Precision Radiation treatment for Epilepsy

Published: 06-09-2023
Last updated: 08-02-2025

Objectives: Primary: to determine whether SRT reduces the seizure frequency resulting in a reduction of at least 75% (RAEC I-III) in patients with drug-resistant focal epilepsy when compared to standard of care. Secondary: Assess quality of life (...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON53258

Source
ToetsingOnline

Brief title
PRECISION

Condition

- Seizures (incl subtypes)

Synonym
epilepsy, seizure

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: ZonMW / Zorginstituut

Intervention

Keyword: curative, epilepsy, non-invasive, radiation

Outcome measures

Primary outcome

Main study parameters/endpoints: Primary endpoint: RAEC I - III after 2 year of follow-up.

Secondary outcome

Secondary endpoints: Seizure frequency, Type epilepsy, Seizure-free days, Quality-of-Life in Epilepsy (EQ-5D 5 Level, AQOL-8D, QOLIE-31), Serious Adverse Events (SAE), anti-epileptic drug use, Cost-effectiveness Resource use iMTA Productivity Cost Questionnaire (iPCQ), iMTA Medical Consumption Questionnaire (iMCQ), iMTA Valuation of Informal Care Questionnaire (iVICQ)], Patient-reported outcome measures (PROMs), Patient-reported experience measures *medische specialistische zorg* (PREM MSZ), neuro-cognition.

Study description

Background summary

The PRECISION trial offers a non-invasive, curative intervention for patients with resistant focal epilepsy who are not eligible for open brain surgery. The intervention will consist of a single LINAC (Linear Accelateror) based stereotactic radiotherapy (SRT) treatment and is given by the radiotherapist-oncologist after detailed localization of the epileptogenic zone (EZ) together with the neurologist, radiologist and neurosurgeon. This intervention is not yet available in the Netherlands and is not reimbursed and in selected patients, who would otherwise be treated palliatively, will offer a non-invasive curative treatment option as a non-competitive alternative to epilepsy surgery. It is expected that the health costs for this curative treatment will not exceed standard treatment, such as lifelong medication and neuromodulation. A cost-effectiveness analysis is performed for this study.

This analysis also includes indirect costs of the informal caregivers of the included epilepsy patients in the PRECISION trial. We assume that: SRT is curative and is a non-inferior treatment option compared with the palliative standard treatment (ie, antiepileptic drugs (AEDs) and neuromodulation), for patients with drug-resistant focal epilepsy, who are not eligible for neurosurgery, which will result in a higher reduction in seizures (with 50% of patients achieving a 75% reduction after 2 years).

Study objective

Objectives: Primary: to determine whether SRT reduces the seizure frequency resulting in a reduction of at least 75% (RAEC I-III) in patients with drug-resistant focal epilepsy when compared to standard of care. Secondary: Assess quality of life (QoL) after SRT, define safety, (serious) adverse effects, AED use and tolerability of SRT, investigate the cost-effectiveness (CEA) of SRT compared to standard of care.

Study design

Randomised waitlist controlled trial in which SRT is the intervention and AED continuation and neuromodulation are the standard treatment with a 1:1 randomization. After 2-year follow up (waitlist) of the controlgroup, patients are offered the intervention (optional).

Intervention

Intervention: LINAC-based Stereotactic Radiotherapy (SRT): Target definition: the target volume is defined as the epileptogenic zone (EZ) on all (non) invasive examinations of the presurgical trajectory. A single fraction SRT with a prescribed isotoxic dose of 24 Gy to the 100% surrounding isodose.

Study burden and risks

Benefit-risk balance: It is not known if SRT is superior to the standard treatment for patients not eligible for curative resective epilepsy surgery (which is the control group: AED and neuromodulation). For the patients in the waitlist-control group there is no additional risk, since they receive the current standard of care treatment during the 2 year waiting/follow-up time. Also the risk for sudden unexpected death in epilepsy (SUDEP) is equal. Given the chronic nature of the epilepsy there is no additional risk.

For the patients treated with SRT the risks are based on the location of the EZ zone. Information is available from treatment of patients with epilepsy, brain metastases or benign brain lesions. Treatment related side effect in patients with epilepsy are based on an update of the review of Eekers et al. 2018.

The most common acute side-effect of SRT is a headache, nausea and/or vomiting caused by reversible intracranial oedema and can be treated with corticosteroids. Long-term side-effects include transient neurological deficits and exacerbation of seizures, magnetic resonance imaging (MRI) changes, expected and mostly asymptomatic superior quadrantanopia (for lesions treated in the temporal lobe), ischemic events, cognitive changes [L. Douw et al., 2009] and radiation necrosis rarely leading to symptomatic oedema or cysts requiring surgical intervention [N.M. Barbaro et al. 2018], [D.B.P. Eekers et al 2018].

