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Non-invasive detection of brain tumour genetic mutations using specialised MRI scans of brain biochemistry in clinical practice

Submission date
30/06/2023

Recruitment status
No longer recruiting

Registration date
22/09/2023

Overall study status
Completed

Last Edited
14/05/2024

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The Isocitrate dehydrogenase I (IDH1) mutation is an important factor in determining the prognosis of adult glioma, a type of brain tumor. It is also a key molecular marker in the WHO 2016 guidelines for brain tumors. The presence of this mutation is independently associated with a positive outcome and a favorable MGMT status, which predicts how well the tumor responds to treatment. Conversely, the absence of this mutation, known as the wild-type IDH genotype, is associated with a poor prognosis, even without the typical aggressive imaging and histology features of the tumor.

IDH1 is found in the cell's cytosol, while another form called IDH2 is located in the nucleus. These enzymes play a role in the oxidation of isocitrate to alpha-ketoglutarate, an intermediary metabolite in the citric acid cycle. They also produce a metabolite called 2-hydroxyglutarate (2-HG), which influences histone demethylation. In the case of IDH mutation, a heterodimer is formed, and the mutant subunit converts alpha-ketoglutarate into 2-HG, which is not present in normal or wild-type tumor cells.

The presence of 2-HG can be detected non-invasively in the body using magnetic resonance proton spectroscopy (MRS). This imaging technique is the first of its kind to specifically target an individual genetic mutation. By using 2D MRS, the spatial distribution of 2-HG can be mapped. Various methods have been developed to quantify the levels of 2-HG, and these have been applied in studies of glioma.

While the presence of 2-HG generally indicates a positive outcome, high or increasing levels of 2-HG are associated with the transformation of less aggressive gliomas into more malignant forms. Conversely, a reduction in 2-HG levels has been observed in response to treatment in longitudinal studies.

Previous research has demonstrated the feasibility of targeting biopsies based on spectroscopic tissue features by incorporating virtual targets into neurosurgical navigation systems.

Although 2-HG-optimized MRS has been used in glioma research elsewhere, it has not been implemented in clinical practice in the UK. Reliable detection of 2-HG can be technically challenging, and the exact mechanisms underlying the quantitative variation in 2-HG and its role in malignant transformation are not fully understood. Additionally, limited data exist on the spatial differences of 2-HG in relation to the IDH mutation within different regions of the tumor.

The proposed study aims to optimize the acquisition of MRS data and develop better methodologies for estimating metabolite levels. It also seeks to evaluate the feasibility and reliability of quantifying 2-HG levels in vivo using MRS. Furthermore, the study aims to validate the quantification of 2-HG in different regions of glioma tumors by comparing it with molecular tissue markers, including IDH1 and IDH2, using targeted biopsies based on 2-HG metabolite maps in a pilot group of patients with diffuse glioma.

The primary goal of this research is to introduce this advanced imaging technique to Edinburgh, providing a platform for investigating the molecular features associated with malignant transformation that affect the levels of 2-HG in specific regions of gliomas. Additionally, the study aims to use this technique in clinical practice as part of a comprehensive imaging protocol to assess the risk of surgery and make informed decisions for patients with low-grade gliomas.

Who can participate?
A participant will only be eligible for inclusion in this study if all the following criteria apply:
• Radiological appearances consistent with diffuse glioma or tissue proven diffuse glioma.
• A signed and dated, informed consent must be obtained prior to study participation.
• Adults aged 18-75 years;
• WHO performance status 0 – 1.
• Measurable disease in the case of post-surgery subjects

What does the study involve?
Patients will be recruited through the Edinburgh Neuroncology MDT or Low grade glioma clinic by one of the clinical members of the direct care team and informed consent obtained by the research nurse or one of the members of the research team.
Patients who have not received treatment at the time of recruitment to the study will undergo research MRI protocol within 6 weeks prior to surgery.
Patients who have previously undergone biopsy and/or surgical resection and have significant residual disease will be imaged within 6 months of tissue sampling.
MRI/MRS data will be acquired at a single timepoint, prior to surgery (or after surgical resection where there is measurable residual disease).
MRI examinations will be acquired on 3T Siemens Prisma MRI system in Edinburgh Imaging RIE facility. The MRI protocol will be setup by a physicist including the following sequences in addition to standard clinical sequences used in glioma assessment: Single voxel SEMI-LASER or MEGA-PRESS localised MRS, optimised for detection of 2HG.
IDH-1, 1p/19q ATRX, P53 and other relevant assays will be carried out on subsequently acquired tissue samples from resection or stereotactic biopsy, as part of standard clinical care; IDH status will be compared with in vivo MRS detected 2-HG.
Patients will have their clinical data recorded for the purpose of the study.

What are the possible benefits and risks of participating?
Benefits: There will be no direct benefit to the research participants. The study findings and implementation may benefit patients with glioma in the future.
Risks: The main burden on participating patient will be the MRI examination.
MRI carries no known risk. The examination requires lying still in a confined environment for up to one hour.

