ANTIEPILEPTIC AND ANTITUMOR TREATMENT IN BRAIN TUMOR PATIENTS: IMPACT ON CLINICAL AND RADIOLOGICAL OUTCOME

MELISSA KERKHOF

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1

Introduction

INTRODUCTION

Gliomas are the most common primary malignant brain tumors in adults.[1] They arise from glial cells, the supportive tissue of the brain. Gliomas are categorized by histological tumor type, WHO tumor grade and molecular biomarkers based on the revised criteria of the World Health Organization (WHO).[2,3] Based on both genotype and phenotype, adult brain tumors are classified into astrocytoma, oligodendroglioma and glioblastoma including the molecular markers isocitrate-dehydrogenase (IDH) and combined loss of heterozygosity (LOH) on chromosomes 1p and 19q. IDH mutations and the presence of 1p/19q co-deletion are both correlated with an improved survival in glioma patients.

Treatment of low-grade gliomas (WHO grade II) consists, when technically possible, of an early maximal safe resection.[4,5] In high risk low-grade glioma patients with unfavorable prognostic factors, postsurgical adjuvant treatment is advised. Unfavorable prognostic factors include age > 40-50 years, residual tumor, astrocytic subtype, diameter tumor ≥ 4-6 cm, neurological deficits or refractory seizures.[6] The postsurgical adjuvant treatment of IDH mutant WHO grade II oligodendroglioma (1p/19q- codeleted) and astrocytoma consists of radiotherapy and, depending on molecular biomarkers, chemotherapy with procarbazine, lomustine and vincristine (PCV) or temozolomide.[7,8] Anaplastic (WHO grade III) IDH mutant astrocytoma and oligodendroglioma (1p/19q- codeleted) are treated with a maximal safe resection followed by radiotherapy and temozolomide respectively PCV chemotherapy.[9,10,11] IDH wildtype astrocytoma can have an aggressive disease course and is treated conform WHO grade IV glioblastoma patients. In glioblastoma the standard treatment is a maximal resection followed by chemoradiotherapy with temozolomide.[12,13]

Estimates of prognosis based on histopathologic diagnosis prior to the 2016 WHO classification ranged widely: patients with low-grade tumors had a median survival of 5-15 years and with high-grade glioma ranging from 14 months to 10 years.[6] Longer follow-up data of trials indicate that survival of 1p/19q- codeleted oligodendrogliomas treated with radiation and PCV is actually closer to 20 years for grade II tumors and 15 years for grade III tumors.[14,15] Patients with a WHO grade II IDH-mutant astrocytoma have a median survival of approximately 11 years.[16] The median survival of WHO grade III IDH mutant astrocytoma is 5-10 years compared to approximately 1.5 years for the IDH-wildtype subtype.[17,16] Glioblastoma patients have a median survival of 14 months, but when the IDH mutation is present median survival is approximately two times longer than that of IDH-wildtype tumors.[16]

Of the intracranial tumors brain metastases represent the most frequent tumors. The incidence of brain metastases has increased over time, as a result of advances in detection of brain metastases and longer survival of cancer patients. In adults, lung (36-64%) and breast (15-25%) tumors and melanoma (5-20%) are the most common sources of brain metastases.[18] The median survival of patients with brain metastases is about nine months,

highly depending on tumor type and patient characteristics.[19] Treatment may involve resection, radiotherapy, systemic treatment, or a combination of these.

To evaluate the effect of brain tumor and cancer therapies on patients functioning, well-being and clinical status, several clinical outcomes can be used like imaging, epilepsy, health-related quality of life (HRQOL), cognition and activities of daily living. Epilepsy may be a sign of cancer either as manifestation of a primary brain tumor or from systemic cancer that presents with brain metastases. It is of major importance to achieve seizure control, as uncontrolled seizures may negatively influence HRQOL.[20] Seizures in brain tumor patients are treated with antiepileptic drugs (AEDs) and are generally initiated after the occurrence of a single seizure attributable to the tumor.
This thesis encompasses questions from the neuro-oncologist's daily practice regarding how to evaluate and define clinical outcomes, particularly with respect to epilepsy and imaging. We aimed to improve patient's clinical outcomes by optimizing AED treatment and improving the radiological assessment after antitumor treatment. To optimize AED treatment, more knowledge about the effects of AED treatment on for example, seizure frequency, side effects, tumor progression and survival is necessary. Another aspect of optimizing AED treatment is the avoidance of overtreatment and side effects, by studying the necessity of continuation of AED treatment after long-term seizure freedom.
Furthermore, to better treat brain tumor patients, improvement of the radiological assessment of tumor progression and pseudoprogression needs more attention. Obtaining high levels of diagnostic certainty is relevant, as tumor progression and pseudoprogression ask for a different treatment approach. The interpretation of neuro-imaging, hampered by treatment-related radiological effects, is still a challenge in neuro-oncology care. Improvement of advanced magnetic resonance imaging (MRI) techniques is therefore of great importance.

Part I of this thesis focuses on the role of antiepileptic drugs on several clinical outcomes, like seizure frequency, tumor progression and survival. Furthermore, the withdrawal of antiepileptic drugs in relation to the radiological follow-up and tumor progression in glioma patients will be discussed.

Part II focuses on the impact of antitumor treatment on clinical and radiological outcomes, with a specific focus on the differentiation between tumor progression versus pseudoprogression, in glioma and brain metastases patients.

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

Seizures in patients with brain tumors are symptomatic and localization-related seizures, manifesting as focal seizures with or without bilateral tonic-clonic seizures. In brain metastases, seizures occur as the presenting symptom in 18% of patients; another 15% develop seizures later in the course of the disease.[21–23] In systemic cancer most seizures are associated with brain or leptomeningeal metastases.[22,24]

In low-grade gliomas, the risk of seizures varies between 65-85% and represents the first clinical symptom in 70% of patients. During follow-up, 6-11% of initially seizure-free patients will develop epilepsy later on.[25] In high-grade glioma patients the incidence of seizures is approximately 30-62%, with two-third occurring at presentation and one third during the course of the disease.[25–28] Low-grade gliomas have a stronger predilection for epileptogenesis than high-grade gliomas. The mechanism is incompletely understood, but it may be explained by the slow growth rate associated with low grade lesions, which favors development of seizure-prone changes like de-afferentation and disconnection of cortical areas leading to denervation hypersensitivity.[29] This slower rate of tumor growth may also permit adaptive change of the surrounding brain tissue to occur, thereby diminishing the development of focal neurological deficits.[23]

There are several pathophysiological mechanisms causing epileptic seizures due to the effect of the tumor itself and changes in the extracellular milieu causing cortical hyperexcitability. Alterations in micro-environment induce swelling and cell damage together with deregulation of sodium and calcium influx with generation of electrical impulses.[23,30] Molecular genotypes also contribute to the development of seizures. One of the first identified genetic factors is a combined loss of heterozygosity (LOH) on chromosomes 1p and 19q. Patients without a deletion of 19q seem to be more likely to present with seizures than those with the deletion.[31] Another biologic marker that has been associated with seizures is the presence of a mutation of IDH1 and IDH2. The more prevalent IDH1 is present in 70–80% of low-grade gliomas.[32] Under normal circumstances, the IDH1 enzyme, which takes part in the Krebs citric acid cycle, catalyzes isocitrate to a-ketoglutarate. If mutated, 2-hydroxyglutarate will be formed instead. This product shows structural similarity to glutamate and may activate N-methyl-D-Aspartate (NMDA) receptors and foster epileptogenesis. In several series of patients with low-grade gliomas, the presence of IDH1/2 mutations showed a higher chance of presenting with seizures as the initial clinical symptom.[27,32] It has also been found that seizure reduction may serve as a surrogate marker for tumor response and precede the radiological response after treatment with temozolomide.[33] Seizures may therefore be considered a prognostic marker for survival in glioma patients.

Chapter 2 focuses on the effect of valproic acid on survival in glioblastoma patients and on the impact of antiepileptic treatment on seizure frequency. Survival of patients

with high-grade glioma treated with chemoradiation has been argued to be positively impacted by the use of valproic acid.[34,35] Potential specific anticancer properties of valproic acid include its action as histone-deacetylase enzyme inhibitor leading to epigenetic modulation. It promotes hyperacetylation of DNA-binding histone proteins together with decondensation of chromatin, and a demethylation process of tumor suppressor genes.[27] Aside from the aforementioned hyperacetylation and demethylation effects, valproic acid may also affect cell differentiation, promote apoptosis and autophagy and lead to growth arrest in cancer cells and the sensitization of malignant cells to radiotherapy and chemotherapy.[27,36] There is also evidence that it downregulates MGMT expression, especially in temozolomide-resistant cell lines.[36]

In chapter 3 we studied the impact of withdrawal of AEDs in glioma patients after long-term seizure freedom. Tumor directed treatments contribute to seizure control in glioma patients.[26,37] Some glioma patients who develop clinically and radiologically stable disease for years fortunately achieve sustained seizure freedom as well. In clinical practice most seizure free glioma patients nevertheless remain on treatment with AEDs. In patients experiencing long-term seizure freedom the question may rise whether AEDs should be continued lifelong or should be withdrawn to reduce side-effects and to eliminate the burden of taking daily AEDs. Other possible reasons to prefer AED withdrawal might be avoidance of teratogenic risk, reducing costs and decreasing the need for follow-up care concerning the epilepsy.[37] Currently, it is unknown if glioma patients and doctors are willing to withdraw AEDs after long-term seizure freedom. More importantly, no prospective data exist on the risk of seizure recurrence in glioma patients after AED withdrawal.

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

The main radiological technique to analyze and monitor a brain tumor is standard MRI with T1-weighted sequence, T2 fluid-attenuated inversion recovery (FLAIR), gadolinium infusion and diffusion-weighted imaging. Although contrast enhancement is generally a strong surrogate for active brain tumor disease, there are restrictions as a result of different treatment related effects.[38] Changes in contrast-enhancement in posttreatment brain tumor imaging alone are non-specific for tumor response, as contrast-enhancement only reflects a disrupted blood-brain barrier (BBB). An increase of contrast-enhancement can be induced by tumor growth but also by several other processes, such as treatment-related inflammation, postsurgical changes, ischemia, radiation effects.[39] Pseudoprogression is a phenomenon of subacute imaging changes subsequent to radiochemotherapy suggestive of tumor progression, with or without clinical symptoms, which resolves spontaneously without further therapy. It is thought to be a treatment related local tissue reaction with inflammation, edema and disruption of the BBB. In 1979 pseudoprogression was first reported.[40,41] After the addition of temozolomide to radiotherapy for newly diagnosed

high-grade gliomas in 2005, pseudoprogression was more frequently encountered.[42] Pseudoprogression occurs predominantly within the first 3-4 months after completing treatment but it may occur from the first week up to 6 months after treatment.[43,44] It is most frequently seen in high-grade gliomas and brain metastases.[45] The incidence varies between 5.5% and 31% depending on the criteria used to define pseudoprogression.[39,46] It appears to be associated with favorable outcome and is more frequent in O6-methylguanine DNA methyltransferase (MGMT) promotor gene methylated GBM patients.[43] According to the literature the definition of pseudoprogression, treatment related effects and radionecrosis vary. Radionecrosis refers to the more severe reaction that occurs at a later stage after therapy and represents a more permanent tissue injury.[45] The distinction between pseudoprogression and tumor progression is critical for predicting prognosis and for future therapy. Changes related to pseudoprogression decrease over time, by definition, so the only way to discern tumor progression from treatment related effects is to perform follow-up examination. The difficulties in assessment of response to therapy have led to the revision of the criteria used to assess tumor response. Nowadays the Response Assessment in Neuro-Oncology (RANO) criteria in high-grade glioma for assessing response to therapy are used.[47,48] However, also with these criteria the conventional MRI is insufficient to reliably differentiate tumor progression from treatment related effects. Aside from brain biopsy being an invasive diagnostic, histopathology is in general not preferred in (asymptomatic) patients due to difficulties in interpreting post-radiotherapy biopsy samples, interobserver variations and inconclusive results due to heterogeneity of the tissue. Therefore, there is a great need for validated non-invasive techniques to assess tumor outcome. Of all advanced MRI techniques especially the quantitative dynamic susceptibility (DSC) perfusion MRI is used in daily clinical practice and shows promising results with high diagnostic accuracy.[49–51] Evidence for the widely used qualitative DSC perfusion technique is limited. Therefore, we studied the interobserver variability of the qualitative perfusion MRI in chapter 4.

With DSC perfusion MRI the angiogenesis can be assessed due to the T2 and T2* shortening effects of gadolinium-based contrast agents and involves rapid imaging to capture signal changes due to the first passage of intravenously administered contrast agent bolus.[45] One of the parameters derived from the DSC MRI is the relative cerebral blood volume (rCBV). It is thought that the rCBV is increased in tumors and decreased in treatment related effects such as pseudoprogression and radionecrosis. In chapter 5 and chapter 6, respectively, the value of perfusion MRI in high-grade glioma and patients with brain metastases is discussed.

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PART I

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


2

Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme

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Abstract

Background: To examine the efficacy of valproic acid (VPA) given either with or without levetiracetam (LEV) on seizure control and on survival in patients with glioblastoma multiforme (GBM) treated with chemoradiation.

Methods: A retrospective analysis was performed on 291 patients with GBM. The efficacy of VPA and LEV and as polytherapy was analyzed in 181 (62%) patients with seizures with a minimum follow-up of 6 months. Cox-regression survival analysis was performed on 165 patients treated by chemoradiation with both temozolomide and VPA for at least 3 months.

Results: Monotherapy with either VPA or LEV was instituted in 137/143 (95,8%) and in 59/86 (68.6%) on VPA/LEV polytherapy as the next regimen. Initial seizure-freedom was achieved in 41/100 (41%) on VPA, in 16/37 (43.3%) on LEV and in 89/116 (76,7%) on subsequent VPA/LEV polytherapy. At the end of follow-up, seizure-freedom was achieved in 77,8% (28/36) on VPA alone, 25/36 (69,5%) on LEV alone, and in 38/63 (60.3%) on VPA/LEV polytherapy with ongoing seizures on monotherapy. Patients using VPA in combination with temozolomide showed a longer median survival of 69 weeks [95% CI:61.7;67.3] as compared to 61 weeks [95% CI 52.5;69.5] in the group without VPA (HR 0.63 [95% 0.43-0.92] p: 0.016), adjusting for age, extent of resection and MGMT promoter methylation status.

Conclusions: Polytherapy with VPA and LEV strongly contributes to seizure control to either of these as monotherapy. Use of VPA together with chemoradiation by temozolomide results in a 2 months longer survival of patients with GBM.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most frequent primary brain tumor in adults and radiochemotherapy with temozolomide (TMZ) leads to a median survival of 14 months.[1,2] This dismal outlook is often aggravated by the presence of epilepsy, occurring between 40%-60% of cases.[3, 4] One difficulty in the management of seizures associated with brain tumors is the development of treatment-resistance in 20-30 % of patients. Another issue is to avoid the use of enzyme-inducing anticonvulsants like carbamazepine or phenytoin in order not to compromise cotreatment with chemotherapeutic agents.[5] Recently, it has been found that combining valproic acid (VPA) with temozolomide leads to an improved survival of patients with glioblastoma multiforme as well as in children with brain tumors.[6] This could possibly be explained by the chemotherapy-sensitizing properties of VPA, including the inhibition of histone deacetylase leading to improved survival. Here, we report on the use of VPA given either with or without levetiracetam (LEV) on seizure control. In addition, we studied the effect of VPA on survival of patients with GBM.

METHODS

The subjects of this retrospective observational study were patients with a histological diagnosis of GBM according to World Health Organization guidelines following biopsy or surgical resection and treatment in the neuro-oncology clinical at the Medical Center Haaglanden in the period July 1999 - September 2011. Patients were studied for the efficacy of anti epileptic therapy on seizure activity and on survival. Baseline-characteristics of patients were collected in a database, including specific information on the site of the tumor, date and type of surgery, subsequent antitumor therapy, MGMT promoter methylation status (from 2008 onwards) and survival data. Data on seizure characteristics and the use of and duration of anticonvulsant therapy were collected as well. Epilepsy was defined as the incidence of at least one seizure during the course of disease. As a rule, patients received either VPA or LEV as a first line anticonvulsant instituted at a maintenance dose of 1000 mg. In case of ongoing seizures, one of these agents was added to the other rather than raising the dose of the initial agent. In case of ongoing seizures on polytherapy with VPA/LEV, one of these was raised at the time, usually ≤2000 mg for each, and as a rule with the help of therapeutic drug monitoring to estimate the therapeutic window. Rarely were doses higher than 2000 mg given for each agent. Patients referred from elsewhere were occasionally taking other anticonvulsants, whose regimens were left unchanged in cases of seizure control and good tolerability.

Seizure frequency before the start of anticonvulsant therapy and following each change in type of anti epileptic drug (AED) use was recorded. Efficacy of AED therapy was studied

in patients who had a minimum follow-up period of 6 months; follow-up was censored in April 2012.

Following biopsy or surgical resection, the first-line antitumor treatment was radiation therapy with concomitant and adjuvant TMZ. Before 2005, a total of 34 patients participated in the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour and Radiotherapy Group trial on concomitant and adjuvant TMZ, and these patients were also included in the study of Weller et al.[1,2,7] Patients >70 years old or patients with Karnofsky performance score of ≤60 received radiotherapy alone.[1] As antitumor therapy, radiation with TMZ was given if they met the inclusion criteria of the schedule designed by the EORTC Brain Tumour and Radiotherapy Group, and they received this schedule as standard treatment for GBM following publication of this schedule.[1] After 2010, patients without MGMT methylation could participate in trials including temozolomide and temsirolimus. Second-line chemotherapy for recurrent glioblastoma consisted of retreatment with TMZ, chemotherapy with procarbazine/CCNU/ vincristine, or combinations of lomustine, bevacizumab and irinotecan.

