CHAPTER 13

Discussion, future perspectives and conclusions


Radiology in the lead: towards radiological profiling for precision medicine in glioblastoma patients? Editorial comment on Glioblastoma patients with a moderate vascular profile benefit the most from MGMT methylation. B.R.J. van Dijken, A. van der Hoorn.

This thesis explored the use of multimodal imaging methods to improve the clinical management of brain tumor patients. The thesis was divided into two parts: Part I discussed the treatment planning and prognostication of brain tumors. Part II emphasized on the treatment follow-up of brain tumor patients with multimodal imaging.

**Part I: Treatment planning and prognostication**

Treatment planning starts with establishing an accurate diagnosis for which imaging is essential. **Chapter 2** discussed the non-invasive diagnosis of lower grade gliomas with advanced MRI. Low grade IDH mutant glioma patients generally have a favorable prognosis and tend to arise in a younger population.\(^1\) Increasing quality of life hence is important for these patients. Noninvasively diagnosing low grade glioma with high accuracy potentially offers several advantages to these patients. Establishing a definitive diagnosis through imaging alone prevents the need of tissue collection. Surgery could then potentially be delayed in stable patients with eloquently located tumors.\(^1\) The IDH mutations of low grade gliomas directly lead to the formation of the oncometabolite 2-HG, which can be measured non-invasively by MR spectroscopy.\(^2\) **Chapter 2** confirmed the excellent diagnostic accuracy of 2-HG MR spectroscopy for IDH mutation detection. Moreover, histological tumor samples were taken during surgery in which the 2-HG concentration was also measured. There was a strong correlation between the 2-HG measurements from MR spectroscopy and the calculated 2-HG concentrations in the tissue samples. The results of **chapter 2** add to a growing body of evidence that 2-HG MR spectroscopy is suitable for non-invasively diagnosing IDH mutant gliomas.\(^3-5\) However, complicated acquisition and post-processing methods have prevented the incorporation of 2-HG MR spectroscopy into clinical practice.\(^2,6\) In **chapter 2** a more straightforward method for 2-HG MR spectroscopy acquisition was used, which potentially increases the usability of this technique.

IDH mutant glioblastomas are on the other side of the spectrum in terms of survival, with a dismal median prognosis of just over one year.\(^7\) Non-invasively establishing features that influence survival can therefore be important to manage patient expectations, as well as selecting appropriate treatment strategies. \(^8\) 11C-MET PET uptake is a marker of proliferation and has the potential of visualizing the aggressiveness of glioblastoma.\(^8\) 11C-MET PET therefore might be a suitable imaging technique for prognostication of glioblastoma patients. However, most studies conducted thus far used conventional PET measuring parameters such as standard uptake values (SUV) and have failed to taking the tumor heterogeneity of glioblastomas into account, leading to inconclusive results.\(^9\) It was hypothesized in **chapter 3** that incorporation of volume-based PET parameters could overcome the limitations
of conventional PET measuring parameters and better evaluates the true tumor burden. **Chapter 3** demonstrated that volume-based 11C-MET PET parameters were indeed associated with survival in a small cohort of glioblastoma patients, in contrast to conventional SUV parameters. These results should be further explored in larger prospective studies. A hurdle to overcome is redefining the optimal tumor delineation method for 11C-MET PET as the delineation method is essential for reliable definition of pathological uptake.

**Chapters 4-6** focused on the relationship between glioblastoma and the subventricular zone. The subventricular zone is the most important neural stem cell containing brain area and has received increasing interest since histological studies have demonstrated similar subpopulations of stem cells within glioma specimens. The subventricular zone is assumed to facilitate gliomagenesis and play an essential role in treatment resistance of glioblastoma. It is thought that the subventricular zone offers an advantageous environment to which glioma stem cells can migrate, thereby escaping treatment and leading to treatment resistance. To further investigate this region, diffusion tensor imaging (DTI) was employed in **chapter 4** to characterize the subventricular zone. The DTI results were indicative of infiltration of the subventricular zone by tumor cells, supporting the notion of migration of glioma stem cells towards the subventricular zone.

The aim of the subsequent chapters was to further study the clinical implications of the subventricular zone in glioblastoma patients. Following the narrative that the subventricular zone offers an advantageous environment to cancer stem cells, it was hypothesized that glioblastomas closer to the subventricular zone would demonstrate more aggressive features and consequently a worse outcome. **Chapter 5** demonstrated a survival difference between patients with ventricle-contacting and patients with non-contacting glioblastomas, with the latter having a significantly better prognosis. This survival difference was also demonstrated in an earlier meta-analysis, where ventricle contact was identified as an independent prognostic factor. Moreover, it was also suggested that ventricle contacting glioblastomas have a higher chance of multifocal and distant recurrence, both unfavorable prognostic features. Due to the supposed clinical importance of the subventricular zone in glioblastoma, several studies have investigated whether including this region in radiotherapy would benefit survival. Results have remained inconclusive and there is a need for a prospective clinical trial.

