Methodology matters: characterization of glioma through advanced MR imaging

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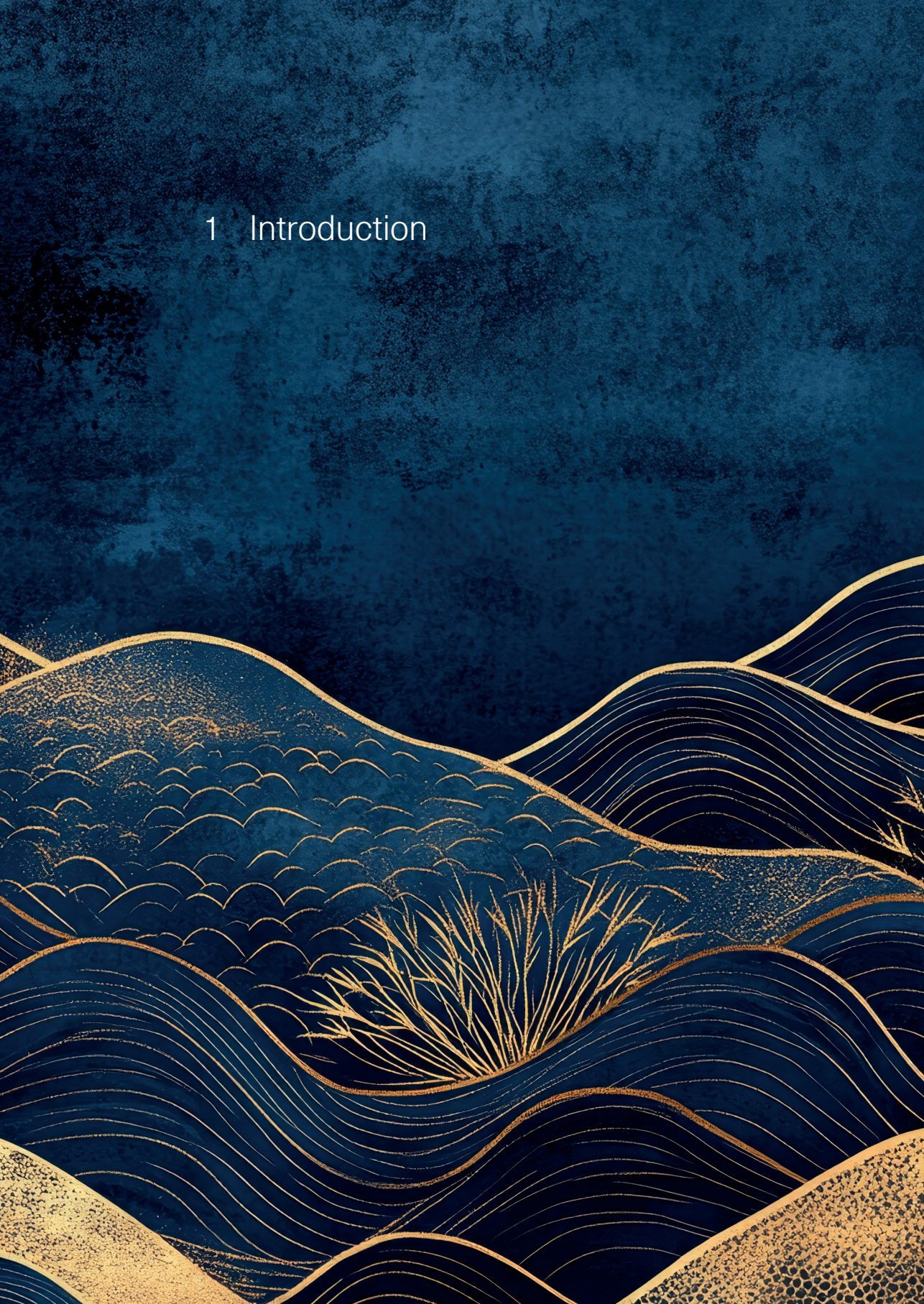
1 Introduction



