Glioma-associated epilepsy

and the treatment with antiepileptic drugs

Kristin M. Knudsen-Baas

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Scientific environment

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- Department of Clinical Medicine, the University of Bergen (UiB), Bergen
- Department of Neurology, Haukeland University Hospital (HUS), Bergen
- Department of Registry, Section for Research, the Cancer Registry of Norway (CRN), Oslo
- The Postgraduate School of Medical Research, the Department of Clinical Medicine 1, UiB
- The Norwegian Research School in Neuroscience (NRSN)

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List of publications

The thesis is based on the following papers:

Paper I:

Does the choice of antiepileptic drug affect survival in glioblastoma patients?

Knudsen-Baas KM, Engeland A, Gilhus NE, Storstein A, Owe JF

J Neurooncol. 2016 Sep;129(3):461-9. Epub 2016 Jul 4.

Paper II:

Antiepileptic and psychiatric medication in a nationwide cohort of patients with glioma WHO grade II-IV

Knudsen-Baas KM, Johannesen TB, Myklebust TÅ, Aarseth JH, Owe JF, Gilhus NE, Storstein AM. J Neurooncol. 2018 Dec;140(3):739-748. Epub 2018 Nov 23.

Paper III:

Status epilepticus secondary to glioma

Knudsen-Baas KM, Power KN, Engelsen BA, Hegrestad SE, Gilhus NE, Storstein A.

Seizure. 2016 Aug;40:76-80. Epub 2016 Jun 23.

Abstract

Background: Gliomas are primary brain tumors with a risk of epileptic seizures that especially depends on subtype. Whether epilepsy or anti-epileptic drugs (AEDs) prolong survival in patients with glioblastoma (GBM) is a matter of debate. Studies of psychiatric drug treatment after a glioma diagnosis are sparse. Previous reports on status epilepticus (SE) secondary to glioma were retrospective or included heterogeneous tumor types.

Objectives: Firstly, we hypothesized that epilepsy is not favorable for the prognosis of GBM but that particular AEDs can improve the overall survival (OS). Secondly, we hypothesized that AED exposure can be associated with drug-treated anxiety or depression and that use of psychiatric medication differ between glioma patients and the general population. Thirdly, we hypothesized that SE secondary to glioma is related to tumor grade, and that the treatment response and outcome is worse with underlying tumor progression.

Material and methods: Data from the Cancer registry of Norway on patients diagnosed with grade II-IV glioma 2004-2010 were linked with the Norwegian Prescription Database and the Norwegian Cause of Death Registry, with a follow-up until 2013. In paper I, we investigated OS in GBM related to AED exposure. In paper II, we examined risk factors for drug-treated anxiety and depression after a diagnosis of grade II-IV glioma. In paper III, we described clinical aspects of SE secondary to grade II-IV glioma diagnosed in two Norwegian Western counties.

Results and conclusions: Neither epilepsy nor the six most commonly used AEDs in our GBM cohort were proven to affect OS. Exposure to levetiracetam was associated with drug-treated anxiety after a grade II-III glioma diagnosis. Fewer received antidepressants among the patients with grade II-III glioma and epilepsy than among the general population. SE was more frequent with higher tumor grade. Patients with tumor progression responded as well to standard SE treatment as patients with no underlying tumor progression, but had a worse outcome.

List of Abbreviations

Alpha-ketoglutarate (α-ketoglutarate)

American Academy of Neurology (AAN)

Anatomical Therapeutic Chemical (ATC)

Antiepileptic drug (AED)

Astrocytoma (Astro)

Body mass index (BMI)

Brain tumor-related epilepsy (BTRE)

Chromosomal co-deletion (Co-del)

Confidence interval (CI)

Cox proportional hazard regression (Cox regression)

Cystine-glutamate transporter system (xCT)

Defined daily dose (DDD)

D-2-hydroxyglutarate (D-2HG)

Diffusion MRI (dMRI)

Diffusion tensor imaging (DTI)

Electroencephalogram (EEG)

Enzyme-Inducing Antiepileptic Drug (EIAED)

Epidermal growth factor receptor (EGFR)

European Association of Neuro-Oncology (EANO)

European Organisation for Research and Treatment of Cancer (EORCT)

Excitatory amino acid transporters (EAAT)

[^{18}F]-fludeoxyglucose (^{18}F-FDG)

Fluid-attenuated inversion recovery (FLAIR)

Glioblastoma (GBM)

Glioma-CpG island methylator phenotype (G-CIMP)

Hazard ratio (HR)

Health related quality of life (HRQOL)

High-grade gliomas (HGGs)

International Classification of Diseases - Oncology, version 3 (ICD-O-3)

International Classification of Diseases, 10th revision (ICD-10)

International Classification of Primary Care, 2nd edition (ICPC-2)

International League Against Epilepsy (ILAE)

Intracranial pressure (ICP)

Isocitrate dehydrogenase gene mutations (IDHmut)

Isocitrate dehydrogenase wild type (IDHwt)

Karnofsky performance score (KPS)

Low-grade gliomas (LGGs)

Magnetic resonance imaging (MRI)

Magnetic resonance spectroscopy (MRS)

Mammalian target of rapamycin (mTOR)

MilliSievert (mSv)

Missing at random (MAR)

Missing completely at random (MCAR)

Missing not at random (MNAR)

N-acetylaspartate (NAA)

Newcastle-Ottawa Scale (NOS)

Non-Enzyme-Inducing Antiepileptic Drug (Non-EIAED)

Odds ratio (OR)

O-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET)

Oligodendroglioma (Oligo)

O^{6}-methylguanine DNA methyltransferase (MGMT)

Overall survival (OS)

Personal identification number (PIN)

Positron emission tomography (PET)

Procarbazin, lomustine and vincristine (PCV)

Progression free survival (PFS)

Quality of life (QOL)

Radiotherapy (RT)

Randomized controlled trial (RCT)

