CHAPTER 1

General introduction


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1. INTRODUCTION

Malignant brain tumors are relatively uncommon tumors in adults, making up less than 2% of all cancer cases.\textsuperscript{1,2} The two major groups are primary brain tumors and cerebral metastases, with the latter being more common.\textsuperscript{3} Although uncommon, brain tumors are responsible for a significant loss of healthy life years and impaired quality of life. Treatment is often aggressive trying to improve this outcome. During and after treatment, patients are monitored with imaging to assess treatment response and to decide whether the current treatment should be continued or not. This thesis focusses mainly on gliomas, the most common primary brain tumor.

1.1 Primary Brain Tumors
Primary intra-axial brain tumors are a heterogenous group of which gliomas are most common (in approximately 80% of the cases), with the majority being grade 4 glioblastoma.\textsuperscript{3} Gliomas arise from glial cells, known as supportive cells within the brain, such as astrocytes or oligodendrocytes. The cause of gliomas remains unknown to date, but neural stem cells, which are abundant in the subventricular zone of the brain, have been named as possible cell of origin in glioblastomas.

To determine the tumor grade of gliomas, historically, the WHO grading system is used, representing a malignancy scale varying from 1 to 4 (previously in Roman numerals I-IV). Grade 1 lesions are regarded as benign tumors due to their low proliferative potential and curative intent of surgical resection alone. Grade 2 and 3 tumors are histologically distinguishable from each other by features of mitotic activity and anaplastic nuclear features in the latter, whilst microvascular proliferation and necrosis are additionally seen in grade 4 tumors. Hence, grade 2 tumors represent low grade tumors and grade 3 and 4 tumors are high grade tumors, often associated with rapid disease evolution and a dismal survival.

Recently, the WHO grading system for brain tumors has been revised. Genetic and molecular markers have now become integral to the grading.\textsuperscript{4} Survival has been shown to be greatly dependent upon these molecular markers.\textsuperscript{5-7} Currently, the most important molecular markers are mutations in the isocitrate dehydrogenase (IDH) genes, most often IDH-1 and sometimes IDH-2, which are associated with a better prognosis in astrocytomas.\textsuperscript{5} IDH mutant astrocytomas are diffusely infiltrating and slow-growing, and are currently defined as IDH-1 or IDH-2 mutated tumors without a 1p/19q codeletion.\textsuperscript{4} Oligodendrogliomas are both IDH-mutant and 1p/19q-codeleted.\textsuperscript{4}

Tumors that lack IDH mutations, IDH wild type tumors, are generally associated with aggressive clinical behavior. Most IDH wild type tumors have malignant
histological features such as microvascular proliferation and necrosis; these tumors are recognized as grade 4 glioblastomas. Additional molecular markers have been identified that define a grade IV tumor, even in absence of malignant histological features. IDH wild type gliomas with increased EGFR amplification, combined whole chromosome 7 gain with whole chromosome 10 loss, or TERT promoter mutation resemble the aggressive clinical course of glioblastomas, and are now also recognized as a IDH wild type glioblastoma, grade IV.

Another important prognostic marker for gliomas is O6-methylguanine methyltransferase (MGMT) gene methylation status. Patients with an MGMT methylated tumor are more susceptible to alkalinizing chemotherapy such as temozolomide and thus have a better survival. 6,7

Peak incidence of lower grade IDH mutant astrocytomas occurs in patients aged between 35 and 45. 8 Patients with glioblastoma have a median age of onset of approximately 60 years. Patients with IDH mutant, grade 2 astrocytomas or 1p/19q-co-deleted oligodendrogliomas have a median survival of 10+ years, patients with IDH mutant WHO grade 3 astrocytomas have a median survival of 5 years. 8 In contrast with patients with IDH wild type glioblastoma grade 4 tumors with a median survival of just over 1 year. Unfortunately, high grade gliomas account for over 70% of newly diagnosed gliomas. 3