For the second analysis on the effect of VPA on survival, we analyzed patients who were treated with concomitant and adjuvant TMZ and received VPA in combination with TMZ. In order to consider the effect meaningful, we required a minimum duration of 3 months of this combination. Other exposure times were analyzed as well. For this part of the study, we compared this group of patients with those patients who had received either none or another anticonvulsant than VPA or had received VPA in combination with TMZ for a period shorter than 3 months. In a subset of our patient group, we reported in 2009 on the efficacy of anticonvulsant therapy in a combined 135 group of patients with low- and high grade gliomas, including 56 patients with GBM.[3] Here we report on patients with GBM only.

Statistics

Descriptive statistics (SPSS v 16.0) were used to define the population and the treatment effect of AEDs on epilepsy frequency. The secondary endpoint was overall survival measured in weeks from diagnosis to death. The minimal follow-up period for survival analysis was 3 months. Patients who were alive at the end of the study were censored at April 2012, or at the day of the last contact. Descriptive statistics were used on defining the population of patients, and statistical evaluation was carried out using both the Chi-square test and Mann-Whitney U-test. Univariate descriptive analysis of overall survival was done with Kaplan-Meier estimates. A log-rank test was used to compare overall survival curves. For multivariate analysis of overall survival, we used Cox proportional hazard models to adjust for confounding factors that may alter the therapeutic effect. We adjusted for known independent prognostic factors: age at tumor diagnosis, extent of resection (complete vs incomplete vs biopsy), and MGMT promoter methylation status. Hazard ratios are presented with 95% confidence intervals (CIs).

RESULTS

In a 12 year period, data were collected on 291 patients who had a newly diagnosed GBM, of whom 181 (62%) had epilepsy. Patients' characteristics are listed in Table 1, showing a slight male preponderance (58.1%) and a median age at tumor diagnosis of 60 years. The median period of follow-up was 9 months (range, 0 - 81). Of 181 patients with epilepsy, 143 had a follow-up of at least 6 months (Fig. 1). The median overall survival was 13 months for the whole study group; 14 months in the group with epilepsy and 8 months in the group without epilepsy (P= .016). At the last follow-up, 18 patients were still alive and 33 were lost to follow-up. During the time of the study, 174 patients had shown progression of tumor.

Table 1. Patient characteristics

Number	**291**
Gender, n (%)	
Male	169 (58.1)
Female	122 (41.19)
Median age at tumor diagnosis, y (range)	60 (24-85)
Overall survival (mo)	13.0
Tumor progression, n (%)	174 (59.6)
PFS* median (mo)	8.5
Received chemoradiation with Temozolomide	165 (56.7)
Patients	
Dead	240 (82.2)
Censored†	18 (6.2)
Alive unknown††	33 (11.3)
Epilepsy‡,n (%)	181 (62.0)
Epilepsy as presenting sign, n (%)	123 (42.1)
Seizure classification, n (%)	181
Partial simple	59 (32.6)
Partial complex	9 (5)
Secondary generalized	74 (40.8)
Combination of partial/generalized	26 (14.4)
Missing	13 (7.2)
Status epilepticus, n (%)	21
Partial	10 (47.6)
Generalized	11 (52.4)
MGMT methylation, n (%)	
Unmethylated	82 (28.2)
Methylated	38 (13.1)
Not defined	171 (58.7)

*Progression-free survival based on MRI. † still alive at last date of follow up (April 2012) ††survival unknown, lost of follow-up ‡ patients with at least one seizure

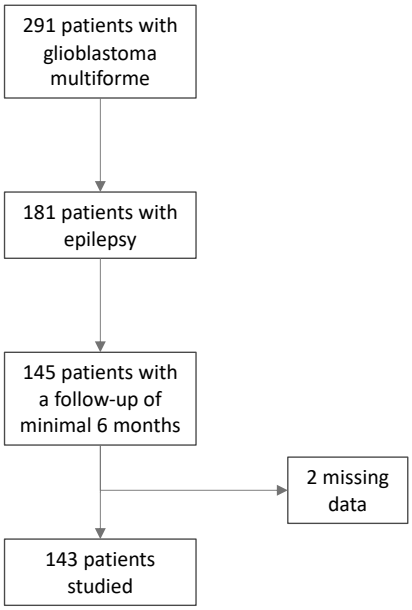

Figure 1. Status of the initial cohort of patients with GBM

Seizure characteristics

A total of 123 of 181 patients (68%) developed epilepsy as presenting sign and 58 (32%) later on (Table 1). Partial seizures occurred in 68 patients (38%), and 74 (40.8%) had partial seizures with secondary generalization. Status epilepticus was observed in 21 patients (11.6%). The most frequently prescribed first AED was VPA in 100; LEV in 37; and another AED in 8 patients (Table 2). During the course of disease, 59 patients (40.7%) needed no alteration in type of AED, excluding adjustments like a lowering or increasing the dose. A change in regimen was performed in the remaining 86 patients (59.3%). In 49 patients LEV was added to VPA because of ongoing seizures (Fig. 2). VPA was discontinued in 10 (10.2%) out of a total of 98 patients due to diverse adverse effects: depression, weight gain, tremor, psychosis, rash, thrombopenia, hepatic function tests abnormalities, or pancreatitis. LEV was given as an alternative in those 10 patients. During the use of LEV, we observed 1 patient with severe fatigue and an allergic reaction, possibly due to interaction with TMZ.

Table 2. Use and effect of AEDs

			Seizure-free, n (%)	Seizure freq < 1 month, n (%)	Seizure freq > 1/month, n (%)
First AED treatment	n (total 145)				
	VPA:	100	41 (41)	33 (33)	26 (26)
	LEV:	37	16 (43.3)	8 (21.6)	13 (35.1)
	Other AED:	8	2 (25)	5 (62.5)	1 (12.5)
	Total		59	46	40
Second AED treatment	n (total 86)				
	LEV + VPA:	59	32 (54.2)	20 (33.9)	7 (11.9)
	LEV mono:	10	7 (70)	2 (20)	1 (10)
	VPA mono:	2	1 (50)	0	1 (50)
	Other combi:	15	7 (46.7)	5 (33.3)	3 (20)
Final AED treatment*	n (total 143)*				
VPA monotherapy	36		28 (77.8)	7 (19.4)	1 (2.8)
LEV monotherapy	36		25 (69.5)	7 (19.4)	4 (11.1)
VPA with LEV ± other AEDs	63		38 (60.3)	16 (25.4)	9 (14.3)
VPA without LEV + other AEDs	2		0	0	2 (100)
LEV without VPA ± other AEDs	4		1 (25)	2 (50)	1 (25)
Other AEDs without VPA/LEV	2		1 (50)	1 (50)	0

*2 missing cases

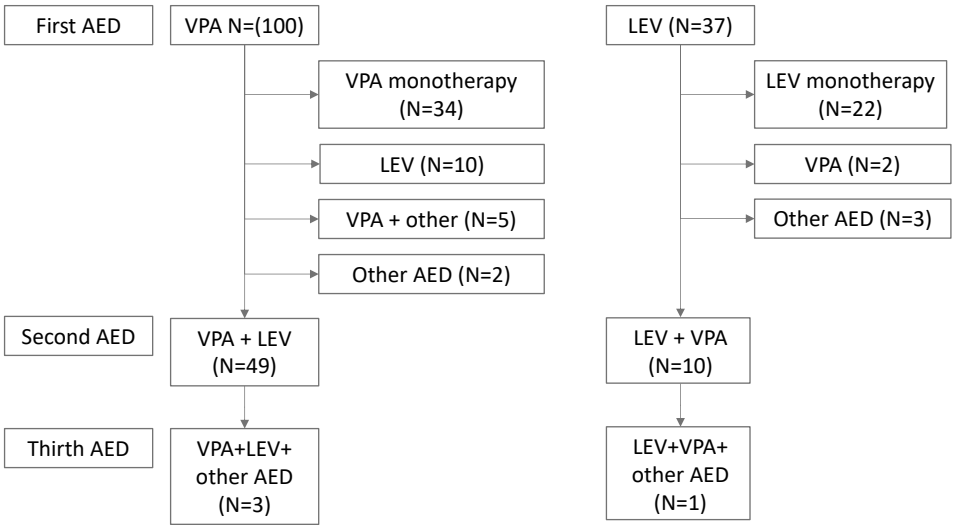

Figure 2. Flowchart. Use of LEV and VPA during the study

Seizure control

The treatment efficacies of different AEDs are summarized in Table 2. Monotherapy with either VPA or LEV was instituted in 95,8% (137/143) of patients with GBM. Seizure-freedom was observed in 41/100 (41%) on initial VPA and in 16/37 (43.3%) on initial LEV monotherapy. A total of 59 out of 86 patients (68.6%) received VPA/LEV polytherapy as next regimen because of ongoing seizure activity, of whom 32/59 (54.2%) became seizure-free. In total, receiving a first and second AED treatment with either VPA or LEV and if necessary subsequent polytherapy, 76.7% of patients (89/116) became seizure free. At the end of the follow-up period, seizure-freedom was observed in 77.8% of patients (28/36) on VPA alone, 25/36 (69.5%) on LEV alone, and 38/63 (60.3%) on VPA/LEV polytherapy.

Of patients who still had ongoing seizure activity at the end of the follow-up period, 7 (16.7%) received VPA alone, 9 (23.1%) LEV alone, and 17 (26.6%) combined VPA/LEV polytherapy. A total of 22 patients (14.9%) received a third AED regimen because of ongoing seizure activity of 2 or more seizures/month. Of these, 18 patients used a combination of VPA/LEV with or without another AED, of whom 7 patients became seizure free, 7 had a seizure frequency of < 1 /month, and 4 had a seizure frequency of > 1 per month.

Survival analysis and determinants

Of the total group of patients with GBM, 165 received radiation with concomitant and adjuvant TMZ for a minimum period of 3 months. Eight patients in this group showed early progression and died in 3 months. In this group we analyzed whether the use of VPA in combination with TMZ had an effect on survival. One hundred eight patients used VPA in combination with TMZ compared to 57 patients in the group not receiving VPA (ie, no or another anticonvulsant) or treatment with VPA during a shorter period than 3 months (Table 3). There were no statistical significant differences between the patient characteristics of these 2 groups, including MGMT promotor methylation status. The median survival of the whole group was 68 weeks. The group using VPA in combination with TMZ during at least 3 months had a significantly longer median survival of 69 weeks [95% CI:61.7-67.3], compared to 61 weeks [95% CI 52.5-69.5] in the group not using VPA (hazard ratio 0.63; 95% CI 0.43-0.92]; P= .016 (Fig. 3), adjusting for age at diagnosis, resection, and MGMT promoter methylation status. The occurrence of early progressive death in any of the 3 groups (receiving TMZ and VPA for 3 months or more; receiving TMZ and VPA for < 3 months; or receiving no AEDs (no seizures)) did not influence the observed differences in survival. As there were only 7 patients who used an enzyme-inducing AED in combination with TMZ, this group was too small to be included for analysis. For progression-free survival, we observed a borderline significant effect with a minimum period of 3 months coexposure of VPA and TMZ (P= .06).

Age at diagnosis was an independent prognostic factor for overall survival (P= .001), while extent of resection and MGMT promoter methylation status were not significant in a multivariate Cox' analysis (Table 4).

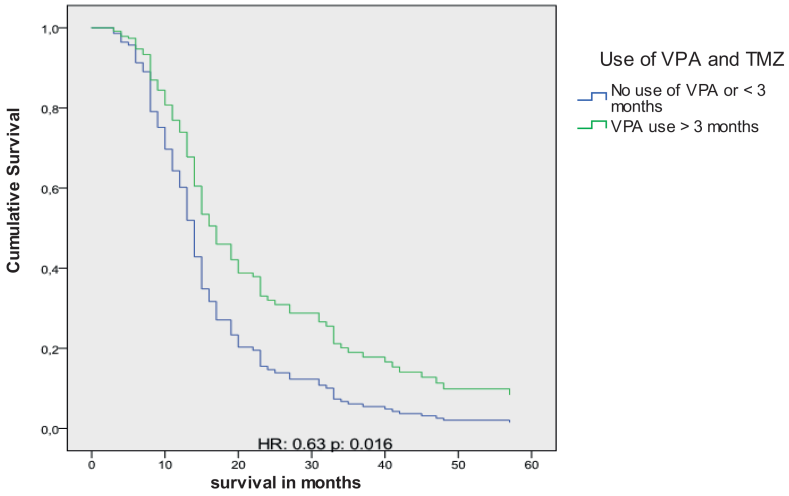

Figure 3. Kaplan-Meier curve of patients treated with chemoradiation with and without VPA for a minimum of 3 months. HR, hazard ratio

Table 3. Characteristics of patients receiving chemoradiation with TMZ

	VPA during 3 months n = 108	No VPA or < 3 months n= 57	P - value
Age at tumor diagnosis,y	58	58	0.97
Extent of surgery			0.08
Total	86	47	
Partial	13	10	
Biopsy	8	0	
MGMT methylation status			0.32
Methylated	16	7	
Unmethylated	31	23	
Missing/inconclusive	61	27	

Table 4. Independent prognostic factors for survival with VPA on multivariate Cox regression analysis

	Hazard ratio (95% CI)	P - value
Overall survival		
VPA during 3 mo	0.63 (0.43-0.92)	0.016
Age, y, at diagnosis	1.03 (1.01-1.05)	0.001
Complete resection vs incomplete vs biopsy	1.36 (0.96-1.93)	0.084
MGMT	1.04 (0.84-1.29)	0.695

DISCUSSION

This study focused on the efficacy of VPA on seizure control and on survival in patients with GBM. Age (median 60 y), sex distribution (58% males), and survival (median 13 mo) corresponded well with recent data of patients with GBM receiving chemoradiation with TMZ.[1,2, 8, 9] The total frequency of seizures we observed was in 62% of patients, which is somewhat higher than reported in 2 earlier, smaller series of patients with GBM, varying between 36 and 60%.[3, 4] Status epilepticus was observed in 21 (11.6%).

In principle, the treatment of seizures in patients with brain tumor does not differ essentially from that of other types of partial epilepsy of adult onset provided that enzyme-inducing AEDs are avoided because of possible interactions with chemotherapy.[5] It was our approach to start with either VPA or LEV monotherapy in low maintenance dose followed by early polytherapy with both anticonvulsants in case of ongoing seizure activity. In brain tumor patients, VPA has been observed to contribute to seizure control[3,4,10] and LEV is known for its absence of drug interactions and its good efficacy and tolerability.[11-14] Possibly, the initial relatively low percentages of seizure freedom on monotherapy are explained by a policy of early polytherapy rather than escalating of the dose of the initial anticonvulsant. At the end of the follow-up period, we observed seizure freedom in 77.8% of patients on VPA alone and 69.5% on LEV alone, corresponding to previous studies in patients with brain tumors.[11-14]

A final percentage of seizure-freedom in 76.7 % of patients compares favorably with other observations of achieving seizure freedom in patients with partial types of epilepsy. Prospective studies on the effect of sequential trials of anticonvulsant indicate that first-line anticonvulsant therapy results in seizure freedom in 47%-63 of patients and another 13%-26% on second line regimen, usually subsequent monotherapy, and that 29%-40% of patients continue to have seizures despite successive treatment attempts.[15-18] Our approach of initial therapy with either VPA or LEV alone and subsequent VPA/LEV polytherapy may seem to compare favorably with other studies on achieving seizure freedom by applying subsequent monotherapy trials with anticonvulsants.[16-18] A number of factors may account for this. In most trials on partial epilepsies, at least 2 seizures

are required for inclusion, while in our study a single seizure was sufficient. All patients underwent active antitumor treatment, which is known to contribute strongly to seizure control. Although epilepsy in brain tumors is known for its treatment resistance, this holds true mainly for low-grade gliomas, particularly with tumors of the medial temporal lobe, including dysembryoblastic tumors and gangliogliomas of childhood.[19]

Nevertheless, our study not only showed the efficacy of anticonvulsants of VPA and LEV as monotherapy, but also showed that combining them resulted in ongoing seizure activity in only 14.9% of the total group of patients with seizures. These observations on the efficacy of anticonvulsant polytherapy may be explained by experimental studies on a synergistic activity of LEV, possibly related to cell-membrane or ion-channel changes associated with the SV2a protein.[20] This seems to be particularly apparent if LEV is combined with AEDs that enhance the gamma-aminobutyric acid-ergic activity or reducing glutamergic neurotransmitter activity, like VPA or benzodiazepines.[21, 22] One advantage of synergistic cotherapy is that lower total dosages of AEDs are sufficient for a similar or better antiseizure effect. Smaller cumulative doses also imply that the risk of drug toxicity will be reduced, including lesser risk on cognitive dysfunction. In patients with brain tumors, the presence of seizures and anticonvulsant therapy are each more unfavorably independent factors for neurocognitive functioning than having had previous surgery or radiation therapy.[23] Our study was retrospective and neither took into account the dosages needed to attain these results nor included a formal analysis of cognitive function. We have observed before that by combining VPA and LEV in a relatively low dose of both, good effects on seizure control can be achieved in combination with maintained cognitive function.[13] Earlier reports on LEV have established its good tolerability with respect to cognitive function, including studies in patients with brain tumors.[24,25] Nevertheless, these impressions need to be substantiated by proper prospective studies.

The use of VPA in patients with GBM has recently drawn attention because of its potential antitumor activity. Based on a post-hoc analysis of data from a prospective trial on the efficacy of chemoradiation in patients with GBM, it appears that the use of VPA in combination with TMZ produces a median gain of 3 months survival compared with use of enzyme-inducing AEDs, the omission of any AED, or use of TMZ alone.[7] In our analysis, we adjusted for age at diagnosis, extent of surgical resection, and MGMT promoter methylation status. We were able to confirm the findings of Weller et al[7] and established a significant median gain of 2 months when both VPA and TMZ were combined for a minimum of 3 months. Possibly, the somewhat shorter survival in our series is explained by the relatively low doses of VPA prescribed. The observed effects of VPA on survival of GBM patients may be explained by the histone deacetylase-inhibiting properties of VPA leading 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.[26,27] The absence of MGMT expression as a predictive factor is

in line with recent findings that enhanced antitumor effects in GBM are associated with valproate-mediated reduced expression of MGMT in TMZ-resistant malignant glioma cell lines.[32] Nevertheless, our results must be interpreted with caution, since it is a selective and retrospective analysis.

These results on effective seizure control and improved survival in patients with GBM seem to provide an extra argument of applying VPA as a first-line anticonvulsant in patients not only in patients with high-grade gliomas but also in those with low-grade gliomas, particularly when one expects that they may be treated with systemic chemotherapy, particularly TMZ. Nevertheless, VPA should be used with caution given its risk for worsening of thrombocytopenia and other bone marrow toxicities associated with chemotherapy, which can be enhanced by the enzyme-inhibiting properties of VPA.[7, 28] In terms of seizure control, a good alternative AED is the use of LEV, based on efficacy, tolerability, and absence of drug-drug interactions.[12, 29] As seizures in brain tumor patients are known to be often treatment resistant for medical therapy with AEDs, synergistic activity by anticonvulsant combination therapy including LEV may provide an important tool to achieve better seizure control and less risk for neurotoxicity and deserves more study.[20, 30, 31]

Recent observations of longer survival for patients with GBM and children with brain tumors receiving both VPA and TMZ are supported by the findings of this analysis.[6, 7] The strength of our study lies in the large number of patients with epilepsy and GBM receiving fairly homogeneous both antiseizure and antitumor therapy. Although these results seem promising, they need further testing in a preferably randomized future study.

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3

Withdrawal of antiepileptic drugs in patients with low grade and anaplastic glioma after long-term seizure freedom: a prospective observational study

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Abstract

Background: When glioma patients experience long-term seizure freedom the question arises whether antiepileptic drugs (AEDs) should be continued. As no prospective studies exist on seizure recurrence in glioma patients after AED withdrawal, we evaluated the decision-making process to withdraw AEDs in glioma patients, and seizure outcome after withdrawal.

Methods: Patients with a histologically confirmed low-grade or anaplastic glioma were included. Eligible patients were seizure free ≥1 year from the date of last antitumor treatment, or ≥ 2 years since the last seizure when seizures occurred after the end of the last antitumor treatment. Patients and neuro-oncologists made a shared decision on the preferred AED treatment (i.e. AED withdrawal or continuation). Primary outcomes were: (1) outcome of the shared decision-making process and (2) rate of seizure recurrence.

Results: Eighty-three patients fulfilled all eligibility criteria. However, in 12/83 (14%) patients, the neuro-oncologist had serious objections to AED withdrawal. Therefore, 71/83 (86%) patients were analyzed; In 46/71 (65%) patients it was decided to withdraw AED treatment. In the withdrawal group, 26% (12/46) had seizure recurrence during follow-up. Seven of these 12 patients (58%) had tumor progression, of which three within 3 months after seizure recurrence. In the AED continuation group, 8% (2/25) of patients had seizure recurrence of which one had tumor progression.

Conclusion: In 65% of patients a shared decision was made to withdraw AEDs, of which 26% had seizure recurrence. AED withdrawal should only be considered in carefully selected patients with a presumed low risk of tumor progression

INTRODUCTION

Low-grade gliomas are a group of primary brain tumors supposedly developing from supportive tissue cells, such as oligodendrocytes and astrocytes, or neural stem cells. In the presence of microvascular proliferation and necrosis, these tumors are designated as anaplastic gliomas. A fundamental shift in the diagnosis of these tumors is effectuated by the increasing importance of molecular markers in the histopathology of these tumors.[1, 2] Most patients with low-grade glioma develop seizures during the course of their disease. In general, patients with low-grade gliomas (World Health Organization (WHO) grade II) appear to have a much higher seizure incidence (up to 60%–90%) compared to patients with anaplastic gliomas (WHO grade III, 40%-60%).[3–6] Epilepsy in patients with glioma may be difficult to treat as 15-50% of patients do not become seizure free despite extensive treatment with anti epileptic drugs (AEDs).[3, 4] Epilepsy in patients with brain tumors is characterized by localization-related seizures, manifesting as focal seizures either with or without focal to bilateral tonic-clonic seizures. In clinical practice, there is no doubt that glioma patients who develop seizures require treatment with AEDs. To achieve adequate seizure control, levetiracetam and valproic acid are the mostly supported treatment options[5], but alternative AEDs as lamotrigine, lacosamide, topiramate, zonisamide or pregabaline also have shown a favorable efficacy and toxicity profile and limited interactions with other drugs such as chemotherapeutic agents.[6–9] Still, in 20-40% of glioma patients AED side-effects occur, such as somnolence, dizziness, fatigue, cognitive disturbances, and mood or behavioral changes.[5, 10] Besides seizures, the tumor itself and antitumor treatments, the cumulative effects of AED treatment are also likely to contribute to cognitive dysfunction, behavioral changes and a decrease in quality of life.[10–13] The potential benefits and harms should therefore be weighted when choosing to start a specific AED.

Evidence exists that antitumor treatment for glioma also contributes to a reduction in seizure frequency; after surgical resection or radiotherapy, respectively 53-87% and 32-75% of patients with low-grade glioma become seizure free.[14] Also chemotherapy treatment results in a ≥50% reduction in seizure frequency in 48-78% of patients.[13,15–19] Consequently, tumor-directed treatments are increasingly recognized as potentially effective options leading to seizure control.[20]

In the light of potential side effects and costs of long-term AED use and the efficacy of antitumor treatment regarding seizures, the question arises whether withdrawal of AEDs after an interval of seizure freedom should be considered.[5] Based on retrospective studies, a seizure recurrence rate after withdrawal between 12.5% and 27% has been reported in patients with mostly intra-axial brain tumors.[5] Currently, it is unknown if glioma patients and their physicians are willing to withdraw AEDs after long-term seizure freedom, and more importantly, no prospective studies exist on the risk of seizure recurrence in glioma patients after AED withdrawal. Therefore, we studied both the decision-making process

of glioma patients and their neuro-oncologists to withdraw or continue AEDs after long-term seizure freedom, as well as the rate of seizure recurrences.

METHODS

Design

A prospective, observational study was conducted. Details on the study design can be found in the published study protocol.[21]

Participants

Participants were recruited from January 2014 until May 2016 from the outpatient clinic in three large tertiary referral centers for brain tumor patients in the Netherlands: Haaglanden Medical Center The Hague, Brain Tumor Center Amsterdam at VU University Medical Center Amsterdam and The Brain Tumor Center at the Erasmus MC Cancer Institute Rotterdam. Consecutive patients visiting the outpatient clinic were screened for eligibility based on information in their medical charts. The inclusion criteria were as follows; 1) adults >18 years of age, 2) histologically confirmed WHO grade II-III glioma, 3) history of epilepsy defined as at least one seizure, except for acute provoked seizures, for which treated with AEDs, 4) clinically and radiologically stable disease for at least 12 months, and 5) seizure freedom for at least 12 months from the date of last surgery, irradiation or chemotherapy cycle, or seizure freedom for at least 24 months from the last seizure when a seizure occurred after the last antitumor treatment. As no formal definition of long-term seizure freedom exists in literature, the current definition (at least >12 months) was based on expert opinion. In case patients fulfilled the inclusion criteria, first the treating neuro-oncologist had to decide if it was safe to withdraw AEDs. If not, the reason for exclusion was registered. In patients in whom it was considered to be safe to withdraw AEDs, the neuro-oncologist and patient needed to make a shared decision on either continuation or withdrawal of AEDs. Patients had to give informed consent prior to inclusion in the study. The medical ethical committees of all participating centers approved the study.

Withdrawal or continuation of AEDs

Patients were included in the withdrawal group in case it was decided to withdraw AEDs, or in the continuation group in case of any objection to withdraw AEDs. The reason for AED continuation was registered separately.

In the withdrawal group, each AED was tapered according to a fixed schedule; a step-wise 50% dose reduction every 2 weeks. In case of using more than one AED, the latest added AED was withdrawn first. In the continuation group, no changes were made in antiepileptic therapy. All participants were evaluated at 3, 6, 12 and 18 months. During these follow-up assessments, data were collected about changes in AED treatment, seizure recurrence,

type and date of seizures, and the date of tumor progression. In case of seizure recurrence, dosages of AEDs were adapted or AEDs were (re)started according to the expertise of the treating neuro-oncologist. The primary outcomes were the decision-making process of AED withdrawal, and the rate of seizure recurrence. Secondary outcomes were type of epilepsy at seizure recurrence, time between inclusion in study and seizure recurrence, and the association between seizure recurrence and tumor progression, WHO grade, time of seizure freedom before inclusion, and time since diagnosis.

Statistical analysis

Baseline patient characteristics and information about seizure and tumor recurrence were reported using descriptive statistics. Differences between groups were assessed with the Chi-Squared test ($\chi 2$) or Fisher's Exact test in case of categorical variables. For continuous variables the independent T-test or Mann-Whitney U test were used, depending on the distribution of the variable. Statistical analyses were performed using SPSS version 23 (SPSS, Chicago, IL). All tests were exploratory, two-tailed, and $P<0.05$ was considered to be statistically significant.

RESULTS

Willingness to withdraw AEDs

A total of 83 patients fulfilled all eligibility criteria. Of these, 71 (86%) were included in the study (Fig. 1).

In 12 patients (14%) the neuro-oncologist had serious objections to AED withdrawal. The reported reasons for exclusion were: a presumed high risk of recurrent seizures due to history of refractory seizures (n=3), severe cognitive dysfunction (n=2), psychologically not stable enough for withdrawal (n=6), and another medical indication for AED use (n=1). Of the 71 patients approved for inclusion by the treating neuro-oncologist, a shared decision to withdraw AED(s) was made in 46 patients (65%) and to continue AED(s) in 25 patients (35%). The most frequently reported reasons to continue AEDs reported by patients were the possibility to lose their driving license in case of a new seizure (n=8), and fear for recurrent seizures (n=8). Four patients reported both the consequences for the driving license as well as fear as reason to continue AED treatment, while five patients did not report any reason.

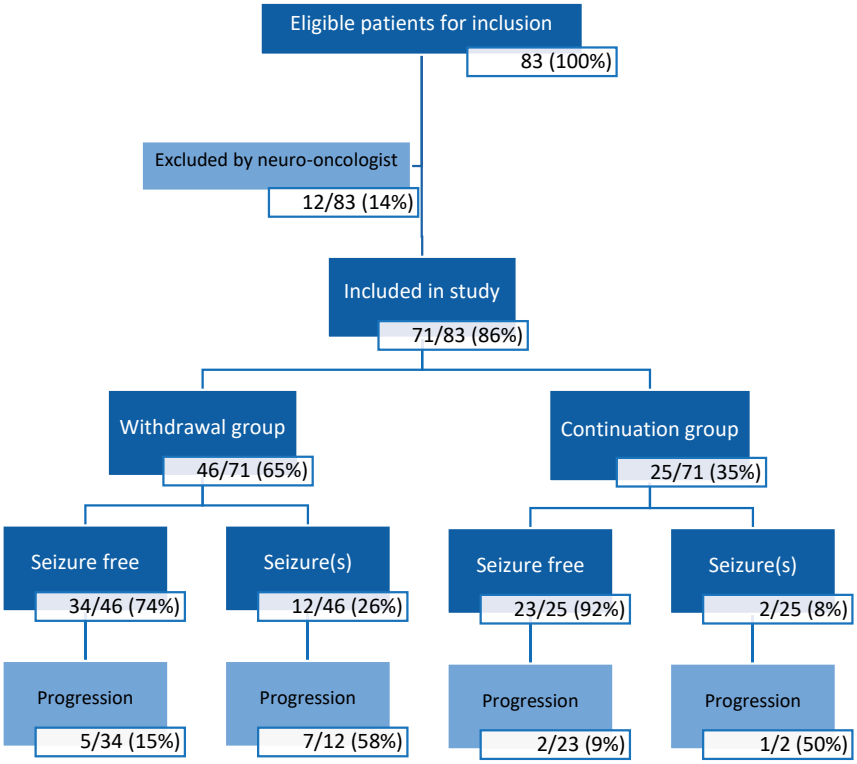

Figure 1. Flowchart patients. Eligibility, AED group and seizure recurrence

Patient and tumor characteristics

The baseline characteristics of the 71 included patients are shown in table 1. Patients in the withdrawal and continuation group were similar with respect to all clinical and sociodemographic variables. The mean age in the withdrawal group was 50 (range: 24-72) years compared to 53 (range: 28-79) years in the continuation group (p=0.24). The withdrawal group and continuation group consisted of 24/46 (52%) and 17/25 (68%) WHO grade II tumors, and 22/46 (48%) and 8/25 (32%) WHO grade III tumors (p=0.20), respectively. In the withdrawal group 18/46 (39%) tumors had loss of 1p/19q versus 11/25 (44%) tumors in the continuation group (p= 0.40). In 20 patients, 15 in the withdrawal and 5 in the continuation group, 1p/19q status was unknown. Before inclusion in the study, 33/71 (46%) patients had focal to bilateral tonic-clonic seizures, 13/71 (18%) had focal seizures, 11/71 (15%) both focal to bilateral tonic-clonic and focal seizures, and for the remaining patients seizure type was unknown (n=14, 20%). Eleven patients (11/46, 24%) in the withdrawal group had at least once tumor progression compared to 3 (3/25, 12%) patients in the continuation group (p=0.12). Most patients used levetiracetam or valproic acid as AED (58% versus 23%), with no differences between groups (p=0.57).

Table 1. Clinical and tumor characteristics

Patient and tumor characteristics	AED withdrawal group (n = 46) (%)	AED continuation group (n = 25) (%)	P - value
Age (mean years, range)	50 (24-72)	53 (28-79)	0.24
Hospital			< .005
VUmc	18 (39)	4 (16)	
HMC	18 (39)	4 (16)	
EMC	10 (22)	17 (68)	
Diagnosed (mean years, range)	7.2 (3.1-19.5)	7.9 (3.8-15.7)	0.12
WHO grade glioma			0.20
Grade II	24 (52)	17 (68)	
Grade III	22 (48)	8 (32)	
LOH 1p/19q			
1p/19q codeleted	18 (39)	11 (44)	0.40
1p/19q not codeleted	13 (28)	9 (36)	
Unknown	15 (33)	5 (20)	
Type epilepsy			0.59
Focal to bilateral tonic clonic	21 (46)	12 (48)	
Focal	10 (22)	3 (12)	
Combination	9 (20)	2 (8)	
Unknown	6 (13)	8 (32)	
Duration seizure-free before inclusion (median years, range)	2.9 (1-12.8)	4.1 (1-20)	0.06
Tumor progression before inclusion			0.12
No progression	35 (76)	22 (88)	
≥ one progression	11 (24)	3 (12)	
Latest antitumor treatment			0.25
Surgery	6 (13)	2 (8)	
Radiotherapy	26 (57)	11 (44)	
Chemotherapy	14 (30)	13 (52)	
AED use			0.57
VPA	10 (22)	6 (24)	
LEV	27 (59)	14 (56)	
LAM	2 (4)	1 (4)	
PHT	3 (7)	0 (0)	
CBZ	3 (7)	4 (16)	
LAC	1 (2)	0 (0)	
Type therapy			0.24
Monotherapy	40 (87)	19 (76)	
Polytherapy (> 1 AED)	6 (13)	6 (24)	

AED antiepileptic drug, *VPA* valproic acid, *LEV* levetiracetam, *LAM* lamotrigine, *PHT* phenytoin, *CBZ* carbamazepine, *LAC* lacosamide

Table 2. Seizure recurrence in relation to tumor progression

	Withdrawal group (n= 46)	Continuation group (n= 25)	P - value
Median duration follow-up (years)	2.2 (range:0.8-3.8)	1.7 (range 0.8-2.9)	0.03
Seizure recurrence, yes	12 (26%)	2 (8%)	0.67
Tumor progression, yes	12 (26%)*	3 (12%)**	0.12

(*) 7/12 with seizure recurrence had tumor progression, (**) 1/2 with seizure recurrence had tumor progression

Follow-up withdrawal group

The median follow-up in the withdrawal group was 2.2 (range: 0.8-3.8) years (Table 2). At the end of follow-up, 12/46 (26%) patients who withdrew AEDs had seizure recurrence (Fig. 1). Of the 12 patients with seizure recurrence, 8 (67%) patients had a focal seizure, 2 patients (17%) had a focal to bilateral tonic-clonic seizure, 1 patient (8%) had a status epilepticus consisting of a focal seizure with impaired awareness, and 1 patient (8%) probably had a nocturnal seizure (Table 3). Seven out of 12 patients (58%) had seizure recurrence within 3 months after the start of withdrawal. In all 12 patients, AED treatment was restarted according to the expertise of the treating neuro-oncologist. Two of these patients had repeated seizures after restarting AED treatment; one patient had one focal seizure while the other patient had frequent focal seizures, even after higher dosages of AEDs. The patient with the status epilepticus was admitted to the hospital for 1 day. Another patient with seizure recurrence during AED withdrawal tapered the AEDs faster than advised. There were no significant differences in WHO grade, time of seizure freedom before inclusion, or time since diagnosis in the group with seizure recurrence compared to the group without seizure recurrence (Table 3). The 1p/19q status of patients without seizure recurrence differed significantly from the patients with seizure recurrence; 44% (15/34) were 1p/19q- codeleted in the group without seizure recurrence versus 25% (3/12) in the group with seizure recurrence (p=0.04).Twenty-six percent (12/46) of patients in the withdrawal group showed tumor progression during the follow-up period. This included 7/12 patients (58%) with seizure recurrence. Of these, three patients had tumor progression within 3 months after seizure recurrence. In the other four patients the interval between tumor progression and seizure recurrence was more than 3 months (range: 4-19) (Table 3). Progression occurred significantly more often in patients with seizure recurrence (7/12, 58%) than in patients without seizure recurrence (5/34, 15%, p=0.006).

Follow-up continuation group

The median follow-up was 1.7 (range: 0.8-2.9) years in the continuation group. In this group, 12% (3/25) showed tumor progression. Two out of 25 (8%) patients in this group had seizure recurrence, which was a focal seizure in both cases. One of the two patients with seizure recurrence had tumor progression 4 months later (Table 3).