Refractory status epilepticus (RSE)

Relative risk (RR)

Serotonin and noradrenaline reuptake inhibitors (SNRI)

Serotonin reuptake inhibitors (SSRI)

Standardized incidence ratio (SIR)

Status epilepticus (SE)

Repetition time msec/echo time (TE)

Telomerase reverse transcriptase (TERT)

Temozolomide (TMZ)

The Anatomical Therapeutic Chemical (ATC)

The Cancer registry of Norway (CRN)

The International Agency for Research on Cancer (IARC)

The Norwegian Cause of Death Registry (CDR)

The Norwegian Institute of Public Health (NIPH)

The Norwegian Prescription Database (NorPD)

World Health Organization (WHO)

1. Introduction

Gliomas develop within the brain parenchyma and the grade of biological aggressiveness is classified by criteria established by the World Health Organization (WHO) (1). While the astrocytoma cells are similar to the astrocytes, the oligodendroglioma cells are similar to the oligodendrocytes (Figure 1). The risk for glioma-associated epilepsy is partly dependent on glioma location and is inversely correlated to WHO grade. In total, 60-90% of patients with grade II-III glioma and 30-60% with grade IV, experience at least one epileptic seizure (2–4). In two-thirds, the epileptic seizure led to the glioma diagnosis (5,6). Brain tumor-related epilepsy (BTRE) and adverse effects from antiepileptic drugs (AEDs) may negatively influence the quality of life (QOL) (7).

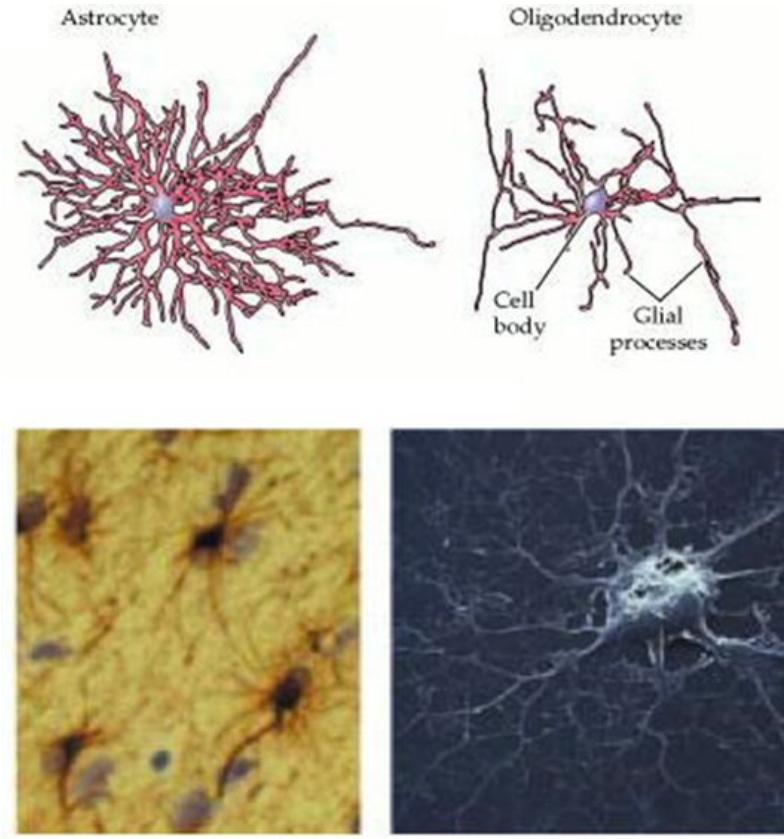


Figure 1 Astrocyte and oligodendrocyte impregnated with silver salts. Astrocytes labeled with an astrocyte-specific protein antibody and a scanning electron micrograph of a single oligodendroglial cell in tissue culture. Given with permission (8).

1.1 Glioma WHO grade II-IV

1.1.1 Diagnosis

Magnetic resonance imaging (MRI) is necessary to investigate the cause of a first epileptic seizure. Advances in MRI and positron emission tomography (PET) imaging have improved the non-invasive characterizing of glioma. As conventional MRI has limitations in distinguishing glioma subtypes, more advanced multiparametric MRI techniques are valuable, such as diffusion MRI (dMRI), diffusion tensor imaging (DTI), MR spectroscopy (MRS) and perfusion MRI (9–11). PET can identify metabolically active glioma tissue. However, PET with the most available tracer [^{18}F]-fludeoxyglucose (^{18}F-FDG), is interpreted with difficulties when used in brain tumor diagnostics because of high physiological glucose uptake in the surrounding cerebral cortex (12). Amino acid PET, especially O-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET) which is a tyrosine analogue tracer, can be useful in distinguishing glioma from other tumors and in molecular subtyping, combined with advanced MRI (12).

Histological diagnosis remains the gold standard for the assessment of gliomas, but even so with important limitations. The interobserver variability in the histological diagnosis of glioma is substantial, regarding both grading and subtyping (13). A free, online classification tool for CNS tumors has therefore been proposed (14). The histological features can differ throughout the tumor, with gradual local malignant transformation (Figure 2).

