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Markers of Aggressive Local Therapy In Newly diagnosed Glioblastomas

Submission date 02/01/2010	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 04/03/2011	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 20/02/2019	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
http://cancerhelp.cancerresearchuk.org/trials/a-study-looking-how-glioma-brain-tumours-behave

Study website
N/A

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
N/A

IRAS number

ClinicalTrials.gov number
N/A

Secondary identifying numbers
NIHR/CS/009/011

Study information

Scientific Title
Magnetic resonance imaging to characterise invasive phenotypes in cerebral gliomas: an observational prospective cohort study

Acronym
MALTING

Study objectives
1. The spectrum of high grade gliomas invasion can be identified using diffusion tensor imaging (DTI). Combining these findings with further information relating to angiogenesis and metabolic activity provided by perfusion magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), will predict patterns of recurrence and the time-to-progression.
2. Tumours with a less invasive imaging pattern will have a better response to aggressive local therapy
3. Regions of extensive invasion will exhibit a biological phenotype characterised by increased extracellular expression of matrix metalloproteinase 2 gene (MMP-2). Vascular endothelial cell growth factor (VEGF) and chemokine stromal cell derived factor-1 (CXCL12) measured using microdialysis and an increased expression of membrane type 1 metalloprotease (MT1-MMP) measured using tumour biopsies.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Prospective observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Screening

Participant information sheet

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

Health condition(s) or problem(s) studied
Glioblastomas

Interventions
This study will include three patient cohorts:

1. Markers of Aggressive Local Therapies in Newly diagnosed Glioblastomas (MALTING):
This project will involve recruiting 95 patients with glioblastomas that are felt by the surgical team to be fully resectable. Patients will be imaged pre-operatively using the standard protocol. Patients will undergo an image-guided craniotomy and tumour debulking, assisted using 5-aminolevulinic acid (5-ALA) fluorescence to improve and standardise tumour resection. Carmustine wafers (Gliadel®) will be inserted according to our local protocol. Patients will be imaged post-operatively to assess the extent of resection. Post-operatively patients will be treated with radiotherapy plus concomitant and adjuvant Temozolomide according to the Stupp protocol. All adverse events (both expected and unexpected) will be recorded in the post-operative period.

2. Correlation of Imaging Parameters with Biological Markers of Invasion:
This cohort will involve 50 patients who are undergoing craniotomy and tumour resection. These numbers should provide 10 - 14 limited invasion and 10 diffusely invasive patients. These studies will be performed in collaboration and will study:
2.1. Microdialysis: This will be performed in conjunction with Mr. Peter Hutchinson and Dr. Keri Carpenter, Department of Clinical Neurosciences. In 50 patients who are undergoing craniotomy and tumour resection, two CMA-71 microdialysis catheters (membrane cut-off of 100 kD) will be inserted at the time of surgery: one catheter in the most invasive region (as defined by DTI) and another in normal brain. They will be perfused at a rate of 0.3 µL min-1. After 6 hours equilibration time, samples will be taken at 8 hourly intervals over a 48 hour period. A post-op imaging will confirm catheter location. Small molecule analysis will be performed using a CMA 600 analyser to measure concentrations of glucose, pyruvate, lactate and glutamate. Urea will also be measured and used as an endogenous reference. Macromolecules will be analysed using a multiplex immunoassay and chemiluminescence detection to measure concentration of VEGF, MMP-2, TIMP-1, CXCL12). The concentration of these proteins will be correlated with imaging measures of invasion.
2.2. Cellular Measures: Using multimodal imaging we will identify surgically accessible regions of potential biological interest and these regions will be biopsied. Cell populations will be derived under serum-free conditions and assayed for tumour competency in the Watts lab using established protocols. Cell populations from multiple patient samples will be evaluated for the expression of therapeutically targetable ligands associated with tumour invasion. In particular we will focus on the expression of MT1-MMP.
2.3. High-Resolution Magic Angle Spinning NMR Spectroscopy (HR MAS): This technqiue images tumour samples and provides a biochemical profile of the tumour that does not destroy the tumour sample. This work will be performed in conjunction with Prof. John Griffiths, CRUK Cambridge Research Institute.
2.4. Genomic Profiling: Gene expression profiles will compare invasive with minimally invasive tumours. Samples will be stored as part of our Brain Tumour Bank and will involve storing both brain tumour samples (image-guided) with 20mls of blood.

Intervention Type

Other

Phase
Not Applicable

Primary outcome measure
Pattern of contrast enhancement at first recurrence. This will be assessed by co-registering anatomical MR's at recurrence with pre-RT and highlighting areas of new contrast enhancement. Invasive GBM's will be defined as radiological evidence of > 80% of the recurrent tumour occurring outside the radiotherapy 95% isodose. For the MALTING study, the percentage of patients surviving 2 years will be the main outcome measure.

Secondary outcome measures
1. Overall survival
2. Time to radiological progression: Radiological progression is defined as per MacDonald criteria i.e. a 25% or greater increase in the size of the tumour (as defined by the product of two perpendiculars of the enhancing component) or the appearances of new contrast-enhancing lesions.
3. Time to clinical progression: This will be defined as the presence of any of the following:
3.1. Neurological deterioration with or without the need for increased steroid use
3.2. Increased steroid requirements for more than 2 weeks including for increasing neurological deficit and/or features of increased intracranial pressure suggestive of tumour progression when other causes have been excluded.
3.3. Deterioration of ? 1 point in WHO performance status, compared with previous assessment
3.4. Increased symptoms of raised intracranial pressure (headache, nausea/vomiting etc.)
4. The extent to which conventionally planned RT volumes encompassed the abnormalities identified using advanced imaging
5. For the MALTING study, patients outcome will be compared to predicted outcome from the prognostic model proposed by Gorlia et al (Lancet Oncology, 2008). This uses a normogram that involves MGMT promoter methylation status, age, performance status, extent of resection, and Mini-Mental State Examination (MMSE) to predict outcome. Using a modified Sliding Dichotomy design, the outcome for each patient is compared to their predicted outcome.

Overall study start date
01/03/2010

Completion date
31/12/2018

Eligibility

Key inclusion criteria
1. Imaging appearances of a high grade glioma
2. Likely to be suitable for radiotherapy (60 Gy) with concomitant and adjuvant temozolomide
3. World Health Organization (WHO) performance status (PS) grade 0 or 2
4. Aged 18 - 75 years, either sex
5. Resection or biopsy (although only those suitable for maximal resection will be considered for the MALTING Trial)

Patients for the MALTING Trial will be felt by their consultant neurosurgeon to be suitable for 5-aminolevulinic acid (5-ALA) fluorescence-guided resection with insertion of carmustine wafers.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Total recruitment of 145 patients with high grade gliomas

Key exclusion criteria
1. Unsuitable for a contrast-enhanced MRI (MR unsafe metallic implants, claustrophobia, allergy to gadolinium contrast agent or severe renal impairment)
2. Pregnant
3. Allergic to aminolevulinic acid
4. Suffering from porphyria. Care will be taken if the patient is taking other photosensitising drugs.

Date of first enrolment
01/03/2010

Date of final enrolment
01/03/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Neurosurgery Division
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Sponsor information

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Sponsor type
Hospital/treatment centre

Website
http://www.cuh.org.uk/research/research_index.html

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research (NIHR) (UK) - Clinician Scientist Award (ref: NIHR/CS/009/011)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration