

Imaging glioblastoma pH using CEST-MRI

Submission date 07/08/2017	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 07/08/2017	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 05/07/2021	Condition category Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

Several studies have demonstrated that acidity is greater within tumours than in normal tissue. This effect is predominantly driven by the hypoxic (low oxygen) environment in the tumour cells, and the build-up of lactic/carboxylic acid as the cells generate energy in the absence of oxygen. Extracellular acidity (outside cells) has been linked to increased tumour invasion and angiogenesis (blood vessel formation), reduced immune function and also resistance to radiation and systemic cytotoxic (anti-cancer drug) treatment. Chemical exchange saturation transfer (CEST) MRI is a non-invasive imaging technique that can give a readout of tissue pH (acidity). Besides pH there is evidence that this technique is also sensitive to protein concentration in tumours. This technique is already being assessed in stroke patients to aid the detection of areas with restricted blood supply and there is also a preclinical program in Oxford to develop this technique to evaluate tumours. The main aim of this study is to evaluate images obtained from CEST MRI in patients with glioblastoma, a type of brain cancer. The CEST-MRI data will also be compared with arterial spin labelling (ASL) perfusion MRI (a non-invasive imaging technique which assesses water and nutrient exchange) and tissue-based testing including pH, protein content and hypoxia markers.

Who can participate?

Patients aged 18 or over with glioblastoma who are scheduled for surgery

What does the study involve?

Participants undergo a CEST-MRI scan and ASL Perfusion MRI scan in addition to their standard care anatomical MRI scan. These may be repeated at the next standard care imaging visit if there are concerns over the time period between imaging and surgery. At surgery, biopsies (tissue samples) are taken for analysis. No visits additional to standard care are anticipated.

What are the possible benefits and risks of participating?

There is not expected to be a clinical benefit to those taking part in the study. There are no known risks or side effects to having a MRI, after proper safety considerations have been addressed. MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). Participants are asked safety questions to help determine if they are able to take part. Some people find that the scanner makes them feel uncomfortable (because they have to keep still for a long time), gives them vertigo (dizziness) or claustrophobic (nervous in small spaces). Such feelings go away once the participant is outside the scanner and there are no after-effects of

having a MRI scan. The main risk associated with biopsy of glioblastoma is haemorrhage (bleeding). However in this setting, biopsy of the tumour during surgery should not carry any increased risk as the participant's tumour will be operated on immediately afterward.

Where is the study run from?
Churchill Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2017 to June 2021

Who is funding the study?
Cancer Research UK

Who is the main contact?
Ms Stasya Ng

Contact information

Type(s)
Scientific

Contact name
Ms Stasya Ng

Contact details
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Oncology Clinical Trials Office
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Roosevelt Drive
Headington
Oxford
United Kingdom
OX3 7DQ

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
35083

Study information

Scientific Title

A single-arm exploratory study examining the feasibility of imaging glioblastoma pH using CEST-MRI

Study objectives

Several studies have demonstrated that acidity within tumours is greater than in normal tissue. This effect is predominantly driven by the hypoxic (low oxygen) environment in the tumour cells, and accumulation of lactic/carboxylic acid as the cells generate energy in the absence of oxygen. Extracellular acidity has been linked to increased tumour invasion and angiogenesis (blood vessel formation), reduced immune function and also resistance to radiation and systemic cytotoxic (anti-cancer drug) therapy.

Chemical exchange saturation transfer (CEST) MRI is a non-invasive imaging technique that can give a readout of tissue pH (acidity). Besides pH there is evidence that this technique is also sensitive to protein concentration in tumour models. This technique is already being assessed in stroke patients to aid the detection of areas with restricted blood supply and there is also a preclinical program in Oxford to develop this technique to evaluate tumours.

The primary objective for this study is to evaluate CEST contrast image obtained from CEST MRI in glioblastoma, a type of brain cancer. As part of this study there are also several exploratory objectives in which the CEST-MRI signature will be correlated with tissue perfusion using arterial spin labelling/ASL perfusion MRI (a non-invasive imaging technique which assesses tissue perfusion/the extent of water and nutrient exchange with tissue) and tissue based testing including pH, protein content and immunohistochemistry to assess for hypoxia markers.

Ethics approval required

Old ethics approval format

Ethics approval(s)

South Central- Oxford A Research Ethics Committee, 18/07/2017, ref: 17/SC/0304

Study design

Non-randomised; Interventional; Design type: Diagnosis, Process of Care, Imaging

Primary study design

Interventional

Secondary study design

Non randomised study

Study setting(s)

Hospital

Study type(s)

Diagnostic

Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied

Brain Cancer

Interventions

Current interventions as of 22/08/2019:

Study participants (previously untreated glioblastoma patients for resection/debulking surgery) will undergo a CEST-MRI scan and ASL Perfusion MRI scan in addition to their standard care anatomical MRI scan. These may be repeated at the next standard care imaging visit if there are concerns over the time period between imaging and surgery. At surgery, biopsies will be taken for analysis prior to tumour resection/debulking. No visits additional to standard care are anticipated.