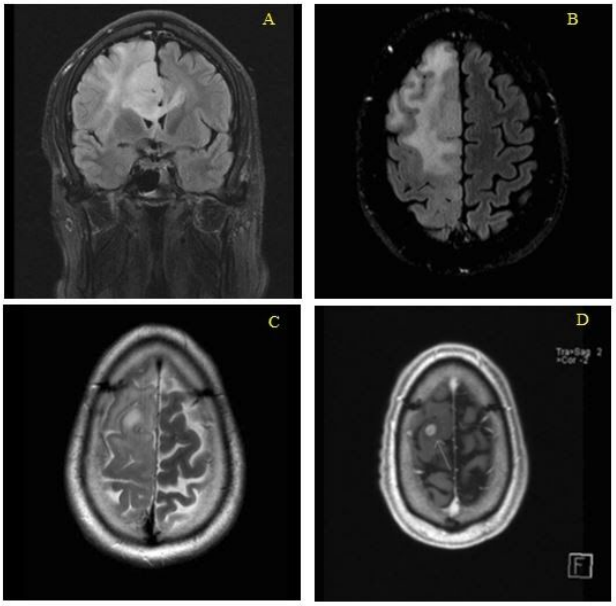
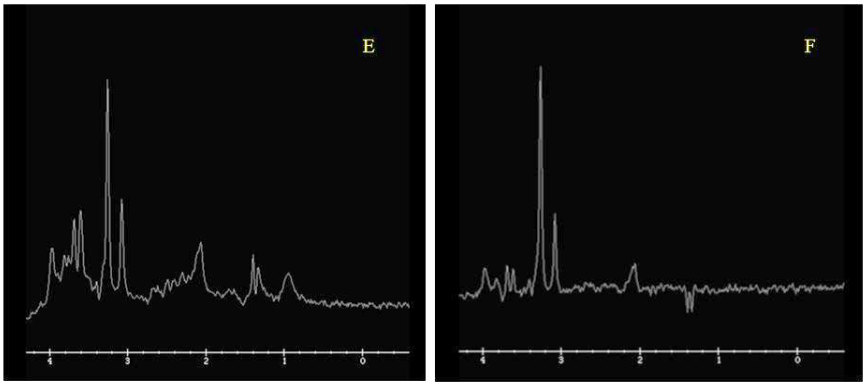


Figure 2 MRI of a 47-year-old man admitted after a focal prolonged seizure, showing a right-sided frontal glioma. **A**: Coronal T1 FLAIR; **B**: Axial FLAIR; **C**: T2; **D**: Contrast-enhanced T1 showing a small focus suspected to be of higher grade.

Figure 2 E: MRS of tumor tissue demonstrates elevated choline relative to NAA, consistent with glioma (TE 35 ms). **F**: The negative double peak (1.33) indicates anaerobic metabolism, consistent with higher grade (TE 144 ms). MRS= MR spectroscopy. NAA= *N*-acetyl aspartate. TE= repetition time msec/echo time.



The tumor was resected and the histology was IDH1 mutated low-grade glioma with malignant transformation to GBM in a small area (D). Given with acknowledgements to the consenting patient and the Department of Radiology, section of Neuroradiology, Haukeland University Hospital providing MRI and MRS with descriptions.

The glioma diagnosis is ultimately based on the neuropathological assessment of tumor tissue from the tumor resection or biopsy with immunohistochemistry and selected molecular tests. Oligodendrogliomas lack parts of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), called 1p/19q co-deletion (15). Early in the development of grade II-III, but rarely in grade IV, genes in isocitrate dehydrogenase (IDH) are mutated (16). IDH is an enzyme catalyzing the oxidative decarboxylation of isocitrate. The mutation may depend on location (17). 1p/19q co-deletion and IDH 1 or 2 gene mutation (IDHmut) increase the specificity of the histological diagnosis and was included in the updated 2016 classification of gliomas (1). Oligodendrogliomas have IDHmut with 1p/19q co-deletion, while astrocytomas have IDHmut without 1p/19q co-deletion. The tumors formerly classified as oligoastrocytoma are now classified either as astrocytoma or oligodendroglioma according to the molecular characteristics (Figure 3). Only 10% of all GBMs have IDHmut and these GBMs are probably developed from a lower grade glioma (18,19).

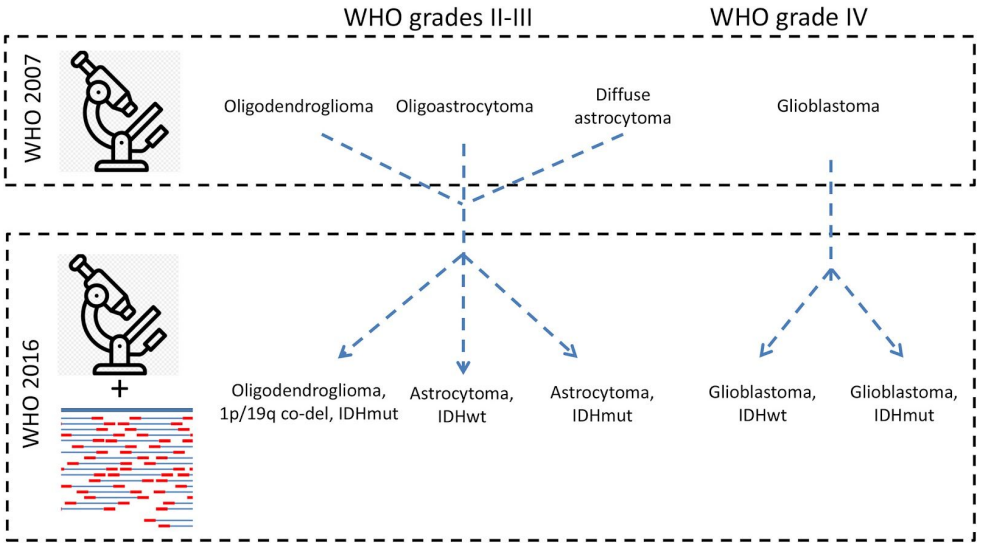


Figure 3 The 2016 update of the WHO classification of CNS tumors. Co-del= co-deletion. IDHmut= IDH gene mutation. IDHwt= IDH wild type. Given with permission (20).

