed estimates(20). The pooled estimates and their 95% confidence intervals (CIs) were then back-transformed and expressed as percentages. An inverse variance method was used for weighting each study in the meta-analysis. Heterogeneity between studies was quantified using the I^2 statistic. We evaluated the publication bias and small-study effects by means of funnel plots and Egger regression symmetry tests. Subgroup analyses were conducted to assess the influence of demographic, procedural and study characteristics on the 1-year all-cause mortality and 1-year HF-related mortality. Kaplan-Meier survival curves were generated for all-cause mortality, HF-related mortality and non-cardiac mortality. P values <0.05 (two-tailed) were considered statistically significant. Data analysis was performed using the packages 'Meta' and 'Metafor' of R statistical software (version 4.2.3).

RESULTS

A total of 1,151 unique citations were screened. Among these, 16 studies met the inclusion criteria and were included in the pooled analysis with a total of 157 patients undergoing a cardiac SBRT procedure for refractory VAs(5–9,21–31). Two studies were excluded from the analysis due to the double inclusion of the same patients in larger cohorts(5,23,32,33). The PRISMA flow diagram illustrating the number and reasons for exclusion of publications from the originally retrieved citations is outlined in *Figure 1*. Main characteristics of the included studies are presented in *Table 1*.

Population characteristics and procedural data

Among the 16 studies, 8 enrolled patients in Europe (84 patients), 6 in North America (63 patients), and 2 in Asia (10 patients). Among the 157 patients included in the analysis, 137 (87.3%) were male and median ages ranged from 56 to 79.5 years old. Regarding the underlying substrate, 80 (51%) patients were treated for refractory VAs in the context of ischemic cardiomyopathy, 76 (48.4%) in the context of dilated cardiomyopathy and one patient for refractory VAs associated with a cardiac fibroma (0.6%). Among the 157 patients,

55 (35%) underwent a SBRT procedure using a Cyberknife system and 102 (65%) using a conventional linear accelerator. The prescribed radiation dose was 25Gy in 141 (89.8%) patients, 20 Gy in 15 (9.6%) patients and 15 Gy in one (0.6%) patient.

One-year mortality after Cardiac SBRT

Among patients included, 157 (100%), 152 (97%) and 139 (86%) completed a 3-month, 6-month and 12-month follow-up, respectively. The 1-year mortality from the random-effects model meta-analyses was 31.9% (95%CI: 23.3-41.0) (*Figure 2*). The 3-month and 6-month mortality rates from the random-effects model meta-analyses were 11.6% (95%CI: 6.0-18.2) and 17.6% (95%CI: 10.7-25.5), respectively (*Supplemental Data*). The 1-year survival after the procedure using Kaplan-Meier estimates is illustrated in *Figure 3, Panel A*. Among the 157 patients included in the review, 46 died within the year after the SBRT procedure. Of note, within the 12 months after the SBRT procedure, 6 (3.8%) patients underwent orthotopic heart transplantation (of whom one died early after the surgery), and 1 (0.6%) patient had implantation of a ventricular assist device. One-year survival without transplant was 59.9% (95%CI: 46.9-72.3) (*Supplemental Data*).

Mode of Death after cardiac SBRT

Among the 46 deaths that occurred within one year of therapy, 24 (52.2%) were considered by the authors to be mainly related to the progression of HF, while 19 (41.3%) deaths were considered to be related to non-cardiac causes. Only 3 (6.5%) deaths were considered to be directly related to refractory VAs (electrical storms and slow VT under the detection threshold of the internal cardioverter defibrillator). Among the 19 patients who died from non-cardiac causes: 5 were due to sepsis (including 2 from Sars-Covid 19 infection), 3 due to kidney or liver failure, 2 to respiratory failure related to amiodarone pulmonary toxicity, 2 due to malignancy, 1 due to stroke, 1 due to an aspiration, 1 due to accidental death, 1 due to an esophago-pericardial fistula, 1 to heart transplantation complications and two patients died of unspecified non-cardiac causes. Details of patients who died from a non-cardiac cause within the year after SBRT are given in *Supplemental Data*. All-cause mortality, heart failure mortality, and noncardiac mortality within the year after SBRT for refractory VAs are illustrated in *Figure 3, Panel B*.

