**Hitting the Mark: Introducing state-of-the-art MRI for precision radiotherapy of glioblastoma**

**Hitting the Mark: Introducing state-of-the-art MRI for precision radiotherapy of glioblastoma**

|  |  |
| --- | --- |
| **Protocol ID** | **NL84994.078.23** |
| **Short title** | **MOSAIC** |
| **EudraCT number** | ***N/A*** |
| **Version** | **1.0** |
| **Date** | **28 July 2023** |
| **Coordinating investigator/project leader** | ***N/A*** |
| **Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)**  ***<Multicenter research: per site>*** | **Alejandra Méndez Romero, PhD, MD**  **Radiation oncologist and assistant professor**  **Department of Radiotherapy**  **Erasmus MC Cancer Institute - University Medical Center, Rotterdam**  **Dr. Molewaterplein 40, 3015 GD Rotterdam**  **The Netherlands**  **Tel: 010-7035792**  **E-mail:** [**a.mendezromero@erasmusmc.nl**](mailto:a.mendezromero@erasmusmc.nl)  **Esther A.H. Warnert, PhD, MSc**  **Assistant professor**  **Department of Radiology & Nuclear Medicine**  **Erasmus MC - University Medical Center**  **Rotterdam**  **E-mail:** [**e.warnert@erasmusmc.nl**](mailto:e.warnert@erasmusmc.nl)  **Patrick L.Y. Tang, MSc**  **PhD-candidate**  **Department of Radiology & Nuclear Medicine**  **Department of Radiotherapy**  **Erasmus MC - University Medical Center**  **Rotterdam**  **E-mail:** [**p.l.y.tang@erasmusmc.nl**](mailto:e.warnert@erasmusmc.nl) |
|  |  |
| **Sponsor (in Dutch: verrichter/opdrachtgever)** | **Erasmus MC, Department of Radiotherapy** |
|  |  |
| **Subsidising party** | **NWO** |
| **Independent expert (s)** | **Prof. dr. Meike W. Vernooij Neuroradiologist Department of Radiology & Nuclear Medicine Erasmus MC – University Medical Center Rotterdam E-mail:** [**m.vernooij@erasmusmc.nl**](mailto:m.vernooij@erasmusmc.nl) |
| **Laboratory sites <*if applicable*>** | ***N/A*** |
|  |  |
| **Pharmacy <*if applicable*>** | ***N/A*** |
|  |  |

**PROTOCOL SIGNATURE SHEET**

|  |  |  |
| --- | --- | --- |
| **Name** | **Signature** | **Date** |
| **Sponsor or legal representative:**  ***Erasmus MC, Department of Radiotherapy***  ***Head of Department of Radiotherapy:***  ***Prof. dr. R.A. Nout*** |  | **28-07-2023** |
| **[Coordinating Investigator/Project leader/Principal Investigator]:**  ***Alejandra Méndez Romero, PhD, MD***  ***Radiation oncologist and assistant professor***  ***Department of Radiotherapy***  ***Erasmus MC Cancer Institute - University Medical Center, Rotterdam*** |  | **27-07-2023** |