1.1.2 Risk factors

Gliomas are more common in Caucasians than in persons of other ethnicity (21). Persons who have a first degree family member with brain cancer have a doubled glioma risk (22). About 5% of gliomas can be explained by hereditary conditions such as neurofibromatosis and tuberous sclerosis, or by gene mutations such as POT1 (23). GBM and lower grade gliomas may have different etiologies explained by observations of involved deregulation of pathways that concern telomere length and epidermal growth factor receptor (EGFR) (24). Most GBMs originate without any known genetic predisposition. The risk for GBM peaks at 75-79 years (25). Most of lower grade gliomas present earlier, in the third or fourth decade of life (26). Body height as risk factor for glioma was hypothesized to be due to insulin-like growth factor as common pathway, while body mass index (BMI) was disproved as risk factor (27,28). The risk for grade III-IV glioma increased for each 100 ml increase in intracranial volume with odds ratio (OR) 1.69 (95% confidence interval (CI) 1.35-2.19) (29). The propensity for glioma in males over females was explained by the higher intracranial volume, and the risk was in fact lower in males than in females after correcting for intracranial volume (29). Higher socioeconomic status and body height as risk factors for glioma were suggested to be related to intracranial volume (29). Exposure to atomic bombs, therapeutic radiation and medical imaging increases the risk for CNS tumors because of ionizing radiation (30,31). Repeated CT scans yield a cumulative dose of ionizing radiation increasing the risk for brain cancer from the lower limit of 10-50 milliSievert (mSv) (32,33). Traffic-related air-pollution has been proposed as a risk factor for malignant brain tumors (34). Non-ionizing radiation from cellular phones has not been proved as a risk factor for glioma, but this is debated because of the possibility of an unknown latency period (35–37). Positive respiratory allergen-specific and total IgE in serum, atopic diseases and asthma have all been found to decrease glioma risk, but these relationships are still not fully uncovered (38,39).

1.1.3 Treatment

Surgical resection is essential in the glioma treatment but initial resection versus biopsy for grade II glioma has been controversial (40). Recent studies support a greater extent of resection for grade II glioma (41,42). Benefit from a more extensive resection might depend on the molecular subtype (43,44), while early surgical resection was more effective than late surgical resection in all molecular subgroups (41). Radiotherapy (RT) and chemotherapy is given depending on glioma subtype, age and Karnofsky performance score (KPS) (Figure 4) (45).

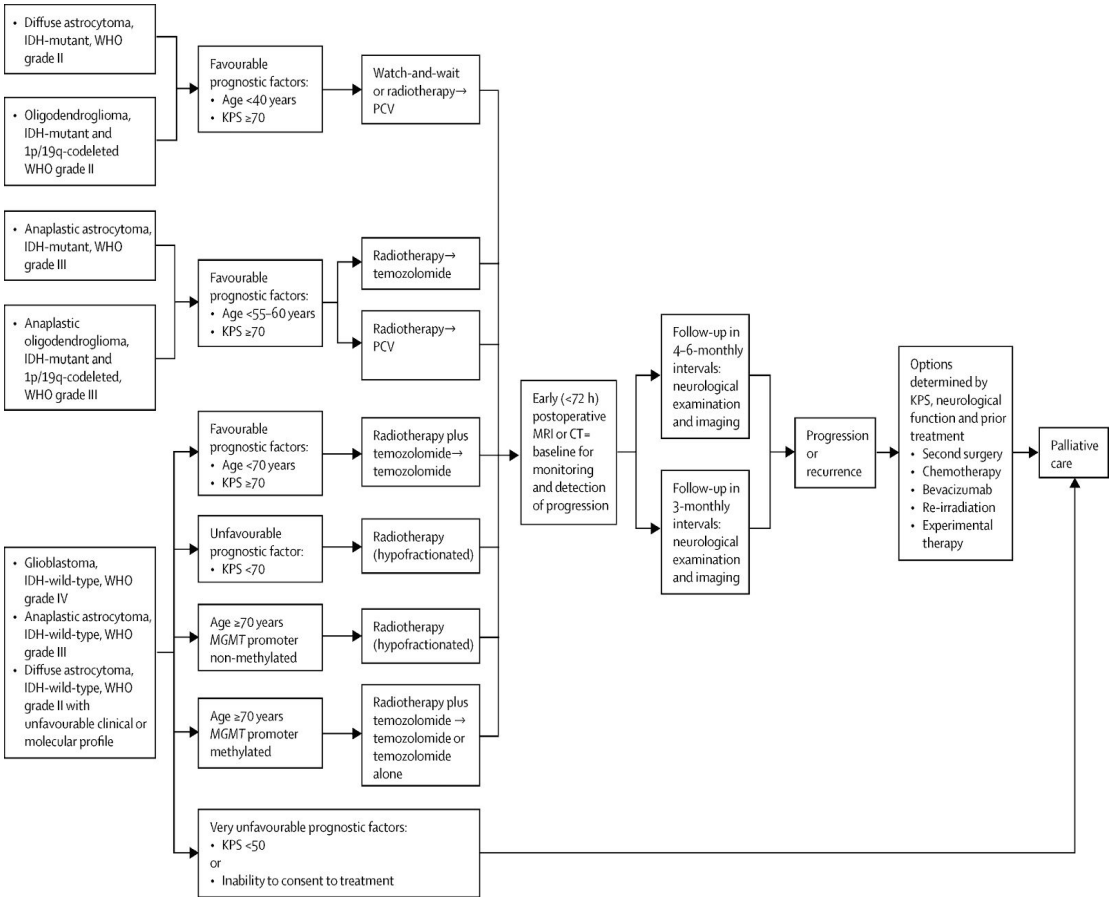


Figure 4 Treatment pathways for WHO grade II-IV glioma. Maximum safe resection is recommended whenever feasible. IDH= isocitrate dehydrogenase. KPS= Karnofsky performance score. MGMT= O^6-methylguanine DNA methyltransferase. PCV= procarbazine, lomustine and vincristine. Given with permission (45).

