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Summary, general discussion and future perspectives

SUMMARY

The goal of this thesis was to provide guidance for the neuro-oncologist's daily clinical practice with respect to tailoring antiepileptic drug (AED) treatment and improving the radiological assessment of tumor response and progression in patients with gliomas and brain metastases. Part I of this thesis focused on the impact of AEDs on clinical outcome, such as survival, and the consequence of AED withdrawal on seizure recurrence and radiological outcome. Part II focused on the impact of antitumor treatment on clinical and radiological outcome, especially regarding the assessment of (pseudo)progression.

PART I: The role of antiepileptic treatment in relation to clinical and radiological outcome

Seizures are common in brain tumor patients and can significantly impact their functioning and quality of life. A seizure frequency of up to 60-90% is seen in low-grade glioma and 25-60% in high-grade glioma patients.[1–3] In **chapter 2**, we investigated the efficacy of valproic acid (VPA) and levetiracetam (LEV) on seizure control in glioblastoma patients during treatment and follow-up. Monotherapy with either VPA or LEV was initially instituted, resulting in seizure freedom in about 40% of patients on either VPA or LEV monotherapy. During follow-up seizure freedom was achieved in 78% of patients on VPA monotherapy, 70% on LEV monotherapy and 60% on combined VPA/LEV treatment if either one was not effective enough. As evidence exists on a potential antitumor effect of VPA, an additional analysis on the effect of VPA on survival was performed. We found that glioblastoma patients using VPA in combination with temozolomide (TMZ) showed a longer median survival of 69 weeks as compared to 61 weeks in the group without VPA (hazard ratio 0.63; 95% CI: 0.43–0.92) when adjusting for age, extent of resection, and O^6-DNA methylguanine-methyltransferase (MGMT) promoter methylation status.

Glioma patients may achieve sustained seizure freedom on AED. Antitumor treatment for glioma can further contribute to a reduction in seizure frequency. After surgical resection or radiotherapy, 53-87% and 32-75% of patients with low grade glioma, respectively, becomes seizure free.[4–9] Chemotherapy treatment results in a ≥50% reduction in seizure frequency in 48-78% of low-grade glioma patients.[10,11] In **chapter 3** we evaluated the need for continuation of AEDs in clinically and radiologically stable low-grade and anaplastic glioma patients with seizure freedom for at least one year after antitumor treatment. We studied the decision-making process on AED withdrawal in patients and physicians as well as seizure recurrence rate. After approval for inclusion by both the patient and their treating neuro-oncologist, they made a shared decision about withdrawal or further continuation of AED treatment. We studied 71 patients, in whom it was decided to withdraw AED treatment in 65% of patients and to continue AED treatment in 35%. Of the patients in the withdrawal group, 26% experienced seizure recurrence during a mean

follow-up of 2.2 years. Of these patients, 58% appeared to have tumor progression, of which 3 patients within 3 months after withdrawal. Only 8% of the patients in the AED continuation group experienced seizure recurrence, of which one patient showed tumor progression.

PART II: The impact of antitumor treatment on clinical and radiological outcome

One of the major challenges in clinical practice is the interpretation of follow-up imaging in brain tumor patients treated with antitumor therapy. Antitumor treatment can induce treatment related effects on imaging which mimic tumor progression. Neuro-oncologists are frequently confronted with the diagnostic dilemma of differentiating progressive disease (PD) from treatment related effects like pseudoprogressive disease (PsPD). Conventional MRI with contrast is insufficient to make the distinction between PD and PsPD. To overcome limitations of conventional MR imaging, advanced MR imaging techniques could offer an alternative for accurate assessment of tumor response.