Table 3. Patients with seizure recurrence and/or tumor progression in both study groups

	Seizure recurrence and progression					
Type tumor	**1p/19q**	**Group**	**Type seizure**	**Inclusion-seizure (mo)**	**Seizure-progression (mo)**	**Inclusion-progression (mo)**
OD II	Codeleted	Withdrawal	Focal	2.5	0	**2.5**
A III	Intact	Withdrawal	Focal	13	1	**14**
OA II	Unknown	Withdrawal	Focal	5.5	18	**23.5**
A II	Intact	Withdrawal	Focal	4.5	0	**4.5**
A II	Intact	Withdrawal	Focal	2	18	**20**
A II	Unknown	Withdrawal	Focal to bilateral tonic-clonic	4	8.5	**12.5**
A II	Intact	Withdrawal	Focal	1.5	19	**20.5**
OD III	Codeleted	Continue	Focal	6	4	**10**
	Seizure recurrence without progression					
A III	Intact	Withdrawal	Focal	30	-	**-**
OD III	Codeleted	Withdrawal	Nocturnal	3	-	**-**
OA III	Intact	Withdrawal	Focal	2	-	**-**
OD II	Unknown	Withdrawal	Status epilepticus	10	-	**-**
OA II	Unknown	Withdrawal	Focal to bilateral tonic-clonic	21	-	**-**
OD II	Intact	Continue	Focal	18	-	**-**
	Progression without seizure recurrence					
OD III	Intact	Withdrawal	-	-	-	**31**
OD II	Unknown	Withdrawal	-	-	-	**20**
OD III	Unknown	Withdrawal	-	-	-	**7**
OD II	Codeleted	Continue	-	-	-	**11**
OD III	Codeleted	Withdrawal	-	-	-	**26**
A II	Intact	Continue	-	-	-	**17**
A II	Intact	Withdrawal	-	-	-	**12**

OD oligodendroglioma, *A* astrocytoma, *OA* oligo-astrocytoma, *II* WHO grade II, *III* WHO grade III, *mo* months

DISCUSSION

In this study, the decision-making process of patients and doctors to withdraw antiepileptic drugs in clinically and radiologically stable low-grade and anaplastic glioma patients that had long-term seizure freedom (>1 year) was studied, as well as the rate of seizure recurrence after AED withdrawal. This is the first study in which the recurrence rate of seizures in glioma patients is evaluated prospectively. In low-grade as well as anaplastic

glioma patients with longstanding stable disease, neuro-oncologists often question whether continuation of AED use is necessary to remain seizure free after years of seizure freedom. Positive outcome of drug withdrawal may include improvement of cognitive functioning and abolishment of (subtle) side-effects of AEDs such as tiredness, which is especially important in this socially active patient population.[22] Although not all patients were deemed eligible for inclusion by neuro-oncologists, we showed that the majority of the eligible patients (65%) were willing to withdraw AED treatment after long-term seizure freedom.

After a mean follow-up of 2.2 years, the recurrence rate of seizures after AED withdrawal was 26% (12/46). The risk of seizure relapse after AED withdrawal in glioma patients appears to be comparable with the general epilepsy population with non-brain tumor related epilepsy.[23–25] In the general epilepsy population, followed for variable periods of time ranging from 3 months to 23 years, a recurrence rate of 12%-66% was reported.[5,25,26] Predictors for seizure recurrence after withdrawal in the general epilepsy population include AED polytherapy, longer duration of active epilepsy, having experienced seizures after the start of AED treatment, and having an abnormal EEG.[26] EEG testing was not performed in this study, as this is not common in brain tumor-related epilepsy. In this patient population, the results of EEG testing typically do not change the decision to alter or withdraw AEDs.[27]

From this study no definite conclusions can be drawn whether AED withdrawal after long-term seizure freedom in glioma patients is advisable as the seizure recurrence rate is still considerable. When making a shared-decision on possible withdrawal of AEDs, the potential positive effects of AED withdrawal should be weighed against the risk of seizure recurrence. Both neuro-oncologists and patients are, in varying degrees, cautious in withdrawing AEDs due to fear for renewed seizures and the potential consequences such as seizure-related injuries. The psychosocial impact of recurrent seizures is also large; seizures can be embarrassing, obstruct professional careers, make patients more dependent on others, and lead to a temporary loss of a driving license.[26] Indeed, the fear for seizure recurrence and the possible loss of their driving license were the two most important reasons for patients to continue AED treatment in our study. The data presented in this prospective study can be used to better inform patients and neuro-oncologists about the risk of seizure recurrence, helping to make well-considered decisions.

In all but one patient, AEDs were withdrawn in line with the study protocol. In this single patient, who experienced seizure recurrence, AEDs were tapered faster than advised. In theory, this quick tapering might have contributed to the recurrence of seizures, warranting caution in the way AEDs are withdrawn in glioma patients. Unfortunately, one patient in our study was admitted to the hospital with a focal status epilepticus. It is noteworthy that this patient fulfilled the eligibility criteria for inclusion. However, it appeared that this patient had a medical history of status epilepticus (twice). Based on

this finding, it could be argued not to withdraw AEDs in seizure free patients with a history of status epilepticus.

It is of interest that more than half of the patients with seizure recurrence (7/12, 58%) in the withdrawal group had tumor progression during study follow-up. Those seven patients were a median of 6.5 years (range: 3.4-13) ago diagnosed with a glioma and two of them had already tumor progression prior to inclusion in the study. Indeed, three of the seven patients had tumor progression within 3 months after seizure recurrence. In these patients, seizure recurrence might have been an indication for progression of the tumor as there is some evidence available that seizures are a surrogate marker for tumor progression.[28–30] Previously, seizure recurrence or worse seizure control was found to be associated with tumor progression following first-line treatment.[31] Furthermore, the risk of tumor progression in low-grade glioma patients is four times higher in case of seizure recurrence.[32] 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 also possible that the study groups were not well-balanced with respect to risk of progression, although no significant differences were found in the baseline patient- and tumor-related characteristics. Moreover, it might be that the higher amount of tumor progression in the withdrawal group is caused by the discontinuation of AED itself, as conflicting evidence exists that valproic acid might have an antitumor effect as well. Several retrospective studies in patients with glioblastoma have suggested that valproic acid moderately improves survival in glioma patients treated with temozolomide, although a larger meta-analysis could not confirm this.[8, 33–35] Interestingly, within the withdrawal group, the subgroup with seizure recurrence had significantly more often tumor progression and the prognostic more unfavorable intact 1p/19q status. Although based on small numbers, seizure recurrence after withdrawal seems to be associated with the absence of 1p/19q codeletion, and is also related to a higher risk of tumor progression within this cohort. In this study, the risk of seizure recurrence after withdrawal was not associated with WHO grade, time after diagnosis, or duration of seizure freedom.

Given the inclusion criteria for our study, with stability of disease for at least a year as a major criterium, we purposely left out glioblastoma patients who have a limited prognosis. For the non-glioblastoma patients, we think that both grade II and grade III patients are of interest, since both low-grade and anaplastic patients with a relatively long survival might specifically benefit from withdrawal of antiepileptic drugs.

Due to the small numbers, a multivariable analysis to assess which factors were independently associated with seizure recurrence could not be performed.

Due to ethical objections to randomize patients with regard to AED withdrawal, a prospective observational study design was chosen, including both the decision-making process and an evaluation of seizure outcome. For the decision to withdraw AEDs, no specific decision-making model was used. Instead, the process depended on the preferred

communication method of the neuro-oncologists.[36, 37] Although both study groups seem to be well-balanced in both patient- and tumor-related characteristics, a risk exists for confounding-by-indication due to the non-randomized study design, which might have influenced the results.

Although not systematically assessed, we did receive positive responses from patients about the withdrawal of their medication. Patients subjectively reported a better concentration or mood. Nevertheless, it would have been interesting to evaluate the impact of seizure recurrence on patients' wellbeing, and to ask patients whether being medication-free outweighs experiencing a new seizure.

CONCLUSION

Neuro-oncologists and glioma patients are now better informed about the risk of seizure recurrence after AED withdrawal. The results presented here can be used in shared decision-making during consultations. Our advice would be to withdraw AEDs only in carefully selected patients. The possible negative side effects of AEDs, the effect of antitumor treatment on seizure frequency, and patients' requests to withdraw medication suggest that an attempt to withdraw AEDs can be considered in patients with low-grade or anaplastic glioma experiencing long-term seizure freedom.

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PART II

The impact of antitumor treatment on clinical and radiological outcome


4

Interobserver variability in the radiological assessment of magnetic resonance imaging (MRI) including perfusion MRI in glioblastoma multiforme

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Abstract

Background: Conventional magnetic resonance imaging (MRI) has limited value for differentiation of true tumor progression and pseudoprogression in treated glioblastoma multiforme (GBM). Perfusion weighted imaging (PWI) may be helpful in the differentiation of these two phenomena. Here we assess interobserver variability in routine radiological evaluation of GBM patients using MRI, including PWI.

Methods: Three experienced neuroradiologists evaluated MR scans of 28 GBM patients during temozolomide chemoradiotherapy at three time points: preoperative (MR1) and postoperative (MR2) MR scan and the follow-up MR scan after three cycles of adjuvant temozolomide (MR3). Tumor size was measured both on T1 post-contrast and T2-weighted images according to the Response Assessment in Neuro-Oncology criteria. PW images of MR3 were evaluated by visual inspection of relative cerebral blood volume (rCBV) color maps and by quantitative rCBV measurements of enhancing areas with highest rCBV. Image interpretability of PW images was also scored. Finally, the neuroradiologists gave a conclusion on tumor status, based on the interpretation of both T1- and T2- weighted images (MR1, MR2 and MR3) in combination with PWI (MR3).

Results: Interobserver agreement on visual interpretation of rCBV maps was good (Kappa = 0.63) but poor on quantitative rCBV measurements and on interpretability of perfusion images (intraclass correlation coefficient 0.37 and Kappa = 0.23, respectively). Interobserver agreement on overall conclusion of tumor status was moderate (Kappa = 0.48).

Conclusion: Interobserver agreement on the visual interpretation of PWI color maps was good. However, overall interpretation of MR scans (using both conventional and PW images) showed considerable interobserver variability. Therefore, caution should be applied when interpreting MRI results during chemoradiation therapy.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumor in adults. Standard treatment consists of maximal surgical resection followed by high-dose radiotherapy (60 Gy in 30 fractions of 2 Gy) with concurrent oral chemotherapy (temozolomide [TMZ]) followed by six adjuvant courses of TMZ. This treatment regimen has increased median overall survival (from 12.1 to 14.6 months) and the 2- and 5- year survival rates compared to treatment with radiotherapy alone.[1;2] With the growing number of additional treatment options, it has become increasingly important to identify early predictors of tumor response and to differentiate treatment response from progression. Serial magnetic resonance imaging (MRI) after standard multimodality treatment in high-grade glioma shows a non-tumoral increase of contrast-enhancement on the first post-radiation MRI in 20-30% of patients.[3] This treatment related reaction, or pseudoprogression (PsPD), is a phenomenon of subacute imaging changes subsequent to radiochemotherapy, which may suggest progression, although it resolves spontaneously without change of therapy. PsPD is especially seen after radiotherapy with concurrent and adjuvant TMZ and occurs most frequently within 3 months of concurrent chemoradiation therapy.[4-7] Obviously, increasing post-contrast enhancement during or after treatment may also be due to tumor progression. The differentiation of PsPD and tumor progression is of major clinical importance, as true tumor progression indicates treatment failure and a need to change therapy, whereas post-treatment radiation effects suggest success of the current treatment. Limitations of conventional MRI have led to the search for new imaging modalities for accurate tumor assessment and for differentiation of true tumor progression and PsPD in glioma patients. Dynamic susceptibility contrast-enhanced perfusion-weighted imaging (DSC PWI) is a technique that can provide physiological information about vascular endothelial proliferation and microvessel density (vascularity) and angiogenesis.[8;9] The cerebral blood volume (CBV) can be calculated from dynamic measurements of changes in signal intensity during first-pass DSC MRI after administration of a bolus of paramagnetic contrast material and is expressed in (quantitative) relative (r) CBV measurements.[10] These rCBV measurements are expressed relative to the normal appearing contralateral white matter and are measured on the unprocessed gray scale images (Fig. 1). Another routinely used way of analyzing perfusion data is by (subjective) visual inspection of the rCBV perfusion color maps (Fig. 1).[11] DSC PWI has been used for grading, histological differentiation and prediction of prognosis in glioma patients.[12;13,14-17] Reliable response assessment also requires acceptable test reproducibility, and information on reproducibility of MRI parameters is of great clinical importance. A previous study in glioma patients demonstrated that the radiological assessment of response to chemotherapy based on conventional MRI alone is susceptible to considerable interobserver variability (intraclass correlation coefficient (ICC) 0.55).[18] To our knowledge, there is no data in literature on the reproducibility of the visual interpretation of DSC PW

images in brain tumor patients. The goal of the current study is to assess interobserver variability in the routine radiological evaluation of MRI including DSC PWI and conventional MRI in GBM patients treated with TMZ chemoradiotherapy.

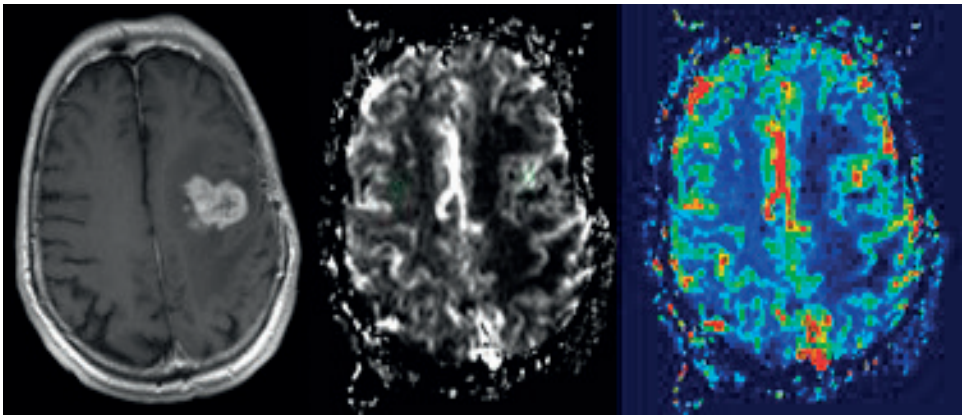

Figure 1. Images obtained in a 73-year old patient with pathologically proven glioblastoma treated with temozolomide chemoradiation
a: axial post-contrast T1-weighted image shows a contrast enhancing lesion seen in the left hemisphere. b: rCBV values derived from unprocessed gray scale perfusion image. c: coloured perfusion map, the CBV map shows increases of the perfusion pixel values in the corresponding area with the contrast-enhancing lesion

METHODS

Patients

This retrospective study included patients with histologically proven GBM who were treated in our center between January 2013 and December 2013. Patient data were collected from the medical records. All patients had undergone tumor resection and had been treated with concomitant and adjuvant TMZ chemoradiation. Patients who had at least finished three adjuvant cycles of TMZ and had undergone adequate MR imaging were included. All patients had undergone conventional MRI preoperatively (MR1) and postoperatively (MR2), with post-operative MRI performed within 48 h after operation. During follow-up, after three adjuvant cycles of TMZ, patients had routinely undergone conventional MRI and additionally DSC perfusion MR imaging (MR3). The medical ethical review board of the Medical Center Haaglanden approved the study.

MR imaging protocol

Conventional MRI

Magnetic resonance imaging studies were performed with a 1.5 Tesla system (Siemens, Symphony, Erlangen, Germany) and a 12-channelled phased array head coil. Standard

doses of 0.1mmol/kg gadolinium were used for the contrast-enhanced images. The imaging protocol consisted of pre-contrast T1-weighted, T2-weighted and fluid attenuated inversion recovery (FLAIR) images followed by PWI/DSC MRI data and finally post-contrast axial T1-weighted images.

Dynamic susceptibility-weighted contrast-enhanced perfusion MRI

Dynamic susceptibility contrast-enhanced MRI scans were acquired with a gradient-echo echoplanner imaging (GE-EPI) technique during the first pass of a standard dose bolus of gadolinium contrast. Before the PWI sequence, a pre-bolus (0,1 ml/kg) of gadolinium was injected to reduce the variance of rCBV by contrast leakage.[19] The time between pre-bolus and the main perfusion was 5 minutes. Imaging parameters were TR 2400 ms, TE 46 ms, flip angle 70°, Matrix 128 x 128, 6 mm slice thickness 10% gap, 20 slices, field of view 225 mm, fat saturation, EPI factor 112. During 50 consecutive EPI scans lasting 2 min, with a 10 s injection delay for baseline signal intensity measurements, an intravenous bolus injection of 20 ml of gadolinium at a flow rate of 4 ml/s followed by a 20 ml saline flush was administered. DSC data were transferred to a Siemens Numaris 4 workstation for post-processing on which CBV values were displayed as a color coded map, using the standard Siemens software available on the workstation.

Evaluation and interpretation of MR images

Three certified and experienced neuroradiologists (REH, BFWK, GJL) independently reviewed all consecutive MR scans (MR1 - MR3) of individual patients after a consensus meeting. All MR scans were assessed anonymously on a PACS workstation, the neuroradiologists being blinded for clinical data. The image interpretability of the perfusion scan was scored by the neuroradiologists and labeled as good or poor. When the perfusion MRI interpretability was scored as poor, the reason for this score was given. Thereafter, tumor size measurements on the T1 post-contrast and T2-weighted images of MR2 and MR3 were performed, and classified in tumor response categories (categorizing complete response, partial response, progressive disease, or stable disease) based on the (radiological) Response Assessment in Neuro-Oncology (RANO) criteria, in which new lesions were taken into account as well and tumor size was defined as the product of the two largest perpendicular transverse T1 enhancing or T2 tumor diameters.

