GENERAL

introduction and outline
INTRODUCTION
Primary brain tumors account for less than 2% of all malignancies, but result in a disproportionate share of cancer morbidity and mortality. Gliomas represent 80% of all primary malignant brain tumors with an incidence of 2-8 per 100,000. The median age at diagnosis of glioma patients varies between 37 and 64 years of age, and men are more often affected than women with a male/female ratio of 1.4.2

Gliomas arise from the supportive tissue of the brain, consisting of glial cells, and are categorized according to cell type and tumor grade, using the World Health Organization (WHO) criteria.3 Gliomas are roughly divided into low-grade (WHO grade I and II) and high-grade tumors (grade III and IV). The main types of low-grade gliomas (LGGs) are pilocytic astrocytoma (grade I), and diffuse astrocytomas, mixed oligoastrocytomas and oligodendrogliomas (grade II). High-grade gliomas (HGGs) mainly consist of anaplastic astrocytomas, oligoastrocytomas and oligodendrogliomas (grade III), and glioblastoma (grade IV).

The median survival of glioma patients largely depends on the phenotype and tumor grade.43 Patients with LGG have a median survival that ranges from 5 to 15 years, whereas in HGGs the median survival ranges from 14 months up to 10 years.4 Clinically favorable prognostic factors include young age, good Karnofsky Performance Status (KPS), as well as macroscopically complete resection of the tumor.5-9 In addition, molecular genetic biomarkers, such as a 1p/-19q co-deletion and a mutation of isocitrate dehydrogenase 1 (IDH1), are established prognostic markers.10-13

Gliomas may cause severe neurological deficits, including symptoms which are directly related to the location of the tumor (such as paresis, sensory disturbances, aphasia, visual problems), more general symptoms (such as attention deficit and cognitive disturbances), and other symptoms that result from an increased intracranial pressure (such as headache, nausea, vomiting and impaired consciousness). Seizures may occur in every type of glioma, although the prevalence of seizures largely depends on the tumor phenotype, its growth rate and location.14-15 Approximately 70-90% of all LGG patients develop epilepsy during the course of the disease, compared to 30-60% of HGG patients.16 Tumors which are located in the frontal or temporal lobe, as well as tumors near the brain cortex tend to be more epileptogenic.17-18

Antiepileptic drugs (AEDs) are essential in achieving seizure control. However, tumor-directed treatment, which includes surgery, radiotherapy and chemotherapy, also contributes to seizure control in a substantial part of glioma patients.19-20 Despite multimodal treatment, 30% of glioma patients with epilepsy will eventually not
Epilepsy and antitumor treatment

Antitumor treatment in glioma patients is primarily aimed at improving survival and achieving symptom control. Treatment in LGGs consists of an early and maximal safe resection, which is thought to postpone malignant transformation and improve survival. Radiotherapy followed by chemotherapy with procarbazine, lomustine and vincristine (PCV) is currently considered the standard of care for LGG requiring postsurgical adjuvant treatment. However, it is still unclear whether treatment with upfront chemotherapy alone while postponing radiotherapy has a similar effect on survival. In case of tumor progression, a re-resection or treatment with temozolomide (TMZ) or PCV chemotherapy should be considered. In patients with an anaplastic glioma, a maximal safe resection followed by radiotherapy, whether or not combined with TMZ or PCV chemotherapy is currently the standard of care. In glioblastoma, surgery followed by radiotherapy with concomitant and adjuvant TMZ is the standard treatment. In case of tumor recurrence of glioblastomas as well as anaplastic gliomas, a second resection may be an option, as well as re-irradiation, or chemotherapy with either TMZ, PCV or bevacizumab.

Improved seizure control has been described after virtually all types of antitumor treatment. Most of these studies included LGG patients who had undergone resection. Other series have shown a significant seizure reduction after radiotherapy and PCV or TMZ chemotherapy as well. Apart from a direct clinical benefit for the patient, the clinical significance of a seizure reduction due to antitumor treatment has been insufficiently explored so far. An objective radiological response to treatment with radiotherapy and chemotherapy is frequently lacking, particularly in LGG patients, seizure outcome might be of value as a clinical marker of tumor response. In addition, in glioma patients with sustained seizure freedom after successful antitumor treatment, the question arises whether, and if yes, for how long AED treatment should be continued.

