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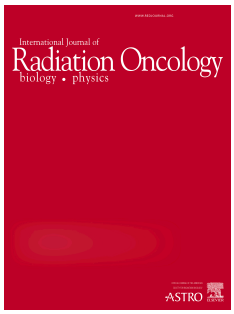

A review of cardiac radioablation (CR) for arrhythmias: procedures, technology and future opportunities

S. Lydiard, G. Hugo, PhD, R. O'Brien, PhD, O. Blanck, PhD, P. Keall, PhD

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A review of cardiac radioablation (CR) for arrhythmias: procedures, technology and future opportunities

Running Title: Cardiac radioablation review

Authors:

Lydiard S, ACRF ImageX Institute, University of Sydney, Sydney, Australia and Kathleen Kilgour Centre, Tauranga, New Zealand

Hugo G, PhD, Department of Radiation Oncology, Washington University School of Medicine, St Louis, USA

O'Brien R, PhD, ACRF ImageX Institute, University of Sydney, Sydney, Australia

Blanck O, PhD, University Medical Center Schleswig-Holstein, Campus Kiel, Clinic for Radiation Oncology and Clinic for Internal Medicine III (Cardiology), Kiel Germany

Keall P, PhD, ACRF ImageX Institute, University of Sydney, Sydney, Australia

Corresponding Author:

Suzanne Lydiard

E: slyd6788@uni.sydney.edu.au

T: +64 21 750696

A: Level 2 ATP Biomedical Building (C81)
1 Central Avenue
Eveleigh
NSW 2015 Australia

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Conflict of Interest:

Dr. Oliver Blanck reports to have been an employee of CyberHeart Inc. (Sunnyvale, CA, USA) from 2008 to 2010, though he reports no financial ties or obligations or conflict of interest to or with the company or its legal successor Varian Medical. (Palo Alto, CA, USA). Dr. Hugo reports personal fees from Varian Medical Systems, grants from Varian Medical Systems, grants from Siemens, grants from ViewRay, Inc., outside the submitted work; In addition, Dr. Hugo has a patent PCT/US2016/000103 licensed to Varian Medical Systems, and a patent PCT/US2018/065278 licensed to Varian Medical Systems. Dr. Lydiard has a patent A patent on an image guidance method for cardiac targeting is in preparation.

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ABSTRACT

Purpose

Cardiac radioablation (CR), a new treatment for cardiac arrhythmias such as ventricular tachycardia (VT) and atrial fibrillation (AF), has had promising clinical outcomes to date. There is consequent desire for rapid clinical adoption. However, CR presents unique challenges to radiotherapy and it is paramount that clinical adoption is performed safely and effectively. Recent reviews comprehensively detail patient selection, clinical history, treatment outcomes, and treatment toxicities but only briefly mention the technical aspects of CR. To address this knowledge gap, this review collates currently available knowledge regarding CR technology choice and procedural details to help inform and guide clinics considering implementing their own CR program, aid technique standardization, and highlight areas that require further development or verification.

Materials and Methods

Original pre-clinical and clinical scientific articles that sufficiently detailed CR technical aspects including pre-treatment electrophysiology and imaging, motion analysis and management techniques, treatment planning, and/or treatment delivery were identified within a comprehensive literature search.

Results

19 pre-clinical and 18 clinical scientific articles performed and sufficiently detailed the technical aspects of CR treatment deliveries on live subjects. The technical aspects of these scientific articles were diverse: pre-clinical treatments have been performed with brachytherapy, photons, protons and carbon ions and clinical treatments have been performed with photons using conventional, robotic and MRI-guided systems. Other technical aspects demonstrated similar variability.

Conclusions

This review summarizes the technical aspects and procedural details of pre-clinical and clinical CR treatment deliveries and highlights the complexity and current variability of CR. There is need for standardized procedural reporting to aid multi-center and multi-platform evaluation and potential for significant technological improvements in imaging, planning, delivery and monitoring to maximize the clinical outcomes for selected arrhythmia patients.

ABBREVIATIONS

3DCT	Three-dimensional computed tomography
4DCT	Four-dimensional computed tomography
AF	Atrial fibrillation
CBCT	Cone-beam computed tomography
CR	Cardiac radioablation
CT	Computed tomography
DVH	Dose volume histogram
EAM	Electroanatomic mapping
ECG	Electrocardiography
ECGI	Electrocardiographic imaging
FFF	Flattening filter free
ICD	Implantable cardioverter-defibrillator
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy treatment
ITV	Internal target volume
LA	Left atrium
MLC	Multileaf collimator
MRI	Magnetic resonance imaging
MU	Monitor unit
MV	Megavoltage
OAR	Organs at risk
PET	Positron emission tomography
PTV	Planning target volume
SBRT	Stereotactic body radiotherapy
SPECT	Single-photon emission computerized tomography
TPS	Treatment planning system
TV	Target volume
VT	Ventricular tachycardia
VMAT	Volumetric modulated arc therapy

INTRODUCTION

Cardiac arrhythmias such as ventricular tachycardia (VT) and atrial fibrillation (AF) are of escalating socio-economic concern. VT, an arrhythmia of the lower chambers of the heart, is commonly associated with heart disease and is the leading cause of sudden cardiac death[1]. With the standard treatments, the current success rate of eliminating scar-related VT is 55 – 89%[2]. AF, an arrhythmia of the upper chambers of the heart, currently affects 2.5 – 4% of all adults[3] and its prevalence is rapidly increasing[3-5]. The current and potential future impact of cardiac arrhythmias on health-care systems is concerning.

Cardiac arrhythmia treatments aim to control heart rate or restore and maintain normal sinus rhythm. Current standard-of-care treatments have their limitations. Drug therapy efficacy may be hindered by toxicities, implantable cardioverter-defibrillator (ICD) interventions can significantly decrease quality of life and catheter ablations can be long procedures with sub-optimal success rates[6,7]. Many of these patients additionally have co-morbidities, for example heart-failure, chronic kidney disease, or pulmonary disease that presents additional challenges to their overall clinical treatment[8]. Patients with specific pathological characteristics or comorbidities currently have limited to no treatment options beyond best-supportive care. Cardiac radioablation (CR), also referred to as stereotactic arrhythmic radioablation or cardiac radiosurgery, is an emerging treatment that could potentially overcome some of the limitations of current standard-of-care treatments. CR aims to mitigate the arrhythmic burden by non-invasively delivering focused high-dose external-beam radiotherapy to the underlying arrhythmogenic substrate. CR has been proposed as a treatment alternative for both VT and AF. However, treatment limitations and reduced quality and length of life is generally more severe for VT and therefore the clinical need and urgency for CR for VT appears more critical.

Radiotherapy is a well-established and successful treatment for oncologic and benign indications. Stereotactic radiosurgery (SRS) and radiotherapy (SRT)[9] have long-proven success for both intracranial tumors and vascular or functional disorders. The success of recent advances in image-guided radiotherapy (IGRT), motion management techniques, and treatment delivery methods are particularly evidenced by favorable clinical outcomes of stereotactic body radiotherapy (SBRT)[9] for small and highly mobile thoracic and abdominal tumors. While most treatment uncertainties for SBRT have been successfully addressed[10], CR brings new challenges to radiotherapy. Because CR treats a non-oncologic disease in an organ usually spared from radiation, high treatment accuracy is required. Yet target motion is more complex than

generally faced in oncology radiotherapy. Figure 1 highlights the extra complexity of CR motion management considerations and outlines possible motion management combinations. Respiratory motion management techniques are frequently utilized in radiotherapy and their accuracy and limitations are well-established[10]. These techniques may also be used to compensate for cardiac motion, which is of higher complexity, smaller magnitude and higher frequency[11-13], but their effectiveness are not yet well-established. The typical CR clinical workflow, as illustrated in Figure 2, is very similar to SBRT but usually requires additional electrophysiological information to aid target delineation, careful selection of suitable motion management techniques, and close collaboration and amalgamation of knowledge between cardiology and radiation oncology personnel.

Because CR treatments to date illustrate promising clinical outcomes, there is consequent desire for rapid clinical adoption. However, safe and effective clinical implementation is paramount. Recent reviews comprehensively detail patient selection, clinical history, treatment outcomes, and treatment toxicities but only briefly mention specific technical aspects of CR[14-18]. This review addresses this knowledge gap by collating currently available knowledge regarding CR technology choice and procedural details to help inform and guide clinics considering implementing their own CR program, aid technique standardization, and highlight areas that require further development or verification.

