Mapping guided Stereotactic ablative Radiotherapy, Hybrid treatment for uncontrollable ventricular tachycardia

Published: 02-01-2020
Last updated: 15-05-2024

Primary objective:To evaluate the clinical efficacy and side effects (adverse events) of a single dose stereotactic radiotherapy on the electro-anatomical arrhythmia substrate, inaccessible by the current state of the art catheter ablation...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON52679

Source
ToetsingOnline

Brief title
Mapping guided Stereotactic ablative Radiotherapy

Condition

- Cardiac arrhythmias

Synonym
cardiomyopathy, life threatening arrhythmias

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Stereotactic-ablative-Radiotherapy, ventricular-tachycardia

Outcome measures

Primary outcome

(1) Number of patients in whom the (presumed) clinical VT(s) causing the presenting symptoms can be eliminated (equals: partial success in RFCA studies) for the study period of one year (after 6 weeks blanking).

(2) Number of patients with the elimination of highly symptomatic VTs (e.g. pre-syncopal VT) or highly symptomatic ICD therapy (e.g. ICD shocks) for the study period of one year (after 6 weeks blanking).

(3) Reduction of any ICD treated VT episodes by >=80% at one year after treatment compared to the year before treatment (including VTs during the 6 weeks blanking)

Secondary outcome

(1) Time to elimination of the clinical VT(s) causing symptoms

(2) Time to elimination of any sustained VT/ VT prompting ICD therapy

(3) Elimination of the targeted arrhythmia substrate indicated by absence of inducible sustained VT at 6 months.

(4) Modification of VT substrate indicated by voltage reduction and non-excitability during electroanatomical mapping at 6 months

(5) number and dosage of class 1 and class 3 AAD at one year

(6) *SUVmax on F18-FDG-PET/CT between baseline, 2 weeks and 6 months after treatment.

Study description

Background summary

1.1 Ventricular tachycardia as an emerging clinical problem

Ventricular tachycardias (VT) are a medical emergency and require immediate termination. VT typically occur in patients with a myocardial scar from myocardial infarction or from non-ischemic cardiomyopathies. In patients with a high risk for VT or who have survived a life-threatening VT an implantable cardioverter defibrillator (ICD) device is recommended. The availability of ICDs has resulted in a marked change in the survival of patients with VT. Patients who formerly would have suffered sudden cardiac death now survive to experience recurrent VT and ICD shocks. Within one year after implantation, approximately 40% of patients will receive appropriate ICD therapy1, 2. This, together with increasing utilization of ICDs (in the Netherlands >30000 ICD recipients + approximately 4000 new implants/year) has resulted in an increasing frequency of patients presenting with recurrent ICD shocks, and the likelihood of a growing problem3. ICD therapy is considered as an adverse event!
Although ICD therapy can be lifesaving it does not prevent VT. Patients with very frequent VT are subject to increased risk of recurrent ICD shocks, progressive heart failure and death4, 5.
Repeated VT and ICD shocks, as most frightening cardiac arrhythmia presentation, result in (1) frequent re-admission to CCU and IC, (2) psychological morbidity (PTSS)2, (3) loss of consciousness with the risk of severe injury before VT is terminated by the device and most important (4) progression of heart failure and increased mortality6. These adverse events have dramatical consequences for the patient and the family in addition to the impact on the costs of the health care system.
There are clinical VT presentations, which are associated with particularly high morbidity and a high risk of (sudden) cardiac death despite the ICD therapy7.
(1) Electrical storms (defined as >=3 ICD shocks within 24h), (2) VTs causing recurrent (pre)syncope despite effective termination by ATP or ICD shocks, (3) recurrent VT (high VT burden) leading to progressive heart failure or (4) symptomatic, incessant VT not detected by the device or reinitiating after ICD therapy. In particular, arrhythmia presentation 3 and 4 may preclude patients with heart failure from LVAD implantation as destination therapy, as the right ventricle is not supported by the assist device.
Despite escalated antiarrhythmic drug (AAD) therapy and advanced catheter ablation technology, up to 50% of patients will experience recurrent VT8. New drugs are not available and current catheter technologies have important and well-recognized limitations in particular to reach deep intramural arrhythmogenic substrates or areas protected by insulated fat or

calcification9-13. Despite the availability of state-of the art technology and highly experienced operators in tertiary referral centers catheter ablation acutely fails to eliminate the electrical storm causing VTs in 9-12% of the patients7. Procedural failure has important prognostic implications during short-term follow-up: sudden death occurs in up to 40% within 3 months despite the ICD, and electrical storm, recurs in almost all7.
For these patients* therapeutic options to eliminate the VT sources inaccessible by current catheter technologies are urgently needed.