If the EZ zone is close to the pituitary, potential risks can be estimated from the literature of treatment of patients with a pituitary tumor. Cerebral infarction has been described as a long-term complication of stereotactic radiotherapy of benign skull base tumors, mainly pituitary tumors (SIR 1.48 - 4.2). When treating the amygdala patients may have a similar risk due to the close relationship with the internal carotid artery [M.G.A. Sattler et al. 2013], [P.D. Brown et al. 2014].

For patients with a pituitary adenoma it is known that hypopituitarism can occur after conventional and stereotactic radiotherapy in 50% of the patients, 10 years after treatment [G. Minniti et al. 2011], [G. Barrande et al. 2000], [N.R. Biermasz et al. 2000]. However, in patients with a non-functional pituitary adenoma population in 37-85% of the patients has already hypopituitarism at the start of diagnosis [C.E. Higham et al. 2016]. Deficit of hormone production after conventional radiotherapy of the pituitary with 45Gy is 45-100% for GH, 18-30% for LH/FSH, 15-22% for ACTH and 25% for TSH [K. H. Darzy et al. 2009], [P.J. Jenkins et al. 2006].

Location in the eloquent cortex is associated with neurological complications in patients with brain metastasis, therefore when the location of the EZ is within the eloquent areas we can limit the dose prescription to 18Gy in order to reduce this risk.

The possible side effects of SRT will be registered carefully and will be weighed against the anticipated gain in quality of life. Side-effects from AED's include nausea and vomiting, ataxia, somnolence and rare, idiosyncratic reactions. DBS involves the surgical placement of neurostimulators in the brain, reducing seizure frequency while in the epileptogenic zone, and has headache, infection, seizure, cerebral haemorrhage, stroke, confusion and difficulty concentrating as potential side-effects. NVS is performed by implantation an electrode coil around the left cervical vagus nerve connected with a subcutaneous lead to the pulsgenerator in a subcutaneous thoracic pocket reducing the seizure frequency up to 50% in two thirds of the patients with hoarseness, bradycardia, infection, paraesthesia and dysphonia as known side-effects [A.D. Farmer et al. 2016].

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

Patients:
1. Age >= 18 years
2 Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations
3. Willingness to use contraception by a method that is deemed effective by the Investigator during the SRT treatment and for at least 30 days following the SRT therapy
4.The patient or caretaker is able to keep an epilepsy diary
5. The patient has a diagnosis of epilepsy established by a dedicated neurologist
6. The patient had at least 3 focal-onset seizures over a 3-month period despite two or more antiepileptic medication trials (according ILAE Task Force

on therapeutic strategies)
7. Video electroencephalography and work-up in the epilepsy surgery working group to determine a well-circumscribed seizure focus is available
8. Evidence (e.g. 3T-MRI or a clear SEEG delineation) of the anatomic region to be targeted with SRT, correlating with the EZ hypothesis;
9. A functional MRI to lateralize language or localize visual, motor and/or sensory eloquent cortex *has been performed in selected patients (if the lesion is expected to be located, based on anatomy, in the language areas).
10.The patient has completed a standard battery of neuropsychological testing
11.The patient been deemed an appropriate candidate for stereotactic radiosurgery by a dedicated Radiation Oncologist and Neurosurgeon/Epileptologist and referred for the study by one of the Dutch regional multidisciplinary epilepsy surgery working groups
12. Patients that were rejected for surgery in an earlier stage can participate in the trial if the last change of the NVS/DBS settings were more than 1 year ago or NVS/DBS was not (yet) tried.

Informal caregivers:
1. Age >= 18 years
2. Understanding of Dutch language

Exclusion criteria

Patients:
1. Pregnancy
2. If a radiation treatment plan without exceeding the constraints for the organs at risk is not feasible.
3. Prior cranial radiotherapy
4. If radiotherapy treatment is not possible for diverse reasons.
5. If the subject has clinically significant and uncontrolled major other medical condition(s) including but not limited to:
- psychiatric illness/social situation that would limit compliance with study requirements
- any medical condition, with the opinion of the study investigator, places the subject at an unacceptably high risk for toxicities
- Progressive co-morbidity which limits overall survival.

Informal caregivers:
1. No signed informed consent

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-01-2024
Enrollment:	188
Type:	Actual

Ethics review

Approved WMO

Date:	06-09-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05182437
CCMO	NL84071.068.23