Among the 26 patients for whom the link between SBRT and death was clearly assessed, in 19 patients deaths were considered as “unrelated” or “unlikely to be related” to the SBRT by the authors, while in 6 patients (5 died from HF and one death on unclear cause)

a link between SBRT and death was considered “possible” or “cannot be excluded. The SBRT procedure was considered to be the direct cause of death in one patient who died from an esophago-pericardial fistula. Death occurred 9 months after a SBRT procedure targeting the substrate of an inferior myocardial infarction(23,34). *Figure 4* illustrates the distribution of main causes of death within the year after the SBRT procedure.

Factors associated with 12-months mortality

Subgroup analyses comparing studies with a median age of the population ≥ 70 yo and < 70 yo identified a significantly higher 12-month mortality for studies with a median age ≥ 70 yo (49.8% versus 26.4%, $p=0.022$), and a non-significant trend toward a higher 12-month HF-related mortality (22.9 vs 9%, $p=0.180$) (*Supplemental Data*). Similarly, when comparing studies with a median LVEF ≤ 25 and > 25 , a trend toward a higher all-cause mortality at 12 months was observed in studies including patient with lower LVEF (42.8% vs 24.9%, $p=0.061$) (*Supplemental Data*). No significant difference in all-cause mortality was observed between studies performing cardiac SBRT using Linear accelerators or Cyber Knife system ($p=0.199$) (*Supplemental Data*). Of note, studies that used larger target volume (mean PTV ≥ 150 cc) for the SBRT procedure did not have higher all-cause mortality nor HF-related mortality at 12 months than studies in which patients were treated with lower target volume (< 150 cc) ($p=0.465$ and $p=0.672$, respectively) (*Supplemental Data*).

Risk of bias assessment

According to the NIH Quality Assessment Tool for Case Series Studies, “According to the NIH Quality Assessment Tool for Case Series Studies, 3 of the included studies were rated as poor in overall quality whereas the 13 remaining studies were deemed to be of good quality. (see *Supplemental Data*). The funnel plots of proportion (Freeman-Tukey arcsine transformation) for the 12-month all-cause mortality is provided in the *Supplemental Data*. Egger’s test did not indicate asymmetry or small-study effect ($p= 0.175$), and thus provided no evidence of significant publication bias related to mortality (*Supplemental Data*).

Sensitivity Analysis

Results remained consistent after restricting the analyses to studies with a low risk of bias according to the NIH Quality Assessment Tool for Case Series, with a 12-months all-cause mortality of 33% and no significant differences when comparing with studies with moderate risk of bias ($p=0.615$) (*Supplemental Data*). On the other hand, study size appeared

to be associated with the all-cause mortality, as demonstrated by the significantly lower 12-month all-cause mortality in studies enrolling more than 10 patients compared with studies enrolling less than 10 patients (25.5% vs 42.2%, $p=0.043$) (*Supplemental Data*)

DISCUSSION

Main findings

To the best of our knowledge, this systematic review is the first to investigate the 1-year mortality and causes of death after cardiac SBRT for refractory VAs. Among 16 studies including 157 patients, the pooled 1-year mortality rate after a cardiac SBRT procedure for refractory VAs was expectantly high (32%), with more than one third of deaths occurring within three months after the radiation therapy. Worsening HF appears to be the leading cause of death (52%) after cardiac SBRT, although non-cardiac mortality remains substantial (41%) in this population. Only one death was reported to be directly related to the SBRT itself. Age ≥ 70 yo was associated with a significantly higher all-cause mortality at one year after the procedure. Neither the size of the target volume nor the SBRT modality appeared to affect the 12-month all-cause mortality or HF-related mortality.