1.2 Novel treatment option for no-option-patients

Non-invasive cardiac radiation, applying a single-fraction stereotactic body radiotherapy (SBRT) has been recently reported as a very promising treatment modality to abolish the source of VTs in patients with structural heart disease and drug- and ablation refractory VT. In 3 series from two centers, including a total of 31 patients, the VT burden could be significantly reduced in the majority of patients with a reasonable safety profile. There was one grade 3 (pericarditis), probably related acute toxicity mentioned in the ENCORE-VT trial, others did not found any acute toxicity 14-16.
The immediate and most important advantage of SBRT is the applicability to reach VT substrates not accessible by any current catheter technologies. This should therefore not be withheld in patients who have today no other therapeutic option.

1.3 The importance of the accuracy and precision of radiotherapy for VT and limitations of prior studies

Despite encouraging first results a significant number of treated patients still had VT recurrence and 16% of these critically ill patients died with recurrent VT in the setting of a worsening overall cardiac status15. It is unclear if there is a lack of durable effect of radiation therapy or if the applied technology is inaccurate. Worsening of the cardiac status can be due to disease progression or late collateral damage to adjacent viable myocardium. The method has great potential but a better understanding of the biological effects is important and accuracy and precision need to be improved.

The major advantage of SBRT, in general, is to noninvasive target a well-defined and demarcated volume of tissue minimizing collateral damage. For efficacy and safety of stereotactic arrhythmia radio ablation (STAR) (1) accurate definition of the part of the scar proven to participate in arrhythmogenicity (accuracy of the method = correct identification, delineation and registration of the source/substrate of VT referred to as target volume), together with (2) optimal tracking of the radiation beam to follow the moving target volume during the respiratory and cardiac cycle (precision of the method), is mandatory.

The published methods to determine the target volume rely on

electrocardiographic imaging (ECGi) which uses multiple body surface electrograms to project epicardial depolarization onto the CT derived surface of the ventricles14, 15.
Noninvasive electrocardiographic mapping in conjunction with cardiac imaging to identify the arrhythmogenic substrate has important limitations:
(1) It can only identify epicardial exits sites during VT of those VTs that are inducible during non-invasive stimulation. However, in up to 35% of patients VTs are not inducible at all and if a VT is induced, the majority of these VT*s, are not clinically relevant or relevant at all17. (2) Recent intraoperative simultaneous endo and epicardial mapping studies during VT in post-MI patients could demonstrate that the epicardial exit site during VT and the critical part of the scar, responsible to sustain VT are spatially distant (mean distance 3.4cm) and discrepant18. The method is highly inaccurate for septal, endocardial and intramural VT substrates and has a poor precision even for epicardial VT sources (median distance from the VT source 3.3cm! (IQR 2.2 -4.6cm))19.

1.4 The rationale for the LUMC

1.4.1 Patient population

The department of cardiology, LUMC, is a national and international tertiary referral centre for ablation of complex VT in structural heart disease. The LUMC VT program is the largest in the Netherlands and among the 5 largest in Europe. As last resort institute we are confronted (in contrast to other institutes) with a high number of patients who have currently no other treatment option to control VT. There is a need to apply and further develop new technologies to reduce VT related morbidity and mortality in a growing patient population.