**TABLE OF CONTENTS**

1. INTRODUCTION AND RATIONALE 11

1.1 Background 11

1.2 Target definition for radiotherapy 11

1.3 State-of-the-art MRI 11

1.4 Rationale 13

2. OBJECTIVES 14

3. STUDY DESIGN 15

4. STUDY POPULATION 18

4.1 Population (base) 18

4.2 Inclusion criteria 18

4.3 Exclusion criteria 18

4.4 Sample size calculation 18

5. TREATMENT OF SUBJECTS 19

5.1 Investigational product/treatment 19

5.2 Use of co-intervention (if applicable) 19

5.3 Escape medication (if applicable) 19

6. INVESTIGATIONAL PRODUCT 20

6.1 Name and description of investigational product(s) 20

6.2 Summary of findings from non-clinical studies 20

6.3 Summary of findings from clinical studies 20

6.4 Summary of known and potential risks and benefits 20

6.5 Description and justification of route of administration and dosage 20

6.6 Dosages, dosage modifications and method of administration 20

6.7 Preparation and labelling of Investigational Medicinal Product 20

6.8 Drug accountability 20

7. NON-INVESTIGATIONAL PRODUCT 21

7.1 Name and description of non-investigational product(s) 21

7.2 Summary of findings from non-clinical studies 23

7.3 Summary of findings from clinical studies 23

7.4 Summary of known and potential risks and benefits 23

7.5 Description and justification of route of administration and dosage 23

7.6 Dosages, dosage modifications and method of administration 23

7.7 Preparation and labelling of Non Investigational Medicinal Product 24

7.8 Drug accountability 24

8. METHODS 25

8.1 Study parameters/endpoints 25

8.1.1 Main study parameter/endpoint 25

8.1.2 Secondary study parameters/endpoints (if applicable) 25

8.1.3 Other study parameters (if applicable) 26

8.2 Randomisation, blinding and treatment allocation 26

8.3 Study procedures 26

8.3.1 Data collection 26

8.3.2 Recurrence volume delineation 26

8.3.3 Pattern of failure analysis and dose to organs at risk comparison 29

8.3.4 Examination of CTVs based on a different combination of aMRI 29

8.3.5 Assessment of the pathophysiological changes detected by aMRI at the site of future tumor recurrence 29

8.4 Withdrawal of individual subjects 30

8.4.1 Specific criteria for withdrawal (if applicable) N/A 30

8.5 Replacement of individual subjects after withdrawal 30

8.6 Follow-up of subjects withdrawn from treatment 30

8.7 Premature termination of the study 30

9. SAFETY REPORTING 31

9.1 Temporary halt for reasons of subject safety 31

9.2 AEs, SAEs and SUSARs 31

9.2.1 Adverse events (AEs) 31

9.2.2 Serious adverse events (SAEs) 31

9.2.3 Suspected unexpected serious adverse reactions (SUSARs) 32

9.3 Annual safety report 32

9.4 Follow-up of adverse events 32

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee] 33

10. STATISTICAL ANALYSIS 34

10.1 Primary study parameter(s) 34

10.2 Secondary study parameter(s) 34

10.3 Other study parameters 34

10.4 Interim analysis (if applicable) 34

11. ETHICAL CONSIDERATIONS 35

11.1 Regulation statement 35

11.2 Recruitment and consent 35

11.3 Objection by minors or incapacitated subjects (if applicable) 35

11.4 Benefits and risks assessment, group relatedness 35

11.5 Compensation for injury 35

11.6 Incentives (if applicable) 36

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION 37

12.1 Handling and storage of data and documents 37

12.2 Monitoring and Quality Assurance 37

12.3 Amendments 37

12.4 Annual progress report 37

12.5 Temporary halt and (prematurely) end of study report 38

12.6 Public disclosure and publication policy 38

13. STRUCTURED RISK ANALYSIS 39

13.1 Potential issues of concern 39

13.2 Synthesis 40

14. REFERENCES 40

**LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

|  |  |
| --- | --- |
| **ABR** | **General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)** |
| **AE** | **Adverse Event** |
| **aMRI** | **Advanced Magnetic Resonance Imaging** |
| **APT** | **Amide Proton Transfer** |
| **AR** | **Adverse Reaction** |
| **ASE** | **Asymmetric Spin Echo** |
| **ASL** | **Arterial Spin Labelling** |
| **CBF** | **Cerebral Blood Flow** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CEST** | **Chemical Exchange Saturation Transfer** |
| **CMRO2** | **Cerebral Metabolic Rate of Oxygen** |
| **CTV** | **Clinical Target Volume** |
| **CTVaMRI** | **Clinical Target Volume based on advanced Magnetic Resonance Imaging** |
| **CV** | **Curriculum Vitae** |
| **DSC** | **Dynamic Susceptibility Contrast** |
| **DSC-HEPI** | **Dynamic Susceptibility Contrast Hybrid Echo Planar Imaging** |
| **DSMB** | **Data Safety Monitoring Board** |
| **DWI** | **Diffusion Weighted Imaging** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **FLAIR** | **Fluid Attenuated Inversion Recovery** |
| **GCP** | **Good Clinical Practice** |
| **GDPR** | **General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)** |
| **GTV** | **Gross Tumor Volume** |
| **Gy** | **Gray** |
| **IC** | **Informed Consent** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)** |
| **MRI** | **Magnetic Resonance Imaging** |
| **qBOLD** | **Quantitative Blood-Oxygenation-Level-Dependent** |
| **OEF** | **Oxygen Extraction Fraction** |
| **PTV** | **Planning Target Volume** |
| **RANO** | **Response Assessment for Neuro-Oncology** |
| **rCBV** | **Relative Cerebral Blood Volume** |
| **(S)AE** | **(Serious) Adverse Event** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical**  **company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **sqBOLD** | **Streamlined Quantitative Blood-Oxygenation-Level-Dependent** |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **UAVG** | **Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG** |
| **VSI** | **Vessel Size Index** |
| **WMO** | **Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

**SUMMARY**

**Rationale:** One of the fundamentals of glioblastoma management is radiotherapy, where ionizing radiation is aimed towards a specific target area in the brain to inhibit further tumor growth. As these brain tumors are notorious for their extensive tumor infiltration, where tumor grows beyond the tumor that is visible on conventional magnetic resonance imaging (MRI), this target area, defined as the clinical target volume (CTV), consists of the visible tumor plus a 1.5-cm isotropic safety margin. In the majority of cases, this unspecific CTV margin adequately covers tumor infiltration, but inevitably also includes considerable amounts of healthy tissue. Radiation-induced side-effects like headaches, nausea, fatigue and cognitive decline can substantially affect the quality of life for these patients.

An opportunity arises to indirectly visualize tumor infiltration with state-of-the-art advanced MRI (aMRI) techniques, providing additional information on physiology rather than only showing anatomical information through conventional MRI. A workflow has been developed to create a CTV based on these aMRI scans (CTVaMRI) rather than an isotropic expansion. With the additional information that aMRI provides, it could be possible to more accurately define what needs to be targeted and thus minimize damage to healthy tissue. In this research, the aim is to assess the potential of integrating aMRI into radiotherapy target delineation for patients with a glioblastoma by comparing the pattern of failure (coverage of first tumor recurrence by the radiotherapy plan) and the expected radiation dose to organs at risk between the CTVaMRI and the 1.5-cm CTV. It is hypothesized that the CTVaMRI can result in decreased radiation dose to organs at risk, whilst having similar pattern of failure.

**Objective**:

*Primary objective*: To illustrate similar pattern-of-failure prediction by a radiotherapy plan generated with a conceptual CTVaMRI compared to the clinical radiotherapy plan (1.5-cm CTV).

*Secondary objective:*

* To illustrate a reduction in dose to organs at risk with a radiotherapy plan based on a conceptual CTVaMRI compared to the clinical radiotherapy plan (1.5-cm CTV).
* To evaluate the synergistic information that each individual aMRI-scan provides for the identification of tumor infiltration.
* To explore the association between pathophysiological changes on aMRI and future tumor recurrence.

**Study design:** In this prospective cohort study, the clinical standard MRI session used for radiotherapy planning of glioblastoma patients will be extended with aMRI techniques that assess altered oxygenation, angiogenesis and increased protein concentration. Radiation treatment (and patient follow-up) will occur according to the clinical standard, i.e. using the 1.5-cm CTV for radiotherapy planning. The aMRI-scans will be used to create a theoretical CTVaMRI and corresponding radiotherapy plan­. Pattern-of-failure analysis and assessment of dose to organs at risk will be done to compare the radiotherapy plan based on the 1.5-cm CTV with the (theoretical) radiotherapy plan based on the CTVaMRI. Additionally, various theoretical CTVs based on different combinations of aMRI-scans are generated to explore the added value of the different aMRI techniques. Lastly, the signal intensities on the aMRI-scans at the site of tumor recurrence are compared with contralateral normal-appearing white matter.

**Study population:** Patients (≥ 18 years), diagnosed with IDH-wildtype glioblastoma, as confirmed by molecular or immunohistochemistry analysis post resection/biopsy and referred to outpatient clinic of the Department of Radiotherapy to undergo standard treatment with radiotherapy. The inclusion comes to an end when 48 study participants have developed tumor recurrence (the majority of patients with glioblastoma develop recurrence within a year).

**Intervention (if applicable)**: Each patient will have an extension to their standard radiotherapy planning MRI-scan taken for regular clinical care (*Brain tumor MRI protocol*: ± 25 minutes). The duration of the extended MRI-scan, which includes the *Brain tumor MRI protocol*, is ± 45 minutes (max. 60 minutes).

**Main study parameters/endpoints:** Pattern of failure and dose to organs at risk by the radiotherapy plan based on the 1.5-cm CTV and the theoretical plan created with the CTVaMRI.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The patients have the burden of prolonged scan time (+ 20 minutes, scan will last at maximum 60 minutes in total) during their standard radiotherapy planning MRI-scan. The remainder of their clinical care will not be altered: Radiotherapy will be given to these patients based on standard 1.5-cm CTVs. Follow-up will follow the clinical protocol. There will be no personal benefit for the patients in this research project.

# INTRODUCTION AND RATIONALE

## Background

Glioblastomas are the most common primary brain malignancies and represent the most aggressive type of gliomas, a heterogeneous group of cancer predominantly arising from glial cells.1 Current standard therapy of newly diagnosed glioblastomas requires a multidisciplinary approach and consists of maximal safe surgical resection followed by concurrent radiotherapy with chemotherapy and, subsequently, adjuvant chemotherapy. Even with extensive treatment, however, patients diagnosed with glioblastoma often face poor prognosis: The median overall survival after initial diagnosis is approximately 15 months.2 One of the reasons why glioblastomas come with a high mortality rate is their microscopic tumor infiltration, where tumor cells grow like thread-like tendrils into normal-appearing brain tissue. Because of this, complete resection is nearly impossible and, although radiotherapy and chemotherapy significantly improve overall survival, tumor recurrence is frequently observed within a year after treatment.3

## Target definition for radiotherapy

Fundamental to glioblastoma treatment is radiotherapy, where ionizing radiation is aimed at an area in the brain to kill tumor cells and inhibit further tumor growth. Accurate definition of this target area is crucial as radiation can also negatively affect healthy tissue. A radiation oncologist uses a combination of computed tomography and conventional magnetic resonance imaging (MRI) to delineate the gross tumor volume (GTV). The conventional MRI-scans used for radiotherapy target delineation include post-contrast T1-weighted MRI, T2-weighted MRI and T2/FLAIR MRI. Typically, the GTV is defined as the resection cavity and any residual contrast enhancement visible on post-contrast T1-weighted MRI. The actual targeted area, however, called the clinical target volume (CTV), consists of the GTV plus a safety margin to cover for tumor infiltration growing beyond the tumor visible on conventional MRI. As glioblastomas are notorious for their microscopic tumor infiltration, this CTV margin is 1.5-cm in every direction for every patient.4 Although effective for targeting significant tumor infiltration, this general isotropic expansion leads to enormous target areas and can also include considerable amounts of healthy tissue. This can result in severe side-effects like cognitive impairment, headache, fatigue and nausea/vomiting and substantially decrease the quality of life during the short time these patients have left.5