Prognosis of patients with high grade gliomas has remained poor for the last decades. Gliomas are infiltrating in nature, often involving eloquent structures, and extend beyond visual borders on imaging, making complete resection without unacceptable damage impossible. 10,11 Nevertheless, surgery remains the cornerstone in glioma treatment. Current clinical practice recommends early surgical resection when safely possible for lower grade gliomas. This is usually followed by both radiotherapy and chemotherapy or – less frequently - a wait and scan policy. 9 Patients with glioblastomas benefit from a greater extent of resection in terms of survival. 12,13 The standard adjuvant treatment in patients in good general and neurological condition, aged up to 70 years is 60 Gy radiotherapy with concomitant temozolomide chemotherapy followed by a six-course regimen of maintenance temozolomide chemotherapy. 14 Recurrence, however, is inevitable due to the inability of radical resection and subsequent resistance to chemoradiation therapy. Currently the median survival after standard treatment of chemoradiation is 14.9 months, with the biggest gain for patients with a methylated MGMT tumor. 14 A lack of standard of care for patients with recurrent glioblastoma further contributes to the poor prognosis for these patients.
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1.2 Brain Metastases

In adults, brain metastases are by far the most common cause of intracranial neoplasms. Brain metastases occur in approximately 20% of the patients with systemic cancer. The incidence of brain metastases has increased over the years due to therapeutic advances for patients with metastatic cancer that are associated with prolonged survival.

Brain metastases originate most commonly, in order of cumulative incidence, from lung, breast, and skin (melanoma) cancers. Although the highest numbers of brain metastases arise from the lung, melanoma has the highest propensity to metastasize to the brain. The distribution of brain metastases correlates with blood flow and tissue volume, with 80% detected in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem. Often, brain metastases are asymptomatic and are seen on staging brain scans. Most patients (80%) present with multiple brain metastases and only a minority of patients (10-20%) have a solitary metastasis.

Therapeutic approaches for brain metastases are resection, radiotherapy and systemic treatment, including immunotherapy. Radiotherapy options can be differentiated into whole-brain radiation therapy (WBRT), which is used less frequently in recent years, and stereotactic radiotherapy (SRT), the primary choice if possible.

2. IMAGING; ROLE AND DILEMMA

Neuroimaging is essential for the diagnosis, prognostication, follow-up and treatment evaluation in brain tumors. Accurate non-invasive diagnosis is important to determine the appropriate treatment strategy and corresponding prognosis. Regular follow-up through neuroimaging aids clinical decision-making about continuation or discontinuation of treatment.

2.1 Role of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the gold standard for neuro-oncology imaging due to its high spatial resolution, allowing detailed visualization of lesions in relation to brain anatomy.

2.1.1 Basic principles of MRI

MRI uses a strong longitudinal magnetic field to measure hydrogen protons, which are abundant in the body due to the high water and fat components. Differences in proton composition between tissues lead to different imaging contrasts. When protons are introduced to the magnetic field, they align in the direction of the magnetic field. A radiofrequency pulse is then applied,
after which the protons absorb the transmitted energy and rotate away from the longitudinal axis. In addition, the radiofrequency pulse causes the protons to precess in phase. After this excitation phase, relaxation occurs in which the magnetization finally returns to its initial state. The restoring of the longitudinal orientation is called T1 relaxation. The T1 relaxation rate differs between tissues and can thus be used to create an image contrast. T1 is defined as the time after which 63% of the longitudinal magnetization is restored. Simultaneously, after administration of the radiofrequency pulse the in-phase protons start dephasing due to spin-spin interactions, which is called T2 relaxation. With this dephasing, the measured transverse magnetization decreases. As with T1 relaxation, the T2 relaxation rate also differs between tissues. T2 is defined as the time after which the transverse magnetization is decayed to 37% of its maximum value. Several MRI parameters (such as time to echo and repetition time) can be used to control the image contrasts due to the different properties of T1 and T2 of different tissues (such as T1-weighted and T2-weighted sequences). White matter has a short T1 time and thus is seen as a lighter contrast on T1-weighted imaging, whilst fluid has a longer T1 time resulting in darker contrasts. Since white matter has a short T2 time, it dephases faster and thus creates a darker contrast on the T2-weighted imaging. Fluid has a longer T2 time and thus slower dephasing which results in lighter contrasts on T2-weighted imaging.