We examined the value of the widely used qualitative assessment of the dynamic susceptibility-contrast (DSC) perfusion MRI in glioma and brain metastases patients in the differentiation of PD from PsPD. DSC perfusion MRI is capable of quantifying vessel blood volume by assessment of the relative cerebral blood volume (rCBV), reflecting the degree of microvascular proliferation in tumor tissue, and might be valuable in the differentiation of PD from PsPD. Discerning PD from PsPD has important clinical and therapeutic consequences in brain tumor patients, as in case of tumor progression a switch of therapy should be considered. To study the value and reproducibility of the widely used qualitative (i.e. visual) method of the DSC perfusion MRI we first assessed the interobserver variability of DSC perfusion MRI in glioblastoma patients treated with TMZ chemoradiotherapy (**Chapter 4**). The interobserver agreement on qualitative interpretation of rCBV maps was labelled as good (κ = 0.63). The interobserver agreement on the interpretability of DSC perfusion MR images was poor (κ = 0.23), however, and only moderate (κ = 0.48) on the overall conclusion of radiological tumor response, taking conventional MRI and DSC perfusion MRI into account (complete response, partial response, PD or stable disease).

Second, in **chapter 5** we examined whether the qualitative assessment of the DSC perfusion MRI can reliably distinguish PD from PsPD in glioblastoma patients during TMZ chemoradiotherapy. The detection of a nodular high perfusion area on the rCBV map (i.e. "high rCBV") within the contrast-enhanced lesion did not reliably indicate PD in patients with glioblastoma (sensitivity and specificity of 72% and 23%, respectively). Furthermore, the qualitative rCBV based DSC perfusion MRI appeared not to be prognostic for survival in glioblastoma patients during TMZ chemoradiotherapy. The median overall survival was similar for the subgroup with high rCBV versus low rCBV.

Subsequently, in **chapter 6** the applicability of the qualitative method of the DSC perfusion MRI was assessed in 26 patients with 42 brain metastases. The changes in DSC perfusion MR images before and after stereotactic radiotherapy (SRT) were evaluated. Almost half of all perfusion images could not be evaluated due to localization near large vessels or the scalp, the presence of hemorrhage artefacts, or due to unmeasurable residual metastases. In most brain metastases (52%) a high rCBV at baseline and low rCBV during follow-up were found. Although non-PD and PsPD could be distinguished from PD after SRT on DSC perfusion MRI, the large proportion of images that could not be assessed due to artefacts and small lesion size severely hampered the practical use of DSC perfusion MRI in predicting tumor response after SRT in brain metastases patients.

GENERAL DISCUSSION

PART I: The role of antiepileptic treatment in relation to clinical and radiological outcome

Achieving sustained seizure control is the main goal of treatment in patients with brain tumor related epilepsy, as a higher epilepsy burden has been shown to negatively affect morbidity, cognition and health-related quality of life (HRQOL).[12,13] The AED treatment of seizures in patients with brain tumors is not different from other types of localization-related epilepsy of adult onset, provided that enzyme-inducing AEDs are generally avoided because of possible interactions with systemic therapy.

Prospective studies on the efficacy of AEDs in the general epilepsy population have indicated that 29%–40% of patients continue to have seizures despite successive treatment attempts.[14–17] As described in chapter 2, to achieve adequate seizure control LEV and VPA are most commonly prescribed in brain tumor patients.[18] The choice for either LEV or VPA as initial treatment mainly depends on the physicians' preference, as evidence from randomized controlled trials supporting the use of one specific AED is lacking. The relatively high percentage of seizure freedom in our study population compares favorably to patients with non-brain tumor related epilepsy.[19] This may be caused by antitumor treatment which is known to contribute strongly to seizure control in studies in low-grade gliomas.[4–9]