## State-of-the-art MRI

An opportunity to indirectly visualize significant tumor infiltration arises with the development of various state-of-the-art advanced MRI (aMRI) techniques. Whereas the conventional MRI-scans mainly describe structure and anatomical changes, these novel techniques provide information on numerous different physiological processes. The combination of four physiological MRI techniques has shown great potential to indirectly visualize significant tumor infiltration for glioblastomas.6 First, quantitative blood-oxygenation-level-dependent (qBOLD) imaging allows for rapid and non-invasive measurement of the oxygen extraction fraction (OEF), which combined with measurement of the cerebral blood flow (CBF) acquired with arterial spin labelling (ASL) results in a cerebral metabolic rate of oxygen (CMRO2) map of the brain.7 *Stadlbauer et al. (2021)* found that CMRO2 mapping could show alterations in oxygenation at the site of future tumor progression 6 months prior to structural changes being visible on conventional MRI, highlighting the potential of this technique for indirect visualization of tumor infiltration in glioblastomas.8 Second, from simultaneous acquisition of gradient- and spin-echo dynamic susceptibility contrast (DSC-HEPI) imaging, it is possible to construct both a relative cerebral blood volume (rCBV) and a vessel size index (VSI) brain map, providing estimations of the microvascular density and microvascular structure, respectively, within the brain.9,10 This reflects early angiogenic activity and thus tumor vascular development and is found to precede anatomical changes on conventional MRI.8,11,12 Finally, a promising MRI technique to visualize elevated protein concentrations in tumor regions is amide chemical exchange saturation transfer (CEST) imaging, also known as amide proton transfer (APT) CEST imaging.13 Hyperintensity on APT-weighted imaging was observed to correlate to increased cellular proliferation, a marker for malignant tumor tissue, indicating the potential of this technique to identify regions with tumor infiltration.14,15

As CMRO2, rCBV, VSI and APT convey complementary information on tumor physiology, combining these four brain maps could enable complete detection of tumor infiltration for improved radiotherapy target delineation.

In the *Imaging for Tumor Environment Mapping (ITEM)* study (MEC-2020-0002) within the Erasmus MC, these aMRI techniques and their corresponding post-processing pipelines have successfully been implemented and validated in human glioma. The individual imaging techniques have been optimized to obtain a sufficiently high signal-to-noise ratio and were integrated in the pre-surgical MRI session of low and high-grade brain tumor patients who were scheduled to undergo either biopsy or resection surgery. Validation of these imaging techniques occurred via stereotactic biopsies of the tumor tissue and analyzing these either for protein content with proteomics (validation of APT) or with immunohistochemistry to assess microvascular structure (validation of VSI) and hypoxia (validation of OEF).

In a collaboration between the Dept. of Radiology & Nuclear medicine and the Dept. of Radiotherapy at the Erasmus MC, a pilot study *Physiological MRI for precision radiotherapy of IDH-wildtype glioblastoma (PhysMRRT)* (MEC-2022-0123) has been initiated with the aim to construct a fully functional workflow that integrates CMRO2, rCBV, VSI and APT imaging into radiotherapy planning of glioblastomas to generate a CTV based on aMRI (CTVaMRI). In this currently ongoing study, a total of ten glioblastoma patients are to be recruited and will undergo an extended MRI protocol, which includes the previously mentioned aMRI techniques and the standard *Brain tumor MRI protocol,* before radiotherapy. The aMRI data of these patients will then be used to further optimize a workflow that uses probability mapping and tumor growth modelling to generate a CTVaMRI­ for glioblastoma,

## Rationale

With aMRI comes the opportunity to introduce additional information on physiological changes in the brain and improve target definition of radiotherapy for glioblastoma. By extending the MRI protocol before radiotherapy with abovementioned aMRI techniques, the 1.5-cm isotropic CTV-margin may be eliminated and the CTV may be defined more accurately through a CTVaMRI. At the Erasmus MC, various promising aMRI techniques have been implemented during the *ITEM* study and a workflow for generation of a CTVaMRI for glioblastoma is being optimized in the *PhysMRRT* study.

In this prospective cohort study, *Hitting the Mark: Introducing state-of-the-art MRI for precision radiotherapy of glioblastoma (MOSAIC)*, the aim is to assess the potential of aMRI and a CTVaMRI for adequate coverage of tumor infiltration and reduced damage to organs at risk.

# OBJECTIVES

**Primary Objective:**

* To illustrate similar pattern of failure prediction by a radiotherapy plan generated with a conceptual CTVaMRI compared to the clinical radiotherapy plan (1.5-cm CTV).

**Secondary Objective(s):**

* To illustrate a reduction in expected dose to organs at risk with a radiotherapy plan generated with a conceptual CTVaMRI compared to the clinical radiotherapy plan (1.5-cm CTV).
* To evaluate the synergistic information that each individual aMRI technique provides for the identification of tumor infiltration.
* To explore the association between pathophysiological changes on aMRI and future tumor recurrence.

# STUDY DESIGN

To assess the potential of these aMRI techniques, a conceptual CTVaMRI and a corresponding radiotherapy plan will be generated in a prospective cohort of glioblastoma patients, scheduled to undergo radiotherapy treatment at the Erasmus MC. This requires extension of the clinical standard MRI session for radiotherapy treatment planning with aMRI. These aMRI-scans include CEST MRI to obtain APT-weighted images, ASL to obtain CBF, qBOLD to obtain the OEF and DSC-HEPI to obtain rCBV and VSI. These imaging biomarkers combined are hypothesized to provide a complete image of significant tumor infiltration. Using the adapted MRI-protocol and workflow already developed in *PhysMRRT*, a conceptual CTVaMRI­ will be generated in all patients and used to create a conceptual radiotherapy plan *(see Fig. 1)*. The duration of the adapted MRI-protocol, which includes the *Brain tumor MRI protocol (± 25 minutes),* is ± 45 minutes (max. 60 minutes) in total.

Note that for all patients, the CTVaMRI and corresponding radiotherapy plan is conceptual and not used for the actual radiotherapy treatment. Radiotherapy treatment will be given according the clinical standard (ESTRO-ACROP guidelines): A radiotherapy plan based on the standard 1.5-cm CTV. This prospective cohort study therefore does not include a change in treatment given to the recruited patients, i.e. there will be no change in the standard of clinical care.

Patient follow-up will occur according the clinical standard, including the standard MRI protocols, for a maximum of 2 years. In the majority of cases, tumor recurrence occurs within 1 year, somewhere within the 1.5-cm CTV.3 The inclusion will come to an end when 48 included patients have developed tumor recurrence. The time point where first tumor recurrence is observed will be marked and the recurrence volume will be delineated. In hindsight, the recurrence volume provides valuable information on the location of significant tumor infiltration. Thereafter, the standard radiotherapy plan (1.5-cm CTV) and the conceptual aMRI radiotherapy plan will be compared regarding pattern of failure (coverage of the tumor recurrence by the radiotherapy plan) and dose to organs at risk/healthy tissue. It is hypothesized that the conceptual aMRI radiotherapy plan would cover tumor recurrence as effectively as the standard radiotherapy plan, whilst decreasing dose to organs at risk/healthy tissue.

|  |
| --- |
| *Fig. 1: Flowchart of the study design. Recruited patients undergo an extended MRI protocol before radiotherapy planning. They will undergo standard radiotherapy treatment using a 1.5-cm CTV; the aMRI-scans are used to generate a conceptual CTVaMRI and corresponding radiotherapy plan. Pattern of failure and dose to organs at risk by both the aMRI radiotherapy plan and the 1.5-cm CTV radiotherapy plan are then analyzed and compared to assess the potential of the CTVaMRI for precision radiotherapy of glioblastoma.* |

In addition to the CTVaMRI (based on all four aMRI-scans), the workflow developed in *PhysMRRT* will be used to generate various CTVs based on three, two or one of the aMRI-scans *(see Table 1)*. A comparison of size and coverage of the delineated recurrence volume will be performed for all CTVs to assess if a CTV based on three or less aMRI techniques may include tumor infiltration as effective as the CTVaMRI. It is hypothesized that the four aMRI-scans offer synergistic information.