2.1.2 MRI characteristics of brain tumors
Low grade gliomas usually (in >90% of cases) demonstrate no or limited contrast enhancement on T1-weighted imaging after gadolinium administration and are best evaluated on fluid-attenuated inversion recovery (FLAIR) and T2-weighted MRI; on the contrary, high-grade gliomas usually have contrast enhancement and are surrounded by high T2/FLAIR signal due to tumor infiltration and extensive vasogenic edema.21 Brain metastases usually present as contrast enhancing lesion on T1-weighted MRI with extensive peritumoral edema visualized on T2/FLAIR-weighted MRI.

2.1.3 Advanced MRI
The rationale behind advanced MRI sequences is a better visualization of biological processes.21,22 The increased cellularity of brain tumors causes impaired diffusivity of water molecules, which is detectable by diffusion-weighted imaging. Tissue perfusion is measurable with perfusion-weighted imaging through means of detectable cerebral blood flow and volume parameters.23 Neovascularization, which is a hallmark of fast-growing neoplasms, generally causes a measurable increase in blood flow and volume on perfusion-weighted imaging. Finally, concentrations of specific metabolites can be calculated with MR spectroscopy. Detectable metabolites include
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N-acetylaspartate (NAA), a marker of neuronal viability and thus intact brain tissue, choline which marks increased cellular proliferation, and lactate which demonstrates anaerobic metabolism and cell death. Increases in choline and lactate with simultaneous decrease in NAA is suggestive of tumor.

2.2 Role of Positron Emission Tomography
Positron Emission Tomography (PET) has recently been recommended by the Response Assessment in Neuro-Oncology (RANO) working group to be of added value in oncological neuroimaging, thereby complementing MRI.24-27

2.2.1 Basic principles of PET
PET imaging is a functional imaging technique which uses intravenously administered radiopharmacons or radiotracers to detect various (patho-) physiological processes, often visualized by a local increased uptake of the radiopharmacon. Radiopharmacons are substances such as glucose or amino-acids which are bound to radioisotopes. The half-life of the radiopharmacon depends on the radioisotope that is used. Most commonly fluorine (18F) and carbon (11C) with a half-life of 109.8 min and 20.3 min, respectively. After being administered, the radiopharmacon will distribute across the body and the isotope will decay. Protons from the nucleus are emitted (hence the name proton emission tomography) and undergo annihilation with electrons, causing two photons to be released in opposite directions. The annihilation photons are detected by crystal detectors. PET is commonly combined with Computed Tomography (CT) imaging (PET-CT) for accurate anatomical coregistration.

The uptake of the PET radiopharmacon can be either visually interpreted or can be quantified. Physiological increased uptake also occurs, dependent on the radiopharmacon used, in various organs such as the brain, kidneys and liver, and should thus be discriminated from pathological uptake. Quantification is therefore often used. Most frequently the standardized uptake value (SUV) and its derivatives such as maximal, minimal, peak, and mean SUV are used. SUV can be calculated dividing the measured activity by the division of the injected radiopharmacon dose by the patient’s weight. Other PET parameters include the tumor-to-background ratio (TBR) and volumetric measurements such as metabolic tumor value (MTV).

2.2.2 FDG PET
[^F]-2-fluoro-2-deoxy-D-glucose (18F-FDG) is glucose-based and to date remains the most widely employed radiotracer in oncology based on an increased glucose consumption of tumors. Despite the fact that 18F-FDG is the most available radiotracer worldwide, its use in oncological neuroimaging is limited
due to the relatively high physiological glucose metabolism of normal brain tissue (Figure 1).