In general, 20-40% of glioma patients experience AED side effects, which is considerably more than in patients with non-brain tumor related epilepsy.[19] This higher frequency of side effects may be caused by interactions with other drugs such as corticosteroids and chemotherapy, but those symptoms can also be attributed to the tumor itself and its treatment. Mood- and behavioral problems, fatigue and cognitive problems are frequently reported side effect of AEDs, commonly misattributed to the underlying disease.[20] In general, VPA is well-tolerated but it may cause severe side effects.[21] In our

study on glioblastoma patients, VPA was discontinued in about 10% due to adverse effects such as depression, weight gain, tremor, psychosis, rash, thrombocytopenia, hepatic test abnormalities or pancreatitis. There are several advantages of LEV in brain tumor patients, including good tolerability and lack of drug-drug interactions. However, approximately 5% of patients on LEV develop behavioral or psychiatric symptoms, such as irritability, aggression or psychosis for which dose adjustment or withdrawal is usually indicated.[22]

Regardless of epilepsy burden, glioma patients experience lower levels of cognitive functioning due to the tumor itself, medication, depression, fatigue and tumor-directed therapy. AEDs unfortunately have an additional negative impact on the already compromised cognitive functioning of brain tumor patients.[12] It is found that patients using AEDs performed worse in almost all cognitive domains than those not using AEDs.

In the study on glioblastoma patients (chapter 2) we intentionally administered early polytherapy in case of ongoing seizures rather than escalation of the dose of the initial AED. [23] One advantage of this synergistic co-therapy is that a lower total dosage of AEDs may be sufficient for a similar or better antiepileptic effect, as toxicity of AEDs may be related to serum AED concentration rather than the number of drugs administered.[12]

Potential antitumor properties of VPA in glioblastoma patients has raised attention from several studies.[24–27] VPA has histone deacetylase–inhibiting properties which may lead to a stronger acetylation of histone proteins together with less methylation activity on promoter sites of many individual genes, including tumor-suppressor genes with ensuing apoptosis and autophagy of cancer cells, particularly if given together with chemotherapeutic agents. Several uncontrolled studies including the study described in chapter 2, have noted an improved outcome in glioblastoma patients treated with TMZ chemoradiotherapy who used VPA for seizure treatment.[26,28] However, a meta-analysis could not confirm a survival benefit for glioblastoma patients using VPA.[29] In this analysis, the effect of AED use at the start of TMZ chemoradiotherapy was studied in more than 1800 newly diagnosed glioblastoma patients. Multivariate analyses did not reveal VPA or LEV use at start of chemoradiotherapy to be associated with improved survival. The lack of confirmation of a survival benefit in this meta-analysis could be caused by several reasons. Previous studies, including our study, had a retrospective design with small patient populations in which few data were available on VPA dosage and duration of use. The lack of data on dosage as well as the length of exposure for the presumed mode of action of VPA to achieve a potential antitumor effect also hamper the meta-analysis. As it stands now, VPA is one of the most effective AEDs to achieve seizure control in glioma patients with epilepsy, but unequivocal evidence for its antitumor properties is lacking.

In our search to optimize AED treatment for brain tumor patients we critically evaluated the need of continuation of AEDs in glioma patients with stable disease and long-term seizure freedom (Chapter 3). The lack of evidence regarding withdrawal of antiepileptic drugs and the fear for renewed seizures often results in cautiousness and mostly a "lifelong policy". Although our study was based on a relatively small group of patients, we think

that patients and neuro-oncologists are now better informed about the risk of seizure recurrence in patients with lower grade gliomas. In our opinion withdrawal should only be considered in carefully selected patients with a presumed low risk of tumor progression. Nevertheless, overtreatment in glioma patients with epilepsy should not be overlooked. Patients should not suffer more heavily from the adverse effects of AED treatment than from the seizures that AED treatment is intended to prevent.[30] It is important to note that considerably more patients had tumor progression in the withdrawal group compared to the continuation group. This finding may have influenced the risk of seizure recurrence in the withdrawal group. It is possible that the study groups were not well-balanced with respect to the risk of progression, although no significant differences were found in the baseline patient and tumor-related characteristics. Another explanation for the higher rate of tumor progression in the withdrawal group is that AED withdrawal may facilitate early diagnosis of tumor recurrence, as one might assume that AED treatment is likely to obscure a seizure as an early sign of disease progression. There is evidence that seizures may serve as a surrogate marker of tumor response; i.e. seizure control, as well as loss of seizure control, can be an early indicator of favorable tumor response, respectively tumor progression.[31–35] Aside from neuroimaging and survival, seizure control could therefore be used as one of the main outcome measures.[36]