*Table 1: Additional CTVs generated in the MOSAIC study.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Generated CTV** | **Based on aMRI-scans** | | | |
| *CMRO2* | *VSI* | *rCBV* | *APT* |
| *CTVaMRI* | x | x | x | x |
| *CTVCMRO2,VSI,rCBV* | x | x | x |  |
| *CTVCMRO2,VSI,APT* | x | x |  | x |
| *CTVCMRO2,rCBV,APT* | x |  | x | x |
| *CTVVSI,rCBV,APT* |  | x | x | x |
| *CTVCMRO2,VSI* | x | x |  |  |
| *CTVCMRO2,rCBV* | x |  | x |  |
| *CTVCMRO2,APT* | x |  |  | x |
| *CTVVSI,rCBV* |  | x | x |  |
| *CTVVSI,APT* |  | x |  | x |
| *CTVrCBV,APT* |  |  | x | x |
| *CTVCMRO2* | x |  |  |  |
| *CTVVSI* |  | x |  |  |
| *CTVrCBV* |  |  | x |  |
| *CTVAPT* |  |  |  | x |

Lastly, the contralateral normal-appearing white matter will be segmented for all patients. On the four aMRI-scans, the mean and maximum signal intensities of the delineated recurrence volumes and the contralateral normal-appearing white matter will be compared to explore the association between pathophysiological changes on aMRI and future tumor recurrence.

# STUDY POPULATION

## Population (base)

Adult patients with glioblastoma, who will be treated with radiotherapy at the Erasmus MC.

## Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

* Written informed consent;
* Adult (18 years or older)
* Diagnosed with IDH-wildtype glioblastoma, as confirmed by pathology including molecular analysis post resection/biopsy.
* Referred to the outpatient clinic of the Dept. of Radiotherapy to undergo standard treatment with radiotherapy (30x2 Gy or 15x2.67Gy) and scheduled for an MRI for radiotherapy planning.

## Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

* Contraindication for (3 Tesla) MRI;
* Contraindication for use of gadolinium-based contrast agent (e.g. subject having renal deficiency or known allergy);
* Referred for treatment of recurrent glioblastoma;
* Previous radiotherapy to the head-and-neck region
* Unable to give informed consent

## Sample size calculation

The primary objective of this study is to demonstrate that the probability for reduced coverage of the recurrence volume by a radiotherapy plan based on a CTVaMRI, compared to the clinical radiotherapy plan (1.5-cm CTV), is lower than 0.20. Reduced coverage of the recurrence volume indicates that a radiotherapy plan based on the CTVaMRI would not be as effective for targeting tumor infiltration as the clinical radiotherapy plan. Any higher number than 0.20 would not warrant further investigation of this workflow for generation of a CTVaMRI in a randomized trial. From each recruited patient, both the clinical radiotherapy plan and a radiotherapy plan based on a CTV­aMRI will be generated and analysed regarding pattern of failure.

The null hypothesis will be that the probability of reduced coverage of the recurrence volume by the radiotherapy plan based on a CTVaMRI, is more than or equal to 0.20. With a sample size of 48 patients whom have developed tumor recurrence, an exact binomial test with a one-sided significance level (alpha) of 0.025 will have 90% power to reject the null hypothesis if the true probability is 0.050.

# TREATMENT OF SUBJECTS

N/A

## Investigational product/treatment

N/A

## Use of co-intervention (if applicable)

N/A

## Escape medication (if applicable)

N/A

# INVESTIGATIONAL PRODUCT

N/A

## Name and description of investigational product(s)

N/A

## Summary of findings from non-clinical studies

N/A

## Summary of findings from clinical studies

N/A

## Summary of known and potential risks and benefits

N/A

## Description and justification of route of administration and dosage

N/A

## Dosages, dosage modifications and method of administration

N/A

## Preparation and labelling of Investigational Medicinal Product

N/A

## Drug accountability

N/A

# NON-INVESTIGATIONAL PRODUCT

In addition to the standard MRI sequences used in clinical practice *(Brain tumor MRI protocol)*, various aMRI sequences will be added to the MRI protocol before radiotherapy. These aMRI sequences have already implemented at the Erasmus MC, but are currently only used in research studies and are therefore not part of the clinical protocol. Note that a brief overview of the MRI-scans (both conventional and research scans) are detailed below. Note as well that, because this data will be acquired during the standard radiotherapy planning MRI session, all scans will be performed by taking into account the standard safety measures for undergoing MRI-scans at the Dept. of Radiology & Nuclear Medicine.

## Name and description of non-investigational product(s)

Conventional imaging *(Brain tumor MRI protocol)*

*Structural MRI-scans*

For glioblastomas, the GTV of the tumor is delineated on a combination of (post-contrast) T1-weighted, T2 propeller and fluid attenuated inversion recovery (FLAIR) structural MRI-scans and expanded by 1.5-cm to generate the CTV. The final steps in reaching the planning target volume (PTV), i.e. the volume to be irradiated, is to minimize dose to organs at risk (important structures include the brainstem, eyes, optic nerves, chiasm, cochlea and lacrimal gland), leading to adjustment of the CTV and adding a final 3-5 mm expansion of the CTV to adjust for uncertainties in beam alignment, patient positioning, organ motion, and organ deformation.

*Diffusion-weighted imaging (DWI)*

DWI is an MRI technique that measures the diffusion of water molecules within biological tissue.16 Hindered water diffusion may be caused by various pathological processes, like cerebral infarction or hypercellularity. Although this MRI technique is not used for radiotherapy target delineation, it is routinely acquired in the *Brain tumor MRI protocol* at the Erasmus MC, as it is particularly useful for tumor characterization and detection of cerebral ischemia.

Physiological imaging *(Research scans in extended MRI protocol)*

*Arterial spin labeling (ASL)*

ASL will be performed to acquire cerebral blood flow (CBF) maps. In this MRI sequence,

blood is non-invasively labelled with a magnetic pulse as it passes through the major brain

feeding arteries and visualized once it has reached the brain/tumor tissue of interest.

Herewith, ASL is a well-established non-invasive manner of assessing CBF, which is currently regularly included in the standard clinical MRI for patients with a brain tumor at the Dept. of Radiology & Nuclear Medicine.

*DSC Hybrid EPI (HEPI) imaging*

For both VSI (vessel size index) and relative cerebral blood volume (rCBV), a DSC hybrid gradient and spin echo EPI sequence is used (DSC-HEPI, available at Erasmus MC on GE Healthcare) with the same injection of a gadolinium-based contrast agent and imaging parameters as those used in the traditional DSC-MRI perfusion imaging. The traditional manner of DSC-MRI acquires either only gradient echo or only spin echo imaging data and is part of the *Brain Tumor MRI protocol* to allow evaluation of the rCBV. At the Erasmus MC, DSC-HEPI has been in use for the past 6 years already as it gives the advantage of simultaneous acquisition.