SEARCH AND REVIEW METHODOLOGY

Original pre-clinical and clinical CR scientific articles were identified within a literature search using OVID Embase, Google Scholar and PubMed. The following search control terms were used: (a) 'cardiac arrhythmia OR atrial fibrillation OR ventricular tachycardia', (b) 'radiosurgery OR radioablation OR radiotherapy OR radiation therapy OR heavy ion OR proton'. No date or species-restrictions were applied. English language restriction was applied. The search was initially performed in December 2019 and updated in February 2020. Further relevant studies were identified by manually searching reference lists and citing articles of identified papers or by direct input from the authors of this review. After an initial redundancy check the identified scientific articles were screened for suitability by experts in the field of CR. An inclusion criterion required articles to sufficiently detail any of the following: planning imaging, motion management, treatment planning, quality assurance, in-room image guidance or treatment delivery. Articles were stratified as either pre-clinical for animal studies or clinical for human treatments.

PRE-CLINICAL STUDIES

Pre-clinical studies were mainly exploratory, investigating the electrophysiological effects of irradiating various regions of rabbit[19,20], pig[21-32] or dog[30,33,34] hearts with different doses. Early studies used Sr^{90} and P^{32} β-emitting sources[21,33]. Later studies utilized external-beam radiation with carbon ions[19,22,26,28,34], protons[35] or photons utilizing CyberKnife[24,29,30] and c-arm linear accelerators[23,25,31,32]. Pre-clinical treatments of live animals are summarized in Table 1, grouped by techniques.

All animals were prepared, planned and treated under general anesthesia and controlled mechanical ventilation[19,22-24,26,27,29,31,32,34,36,37]. Computed tomography (CT) imaging was always used for treatment planning[22-24,26,27,29,31,32,35,36]. Respiratory motion management techniques included direct tracking of gold fiducials or a temporary implanted catheter tip[24,29,30], internal target volume (ITV)[22,31,32], or breath-hold during paused ventilation[25,26,28,35]. An ITV derived from an cardiac-gated CT was commonly used to mitigate cardiac motion[22,23,26,28,29,31,32,35] but a pre-defined isotropic margin expansion was also used[25]. 3–5 mm isotropic treatment planning margin expansions were utilized in CyberKnife and c-arm linear accelerator treatments to compensate for treatment delivery uncertainties[23,25,27,31,32,36]. For AF, the right superior pulmonary vein was mainly targetted[24,26,31,32] due to other pulmonary veins exhibiting larger mobility or extensive branching in animal models and/or having limited catheter accessibility for electrophysiology investigation[24,31,32].

Pre-clinical studies have irradiated the left ventricle, cavotricuspid isthmus, atrioventricular node, left atrial appendage, and pulmonary veins. Doses between 5-160 Gy have been used to investigate pathological and electrophysiological effects of CR. Healthy animals were mostly used. A non-transmural myocardial infarction pathophysiology model via intracoronary injection of microspheres has been used and the effect of CR on the propensity to VT or ventricular fibrillation was evaluated[19,20,34]. The dose-effect and toxicity findings of pre-clinical studies have been extensively discussed in previous reviews[14,38]. To briefly summarize, doses of 30 Gy or more was ~~is~~ needed to block electrical conductivity[31]. Electrophysiological effects without complete electrical conductivity block were observed at doses between 20-25 Gy[22,23,25,26,29].

In-vivo dosimetry data are scarce. Thermoluminescent and metal-oxide-semiconductor field-effect transistor dosimeter measurements performed in pig and canine CyberKnife treatments using fiducial respiratory tracking indicated that target or near-target doses were on average 5-6% lower than planned[30]. A phantom feasibility study using diode-array measurements, 4D dose reconstruction and multileaf collimator (MLC) tracking for combined cardio-respiratory motion management reported that target doses were on average

8% lower than planned[39]. In-beam positron emission tomography (PET) imaging has been used to monitor dose deposition in carbon ion treatments[26].

CLINICAL TREATMENTS

Clinical CR treatments have mostly been for VT patients who were refractory or contraindicated to catheter ablation with limited or no alternative treatment options. Publications report 44 VT CR treatments within clinical trials[40-45], 10 VT CR treatments within single-patient case-studies[46-55], and 3 AF CR treatments[56,57]. Technical aspects of clinical CR treatments delivered on CyberKnife and c-arm linear accelerators are summarized in Table 2 and Table 3 respectively.

Pre-planning

Target localization for VT CR relies on a combination of electrophysiology and anatomical scar information to identify the arrhythmogenic substrate and intended target location. Using both electrophysiology and anatomical information allows preferential irradiation of scar tissue, ensures the arrhythmogenic target is sufficiently irradiated, and minimizes damage to viable myocardium. Target localization for AF CR may rely on anatomical information alone (e.g., the pulmonary vein antrum for paroxysmal AF) or on a combination of both electrophysiology and anatomical information (e.g., refractory AF).

Electrophysiology information

12-lead electrocardiography (ECG)[40,41,43-45,49,52,55] and programmed stimulation[40,41,44,45,53] involving VT induction via the ICD under light sedation were commonly used to locate the general proximity of the VT arrhythmogenic substrate. Electroanatomical maps (EAM) acquired during prior invasive catheter ablation procedures were most commonly used for target definition as these provide more detailed electrical information[41-43,49-55,58]. An alternative non-invasive CT-based surface electrocardiographic imaging (ECGI) method that identifies the arrhythmia exit site has been proposed[40,44,45]. The accuracy and suitability of this non-invasive technique for CR arrhythmogenic substrate localization when used as sole substrate location method has not been established[48]. Nevertheless, clinical results using ECGI-based CR in combination with anatomical imaging have been very promising[40,44,45].

Anatomical scar imaging

Contrast-enhanced CT[40,43-45,52,53], magnetic resonance imaging (MRI) [40,44,45,50,52,58], echocardiography[40,44,45,49,50], single-photon emission computerized tomography (SPECT) [40,44,45] and PET CT[45,49] have been used to image and localize myocardial scarring and guide arrhythmia substrate definition. ECG-triggering and intravenous (IV) contrast were nearly always used, provided renal function allowed, to enhance visualization of myocardial scarring and thinning in CT and MRI images[40-42,44,45,58]. MRI is generally superior for scar detection[59-61], but many patients were contraindicated to MRI due to their ICDs.

Motion analysis

Target motion can vary between patients and target locations. As illustrated in Figure 2, target motion was most commonly assessed within the planning imaging appointment. Free-breathing four-dimensional CT (4DCT) was most commonly used to assess combined cardio-respiratory target motion[40,44,45,58]: combined because the time-binned CTs are blurred from cardiac contraction due to the lack of ECG-triggering during imaging. Studies are underway to overcome this 4DCT limitation[62]. For treatments utilizing gating or tracking, planning imaging was performed in expiratory breath-hold and target motion was instead evaluated within the treatment delivery process[41,43]. To additionally assess cardiac-induced target motion, ECG-triggered CT scans in both systole and diastole[41], transthoracic echocardiography[50] and fluoroscopy imaging of ICD leads during transient breath-holds[49,55] have been used. An MRI-guided gated treatment used single-slice 2D sagittal cines acquired with balanced steady-state precession (TrueFISP) to assess target motion and exhalation reproducibility[47]. MRI has also been used to assess atrial motion in pre-clinical human imaging studies[63,64].

Observed target motion magnitude was rarely described beyond single case-studies. One larger study[45] reported median maximum target displacements in 4DCT for patients with abdominal compression to be 4.4 mm (range 3.0–11.0 mm), 4.7 mm (range 1.6–12.0 mm), and 3.0 mm (range 1.0–7.2 mm) in axial, coronal, and sagittal planes respectively. Pre-clinical human imaging studies report average pulmonary vein or left atrial respiratory-induced displacements in the range of 5.0–16.5 mm in the superior-inferior direction or 17.8–19.1 mm three-dimensional[63-66] and average cardiac-induced displacements in the range of 3.3–4.5 mm and maximum cardiac-induced displacements up to 12.3 mm[12,64,66].