PART II: The impact of antitumor treatment on clinical and radiological outcome

The second part of this thesis addressed the impact of antitumor treatment on clinical and radiological outcomes in patients with glioma and brain metastases. We focused on the value of the qualitative method of DSC perfusion MRI in differentiating PD from PsPD in brain tumor patients treated with (chemo)radiation (chapter 4, 5, 6). As a reliable diagnostic test requires acceptable test reproducibility, we first assessed the interobserver variability of the qualitative assessment of DSC perfusion MRI and conventional imaging. Although reproducibility of qualitative interpretation of perfusion MR images by neuroradiologists was labeled as good, we found that the interobserver agreement on the overall interpretation of MR imaging (using both conventional and perfusion images) was rather disappointing (Chapter 4). The main problem of the relatively low interobserver agreement on overall interpretation of MR imaging is the low interobserver agreement on perfusion imaging interpretability, i.e. that the neuroradiologists disagreed on whether perfusion images should have been selected for the interpretation. There are several causes for the observed interobserver disagreement. First, the visual score was based on a crude yes/no rating, labelling the presence or absence ("black hole") of highly vascularized areas within the contrast-enhanced lesion relative to the contralateral hemisphere as high rCBV versus low rCBV. The choice of the particular slice and location of labelling within the area with contrast leakage depended on the individual neuroradiologist. Second, lesions are

likely to contain a mixture of tumor and treatment related effects, resulting in different rCBV within a single contrast-enhancing lesion. Third, rCBV maps had a lower resolution than the conventional MR images. This makes the interpretation of contrast enhancement in close proximity to structures of the brain with higher rCBV values (cortex, blood vessels, focal hemorrhages) challenging.

A reliable radiological assessment of PD and PsPD is of major importance as the clinical distinction between PD and PsPD can be difficult, although, glioma patients with PsPD tend to be younger and are less often symptomatic than patients with PD.[37] Furthermore, tumors of patients with PsPD are more often MGMT promotor methylated and isocitrate dehydrogenase (IDH) mutated.[37–41] In our patient group, additional qualitative DSC perfusion MRI could not more reliably distinguish PD from PsPD, nor did it provide prognostic information regarding survival in glioblastoma patients during TMZ chemoradiation (Chapter 5). We also applied the qualitative DSC perfusion MRI in patients with brain metastases treated with SRT, to potentially better differentiate PD from PsPD (Chapter 6). The applicability of DSC perfusion MR imaging in patients with brain metastases was assessed and the changes of perfusion imaging before and after stereotactic radiotherapy (SRT) were evaluated and correlated to tumor response on conventional MRI. We have found that a large proportion of perfusion images could not be assessed due to artefacts and small tumor size, which severely hampered the ability to differentiate PD from PsPD.

Advanced quantitative MRI including DSC perfusion imaging showed high diagnostic performance in treatment response assessment in glioma patients demonstrating sensitivity of 71–92 % and specificity of 85–95 % using diffusion-weighted imaging (DWI), DSC, dynamic contrast-enhanced imaging (DCE) or MR spectroscopy (MRS).[42] DSC perfusion MRI had the second-best sensitivity of 87% (95%CI 82–91) and a specificity of 86% (95%CI 77–91). The findings in literature on quantitative DSC perfusion imaging with high diagnostic accuracies, are discrepant with the results from our studies. It is important to note that the qualitative technique studied is a derivative of the quantitative method and is a more simple, visual interpretation of the rCBV maps and is therefore far more used in the clinical setting.