1.4.2 Technical requirements

The current limitations of accurate substrate delineation and target volume determination can be solved by combining current gold standards of catheter mapping and ablation of scar related VT as a hybrid procedure to accurately determine and potentially restrict the volume of interest to the area not accessible by RFCA. As RFCA is the recommended treatment modality in the described scenarios 1-4 this data is available from the clinically indicated procedure.
Accurate delineation of a well-defined target volume and highly focused radiation therapy allows to better determine and to improve the efficacy of the novel treatment. We have developed a method of real-time registration of electro anatomical mapping data (gold-standard to identify the VT source) and cardiac imaging (CT and CE-CMR) and we are able to accurately define, delineate and register the VT substrate, with a registration error of <0.3cm!12, 20, 21
The required knowledge and technologies to apply STAR with already higher accuracy than previously described are available in the LUMC and we have successfully treated the first two *no-option* patients in Leiden (April and June, 2019).

1.5 Unsolved questions

1.5.1 The acute and long-term biological effects and the time-to-effect (acute and long-term efficacy) are poorly understood.
The exact underlying mechanisms of the time-dependent effects of radiotherapy on the VT substrate are unknown. Reported time-to-effect was highly variable (from acute effects to weeks to months).
In many patients* immediate effects (within the blanking period) have been described with no reported ICD shocks after one month following the radiation15. Since scar formation/fibrosis due to radiotherapy normally takes months/years, one hypothesis is that acute inflammatory responses may contribute to the beneficial effect of radiotherapy on the VT substrate. To evaluate the exact time-to-effect is very important. Acute effects would allow the treatment of patients with arrhythmias only controllable in a clinical setting (requiring i.v. drugs/ hemodynamic support). The exact mechanism and type of tissue destruction is yet not clear. Based on limited animal studies some biological effects require a longer period (gradual apoptosis, vascular injury and fibrotic remodeling)22. The optimal effect in patients with scar-related VT would be scar homogenization. However, if this can be achieved and will be durable is unknown.

1.6 Summary of Rationale

There is an urgent need to demonstrate the clinical efficacy and safety of a single dose stereotactic radiotherapy of an accurately determined substrate for ventricular tachycardia, inaccessible by the current state of the art catheter ablation techniques in the LUMC for several reasons:
(1) The number of patients who present with VT and without any other treatment option to control these VTs is increasing.
(2) For these patients* therapeutic options to eliminate the VT sources inaccessible by current catheter technologies are urgently and acutely needed.
(3) SBRT is an existing treatment modality which has the potential to reach VT substrates not accessible by any current catheter technologies. The acute toxicity is very low. The therapy should therefore not be withheld in patients who have today no other therapeutic option.
(4) The knowledge and the technology required to apply SBRT with high accuracy and precision is already available and can be further improved.
(5) The risk profile is low as these patients have a limited life expectancy due to the underlying disease and co-morbidities and are unlikely to experience potential late cardiac toxicity.
(6) The clinical efficacy in *no-option* patients and the time to effect needs to be evaluated for optimal patient selection

Study objective

Primary objective:

To evaluate the clinical efficacy and side effects (adverse events) of a single dose stereotactic radiotherapy on the electro-anatomical arrhythmia substrate, inaccessible by the current state of the art catheter ablation techniques, in highly symptomatic patients with drug-refractory ventricular tachycardia.

Secondary objective:
To evaluate the efficacy and the time-to-effect of a single dose stereotactic radiotherapy to control clinical VTs and to modify the electro-anatomical arrhythmia substrate.
To evaluate formation and duration of an inflammatory response after a single high dose radiation on the VT-substrate

Study design

The study is a single centre (Phase IIA) pre-post intervention, single arm (12 patients) pilot study using routinely acquired data of real-time integration of electro-anatomical mapping data with cardiac imaging (including cardiac CT) to determine the part of the VT substrate (target volume) inaccessible by catheter ablation in highly symptomatic patients without any remaining established treatment option. The identified volume will be targeted by precise stereotactic radiotherapy. The study is designed to define the efficacy and safety of this novel treatment option using mapping guided radiation and to determine the time-to-effect and efficacy to abolish the delineated VT substrate based on state of the art electro-anatomical mapping techniques with real-time image integration.