GBM in adults ≤ 70 years of age is maximally safely resected before RT. Temozolomide (TMZ) is an alkylating chemotherapy agent which prolongs median overall survival (OS) from 12.1 months with RT alone to 14.6 months (46). TMZ is given concomitant with RT, followed by five days of adjuvant TMZ given every 28 days, usually for six cycles (45). O^6-methylguanine DNA methyltransferase (MGMT) is a DNA repair protein. When methyl molecules are attached to the promoter region, the transcription of MGMT is silenced which improves OS because of better effect from TMZ (47). Median OS is 23.4 months with methylated MGMT and 12.6 months with unmethylated MGMT (48,49). However, this might be more complex as global methylation and point mutations in the promoter of telomerase reverse transcriptase (TERT) gene might affect TMZ effect (50). A recent randomized controlled trial (RCT) showed improved median OS in GBM patients 18-70 years of age with methylated MGMT and KPS ≥70 from 31.4 months with TMZ alone to 48.1 months with lomustine-TMZ combination (51). Elderly GBM patients more often have treatment complications like neurocognitive dysfunction after RT (52) and adverse effects from TMZ (53). Hypofractionated RT without TMZ is standard treatment of GBM in adults >70 years of age with unmethylated MGMT (46,48,54).

1.1.4 Prognosis and follow-up

Grade II glioma gradually progresses with malignant transformation. The tumor usually grows continuously, but can remain stable for prolonged periods (55). Rapid volumetric expansion indicates a higher malignancy potential (56,57). Molecular differences explain the heterogeneous outcome (Table 1).

Table 1 Molecular classification and survival in WHO grade II glioma.

Grade II glioma	Prognostic biomarkers		Median PFS years	Median OS years	Reference
	1p/19q codel	IDHmut			
Astrocytoma	**(-)**	**(-)**	**1.7**	**≤5**	(58–61)
Astrocytoma	**(-)**	**(+)**	**4.0**	**>7**	(60-62)
Oligodendroglioma	**(+)**	**(+)**	**5.2**	**>12**	(60–62)

Table 1 Grade II glioma with 1p/19q co-deletion has the most favorable outcome while intact 1p/19q and IDHwt has the shortest survival. Codel= chromosomal co-deletion. IDHmut= isocitrate dehydrogenase 1 or 2 gene mutation. OS= overall survival. PFS= progression free survival. Modified with permission (63).

In grade II-III glioma, 1p/19q co-deletion predicts a favourable response to RT and chemotherapy (64). Patients with IDHmut live longer independently of tumor grade II or III, while IDH wild-type (IDHwt) has a worse prognosis (65,66). Survival differs by histological subtype alone as well as by molecular genetic subgroups (Figure 5). Genome-wide DNA methylation, termed glioma-CpG island methylator phenotype (G-CIMP), has been related to an improved prognosis and may become a future glioma subtype (67).

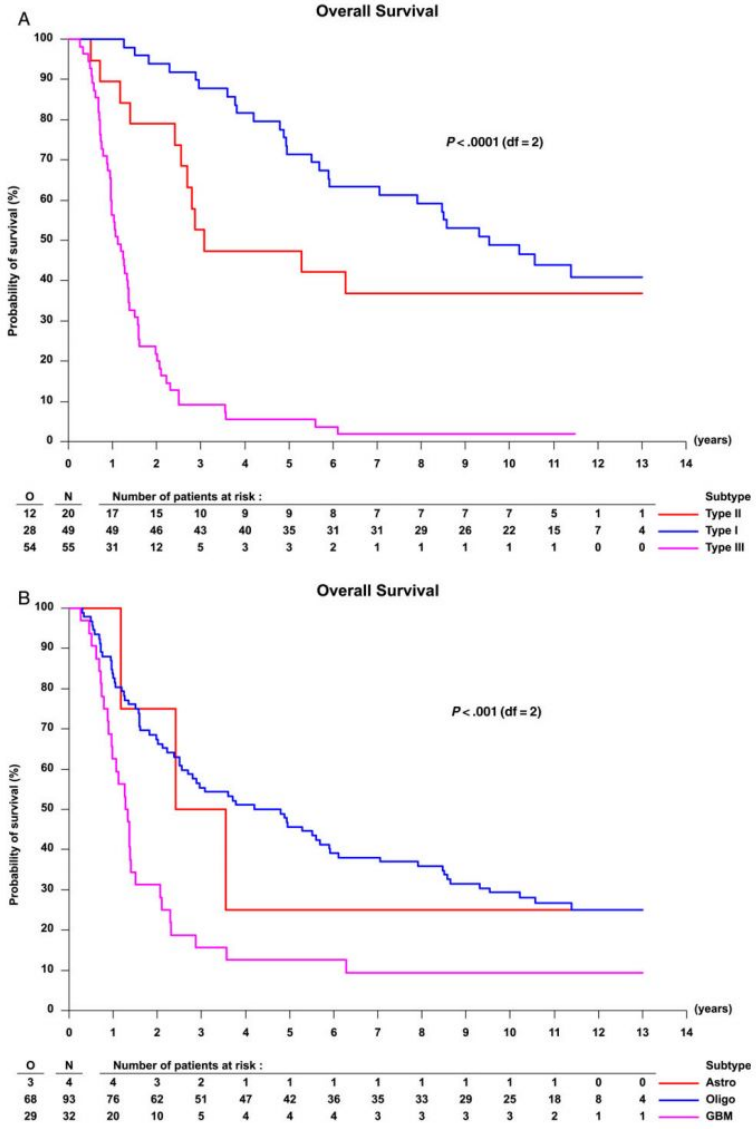


Figure 5 Kaplan-Meier OS curves for patients in the EORTC 26951 study. (A) According to the molecular genetic analysis: Type I with 1p/19q co-deletion (entire 1p and 19q arm). Type II with IDHmut without 1p/19q co-deletion. Type III with TERT mutation without 1p/19q co-deletion or 10q loss and either EGFR amplification or chromosome 7 imbalance. (B) According to the histological subtypes "oligodendroglioma", "astrocytoma" or "GBM" diagnosed by the central study pathologist. O= observed events. N= number of patients. Given with permission (68).