Choice of motion management

As illustrated in Figure 1, there are multiple possible motion management technique combinations for combined cardio-respiratory motion, not all of which have been used clinically. All CyberKnife treatments utilized x-ray based marker tracking for respiratory motion management[41,43,46,49-51,55-57]. Temporary (for CR only) or permanent (unrelated to CR) markers have included ICD leads or cardiac resynchronization therapy leads located in the left ventricle (coronary venous system)[51] or the right ventricle (interventricular septum or apex)[41,50], a temporary transjugular active fixation lead positioned in the interventricular septum[43,49,57], and stimulation electrodes within the coronary sinus[51]. Unfortunately, minimal to no data exist regarding the surrogate accuracy and stability of these markers in humans. Marker-less tracking using the current CyberKnife x-ray imaging system is currently not achievable but a feasibility study illustrated that ultrasound tracking may provide marker-less real-time tracking in the future[11]. CyberKnife treatments frequently incorporated an ITV derived from ECG-triggered CT[41] or fluoroscopic imaging[49] to compensate for cardiac motion. One study used a pre-defined 3mm target margin expansion in all patients as an 'average' cardiac motion ITV[43] and another study used no ITV after evaluating 'low' magnitude cardiac motion with transthoracic echocardiography[50]. The AF CR treatments did not discuss cardiac motion management[56,57].

The majority of c-arm linear accelerator treatments utilized a combined cardio-respiratory ITV derived from free-breathing or motion-compressed respiratory-gated 4DCT[40,42,44,45,53,54,58]. Krug *et al.*[53] additionally incorporated information from cardiac-gated CT for cardiac margin generation. Conversely, one respiratory-gated treatment delivery was performed using an external surrogate but cardiac motion management was not explicitly described[52].

One VT treatment has been performed on an MRI-Linac utilizing breath-holds and MRI-guided respiratory-gating[47]. Neither the target area in the heart nor the esophagus could be used as gating structures due to artifacts from the ICD leads and finally the liver dome was used. Cardiac motion management was therefore not addressed.

Initial feasibility studies investigating combined cardio-respiratory motion MLC tracking tracking[39] and/or marker-less target tracking on MRI-Linacs[63,64,67] are promising. A cardiac-gated treatment delivery is conceptually feasible[68] but has not been used clinically.

Treatment planning & design

Planning imaging & immobilization

Treatment planning was always performed on 3D and/or 4DCT acquisitions. Limited information was provided regarding how the primary planning CT was derived (e.g., maximum intensity projections, averages, specific phase) when 4DCT data was used. Slice thicknesses of 1 mm–3 mm[42,43,45,53 40,44] were reported. One study co-registered a prior-acquired diagnostic contrast-enhanced cardiac-gated CT to a non-contrast planning CT[53] and another used a pre-acquired diagnostic CT for planning[51]. Many studies correlated or directly registered available anatomical images (MRI, PET, etc.) to the planning CT to aid target delineation[43,45,53]. The time lapse between planning imaging and treatment delivery has varied from 2 hours[57], the same clinical day[54], on average 13.5 days[45], and up to 33 days[45].

Patient immobilization was usually consistent for planning imaging and treatment delivery and comparable to standard thoracic and abdominal SBRT immobilization, including rigid or vacuum-based immobilisation[40,42,44,52] in supine position and in some cases with the arms overhead[45,47]. Abdominal compression[44,45] and an external thermoplastic shoulder mask[58] have also been used. Some critical patients were treated under general anaesthetic[50] or deep sedation[54].

Target volume (TV) generation

Electrophysiology information (e.g., ECG, EAM, ECGI) and anatomical scar imaging (e.g., contrast CT, MRI, PET, SPECT) used to identify the VT arrhythmogenic substrate need to be incorporated or transferred into the radiotherapy treatment planning system (TPS) to aid TV generation. However, importing electrophysiology information into commercial TPS is currently only feasible through non-commercial conversion methods[69]. To overcome this current limitation, manual TV contouring was commonly performed via a dual registration method that involved co-registering the endo- and/or epicardial- and/or non-invasive EAM to pre-planning volumetric imaging using either standard electrophysiology or non-commercial visualization software[42,43,49,51], followed by the registration of pre-planning volumetric imaging to the planning imaging within the TPS[41,42,50,54,55]. Instead of dual-registration, a currently non-commercial anatomical radioablation contouring software (CardioPlan, CyberHeart now Varian, Palo Alto, CA, USA) has been used to generate TV contours, which were then automatically transferred to the TPS [43,49]. Another group used the American Heart Association 17-segment left ventricle model to identify the critical regions on each individual dataset (ECG, EAM, ECGI, scar imaging) and combined this information to generate a

probability mask for the arrhythmogenic substrate [40,44,45]. TV generation requires transmural ventricle wall expansion because EAM only provides epi- or endocardial surface information and one study additionally expanded the TV 5-8 mm beyond the ventricular wall to include adjacent myocardial tracts[58]. AF treatments used only CT anatomical information for TV generation within CardioPlan software[57].

TVs prior to additional motion or uncertainty margin expansions have been reported in the range of 3.5-89.0 cc[40,44,47,53,54] for VT and 48.9-54.5 cc[57] for AF. A CR treatment planning study for proximal AF reported separate left and right TVs of 4.2-11.9 cc (median 6.9 cc) and 4.6–18 cc (median 9.8 cc) respectively[11].

Planning target volume (PTV) expansion

The TV or ITV is expanded to generate a planning target volume (PTV), which accounts for treatment uncertainties including incomplete target motion and deformation modelling, differential surrogate-to-target motion and variability during patient set-up and radiation delivery. The PTV margin dimensions are dependent on the choice of motion management, treatment delivery unit, immobilization and in-room image-guidance and are generally addressed jointly.

Early CyberKnife treatments did not utilize additional PTV margins despite uncompensated cardiac target motion[41,50,51]. It is consequently difficult to compare the prescription and delivered doses in these early studies to consequent studies that utilized margin expansions and/or different motion management or delivery techniques. Later CyberKnife studies utilized 3 mm isotropic PTV margins based on the reported accuracy of CyberKnife for lung/abdominal SBRT and CR[11,24,29,37]. The majority of c-arm linear accelerator VT treatments utilized 5 mm (range 1-8 mm) isotropic PTV margins[40,42,44,45,53,54,58]. The MRI-guided VT treatment utilized margin expansions of 2 mm in the vertical and lateral directions and 3 mm in the longitudinal direction[47]. C-arm linear accelerators have not yet been used for AF treatments, but a planning study for paroxysmal AF proposed that 3 mm is the maximum tolerable PTV margin to ensure critical surrounding structures are adequately spared[63]. Another study suggested that a greater margin in the superior-inferior direction may allow better target coverage in AF CR while still protecting the esophagus[70].

PTVs sizes of 21-193 cc have been reported for CyberKnife treatments[41,43,50,55] and 42-299 cc for c-arm linear accelerator treatments[42,44,47,53,54,58]. A single case-study of a right ventricular target utilizing amplitude-based respiratory-gating on a c-arm linear accelerator had a small PTV, approximately 3.5 cc[52].

Prescription and maximum dose

Nearly all published clinical CR treatments prescribed 25 Gy to the PTV in a single session delivery[40-46,49-54,56-58]. One group prescribed 24 Gy in three sessions because it was the first attempt to treat VT secondary to cardiac lipoma[55]. Many groups prescribed to the 80% isodose line (31.25 Gy maximum dose) but 66-85% prescription isodoses (29.4-37.9 Gy maximum doses) have been reported[41,46,47,51,53,54] and differing levels of PTV dose heterogeneity may cause differing pathological effects with respect to local scarring[31]. Contrary to the recommendations of the International Commission on Radiation Units and Measurements (ICRU) report 91[71], doses to 98%, 50% and 2% of the PTV ($D_{98\%}$, $D_{50\%}$ and $D_{2\%}$) were rarely reported. This significantly limits the comparability between studies utilizing different procedures and technology choice and the CR community is therefore urged to follow ICRU report 91 guidelines[72] to generate consistent and comparable data.

A common planning objective for CR was for >95% of the PTV to receive the prescription dose and the actual PTV coverage was reported to be in the range 61–97%[43,51,55-57]. Gianni *et al.*[43] reported low PTV coverage in two VT patients (61% and 66%) and stated that target dose coverage was reduced to limit doses to the proximal conduction system and stomach respectively. Clinical AF CR treatments reported 89%[56,57] and 96%[57] PTV coverage. AF CR treatment planning studies assumed 25 Gy to be the scar generating dose and used a planning goal to achieve >97%[70] or >99%[11] PTV prescription dose coverage, acknowledging the importance of achieving full circumferential transmural scarring for this arrhythmia.