**Figure 1**

Treatment follow-up with 18F-FDG PET in a 62-year-old female patient with multiple brain metastases of a small cell lung cancer. Gadolinium-enhanced MRI (A) was performed after WBRT and demonstrated multiple contrast enhancing lesions, with two larger lesions frontally on the left side (white circle) and several smaller lesions (white arrows). 18F-FDG PET (B and C) demonstrated high physiological uptake throughout the brain but failed to clearly localize most contrast enhancing MRI lesions as demonstrated by the white arrows on co-registration of 18F-FDG PET images with MRI (B). This case demonstrates the lack of diagnostic sensitivity of 18F-FDG PET for treatment response evaluation in brain tumors.

2.2.3 Amino PET

Cellular proliferation associated with malignant tumors activates increased protein synthesis. Amino acids function as essential compounds of proteins and thus amino acid transport and protein synthesis are vastly increased in malignant proliferating cells and higher compared to normal healthy tissue. Radiolabeled amino acids and amino acid analogs have different metabolic fates depending on their chemical structures. Amino acid traces are predominantly based on L-type amino acid transporters (LAT), LAT-1 and LAT-2. The most frequently used radiolabeled amino acids are \[^{11}C\]-methyl-L-methionine (11C-MET) (Figures 2 and 3), O-(2-[\(^{18}\)F]-fluoroethyl)-L-tyrosine (18F-FET), and 3,4-dihydroxy-6-[\(^{18}\)F]-fluoro-L-phenylalanine (18F-FDOPA) (Figure 4).\(^{28,30}\)
Example of 11C-MET PET follow-up in a 49-year-old patient with an anaplastic astrocytoma (WHO grade III) after treatment with surgical resection followed by radiotherapy and temozolomide chemotherapy. One year after surgery, follow-up gadolinium-enhanced MRI (A) showed new contrast enhancement (white arrow). The differentiation between tumor progression and radionecrosis could not be made and 11C-MET PET was performed (B and C). 11C-MET PET (C) demonstrated high uptake (white arrow) suggestive of tumor progression. Co-registration of 11C-MET PET images with MRI (B) shows good agreement of the contrast enhancing lesion and increased uptake.

Physiological uptake of amino acid radiotracers in the brain is generally low, depending on anatomical region and age. The high tumor uptake in combination with low background uptake is associated with straightforward visual assessment of amino acid PET radiotracers. Therefore, the tumor detection rate and tumor delineation is thought to be better compared to 18F-FDG. Images can be interpreted visually or quantitatively. The most often used calculation method is the tumor-to-normal-background ratio (T/N ratio) that compares tumor uptake to physiological uptake in the contralateral hemisphere. Uptake may also be defined by the standardized uptake value (SUV), a unit normalized to injected tracer dose per kilogram of body weight.

2.3 Dilemma of treatment induced changes

The extensive treatment regimen of malignant brain tumors, especially high dose radiotherapy with or without concomitant chemotherapy, can produce adverse events. Damage to healthy brain tissue may lead to radiological suspicion of tumor progression (Figure 3) which can even be accompanied by clinical symptoms indistinguishable from tumor progression. It is important to timely identify the nature of the radiological changes. True progression is indicative of failing treatment whilst treatment induced changes in fact conforms with a desired response to the given treatment.
These treatment induced changes, often called pseudoprogression in literature, are resulting from blood-brain barrier dysfunction, vasodilation and subsequent vasogenic edema due to damage from given radiotherapy with or without chemotherapy. Typically, these changes occur within 3 months after treatment and will ultimately stabilize or decrease in size. Therefore, early posttreatment progression should not automatically lead to interruption of current treatment and start of second line regimens. Delayed and longer lasting effects, 6 months to several years after treatment, can sometimes also be seen and are then referred to as radiation necrosis. Pseudoprogression and radiation necrosis are different clinical entities, although within the same pathological spectrum.