1.2 Glioma-associated epilepsy

1.2.1 Epileptogenesis

The pathogenesis of tumor-related epilepsy is multifactorial and not completely understood. Alterations in the peritumoral zone is an acknowledged driver of glioma epileptogenicity (69,70). That seizure frequency differs between tumors of the same histopathology can be explained by tumor location, but also by functional changes such as increased extracellular K+ and altered function of peritumoral glial gap junctions (71,72). Normal astrocytes manage to maintain a stable level of extracellular glutamate through Na+-dependent glutamate transport. In glioma cells, the cystine-glutamate transporter system (xCT) releases extracellular glutamate and there is a reduced Na+-dependent glutamate transport (73). Glutamate released by xCT from GBM in mice led to epileptiform hyperexcitability with spread into surrounding brain tissue (74). Elevated total glutamate concentration in the tumor and peritumoral brain and altered glutamate transporter expression is associated with epileptic seizures in patients with grade II-IV glioma (75). The glutamate hypothesis (71,76) is an explanatory model for the carcinogenesis of glioma and the glioma-associated epileptogenesis (Figure 6) (77). In addition to initiate epileptic seizures, glutamate may enhance glioma proliferation and invasion (78).

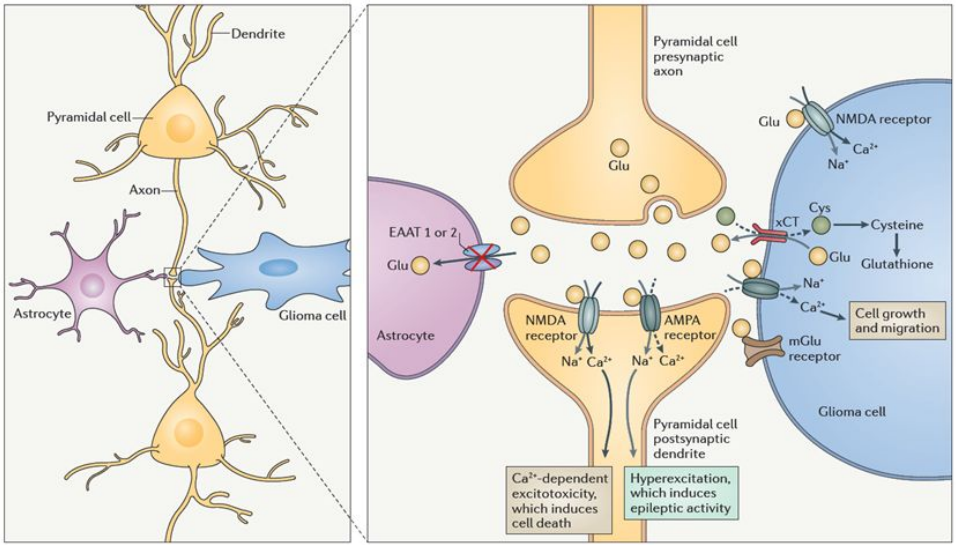


Figure 6 Model for common pathway of glioma epileptogenesis and tumorigenesis. The glioma cell releases glutamate with the cystine-glutamate transporter system (xCT) and uses cystine to produce the antioxidant glutathione which protects the glioma cell. The increased extracellular glutamate levels are further increased by impairment of excitatory amino acid transporters (EAAT) in the astrocytes. In the synaptic cleft, glutamate activates neuronal postsynaptic receptors and glioma cell receptors inducing intracellular Ca2+ signalling cascades which promote neuronal death, and glioma cell growth and migration. Given with permission (77).

Alternative hypotheses for glioma epileptogenesis include both intratumoral- and peritumoral pathways (71,79,80). Mammalian target of rapamycin (mTOR) is increased in peritumoral neurons and contributes to glioma epileptogenesis (81). Low-grade gliomas (LGGs), often defined as WHO grade II, grow slower and cause more chronic functional changes in the peritumoral cortex than high-grade gliomas (HGGs), defined as WHO grade III-IV (71). The higher epileptogenic propensity of grade II glioma can also be explained by more limited neuronal death, interacting glial cells and remodeled brain networks with imbalance between inhibition and excitation, leading to epileptic seizures (78). One known triggering mechanism of glioma-associated epileptic seizures is dysregulation of neuronal chloride reducing inhibitory GABA signalling and enhancing excitatory glutamatergic signalling (77,82). Brain network disturbances in glioma have been proved (83,84), are hypothesized to be due to altered protein

expression (85), and differ between grade II gliomas and HGGs (86). Damaged neuronal networks in HGGs may reduce the possibility of epileptic discharges and thus contribute to a lower epilepsy risk than in grade II gliomas (77). Glioma epileptogenesis is also affected by mechanical mass effect, inflammation and edema, in addition to vascular, astrocytic and microglial dysfunction (82). Grade II gliomas are larger when presenting with seizures than with other symptoms on the contrary to epileptogenic HGGs having smaller tumor size than non-epileptogenic HGGs (87). Epileptogenic gliomas are more often located temporally and frontally than in deep or midline areas (2,87–89). Insular cortical tumors often present with epileptic seizures, explained by these tumors being clinically silent until the first seizure (87). Oligodendroglial tumors mostly involve the cortex with a higher propensity of seizures, while astrocytomas can be located also in the white matter (82). Up to 70-80% of grade II gliomas are IDHmut and thereby associated with increased risk of epileptic seizures (75,90–92). With IDHmut, isocitrate is converted to D-2-hydroxyglutarate (D-2HG) instead of the antiepileptic alpha-ketoglutarate (α-ketoglutarate) (93). D-2HG accumulates in the glioma cells and binds to and activates glutamate receptors (94). In this way, D-2HG also affects synaptic clearance (95,96). There is supporting evidence for downregulation of inhibitory neurotransmission (97,98). In a retrospective cohort study, 30.5% of 59 glioma patients with seizures at glioma diagnosis and 17.8% of 151 glioma patients without seizures had high xCT expression ($p=0.05$, X^2 test) and high xCT expression was not associated with refractory epilepsy requiring more than three AEDs (99). xCT was more highly expressed in IDHwt HGGs than in IDHmut grade II gliomas (99), suggestive of this mechanism being especially important for the HGGs epileptogenesis.