Organs-at-risk (OAR) and dose constraints

There is limited data on definitive CR radiation-induced toxicities, particularly long-term toxicities and the specific effect of high radiation doses on healthy intra-cardiac structures. Most clinical CR treatments used organ-at-risk (OAR) dose constraints based on hypo-fractionated mediastinal and pulmonary treatments that generally comprised of extra-cardiac OAR constraints[11,39,47,70]. One group recently published specific intra- and extra-cardiac dose constraints and recommendations for a VT CR multi-center trial[38]. Extra-cardiac structures delineated in the evaluated literature included: esophagus, stomach, spinal cord/canal, airways, great vessels (e.g., descending aorta), lungs, liver, large and small bowel, phrenic nerve, chest wall, ribs and skin[40,42-45,49,50,52,53]. Furthermore, the following intra-cardiac sub-structures besides the whole heart were reported: left and right atrium, left and right ventricle, inferior and superior vena cava, coronary arteries, left

circumflex and anterior descending arteries, pulmonary trunk and arteries, healthy myocardium and pericardium, ascending aorta and aortic valve, pulmonic valve, mitral valve, coronary sinus and atrioventricular node[43,45,52,53,73].

Most extra-cardiac OAR dose constraints were easily achieved in planning studies and treatment reports for VT CR[11,39,63,70]. Knutson *et al.*[45] reported that one treatment plan exceeded stomach dose constraints and the patient consequently fasted prior to treatment. Krug *et al.*[53] also reported a somewhat higher, yet acceptable, stomach maximum dose (13.8 Gy) due to utilizing an ITV for larger respiratory-induced target motion. Repeat VT CR has already been reported[42]. Contrastingly, proximal AF CR treatment planning studies targeting the pulmonary vein antrum found it most challenging to meet esophageal dose constraints[11,39,63,70]. One study[70] used an esophagus planning risk volume that incorporated a 2 mm margin expansion to account for cardiac-induced esophagus motion and found that this was in direct contact and/or overlay with the PTV in 75% of patients. Another study[11] found that the esophagus was in direct contact with the ideal target lesion location in 50% of patients. Airways, great vessel, lung and whole heart dose constraints were also occasionally exceeded in these human planning studies[11,39,63,70], which may indicate intolerable side effect risks for a larger number of potential AF CR patients.

No clear consensus recommendations exist for CR dose constraints for intra-cardiac structures beyond common dose limits for coronary arteries[38,50]. A recent large study on intra-cardiac structure dose constraints from lung radiotherapy revealed that the cardiac region encompassing the right atrium, right coronary artery and ascending aorta had the greatest impact on patient survival[74]. Knutson *et al.*[45] reported planned median doses, interquartile range and 2 Gy equivalent doses for a large range of intra-cardiac substructures for their clinical VT CR treatments that could be used for future benchmarking. This study found that the pulmonary artery and superior vena cava generally received the lowest doses and the left anterior descending artery and left ventricle received the highest doses. Heart minus PTV dose was also reduced after changing the planning protocol to include dose optimization of this structure and it was observed that as the study progressed steeper dose gradients outside the target were achieved whilst still maintaining target dose conformity.

Clinical treatments utilizing the planning dose constraints discussed above observed few toxicities. Observed side effects have been comparable amongst the different treatment delivery units and studies. No serious acute toxicities or malfunction of the ICDs have been observed during or immediately after treatment

delivery. One study found most observed short-term toxicities were grade 1 or 2 but 10.5% of patients developed serious adverse events in the 3 months post-treatment[44]. There has been no evidence of short-term toxicities in the esophagus, phrenic nerve, coronary arteries nor significant degradation of cardiac contractility and currently no long-term data on long-term toxicities exists.

The ICD electronics have been treated as a structure that should receive minimal dose[45,53] and kept below the 2 Gy limit recommended by the American Association of Physicists in Medicine (AAPM)[45]. One study reported median planned ICD electronic doses of 0.13 Gy (range 0.03-0.60 Gy)[45] and another reported 0.2 Gy maximum dose to the ICD electronics. No reports have been found for dose to the ICD leads and/or ICD lead tips which are generally close to or directly inside the PTV. No ICD malfunctions or adverse changes in lead thresholds or impedances during or after treatment delivery have been reported so far for CR.

Beam-delivery technique planning

CyberKnife treatments utilized cylindrical collimator sizes in the range of 7.5–25 mm[41,56,57], 45–94 beam directions[11,51,55,56], 84–269 beams[11,43,51,55-57] and 22000–48000 MU[11,41,43,51,55-57]. C-arm linear accelerator treatments most commonly used volumetric modulated arc therapy (VMAT)[39,40,42,44,45,54,58,70,73] but fixed field intensity modulated radiotherapy treatment (IMRT)[40,44,47,63] and dynamic conformal arcs[52,53] have also been used. 6 MV photon beam energy, more commonly flattening filter free (FFF)[43,45], was nearly always used due to treatment recommendations for patients with ICDs[45]. The well-known reduction in treatment time when using 6 MV FFF (dose rate 1400 MU/min) compared to flattened beams (dose rate 600 MU/min) has been reported for CR[45]. One study used 10 MV FFF[52]. Plan metrics such as conformity index, homogeneity index, R50 (the ratio of 12.5 Gy isodose volume to the PTV volume), MU ratio and gradient measures (average distance between the 12.5 Gy and 25 Gy isotropic spherical volumes) were used to assess plan quality[41-43,45,50,51].

Besides already known advantages of the various SBRT delivery systems[75], a CR treatment planning study compared CyberKnife and c-arm linear accelerator treatment plans using a variety of planning techniques and reported that target dose coverage, dose homogeneity, and dose fall-off beyond the TV was superior with CyberKnife but distant critical structures were spared less in comparison[73].

Monte Carlo, raytracing, pencil beam, pencil beam convolution superposition and collapsed cone convolution dose calculation algorithms have been used in various TPS. For patients with an ICD or pacemaker, a study[41]

reported that metal artefacts caused by the pacing leads affected the dose distribution by <1%. For targets distal in the ventricle and hence in direct proximity to the left lung, a study[41] reported that the dose calculation accuracy with a type-A algorithm was affected less than 3% compared with Monte Carlo simulation. Conclusive studies are lacking, but it may be assumed that dose calculation errors from artefacts and tissue heterogeneities in the heart for CR are small; however distal PTVs extending into the lungs may require further investigation.

Patient specific quality assurance

Detailed information regarding patient-specific quality assurance for CR was rarely reported beyond general SBRT quality-assurance processes[40,44,45,53]. One study reported pre-treatment verification using a static diode-array detector passing >98% with a 3%/2 mm gamma evaluation criteria[47]. Knutson *et al.*[45] described their quality assurance processes in more detail. An ion-chamber measurement within a plastic water phantom, EPID-based dosimetry and treatment log-file comparison using in-house software was performed for all patients[45]. Film planar measurements were performed for the initial eight patients. For plan acceptance, point dose measurements had to be within 3% of the calculated dose and <10% and <5% of the planar measurement points had to fail 2%/2 mm and 3%/3 mm gamma-index criterion. They reported that all ion-chamber point dose measurements were within 2.9% of the predicted dose, with a median difference of 1.4%. The number of points failing 2%/2 mm gamma-index criterion was <8.0% (median 3.0%) in EPID dosimetry and <4.3% in film measurements.

Knutson *et al.*[45] also performed extensive treatment plan and treatment data review throughout their clinical trial. All dose-volume-histogram (DVH) data of clinically significant structures were compared to DVH data for all previously treated patients using dedicated in-house software. Patient setup shift data, plan delivery times, and elapsed time between simulation and treatment were also tracked. Control charts and statistical processes were used to evaluate changes in these parameters as the clinical trial progressed and the Shewhart 3-sigma method was used to establish upper and lower control limits for many planning and treatment parameters[45]. Quality assurance dose simulation under realistic cardio-respiratory motion has not been reported besides preliminary investigations[39,76].