Mortality in HF patients with VAs

Chronic HF is characterized by a progressive course of increasing symptoms, recurrent hospitalizations, and shortened survival, all mediated by ventricular remodeling(35). Relationship between HF and VAs is complex and multifaceted. Adverse myocardial changes that come with the progression of HF lead to the development of an electrophysiologic substrate promoting the occurrence of VAs(36). On the other hand, occurrence of VAs may worsen structural myocardial changes and impair the cardiac pump function, resulting in clinical deterioration of HF. In our pooled analysis, all patients had VAs in the context of SHD and the median LVEF was $< 30\%$ in 10 of the studies, reflecting the severity of structural damage and the advanced stages of HF in the population treated with cardiac SBRT for refractory VAs. Burden and type of VAs are also important factors that influence mortality patients with SHD. Thus, clustered pattern of VAs in patients with internal cardioverter defibrillator were shown to be independently associated with the risk of subsequent death (mostly non sudden cardiac deaths)(15,37). Exner et al. shown that electrical storm (3 or more

VA episodes in 24 h) was a major risk factor for subsequent death, particularly within the first 3 months after its occurrence and independently of LVEF and other prognostic variables (relative risk 2.4; 95% CI: 1.3 to 4.2; P=0.003)(37). Thus, one-year mortality after hospitalization for electrical storm is dramatically high, around 35% and even higher (40-45%) in patients unsuccessfully treated by CA³⁴⁻³⁷. The high comorbidity of patients undergoing a cardiac SBRT procedure as a last-resort, palliative, or compassionate use strategy (advanced SHD and VAs refractory to medical therapy and CA) most likely accounts for the substantial 1-year mortality observed in this population.

Mortality after CA procedures

Radiofrequency CA has become an established therapy in managing recurrent, drug-refractory VTs, with a critical role in patients with incessant or life-threatening VAs(39,41). However, several factors still contribute to make this procedure complex, such as hemodynamic instability, complex arrhythmia substrate, multiple VTs, noninducibility, or uncertainty over the best ablation strategy to undertake(42,43). Mortality after CA for VT in patients with SHD remains non-negligible, estimated around 5% within the first 30 days and between 9 and 15% at one year(16,17,44). Age, low LVEF, chronic kidney disease and mechanical hemodynamic support were shown to be independent predictors of early mortality after the procedure(17,44). Death due to worsening HF is common in this population, and predictors of death in patients undergoing CA for VT are also predictors of death in advanced HF(45). On the other hand, procedure failure itself has been described as an independent predictor of early mortality in SHD patients undergoing CA for VT(44,46). In this analysis, all patients included had a history of (at least one) failed CA procedures before cardiac SBRT except in case of contraindication, highlighting the significant vulnerability that characterizes the population for which SBRT is intended. Procedure-related complications are also non-negligible in conventional CA for VTs, as up to 12% of early death after the procedure appeared to be related to a major complications of the ablation procedure(17). Among the 46 deaths reported in the 16 studies, only one was clearly a complication of the SBRT procedure (esophago-pericardial fistula)(34). However, longer-term follow-up data will be needed to identify possible late complications of SBRT.

Mortality after cardiac SBRT

It is noteworthy that among all the patients who died within the year after the SBRT

procedure, only 3 deaths were reported to be related to VAs (electrical storms, and VT under the detection threshold). Thus, the majority of deaths were related to worsening HF/hemodynamic death reflecting the advanced HF condition of these patients, even when the VA burden is reduced. However, since there is no information on the circumstances of death in some patients, we cannot exclude more cases of slow VAs that deteriorated HF. On the other hand, deaths from noncardiac causes also appear to be a substantial in this population with numerous comorbidities. Thus, sepsis (2 Covid infections), other organs dysfunction (kidney and liver failures), cancer or accident accounts for nearly 40% of one-year mortality after cardiac SBRT, highlighting the overall frailty of this population. The significantly lower rate of death in studies including more than 10 patients may be explained by the fact that with increasing experience in the technique and number of treated patients, SBRT centers tend to treat less elderly patients with fewer comorbidities and better cardiac condition, while teams with little experience usually start treating extremely fragile patients.