The PWI scan was evaluated by (subjective) visual inspection of the rCBV map together with the post-contrast conventional MR series, and by a quantitative rCBV measurement in a region of interest (ROI) which was placed by the examiner in the contrast-enhanced area of maximal perfusion. The visual score was based on presence or absence ("black hole") of highly vascularized areas within the contrast-enhanced lesion relative to the contralateral hemisphere and irrespective of areas indicative of necrosis, and was defined as high rCBV versus low rCBV, reflecting viable tumor tissue or treatment related effects, respectively, or as not assessable in case of no visible residual tumor on T1 post-contrast.

The quantitative rCBV measurements were expressed relative to the normal appearing contralateral white matter and were measured on the unprocessed gray scale images. The neuroradiologists inspected the raw perfusion images and the conventional MR images simultaneously. For quantitative measurements, each observer placed a ROI on PW images within the enhancing areas containing the region with highest tumor perfusion. The CBV values of each ROI were recorded and rCBVs were calculated and used for interobserver agreement analyses. The size of each ROI was at least 40 mm^2. No quantitative perfusion measurements were performed when the lesion was too small for measurement or when the image interpretability of the perfusion MRI was labeled as poor. Finally, the neuroradiologists gave an overall conclusion on tumor status based on the post-contrast T1- and T2-weighted images of MR1, MR2 and MR3, in combination with the perfusion data of MR3, categorizing definite progressive disease, possible progressive disease, possible stable, or definite stable disease.

Statistical analysis

The interobserver variability was assessed by using Kappa statistics and ICCs. This is a true index of agreement between observers. Kappa values were calculated for categorical items and for continuous variables ICCs were calculated. The interobserver variability is derived from a two-way mixed analysis of variance with subjects treated as a random effect and observer treated as a fixed effect. The strength of agreement was categorized as follows: ICC/Kappa value ≤ 0.40 poor to fair agreement; 0.41 - 0.60 moderate agreement; 0.61 - 0.80 substantial agreement; 0.81 - 1.00 almost perfect agreement.[20]

RESULTS

Patient characteristics

Thirty-eight patients had been treated with TMZ chemoradiation between January 2013 and December 2013, of whom 28 were included. In 10 patients adequate MRI including PW images were missing. The mean age at diagnosis was 56 years.

Interobserver agreement analyses

Results of interobserver agreement analyses are demonstrated in Table 1. All ROIs compromised an area of 40-70 mm^2. 42% of the PW images had a low perfusion and 58% a high perfusion. The interobserver agreement on the visual interpretation of the PWI color maps (high versus low rCBV) reflecting viable tumor tissue or treatment related effects was good (Kappa = 0.63). Regarding quantitative rCBV measurements, of all PWI evaluations (N = 3x28 = 84), 12 were missing; in 9 PWI evaluations there was no visible residual tumor on T1 post-contrast, and in 3 PW images rCBV was not measured due to poor image interpretability. The interobserver agreement on quantitative rCBV measurements (N = 72)

of perfusion MRI was poor to fair (ICC = 0.37). The Kappa for the assessment of the image interpretability of the perfusion MRI was 0.23, indicating poor interobserver agreement. Several reasons were given for the poor image interpretability of the perfusion MRI, including close proximity to the cortex, blood (vessels) or skull base. The reproducibility of measuring changes in tumor size on T1 and T2 weighted imaging was relatively good (ICC = 0.80 and 0.64, respectively), whereas the interobserver agreement on response classification according to the (radiological) RANO criteria was only moderate (Kappa = 0.56). Finally, the interobserver agreement on overall conclusion on tumor status based on T1- and T2-weighted images including perfusion MRI was moderate as well (Kappa = 0.48). When the four response categories of the overall conclusion (definite progressive disease, possible progressive disease, possible stable disease and definite stable disease) were dichotomized into progressive disease versus stable disease, the interobserver agreement was slightly better (Kappa = 0.62, 95% CI 0.40-0.83), indicating substantial agreement. Selecting only those perfusion MR scans labeled as having good image interpretability by all three neuroradiologists (N = 15/72), the interobserver agreement on visual interpretation of the perfusion maps is slightly better (Kappa = 0.72, 95% CI: 0.50-0.94) and the overall conclusion on tumor status remains moderate (Kappa = 0.59, 95% CI: 0.40-0.80). The neuroradiologists agreed on overall conclusion on tumor status in 87% when the perfusion image interpretability was interpreted as good. When one of the three neuroradiologists labeled the perfusion MRI as poor image interpretability, full interobserver agreement dropped to only 54%.

Table 1. Interobserver variability of MRI parameters including dynamic susceptibility contrast-enhanced perfusion imaging in glioblastoma patients treated with temozolomide chemoradiation

Interobserver variability	Method	Result	P - value	95% CI
	Visual score (pMRI)	0.63	<0.0001	0.46-0.81
Kappa	Quality perfusion (pMRI)	0.23	0.019	0.04-0.43
	RANO (cMRI)	0.56	<0.0001	0.41-0.70
	Overall conclusion (pMRI + cMRI)	0.48	<0.0001	0.34-0.61
	rCBV (pMRI)	0.37	0.003	0.10-0.63
ICC	change tumor size T1 (cMRI)	0.80	<0.0001	0.67-0.90
	change tumor size T2 (cMRI)	0.64	<0.0001	0.44-0.80

CI, confidence interval; ICC, intraclass correlation coefficient; pMRI, perfusion MRI; cMRI, conventional MRI.
Interpretation value ICC/kappa: ≤ 0.40: poor/fair agreement; 0.41 - 0.60 moderate agreement; 0.61 - 0.80: good agreement; 0.81 - 1.00: very good agreement

DISCUSSION

In routine neuro-oncology practice, differentiating tumor progression from PsPD is a major diagnostic challenge. PWI may be helpful in the differentiation of these two phenomena. There are different ways of interpreting perfusion data, with the visual inspection method of the colored CBV maps being widely used in daily practice. In the current study, our interest was in the reproducibility of this qualitative method of interpreting perfusion data by neuroradiologists, and additionally the reproducibility of other conventional and perfusion MRI techniques was assessed. It was found that the interobserver agreement on perfusion image interpretability was rather disappointing in the current study, indicating that the neuroradiologists disagreed on whether perfusion images could be taken into account in the interpretation. Discrepancies in interpretability of the perfusion MR images came up as well during the review process of the MR scans in the overall conclusion on tumor status. Increase in contrast enhancement on post-contrast T1-weighted images in combination with low rCBV values on perfusion images, for example, suggests PsPD rather than tumor progression. When the neuroradiologist labeled the perfusion MRI as having poor interpretability, this perfusion MRI was not taken into account in the analyses and the radiologist concluded progression instead of PsPD. It is important to notice that rCBV maps have a lower resolution than conventional MR images, which may give rise to controversy especially when the contrast enhancement is in close proximity to structures of the brain with higher rCBV values, like the cortex and blood vessels. The reproducibility of the evaluation of perfusion MR images increased when all neuroradiologists agreed on good interpretability of the images.

Interobserver agreement on quantitative rCBV measurements was only poor, which can possibly be explained by the lack of experience of the neuroradiologists to perform such quantitative rCBV measurements in clinical practice and, additionally, by intratumor heterogeneity at cellular and molecular level, possibly leading to different perfusion region results. Since the neuroradiologists are not trained for the quantitative analysis, no standardized method was used where to place the ROI in the tumor. The observers outlined different areas of the tumor, but the variance of rCBV measurement was high within the same tumor, so ROI placement in different areas of the tumor gave a variance in the rCBV measurements. To avoid the variance in ROI placement a protocol for ROI size and placement should be used in future research. Aforementioned observation would ask for stricter radiological criteria whether or not to include perfusion MR images in the overall conclusion on tumor status. As such, a statement about image interpretability of PWI data should be included in every radiological report.

In the current study the single value measurement of rCBV is used to evaluate interobserver variability, but recently published research suggested that longitudinal trends in rCBV may be more useful than one absolute rCBV in distinguishing PsPD from progression in chemoradiation treated high-grade glioma patients.[19] This additional value of longitudinal

trends in rCBV is beyond the scope of this manuscript, but the interobserver variability of measured change in rCBV between two time points including the effect on response assessment might be of interest as well. Contrast extravasation in DSC MRI increase inaccurate estimates of rCBV. To reduce the variance of contrast leakage a pre-bolus of gadolinium was given. In this study no additional post-processing techniques were used. Of particular interest also are as the data on interobserver agreement between measurements of (conventional) tumor size and classification according to the radiological RANO criteria. A discrepancy between the observed good agreement on measurements of change in tumor size on post-contrast T1-and T2-weighted images (ICC = 0.80 and 0.64, respectively) and only moderate agreement on response classification according to the radiological RANO criteria (Kappa = 0.56) was observed. This discrepancy may (partially) be explained by the method for calculating Kappa. When calculating Kappa statistics, the agreement occurring by chance, or the *a priori* chance, is taken into account. A category commonly used, in this case progression, may therefore lead to an underestimation of interobserver agreement. Besides, the artificial subdivision of percentage increase or decrease of tumor size in only four response categories may by itself lead to variability. A minor difference in measured change in tumor size of a few percentages, for example, can make a distinction between two response classes. Another potential cause for the difference in interobserver agreement is that, irrespective of tumor size measurements, the interpretation of new enhancing lesions may be reason for disagreement. In 2003 Vos *et al*. found that the interobserver variability of the radiological assessment of response to chemotherapy in patients with recurrent glioma was moderate for change in tumor size (ICC = 0.50) as well as for the Macdonald response criteria (weighted Kappa = 0.55), taking new lesions into account.[18]

In conclusion, in this study the reproducibility of visual interpretation of perfusion MR scans by neuroradiologists was good. However, the overall interpretation of MR scans (including perfusion and conventional images) on tumor status was prone to considerable interobserver variability. This can partly be explained by disagreement of neuroradiologists regarding perfusion MR image interpretability, resulting in varying contribution of perfusion imaging data in overall interpretation. Perfusion MRI may provide supplemental information in addition to conventional MR images and may be especially helpful when the perfusion images are not disturbed by close proximity of the cortex, blood (vessel) and skull base. Optimization of the radiological interpretation of MR perfusion data is necessary, and requires further research. Further, given the rather high interobserver variation found in our study, the radiological report should be only part of the overall judgement on the clinical status of the patient.

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5

Visual inspection of MR relative cerebral blood volume maps has limited value for distinguishing progression from pseudoprogression in glioblastoma multiforme patients

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Abstract

Background: We examined whether visual interpretation of relative Cerebral Blood Volume (rCBV) colour maps made with dynamic susceptibility-weighted perfusion MRI, can reliably distinguish progressive disease (PD) from pseudoprogression (PsPD) in glioblastoma patients during treatment with temozolomide chemoradiation.

Methods: Magnetic resonance (MR) perfusion-weighted images were evaluated based on visual inspection of rCBV maps. Sensitivity and specificity was calculated to assess if rCBV can reliably differentiate between PD and PsPD, during standard chemoradiation therapy.

Results: Evaluation of dynamic susceptibility-weighted contrast-enhanced perfusion MRI by visual interpretation of rCBV maps did not differentiate PD from PsPD (sensitivity=72%; specificity=23%). Furthermore, the interpretation of the rCBV maps had no prognostic value regarding survival.

Conclusions: Qualitative rCBV-based dynamic susceptibility-weighted contrast-enhanced perfusion MRI does not reliably differentiate PD from PsPD, and is not prognostic for survival in glioblastoma patients during treatment with temzolomide chemoradiation.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and most aggressive primary malignant brain tumor in adults. The standard treatment at initial presentation consists of maximal surgical resection followed by high-dose radiotherapy with concurrent oral chemotherapy (temozolomide [TMZ]) followed by six adjuvant courses of TMZ. There is no universally accepted standard second-line treatment for recurrent GBM, and for patients in (relative) good clinical condition, reoperation, reirradiation, alternative cytotoxic and targeted therapy regimens can be considered possible treatment options if a relapse is suspected.[1-3] Response monitoring using MRI after standard multimodality treatment in GBM patients has shown that 20-30% of patients develop an increase of contrast-enhancement on their first post-radiation MRI, in the absence of tumor progression, so-called pseudoprogression (PsPD).[4] This phenomenon may occur with or without new or progressive clinical symptoms. It is thought to be a treatment related reaction, due to alterations of the blood- brain barrier. In general, it has a self-limiting course without necessity to change therapy. Usually, PsPD occurs within 3 months after concurrent chemoradiation therapy.[5-8] Currently available data suggest a better clinical outcome in patients with PsPD, apparently due to a strong correlation with O6-methylguanine-DNA methyltransferase (MGMT) status, compared with patients with true early tumor progression and compared to patients with no PsPD, however, a significant survival benefit has yet to be established in larger patient cohorts.[5,8-11]

Evaluation of conventional MR imaging may be insufficient in differentiating PsPD from progressive disease (PD, i.e. tumor progression) in GBM patients. This may have important consequences for both expected prognosis and decisions on treatment adjustments.[4,6,12] Advanced MRI techniques may offer a noninvasive alternative for more accurate assessment of tumor response during treatment. One of these techniques is dynamic susceptibility-weighted contrast-enhanced (DSC) perfusion MRI, which 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.[13-15] It has been used for tumor grading, distinction of tumor progression versus treatment-induced changes and for prediction of survival in glioma patients, although larger studies are still needed to assess its utility and reproducibility.[16-27] Many studies have used quantitative rCBV analysis, while visual assessment of rCBV color maps is currently routinely used in daily practice. In brain metastasis, the visual assessment of perfusion-weighted imaging (PWI) analysis was unfortunately not reliable enough to predict (pseudo)progression.[28]

In clinical practice, radiological progression in combination with a high rCBV on perfusion MRI may in some patients result in a change of the treatment regimen based on presumed tumor progression. The radiological and clinical development during follow-up of these patients is therefore, highly relevant. The aim of the current study was to assess the value of routine assessment of rCBV color maps in GBM, to differentiate PsPD from PD.

METHODS

Study Population

Patients included in this study were treated between January 2009 and December 2012 at the Department of Neuro-Oncology, Haaglanden Medical Center (The Hague, The Netherlands). Patients were eligible if they were diagnosed with histologically proven primary GBM (World Health Organization classification grade IV), were aged ≥18 years and had been treated with postoperative radiotherapy (60 Gy in 30 fractions of 2 Gy during 6 weeks) with concurrent TMZ (75mg/m^2/day), followed by (intention to treat with) six adjuvant TMZ cycles at a dose of 150-200 mg/m2 in a 5/28 schedule, according to the Stupp protocol.[29] Patients were included who had had (at least) finished the concurrent phase and had undergone MRI including PWI at the time of first radiological tumor progression or within 2 months thereafter. Radiological tumor progression was based on the Response Assessment in Neuro-Oncology (RANO) criteria (time of progression, T_p).[12] Based on the presumed diagnosis made by their treating neurooncologist at Tp, patients either continued or discontinued their initial treatment. Information was obtained concerning patient demographics (age, gender and survival), the type and extent of surgery performed, MGMT methylation status, Karnofsky Performance Status, time of suspected radiological and clinical progression, corticosteroid (dexamethasone) use and treatment regimens. Relative changes in (conventional) tumor measurements were used to assess tumor response or progression at follow-up MRI 3 months after Tp (T_{FU}). Research was conducted according to the principles of the Declaration of Helsinki, and according the regulations of the local medical ethics committee.

Definition of outcome variables

Suspected Radiological progression at T_p and radiological progression at T_{FU} (in comparison with T_p) were based on the RANO criteria[12], defined by an increase in size of the contrast-enhancing lesion and the T2/fluid-attenuated inversion recovery lesion and/or the presence of new contrast-enhancing lesion(s).

Progressive Disease (PD; i.e. tumor progression) was defined by either histologically proven tumor progression within 4 months after T_p, death within 4 months after T_p not caused by other (comorbid) conditions, or further radiological progression (on conventional MR imaging) at T_{FU} compared to T_p.

Pseudoprogression (PsPD) was defined by either pathological confirmation of necrosis without presence of viable tumor cells obtained by re-resection within 4 months after T_p, or stable or decreased (conventional) MRI abnormalities at T_{FU} compared to T_p.

Overall survival (OS) was defined as the interval between the date of initial surgery or biopsy and date of death.

Progression free survival (PFS) was defined as the interval between date of initial surgery or biopsy and date of clinical progression (derived from the RANO criteria, based on clinical status and use of corticosteroids).

MR Imaging

MRI studies were performed with a 1.5 Tesla system (Siemens, Symphony, Erlangen, Germany) and a 12-channel phased array head coil. Standard doses of 0.1 mmol/kg gadolinium were used for the contrast-enhanced images. The imaging protocol consisted of precontrast conventional axial T1-weighted, T2-weighted and fluid attenuated inversion recovery images followed by perfusion- weighted imaging/DSC MRI data and finally postcontrast axial T1-weighted images. DSC perfusion MR scans were acquired with a gradient-echo echoplanar imaging (GE-EPI) technique during the first pass of a standard dose bolus of gadolinium contrast. Before the PWI sequence, a prebolus (0,1 ml/kg) of gadolinium was injected to correct for leakage. Imaging parameters were: TR 2400ms, TE 46 ms, flip angle 70º Matrix 128 2, 6mm slice thickness 10% gap, 20 slices, field of view (FOV) 225 mm, fat saturation, EPI factor 112. During 50 consecutive EPI scans lasting 2 min, with a 10 s injection delay for baseline signal intensity measurements, an intravenous bolus injection of 20 ml of gadolinium at a flow rate of 4 ml/s followed by a 20 ml saline flush was administered. DSC data were transferred to a Siemens Numaris 4 workstation for postprocessing on which CBV values were displayed as a color-coded map. Conventional tumor size was defined as the product of the two largest perpendicular transverse-enhancing tumor diameters measured on a postcontrast T1-weighted image. MR perfusion-weighted rCBV color maps were independently scored based on subjective evaluations by two experienced neuroradiologists (REH, GJL), who were blinded to the clinical information and outcome. Discordant results between the radiologists were resolved by consensus. Adapted from Hoefnagels *et al*., we determined a subjective visual score of the rCBV color map.[30] For a reliable interpretation, the rCBV map was evaluated beside the conventional MR images to detect and account for magnetic susceptibility, motion, bolus timing and other artifacts. On visual inspection, lesions with a relative high rCBV compared to the contralateral normal appearing white matter and irrespective of areas indicative of necrosis were scored as 'high rCBV'. This was based on the presence of nodular highly vascularized areas within the contrast-enhanced lesion. In the absence of any high angiogenic intratumoral area a 'low rCBV' was scored.