Treatment delivery

Treatment systems

VT patient treatments have been delivered with the CyberKnife[41,43,46,49-51,55] (Accuray, Sunnyvale, USA), c-arm linear accelerators including the TrueBeam (Varian) [40,42,44,45,52,58], Edge (Varian)[40,44,45], and VersaHD (Elekta AB, Stockholm, Sweden)[54] and an MRI-Linac (ViewRay, Mountain View, CA, USA)[47]. AF patient treatments were delivered with the CyberKnife[56,57]. Pre-clinical studies demonstrated the feasibility of using protons and heavy-ions and a first human treatment for AF with protons has been reported from Italy (via press release). Proton and heavy-ion treatments can vary the depth of maximum dose deposition, which may be advantageous compared to photon treatments, but motion management may be more challenging with current systems.

Treatment delivery times were longer with CyberKnife (45–114 minutes[41,43,49-51,57,73]) than c-arm linear accelerators (4–32 minutes[40,44,45,52-54,73]). Overall linear accelerator treatment appointment times (treatment set-up, IGRT, delivery) have been in the order of 30–60 minutes[42,53,54]. The MRI-Linac treatment delivery was the longest; 24 minute beam-on time, 46 minute treatment delivery time due to beam-gating and 148 minute overall treatment time including multiple re-setups due to tracking interruptions, positioning checks and a patient toilet break[47]. This potential problem is particularly relevant for CyberKnife treatments of complex target shapes with fixed cylindrical collimators[11] and current MRI-Linac treatments with a non-optimized CR workflow[47] but could be overcome with smart sequencing and/or MLC tracking and/or workflow optimization. The clinical significance of this hypothesized high cellular repair rates for CR can only be speculated at this stage due to the current lack of comparable data. Detailed analysis and future studies are warranted.

Target volume localization and repositioning

The CyberKnife CR workflow generally involved an initial translational and rotational spine alignment using the in-room stereoscopic x-ray imaging system to align the patient into the treatment position and the Synchrony system (Accuray) to track available pacing lead tips for respiratory motion management[41,43,49-51]. An ITV and spine tracking combination is feasible with CyberKnife[77] but requires further investigation for CR as the relationship between the heart and the spine may vary over time.

3D or 4D cone-beam CTs (CBCTs) were acquired within the c-arm linear accelerator CR workflow to aid patient set-up[40,42,44,45,52,54,58] and a treatment couch capable of 6 degrees of freedom motion has additionally

been used[45]. Bony landmarks[42] and/or ICD leads[42,53] were used to guide the registration between the CBCT and planning CT[42]. Fluoroscopy[40,44,45] or portal imaging[54] were often additionally used to confirm couch shifts[40,44,45]. Fluoroscopy has also been used to verify target motion consistency with planning imaging by ensuring that the cardiac silhouette did not leave the PTV projection[45]. One study further repeated CBCT imaging during treatment delivery (e.g. after the delivery of the first arc)[53]. One patient was treated with mechanical ventilation and settings were evaluated and adjusted when the patient was on the treatment couch to confirm the target motion was consistent with planning imaging[54]. Another study acquired a dynamic multi-frame volumetric cine CT on the day of the treatment to ensure target motion consistency[58].

The MRI-Linac CR workflow[47] utilized a 3-dimensional TrueFISP MRI scan to match the target to the planning images and verify that the PTV, heart, and lung contours were aligned. Single-slice 2-dimenstional sagittal cine TrueFISP 60 second acquisitions was then performed to evaluate and set-up the MRI-guided gating during treatment.

Real-time motion management

Most CyberKnife treatment deliveries utilized real-time respiratory motion management (Synchrony, Accuray) using x-ray-based pacing lead tip tracking. This methodology creates a correlation model between the respiratory pacing lead tip and chest wall motion prior to treatment delivery, which is then monitored and adapted during treatment delivery. This system accounts for translational and dynamic respiratory motion and the additional cardiac motion will appear as sporadic correlation errors during modelling and update but will otherwise not influence treatment delivery. Respiratory-gating using an external chest surrogate marker has been performed for one c-arm linear accelerator treatment delivery[52]. The MRI-Linac treatment used the available MRI-guidance and the motion of the liver-dome to perform respiratory-gated beam delivery[47]. The patient performed 55 expiration breath-holds of >10 second duration for part of the treatment delivery. The authors mentioned tracking difficulties and low tracking correlation due to ICD-induced MRI artefacts. Distortion artefacts did not significantly impact the geometric accuracy, but ring artefacts caused by the device itself partly overlaid the target area and detrimentally impacted tracking ability.

Implantable Cardioverter Defibrillator (ICD)

A cardiac rescue team was usually on standby for CR deliveries[53] and ICD performance during treatment delivery was assessed via remote monitoring[40,44,45,55,58]. There appears to be limited consensus on how best

to handle the ICD during treatment delivery: ICDs have been disconnected[52], temporarily programmed to monitor-only[43] or left in regular mode[53]. Older ICD devices and electromagnetic radiation from the linear accelerator heads appear to raise the most concern as doses to the ICDs can generally be kept well below recommended thresholds[78]. The majority of studies interrogated the ICDs directly after treatment delivery and reconnected, re-programmed, or slightly modified ICD settings to appropriately detect VT episodes[40,41,43-45]. The patient treated on the MRI-Linac had a non-MR compatible ICD and extensive testing was performed to ensure the safety of the device[47]. There have been no reports of ICD damage from CR so far with mostly 6 MV photon CR treatments.

Follow up

Imaging and electrophysiology procedures used for post-treatment monitoring to date has been variable and has included ICD interrogation to assess the reduction or elimination of VT episodes compared to pre-treatment[40,41,43-45], ECG[44,54,55], chest x-rays[43,55], chest CT[40,41,43-45], echocardiography[41,43,47,54,55,57,58] and MRI[47,52,56-58]. 1.5 T contrast-enhanced cardiac MRI has been used in one VT[47] and one AF[56] CR study to assess both pre-treatment and post-treatment fibrosis and edema.

DISCUSSION & FUTURE DIRECTIONS

The complexity and variability in technology and procedural details currently utilized in clinical CR treatments makes it difficult to conclude whether treatment outcomes are correlated to CR procedures and technology choice even if the same dose is prescribed. Incomplete reporting in publications, lack of extra-institutional standardization of CR protocols, scarce evaluation of delivered dose to verify motion management and treatment delivery accuracy and limited pre- and post-treatment electrophysiology and anatomical imaging comparisons also compound this uncertain link between technology and outcomes. Improvements in these key areas would significantly advance scientific knowledge and improve the confidence in CR treatments.

The initial clinical cohort of patients receiving CR have mostly had scar-related VT, no alternative treatment options and significantly impaired quality of life or limited life expectancy. The clinical need and urgency for technique advancements appears more apparent for CR for VT. CR for AF may have differing technical requirements and/or challenges as it targets the thinner-walled atria, generally requires sustained electrical isolation of the pulmonary veins from the atria for therapeutic benefit and presents a different clinical risk-benefit scenario.

Recent reviews have comprehensively detailed patient selection, clinical case-histories, the dose-effect, treatment outcomes and treatment toxicities[14,16-18]. While out of the scope of this review, it is important to note that there are gaps in clinical knowledge that remain to be fully investigated and addressed. Better understanding of the underlying radiobiological mechanism, optimal treatment target definition, and the required dose to achieve therapeutic effect in arrhythmic humans is required. An arrhythmic pre-clinical model may help specifically investigate the dose-effect of CR for arrhythmias. Pre-clinical studies have investigated VT inducibility after myocardial infarction but currently no VT or AF pre-clinical model exists. Further long-term data on treatment outcomes and toxicities may also better inform clinicians on the risk-benefit profile of CR.

Areas that could benefit from further validation and/or development that are specifically related to procedure and technology choice are described in the sections below.

Pre-planning

Invasive EAM is well-established and routinely used within catheter ablation procedures, however, if proven to have comparable accuracy, alternate non-invasive electrophysiology mapping procedures such as ECGI, would greatly advance the overall CR clinical applicability and patient experience and may reduce required resources. Further analysis and comparison of electrophysiology mapping spatial and temporal uncertainties may help inform optimal treatment volume margin expansions and improvements in anatomical and physiology data acquisition in the presence of cardio-respiratory motion may reduce target delineation uncertainties.

Respiratory-gated 4DCT was often used to evaluate target motion and create ITVs, but it is not yet confirmed that this imaging modality accurately captures cardiac-induced target motion. Further cardio-respiratory target motion magnitude analysis (cardiac-induced and respiratory-induced target motion magnitude and trajectory, intra-patient and inter-patient variability, variability between ischemic and non-ischemic patients and variability between arrhythmic and normal sinus rhythm states) requires urgent investigation and would better advise optimal imaging modalities and motion management techniques.