Finally, although most studies considered the direct link between death from worsening HF and the SBRT procedure to be unrelated or unlikely, it is currently impossible to completely rule out this hypothesis, and long-term randomized data will be needed to clarify the question and not to overlook a possible effect of radiation therapy as a precipitating factor in the deterioration of cardiac function (e.g. decline in systolic or diastolic function, changes in neurohormonal regulation).

Association between treatment volume and mortality

It is important to note that in the field of thoracic radiotherapy for tumor-related indications, an association has been demonstrated between the total radiation dose received by the cardiac structure and survival after treatment(47,48). For instance, Kim et al. recently reported that irradiation of the sinus node region with a cumulative dose exceeding 53 Gy was associated with a higher mortality in patients with lung cancer(49). However, the association may not be applicable in cardiac SBRT, as the irradiation modalities differs a lot from tumor-related indications. Cardiac SBRT involves a single dose of 20 or 25 Gy, significantly lower than the cumulative doses reported for tumor-related irradiations (up to 75Gy). Moreover, the area receiving the dose is typically a very limited volume of myocardium, already affected by the presence of scar tissue. This is in contrast to studies related to tumor-related indications, which measure cumulative doses over a larger volume of a healthy heart. Nevertheless, despite that our pooled analysis does not reveal an association between the planning target volume and early mortality after cardiac SBRT, caution is warranted on this point. Large prospective data,

with individual patient data analyses will be needed to investigate appropriately this possible association.

Clinical implications

Cardiac SBRT has recently emerged as a promising non-invasive alternative for patients with VAs resistant to conventional therapies(4–6,50). Short term safety profile of cardiac SBRT is commonly reported as favorable, even though the current clinical experience remains limited(7). Despite the fact that a high mortality rate might not be surprising in this population, data on early mortality are critical in a field where clinical decision making is tenuous, mainly related to the difficult question of the perceived risk of long-term side effects of radiation therapy. Indeed, the risks of radiation therapy are both short- and long-term. One of the major future challenges for the technique will be to quantify whether or not the long-term safety is as high as the clinical benefit expected. Nevertheless, this long-term risk of radiation also needs to be taken in context. Just as late effects of radiation in patients with incurable cancers may be an irrelevant concern, it is likely that in the most fragile and severe patients treated with cardiac SBRT for refractory VAs, these long-term issues may also be irrelevant given the short-term mortality in this population. Thus, in older patients with advanced SHD, low LVEF and numerous comorbidities, the therapeutic ratio appears to be fairly favorable for the use of radiation when facing a therapeutic impasse with refractory VAs. In patients with relatively short life expectancy, cardiac SBRT may also have a role for reduction of VA burden in the short term for the purpose of improving quality of life. However, randomized trials and long-term follow-up data will be needed to further explore the benefit-risk ratio of this therapy in younger, healthier patients.

Limitations

Our mortality estimates were obtained after exclusion of case reports and case series including less than 3 patients and may be more representative of the expected mortality in the context of much larger cohorts. However, cardiac SBRT remains a very recent technique, usually performed by centers already expert in VT ablation, making sporadic implementation of cardiac SBRT rare. The decision to exclude case reports from the pooled analysis was driven by the fact that case reports often provide valuable insights into individual clinical experiences; however, inclusion of case reports may introduce a substantial additional level of heterogeneity regarding the implementations of the technique that could impact the precision and reliability of the analyses. Individual patient data were not available for all variables, and our study