To provide a possible explanation for the survival difference between patients with ventricle-contacting glioblastoma and patients with non-contacting tumors, **chapter 5** investigated the peritumoral area of both patient groups.
Chapter 13

with perfusion MRI as a sign of tumor aggressiveness. Ventricle-contacting glioblastomas demonstrated higher peritumoral perfusion than non-contacting tumors. In addition, 11C-MET PET was employed as an indicator for increased proliferation in chapter 6 to confirm these findings. Ventricle-contacting glioblastomas indeed demonstrated a higher methionine uptake, and thus proliferation, than non-contacting glioblastomas.

Part II: Treatment follow-up
Treatment induced imaging changes such as pseudoprogression and radiation necrosis mimic tumor progression on conventional follow-up imaging and thereby hinder a reliable treatment response evaluation. The relatively poor diagnostic accuracy of conventional MRI follow-up in high grade glioma patients was confirmed in chapter 7. This chapter furthermore studied the diagnostic accuracy of several advanced MRI sequences. Meta-analysis showed a sensitivity and specificity for diffusion-weighted imaging of 71% (95%CI 60-80) and 86% (95%CI 76-92), respectively. For perfusion-weighted imaging this was 87% (95%CI 82-91) and 86% (95%CI 77-91). MR spectroscopy demonstrated the highest diagnostic accuracy with a sensitivity of 91% (95%CI 79-97) and specificity of 95% (95%CI 65-99). As MR spectroscopy is time consuming, with risk of movement artefacts, perfusion-weighted imaging is the most applicable sequence to aid in the differentiation of tumor progression from treatment induced changes in high grade glioma patients. Studies on the diagnostic value of advanced MRI in brain metastases after treatment are limited. Perfusion-weighted imaging and MR spectroscopy demonstrate most promising results thus far. Diagnostic accuracy seems to be in a similar good range as seen for gliomas. However, a drawback of MR spectroscopy is the relatively large voxel size, making differentiation of tumor progression from treatment induced changes in smaller metastases difficult. Perfusion MRI thus emerged as the most reliable and applicable imaging technique for differentiating tumor progression from treatment effects in brain tumor patients. Chapter 8 explored the various available perfusion methods, as well as the advantages and drawbacks of the different techniques.

MRI to date remains the mainstay of treatment response assessment in brain tumor patients. However, several neuro-oncology working groups have recommended the use of PET imaging for the differentiation between treatment induced imaging changes and tumor progression in addition to MRI. Despite that 18F-FDG PET has traditionally been the most commonly employed radiotracer in general oncology, its role in neuro-oncology has remained limited due to the high physiological background uptake. Most emphasis has therefore been placed on amino acid PET radiotracers which demonstrate low background uptake of normal brain tissue and thus create higher imaging
contrasts between tumor and normal brain tissue. The diagnostic accuracy of different PET radiotracers for the differentiation of tumor progression from treatment effects in high grade gliomas was studied in chapter 9. This meta-analysis included 39 studies and confirmed a lower diagnostic accuracy for 18F-FDG than for the two most common amino acid radiotracers, 18F-FET and 11C-MET. 18F-FDG reached a sensitivity of 84% (95%CI 72-92) and specificity of 84% (95%CI 69-93), whilst 18F-FET, sensitivity 90% (95%CI 81-95) and specificity 85% (95%CI 71-93), and 11C-MET, with a sensitivity and specificity of 93% (95%CI 80-98) and 82% (95%CI 68-91), respectively, performed significantly better. 18F-FDOPA was a less studied radiotracer, with only four known studies being published in this chapter, but demonstrated a comparable diagnostic accuracy with a sensitivity ranging from 85% to 100% and specificity ranging from 72% to 100%.28-31 The diagnostic accuracy of the different amino acid PET radiotracers thus seems comparable, although FDOPA is somewhat understudied compared to 11C-MET and 18F-FET PET. There is less literature available on the diagnostic accuracy of different PET radiotracers for differentiating tumor progression from treatment induced changes in brain metastases.32-36 As expected, the accuracy of amino acid PET is superior to 18F-FDG PET. 18F-FDG PET only marginally improved accurate differentiation between tumor progression and treatment induced changes after an ambiguous MRI.37,38 The improved accuracy of amino acid PET was also shown in Chapter 10, which demonstrated that 11C-MET is capable of distinguishing between treatment induced changes and tumor progression in a retrospective cohort of 26 brain metastases patients. In general, most experience for amino acid PET treatment follow-up in brain tumor patients is gathered with 11C-MET. However, 11C-MET is impractical since it demands a cyclotron due to its very short half-life (20 minutes). 18-F labeled FET has gained ground due to its longer half-life (109.7 minutes).