Verification of accurate dose delivery will be vital to evaluate the suitability of motion management techniques and overall treatment delivery accuracy, including whether cardiac-induced target motion management is required and whether current oncology motion management techniques are suitable.

Other potential advancements include: development of direct tracking for cardiac-induced target motion management, analysis of surrogacy errors to verify the suitability of tracking surrogates and for incorporation into treatment margins, analysis of the suitability of motion restriction devices such as abdominal compression and evaluation of cardiac-induced tissue deformation.

Treatment planning & design

Increased compatibility between commercial cardiology electrophysiology contouring and radiation oncology TPS software or the commercialization of non-commercial software products currently used for target delineation would help reduce target delineation uncertainty and improve the efficiency of CR planning. Further assessment of electrophysiology-anatomical and anatomical-anatomical registration errors would advise suitable margin expansions.

PTV prescription dose coverage and heterogeneity has been variable and there has been limited reporting of ICRU 91 target constraints. Reporting standardization is urgently recommended as well as data sharing. Data collection projects are being initiated on an international scale and participation of centers performing cardiac radioablation is highly recommended.

Other required advancements include: long-term toxicity data to inform appropriate dose limits for OARs, particularly intra-cardiac structures, guidance regarding appropriate patient-specific quality assurance processes and potentially the development of a niche patient-specific quality assurance phantom tailored to CR.

Treatment delivery

Variation in technology and procedural details used in clinical CR treatments makes it difficult to determine superiority or inferiority of any treatment system. CyberKnife treatment delivery times were longer than linear accelerator treatments but overall CR treatment times were comparable to the duration of oncology treatments on the respective treatment systems.

MRI-linacs provides an avenue for treatment with state-of-the-art soft tissue imaging. However, the reported MRI-Linac case-study describes limitations in the MRI-guided gating software, did not directly compensate for cardiac-induced target motion, performed delivery mainly in breath-hold rather than free-breathing, and had a long treatment time. If these limitations could be overcome, even for patients with ICD leads, MRI-

guided treatment deliveries with real-time target visualization and motion compensation could greatly advance CR.

Proton or heavy-ion CR treatments have not yet been clinically realized but a recently published photon and proton CR plan comparison illustrates the conceptual benefit of proton CR treatments[79]. CR particle therapy application warrants further investigation because the potential dosimetric benefits are alluring but motion management in the presence of cardio-respiratory motion would need to be carefully accounted for.

Evaluation of the accuracy and spatio-temporal error of current motion management strategies, including targeting and imaging methods would aid margin calculations, help advise optimal imaging frequency during treatment delivery and evaluate the suitability of internal-external correlation models. Further development of targeting and intrafraction imaging methods including non-invasive real-time adaptive targeting tools may improve treatment delivery accuracy as well as broaden the suitability of targeting techniques to a larger cohort of patients without ICDs.

Data verifying treatment delivery accuracy are scarce, making it difficult to compare the results of studies utilizing different treatment delivery systems and motion management techniques. This additionally confounds the results of studies investigating the required treatment dose for therapeutic effect. Determining the uncertainty in delivered doses requires attention[80] and it is likely that the development and/or verification of alternative and potentially better suited methods, for example dose reconstruction, will be needed for evaluating CR delivered doses. Prospective real-time motion-including dose reconstruction has been demonstrated during liver radiotherapy treatment delivery[81] and this technology shows potential applicability for CR.

Follow-up

Potential advancements include: consistent and detailed reporting to enable comparability between CR treatments using different procedures and technology, multi-center multi-platform clinical trials with higher patient numbers and longer follow-up to compare methods and technology against treatment efficacy and safety, new follow-up procedures including the registration of pre- and post-electrophysiology and anatomical and functional imaging to the treatment plan to correlate results and treatment outcomes to procedural planning and design, and the development and verification of imaging biomarkers that are predictive of long-term therapeutic effect.

CONCLUSION

This review summarizes the technical aspects and procedural details of pre-clinical and clinical CR treatment deliveries and highlights the complexity and current variability of CR. There is need for standardized procedural reporting to aid multi-center, multi-platform evaluation. CR is an emerging field and there is potential for significant technological improvements in imaging, planning, delivery and monitoring to maximize the clinical outcomes for selected arrhythmia patients.

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FIGURE CAPTIONS

Figure 1: Summary of motion and motion management considerations for cardiac radioablation treatments. Both respiration-induced and cardiac-induced target motion needs to be carefully assessed. Respiratory motion management techniques such as breath holds, gated deliveries, internal target volumes (ITV) and x-ray based tracking are well established. Cardiac motion is of higher frequency and smaller magnitude and limited data exists on the requirements and suitability of currently available motion management techniques. Direct tracking or gating of cardiac or combined cardio-respiratory motion has been conceptually proposed or utilized in phantom studies but have not yet been used in clinical treatments.

Figure 2: Illustration of a typical clinical cardiac radioablation workflow. This workflow is comparable to radiation oncology SBRT treatments with the addition of electrophysiology (e.g., for ventricular tachycardia) and/or scar anatomical imaging (e.g., for ventricular tachycardia and atrial fibrillation) that is usually acquired to assist target delineation.

Table 1: *Summary of procedural and technical details of pre-clinical studies that performed treatment deliveries on live animals, grouped by technique.*

Study	Subjects	Treatment type	Dose	Target definition	Planning imaging	Motion management: cardiac	Motion management: respiration	Planning margins	Fiducial	Electrophysiological outcome	Adverse effects observed
Guerra *et al*. 2004	Dogs	β (Sr/Y^{90})	25 or 50 Gy	Cavotricuspid isthmus	Not reported	Not applicable	Not applicable	Not applicable	Not applicable	Conduction block in 88% of animals.	None
Perez-Castellano *et al*. 2006	Mini-pigs	β (P^{32})	60 Gy at 1mm	Superior wall of right PV trunk	Not reported	Not applicable	Not applicable	Not applicable	Not applicable	Transmural lesions in 60% PVs. AF remained inducible in 20% of animals	2 animals died; 1 electively euthanized, 1 animal suffered VF during catheterization
Amino *et al*. 2006 Amino *et al*. 2009 Amino *et al*. 2017	Rabbits Dogs	Carbon ions	5-15 Gy	Antero-lateral LV free wall	Not reported	Not reported	Artificial ventilation and GA	Not reported	Not reported	75%[32,62]-100%[18] reduction in VT/VF inducibility	Skin reactions and hair loss
Prall *et al*. 2015*	Pigs	Carbon ions	90- 160 Gy	AV node	3DCT	ITV, beam range changes, re-scanning multiple fractions	Not reported	15 mm isotropic	Clips for target delineation	AV block in 67% animals. Heart treated with 160Gy showed complete AV block	None
Lehmann *et al*., 2016, 2019* Rapp *et al*.,2019*	Pigs	Carbon ions	20 – 55 Gy	LV, AV node, or PV	Cardiac-gated, contrast-enhanced CT end-expiration under GA and ventilation	ITV from CT	Expiratory breath-hold, using ventilator	5 mm isotropic	None	AV block dose dependent, observed in 40%[24] and 67%[26] of animals. Reduction in EP parameters at RSPV-LA junction	None
Hohmann *et al*.,2019*	Pigs	Protons	30 or 40 Gy	LV (anterior wall, inferior wall, or apex)	Cardiac-gated, contrast-enhanced CT end-expiration	ITV from CT	Expiratory breath-hold, using ventilator	5 mm isotropic	None	Reduction in LV ejection fraction and LV dilation	6 animals receiving high dose to 3 targets died suddenly with no known cause of death
Sharma *et al*., 2010** Gardner *et al*., 2012** Zei *et al*., 2018 *Maguire et al*., 2011**	Canine & Mini-pig	Photons, CyberKnife	15 – 50 Gy	AV node, PV, left atrial appendage, cavotricuspid isthmus	Cardiac-gated, contrast-enhanced CT at end expiration and inspiration	ITV based on CT	Fiducial tracking	3 mm isotropic	Gold fiducials or catheter tip	Reduced EP parameters in 100% animals. Complete electrical block in 89% of animals. Doses >25Gy resulted in conduction block 100% animals	Myocardium infraction n=1, mild LV dysfunction n=3, trace mitral valve regurgitation n=1
Blanck *et al*., 2014 & Bode *et al*., 015	Mini-pig	Photons, c-arm linear accelerator	17.5 – 40 Gy	PV	Cardiac-gated, contrast-enhanced CT at end-expiration & end-inspiration for end-systole and end-diastole, under sedation and ventilation	ITV from 4DCT	ITV	5 mm isotropic	None	Reduced EP parameters in 83% animals. >32.5 Gy needed to achieve circumscribed scars and electrical conduction block	Unintentional AV block observed in 40 Gy animal, bronchial-mediastinal fistula in 37.5 Gy animal
Lehmann *et al*., 2017, Prall *et al*., 2017, Richter *et al*., 2017	Pigs	Photons, c-arm linear accelerator	25 – 55 Gy	AV node	Cardiac-gated, contrast-enhanced CT end-expiration under GA and ventilation	Anisotropic margin expansion (1mm left-right, 4mm superior-inferior, 4mm anterior-posterior)	Expiratory breath-hold, using ventilator	4 mm isotropic	None	Complete AV block in 86% animals. Reliable ablation achieved with >40 Gy	None

