Assessing and Predicting Radiation Influence on Cognitive Outcome using the cerebrovascular stress Test

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Observational non invasive

Summary

ID

NL-OMON52427

Source
ToetsingOnline

Brief title
APRICOT

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym
Brain metastases, metastatic brain disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF

Intervention

Keyword: Brain metastases, Cognitive outcome, Prediction

Outcome measures

Primary outcome

The main endpoints will be the change in neurocognitive test score between pre- and post-radiotherapy in relation to cerebrovascular reactivity as measured with MRI before the start of radiation treatment.

Secondary outcome

1. The changes in cerebral hemodynamics (CVR and cerebral blood perfusion) in relation to the changes in cognitive performance 3 months after radiotherapy.

2. The spatial distribution of cerebral hemodynamics in relation to change in cerebral hemodynamics 3 months after radiotherapy.

3. The spatial relationship between dose distribution and regional cerebral hemodynamics changes 3 months after radiotherapy.

4. The spatial relationship between dose distribution and cerebral morphological changes 3 months after radiotherapy.

5. Relation between patient reported QoL and performance on the NCA both before and 3 and 11 months after radiotherapy.

6. Relation between changes in brain morphology (e.g. cortical thickness or white matter tract integrity) and changes in cerebral hemodynamics and cognitive performance.

7. Comparison of the WBRT and SRS group regarding cognitive performance and cerebral hemodynamics.

8. Relation of compliance with both the CST and NCA in patients receiving

radiotherapy.

Study description

Background summary

Whole brain radiotherapy (WBRT) is a common therapy for the treatment of brain metastases, or as prophylaxis to prevent intracranial metastases. An alternative for the treatment of brain metastases is stereotactic radiosurgery (SRS). The median overall survival time of patients with intracranial metastases is approximately seven months with systemic and local treatment. After brain irradiation patients may suffer from radiation induced brain injury and neurocognitive deficits. Since cognitive functions are essential for our daily social, occupational and personal life, impaired cognitive functioning consequently affects quality of life (QoL) during the remaining life span of these patients. It is currently not possible to predict the impact of radiotherapy on individual patients. The pathogenesis of this radiation-induced cognitive impairment is not fully understood, but some evidence suggests that it could be considered a type of vascular dementia. The hypothesis is that radiation damage to cerebral vessels leads to a reduced blood supply and subsequent damage to brain tissue. Additionally, patients with impaired vascularisation of the brain at start of radiotherapy have less reserve to maintain the required blood supply. A reliable method to measure the hemodynamic status of the cerebral vessels is cerebrovascular reactivity (CVR) as measured during the cerebrovascular stress test (CST), which uses respiratory challenges to estimate the reserve capacity of the microvasculature of the brain. Our findings will work towards identifying risk factors for radiation-induced cognitive changes. In the future this knowledge could be of value in making treatment decisions.

Study objective

The main goal is to identify risk factors for radiation induced cognitive changes. Therefore, cerebral hemodynamic status of the patient, measured as cerebrovascular reactivity (CVR) with magnetic resonance imaging (MRI), at the start of radiation therapy will be studied in relation to the change in cognitive performance before and 3 and 11 months after radiotherapy. In addition, changes in cerebral hemodynamics, radiation dose (spatial) response relationship and patient compliance will be studied.

Study design

A prospective study.

Study burden and risks

Subjects will have no direct benefit from participating in this study. The NCA has no risks. The only risk of this study is the chance of a transient increase of the intracranial pressure during the hypercapnic stimulus. Therefore, suspected increased intracranial pressure (defined as non-prophylactic >4 mg dexamethasone use) is an exclusion criterion. Furthermore, an independent blood oxygen saturation and respiratory rate monitoring will be performed during the MRI measurements with fingertip pulse oximetry and a pressure sensor for the respiratory rate. The controlled gas breathing will be administered using the reliable RespirAct RA-MRTM MRI UNIT which has an open breathing system. Subjects have to breathe through a mask. The increase in end-tidal CO2 (PetCO2) we will apply will be within physiological ranges, experienced repeatedly during a normal day and night and also occur spontaneously in patients with gliomas while under (local) anaesthesia before resection. Nevertheless if subjects do experience discomfort because of high arterial CO2 levels, the operator can switch instantly to room air when the red button on the front of the gas blender is activated. In the MRI, subjects can squeeze the panic button.
Before participating in this research, all subjects will receive an extensive explanation about the device and the procedure. We will administer the entire respiratory protocol outside of the MRI scanner first, to see how the subject reacts to the hypercapnic stimuli. Only when we are sure the subject is comfortable with the respiratory challenges, we will perform the test in the MRI. Subjects will be able to practice squeezing the MR panic button once positioned on the scanner bed. The subjects will be able to withdraw themselves at any moment throughout the study.
Additionally, the RespirAct RA-MRTM MRI UNIT that will be used to administer the breathing challenges is a plug-and-play device and as such does not require special training for operation. System failsafes, and the fact that subjects are always open to room-air ensures that there is no possibility for accidental hypoxia. Nonetheless all staff operating the RespirAct RA-MRTM MRI UNIT has received official training by the manufacturer (Thornhill Research). Also, the research group performing this research (including Dr. A. Bhogal) has extensive experience with both the device and similar breathing protocols, thereby ensuring maximum safety for participants.

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

For patients:
- Age >= 18 years;
- Expected survival >= 5 months, as determined by Graded Prognostic Assessment (GPA) score;
- Either radiographic and/or histologic proof of metastatic brain disease eligible for cranial irradiation;
- Eligible for brain irradiation for prophylaxis or treatment;
- Signed informed consent;
- Sufficient knowledge of the Dutch language to allow reliable use of the standardized tests and understand the study information;
- Participation in the COIMBRA cohort, with given consent for filling in QoL questionnaires.

For healthy volunteers:
- Age >= 18 years;
- Signed informed consent;
- Sufficient knowledge of the Dutch language to understand the study information.

Exclusion criteria

For patients and healthy volunteers:
- Unwilling or unable to cooperate with breathing manoeuvres or keeping still;
- Medical contraindications to limited hypercapnia (known metabolic acidosis or alkalosis);
- Standard contraindications for 3T MRI scanning;
- Standard contraindications for using the RespirAct RA-MRTM MRI UNIT;
- Noncompliance with prescribed anti-seizure medication;
- Severe current neurological or psychiatric diseases (including pre-existent dementia or other cognitive disorders as diagnosed by a neurologist, psychiatrist or gerontologist), not related to the primary malignancy or cerebral metastases;
- History of cerebrovascular disease (ischaemic stroke or intracranial haemorrhage);
- Non-prophylactic use of >4 mg dexamethasone on the day of the cerebrovascular stress test;
- Cardiovascular disease: congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, and myocardial infarction within past 6 months as diagnosed by a cardiologist;
- Pulmonary disease as diagnosed by a pulmonologist: oxygen dependency at rest or with exercise, restrictive lung disease with resting respiratory rate over 15 breaths/min;
- Concurrent severe or uncontrolled medical disease (e.g., active systemic infection);
- History of bleomycin treatment;
- Body weight <30 kg, >100 kg;
- Pregnancy.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2019
Enrollment:	145
Type:	Actual

Medical products/devices used

Generic name:	RespirAct RA-MRTM MRI UNIT
Registration:	No

Ethics review

Approved WMO Date:	28-08-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	01-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	METC NedMec

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
CCMO	NL67227.041.18