Advanced MRI and amino acid PET thus seem to perform similar for differentiating treatment induced changes from tumor progression in brain tumor patients. However, only few studies have compared MRI and PET directly, and thus far results have remained inconclusive.39-42 More studies directly comparing advanced MRI sequences with amino acid PET for treatment evaluation of brain tumors are therefore warranted.

Despite the high diagnostic accuracy of the various advanced MRI sequences and amino acid PET radiotracers, these techniques have not made it into clinical routine yet. Most treatment follow-up imaging in brain tumor patients is done with conventional MRI with the addition of diffusion-weighted imaging.43-45 Perfusion MRI is part of the standard neuro-oncology imaging protocol in approximately half to two thirds of centers.46,47 No standardized or uniform imaging protocol for treatment follow-up of brain tumor patients exists.
Furthermore, there is a lack of consensus concerning the optimal interval in which follow-up imaging takes places during treatment. For gliomas, most centers have adopted a 2-3 monthly interval imaging protocol during standard treatment. Chapter 11 questioned whether this pragmatic strategy would actually be beneficial to the patient. The consequences of scheduled and unscheduled follow-up scans on treatment decisions during standard treatment in glioblastoma patients were evaluated over a 15-year period. Scheduled follow-up scans during treatment rarely led to early determination of treatment. However, due to the occurrence of pseudoprogression, scheduled scans often introduced diagnostic uncertainty. The use of perfusion MRI did not influence decisions about continuation or discontinuation of treatment, but perfusion MRI did significantly reduce diagnostic uncertainty. The results of chapter 11 did not support the current pragmatic approach of 2-3 monthly scheduled MRI scans. One or more of the scheduled scans might rather be replaced by unscheduled scans in symptomatic patients, which were shown to result in significantly more treatment consequences.

Treatment induced changes such as pseudoprogression occur in about one third of brain tumor patients, representing a radioclinical challenge in neuro-oncology management. However, treatment with radiotherapy and, in lesser degree, chemotherapy also lead to other neurotoxic effects, which are not always easily detected with imaging. It is known that some degree of neurocognitive decline occurs in a vast majority of treated brain tumor patients. This might be due to structural brain changes caused by treatment which can occur even distant to the irradiated tumor area. Standard chemoradiotherapy for glioblastoma patients could cause a decline in white matter volume of the contralateral tumor-free hemisphere, as chapter 12 demonstrated. The found white matter volume loss developed in the early-delayed phase, approximately 16 weeks post-radiotherapy, which is comparable to the occurrence of pseudoprogression. Chapter 12 used a voxel based morphometry (VBM) approach to study volume changes on a group level. Several clusters were identified in which most volume loss was observed, mainly throughout the frontal and parietal lobes, which showed a clear relationship with the delivered radiation dose. In addition, certain areas such as the frontal lobe and insula received a relatively lower radiotherapy dose, but did experience significant white matter volume loss. Such areas are possibly more sensitive to radiotherapy-induced injury. An increased likelihood of pseudoprogression occurrence in patients with tumors located in the frontal lobe or insula was also described in a different study, supporting the hypothesis of increased radiosensitivity of these areas. Identification of vulnerable brain areas to radiotherapy is important as it can aid treatment planning in
minimizing white matter injury and can also provide cues to the likelihood of pseudoprogression occurrence.

**FUTURE PERSPECTIVES**

**Novel treatments**
The last significant step forward for glioblastoma patients came with the incorporation of temozolomide chemotherapy in standard treatment protocol in 2005, increasing the median overall survival with 2.5 months when compared to radiotherapy alone. And despite an increasing number of targeted therapies and immunotherapies becoming available for systemic cancers with brain metastases, the outcome of many brain metastases patients has remained poor. A need for novel treatment strategies for brain tumor patients thus clearly remains. Novel treatments, however, will come with their own imaging challenges, including pseudoprogression and pseudoresponse. How this influences current and future imaging techniques should therefore be further investigated.

**Hybrid imaging**
It has been suggested that hybrid PET/MRI cameras could lead to a jump forward in the imaging of brain tumors. Combining both modalities might overcome a number of individual limitations and avoids the necessity of additional scanning. This would enable an absolute match between tissue information of both modalities under the same physiological conditions and may thus lead to better localization of the PET signal within the soft tissues. However, the economic cost of hybrid PET/MRI scanners is substantial. The first studies have been published and indeed demonstrate the feasibility of using combined PET/MRI machines. However, most of these studies are limited to FDG PET, which has insufficient value in brain tumor imaging, and carbon-bound MET PET, which is not feasible in many centers. A first study combining DWI and FET on a hybrid PET/MRI scanner demonstrated promising results. Therefore, more PET/MRI studies with emphasis on treatment evaluation of gliomas and brain metastases using fluorine-bound amino radiotracers are desired.