First of all, the gradient echo imaging data allows for traditional DSC-MRI perfusion to be acquired according to the guidelines set out by the EORTC: A preload contrast bolus of 0.05 mmol/kg bodyweight Gadolinium-containing contrast agent is given approximately 5 min prior to a bolus injection of 10 mmol at a rate of minimum 3 ml/s followed by a 20 ml saline flush. From the gradient echo imaging data, a map of the rCBV can be calculated. Although rCBV is routinely acquired in the *Brain Tumor MRI protocol*, it is not used for radiotherapy target delineation of glioblastomas. To calculate the VSI map, the gradient *and* spin echo data will be used acquired by this HEPI acquisition. Previously established post-processing will be done in which the gradient and spin echo signal perturbations from the injection of the gadolinium based contrast agent are used to generate maps of microvascular density (rCBV) and vessel size (VSI).10

*Chemical exchange saturation transfer (CEST) imaging*

CEST image acquisition and analysis will be done according to previously developed and published methods, which includes using in-house developed pipeline to obtain voxel-wise maps of amide proton transfer (APT) and nuclear Overhauser enhancement effects.17

*Asymmetric Spin echo (ASE) for qBOLD*

The other technique that is going to be included in this study, is called streamlined

quantitative BOLD (sqBOLD), which is developed to model the BOLD magnitude signal in tissue and map baseline oxygenation.18 In this approach, “asymmetric spin echo (ASE)” pulse sequence will be utilized, where the 180° refocusing pulse of a standard spin echo pulse sequence is shifted towards the 90° excitation pulse by a different time shift. This technique is able to provide valuable information about the metabolic profile, represented by the local oxygen extraction fraction (OEF); the OEF can be combined with a CBF map to assess the CMRO2 of brain tissue.19

Post-processing of aMRI

An in-house developed post-processing pipeline, already validated in *ITEM* and *PhysMRRT*, will be used to generate the aMRI biomarker maps (CMRO2, VSI, rCBV and APT).

## Summary of findings from non-clinical studies

N/A

## Summary of findings from clinical studies

First, qBOLD imaging allows for rapid and non-invasive measurement of the OEF, which combined with measurement of the CBF acquired with ASL results in a CMRO2 map of the brain.7 *Stadlbauer et al. (2021)* found that CMRO2 mapping could show alterations in oxygenation at the site of future tumor progression 6 months prior to structural changes being visible on conventional MRI, highlighting the potential of this technique for indirect visualization of tumor infiltration in glioblastomas.8 Second, from DSC-HEPI imaging, it is possible to construct both an rCBV as well as a VSI brain map, providing estimations of the microvascular density and microvascular structure, respectively, within the brain.9,10 This reflects early angiogenic activity and thus tumor vascular development and is found to precede anatomical changes on conventional MRI.8,11,12 Finally, a promising MRI technique to visualize elevated protein concentrations in tumor regions is amide CEST imaging, also known as APT CEST imaging.13 Hyperintensities on APT-weighted imaging were observed to correlate to increased cellular proliferation, a marker for malignant tumor tissue, indicating the potential of this technique to identify regions with significant tumor infiltration.14,15

As CMRO2, rCBV, VSI and APT convey complementary information on tumor physiology, combining these four brain maps could enable complete detection of significant tumor infiltration.

## Summary of known and potential risks and benefits

Risks associated with this project include the risks of undergoing an extended MRI (± 20 minutes longer). To prevent any potential risks or filter out contraindications for MRI, all participants will be screened with standardized screening forms present within the Dept. of Radiology & Nuclear medicine. There will be no personal benefit for participants in this research project.

## Description and justification of route of administration and dosage

To assess DSC-HEPI, the clinically applicable dose of gadolinium-based contrast agent will be intravenously administered according to standard clinical practice. As standard clinical practice already requires administration of contrast agent for post-contrast T1-weighted imaging and traditional DSC-MRI, no additional contrast is needed for DSC-HEPI acquisition.

## Dosages, dosage modifications and method of administration

The total amount of contrast media to be injected will not exceed the dose used in clinical practice *(Table 2).*

*Table 2: Adapted from the standard Brain tumor MRI protocol (code 941390D).*

***Instructions to radiographers:***

|  |
| --- |
| * Laat een roze infuusnaald inbrengen t.b.v. de injector. * Zuig 15 cc gadovist op in A en 50 cc NaCl 0.9% in B. * Patiënt in rugligging, headfirst. * Geef de patiënt de alarmbel en oordoppen. |

## Preparation and labelling of Non Investigational Medicinal Product

N/A

## Drug accountability

N/A

# METHODS

## Study parameters/endpoints

### Main study parameter/endpoint

The main study endpoint is pattern of failure by the clinical radiotherapy plan (1.5-cm CTV) and the radiotherapy plan generated with the CTVaMRI. For both the clinical radiotherapy plan and the aMRI radiotherapy plan of each patient, the recurrence volumes will be classified as in-field, marginal, or distant recurrence if more than 80%, 20-80%, or less than 20% of the recurrence volume falls within the 95% isodose line, respectively.21 The 95% isodose line describes the region that receives 95% of the target dose; for a target dose of 60 Gy, that would be the region that receives at least 57 Gy. Reduced coverage by the aMRI radiotherapy plan occurs in three scenarios *(see Table 3);* this indicates the aMRI radiotherapy plan would not have targeted tumor infiltration as effectively as the clinical radiotherapy plan.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Table 3: Reduced coverage of the recurrence volume occurs in three scenarios.*   |  |  |  | | --- | --- | --- | | **Pattern of failure** | | | | ***Clinical radiotherapy plan  (1.5-cm CTV)*** | ***aMRI radiotherapy plan (CTVaMRI)*** | ***Recurrence coverage*** | | *In-field* | *In-field* | *Similar* | | *In-field* | *Marginal* | *Reduced* | | *In-field* | *Distant* | *Reduced* | | *Marginal* | *Distant* | *Reduced* | |

### Secondary study parameters/endpoints (if applicable)

* The difference in expected dose to important organs at risk between the clinical radiotherapy plan (1.5-cm CTV) and the aMRI radiotherapy plan (CTVaMRI). Important organs at risk include the brainstem, optic nerves, eyes, lenses, cochlea and optic chiasm.
* The differences in tumor recurrence coverage and size between the CTVaMRI (based on all four aMRI-scans) and CTVs based on individual or other combinations of aMRI, i.e. based on three, two or one aMRI-scan(s).
* The difference in mean and maximum signal intensity on the individual aMRI-scans between the tumor recurrence site and the contralateral normal-appearing white matter.

### Other study parameters (if applicable)

N/A

## Randomisation, blinding and treatment allocation

N/A

## Study procedures

### Data collection

Recruited patients will undergo an extension of their clinical MRI session used for radiotherapy planning *(extended time: ± 20 minutes)*. In this scan session, additional MRI-scans will be collected (highlighted in orange in *Fig. 2*) that assess different aspects of cerebral and tumor physiology.

|  |
| --- |
| *Fig. 2: The standard patient’s trajectory (from surgery/biopsy onward) for patients with newly diagnosed glioblastoma is shown in blue. Instead of the standard clinical MRI protocol for radiotherapy, recruited patients will undergo an extended MRI protocol, which consists of the standard MRI sequences plus the aMRI sequences. Note that there are no changes regarding the actual radiation treatment (based on 1.5-cm CTV) or follow-up, meaning treatment will not be altered/affected.* |

In the recruited patients, the CTVaMRI will be generated using the workflow developed in *PhysMRRT.* Instead of an isotropic 1.5-cm CTV expansion, this workflow generates a CTV by defining high-risk regions for tumor infiltration using unsupervised learning (applied on the aMRI-scans) and tumor growth modelling (applied on conventional MRI). The CTVaMRI will then be used to generate a conceptual aMRI radiotherapy plan according to standard clinical guidelines.