In high grade gliomas the incidence of treatment induced changes is as high as 36%. Advances in radiotherapy planning techniques enables a high conformal dose distribution around the target volume, however, radiation dose to healthy brain tissue is unavoidable due to the infiltrative behavior of gliomas. Furthermore, treatment induced changes are more frequent in IDH wild type and MGMT methylated tumors.

The incidence of treatment induced changes in brain metastases after hypofractionated stereotactic radiotherapy (HFSRS) or radiosurgery (SRS) is approximately 15%, but some studies have suggested higher percentages. Factors related to the development of radiation necrosis, especially after SRS, include dose, treated volume, and volume of the brain receiving a specific dose. An increase in the occurrence of treatment induced changes is also expected with immunotherapy. The first studies have shown that immunotherapy alone or in addition to radiotherapy can lead to pseudoprogression and pose a new challenge for follow-up of brain metastases.
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Figure 3

Example of 11C-MET PET follow-up in a patient with a brain metastasis. Case of a 54-year-old male with right frontal solitary brain metastasis from a fibrosarcoma. The patient was treated with surgical resection and stereotactic radiosurgery. After treatment, follow-up gadolinium-enhanced MRI showed a new contrast enhancing lesion (white arrow). 11C-MET PET was performed which did not demonstrate increased uptake at the lesion site. The contrast enhancement was in this case shown to be due to treatment induced changes.

Conventional MRI cannot reliably differentiate between tumor recurrence and treatment induced changes. Both tumor progression (Figures 2 and 4) and treatment induced changes (Figure 3) demonstrate contrast enhancement on T1-weighted MRI with surrounding T2/FLAIR hyperintensities.

Figure 4

Example of 18F-FDOPA PET follow-up in a patient with a glioblastoma. Follow-up imaging of a 26-year-old female glioblastoma patient, after surgical resection and chemoradiotherapy. Gadolinium-enhanced T1-weighted MRI (left image) 5 months after surgery was suggestive of tumor progression (white arrow). 18F-FDOPA PET was performed for other reasons (middle and right images) and demonstrated increased uptake (white arrows), also suggesting tumor progression. Co-registration of 18F-FDOPA PET and MRI (middle image) showed increased uptake at the site of enhancement on MRI. Subsequent follow-up MRI later showed further growth, confirming this case of tumor progression. The patient deceased within a year after the 18F-FDOPA PET scan.
To assist the clinician in the problematic differentiation of tumor progression and treatment induced changes, the RANO criteria for gliomas and for brain metastases have been established.\textsuperscript{39,40} According to the RANO criteria, progression on conventional imaging within 3 months after chemoradiotherapy is only certain if there is new enhancement outside of the radiation field or after pathological confirmation.\textsuperscript{39} These criteria are similar for gliomas and metastases.\textsuperscript{39,40} However, in clinical practice, pathological confirmation is often not acquired in asymptomatic patients since this requires a neurosurgical intervention with a chance of morbidity. As a consequence, follow-up with imaging is usually chosen. However, this is time consuming and can potentially expose a patient to a failing, but possibly toxic, treatment, or delay the start of a second line treatment. More advanced MRI sequences and PET radiotracers have therefore received increasing interest to potentially overcome the limitations of conventional MRI, and are further studied in this thesis.

### 3. STRUCTURE OF THIS THESIS

**Part I** of this thesis discusses the treatment planning and prognostication of brain tumors. The studies included in this first part focus on multisequence imaging in the preoperative stage of brain tumors. **Part II** of this thesis is aimed at improving the imaging treatment follow-up of brain tumors.

