Non-invasive genotyping and grading of glioma using advanced MR imaging, histopathology and AI: the iGENE2.0 study

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

Summary

ID

NL-OMON57298

Source
ToetsingOnline

Brief title
iGENE2.0

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Head and neck therapeutic procedures

Synonym
Advanced imaging in brain tumors

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: (ZonMW) Subsidiebesluit over dossiernummer 09150182210019

Intervention

Keyword: Genotyping, Glioma, MRI

Outcome measures

Primary outcome

The primary study parameter is the diagnostic accuracy with which we can

predict glioma genotype, based on pre-operative advanced MRI techniques in

combination with our previously developed *PrognosAIs* algorithm.

Secondary outcome

The secondary parameter is the association between MRI signal and tissue

features (both at the cellular and molecular level).

Study description

Background summary

The iGENE2.0 project challenges the current diagnostic paradigm that entirely relies on tissue for diagnosis and management of patients with a brain tumour, with the ultimate aim to determine tumour genotype non-invasively from MRI only.

Roughly 1,000 new cases of adult primary brain tumours are diagnosed each year in the Netherlands. These are most often diffuse glioma, and outcome is largely dismal. Prognosis and treatment decisions rely on tissue diagnosis of tumour (geno)type and grade. Glioma typing is based on the presence or absence of mutation in the isocitrate dehydrogenase (IDH) gene: IDH mutated (IDHmut) respectively IDH wild type (IDHwt). In the presence of other specific, genetic alterations, IDHwt tumours are classified as *glioblastoma, IDHwt* (GBM). IDHmut tumours are further divided into those with versus without 1p/19q co-deletion: *oligodendroglioma, IDHmut and 1p/19q co-deleted* respectively

astrocytoma, IDHmut.

Gross total surgical resection is treatment of first choice, but is often not feasible, for instance due to tumour location or extent of infiltration in the brain or due to patient frailty. In such cases, diagnostic biopsy is performed, solely to obtain tissue for diagnosis. For patients, these are procedures with high impact, have complication risks, and require hospitalisation. They are therefore rarely performed in the setting of tumour recurrence, let alone at intermediate time points. This means that in most patients there is no tumour tissue available for assessing - altered - tumour characteristics to rationally determine treatment switch or inclusion in trials along the course of their disease. The non-invasive characterisation of brain tumours is thus clinically highly relevant not only at first diagnosis - especially in patients not qualifying for surgical resection - but particularly upon recurrence.

In our previous work, it has been shown that non-invasive genotypical classification of adult-type glioma with only conventional MRI techniques can be achieved using artificial intelligence (AI) with accuracies of ~85%. This is not yet sufficient to replace surgical biopsy. One way to improve the diagnostic accuracy is by computationally exploiting more advanced MRI data. For example, in our previous work we found that with a combination of more advanced MRI techniques such as diffusion weighted (DWI) and perfusion MRI (PWI), reflecting cellularity and vascularisation respectively, IDHwt glioma can be distinguished from IDHmut 1p/19q intact glioma. More recent advanced MRI techniques such as Chemical Exchange Saturation Transfer (CEST) MRI, which reflects cellular proliferation, have been shown to correlate well with a tumour*s aggressiveness. This work underlies the hypothesis that MRI can be sensitised to specific glioma tissue features. Also, current classification predictions only scratch the surface of tumour biology, of which the micro-environment is of particular interest in view of new treatment targets. Computational analysis techniques based on radiological imaging (*radiomics*) have taken a huge flight in the past decade and are increasingly successful in disease detection, characterisation, and surveillance. Given the clinical implications, a large body of work has focused on the prediction/correlation of glioma genotype from/with imaging phenotypes: *radiogenomics*. Some exploratory work indicates that MRI can also predict the tumour*s immune micro-environment phenotype.

By leveraging the biological association between morphological tissue properties and (advanced) MRI signal on the one hand, and genetic alterations on the other, we expect to make clinically meaningful diagnostic predictions based on pre-operative MRI alone, and thus eventually not requiring tumour tissue currently only obtainable through invasive surgical procedures. In this study, we assess whether we can improve such diagnostic predictions by combining our previously developed algorithm *PrognosAIs* with advanced MRI. Additionally, we aim to gain a better understanding of the relationship between the (advanced) MRI signal on the one hand and the tumour tissue characteristics

(both on the cellular and molecular level) on the other hand. Such insights are essential for the future development of AI models by indicating which of the advanced MRI technique(s) have the highest potential and strongest biological foundation to eventually make a fully MRI-based glioma diagnosis possible.