### Recurrence volume delineation

As the site of the recurrence volume can, in hindsight, provide valuable information on the location of tumor infiltration, standard follow-up data of the recruited patients will be analyzed to determine the time point of recurrence (which is expected to happen within two years after radiotherapy treatment has finished at maximum).3 The time point that progressive disease is first established in the neuro-oncological multidisciplinary consultation/clinical practice will be marked; this is determined by the clinicians according to the clinical standard *Response Assessment for Neuro-Oncology (RANO) criteria* *(Table 4).*20 One of the challenges of response assessment in clinical practice, however, is the presence of *pseudoprogression*: New or increasing contrast-enhancement and/or T2-weighted hyperintensity after treatment with radio- or chemotherapy, implying progressive disease at first, but eventually subsiding without any therapeutic interaction. In clinical practice, it is not yet possible to reliable distinguish between *pseudoprogression* and true tumor progression. In a research setting, however, it is possible to look back/forward in time and establish if abnormalities on follow-up MRI were *pseudoprogression* or actual tumor progression. In this study, this approach (under supervision of a radiologist) will be used to mark the time point of first tumor recurrence. Two possible scenarios have been visualized in *Fig. 3*. After determination of the time point of first recurrence, the recurrence volume will be delineated in MIM Maestro®, the delineation software used at the Dept. of Radiotherapy, under supervision of a radiation oncologist.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Table 4. Criteria for response assessment incorporating MRI and clinical factors20* | | | | |
| **Criterion** | **CR** | **PR** | **SD** | **PD** |
| T1-Gd + | None | 50% | 50% to < 25% | 25% † |
| T2/FLAIR | Stabler or | Stable or | Stable or | † |
| New lesion | None | None | None | Present† |
| Corticosteroids | None | Stable or | Stable or | NA‡ |
| Clinical status | Stable or | Stable or | Stable or | † |
| Requirement for response | All | All | All | Any† |
| Summary of HGG response criteria | Requires all of the following:  complete disappearance of all  enhancing measurable and  nonmeasurable disease  sustained for at least 4 weeks;  no new lesions; stable or  improved nonenhancing  (T2/FLAIR) lesions; patients  must be off corticosteroids (or  on physiologic replacement  doses only); and stable or  improved clinically. Note:  Patients with nonmeasurable  disease only cannot have  achieved CR; the best response  possible is SD | Requires all of the following:  ≥50% decrease compared with  baseline in the sum of products  of perpendicular diameters of  all measurable enhancing  lesions sustained for at least  4 weeks; no progression of  nonmeasurable disease; no  new lesions; stable or improved  nonenhancing (T2/FLAIR)  lesions on same or lower dose  of corticosteroids compared  with baseline scan; the  corticosteroid dose at the time  of scan evaluation should be no  greater than the dose at time  of baseline scan; and stable or  improved clinically | Requires all of the following:  Does not qualify for CR, PR or  progression; stable  nonenhancing (T2/FLAIR)  lesions on the same or lower  dose of corticosteroids  compared with baseline scan.  In the event that the  corticosteroid dose was  increased for new symptoms  and signs without confirmation  of disease progression on  neuroimaging, and subsequent  follow-up imaging shows that  this increase in corticosteroids  was required because of  disease progression, the last  scan considered to show SD will  be the scan obtained when the  corticosteroid dose was  equivalent to the baseline dose | Defined by any of the following:  ≥25% increase in the sum of the  products of perpendicular  diameters of enhancing lesions  compared with the smallest  tumor measurement obtained  either at baseline (if no decrease)  or best response on stable or  increasing doses of  corticosteroids†; significant  increase in T2/FLAIR  nonenhancing lesion on stable or  increasing doses of  corticosteroids compared with  baseline scan or best response  after initiation of therapy† not  caused by comorbid events  (e.g., radiation therapy,  demyelination, ischemic injury,  infection, seizures, postoperative  changes or other treatment  effects); any new lesion; clear  clinical deterioration not  attributable to other causes apart  from the tumor (e.g., seizures,  medication adverse effects,  complications of therapy,  cerebrovascular events, infection,  etc.) or changes in corticosteroid  dose; failure to return for  evaluation as a result of death or  deteriorating condition; or clear  progression of nonmeasurable  disease |
| †Progression occurs when this criterion is met.  ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.  ↓: decrease; ↑: increase; CR: Complete response; FLAIR: Fluid-attenuated inversion recovery; HGG: High-grade glioma; NA: Not applicable; PD: Progressive disease; PR: Partial response;  SD: Stable disease; T1-Gd +: T1 postgadolinium.  Modified with permission from (16) © American Society of Clinical Oncology (2017). All rights reserved. | | | | |

|  |
| --- |
| *Fig. 3: In the first scenario (a), a new abnormality was first observed on 6-month follow-up MRI, however, according to the RANO criteria it was not yet defined as true progressive disease. Only at 9-month follow-up, true progressive disease was established in clinical practice. In this research, this time point is first marked. Subsequently, follow-up MRI before and after this time point are re-evaluated to determine if it was true progressive disease and if the recurrence was already visible on earlier MRI-scans. In this case, progression persisted in the MRI-scan at 12-month follow-up. Additionally, now it is known that the abnormality at 6-month follow-up was true progressive disease; this time point can then be marked as time point for first recurrence.*  *In the second scenario (b), progressive disease according the RANO-criteria was first observed at 12-month follow-up. At 9-month follow-up MRI, there were no abnormalities at that site; therefore, 12-month follow-up is defined as the time point of first recurrence. In hindsight, the abnormality at 6-month follow-up was found to be pseudo-progression.* |

### Pattern of failure analysis and dose to organs at risk comparison

To test the hypothesis that a radiotherapy plan based on a CTVaMRI, would adequately encompass tumor infiltration, the recurrence volume will be used to assess the pattern of failure. Pattern of failure analysis (i.e. recurrence coverage) will be performed in MIM Maestro® and quantified by categorizing the recurrence volume of each patient based on its location. For both the clinical radiotherapy plan (1.5-cm CTV) and the aMRI radiotherapy plan, the recurrence volumes will be classified as in-field, marginal, or distant recurrence if more than 80%, 20-80%, or less than 20% of the recurrence volume falls within the 95% isodose line, respectively.21 A comparison of recurrence coverage by the two radiotherapy plans can be indicative for the effectiveness of the CTVaMRI. Additionally, the expected radiation dose delivered to important surrounding organs at risk (including the brainstem, optic nerves, eyes, lenses, cochlea and chiasm) by both the radiotherapy plans will be compared to assess the potential risk of side-effects of each plan.

### Examination of CTVs based on different combinations of aMRI

In addition to the CTVaMRI, CTVs based on three, two and one of the four aMRI-scans will be generated for all patients using the pipeline developed in *PhysMRRT (see Table 1).* Size of the CTVs and coverage of the recurrence volume are compared to assess if a CTV based on three or less aMRI techniques may include tumor infiltration as effectively as the CTVaMRI and if the aMRI techniques offer complementary information.

### Assessment of pathophysiological changes detected by aMRI at the site of future tumor recurrence

Using FMRIB Software Library (FSL), the contralateral normal-appearing white matter is segmented for all patients. On the four aMRI-scans, the mean and maximum signal intensities of the recurrence volume and the contralateral normal-appearing white matter are then compared to explore the association between pathophysiological changes on aMRI and future tumor recurrence.

## Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

### Specific criteria for withdrawal (if applicable) N/A

## Replacement of individual subjects after withdrawal

Should a subject decide to withdraw consent afterwards, a replacement subject will be added to the study. The standard follow-up received by the patient will not change and will not be used for further analysis.

## Follow-up of subjects withdrawn from treatment

The standard follow-up of subjects withdrawn from the study will not change.

## Premature termination of the study

During this study, the standard care for patients diagnosed with glioblastoma will not be affected; no intervention will be applied that could possibly influence (clinical) outcome of the patients. The only change is that aMRI sequences will be added to the standard MRI protocol used for treatment planning in the recruited patients, extending this MRI-scan time to ± 45 minutes (maximum of 60 minutes). Therefore, no premature termination of this study is expected.

# SAFETY REPORTING

## Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## AEs, SAEs and SUSARs

### Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or her staff will be recorded.

The adverse events will be recorded in the online environment (PaNaMa), where the monitoring takes place.

### Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

* results in death;
* is life threatening (at the time of the event);
* requires hospitalisation or prolongation of existing inpatients’ hospitalisation;
* results in persistent or significant disability or incapacity;
* is a congenital anomaly or birth defect; or
* any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

Acute adverse events after injection gadolinium are rare (0.07% to 2.4%). The vast majority of these reactions are mild, including coldness at the injection site, nausea with or without vomiting, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching. “Allergic” responses are very unusual and vary in frequency from 0.004% to 0.7%. A rash hives, or urticaria are the most frequent of this group, and very rarely there may be bronchospasm. Severe, life-threatening anaphylactoid or non-allergic anaphylactic reactions are exceedingly rare (0.001% to 0.01%).

MRI personnel are trained to recognize potential symptoms of an adverse reaction to gadolinium. In collaboration with the Dept. of Anesthesiology, a plan of action is available in a dedicated quality management system protocol (“Kwaliteitsmanagementsysteem”) at the Erasmus MC ([Verdenking contrastreactie volwassenen Centrumlocatie, flowchart Radiologie & Nucleaire Geneeskunde](https://kms.erasmusmc.nl/Portal/" \l "/document/692671c8-3846-4db4-8db0-8ce77783eaf3" \t "_blank))

The investigator will report all SAEs that are considered possibly or definitely related to the additional MRI sequences to the sponsor without undue delay after obtaining knowledge of the events. All other SAEs will not be reported, as collection of toxicity data following standard treatment falls outside the scope of this research.

The sponsor will report only the SAEs that are considered possibly or definitely related to the additional MRI sequences through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

### Suspected unexpected serious adverse reactions (SUSARs)

N/A

## Annual safety report

N/A

## Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

## [Data Safety Monitoring Board (DSMB) / Safety Committee]

N/A

# STATISTICAL ANALYSIS

The aim of this study is to illustrate similar pattern of failure and reduced dose to organs at risk by a radiotherapy plan generated with a CTVaMRI, when compared to the clinical radiotherapy plan (1.5-cm CTV).

## Primary study parameter(s)

For both the clinical radiotherapy plan and the aMRI radiotherapy plan of each patient, the recurrence volumes will be classified as in-field, marginal, or distant recurrence if more than 80%, 20-80%, or less than 20% of the recurrence volume falls within the 95% isodose line, respectively.21 Reduced coverage of the recurrence volume by the aMRI radiotherapy plan can occur in three scenarios *(see Table 3).* An exact binomial test with a one-sided significance level (alpha) of 0.025 will be performed to test the null hypothesis that the probability of reduced coverage of the recurrence volume by the radiotherapy plan based on a CTVaMRI, is more than or equal to 0.20.

## Secondary study parameter(s)

* A two-sided paired t-test will be used to test if the expected dose to important organs at risk differ between the clinical radiotherapy plan (1.5-cm CTV) and the aMRI radiotherapy plan (CTVaMRI); a p-value < 0.05 will be considered statistically significant. Important organs at risk include the brainstem, optic nerves, eyes, lenses, cochlea and optic chiasm.
* An analysis of variance (ANOVA) is used to test if CTVs based on three or less aMRI-scans are as effective for coverage of tumor infiltration as the CTVaMRI (based on all four aMRI-scans).
* A paired t-test will be used to test if the mean or maximum signal intensities on aMRI (CMRO2, VSI, rCBV and APT) are different at the site of the recurrence volume and the contralateral normal-appearing white matter; a p-value < 0.05 will be considered statistically significant.

## Other study parameters

N/A

## Interim analysis (if applicable)

N/A

# ETHICAL CONSIDERATIONS

## Regulation statement

The study will be performed according to the principles of the Declaration of Helsinki

(Fortaleza, Brazil, October 2013), of Good Clinical Practice, and the applicable laws and

regulations of the Netherlands, including but not limited to the Medical Research Involving Human Subjects Act (WMO) and the General Data Protection Regulation (UAVG).

## Recruitment and consent

Patients will be recruited by the radiation oncologist when eligible patients visit the outpatient clinic of the Dept. of Radiotherapy. Candidate patients are asked by the radiation oncologist (dr. Alejandra Méndez Romero and colleagues) if they can be approached by the researcher. If permission is given, the researcher (Patrick L.Y. Tang) discusses this study with the patient. If needed, patients receive a reflection time that may vary between 1 and 3 days, after which telephone contact takes place in which the patient indicates whether he/she wants to participate in the study. Thereafter, the extended MRI-scan is planned. On the day of the extended MRI-scan, before the MRI scan will be performed, and after all questions of the patient about study participation are answered satisfactorily, written informed consent is given to the researcher (Patrick L.Y. Tang) by the patient.

## Objection by minors or incapacitated subjects (if applicable)

N/A

## Benefits and risks assessment, group relatedness

The patients participating in this study will not have personal benefit of taking part.

There are negligible additional risks for patients taking part in this study. Note that added risks of the additional MRI-scan time are limited, since this is an extension of the already planned MRI-scan, in which contrast agent is already injected (to obtain the conventional post-contrast T1-weighted MRI–scan and traditional DSC-MRI).

## Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

Since participating in this study only brings negligible risks, the accredited METC has given dispensation from the statutory obligation to provide insurance for damage to research subjects through injury or death caused by the study.

## Incentives (if applicable)

N/A

# ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

## Handling and storage of data and documents

All data will be handled confidentially and pseudonymized. Raw MRI data will be stored pseudonymized on the (research) XNAT folder at the Dept. of Radiology & Nuclear medicine; radiotherapy treatment plans will be stored in a dedicated research folder in MIM Maestro® at the Dept. of Radiotherapy and clinical data (e.g. age, molecular markers, performance status) will be transferred into a Castor database. (Post-)processed data will be stored through the data storage environment for research provided by the Dept. of Radiology & Nuclear medicine. Every subject will get an identification code. The code is not based on the patient’s initials or birth-date. The *Outcome Unit (Trial office)* from the Dept. of Radiotherapy will safeguard the key to the code. Where it is necessary to be able to trace data to an individual subject, a subject identification code list can be used to link the data to the subject. Informed consent and contra-indications forms will be held at the Dept. of Radiotherapy for at least 15 years. In addition, all study data will be held for 15 years according the archiving guidelines of the Dept. of Radiotherapy (radiotherapy treatment plans, delineations and the Castor database) or the Dept. of Radiology & Nuclear medicine (pre- and post-processed imaging data).

The handling of personal data will comply EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG, UAVG). The patients are asked for permission to share anonymized images with the MRI vendor (GE Healthcare) that has provided the new sequences.

## Monitoring and Quality Assurance

Monitoring of the conduct of the study will be done according to monitoring plan from the *Outcome unit* at the Dept. of Radiotherapy.

## Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

Both substantial and non-substantial amendments will be notified to the METC and to the competent authority.

## Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

## Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.  
  
 Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

<*In case the final study report will not be available within one year, another term should be defined including the reasons.*>

## Public disclosure and publication policy

Erasmus MC is the sponsor of the study. Results of this study will be presented at (inter)national conferences and in open access, peer-reviewed scientific articles.

# STRUCTURED RISK ANALYSIS

Some aMRI sequences used in this study are not yet in commercial distribution. The software used for these aMRI sequences is CE-marked for evaluation use only. It has been verified to not affect the safe operation of the MRI scanner. The standard procedures for screening of MRI-contraindication is in place. For these reasons, application in patients is acceptable. Accompanied with this protocol is a letter from the head of the Dept. of Radiology & Nuclear Medicine (and a statement from GE Healthcare). In this letter, a declaration is given that approves the use of these aMRI research sequences for internal research purposes. This letter was also provided for the approval of *PhysMRRT (MEC-2022-0123).* Note that *PhysMRRT* had a similar patient burden/study setup, where patients with a glioblastoma undergo the same extended MRI-protocol before radiotherapy.