1.2.2 Classification of epileptic seizures and status epilepticus

The classification of epileptic seizures was revised by the International League Against Epilepsy (ILAE) in 2017 (100). The previous term “simple partial” became “focal aware”, “complex partial” became “focal with impaired awareness”, and “secondary generalization” became “focal to bilateral tonic clonic” (Figure 7). In addition to “focal onset” and “generalized onset”, the category “unknown onset” was established. In the new classification, all seizure types are

subdivided into “motor” or “non-motor” (Figure 8). When onset is unknown together with lack of information or inability to categorize otherwise, the seizure type is “unclassified”.

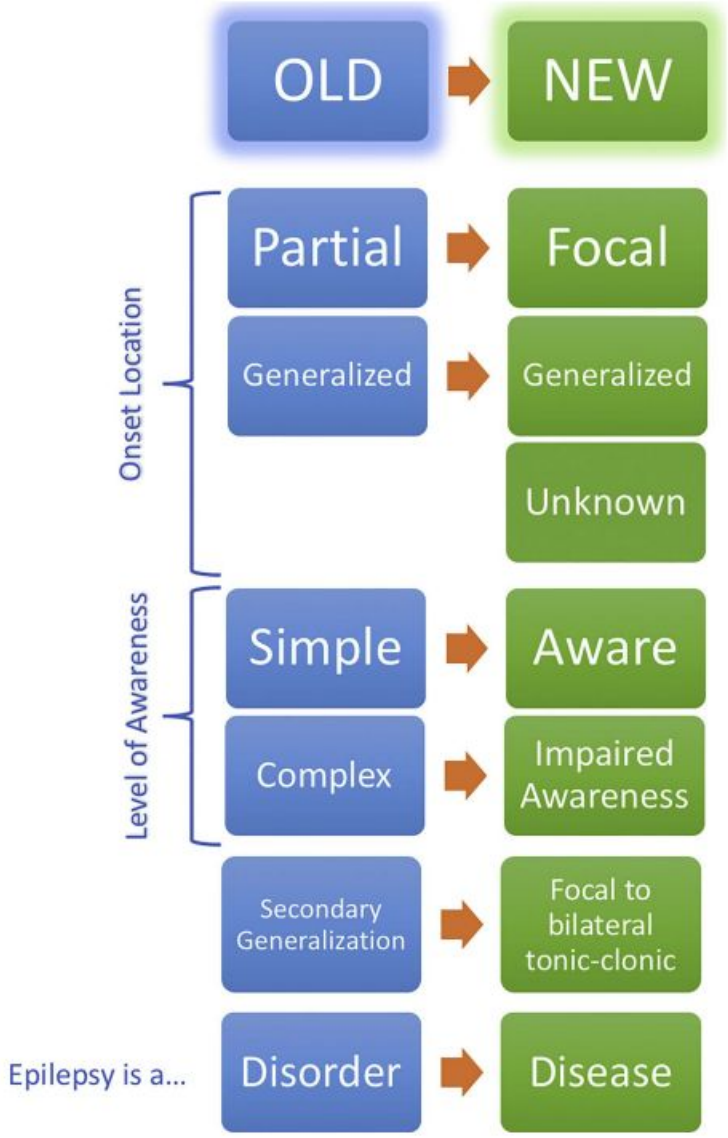


Figure 7 The old and the new definitions and classifications of seizures and epilepsy. Given with permission (101).

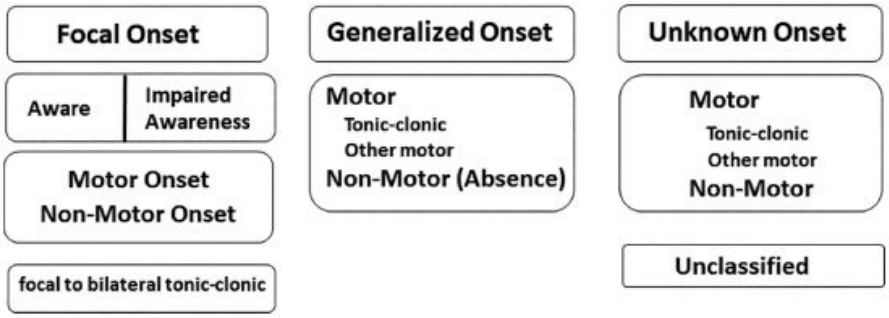


Figure 8 The updated 2017 version of ILAE operational classification of epileptic seizure types. Given with permission (100).

In grade II glioma, independently of timing, the epileptic seizures are focal to bilateral tonic-clonic in 69.7%, focal aware in 23.7%, and focal with impaired awareness in 6.6% (4). In GBM, the early epileptic seizures are focal to bilateral tonic-clonic in 40%, focal aware in 28-37%, and both focal and focal to bilateral tonic-clonic in 14% (5,89,102–108). Grade II-III glioma is associated with more focal to bilateral tonic-clonic seizures than GBM (109).

An epileptic seizure normally ends between 15 seconds and two minutes after onset (110). When the mechanisms that terminate the seizure fail, SE (Status epilepticus) evolves. For research on outcome of SE, a time frame of 30 minutes has traditionally been used, while a time frame of five minutes has been introduced to evaluate emergency treatment (111). In 2015, ILAE proposed a new definition of SE: *"SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures"(111)*. In this definition, there are two operational dimensions based on animal experiments and clinical research with various

time for different forms of SE (Table 2). The semiological classification of SE was also revised in 2015 (Table 3). SE has been reported to occur in 12-15% of patients with grade III-IV glioma (6,112). Few studies have investigated SE in glioma patients.

Table 2 Operational SE dimensions.