methodology did not provide the opportunity to analyze the association between mortality and other important clinical or procedural variables. Moreover, the substantial heterogeneity regarding the efficacy endpoints used in the different case series did not allow us to perform an analysis of the mortality according to the success of VAs elimination (residual VA burden). The lack of detailed data regarding this relationship is a limitation of the current study, and more targeted and specific future researches will be needed to elucidate this matter. Finally, some of the data extracted, such as the accurate date of death, may have been surrounded by an error margin in some studies. Similarly, the determination of the cause of death is difficult in this high morbidity population, and results accuracy is limited by the information provided by the different studies, which presented more or less comprehensive information regarding the surrounding circumstances of death. However, more than establishing strong inferences, the purpose of this systematic review was rather to provide an overall picture of the early mortality observed after implementation of this new ablation technology.

CONCLUSION

One-year mortality in patients undergoing cardiac SBRT for refractory ventricular arrhythmias is high (~32%), with more than one third of these deaths occurring within the first 3 months after the procedure. Worsening heart failure and non-cardiac causes accounted for the majority of deaths in this population. Neither target volume size nor SBRT modality appeared to be associated with the 1-year mortality. Multicenter prospective studies will be needed to confirm these results.

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Table 1: Main characteristics of the included studies

Study	N Sex M/F	Radiation Therapy Device	Median [Min-Max] Age, yo	Median [Min-Max] LVEF, %	Cardiomyopathy	Mean [Min-Max] PTV, cc
Cuculich et al, 2017	5 4/1	Linear accelerator	62 [60-83]	22 [15-37]	2 ICM 3 NICM	49.4 [17-81]
Robinson et al, 2019	19 17/2	Linear accelerator	66 [49-81]	25 [15-58]	11 ICM 8 NICM	98.9 [60-299]
Gianni et al, 2020	5 5/0	Cyber Knife	67 [45-76]	25 [20-55]	4 ICM 1 NICM	143.5 [80-184]
Gordon Ho et al, 2021	6 5/0	Linear accelerator	72.5 [64-81]	26 [23-46]	2 ICM 4 NICM	120.5 [66-193]
Chin et al, 2021	8 8/0	Linear accelerator	74 [65-86]	20 [15-31]	4 ICM 4 NICM	121.4 [21-190]
Carbucicchio et al, 2021	7 7/0	Linear accelerator	72 [59-78]	21 [20-44]	3 ICM 4 NICM	183 [88-239]
Lee et al, 2021	7 4/3	Linear accelerator	70 [60-70]	25 [20-45]	5 ICM 2 NICM	94.5 [57-121]
Peichl et al, 2021	33 30/3	Cyber Knife	66 NA	30 NA	19 ICM 14 NICM	NA NA
Li-Ting Ho et al, 2021	7 7/0	Linear accelerator	56 [23-80]	43 [30-66]	0 ICM 3 NICM	54.5 [14.4-92.6]
Yugo et al, 2021	3 2/1	Linear accelerator	68 [65-83]	44 [20-59]	0 ICM 3 NICM	83.3 [63-106]
Qian et al, 2022	6 6/0	Linear accelerator	72 NA	20 NA	6 ICM 0 NICM	308 [170-443]
Ninni et al, 2022	17 13/4	Cyber Knife	68 [30-83]	35 [20-47]	10 ICM 7 NICM	62.4 [20-186]
Wight et al, 2022	14 10/4	Linear accelerator	59.5 [50-78]	NA NA	5 ICM 8 NICM	NA NA
Molon et al, 2022	6 5/1	Linear accelerator	79.5 [61-85]	26.5 [20-42]	4 ICM 2 NICM	NA NA
Aras et al, 2022	8 8/0	Linear accelerator	61.5 [33-85]	25 [10-30]	2 ICM 6 NICM	157 (median) [70-273]
van der Ree et al, 2023	6 6/0	Linear accelerator	73 [54-83]	38 [24-52]	6 ICM 0 ICM	187 [93-372]

Figure 1: The Preferred Reporting Items for Systematic Review and Meta-analysis flow-chart of studies included in the meta-analysis.