The interpretation of both qualitative as well as quantitative DSC perfusion imaging to discern PD from PsPD remains challenging. First, the clinical definition of PsPD varies considerably with no clear distinction with other treatment related effects.[43] PsPD is mostly used related to early delayed and reversible radiation injury. However, also radiation necrosis, an irreversible and late complication of radiation to the brain, may be regarded as a (late) expression of PsPD. In literature these terms are used interchangeably.[44,43] Second, there is lack of standardization how to perform and interpret DSC perfusion MRI. Differences include for instance the time of scanning after contrast-injection, identifying regions of interest (ROIs), pre- and post-processing, reference tests and in case of the

quantitative studies, the cut-off values and calculations of rCBV.[43,45] These methodological differences preclude a fair comparison between different studies.

The strength of the study described in chapter 6, is that specifically the applicability of the DSC perfusion was studied, which included the pitfalls of producing the perfusion MRI in a clinical setting. All patients, independent of their tumor response and of the quality of perfusion images were included, whereas most other studies on perfusion imaging included only patients with radiological progression and a technically well performed perfusion MRI.[45–48] There is, in contrast to PsPD in glioma patients, a lack of evidence in literature on PsPD in brain metastases. This study contributed to the understanding of PsPD in brain metastases.

Newer therapies like treatment with immune checkpoint inhibitors, targeted therapy and proton therapy do not seem to obviate the need to better differentiate treatment-related effects from tumor progression.[49,50] Immunotherapy, currently investigated for glioblastoma, has established itself in a variety of metastatic solid cancers including selected patients with brain metastases.[51] Pseudoprogression after immunotherapy in extracranial solid tumors is described in 5-10% of patients. The time interval for immunotherapy-associated PsPD in brain metastases spans from the first weeks after initiation to a maximum of 6 months.[52] It is thought that PsPD after immunotherapy in patients with brain metastases is highly variably and somewhat different in kinetics, frequency and overall impact than PsPD after standard (chemo)radiation in glioma and brain metastases patients.[52] An increased risk cannot be excluded when immunotherapy is combined with radiotherapy in this patient group.

Further, proton therapy instead of standard photon therapy is recently introduced for a selected group of glioma patients. There is some conflicting evidence that proton therapy might increase the frequency of PsPD in (pediatric) brain tumors, such as glioma patients.[53–56] Based on a recent retrospective study in low-grade and anaplastic glioma patients no difference was found in the rate of PsPD after proton beam therapy compared to photon therapy.[54] It is of interest that in the subgroup of oligodendroglioma patients treated with proton beam therapy PsPD developed sooner than in patients who received photon therapy. In another study in low-grade glioma patients treated with proton beam therapy PsPD was more often seen when temozolomide was added compared to proton beam therapy alone (HR 2.2, p= 0.006).[53]

Over the last decades, additional imaging techniques next to quantitative and qualitative DSC perfusion MRI have been tested to differentiate PD from PsPD. These imaging techniques include DWI, diffusion tensor imaging (DTI), DCE, arterial spin labelling (ASL), metabolic PET imaging and MRS.[57,58] Of the advanced MRI techniques, MRS has the highest pooled sensitivity and specificity. Several practical limitations, like prolonged duration of scan times, small tumors and signal contamination from adjacent tissue of the tumor challenge the incorporation in clinical practice. ASL MRI has the main advantage of being a non-invasive perfusion technique. It measures blood flow by using magnetically

labeled arterial blood water protons as an endogenous tracer. Compared to DSC, CBF values acquired from ASL are unrelated to disruptions of the blood-brain barrier. However, until now there is insufficient evidence to conclude whether the diagnostic accuracy of ASL is superior to DSC perfusion in differentiating PD from PsPD in patients with brain tumors.[42,57,59–63] So far, advanced MRI techniques are not (yet) incorporated in the Response Assessment in Neuro-Oncology (RANO) criteria. Amino acid PET, like 11C-MET, 18F-FET, or 18F-FDOPA PET have also been demonstrated to be useful to discern PD from PsPD in glioma and brain metastases.[58,64,65] Practice guidelines and procedure standards for implementation of PET have already been developed.[58,64]

FUTURE PERSPECTIVES

Epilepsy and imaging are two of the most important outcome measures in brain tumor patients. Future research should focus on these outcome measures to further increase their applicability and eventually improve patients' clinical outcomes. In order to achieve this the following topics need more attention in future research.