**Part I: Treatment planning and prognostication**

**Chapter 2** aims at the non-invasive diagnosis of lower grade gliomas with advanced MRI. Lower grade gliomas, with the majority being grade 2 IDH mutant, can usually be fairly reliably detected on MRI. However, it is important to distinguish these tumors from other differential diagnoses such as tumefactive multiple sclerosis or higher grade lesions without typical contrast enhancement. Hence, histology remains necessary to definitely diagnose these patients. However, the IDH mutation present in most lower grade gliomas leads to the formation of 2-hydroxyglutarate (2-HG), an oncometabolite. In **chapter 2** MR spectroscopy is employed to non-invasively detect 2-HG produced by IDH mutant gliomas.

Prognostication of IDH wildtype glioblastomas with 11C-methionine PET is centralized in **chapter 3**. Glioblastomas are highly malignant tumors with known high intratumoral heterogeneity, contributing to the therapy resistance and poor prognosis. Conventional PET parameters such as standardized uptake values (SUV) are unable to detect this intratumoral heterogeneity and are thus suboptimal for reliable prognostication. **Chapter 3** investigates the prognostic value of volumetric PET parameters, including a novel parameter...
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which combines volumetric data with metabolic information, compared to conventional SUV parameters.

**Chapters 4-6** have a special focus on the subventricular zone and its role in glioblastoma. Since stem cell subpopulations were identified within glioblastoma samples, the stem cell harboring subventricular zone has received increasing interest. In **chapter 4** the subventricular zone is characterized with diffusion tensor imaging to demonstrate its involvement in glioblastoma. Subsequently, the survival impact of the location of glioblastomas in relation to the ventricles is discussed in **chapter 5**. Furthermore, tumoral differences between glioblastomas with and without ventricle contact are studied with advanced MRI sequences (**chapter 5**) and 11C-methionine PET (**chapter 6**).

**Part II: Treatment follow-up**

Treatment effects such as pseudoprogression occur often during the treatment of brain tumors and hinder a reliable treatment response assessment. Since conventional imaging is limited in differentiating treatment effects from tumor progression, it is important to establish more accurate treatment techniques. In **chapter 7** a meta-analysis is performed on the diagnostic accuracy of different MRI sequences for the treatment response evaluation of high grade gliomas. Perfusion MRI emerges as one of the most reliable and promising techniques, which is further discussed in **chapter 8**. In addition to MRI, the same analysis is undertaken for different PET radiotracers among high grade glioma patients in **chapter 9**. As it is known that treatment effects also occur in patients with brain metastases after radiotherapy, 11C-methionine is employed for the diagnosis of such treatment effects against tumor progression in brain metastases in **chapter 10**.

Despite the promise of various advanced imaging techniques, conventional imaging for brain tumor follow-up imaging has remained standard clinical practice for a long time. Moreover, there is a lack of uniformity among MRI protocols and imaging interval during treatment. Often, a pragmatic approach is chosen with several scheduled follow-up MRI scans during the different stages of standard treatment. However, the interpretation of such scheduled scans is complicated by the presence of treatment effects, which occur in a large number of treated brain tumor patients. **Chapter 11** studies if, and how, standard scheduled follow-up MRI scans influence clinical decision making about continuation or discontinuation of treatment in glioblastoma patients.

Finally, the adverse effects of standard treatment, including chemotherapy and radiotherapy, on the brain are discussed. **Chapter 12** provides an insight into the mechanism of treatment-induced damage in high-grade glioma patients.
This chapter also aims at identification of vulnerable brain regions for which caution should be taken during treatment planning to minimize injury to healthy brain tissue.

This thesis aims at improving the diagnostic process, treatment planning and the treatment follow-up, through multimodal imaging in brain tumor patients. By incorporating novel regions of interest, imaging parameters, and imaging techniques, the clinical decision-making process could be enhanced. Ultimately, this would lead to an increase in the quality of life for brain tumor patients.
4. References


Chapter 1


PART I

Treatment planning and prognostication