**Artificial intelligence**
An expansion of artificial intelligence applications in neuro-oncology is expected in in the upcoming years. Software that allows for automatic delineation of brain tumors, including different imaging contrasts and sequences, is already available. Ongoing improvement and availability of such delineation methods, will lead to inclusion of more advanced imaging methods to result in a more reliable delineation of the tumor extent and different tumor components. Machine learning uses self-learning and self-
improving algorithms which allows for classification of data. Improvement of these machine learning algorithms could potentially lead to an automatic differentiation between tumor progression from treatment induced changes, based on certain imaging characteristics. Radiomics also uses extracted quantitative imaging features but combines these with clinical information and molecular markers. A growing integration of imaging with clinical, genetic, and molecular data is expected. Quantification of imaging data, for which standardization thus is essential, will become more and more important for this so-called multiomics. Multiomics is therefore promising for enhancing personalized treatment.

Radiological profiling for precision medicine in neuro-oncology

The paradigm shift of “one fits all” to “all fit one” associated with precision medicine has also emerged in neuro-oncological treatment schemes in recent years. After all, it is rather peculiar to implement homogeneous treatment protocols for such a heterogeneous population. Molecular markers and genetic profiles now play a pivotal role in the management of glioblastoma. Certain molecular parameters such as TERT promoter mutation, EGFR gene amplification, or chromosome 7 gain now define glioblastoma, even if histologically the tumor is suggestive of a lower grade tumor. Most recent guideline updates have started to emphasize the heterogeneity and interpatient variability of brain tumors.

Currently, one of the most widely accepted molecular markers for prognostication and treatment decision-making in glioblastoma is O6-methylguanine-DNA methyltransferase (MGMT) methylation status. MGMT-methylated tumors are more susceptible to alkylating chemotherapeutic agents such as temozolomide, leading to an improved prognosis. As a result, the addition of temozolomide complementing radiotherapy is now recommended for elderly patients (> 70 years) with MGMT-methylated glioblastoma only. A retrospective multicenter study, however, has found that the prognostic impact of MGMT methylation might be influenced by the tumor’s vascularity. This study among 96 glioblastoma patients, has demonstrated that there is a beneficial effect of MGMT methylation in tumors with a moderately vascular status only. Not considering such information could potentially induce bias in future clinical studies. This study identified different vascular regions (habitats) within the tumor based on conventional anatomical sequences as well as perfusion MRI. The habitat approach is drawn from the idea that glioblastoma is not a homogenous entity but a rather heterogeneous tumor. Habitat approaches based on advanced MRI sequences such as perfusion or diffusion have been successfully applied by other studies. Certain habitats
experience more aggressive features such as high perfusion and low diffusion, suggestive of a highly vascularized and cellular tumor component.

Presence of such aggressive tumor habitats have been shown to have a negative impact on survival and treatment response.66,67 In addition, certain habitats have been suggested to play a role in resistance to chemotherapy and radiotherapy and thus might in part be responsible for treatment failure.68 Identification of such tumor habitats and thus radiological “profiling” of the individual tumor could potentially guide subsequent treatment in addition to molecular biomarkers.

To conclude, certain biomarkers such as MGMT methylation status have been given a more prominent role in the management of glioblastoma patients over recent years. However, in addition to this interpatient heterogeneity, intratumor heterogeneity also plays an important role in glioblastoma. When moving towards a precision medicine approach, such information should indeed be considered, both in future clinical studies but also in the multidisciplinary management of glioblastoma patients. Perhaps the radiologist should be in the lead to allow personalized treatment?

**CONCLUSION**

Imaging plays a pivotal role in the management of brain tumor patients. Conventional imaging methods, however, have several limitations which hinder adequate treatment planning and treatment response evaluation. This thesis demonstrated that multimodal imaging with advanced MRI and PET methods provides a plethora of additional information that can aid in clinical decision making in brain tumor patients.
Chapter 13

REFERENCES


Discussion, future perspectives and conclusions


42. Tomura N, Kokubun M, Saginoya T, et al. Differentiation between Treatment-Induced Necrosis and Recurrent Tumors in Patients with Metastatic Brain Tumors: Comparison among 11C-Methionine-PET, FDG-PET, MR Permeability Imaging, and MRI-ADC—Preliminary Results. AJNR 2017;38:1520-1527.


Discussion, future perspectives and conclusions
APPENDICES