Refaat *et al*. 2017	Pig	Photons, c-arm linear accelerator	35-40 Gy	AV node	Cardiac gated CT (diastolic & systolic) under GA	ITV from 4DCT	Not reported	5 mm isotropic	None	Complete AV block in 100% animals	None

*Same technique utilized and therefore these studies have been grouped (dashed lines), **Same animals used and therefore these studies have been grouped.

3DCT = three-dimensional computed tomography, 4DCT = four-dimensional computed tomography, AF = atrial fibrillation, AV node = atrioventricular node, β = beta radiation, CT = computed tomography, EP = electrophysiology, GA = general anesthetic, ITV = internal target volume, LA = left atria, LV = left ventricle, P = phosphorous, PV = pulmonary vein, RSPV = right superior pulmonary vein, Sr = Strontium, VT = ventricular tachycardia, VF = ventricular fibrillation, Y = yttrium.

Table 2: *Summary of procedural details and technology choice for human ventricular tachycardia (VT) and atrial fibrillation (AF) cardiac radioablation treatments using CyberKnife.*

Study	Number of participants	Pre-planning EP & scar imaging	Imaging for planning	Arrhythmia	Prescription	Respiratory motion management	Cardiac motion management	Treatment motion management	Target volume size (range)	Treatment time
Neuwirth *et al*., 2019	10	EAM	Contrast-enhanced 3DCT x2 (ECG gated) in expiratory breath-hold	VT	25 Gy/1 fraction	Fiducial tracking (ICD lead)	ITV based on systole & diastole ECG-gated CT	kV orthogonal oblique planar intra-fraction imaging, & fiducial tracking (Synchrony).	TV: 14.2 – 29.6 cc (range) PTV: 14.2 – 29.6 cc (range)	Mean treatment time 68 min (range 45-80 min)
Gianni *et al*., 2020	5	EAM, ECG, contrast-enhanced CT	Contrast-enhanced cardiac CT in expiratory breath-hold	VT	25 Gy/1 fraction	Fiducial tracking (Temporary pacing lead)	Pre-defined 3mm target volume margin expansion	kV orthogonal oblique planar intra-fraction imaging & fiducial tracking (X-sight spine tracking & Synchrony)	PTV: 80 – 184 cc	Mean treatment times 82 min (range 71-93 min)
Loo *et al*., 2015	1	12-lead ECG, ECHO, PET-CT	3DCT in breath-hold & fluoroscopy images of cardiac fiducials in breath-hold	VT	25 Gy/1 fraction	Fiducial tracking (Temporary pacing wire)	ITV based on breath-hold fluoroscopy of cardiac fiducials.	kV orthogonal oblique planar intra-fraction imaging & fiducial tracking (Synchrony)	Not reported	90 min (approx.)
Jumeau *et al*., 2018	1	EAM, MRI, ECHO, PET	Non-contrast CT under GA & transthoracic echocardiography	VT	25 Gy/1 fraction	Fiducial tracking (ICD lead)	Motion assessed by transthoracic echocardiography	kV orthogonal oblique planar intra-fraction imaging & fiducial tracking (Synchrony)	TV: 21 cc	45 min (approx.)
Cvek *et al*., 2014	1	EAM, CT	3DCT (pre-acquired diagnostic scan)	VT	25 Gy/1 fraction	Fiducial tracking (LC electrode of stimulation system)	ITV based on systole & diastole	kV orthogonal oblique planar intra-fraction imaging & fiducial tracking (Synchrony)	Not reported	114 min
Zeng *et al*., 2019	1	12-lead ECG and EAM	3DCT & fluoroscopy In breath-hold	VT	24 Gy/3 fractions	Fiducial tracking (Active-fixation pacing lead)	ITV based on breath-hold fluoroscopy of cardiac fiducials.	kV orthogonal oblique planar intra-fraction imaging & fiducial tracking (Synchrony) assumed	PTV: 71.2 cc	Not reported
Monroy *et al*., 2016	1	None	CT	AF	25 Gy/1 fraction	Fiducial tracking	None (assumed as no mention)	kV orthogonal oblique planar intra-fraction imaging, & fiducial tracking	Not reported	Not reported
Qian *et al*., 2019	2	None	Contrast-enhanced cardiac CT	AF	25 Gy/1 fraction	Fiducial tracking (Active fixation lead in interatrial septum)	None (assumed as no mention)	kV orthogonal oblique planar intra-fraction imaging, & fiducial tracking	PTV: 48.9 – 54.5 cc	90 min (approx.)

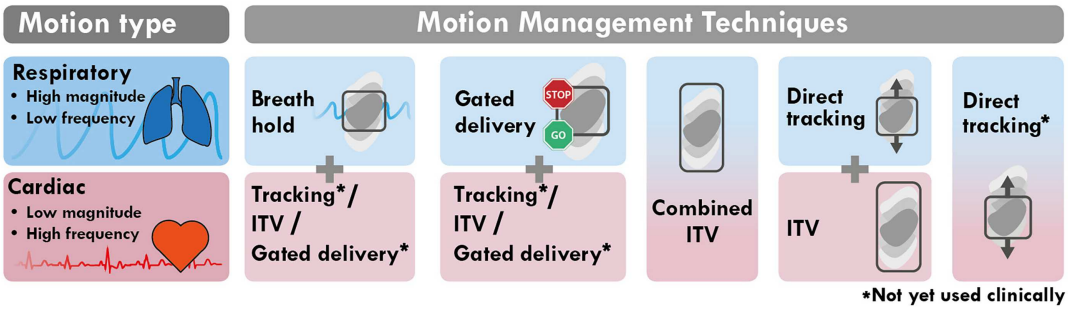
3DCT = three-dimensional computed tomography, AF = atrial fibrillation, CT = computed tomography, EAM = electroanatomical mapping, ECG = electrocardiography, ECHO = echocardiography, GA = general anesthetic, ITV = internal target volume, kV = kilovoltage, MRI = magnetic resonance imaging, PET = positron emission tomography, PTV = planning target volume, TV = target volume, and refers to the contoured treatment target without any margin expansions, VT = ventricular tachycardia