Some of the MRI sequences generate significant noise. Patients will be provided with earplugs to reduce noise levels experienced. The spectroscopy sequences themselves are relatively quiet, compared with standard MRI acquisitions.
Intravenous gadolinium-based contrast agent will be administered. This is part of standard clinical tumour imaging protocols that are used routinely in diagnosis, surgical planning and follow up of brain tumours. Historically-used linear gadolinium based agents have been associated with nephrogenic systemic fibrosis (NSF; a rare but serious life-limiting condition) and gadolinium deposition in the brain (of unknown significance). The more chemically stable macrocyclic agents currently used in clinical practice have not, however, been associated with these complications.
For this project, subjects will have at most one additional contrast enhanced MRI. In the majority of patients this will replace a routine pre-operative planning MRI and therefore involve no additional contrast agent exposure. In those patients who have are due to have surgical tumour resection, the spectroscopy MRI will be combined with the pre-operative MRI (adding approximately 30 mins to a total duration of 60 mins). Those who have proven LGG from previous biopsy or resection will have a 60 minute MRI spectroscopy scan.
Additional biopsy obtained at the time of surgical resection will prolong the overall procedure by approximately 20 minutes. It is not associated with significant excess morbidity or mortality above and beyond the usual surgical risks associated with glioma resection, and has been used in previous similar ethically-approved studies.

Where is the study run from?
The study will be run from both the NHS Lothian/University of Edinburgh at the Department of Clinical Neuroscience, Royal Infirmary of Edinburgh and Edinburgh Imaging RIE facility, and NHS Greater Glasgow and Clyde/University of Glasgow at the Imaging Centre of Excellence (ICE) at the Queen Elizabeth University Hospital, in Edinburgh and Glasgow, Scotland, respectively.

When is the study starting and how long is it expected to run for?
July 2023 to December 2024

Who is funding the study?
1. The Melville Trust for the Care and Cure of Cancer (UK)
2. Edinburgh Brain Cancer 'Jonathan Haw Fund' (University of Edinburgh) (UK)

Who is the main contact?
Prof Adam Waldman
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Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
252870

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 252870

Study information

Scientific Title
Magnetic resonance spectroscopy of 2-hydroxyglutarate for the identification of IDH mutations status in glioma

Acronym
IDH MRS

Study objectives
In vivo quantification of 2-hydroxyglutarate (2-HG) in different tumour regions using magnetic resonance spectroscopy methods can reliably perform as a molecular tissue biomarker (including IDH1 mut, IDH2 mut). This method can be confirmed using targeted biopsies based on 2-HG metabolite maps in a pilot cohort of diffuse glioma.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 30/04/2024, East of England - Cambridge South Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)2071048084; cambridgesouth.rec@hra.nhs.uk), ref: 24/EE/0081

Study design
Observational cohort study

Primary study design

Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Patients with radiological appearances consistent with diffuse glioma or tissue-proven diffuse glioma

Interventions
Patients with radiological appearances consistent with diffuse glioma or tissue-proven diffuse glioma will undergo magnetic resonance spectroscopy scanning to assess IDH mutation status via the presence of 2-hydroxyglutarate (2-HG).

MRI/MRS data will be acquired at a single time point prior to surgery (or after surgical resection where there is measurable residual disease). IDH-1, 1p/19q ATRX, P53 and other relevant assays will be carried out on subsequently acquired tissue samples from resection or stereotactic biopsy, as part of standard clinical care; IDH status will be compared with in vivo MRS detected 2-HG. Additional proteomic, metabolomic and gene expression tissue analysis will also be performed.

Intervention Type
Other

Primary outcome(s)
2 hydroxyglutarate concentration determined using in vivo MR spectroscopy at the time of MRI examination

Key secondary outcome(s))
IDH mutation status as determined by immunohistochemistry and gene sequencing from tissue samples collected at the time of surgery

Completion date
31/12/2024

Eligibility

Key inclusion criteria
1. Radiological appearances consistent with diffuse glioma or tissue proven diffuse glioma
2. A signed and dated, informed consent must be obtained prior to study participation
3. Adults aged 18 - 75 years
4. WHO performance status 0 – 1
5. Measurable disease in the case of post-surgery subjects

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
20

Key exclusion criteria
1. Participants for whom MRI is contraindicated
2. Patients with tumours in locations that preclude tissue sampling by biopsy or surgical resection.
3. Patients whose co-morbidities or functional status precludes tissue acquisition by biopsy or surgical resection.

Date of first enrolment
31/07/2023

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital

1055 Great Western Road Glasgow
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Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Charity

Funder Name
The Melville Trust for the Care and Cure of Cancer

Funder Name
Edinburgh Brain Cancer ‘Jonathan Haw Fund’ (University of Edinburgh)

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.
The principal means of data collection from patient visits will be imaging data in DICOM format, this will be stored without patient identifiers on a secure server within UoE. Patient data will be collected on a case report forms (CRF) and then inputted onto an electronic database held on a secure, password protected computer within Imperial College Healthcare Trust.
Subject’s consent forms will be filed in study number order, in a secure office at each investigating site and will link the study number with the patient details.
The Investigator must retain essential documents until notified by the Sponsor and at least for five years after study completion in line with ICH Directive 2005/28 /EC Article 17 (ICH GCP, 2005) subject files and other source data must be kept for the maximum period of time permitted by the institution, which in this case is ten years. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. The data for this study will be

maintained on a secure, password protected East Lothian NHS Trust computer, with only authorised personnel having access to them.
No study document will be destroyed without prior written agreement between the Sponsor and the PI. Should the PI wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Patient (post surgery) version 2.3	17/07/2023	18/07/2023	No	Yes
Participant information sheet	Patient (pre surgery) version 2.3	17/07/2023	18/07/2023	No	Yes
Participant information sheet	version 1.1	16/04/2024	14/05/2024	No	Yes
Protocol file	version 1.0	18/03/2024	14/05/2024	No	No