Statistical methods

Differences between categorical factors were assessed by the Chi-Squared test (χ^2). For the association between continuous and categorical (nominal) factors, the Mann-

Whitney-U test was used. OS and PFS were evaluated according to the Kaplan-Meier method. The Log-Rank test was used to compare OS and PFS between patient groups (PD vs PsPD, and high vs low rCBV). Univariable and multivariable survival analyses were conducted using Cox proportional hazard models to identify prognostic factors for OS and PFS. Sensitivity and specificity were calculated to examine if the subjective rCBV map could reliably classify the clinical diagnosis (PD or PsPD). All data analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (NY, USA). P-values less than 0.05 were considered to be statistically significant.

RESULTS

Patients Characteristics

Fifty-eight out of 200 consecutive adult patients with newly diagnosed GBM and adequate MR follow-up including PWI, who had been treated with concurrent TMZ chemoradiation followed by adjuvant TMZ between January 2009 and December 2012 were enrolled in the present study (Table 1). At the time of first increase of contrast-enhancement after concurrent chemoradiation (T_p), 23/58 (40%) patients continued their treatment with adjuvant TMZ because of suspected PsPD (based on both conventional and perfusion MR imaging and clinical performance). The remaining 35/58 (60%) patients were diagnosed with presumed PD and received a new type of therapy. A re-resection was performed in 12/58 (21%) patients. In total, 6/58 (10%) patients received no further treatment at the time of T_p: 2/6 patients did not continue current treatment because of ongoing thrombocytopenia and only underwent follow-up imaging, and in 4/6 patients there were no more treatment options due to worsening of their clinical condition. The majority of all patients (39/58; 67%) reached $T_p \leq 3$ months after completion of concurrent chemoradiation. T_p preceded clinical progression in 47/58 (81%) patients, with a median difference of 4 (range: 0-25) months.

PD and PsPD on follow-up

During follow-up, PD was diagnosed in 32/58 patients (55%), and PsPD was diagnosed in 26/58 patients at Tp (45%). Regarding the 32 patients with PD, 16 (50%) showed increase of the enhancing lesion or the appearance of new enhancing lesion(s) on T_{FU}, 10/32 patients (31%) had histologically proven tumor progression and 6/32 (19%) patients died within 4 months of T_p (not caused by other comorbid conditions) (Table 2). At T_{FU}, 24/26 (92%) patients demonstrated partial response or stable disease, based on the change in enhancing tumor size, and in 2/26 (8%) patients pathological examination revealed findings associated with treatment-related necrosis without viable tumor cells, resulting in 26 patients diagnosed with PsPD (Table 2). A decrease of Karnofsky performance status was found in 24/58 patients (41%). Of these 24 patients, 9 patients (38%) demonstrated

PsPD and 15 (63%) demonstrated PD. From the patients classified as having PsPD, 13/26 (50%) had a methylated MGMT promoter, whereas only 7/32 patients (22%) who were classified as having PD had a methylated MGMT promoter (p=0.08). Further analysis revealed that a majority of patients with PsPD (17/26; 65%) showed an early T_p (≤ 2 months), compared with PD patients (10/32 patients (31%), p=0.01). Only five of 26 PsPD patients developed PsPD after 3 months.

Table 1. Patient characteristics population (n=58)

Characteristic	
Male/female (n)	41/17
Median age at baseline (y)	60 (range 36-78)
Median KPS at baseline	90 (range 50-100)
Corticosteroid therapy at baseline (n)	
Yes	8 (14%)
No	47 (81%)
Missing	3 (5%)
Biopsy or resection at primary diagnosis (n)	
Biopsy	4 (7%)
Resection	54 (93%)
MGMT promoter methylation status (n)	
Methylated	20 (35%)
Unmethylated	30 (52%)
Missing	8 (14%)
Median number of adjuvant TMZ courses	6 (range 0-6)
T_p (n)	
0-3 months after concurrent chemoradiation	39 (67%)
3-6 months after concurrent chemoradiation	6 (10%)
>6 months after concurrent chemoradiation	13 (22%)
T_{fu} (n)	44 (76%)
Median tumor size at T_p (mm^2)	1642 (range 189-4025)
Therapy after T_p (n)	
Reoperation	12 (21%)
Reirradiation	1 (2%)
Chemotherapy	
TMZ	23 (40%)
Other	11 (19%)
Other	
Bevacizumab monotherapy	4 (7%)
Cediranib monotherapy	1 (2%)
None	6 (10%)

KPS Karnofsky Performance Status, *MGMT* O^6 –methylguanine-DNA methyltransferase, *TMZ* Temozolomide, T_p Time of first suspected radiological progression after chemoradiation, T_{fu} follow-up 3 months after Tp

Table 2. Criteria for Progressive Disease (PD) or Pseudoprogression (PsPD) at T_{FU} (n=58)

Progressive Disease (n=32)	**n(%)**
Radiological progression [a]	
Increase in size of enhancing tumor	13 (41%)
New lesions on post-contrast T1-weighted imaging	3 (9%)
Histological proven tumor [b]	10 (31%)
Death [b]	6 (19%)
Pseudoprogression (n=26)	
Radiological partial response (>50% decrease) [a]	5 (19%)
Radiological stable disease (0-50% decrease)[a]	19 (73%)
Histological proven necrosis [b]	2 (8%)

a) Relative change in tumor size based on the two largest perpendicular transverse-enhancing tumor diameters: T_{FU} compared with T_P
b) within 4 months after radiological progression (T_p)
Tfu: follow-up 3 months after Tp; Tp: time of progression

MR Perfusion Analysis

Concordant perfusion image results were found in 86% of the perfusion images (50/58) before the neuroradiologists reached consensus. On visual inspection of rCBV color maps, 43/58 lesions (74%) showed relative hypervascularity suggestive for viable tumor (high CBV) and 15/58 lesions (26%) showed no high vascularized intratumoral areas (low CBV), suggesting no viable tumor. No significant difference (p=0.66) in rCBV was found between patients with PsPD and PD; high rCBV was found in 20/26 patients with PsPD (77%) and in 23/32 (72%) of the patients with PD. MR images of a case of PD are shown in Figure 1, and of a case of PsPD in Figure 2. Sensitivity and specificity analyses were performed to calculate whether the rCBV color map in itself is capable of predicting PD. This showed a sensitivity and specificity of 72% and 23%, respectively. When the subgroup of patients with a histologically confirmed diagnosis of PD (n= 10/32) or PsPD (n=2/26) were evaluated, analysis of the subjective rCBV maps demonstrated a slightly better sensitivity (70%) and specificity (50%).

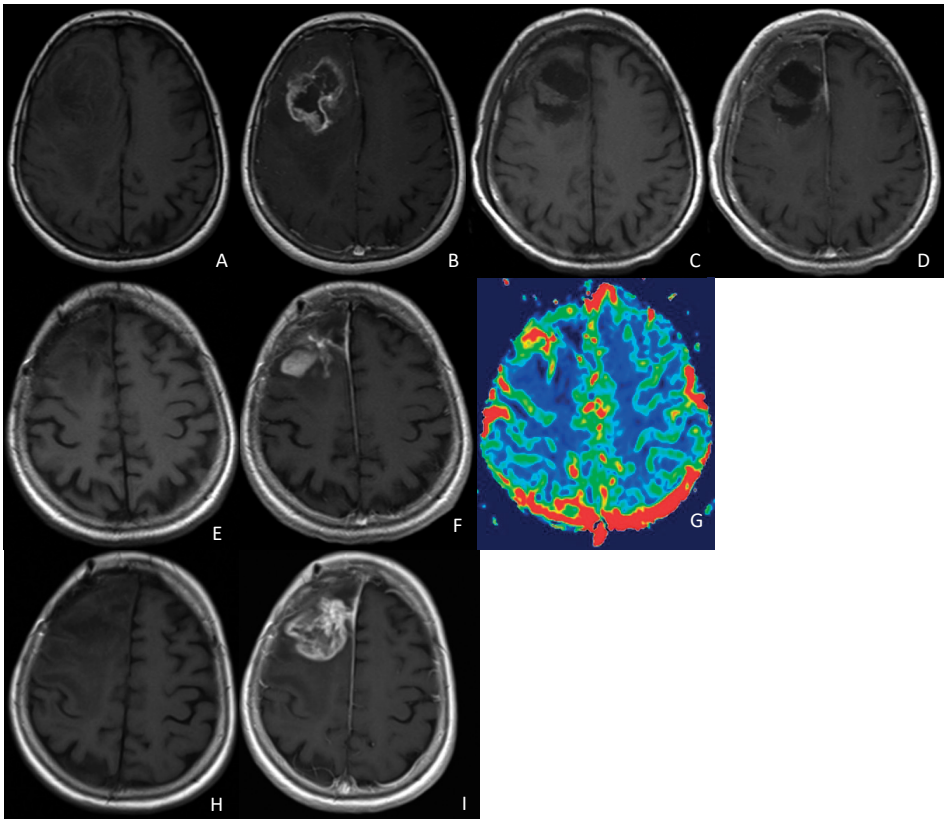

Figure 1. Progressive disease
A and B: pre-surgery T1-weigthed MR images pre- and post-contrast respectively. C and D: post-surgery T1-weigthed MR images pre- and post-contrast respectively. E and F: T1-weigthed MR images pre- and post-contrast respectively, showing TP 4 months after concurrent chemoradiation. G: rCBV perfusion map showing high rCBV within the contrast-enhanced lesion on visual inspection. H and I: T1-weigthed MR images pre- and post-contrast respectively at T_{FU}, showing an increase in the contrast-enhancing lesion consistent with PD. MR: magnetic resonance; PD: progressive disease; rCBV: relative cerebral blood volume; T_{FU}: follow-up 3 months after Tp; Tp: time of progression

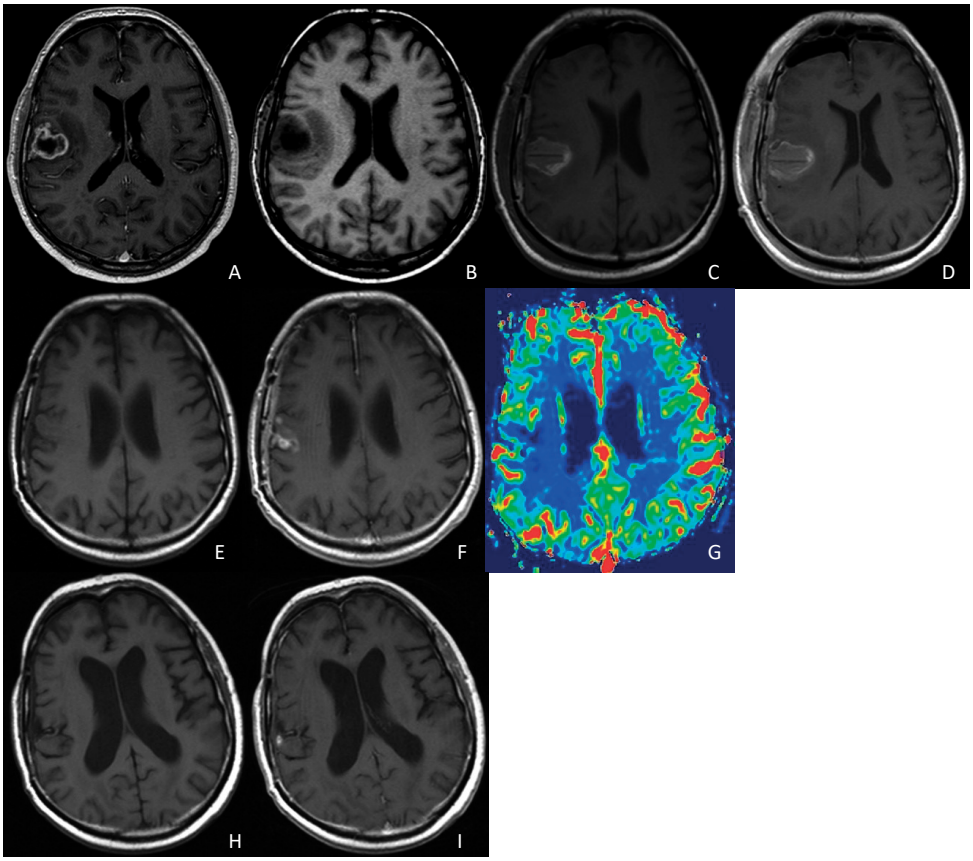

Figure 2. Pseudoprogression
A and B: pre-surgery T1-weigthed MR images pre- and post-contrast respectively. C and D: postsurgery T1-weigthed MR images pre- and post-contrast respectively. E and F: T1-weigthed MR images pre- and postcontrast respectively, showing TP 4 months after concurrent chemoradiation. G: rCBV perfusion map showing low rCBV within the contrast-enhanced lesion on visual inspection. H and I: T1-weigthed MR images pre- and postcontrast respectively at TFU, showing a decrease in the contrast-enhancing lesion consistent with PsPD. MR: magnetic resonance; PsPD:pseudoprogression; rCBV: relative cerebral blood volume; Tfu: follow-up 3 months after Tp; Tp: time of progression.

Progression free and overall survival

At the time of analysis, 57/58 (98%) patients were clinically progressive. Median PFS was 10.5 months (Table 3). Median PFS for the subgroup of patients with high rCBV was 9 months, whereas patients with low rCBV showed a median PFS of 14 (range 5-29) months (p=0.77). Median PFS for patients experiencing PD or PsPD was not statistically different: 9.5 months versus 12.5 months, respectively (p=0.86). In univariable analyses, MGMT status was significantly associated with PFS, with a median PFS of 17 (range 3-29)

months in MGMT promoter methylated patients versus 8.5 (range 3-37) months in MGMT promoter unmethylated patients (p<0.01). Median PFS was also significantly associated with (conventional) tumor size at T_p (<1642 mm2 vs ≥1642 mm2; 14.0 versus 6.0 months; p=0.04), and by the number of adjuvant TMZ cycles administered (<4 vs ≥4 cycles; 6.0 vs 14.5 months; p<0.01). Only MGMT promoter methylation status was independently associated with PFS in multivariable analysis (HR 0.36; p=0.03). At the time of completion of the study all patients had died. One patient had died due to aspiration pneumonia, though without signs of preceding clinical progression. For all patients, the median OS from baseline was 17 (range 4-42) months (Table 3).

Table 3. Median (Progression Free and Overall) survival times (n= 58)

Characteristic	PFS (months)	P - Value[a]	OS (months)	P-Value[a]
Median (range)	10.5 (2-37)		17 (4-42)	
MGMT promoter status		<0.01[b]		0.01[b]
Methylated	17 (3-29)		22 (6-38)	
Unmethylated	8.5 (3-37)		15 (4-39)	
PD or PsPD at T_{FU}		0.86		0.36
PD	9.5 (2-37)		15.5 (4-42)	
PsPD	12.5 (3-29)		19.5 (6-38)	
High or Low rCBV map at T_p		0.77		0.59
High rCBV	9 (2-37)		17 (4-42)	
Low rCBV	14 (5-29)		16 (8-32)	

Data are presented as median (range)
PFS Progression Free Survival; *OS* Overall Survival; *MGMT* O^6 –methylguanine-DNA methyltransferase; *PD* Progressive Disease; *PsPD* Pseudoprogression; *rCBV* relative cerebral blood volume; *Tfu* follow-up 3 months after Tp; *TP* time of progression
a) Log-Rank test
b) Statistical significant difference

Survival from the time of clinical and radiological progression (T_p) was 5 (range 0-29) and 9 (range 0-34) months, respectively. Median OS was similar for the subgroup with high rCBV and low rCBV, 17 (range 4-42) months versus 16 (range 8-32) months respectively (p=0.59). Median OS in patients with PD was 15.5 (range 4-42) months, whereas patients with PsPD had a median OS of 19.5 (range 6-38) months (p=0.36). In multivariable analyses, OS was independently associated with MGMT promoter methylation status (HR 0.48; p=0.03).

DISCUSSION

At the moment of 'first radiological progression', in other words, a growing enhancing lesion on standard MR images, it would be very useful to be able to predict the subsequent clinical course. We assessed in a group of 58 homogeneously treated GBM patients whether DSC perfusion MRI may predict a PsPD or PD course, and whether abnormalities on rCBV colour maps may have overall predictive value. In our study, the detection of nodular high perfusion areas on the rCBV map (i.e. 'high rCBV') did not reliably predict a subsequent PD course (sensitivity and specificity of 72% and 23%, respectively). Twenty-nine out of 58 patients (50%) were misclassified based on evaluation of the rCBV maps: 9 patients with a PD course demonstrated a low rCBV at Tp and more interestingly 20 patients with a PsPD course had demonstrated high rCBV abnormalities at Tp. The possible mechanisms underlying this under- and overestimation of rCBV might include the following: GBM is a heterogeneous lesion with a possible mixture of tumor and (avascular) radiation-induced necrosis; beside endothelial injury, therapy-induced lesions can show vascular abnormalities, such as telangiectasis.[25] These vascular abnormalities may result in an increased rCBV within the necrotic lesion; rCBV assessment of cortical areas is difficult. rCBV in the cortical area is higher than that in the white matter and, subsequently, can lead to confusion in interpretation. Also, lesions are often located on the junction of gray and white matter. Since the rCBV map has a lower resolution than the conventional MRI, this might result in discussion whether the area of high perfusion is due to progression of the tumor in the white matter, or representing the normal surrounding gray matter; artefacts due to focal hemorrhage.

In our analyses, no significant association was found between abnormalities found on rCBV color maps and (overall and progression free) survival. As such, rCBV-based DSC perfusion MRI was not prognostic for survival.