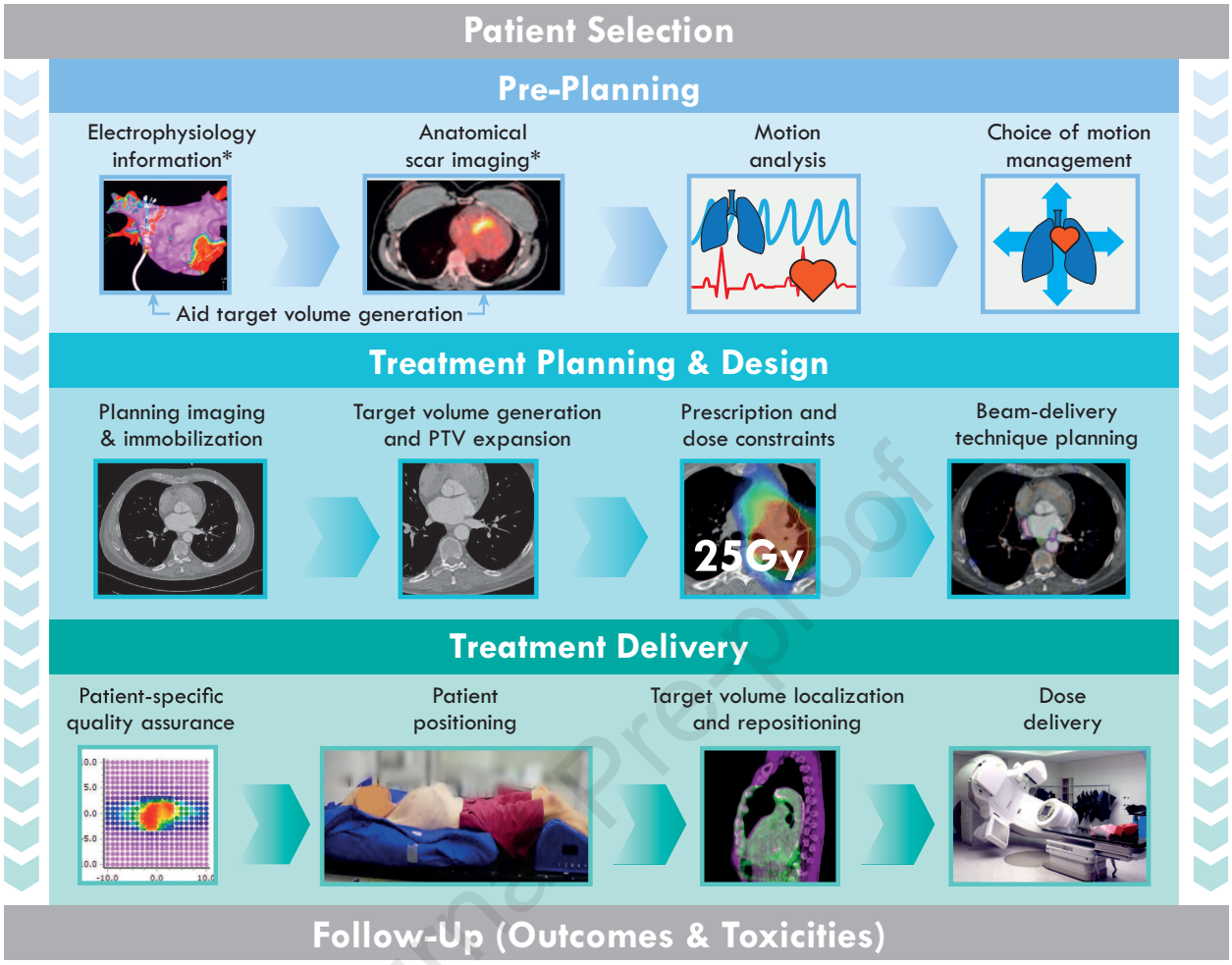
Table 3: *Summary of procedural details and technology choice for human ventricular tachycardia (VT) cardiac radioablation treatments using c-arm linear accelerators. No cardiac radioablation treatments for atrial fibrillation (AF) have been performed on c-arm linear accelerators.*

Study	Number of participants	Pre-planning EP & scar imaging	Imaging for planning	Arrhythmia	Prescription	Motion management	Treatment planning margins	Linac & treatment type	Immobilization	Treatment set-up /IGRT	Target volume size (range)	Timeframes
*Cuculich *et al*., 2017 *Robinson *et al*., 2019 *Knutson *et al*., 2019	19 (combined total)	Multi-electrode vest with CT registration, EAM, CT, contrast-enhanced MRI, ECHO, PET-CT	Contrast-enhanced 3DCT & 4DCT free-breathing	VT	25 Gy/1 fraction	Cardiac & respiratory: combined ITV. Abdominal compression used as needed.	ITV from 4DCT 5 mm ITV-PTV expansion	Varian TrueBeam or Edge 6 MV flat or FFF VMAT or IMRT	Vacuum-assisted cushion with vacuum-sealed layer or foam cushion with abdominal compression Overhead arm extension	Pre-fraction CBCT registered to respiratory-averaged planning CT, fluoroscopy to confirm shifts, 6dof couch	TV: 11.5 - 54.9 cc ITV: 17.7 – 81.6 cc PTV: 66 – 208.5 cc	Simulation on average 13.5 days before treatment, mean treatment delivery time 14 min (5.4-32.3 min)
Lloyd *et al*., 2019	10	At least 1 3D anatomical imaging and 1 EP study with EAM	Contrast-enhanced 3DCT & 4DCT free-breathing	VT	25 Gy/1 fraction	Cardiac & respiratory: combined ITV	1-5 mm scar to PTV expansion	Varian TrueBeam VMAT	Rigid immobilization consistent with Lung SBRT treatments	Pre-fraction kV planar & CBCT matched to bony anatomy and ICD leads	PTV: 29 – 238 cc	One hour between departure and return to clinical care unit. RT appointment 30 min
Marti-Almor *et al*., 2019	1	Previous EAM, MRI, CT	Unclear	VT	25 Gy/1 fraction	External surrogate amplitude-based respiratory gating	Not reported	Varian TrueBeam 10FFF DCA & static fields	Vacuum assisted device	Pre-fraction CBCT	Not reported	4 min treatment delivery
Bhaskaran *et al*., 2019	1	EAM, MRI	Contrast-enhanced 3DCT & 4DCT free-breathing	VT	25 Gy/1 fraction	Cardiac & respiratory: combined ITV	ITV from 4DCT 5-8 mm margin to include adjacent myocardial tracts, 5 mm ITV-PTV expansion	Varian TrueBeam 6FFF VMAT	Supine position with external thermoplastic shoulder immobilization	Volumetric cine on day of treatment (Canon Genesis 320 slice scanner) to verify planning margins adequate & pre-fraction CBCT	PTV: 52 cc	5 min treatment delivery
Krug *et al*., 2019	1	EAM, cardiac-gated CT	Non-contrast 4DCT free-breathing	VT	25 Gy/1 fraction	Cardiac & respiratory: combined ITV	ITV from cardiac-gated and free-breathing planning 4DCT, 5 mm ITV-PTV expansion	Varian TrueBeam 6FFF Co-planar DCA	Supine position with elevated arms. No vacuum bag or abdominal compression	Pre-fraction and between arcs CBCT, using ICD lead as reference for image registration	TV: 8.1 cc PTV: 42.2 cc	Patient positioning and setup of monitoring equipment approx. 40 min. Treatment and image guidance time approx. 15 min
Scholz *et al*., 2019	1	EAM, coronary angiography, LV angiography	4DCT	VT	25 Gy/1 fraction	Cardiac & respiratory: combined ITV with mechanical ventilation	ITV from 4DCT, 2 mm ITV-PTV expansion	Elekta VersaHD 6FFF VMAT	Deeply sedated and mechanical ventilation	Pre-fraction 4D CBCT and kV planar	ITV: 55.8 cc PTV: 82.4 cc	30 min treatment appointment, 5 min for image guidance, 5 min for delivery
Mayinger *et al.,* 2020	1	Contrast-enhanced MRI, non-contrast MRI, surface ECG, invasive EAM	CT & 3D MRI	VT	25 Gy/1 fraction	MRI-guided tracking of liver-dome with automatic beam gating & breath-hold	PTV 2 mm vertical and lateral, 3 mm longitudinal expansion	Hybrid MRI-Linac 6FFF IMRT	Supine position, arms raised above head	3D MRI matching TV to planning images, 2D single-slice sagittal cine for MRI-guided tracking	VT: 73.6 cc	Total duration 148 min; patient set-up 24 min, target localization & set-up 6 min, MR cine tracking 46min, beam on time 24 min

*Same group

3DCT = three-dimensional computed tomography, 4DCT = four-dimensional computed tomography, AF = atrial fibrillation, CBCT = cone-beam computed tomography, CT = computed tomography, DCA = dynamic conformal arc, dof = degrees of freedom, EAM = electroanatomical mapping, ECG = electrocardiography, ECHO = echocardiography, FFF – flattening filter free, GA = general anesthetic, ICD = implantable cardioverter defibrillator, IMRT = intensity modulated radiotherapy treatment, ITV = internal target volume, kV = kilovoltage, MRI = magnetic resonance imaging, MV = megavoltage, PET = positron emission tomography, PTV = planning target volume, TV = target volume, and refers to the contoured treatment target without any margin expansions, VMAT = volumetric modulated arc therapy, VT = ventricular tachycardia





*Not always used in cardiac radioablation workflows