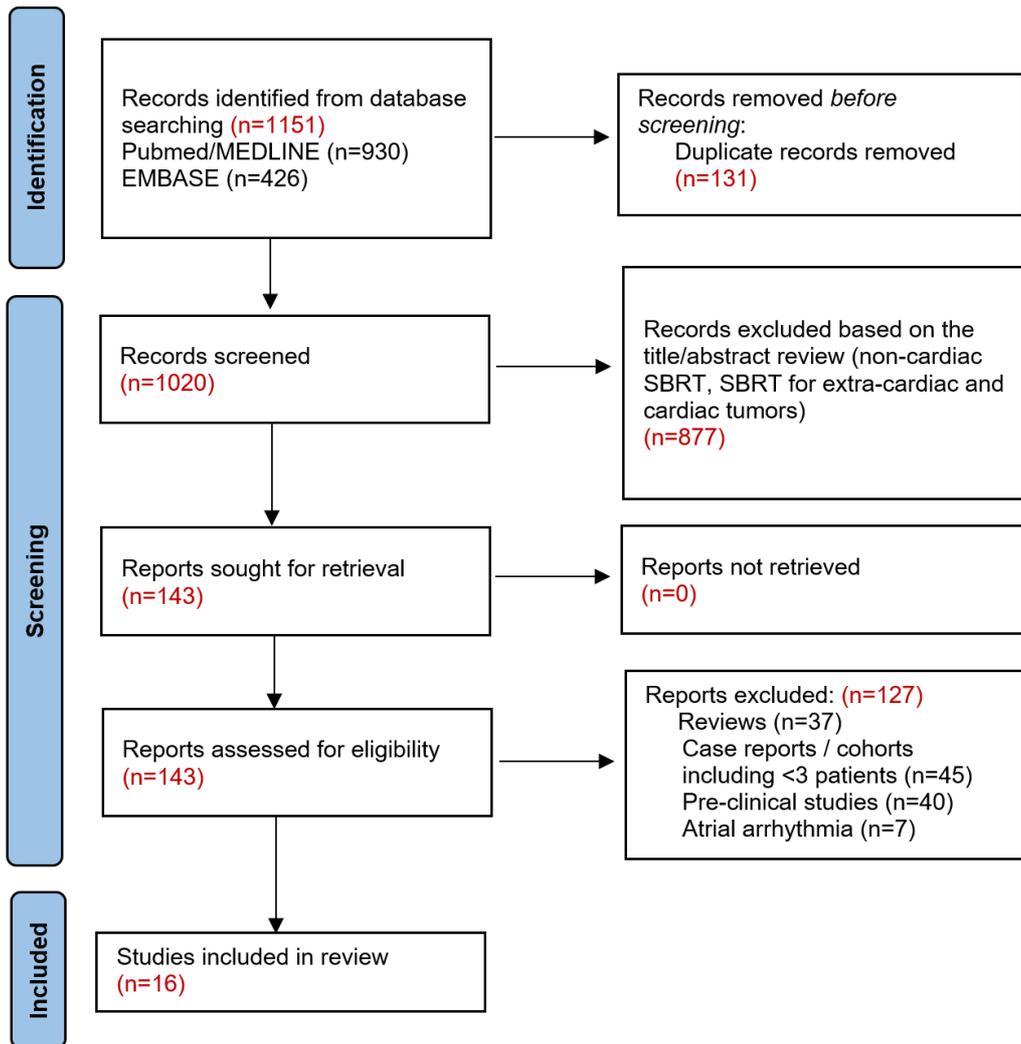


Figure 2: Forest plot from the random-effects meta-analysis of the 12-month overall mortality