1.1 Glioma disease background

Gliomas are the most common form of adult primary brain tumors, accounting for approximately 25% of the total of primary brain tumors and 81% of all adult malignant brain tumors[1]. Gliomas originate from glial cells, which provide physical and chemical support to neurons, including astrocytes, oligodendrocytes, microglia and ependymal cells [2–4]. Despite being relatively rare, gliomas still pose one of the biggest challenges in neuro-oncology. Due to their infiltrative growth these tumors tend to recur after antitumor treatment and prognosis is generally poor, particularly for the higher grade gliomas. Currently, despite extensive treatment, patients with glioblastoma (the most malignant and most commonly occurring glioma) have a median overall survival between 12 and 15 months[5]. Lower-grade gliomas have a slower growth rate and have a 5-year overall survival rate between 70% and 97%[6]. The cause of gliomas is still poorly understood, and identifying the triggers for the onset of these tumors could help in its prevention. However, as of today, only a few risk factors have been confirmed and are widely accepted[1]. For instance, a family history of glioma is a known risk factor, although it accounts for only a small percentage (5-10%) of cases[7]. Another risk factor is the exposure to ionizing radiation. A few studies have investigated the relationship between intensity of radiation obtained during childhood and the development of central nervous system tumors. These studies found a sevenfold increased risk to develop a glioma after exposure to radiation[8,9].

The diagnosis of a glioma typically involves a combination of clinical (symptom) assessment, lesion visualization by means of imaging methods, and importantly, pathological and genetic/molecular tissue examination[10]. Tissue collection through surgery is performed by means of a resection or a biopsy[11]. Tumor resection is usually aimed at the maximal safe removal of the tumor, while a biopsy is performed when surgery is contraindicated. Contraindications include situations where a substantial part of the tumor is located in or near brain regions where tumor resection could significantly impair the patient's neurological functions.

Following surgery and determining the integrated tissue diagnosis including both histopathological and molecular-genetic characteristics, patients typically undergo radiotherapy, chemotherapy with temozolomide or PCV (procarbazine, CCNU, and lomustine), or targeted therapy. In case of tumor recurrence, similar antitumor treatment options can be weighed against each other, depending on the efficacy of previous treatment, performance score, and the availability of experimental treatments[12].

1.2 MR imaging in the clinical workflow of gliomas

Magnetic resonance imaging (MRI) is the most commonly used imaging method to diagnose and follow-up gliomas. Advantages of MR imaging for gliomas include its good soft tissue contrast, detailed visualization through high-resolution images, its non-invasiveness and lack of any ionizing radiation. Different modalities are available, allowing to characterize, for example, tumor vascularity and metabolism, as well as to perform functional imaging to assess

brain activity to support surgical planning. Standard MRI protocol recommendations have been outlined by the European Organization for Research and Treatment of Cancer (EORTC) and the United States National Brain Tumor Society (NBTS)[13]. These include anatomical images such as 3D T_1-weighted imaging (pre-contrast), which suppresses any signal from water (like edema) while maintaining fat tissue contrast. Moreover, T_2 fluid-attenuated inversion recovery (FLAIR) suppresses free fluid, such as edema, while maintaining a hyperintense appearance from the solid tumor tissue. On T_2-weighted imaging, the solid component of the tumor also appears hyperintense, most likely due to its protons' longer relaxation times, which also make any water component appear brighter, in contrast to T_2-FLAIR images. Other modalities, such as diffusion-weighted imaging, are also recommended due to their ability to non-invasively estimate tumor cellularity and grade[14]. Lastly, post-contrast 3D T_1-weighted images are recommended, most commonly using gadolinium-based contrast agents. The contrast agent travels to the newly developed capillaries surrounding the tumor, which tend to be leakier than regular blood vessels, leading to extravasation of contrast agent into the extracellular space. This causes a shortening of the longitudinal proton relaxation time (T_1), resulting in a hyperintense signal. The resulting hyperintensity can indicate malignancy due to the neovascularity fueling tumor cells.

Conventional imaging allows visualization of different tumor components, such as the necrotic core, edema, and gadolinium contrast enhancing and non-enhancing lesions. However, conventional imaging has a few disadvantages. For example, it can be challenging to differentiate between edema and the non-enhancing component of the tumor, as both appear hyperintense on T_2 MR images. Another current challenge is delineating tumor borders. Gliomas tend to be diffuse and in most cases their lesion is not clear and well differentiated due to their infiltrative growth. This in turn makes it extremely difficult to define a clear-cut boundary. In the monitoring of response after antitumor treatment, it can be hard to differentiate between tumor recurrence and treatment-related effects, often referred to as progression and pseudo-progression, respectively. Another challenge includes differentiating between pseudo-progression and radiation necrosis. The former mimics tumor progression through treatment induced inflammation, whereas the latter is caused by radiation damage to the brain and blood vessels. However, on conventional MRI such as T_2 weighted images, both appear hyperintense.

