

General Introduction

GLIOMAS

Gliomas are primary brain tumors in adults and are categorized by the World Health Organization (WHO) as grade I and II (low-grade gliomas), grade III (anaplastic) and IV (glioblastoma)¹. Glioblastoma encompass 15% of all brain and central nervous system tumors and almost half of all primary brain tumors². Astrocytoma and glioblastoma are categorized by the mutational status of the gene encoding for isocitrate dehydrogenase (*IDH*): *IDH*-mutant (*IDHmt*) and *IDH* wild-type (*IDHwt*). By definition, oligodendrogloma is both 1p19q codeleted and *IDHmt*¹. While the exact diagnosis and tumor grade is determined by assessment of molecular markers and histology, Magnetic Resonance Imaging (MRI) can give information on the diagnosis as well. General features that can help predict glioma grade are presence or lack of contrast-enhancement and necrosis. More advanced measures such as Apparent Diffusion Coefficient (ADC) derived from Diffusion Weighted Imaging (DWI)^{3,4} and regional cerebral blood volume (rCBV) from perfusion imaging can also have added value and are therefore often included in clinical glioma scanning protocols^{5,6}.

MRI METHODS

MRI images are constructed by inducing alignment of hydrogen nuclei (protons) using a strong magnetic field (usually 1.5 or 3.0 tesla), after which the alignment is disturbed with a radiofrequency (RF) pulse. When the RF-pulse has ended, the protons realign themselves and emit signals while doing so. The exact location of every signal can be determined with the help of magnetic gradients and frequency encoding, which make sure that every voxel emits a slightly different signal. The signals are then processed to form an image.

The realignment signals are two-fold: there is the T1 signal (recovery of longitudinal relaxation) and the T2 signal (decay of transverse magnetization). The main MRI sequences are therefore T1-weighted and T2-weighted images. Differences in T1 and T2 relaxation times between different tissues allow distinction between tissues. Images can be reconstructed as well using more advanced techniques. For instance, when the water signal is nulled in a T2-weighted sequence, we are left with a T2-weighted FLuid Attenuation Inversion Recovery (FLAIR) image, which is a very useful image when looking at white matter abnormalities.

If a gadolinium-based contrast-agent is administered and a T1-weighted image is acquired, blood vessels and areas with a defective blood-brain-barrier (as is the case many tumors) enhance. Contrast-enhanced scanning can also be used for the evaluation of brain perfusion. There are several different methods to measure brain

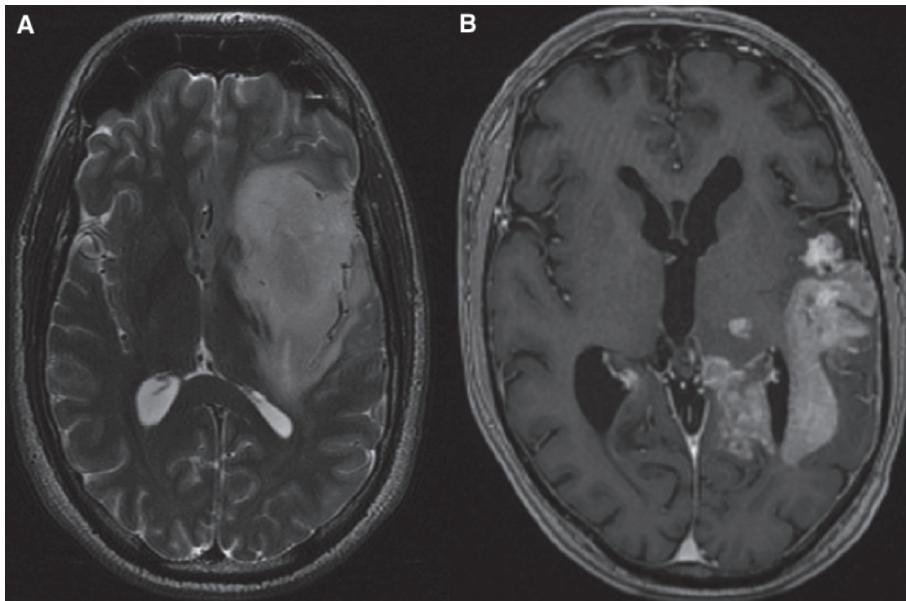


Figure 1. (A) Example of a low-grade glioma on a T2-weighted image. (B) Contrast enhancement of glioblastoma on a post-contrast T1-weighted image.

perfusion, and the method used in this thesis is Dynamic Susceptibility Contrast (DSC) MR perfusion, from which relative cerebral blood volume (rCBV) can be estimated. Examples of gliomas on structural imaging and perfusion imaging can be seen in *figure 1* and *figure 2*.

Diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) are MRI methods in which the degree of diffusion of water molecules within a voxel is measured. Certain tissues are more dense than others, affecting diffusion. Isotropic diffusion means that a water molecule can move freely in any direction, while anisotropic diffusion indicates one or more barriers preventing free diffusion. The anisotropy can also be used to determine the general direction of diffusion within a voxel and after linking voxels together, the general direction of white matter fibers can be determined⁷.

Response assessment and follow-up of patients with brain tumors can include structural MRI (T1-weighted, T2-weighted and FLAIR images), advanced MRI (diffusion, perfusion and spectroscopy) and nuclear medicine imaging (Single-Photon Emission Computed Tomography or SPECT and Positron Emission Tomography or PET), and is described in more detail in *chapter 3.1*.

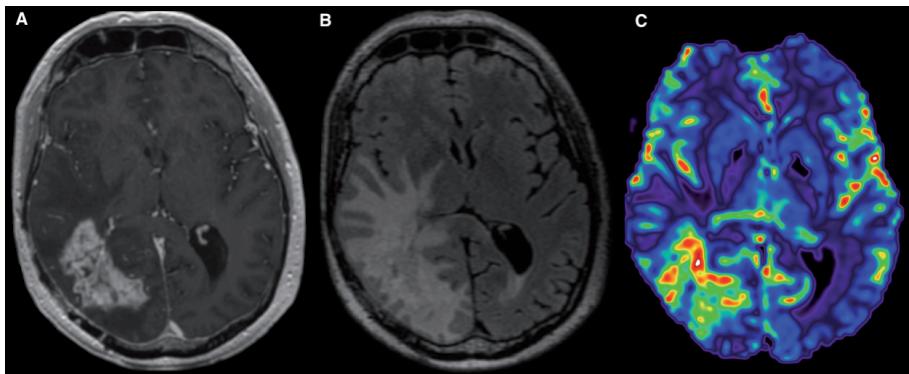


Figure 2. (A) Example of a recurrent glioblastoma with enhancement on the T1-weighted post-contrast image, (B) surrounding non-enhancing abnormalities on the FLAIR-image and (C) a DSC-perfusion-derived standardized and leakage-corrected rCBV map depicting increased rCBV in the enhancing tumor area.

PRE-TREATMENT ASSESSMENT IN GLIOMAS

Before surgery, Diffusion Tensor Imaging (DTI) scans can be made for localization of important fiber tracts. Further post-processing of DTI-scans provides a variety of parameter maps, such as Mean Diffusivity (MD), Fractional Anisotropy (FA), pure isotropy (p) and anisotropy (q). The p and q maps have been used by Price et al.^{8,9} to determine the extent of infiltrative growth of glioblastoma along white matter tracts in association with IDH-mutation status. In **chapter 2**, Price's method is replicated and applied to non-enhancing gliomas (i.e. presumed low-grade) to see if it allows prediction of *IDH*-mutation status and 1p19q codeletion status in this specific patient group.

POST-TREATMENT ASSESSMENT IN GLIOMAS

While **chapter 2** focuses on pre-treatment characteristics in non-enhancing gliomas, **chapter 3** focuses on response assessment after treatment. Treatment of glioma includes surgery, radiotherapy and chemotherapy at first diagnosis¹⁰. At recurrence, other and sometimes experimental treatment options are considered, including nitrosoureas, retreatment with temozolomide, and angiogenesis inhibitors. Tumors need a steady supply of nutrients and oxygen to grow. Normal blood vessels in the area of the tumor are insufficient to fulfill the demands of the tumor and so the tumor induces growth of new blood vessels: angiogenesis. Angiogenesis can be blocked by targeting endothelial cells directly or by inhibiting specific signal-mole-