Based on the criteria applied in this study, a PD course after Tp was seen in 55% of our patients, while a PsPD course was seen in 45% of patients with presumed radiological progression (T_p). This percentage of patients with PsPD is higher than reported in literature, which will be related to the selection of patients with radiological progression according to the RANO criteria, instead of including all patients after chemoradiation. In our study population, we detected a survival benefit favoring the PsPD group. The presence of methylation of the MGMT promoter in GBM had been found to be strongly associated with PsPD.[5] We indeed found that patients with PsPD had more often methylated MGMT promoter than patients with PD (50 vs 22%, p=0.08) and MGMT promoter methylation status was independently associated with both OS and PFS.

A limitation of the current study is the methodology of perfusion MR analysis, which was based on visual inspection, instead of using quantitative rCBV measurements or measurement of the parametric response map. However, the applied visual interpretation technique of perfusion MRI resembles routine daily clinical practice, and is therefore

highly relevant. Furthermore, different therapy modalities were applied in patients once they had experienced (presumed) radiological progression and this difference may have influenced subsequent MRI results at T_{FU}. Nevertheless, these considerations also hold true in daily clinical practice. Finally, the interval of 3 months (T_{FU}) after radiological progression (T_P) to define PsPD is arbitrary, but in accordance with other literature on this topic. Also, given the aggressive nature of GBMs, we hypothesized that PD would result in further radiological progression within 3 months of first radiological progression (or death within 4 months).

In conclusion, with a reported relatively high incidence of PsPD after concurrent TMZ chemoradiation in GBM patients, a timely and reliable differentiation of PsPD and true PD is crucial for appropriate treatment decision making, both in daily clinical practice and in clinical trials. Unfortunately, in this retrospective study, we found that qualitative scoring of DSC MR perfusion rCBV maps did not reliably differentiate PsPD from PD and is not a prognostic factor for survival in GBM patients treated with TMZ chemoradiation. Currently, we are planning to perform analyses with a revised quantitative rCBV measurement technique to substantiate our findings. If the prognostic value of perfusion MRI (rCBV) indeed seems to be limited in GBM patients treated with TMZ chemoradiation, this may obviate the use of this imaging modality in this setting.

Practice points

- Pseudoprogression (PsPD) is increasingly encountered in patients with glioblastoma multiforme (GBM) since the introduction of chemoradiation with temozolomide (TMZ)
- Evaluation of conventional MR imaging can be insufficient in differentiating PsPD from PD in glioma patients
- Dynamic susceptibility-weighted contrast-enhanced (DSC) perfusion MRI is capable of quantifying vessel bloodvolume by assessment of the relative cerebral blood volume (rCBV), reflecting the degree of microvascular proliferation in tumor tissue
- Qualitative rCBV-based DSC perfusion MRI does not reliably differentiate PsPD from PD in patients treated with TMZ chemoradiation
- Qualitative rCBV-based DSC perfusion MRI is not prognostic for survival in GBM patients treated with TMZ chemoradiation

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6

Clinical applicability of and changes in perfusion MR imaging in brain metastases after stereotactic radiotherapy

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Abstract

Background: To assess the applicability of perfusion-weighted (PWI) magnetic resonance imaging (MRI) in clinical practice, as well as to evaluate the changes in PWI in brain metastases before and after stereotactic radiotherapy (SRT), and to correlate these changes to tumor status on conventional MRI.

Methods: Serial MR images at baseline and at least 3 and 6 months after SRT were retrospectively evaluated. Size of metastases and the relative cerebral blood volume (rCBV), assessed with subjective visual inspection in the contrast enhanced area, were evaluated at each time point. Tumor behavior of metastases was categorized into four groups based on predefined changes on MRI during follow-up, or on histologically confirmed diagnosis; progressive disease (PD), pseudoprogression (PsPD), non-progressive disease (non-PD) and progression unspecified (PU).

Results: Twenty-six patients with 42 metastases were included. Fifteen percent (26/168) of all PW images could not be evaluated due to localization near large vessels or the scalp, presence of hemorrhage artefacts, and in 31% (52/168) due to unmeasurable residual metastases. The most common pattern (52%, 13/25 metastases) showed a high rCBV at baseline and low rCBV during follow-up, occurring in metastases with non-PD (23%, 3/13), PsPD (38%, 5/13) and PU (38%, 5/13). Including only metastases with a definite outcome generally showed low rCBV in PsPD or non-PD, and high rCBV in PD.

Conclusion: Although non-PD and PsPD may be distinguished from PD after SRT using the PW images, the large proportion of images that could not be assessed due to artefacts and size severely hampers value of PWI in predicting tumor response after SRT.

INTRODUCTION

About 10–30% of patients with systemic cancer develop brain metastases. The overall median survival in 3940 patients with newly diagnosed brain metastases was 7.2 (range 2.8–25.3) months depending on tumor type, number of brain metastases, presence of extracranial metastases and patient-related factors such as age and performance status.[1] Treatment may involve resection, radiotherapy (stereotactic techniques or whole brain radiotherapy), systemic treatment or a combination of these. Radiotherapy may result in adverse radiation effects (ARE) comprising a spectrum of radiation effects with (temporary) enlargement of the area of contrast-enhancement in tumor and surrounding normal brain tissue, which may be reversible or irreversible.[2] The term pseudoprogression is used when there is an early delayed injury and when this is a reversible reaction. The other end of the spectrum is radiation necrosis, which is an irreversible reaction and late complication of radiation to the brain.[3] In literature, these terms are used interchangeably, but in this study the AREs are referred to as pseudoprogression. MRI for follow-up after radiotherapy may either show stable or a decreased area of contrast enhancement (i.e., non-progressive disease; non-PD), or increased contrast enhancement [i.e., progressive disease (PD) or pseudoprogression (PsPD)]. However, the distinction between PD and PsPD cannot be made easily with conventional MRI. Several advanced imaging methods based on MRI, such as delayed-contrast MRI to calculate treatment response assessment maps (TRAMs), proton magnetic resonance spectroscopy (MRS), and positron-emission-tomography (PET) are studied in patients with brain metastases.[4-8] With the TRAMs approach, to differentiate tumor from nontumor tissue, a sensitivity and positive predictive value of 100% respectively 89% was found in patients with brain metastases.[7] To distinguish between PD and PSPD MRS demonstrated to have sensitivity between 33 and 50% and a specificity of 100%.[8] Another advanced technique is perfusion MRI which may provide additional information necessary to make the distinction between PD and PSPD. The capability of perfusion-weighted imaging (PWI) to differentiate tumor recurrence from PsPD of cerebral metastases after radiotherapy has been described before in four studies evaluating predictive value of PWI in brain metastases treated with radiotherapy.[9-12] For predicting tumor recurrence, visual inspection of the relative cerebral blood volume (rCBV) map yielded a sensitivity and specificity of 70 and 93%, respectively,[9] while quantitative PWI analysis resulted in a sensitivity between 70 and 91% and a specificity between 73 and 100%.[9, 10] Moreover, a decrease in rCBV of > 15% six weeks after radiotherapy was found to be predictive of tumor response after six months, with a sensitivity of 91% and specificity of 71%.[11] Similarly, a decreased rCBV after 1 week of treatment with SRT or WBRT ($p < 0.05$) was found to be predictive of tumor response 1 year post-treatment at last available follow-up.[12] Interestingly, in this study a reduction of rCBV after one month was also seen in patients with PD (sensitivity 74%, specificity 82%). Although the previous studies found that perfusion MRI is a useful tool in the distinction

of PD and PsPD, these studies only described the changes of perfusion MR parameters in patients with radiological progression. However, it is currently unknown if these patterns are unique for patients with progression and do not occur in patients with radiologically stable lesions. In order to get better insight in the effect of radiotherapy on perfusion MRI parameters, we also included patients with radiologically stable disease in our study. The aim of this study was therefore to evaluate the applicability of the PW imaging technique and changes in PWI in brain metastasis after SRT and to study the rCBV patterns in relation to changes in the area of contrast-enhancement.

METHODS

Patient population

We retrospectively studied patients with one to three brain metastases who received SRT between January 2011 and December 2013 at the Radiotherapy Center West in The Hague, The Netherlands. Only patients with baseline conventional and perfusion MR and at least at 3 and 6 months follow-up were included. Patients with prior resection or radiotherapy, and patients who received subsequent (whole brain) radiotherapy within 6 months post-SRT, were excluded. Recorded demographic and clinical parameters included age, gender, date of birth, age at diagnosis, diagnosis and location of primary tumor, date of diagnosis, date of first SRT and metastases location.

Radiation therapy

Patients were treated with Dynamic Arc Technique. Prescribed doses, specified on the 80% isodose, were 1×18, 1×21, 3×8 Gy or 3×8.5 Gy, depending on the volume of the planning target volume (PTV). A CTV (clinical target volume)-PTV margin was given to all patients. Patients received dexamethasone (6 mg twice a day) from the day before SRT until 1 day after SRT. Depending on previous use, dexamethasone was either stopped or tapered based on symptoms.

Magnetic Resonance Imaging

MRI of the brain was performed (1.5 T, Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany) according to the brain tumor protocol of the hospital. Imaging included T1-weighted (T1WI) pre- and postcontrast images, T2-weighted images (T2WI) and PWI. PWI was acquired using a gradient echo echoplaner sequence (GE-EPI). Slice thickness of T1WI is 1.3 mm. A contrast prebolus 0,1 ml/kg gadolinium followed by 10 cc NaCl (2 cc/s) was given to correct for contrast leakage. PW images were obtained during the first pass of gadolinium (20 cc, 4 cc/s) with an injection delay of 10 s. Imaging parameters of PWI were: repetition time/echo time (TR/TE) 1490/30 ms, slice thickness 5.0

mm, field of view 230, acquisition matrix 128/128, flip angle 90°. MRI was performed at baseline, 3 and 6 months after SRT. MR images were anonymized before evaluation.

Assessment of MR images: lesion size

Baseline and standard follow-up metastatic size at 3, 6 and when available 9 and 12 months after SRT were evaluated. Measurements of the estimated area of contrast-enhancement were obtained from axial postcontrast T1-weighted images by selecting the largest tumor diameter and the greatest perpendicular diameter.[13, 14] The tumor responses of metastases were categorized into four groups based on changes in contrast enhancement on T1-weighted images during followup or based on a histologically confirmed diagnosis; (1) progressive disease (PD), (2) pseudoprogression (PsPD), (3) non-progressive disease (non-PD) and (4) progression unspecified (PU). All metastases showing a decrease of at least 5% (to ascertain a true change in tumor size, whether or not clinically relevant) in tumor size over time were categorized as non-PD. Metastases with an initial increase in size (≥ 5%), but without a subsequent decrease in size (≥ 5%), were categorized as PU. This group may include both PsPD and PD, which could not be further specified based on (missing) histology or follow-up. PsPD was defined as a decrease of size on T1WI after an initial increase of contrast enhancement of at least 5%. Definite PD was based on a histological diagnosis consisting of viable tumor tissue.

Assessment of MR images: PW imaging

rCBV was assessed by subjective visual inspection of the rCBV maps in the contrast-enhanced area. This visual score was based on presence or absence of highly vascularized areas within the contrast-enhanced lesion relative to the contralateral hemisphere and was defined as high rCBV versus low rCBV, reflecting viable tumor tissue or treatment related effects, respectively, or as not assessable. The cut-off used to define a metastasis as unmeasurable was < 60 mm.[2] All MR assessments were performed independently by two experienced neuroradiologists (GL, BH). Parameters included in the evaluation were the quality of the scan, T1-assessment of contrast enhancement, and PW images results. Discordant results on the scoring form between the two radiologists were resolved by consensus. For PWI pattern analysis, a minimal of two PWI follow-up time points (3 and 6 months) were necessary. PWI patterns for perfusion changes in relation to the estimated area of contrast-enhancement where studied for all four categories. Additionally, we performed a PWI subanalysis in which we only included those metastases with a definite outcome.

Statistical analysis

Descriptive statistics were used to define the patient population. Survival time was calculated from the first day of SRT until the date of death or the last date of follow-up when the patient was still alive. Descriptive statistics were also used to study the rCBV patterns for perfusion changes in relation to the estimated area of contrast-enhancement during follow-

up. Statistical analysis was performed using SPSS version 23 (SPSS, Chicago, IL). Differences between categorical factors were assessed by the Chi-Squared test ($\chi 2$) or Fisher's Exact test. All tests were two-tailed, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient selection, clinical outcome and survival

A total of 133 patients with 224 metastases were treated with SRT between 2011 and 2013. Of these, 26 patients with 42 metastases were eligible according to our inclusion criteria (Table 1). More than half of the patients were female (54%) and the median age was 66 years (range 40–84 years). Primary cancer sites included non-small cell lung carcinoma (NSCLC) (46%), breast cancer (19%) and others (36%) (melanoma, gastro-intestinal cancer and urogenital cancer). The median survival time was 17 (range 10–22) months. After 1 year of follow-up, four patients (15%) were still alive. Eleven out of 26 patients (42%) had multiple metastases. The dosage of radiation varied from 18 to 25,5 Gy depending on metastasis size and location, with a median of 21 Gy.

Table 1. Patient characteristics

Gender, n (%)	
Male	12 (46)
Female	14 (54)
Dosage SRT (Gy)	
Median	21
Range	21-24
Age (years)	
Median	65
Range	40 – 84
Primary tumor, n (%)	26
NSCLC	12 (46)
Breast cancer	5 (19)
Other	9 (36)
Metastasis per primary tumor, n (%)	42
NSCLC	20 (48)
Breast cancer	9 (21)
Other	13 (31)
Amount of metastases, n (%)	
1	15 (58)
2	6 (23)
3	5 (19)
Metastasis location, n (%)	
Supra-tentorial	36 (86)
Infra-tentorial	6 (14)

n number; *NSCLC* non-small cell lung carcinoma

MR lesion size

Changes in the estimated area of contrast-enhancement on T1W1 with gadolinium were evaluated on a group level after 3 (n=42), 6 (n=42), 9 (n=25) and 12 (n=16) months follow-up (Table 2). The median metastases size before SRT was 290 mm^2 (range 77–591 mm^2). Median size 3 and 6 months post-SRT was 86 mm^2 (30–356 mm^2) and 149 mm^2 (range 12–500 mm^2) respectively. Three months after SRT, 79% (33/42) of the metastases decreased in size or remained stable in size compared to the size at baseline, whereas 6 months after irradiation only 60% (25/42) showed a decrease in size or had a stable size compared to the size at 3 months. After 9 and 12 months follow-up, 44% (11/25) and 69% (11/16) showed a decrease in size or remained stable compared to the size at 6 and 9 months follow-up, respectively. From baseline until 6 months after radiotherapy, 26% (11/42) of the metastases showed an increased area of contrast-enhancement and 74% (31/42) showed a decrease in size on T1WI with gadolinium. At the end of follow-up, 18 out of 42 metastases were classified as PU (43%), 15 as non-PD (36%), eight as PsPD (19%) and one metastasis as PD (2%).

Table 2. Changes in the estimated area of contrast-enhancement on T1WI with gadolinium, compared to the previous time point.

Changes T1WI with gadolinium	3 months FU (n= 42)	6 months FU (n=42)	9 months FU (n=25)	12 months FU (n=16)
Decrease	33 (79%)	24 (57%)	9 (36%)	10 (63%)
Increase	9 (21%)	17 (41%)	14 (56%)	4 (25%)
Stable	-	1 (2%)	2 (8%)	1 (6%)

An increase is defined as ≥5% increase in the area of contrast-enhancement compared to previous time point and a decrease as <5% decrease in the area of contrast-enhancement compared to the previous time point.

MR PW imaging

A total of 168 PW images at baseline and follow-up were reviewed. Up to forty-six percent (78/168) of all PW images could not be used for PWI analysis; thirty-one percent (52/168) could not be evaluated due to unmeasurable residual metastases (< 60 mm^2), while the other fifteen percent (26/168) could not be evaluated due to localization near large vessels or the scalp (n = 13), or due to the presence of hemorrhage artefacts (n = 13). The lesions which could not be used were not included in further PWI results. Thirty-two metastases (76%, 32/42) remained for baseline PWI analyses and twenty-five metastases (60%, 25/42) remained for follow-up PWI pattern analyses with a minimum of two PWI follow-up time points (3 and 6 months); 21/42 (50%) PWI analyses at 3 months and 22/42 (52%) at 6 months follow-up. At 9 and 12 months follow-up, only 13/42 (31%) and 6/42 (14%) PWI analyses were available. No association was found between primary tumor type and rCBV 3 and 6 months after irradiation ($p = 0.484$ and $p = 0.940$, respectively). Of the metastases suitable

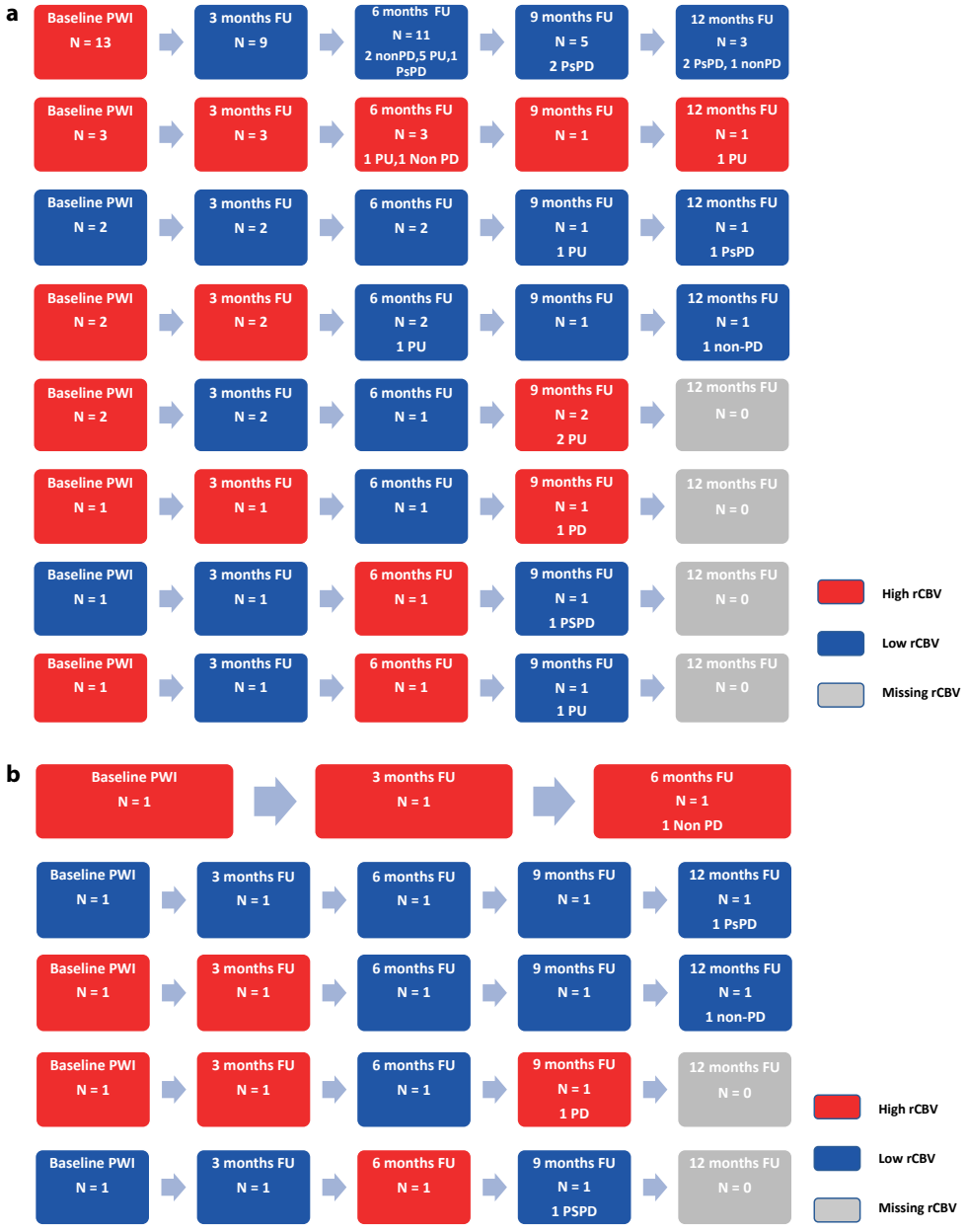

Figure 1 a) PWI pattern analysis (n=25) and b) PWI subanalysis (n=13) showing high or low rCBV at baseline and during follow-up.

Numbers of metastases evaluated at each time point are added as well as the number of patients with PsPD, non-PD, PU and PD in case it is their last follow-up moment. Red colour high rCBV, blue colour low rCBV, PWI perfusion weighted image, FU follow-up, PsPD pseudoprogression, non-PD no progressive disease, PU progression unspecified (progressive disease or pseudoprogression), PD progressive disease

for analysis at baseline, 84% (27/32) showed high rCBV. Three months post-SRT, only 29% (6/21) showed high rCBV. At 6,7,9 and 12 months, 23% (5/22), 31% (4/13) and 17% (1/6) showed high rCBV, respectively. For each metastasis, we have also evaluated the individual pattern of rCBV flow (Fig. 1a). After radiotherapy, the most frequent pattern (52%, 13/25 metastases) showed a high rCBV at baseline and low rCBV during follow-up. However, this pattern was independent of the subsequent tumor status category: 3/13 (23%) were subsequently categorized as non-PD, 5/13 (38%) as PsPD and 5/13 (38%) as PU. The other metastases did not fit into any pattern and were not related to specific categories based on the change of contrast-enhancement. Of the seven metastases in the PWI analyses categorized as PsPD, six (86%) had a continuously low rCBV during follow-up. Of the five metastases categorized as non-PD, three showed a continuously low rCBV during follow-up (60%). The patient with histologically confirmed PD was found to have a low rCBV at 6 months and a high rCBV at 3 and 9 months of follow-up. The subanalysis contained only the metastases with a definite outcome; PsPD, PD and non-PD. A total of 13 metastases were included. In 12/13 (92%) the follow-up PWI demonstrated a concordant result with the changes in the estimated area of contrast enhancement; low rCBV in case of PSPD or non-PD and high rCBV in case of PD (Fig. 1b). However, one metastasis categorized as non-PD demonstrated a high rCBV at baseline and at 3 and 6 months of follow-up.

DISCUSSION

The differentiation between PsPD and PD in patients with brain metastases after SRT may have clinical implications. If PD could be diagnosed reliably, patients can receive timely and appropriate additional antitumor treatment, whereas patients with PsPD should not be treated in the same way. Although some authors have suggested that all lesions increasing in size resulting in neurological problems should be treated, it is a matter of debate whether this should be done with antitumor or supportive treatment. The use of quantitative perfusion MRI for this indication showed promising results, but evidence for the widely used visual technique in clinical practice for PWI interpretation is limited. [9–13] In addition, previous studies investigating the use of quantitative perfusion MRI only described the changes of perfusion MR parameters in patients with radiological progression, limiting generalizability of these findings.

In the current study we described the change of the estimated area of contrast-enhancement in brain metastases from baseline up to a minimum of 6 months after irradiation. This selection criterion impacted the overall survival of this study population, which is high compared to the median survival of a general brain metastases patient population. Six months after radiotherapy most of the metastases in our study initially decreased in size compared to baseline (74%). Based on the change of the area of contrast-enhancement over time (and when available based on histology) metastases were

categorized as PD, PsPD, non-PD or PU. Contrary to other studies on this subject, the lesions that increased over time without histological confirmation or a subsequent decrease of contrast-enhancement were categorized as the unspecified (PU) cases. To eliminate the risk of false classification, we chose to not further specify the tumor status.[9,10]

In the literature, an occurrence of 20% PsPD was described in glioma patients treated with temozolomide chemoradiation.[14] Of the brain metastases patients with progressive contrast enhancement during follow-up, 25-41% were classified as PsPD.[9,10,15,16] Diagnoses were based on histology, definite radiological decrease or a combination of radiological and clinical follow-up. We found a significant reduction in the area of contrast-enhancement in 79% of the metastases three months after SRT. However, 6 months after irradiation, in a large number of metastases (40%) the area of contrast-enhancement increased again due to either PD or PsPD. In the clinical setting this can be a difficult moment in decision-making. Most studies attempting to make the distinction between these two entities, describe only 3 months of follow-up.[9–11] However, we demonstrated that 4% of lesions do increase after this follow-up interval.

The strength of this study is that all patients, independent of tumor status, were included, whereas most studies on perfusion imaging included only patients with radiological progression. Sixty percent of the metastases categorized as non-PD had a continuously low rCBV during follow-up

Study limitations

Unfortunately, almost half of the metastases (43%) in our study were categorized as PU, making drawing conclusions hardly possible. This limitation is partly due to the lack of histology in almost all patients. On the other hand, this reflects clinical practice, in which treatment choices have to be made on the limited available evidence.

Furthermore, PWI were assessed using the visual method, which is a subjective method widely used in clinical practice. Although widely used, large interobserver variability, observed in evaluating rCBV in patients with glioblastoma, questions the value of this method.[13] Moreover, the perfusion MRI was not applicable in several metastases; in almost half of the PW images the rCBV could not be determined due to small lesion size or artefacts, which is a major limitation. Artefacts in PWI may be based on localization of the metastases near large vessels, localization in the posterior cranial fossa, necrosis or hemosiderin deposition. The latest is thought to be due to small haemorrhages in the tumor bed, caused by radiation therapy.[17] A hemosiderin rim could indicate radiation-induced damage to the metastases. The rCBV may not be reliable when bleeding has occurred, because bleeding within the tumor could cause false increase or decrease in rCBV.[18] Therefore, caution in interpretation is warranted in case of haemorrhage. After excluding metastases with impeding artefacts and metastases too small for assessment, only 22 patients with 25 metastases remained available for further PWI analysis. The

sample size is an important limitation of the study and limited the interpretation of the study results.

CONCLUSION

Most metastases showed a decrease in the area of contrast-enhancement 3 months after irradiation, reflecting the known efficacy of SRT. The follow-up MRIs learnt us more about rCBV development after SRT. The majority of brain metastasis (52%) had a high baseline and low follow-up rCBV, independent of the eventual tumor status: low perfusion during follow-up is seen in patients with both PD, non-PD and PsPD. Based on these results it can be concluded that the visual method of PWI analysis does not provide unequivocal guidance in predicting progression of metastasis. However, when excluding metastases that were classified as having PU from the analysis, results of the PWI subanalysis were concordant with the changes in the area of contrast-enhancement in almost all patients, with low rCBV in case of PSPD or non-PD and high rCBV in case of PD in 12 out of 13 patients. This suggests that non-PD and PsPD may be distinguished from PD based on the visual method of the PWI analysis. Nevertheless, the large proportion of PW images that could not be assessed due to artefacts and size severely hampers the ability to predict tumor response.

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7

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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A

Appendix

Samenvatting
(Summary in Dutch)

List of publications

Dankwoord
(Acknowledgements in Dutch)

About the author

NEDERLANDSE SAMENVATTING

Met dit proefschrift heb ik geprobeerd een leidraad te geven voor de dagelijkse neuro-oncologische praktijk. Enerzijds heb ik mij gericht op behandeling van epilepsie bij patiënten met een glioom, anderzijds op de beoordeling van de beeldvorming na behandeling van patiënten met een glioom of hersenmetastase(n).
Deel I van dit proefschrift richtte zich op de rol van de epilepsie behandeling bij glioom patiënten in relatie tot klinische uitkomstmaten zoals overleving en de gevolgen van het stoppen van anti-epileptica op recidief epileptische aanvallen in relatie tot de radiologische uitkomst.
Deel II van dit proefschrift richtte zich op de impact van de hersentumor behandeling op klinische en radiologische uitkomsten, in het bijzonder op het vaststellen van (pseudo) progressie.

Deel I: De rol van de epilepsie behandeling in relatie tot klinische en radiologische uitkomsten

Epileptische aanvallen komen frequent voor bij patiënten met een hersentumor en kunnen grote invloed hebben op functioneren en kwaliteit van leven. Epileptische aanvallen komen voor bij 60-90% van de patiënten met een laaggradige glioom en bij 25-60% van de patiënten met een hooggradige glioom. In **hoofdstuk 2** bestudeerden we het effect van valproaat (VPA) en levetiracetam (LEV) op de aanvalscontrole in patiënten met een glioblastoom. Er werd gestart met VPA- of LEV- monotherapie, wat in 40% van de patiënten heeft geleid tot aanvalsvrijheid. In de loop van de ziekte werd aanvalsvrijheid bereikt in 78% van de patiënten op VPA-monotherapie, in 70% op LEV-monotherapie en in 60% op de combinatie van VPA en LEV indien één van beiden niet effectief was. Er werd, gezien het potentiële antitumor effect van VPA, een aanvullende analyse verricht naar het effect van VPA op de overleving. We vonden dat patiënten met een glioblastoom die VPA in combinatie met temozolomide (TMZ) gebruikten, een langere mediane overleving hadden van 69 weken in vergelijking met 61 weken in de groep zonder VPA (hazard ratio 0.63; 95% CI: 0.43–0.92), na correctie voor leeftijd, mate van resectie en O^6-DNA methylguanine-methyltransferase (MGMT) promotor methylatie.
Glioom patiënten kunnen met anti-epileptica aanvalsvrijheid bereiken. De hersentumor behandeling kan daarnaast ook bijdragen aan afname van de aanvalsfrequentie. Na resectie en radiotherapie wordt respectievelijk 53-87% en 32-75% van de laaggradig glioom patiënten aanvalsvrij. Chemotherapie resulteert in een ≥50% aanvalsreductie in 48-78% van de laaggradig glioom patiënten. In **hoofdstuk 3** onderzochten we de noodzaak om anti-epileptica voort te zetten in klinisch en radiologisch stabiele laaggradige en anaplastische glioom patiënten die ten minste één jaar aanvalsvrij waren, gerekend vanaf het einde van de laatste hersentumor behandeling. We bestudeerden

zowel het proces van 'shared decision making' tussen patiënt en arts ten aanzien van het stoppen van anti-epileptica, als het effect van stoppen van anti-epileptica op recidief epileptische aanvallen. Na overeenstemming tussen zowel patiënt als behandelend neuro-oncoloog tot participatie in de studie, werd een gezamenlijk besluit genomen ten aanzien van het al dan niet stoppen van de anti-epileptica. Bij 65% van de in totaal 71 patiënten werd besloten de anti-epileptica te stoppen en bij 35% van de patiënten om de anti-epileptica te continueren. In de groep die de anti-epileptica stopte, kreeg 26% een recidief epileptische aanval na een mediane follow-up van 2.2 jaar. Van deze patiënten bleek 58% tumorprogressie te hebben, waarvan 3 patiënten al binnen 3 maanden na het stoppen van de anti-epileptica. Slechts 8% van de patiënten in de groep die anti-epileptica continueerde had een recidief epileptische aanval, waarvan één patiënt ook tumorprogressie had.

Deel II: De impact van de hersentumor behandeling op klinische en radiologische uitkomsten

Eén van de grootste uitdagingen in de neuro-oncologische praktijk is de interpretatie van de beeldvorming na hersentumor behandeling. De behandeling kan namelijk behandelingsgerelateerde effecten op de beeldvorming induceren, lijkend op tumorprogressie, wat ook wel pseudoprogressie wordt genoemd. De conventionele MRI met contrastmiddel is helaas onvoldoende geschikt om het onderscheid te maken tussen tumorprogressie en pseudoprogressie. Geavanceerde MRI-technieken zijn mogelijk meer geschikt om accuraat de status van de hersentumor na behandeling vast te stellen.
We bestudeerden om die reden de waarde van de veelgebruikte kwalitatieve beoordeling van de dynamische susceptibiliteits contrast (DSC) perfusie MRI bij hersentumorpatiënten. De DSC-perfusie MRI maakt het mogelijk het cerebraal bloedvolume zichtbaar te maken door beoordeling van het relatieve cerebraal bloedvolume (rCBV), wat een maat is voor microvasculaire proliferatie in tumorweefsel. De kwalitatieve DSC-perfusie MRI kan gebruikt worden om tumorprogressie van pseudoprogressie te onderscheiden. Dit onderscheid heeft belangrijke klinische en therapeutische consequenties, aangezien in geval van tumorprogressie vaak een aanpassing van de hersentumor behandeling moet worden gedaan. Om de waarde en de reproduceerbaarheid van de kwalitatieve beoordeling van de DSC-perfusie MRI te bestuderen stelden we eerst de interobserver variabiliteit van DSC-perfusie MRI-parameters vast in glioblastoom patiënten behandeld met TMZ-chemoradiatie (**hoofdstuk 4**). Er werd een goede interobserver overeenkomst gevonden bij de kwalitatieve beoordeling van de rCBV overzichten (kappa waarde = 0.63). De interobserver overeenkomst van de interpretatie van de DSC-perfusie MRI daarentegen was veel slechter (kappa waarde = 0.23). De uiteindelijke radiologische beoordeling van de status van de tumor (volledige tumor respons, partiele tumor respons, progressieve ziekte of stabiele ziekte) waarbij zowel de standaard MRI als de DSC-perfusie MRI-beelden

werden meegewogen, resulteerde in een matige interobserver overeenkomst (kappa waarde = 0.48).

Vervolgens onderzochten we in **hoofdstuk 5** of de kwalitatieve beoordeling van de DSC-perfusie MRI accuraat tumorprogressie van pseudoprogressie kon onderscheiden in patiënten met een glioblastoom tijdens behandeling met TMZ-chemoradiatie. Het vaststellen van een gebied met hoge perfusie op het rCBV overzicht (hoge rCBV) binnen het gebied met contrast aankleuring kon echter niet betrouwbaar tumorprogressie voorspellen (sensitiviteit 72%, specificiteit 23%). Verder bleek deze kwalitatieve rCBV niet prognostisch te zijn voor overleving van glioblastoom patiënten. De mediane overleving was gelijk voor de subgroepen met hoge rCBV en lage rCBV.

Daarna stelden we in **hoofdstuk 6** de toepasbaarheid van de kwalitatieve beoordeling van de DSC-perfusie MRI in 26 patiënten met 42 hersenmetastasen vast. De verandering van de DSC-perfusie MRI-beelden voor en na stereotactische radiotherapie (SRT) werd geëvalueerd. Vijftien procent van de perfusie beelden kon niet geëvalueerd worden ten gevolge van de ligging van de hersenmetastasen nabij grote bloedvaten of de schedel, of de aanwezigheid van artefacten ten gevolge van bloedingen, en nog eens 31% door te kleine afmeting van de resterende hersenmetastase. In de meeste hersenmetastasen (52%) werd een hoge rCBV gevonden op de eerste MRI na bestraling en een lage rCBV tijdens vervolg MRI onderzoeken. Ondanks dat met hulp van de DSC-perfusie MRI pseudoprogressie en 'geen progressie' (gedefinieerd als tenminste stabiele ziekte) redelijk goed van tumorprogressie kon worden onderscheiden, heeft het grote aandeel niet te beoordelen perfusie beelden de toepasbaarheid van de DSC-perfusie MRI als voorspeller van de radiologische status van de hersenmetastase na SRT ernstig belemmerd.

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Melissa Kerkhof was born in Zwijndrecht on December 13, 1985. She passed her secondary school exam (Gymnasium) at the 'Walburg College' in 2004. After graduating she started her medical study at the Medical Faculty of the Erasmus University of Rotterdam. During her training she was invited to participate in an honours program for excellent medical students. As part of this program, she started a Master in clinical epidemiology, for which she attended epidemiology courses at the Johns Hopkins School of Public Health, USA. In 2009 she obtained her Master of Science degree in clinical epidemiology. Two years later Melissa obtained her Medical Doctorate cum laude. She worked from 2011 as a neurology resident in Haaglanden Medical Center in the Hague and started in 2012 with her specialist registrar neurology training. In addition, she worked on several clinical research projects, including the work described in this thesis. In 2018 she started as certified neurologist at the Haaglanden Medical Center.

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