Advanced imaging techniques provide an opportunity to aid in differentiating between true tumor progression, pseudo-progression and radiation necrosis. For example, it could allow to visualize tumor specific metabolic and perfusion changes. The further refinement of imaging techniques might contribute to better decision-making and subsequently a better prognosis for patients[56].

1.3 Advanced MR imaging for gliomas

The advancement of MR imaging techniques has brought new opportunities to non-invasively characterize gliomas and surrounding tissue[15]. Capturing more detailed tumor characteristics could aid in a more complete diagnostic understanding of the different glioma molecular

subtypes recently established by the WHO[10]. For treatment it could mean establishing a more targeted treatment plan based on the tumor's genetic and molecular makeup. For treatment follow-up more accurately distinguishing true tumor progression, pseudo-progression and radiation necrosis is of the highest importance. The opportunities for advanced MR imaging techniques in improving glioma standard of care are well recognized. This is why extensive research has also been carried out on trying to image pathophysiological characteristics of gliomas: increased vascular needs and abnormal metabolism[16–19].

One of the hallmarks of cancer includes neo-angiogenesis where new blood vessels are formed to provide enough oxygen and nutrients for tumor growth[20]. Perfusion imaging is one of the advanced MR imaging techniques that seeks to measure the blood flow to tumors. This indirect measure of tumor vascularity has shown to be valuable for characterizing gliomas using modalities such as dynamic susceptibility contrast (DSC) and arterial spin labeling (ASL) MRI.

DSC is based on monitoring the first passage (or more precisely approximately the first 1-2 minutes after injection) of contrast agent through tissue. From DSC it is possible to estimate the relative cerebral blood volume (rCBV), and the ratio with contralateral tissue has been shown to help predict tumor-grades and stratify patients based on their survival prognosis[21,22], as well as identifying differences regarding IDH1 mutation and MGMT status[23]. An interesting case report has also shown through histopathology that aggressive recurrent tumor tissue exhibits high rCBV, while low rCBV corresponded to non-tumorous tissue[24]. Lastly, DSC has shown to have one of the highest diagnostic accuracies for differentiating between true- and pseudo-progression in high-grade gliomas, and the highest specificity (0.88 [0.70 – 0.96])[25].

ASL allows to non-invasively quantify cerebral blood flow (CBF) by using the blood as endogenous tracer. ASL-based perfusion maps are generally found to show increased signal-intensities in gliomas compared to the healthy appearing brain[26]. Studies have demonstrated the ability to differentiate between tumor grades based on maximum signal intensity in the tumors region compared to contralateral healthy tissue. It is known that glioblastomas have an increase in metabolic demands and therefore perfusion, compared to lower grade tumors which typically have a lower blood flow[27,28]. ASL has also been shown to be useful to predict IDH1 mutation and MGMT promoter status, which are relevant concerning survival prognosis and treatment response, respectively[29]. Although deemed valuable and already applied in some clinical centra, these advanced perfusion modalities are not yet widely available, partly due to technical constraints and lack of standardization[16,18]. ASL has also shown to increase sensitivity and specificity to distinguish between true- and pseudo progression, especially when combined with DSC[25]. One study has even concluded that ASL has sufficient diagnostic accuracy to potentially replace DSC-MRI and in this way avoid higher doses of contrast agent[30].

Another hallmark of cancer is deregulated cellular metabolism, where the metabolic needs and byproducts differ from those of healthy cells[20]. Consequently, advanced MR imaging can be valuable for capturing the abnormal metabolic behavior of gliomas. Proton magnetic resonance

spectroscopy (1H-MRS) is an MR modality that can non-invasively measure metabolites in gliomas. It is useful, for instance, in differentiating between glioblastoma and lower-grade gliomas[31]. Additionally, the oncometabolite 2-hydroxyglutarate (2-HG), which accumulates due to the IDH mutation, has recently gained attention for its significant diagnostic performance when measured with 1H-MRS[32].

A more recent technique, chemical exchange saturation transfer (CEST), is another modality which allows to indirectly measure metabolites[33]. In Chapter 2 this technique is introduced in more detail, including its methodology and value in glioma imaging.