Further analysis will explore, by carrying out genomic, transcriptomic and metabolomic profiling of the tumour samples, how the hypoxic tumour signature relates to the degree of CEST imaging contrast. This latter work will focus on transcriptomic metagene approaches to assess for example the expression of a validated hypoxia metagene and its relationship to the CEST MRI signature as well as characterisation of glutamine metabolism and its activation under hypoxic conditions (and hence relationship to the CEST MRI imaging signature).

Previous interventions:

Study participants (previously untreated glioblastoma patients for resection/debulking surgery) will undergo a CEST-MRI scan and ASL Perfusion MRI scan in addition to their standard care anatomical MRI scan. These may be repeated at the next standard care imaging visit if there are concerns over the time period between imaging and surgery. At surgery, biopsies will be taken for analysis prior to tumour resection/debulking. No visits additional to standard care are anticipated.

Intervention Type

Other

Primary outcome measure

pH-weighted CEST MRI signal, assessed using amide proton transfer ratio analysis, taken at the patient's imaging visit

Secondary outcome measures

Current secondary outcome measures as of 22/08/2019:

1. Protein levels obtained from tissue-based assay using biopsies obtained on the surgery date
2. pH levels obtained from tissue-based assay using biopsies obtained on the surgery date
3. Hypoxia markers obtained from immunohistochemistry using biopsies obtained on the surgery date
4. Cerebral blood flow and bolus arrival time from ASL MRI perfusion scan, taken at the patient's imaging visit
5. Correlation of tumour metabolite levels and functional genetic pathway expression with CEST-MRI imaging signal

Previous secondary outcome measures:

1. Protein levels obtained from tissue-based assay using biopsies obtained on the surgery date
2. pH levels obtained from tissue-based assay using biopsies obtained on the surgery date
3. Hypoxia markers obtained from immunohistochemistry using biopsies obtained on the surgery date
4. Cerebral blood flow and bolus arrival time from ASL MRI perfusion scan, taken at the patient's imaging visit

Overall study start date

23/02/2017

Completion date

15/06/2021

Eligibility

Key inclusion criteria

1. Participant is willing, capable of cooperating with the protocol and able to give informed consent for participation in the study
2. Male or female, aged 18 years or above
3. Diagnosed with glioblastoma and scheduled for neurosurgical resection or debulking

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

Planned Sample Size: 20; UK Sample Size: 20

Total final enrolment

19

Key exclusion criteria

Current exclusion criteria as of 16/02/2018:

1. Intolerant of MRI brain (for example: claustrophobia)
2. MRI brain contraindicated (for example: implanted electric and electronic devices, heart pacemakers, insulin pumps, implanted hearing aids, neurostimulators, intracranial metal clips, metallic bodies in the eye)
3. Neoadjuvant chemotherapy/radiotherapy treatment for glioblastoma which would interfere with the interpretation of trial results
4. Pregnancy
5. Other psychological, social or medical condition that the investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results

Previous exclusion criteria:

1. Intolerant of MRI brain (for example: claustrophobia)
2. MRI brain contraindicated (for example: implanted electric and electronic devices, heart pacemakers, insulin pumps, implanted hearing aids, neurostimulators, intracranial metal clips, metallic bodies in the eye)

- 3. Prior treatment for glioblastoma
- 4. Pregnancy
- 5. Other psychological, social or medical condition that the investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results

Date of first enrolment

24/10/2017

Date of final enrolment

31/05/2019

Locations

Countries of recruitment

England

United Kingdom

Study participating centre**Churchill Hospital**

Old Road

Headington

Oxford

United Kingdom

OX3 7LE

Sponsor information

Organisation

University of Oxford

Sponsor details

Clinical Trials & Research Governance

Joint Research Office

Boundary Brook House

Headington

Oxford

England

United Kingdom

OX3 7GB

Sponsor type

University/education

ROR

Funder(s)

Funder type

Charity

Funder Name

Cancer Research UK

Alternative Name(s)

CR_UK, Cancer Research UK - London, CRUK

Funding Body Type

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United Kingdom

Results and Publications

Publication and dissemination plan

The intention is to publish this research in a specialist peer reviewed scientific journal.

Intention to publish date

15/06/2022

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.

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?
HRA research summary			28/06/2023	No	No