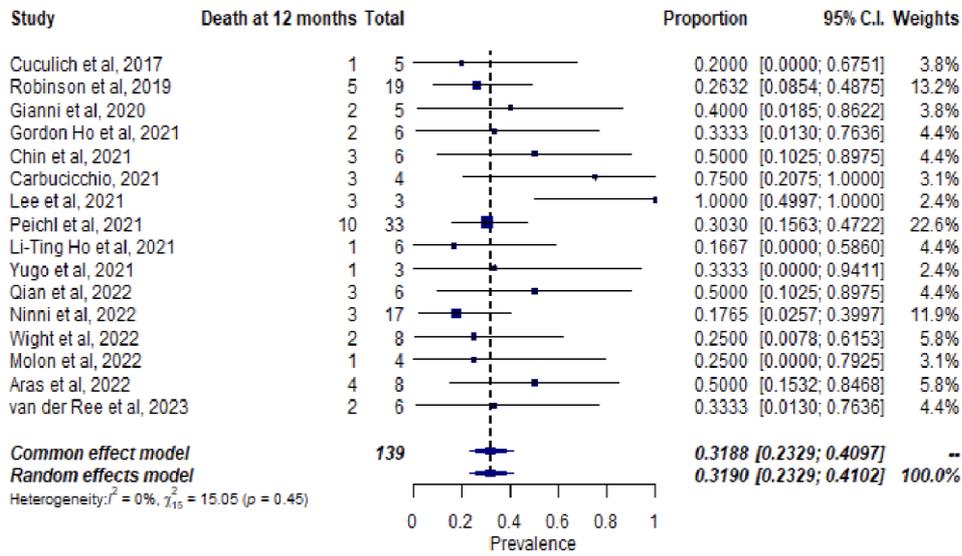


Figure 3: Panel A, Kaplan-Meier estimate of the one-year survival after cardiac SBRT for refractory VAs. Panel B, Kaplan-Meier estimates of the one-year overall mortality, HF-related mortality, non-cardiac mortality and mortality related to refractory VAs after cardiac SBRT for refractory VAs