1.4 Ultra-high field imaging

Another advancement in glioma imaging has been the utilization of ultra-high field (UHF) MR. UHF systems operate at magnetic field strengths of 7 Tesla and above[34]. With stronger MRI systems, it is possible to obtain images with higher spatial resolution, larger spectral resolution and increased sensitivity[34]. These advantages stem from improvements in signal-to-noise ratio (SNR), which scale super-linearly with the magnetic field (B_0)[34].

The benefits of UHF MR imaging for gliomas have been recently outlined[35]. The main findings indicate that 7T MR imaging enhances the visualization of microbleeds, allows for quantification and characterization of blood vessels in glioblastomas, improves contrast between gray and white matter, and can refine radiotherapy planning[36–38]. The latter was investigated by comparing the ability to delineate radiotherapy targeted volumes between clinical MRI scans and 7T T_2-FLAIR. The 7T image allowed to significantly reduce the targeted volume leading to the idea that healthy tissue can in this way be spared during treatment[37].

Additionally, advanced MR imaging modalities, such as CEST, can also benefit from the increased magnetic field strength due to enhanced spectral resolution, specificity to protons with high exchange rates, and longer water T_1, which amplifies the CEST effect[39]. These characteristics can improve the specificity to the proton group of interest when acquiring CEST images. Few clinical studies have explored these advantages for glioma endogenous CEST contrasts at 7T[40–47]. Nuclear Overhauser effect (NOE)-mediated and amide protein transfer (APT) CEST contrasts were found to be higher in the tumor areas and overlapped with gadolinium weighted T_1 tumor lesions, respectively[40,41]. Moreover, NOE-CEST contrast at 7T has been found to aid in differentiating between high and low-grade gliomas[43]. Conversely, NOE suppressed APT-CEST at 7T has shown potential in predicting Isocytrate Dehydrogenase (IDH) mutation status and differentiating between high and low-grade gliomas, although it did not predict MGMT promoter methylation status[42,44]. Interestingly, APT-CEST was found to provide higher contrast in gliomas located in the right hemisphere compared to the left. Finally, NOE-suppressed APT-CEST contrast at 7T appears to significantly differ according to patient's response to treatment[46]. Recently, glutamate-CEST at 7T was shown to be significantly associated with recent epileptic seizure and drug-refractory epilepsy, suggesting glutamate's role in glioma-associated seizures[45].

1.5 Goals and outline of this thesis

The overarching goal of this thesis is to explore the value of advanced MRI modalities for imaging gliomas. The first goal is to evaluate the use of CEST at ultra-high-field at 7T to characterize these brain tumors. The second goal is to investigate how ultra-high-field imaging at 7T can aid in answering current clinical challenges in the assessment of gliomas.

This thesis starts with a Chapter introducing CEST imaging, reviewing recent literature and contextualizing its clinical relevance for gliomas (Chapter 2). This Chapter is part of an extensive literature overview on advanced MRI techniques for preoperative glioma characterization.

Hereafter the thesis dives into the methodology of CEST, where the feasibility of a novel and advanced image analysis technique, variable delay multi pulse (VDMP) is investigated to separately assess the different CEST pools in the human brain (Chapter 3). The goal of Chapter 4 was to determine what the most optimal image acquisition protocol parameters would be to image the CEST amines pools. Initially simulations and phantom work were performed. From these *in vitro* findings, the acquisition parameters were then applied for image acquisition *in vivo*. Together with MRS the metabolite contributor to the amines CEST contrast observed was determined. The final chapter (Chapter 5) on CEST consisted of investigating the use of 2 ppm CEST pool contrast to non-invasively differentiate between the enhancing and non-enhancing (parts of) glioma lesions.

The second part of the thesis aimed at exploring novel modalities to respond to current clinical challenges, namely treatment planning and the differentiation between true- and pseudo-tumor progression. Chapter 6 addresses the comparison between high-quality 7T MR imaging and clinical MRI in assessing tumor extension, volume and shape characteristics of the hyperintense component of gliomas. In Chapter 7 a clustering analysis method was applied based on radiological perfusion characteristics retrieved from clinical DSC and ASL imaging to identify different phenotypes of gliomas. Ultimately the goal was to form groups on the basis of these phenotypes which would share similar clinical outcome.