Epilepsy

- *Development of an accurate seizure scale.* There is a great need for a more homogeneous seizure scale including relevant data like seizure qualities and seizure severity. A standardized assessment of the frequency and severity of seizures will facilitate accurate monitoring of seizures in clinical trials. This seizure scale can also facilitate the use of epilepsy as outcome measure in clinical trials. Current end points, such as a >50% seizure reduction in seizure frequency, omit important information regarding seizure qualities like intensity, duration and associated symptoms, and the severity of seizures. The RANO seizure working group proposed a seizure scale to quantify seizure control, however, further prospective studies are needed for implementation in therapeutic trials.[66]

- *Clinical trials on brain tumor-related epilepsy*

- *More evidence preferred AED(s)*. The effectiveness, HRQoL and side-effects of treatment of frequently used AEDs in brain tumor patients' need more attention in clinical trials. This will result in better evidence-based decisions regarding preferred choice of AED(s) in brain tumor patients. The Seizure Treatment IN Glioma (STING) study is such an initiative comparing the effectiveness of treatment with levetiracetam and valproic acid in glioma patients in a randomized controlled setting.
- *Withdrawal of AED*. The results of our study on the withdrawal of AEDs motivate future research to study the effect of AED withdrawal on cognition and quality of life. The standardized questionnaires QLQ-C30 and QLQ-BN20 can be used to quantify this.

Regarding the decision to withdraw AEDs in glioma patients, it would also be of interest to study what the effect is of seizure recurrence on patient's wellbeing and whether being medication-free outweighs the risk of experiencing a new seizure.

- *Epilepsy as surrogate endpoint for progression*. It is important to consider epilepsy as an additional outcome measure in every brain tumor clinical trial. In clinical trials, survival and neuroimaging are the usual outcome measures. However, seizure outcome may reflect the patient's response to antitumor treatment at an early stage.[31–34] The aforementioned epilepsy scale will be a step forward to help introducing epilepsy as an outcome measure in clinical trials. In addition, more research must be performed to elucidate the exact role of epilepsy as surrogate marker of tumor response. When it is in fact possible to use epilepsy (changes) as a surrogate tumor marker in certain patients, perhaps the radiological monitoring schemes will change.

Imaging

- *Standardization of the DSC perfusion technique*. The greatest disadvantage of the DSC perfusion MRI is the lack of protocol standardization. Variations in for example instrumentation, imaging protocols (i.e. injection time, dose, speed of injection, echo time, slice thickness) and processing of data influence the results and accuracy of the perfusion technique.[43] One of the options to achieve a better radiological assessment of PD and PsPD is to improve the use of the qualitative assessment of the DSC perfusion technique by standardization. When used properly and with awareness of the pitfalls of the technique, the qualitative DSC perfusion MRI has value in the assessment of tumor response. Recommendations from the RANO working group for the standardized use of the DSC perfusion technique would be helpful to compare study results and for the use in clinical practice.
- *Application in new treatments*. It is thought that the development of PsPD after immunotherapy and proton radiotherapy is somewhat different than after standard (chemo)radiation, although data is limited. More research is necessary to explore the effect of new therapies on PsPD using advanced MRI techniques and PET.
- *Artificial intelligence*. Until now most studies focus on one advanced technique to radiologically assess tumor response. Another option to improve the assessment of PD and PsPD is to focus more on the combination of different (MR/PET) imaging modalities. Since there are so many different imaging modalities available questions arises whether clinical image interpretation is still sufficient to interpret all acquired digital data. In the future there will be a more prominent role for machine learning techniques or artificial intelligence to analyze this complex data.[67]

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