Study objective

The primary objective is to improve the accuracy to predict glioma genotype of our previously developed algorithm *PrognosAIs* by adding advanced MRI acquired before surgery. The secondary objective is to learn the relationship between MRI signal formation and tissue characteristics, both at the cellular and molecular level. Both these objectives contribute to guiding the future development of artificial intelligence (AI) models, indicating which of the advanced MRI technique(s) have the highest potential and strongest biological foundation to eventually make a fully MRI-based glioma diagnosis possible.

Study design

In this prospective observational study, prospective data will be collected, which will start once ethical approval is in place.

For the primary objective of this study, patients will be scanned with advanced MRI techniques, from which quantitative parameters will be obtained which will be investigated as predictors of brain tumour genotype. These predictors will be combined with the prediction from our previously developed AI algorithm *PrognosAIs*, through regression analyses. In parallel to this project, *PrognosAIs* is further developed with retrospective data (MEC-2024-0211). Future iterations of PrognosAIs will likely become available during the course of this project and will similarly be combined with the advanced MRI predictors.

Once included (after informed consent is given by the patients), patients will be scanned at the department of Radiology & Nuclear Medicine at Erasmus MC with a pre-operative MRI scan as part of the standard clinical care (30 minutes). Additionally, advanced MRI sequences will be added to this scan session (max 30 minutes).

For the secondary objective of the project, targeted stereotactic biopsies will be performed during surgery at specific tumour locations identified based on the pre-operative MRI scans. This enables to establish a spatial relationship between advanced MRI parameters and tissue characteristics, which is important because of tumour heterogeneity both in terms of MRI signal and tumour histology. However, since this procedure carries an - albeit limited - additional risk to the patient while it is at the same time not essential for the primary objective of the study, patients are given the opportunity to opt

out of this aspect of the study. In these cases, the location of the diagnostic biopsies performed as part of the standard clinical routine will be recorded during the surgery, such that a relationship between the clinically acquired and assessed tissue sample and the MRI signal can still be investigated.

The collected tissue samples will - in addition to routine clinical analysis - be subjected to (advanced) immunohistochemical staining and molecular analyses such as next-generation sequencing (NGS), for tumour microenvironment mapping respectively genetic profiling (e.g., IDH mutation status). These quantitative tissue data will be correlated with the advanced MRI parameters, with the known locations from the pre-operative scan.

Patients will be followed up for disease progression and survival in routine clinical practice, and their quality of life and experience during the study will be recorded. No additional observations beyond those in routine clinical care will be conducted in the context of this study.

Study burden and risks

No additional benefits are associated with patient participation in this study. However, patient participation could help the development of techniques capable of diagnosing primary brain tumours without the need for invasive procedures, therefore helping future patients.

One possible burden for participating patients is that they will be subjected to longer MRI scanning times than usual, as aside from the conventional MRI scans that patients with glioma undergo, they will be scanned with several advanced MRI techniques. The total additional scan time is 30 minutes.

The surgeries that these patients will undergo (either for diagnostic biopsy or a resection) are part of the standard medical procedure. However, in patients opting to undergo targeted biopsies, the surgical time will be extended by a maximum of 15-30 minutes depending on the intended procedure (diagnostic biopsy or resection respectively). The additional targeted biopsies carry a - limited - risk of haemorrhage (1.5%). These risks will be mitigated by careful pre-operative planning with the aim to take all diagnostic and targeted biopsies from within the same trajectory whenever possible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Participant must be an adult (18 years or older)
Participant must be scheduled for surgery (resection or biopsy) of a (presumed) primary brain tumour
Participant must give written informed consent conform ICH-GCP

Exclusion criteria

Contra-indication for MRI (implanted metal parts, e.g. stents, vascular clips, pacemakers, claustrophobia)
Inability to give consent
Having received/receiving chemotherapy for a brain tumour at time of MRI, prior to surgery

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	17-02-2025
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO

Date:	17-02-2025
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL87585.078.24