The first part of this thesis focuses on the clinical significance of the effect of antitumor treatment on epilepsy. We have explored the current literature on seizure outcome after radiotherapy and chemotherapy and we have analyzed the prognostic significance of seizure reduction. Further, we have proposed to re-evaluate AED treatment in case of sustained seizure freedom after antitumor treatment.

Epilepsy as a major symptom in the end of life phase

When antitumor treatment is no longer effective for glioma patients, and care is primarily aimed at decreasing the symptom burden and maintaining quality of life, patients have entered the EOL phase. This phase may start a few days to even months before death and is commonly characterized by significant neurological deterioration. Physical symptoms, such as focal neurological deficits, seizures and loss of consciousness, together with the patient’s personality changes and cognitive deficits may cause a high level of distress among caregivers during the patient’s EOL phase. In addition, EOL care may involve complex medical decisions for the prevention and relief of suffering.

Although epilepsy in glioma patients has been extensively studied, little is known about the occurrence of seizures in the EOL phase. Previous series showed that patients and their relatives fear seizures in the EOL phase and that seizures often diminish patient’s quality of life. A study on symptom prevalence in the EOL phase revealed that 28% of patients experienced seizures during the last week before death. Loss of consciousness, one of the most common symptoms during the final stage of life in brain tumor patients, may be one of the main reasons, as it interferes with the regular oral administration of AEDs. Thus, preventing and treating seizures in the EOL phase is a major challenge.

Since no treatment guidelines exist for the EOL phase, the decision on optimal AED treatment currently depends on the physician’s experience. For adequate management of epilepsy in the EOL phase, knowledge of seizure prevalence, related EOL symptoms, and the type of EOL care is needed. In patients with other types of cancer the organization of EOL care appears to differ widely between countries, due to cultural-historical differences in attitudes towards medical interference in the EOL phase. However, the organization of EOL care for glioma patients as well as their experiences with EOL care have never been examined.

In order to develop more specialized EOL care for the treatment of epilepsy in glioma patients, a guideline is needed that takes into account the specific aspects of the EOL phase. Before discussing the management of epilepsy in the EOL phase, the second part of this thesis first focuses on the current literature on epilepsy in the EOL phase, followed by an analysis of the prevalence of EOL symptoms and organization of EOL care throughout Europe.
THESIS OUTLINE

PART I: Epilepsy and antitumor treatment
Chapter 2 systematically addresses the existing literature on seizure outcome after radiotherapy and chemotherapy, and explores the relationship between seizure reduction and radiological response. In Chapter 3 a retrospective analysis of seizure outcome in a cohort of LGG patients who received TMZ chemotherapy is described. We explore the seizure reduction rate after TMZ treatment and the relation factors associated with seizure reduction as well as the relation between seizure reduction and survival. Chapter 4 expands further on the possible association between seizure reduction and survival and addresses the value of brain tumours as a prognostic marker of survival and its relation with the response on MRI. To gain insight into seizure reduction as a possible surrogate marker for tumor response, we specifically focus on progressive LGG patients with uncontrolled epilepsy. In case antitumor treatment has been successful both in terms of tumor control and seizure freedom, the question arises whether AEDs should be continued. In Chapter 5 the design of a prospective observational study on AED withdrawal in patients with low-grade or anaplastic glioma with long-term seizure freedom is described. As the safety of withdrawal has never been prospectively assessed in glioma patients, we have chosen for a non-randomized study design, where the patient and the treating physician make a shared decision to either withdraw or continue AED treatment.

PART II: Epilepsy as a major symptom in the end of life phase
Chapter 6 retrospectively explores EOL care for HGG patients in three European countries with clearly distinctive health care systems: The Netherlands, Austria and Scotland. We analyze patient’s preferences regarding EOL care, patient’s treatment and survival. The design of a feasibility study on the use of AEDs that can easily be applied in the out-of-hospital setting during the EOL phase. A retrospective analysis of seizure outcome in a cohort of HGG patients. Next, the epidemiology of epilepsy in the EOL phase are outlined. This chapter forms the basis for the design of a prospective observational study on AED withdrawal in patients with low-grade or anaplastic glioma with long-term seizure freedom is described. As the safety of withdrawal has never been prospectively assessed in glioma patients, we have chosen for a non-randomized study design, where the patient and the treating physician make a shared decision to either withdraw or continue AED treatment.

REFERENCE LIST
Introduction and outline