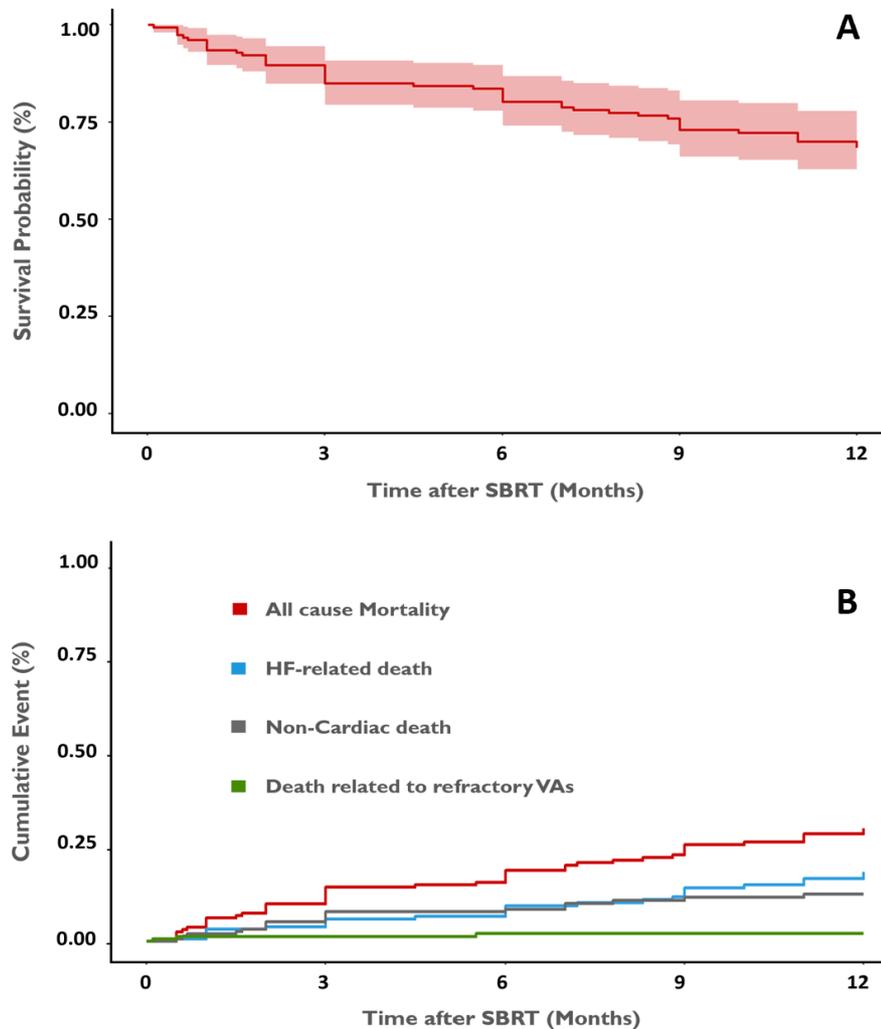
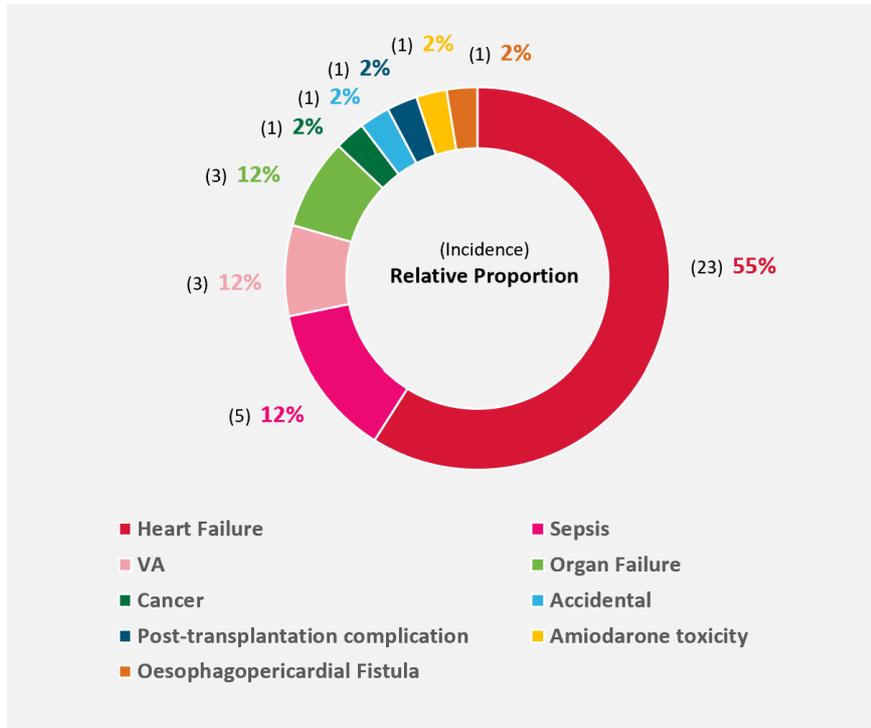


Figure 4: Causes of death at one year after cardiac stereotactic radiation therapy for refractory ventricular arrhythmias

VA: Ventricular arrhythmia;



Ethical Statement

Hereby, I / **Karim Benali** / consciously assure that for the manuscript / **One-Year Mortality and Causes of Death after Stereotactic Radiation Therapy for Refractory Ventricular Arrhythmias: A Systematic Review and Pooled Analysis** / the following is fulfilled:

- 1) This material is the authors' own original work, which has not been previously published elsewhere.
- 2) The paper is not currently being considered for publication elsewhere.
- 3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
- 4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
- 5) The results are appropriately placed in the context of prior and existing research.
- 6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
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I agree with the above statements and declare that this submission follows the policies of Trends in Cardiovascular Medicine as outlined in the Guide for Authors and in the Ethical Statement.

Conflict of interest

No