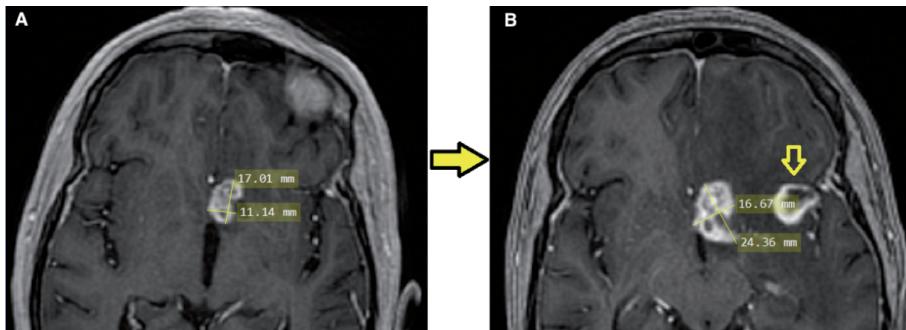


Figure 3. Example of 2D RANO measures in enhancing glioblastoma at baseline (A) and follow-up (B). There is progressive disease (PD) because the enhancing lesion has grown in size and a new enhancing lesion has appeared next to it.

cules released by the tumor. An important signal-molecule, produced in abundance by glioblastoma, is Vascular Endothelial Growth Factor (VEGF)¹¹. The most commonly used angiogenesis inhibitor in glioblastoma is the VEGF- inhibitor bevacizumab (or Avastin®), which has been granted full approval by the United States Food and Drug Administration (FDA) in 2017 for second-line treatment in recurrent glioblastoma¹². Bevacizumab is often given in combination with a chemotherapeutic agent.

Whether a recurrent glioblastoma is responding to treatment is based on MRI and clinical features. The Response Assessment in Neuro-Oncology (RANO) criteria include 2D measurements of enhancing tumor and an estimation of change in non-enhancing abnormalities. Additionally, the appearance of new lesions, steroid use and clinical status are taken into account¹³ (see **Figure 3**). There are two main problems when it comes to response assessment: 1) pseudo-response, and 2) pseudo-progression. Pseudo-progression is an increase in enhancement on the T1-weighted post-contrast scan caused by prior radiotherapy. It mimics actual tumor growth, while in fact it reflects radionecrosis. In **chapter 3.1**, imaging of pseudo-progression is described in detail.

Pseudo-response is seen after treatment with angiogenesis inhibitors and describes the decrease in enhancement of the tumor and also a decrease in non-enhancing abnormalities without an actual decrease in tumor size. As the effect of pseudo-response is seen early after start of treatment, early radiological treatment response assessment can be a challenge. Early assessment is important because it provides valuable information on whether the tumor is responding to treatment or not. If a treatment is ineffective, there is no reason to continue, especially in the light of potential serious side effects. A different treatment might be considered in some patients. Additionally, radiological measures can provide information on the patient's prognosis. Measuring this early treatment response with the 2D RANO criteria in

those with pseudo-response is suboptimal at best and therefore we evaluated a variety of different methods for determining treatment response in this patient group.

It has been argued that volumetric measures are an improvement over 2D measures, especially in glioblastoma, because these heterogeneous tumors with asymmetrical growth could be measured more reliably with a volumetric approach, and also because semi-automated volumetric tumor segmentation was shown to have lower intra- and interrater variability than manual measures^{14,15}. In **chapter 3.2**, the 2D RANO criteria were compared with volumetric measures in recurrent glioblastoma treated with classical chemotherapy and/or bevacizumab. Change in tumor volume was measured between baseline (before treatment) and first/second follow-up. In **chapter 3.3**, the quantitative approach to this volumetric response assessment is explored.

Measures other than tumor size might provide more information on treatment response (or lack thereof) in those treated with bevacizumab. Previous studies have shown that low values of Apparent Diffusion Coefficient (ADC) derived from DWI at baseline and after treatment (i.e. diffusion restriction) may be predictive for survival^{16,17}. Studies that look at perfusion imaging derived, relative Cerebral Blood Volume (rCBV) find that an increase in rCBV from pre- to post-treatment decreases survival, while a decrease improves survival¹⁸. Early changes in diffusion after therapy in recurrent glioblastoma are discussed in **chapter 3.4**.

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