According to our standard clinical protocol for mapping and ablation of complex scar related VTs, (contrast) echo (right and left ventricular function, valvular disease, intracardiac thrombus), CE-MRI and/or CT and coronary angiogram if considered appropriate, is routinely performed prior to ablation, followed by real-time image integration with electro-anatomical mapping data during the clinically indicated procedure. Accordingly, determination of the arrhythmogenic substrate, inaccessible by catheter ablation, which can be post-procedurally extracted from the 3D mapping system is clinical standard and not part of a study protocol.

The patient study duration will start after informed consent for STAR as a bail-out strategy.
Additional assessment of safety endpoints includes a pulmonary function test. Subsequently, patients will undergo a contrast enhanced 4D-CT-scan for radiation treatment planning purposes. The radiation oncologist and the cardiologist-electrophysiologist will in close cooperation delineate the target area for treatment. After radiotherapy planning, the radiotherapy treatment will be performed. After the treatment with radiotherapy patients will be monitored for at least 24 hours. Afterwards the patient undergoes follow-up for the primary and secondary efficacy and safety endpoints. Follow up will be scheduled at 2, 4 and 12 weeks and at 3-months intervals thereafter. The

evaluation will include history, clinical examination, ECG and ICD interrogation. For safety endpoints blood samples, transthoracic echo (at 3, 6 and 12 months) and a pulmonary function test (at 3 and 12 months) will be performed. For evaluation of presence and duration of an inflammatory response F18-FDG-PET/CT will be performed at 2 weeks and 6 months. For efficacy and time to effect evaluation patients will be readmitted (one-to-two day admission) at 6 months for PES and endocardial electro-anatomical remapping of the target area.

The endpoints are finalized at one year. Follow up will continue as a standard of care thereafter which includes a minimum ICD interrogation every 6 months and yearly clinical evaluation.

Intervention

Patients are treated with a single radiotherapy fraction of 25 Gy targeting specifically the part of the identified VT substrate, which was not accessible by the current state of the art catheter ablation techniques (all maneuvers that are known to enhance lesion depth). Substrate identification is performed using the current state of the art techniques including real-time integration of electro-anatomical mapping data with cardiac imaging, including cardiac CT. This technique allows precise determination of the radiation volume by extracting mapping data together with the anatomical location on CT which can be used for the radiation planning

Study burden and risks

Possible disadvantages of participating in this study could be:
- The possible adverse effects that are related to the new treatment in both the short and the long term (after 10-15 years)
- Possible inconveniences of the measurements
- Unexpected findings that may be detected in the additional investigations.
- Time investment
- Patient will undergo additional examinations
- Patient will be admitted for at least 24 hours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age >=18
- Implanted ICD
- Structural heart disease with myocardial scar
- World Health Organization (WHO) / Eastern Cooperative Oncology Group (ECOG) performance status grade 0-3 in the past 3 months, or grade 4 if related to the ar-rhythmic presentation (from fully active to capable of limited self-care, see below for full explanation)

- Presenting with at least one of the following
* Within the past 3 months: electrical storm (defined as >=3 ICD shocks within 24h)
* Within the past 3 months: 3 or more episodes of highly symptomatic sustained VT (either requiring ICD shocks, or leading to (pre)syncope)
* Recurrent VT (high VT burden) leading to progressive heart failure
* Symptomatic, incessant VT not detected by the device or reinitiating after ICD therapy
* Progressive heart failure and indication for LVAD, in whom recurrent VT preclude LVAD implantation
- Despite all of the following

* Optimal medical treatment according to current guidelines
* Failure of recommended antiarrhythmic drugs including failure of amiodarone
* Failure of catheter ablation using the current state of the art catheter ablation techniques to modify the VT substrate

- Able and willing to undergo all necessary evaluations, treatment and follow-up for the study and of follow-up thereafter
- Informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Pregnancy
- Interstitial pulmonary disease
- Irreversible renal insufficiency with a glomerular filtration rate <30ml/min (not related to the high VT burden)
- Life expectancy <12 months in the absence of VT
- Refusal or inability to provide informed consent or to undergo all necessary evaluations, treatment and follow-up for the study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-02-2020
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	02-01-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27436
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL70844.058.19
OMON	NL-OMON27436