## Potential issues of concern

a. Level of knowledge about mechanism of action

The registered NIMP (MRI) will be used within the indication and not in combination with other products. Patients will be screened for metal and asked to remove all metal items they carry and to change into scrubs, should their clothing contain metal. This is in accordance with the standard MRI safety guidelines of the Dept. of Radiology & Nuclear medicine.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

N/A

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

N/A

d. Selectivity of the mechanism to target tissue in animals and/or human beings

N/A

e. Analysis of potential effect

N/A

f. Pharmacokinetic considerations

N/A

g. Study population

Adult patients diagnosed with glioblastoma, scheduled to undergo radiotherapy treatment.

h. Interaction with other products

Gadolinium-based contrast agent will be used during the MRI scanning, as part of the regular care patients are to undergo.

i. Predictability of effect

Adverse effects of gadolinium-based contrast agent can occur in subjects with kidney insufficiencies. Safety risks and management of this is part of the standard of clinical care at the Erasmus MC. (See Section 9.2.2)

j. Can effects be managed?

To prevent adverse effects of gadolinium-based contrast agent, patients with kidney insufficiencies will not be included in this research.

## Synthesis

Standard use of the MRI and gadolinium-based contrast agent will be performed within this study. Extending the MRI-scan time is not known to lead to any additional risk to the patients.

To prevent metal from entering the MRI-scan room, patients are screened upfront. Should their clothing contain any metal, patients are asked to change into scrubs provided by the hospital.

Based on the 2020 guideline by the NFU (Dutch Federation of University Medical Centres) about quality insurance in human research (“Kwaliteitsborging van mensgebonden onderzoek”) we qualify the risk of this study as ‘low’, meaning it has a neglectible chance of serious damage.

# REFERENCES

1. Tamimi, A. F., & Juweid, M. (2017). Epidemiology and outcome of glioblastoma. *Exon Publications*, 143-153.
2. Stupp, R., Mason, W. P., Van Den Bent, M. J., Weller, M., Fisher, B., Taphoorn, M. J., ... & Mirimanoff, R. O. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England journal of medicine*, 352(10), 987-996.
3. Ballman, K. V., Buckner, J. C., Brown, P. D., Giannini, C., Flynn, P. J., LaPlant, B. R., & Jaeckle, K. A. (2007). The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro-oncology*, 9(1), 29-38.
4. Weller, M., van den Bent, M., Preusser, M., Le Rhun, E., Tonn, J. C., Minniti, G., ... & Wick, W. (2021). EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nature reviews Clinical oncology,* 18(3), 170-186.
5. Lawrence, Y. R., Li, X. A., El Naqa, I., Hahn, C. A., Marks, L. B., Merchant, T. E., & Dicker, A. P. (2010). Radiation dose–volume effects in the brain. *International Journal of Radiation Oncology\* Biology\* Physics*, 76(3), S20-S27.
6. Tang, P., Méndez Romero, A., Jaspers, J., & Warnert, E. (2022). The potential of advanced MR techniques for precision radiotherapy of glioblastoma. *Magma (New York, N.Y.),* 35(1), 127–143. <https://doi.org/10.1007/s10334-021-00997-y>
7. He, X., & Yablonskiy, D. A. (2007). Quantitative BOLD: mapping of human cerebral deoxygenated blood volume and oxygen extraction fraction: default state. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 57(1), 115-126.
8. Stadlbauer, A., Kinfe, T. M., Eyüpoglu, I., Zimmermann, M., Kitzwögerer, M., Podar, K., ... & Marhold, F. (2021). Tissue Hypoxia and Alterations in Microvascular Architecture Predict Glioblastoma Recurrence in Humans Physiologic MRI of Glioblastoma Recurrence. *Clinical Cancer Research*, 27(6), 1641-1649.
9. Sadeghi, N., D'Haene, N., Decaestecker, C., Levivier, M., Metens, T., Maris, C., ... & Goldman, S. (2008). Apparent diffusion coefficient and cerebral blood volume in brain gliomas: relation to tumor cell density and tumor microvessel density based on stereotactic biopsies. *American journal of neuroradiology*, *29*(3), 476-482.
10. Kellner, E., Breyer, T., Gall, P., Müller, K., Trippel, M., Staszewski, O., ... & Mader, I. (2015). MR evaluation of vessel size imaging of human gliomas: Validation by histopathology. *Journal of Magnetic Resonance Imaging*, *42*(4), 1117-1125.
11. Stecco, A., Pisani, C., Quarta, R., Brambilla, M., Masini, L., Beldì, D., ... & Carriero, A. (2011). DTI and PWI analysis of peri-enhancing tumoral brain tissue in patients treated for glioblastoma. *Journal of neuro-oncology*, *102*(2), 261-271.
12. Blasel, S., Franz, K., Ackermann, H., Weidauer, S., Zanella, F., & Hattingen, E. (2011). Stripe-like increase of rCBV beyond the visible border of glioblastomas: site of tumor infiltration growing after neurosurgery. *Journal of neuro-oncology*, *103*(3), 575-584.
13. Zhou, J., Lal, B., Wilson, D. A., Laterra, J., & Van Zijl, P. C. (2003). Amide proton transfer (APT) contrast for imaging of brain tumors. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, *50*(6), 1120-1126.
14. Jiang, S., Eberhart, C. G., Zhang, Y., Heo, H. Y., Wen, Z., Blair, L., ... & Zhou, J. (2017). Amide proton transfer-weighted magnetic resonance image-guided stereotactic biopsy in patients with newly diagnosed gliomas. *European Journal of Cancer*, *83*, 9-18.
15. Jiang, S., Eberhart, C. G., Lim, M., Heo, H. Y., Zhang, Y., Blair, L., ... & Zhou, J. (2019). Identifying Recurrent Malignant Glioma after Treatment Using Amide Proton Transfer-Weighted MR Imaging: A Validation Study with Image-Guided Stereotactic Biopsy Identifying Recurrent Glioma with APTw MRI. *Clinical Cancer Research*, *25*(2), 552-561.
16. Baliyan, V., Das, C. J., Sharma, R., & Gupta, A. K. (2016). Diffusion weighted imaging: Technique and applications. *World journal of radiology*, 8(9), 785–798. <https://doi.org/10.4329/wjr.v8.i9.785>
17. Warnert, E., Wood, T. C., Incekara, F., Barker, G. J., Vincent, A., Schouten, J., Kros, J. M., van den Bent, M., Smits, M., & Tamames, J. (2022). Mapping tumour heterogeneity with pulsed 3D CEST MRI in non-enhancing glioma at 3 T*. Magma (New York, N.Y.),* 35(1), 53–62. <https://doi.org/10.1007/s10334-021-00911-6>
18. Stone, A. J., & Blockley, N. P. (2017). A streamlined acquisition for mapping baseline brain oxygenation using quantitative BOLD. *NeuroImage*, 147, 79–88. <https://doi.org/10.1016/j.neuroimage.2016.11.057>
19. Borghammer, P., Cumming, P., Østergaard, K., Gjedde, A., Rodell, A., Bailey, C. J., & Vafaee, M. S. (2012). Cerebral oxygen metabolism in patients with early Parkinson's disease. *Journal of the neurological sciences*, 313(1-2), 123–128. <https://doi.org/10.1016/j.jns.2011.09.010>
20. Chukwueke UN, Wen PY. Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. *CNS Oncol.* 2019 Mar 1;8(1):CNS28. doi: 10.2217/cns-2018-0007. Epub 2019 Feb 26. PMID: 30806082; PMCID: PMC6499019.
21. Gebhardt, B. J., Dobelbower, M. C., Ennis, W. H., Bag, A. K., Markert, J. M., & Fiveash, J. B. (2014). Patterns of failure for glioblastoma multiforme following limited-margin radiation and concurrent temozolomide. *Radiation oncology (London, England),* 9, 130. https://doi.org/10.1186/1748-717X-9-130