SE type	**Operational dimension 1* Time 1 (t_1)**	**Operational dimension 2¤ Time 2 (t_2)**
Tonic clonic	5 min	30 min
Focal with impaired consciousness	10 min	>60 min
Absence	10-15 min	unknown

*When a seizure is likely to be prolonged, leading to continuous seizure activity
¤When a seizure may cause long-term consequences

Table 2 Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 indicating the time at which long-term consequences may be expected. Given with permission (111,113).

Table 3 Semiological classification of SE.

A With prominent motor symptoms

A1 Convulsive SE (CSE, synonym: tonic-clonic SE)
a. Generalized convulsive
b. Focal onset evolving into bilateral convulsive
c. Unknown whether focal or generalized

A2 Myoclonic SE (prominent myoclonic jerks)
a. With coma
b. Without coma

A3 Focal motor SE
a. Repeated focal motor seizures (Jacksonian)
b. Epilepsia partialis continua (EPC)
c. Adversive status
d. Oculoclonic status
e. Ictal paresis (i.e., focal inhibitory)

A4 Tonic SE

A5 Hyperkinetic SE

B Without prominent motor symptoms (i.e. NCSE)

B1 NCSE with coma (including "subtle" SE)

B2 NCSE without coma
a Generalized
a. Typical absence
b. Atypical absence
c. Myoclonic absence

b Focal
a. Without impairment of consciousness
b. Aphasic
c. With impaired consciousness

c Unknown whether focal or generalized
a. Autonomic

Table 3 The most recent classification of SE. Given with permission (111,113). (B) "SE without prominent motor symptoms" replaces the previous "Non convulsive SE" (NCSE), of which (B2) by some is referred to as "NCSE proper" as (B1) co-exists with coma (114).

1.2.3 Epilepsy treatment in glioma

Most patients with grade II glioma experience epileptic seizures. At the time of grade II glioma diagnosis, 65-85% have epileptic seizures, and additionally 6-11% have their first epileptic seizures later during the disease (4,5). The oncological therapy has antiepileptic effects. Without tumor resection, the epilepsy often worsen, also under treatment with AEDs (102). At six months after tumor resection, 71% of patients with grade II glioma and associated epilepsy were seizure free (115). At ≥two years after tumor resection, 71% with temporal lobe grade II-III glioma and treatment refractory epilepsy were seizure free or without disabling seizures (116). Focal aware seizures and preoperative refractory epilepsy predicted postoperative refractory epilepsy (115). More patients obtain seizure freedom after total or subtotal resection than after partial resection or biopsy (102). Seizure onset <one year before surgery and total resection were predictors for postoperative seizure freedom (115). Presurgical evaluation with video-electroencephalogram (video-EEG) can improve identifying the epileptogenic zone (117). After partial resection, intraoperative functional mapping during the next surgery can contribute to reduce epileptic seizures (118). Reduction of epileptic seizures early during RT did not correlate to tumor reduction on imaging, indicating different mechanisms for effects on epilepsy and tumor tissue (119). After chemotherapy, epileptic seizure control improved in 48-100% of patients with grade II glioma, and seizure freedom was obtained in 20-40% (120–128). After TMZ treatment for grade II glioma, seizure reduction correlated with volume reduction of metabolically active tumor on amino acid PET, but not with volume reduction of tumor on MRI, indicating that reducing the metabolic imbalance is of importance for seizure control (129).

Treatment with AEDs is recommended after the first epileptic seizure in all glioma patients. The American Academy of Neurology (AAN) disapprove of prophylactic AED treatment for patients with a brain tumor without a history of seizures (130). In 2006, the treatment recommendations from ILAE for focal epilepsies were phenytoin and carbamazepine for adults, and oxcarbazepine for children (131). Phenytoin, carbamazepine and oxcarbazepine are enzyme-inducing

antiepileptic drugs (EIAEDs). Because drug-drug interactions with some chemotherapeutic agents may lead to impaired anti-tumor effects and bone marrow suppression, EIAEDs are not recommended for glioma patients (132,133). Valproate is an enzyme-inhibiting AED and has also been reported with serious hematological adverse effects when combined with chemotherapy (134–136). Reports on efficacy from levetiracetam on BTRE and synergistic effects when combining levetiracetam with valproate, led to these AEDs being proposed as primary treatment options (5,137,138). However, a Cochrane review in 2011 identified only one RCT with available data and concluded on a lack of high-quality evidence for recommending particular AEDs for BTRE (139). The one RCT concluded that switch from phenytoin into levetiracetam after glioma resection is safe (140), and levetiracetam became first line treatment (139). One RCT in 2014 concluded that levetiracetam and pregabalin are efficacious and safe as monotherapy for grade II-IV glioma patients under oncological treatment (141). Seizure reduction >50% was reported in 65-100% of glioma patients with levetiracetam add-on, while seizure freedom was reported in 20-77% with levetiracetam add-on and in 70-91% with levetiracetam monotherapy (3,6,142). Seizure freedom was reported in 60% of glioma patients with valproate add-on and in 30-78% with valproate monotherapy (3,6,143). Oncological treatment probably contributed to all seizure reduction rates. Levetiracetam is still first line AED for managing seizures in cancer patients (82).

1.2.4 Antiepileptic drug treatment and glioma survival

It has been a matter of debate whether particular AEDs affect OS in glioma patients. Valproate is a histone deacetylase inhibitor, and stronger acetylation of histone proteins with less methylation of the promoter in tumor-suppressor genes leads to slower glioma cell growth in vitro and in vivo (144,145). There are several studies of valproate and OS in patients with GBM (6,146–149). One theory for improved survival with valproate was interactions with TMZ, and TMZ clearance was reported to be decreased by 5% when combined with valproate (134,146). Levetiracetam was reported to improve the effect from TMZ by inhibiting the transcription of MGMT (150).

Survival benefit from levetiracetam in combination with TMZ in GBM patients was found in one retrospective study (151). A pooled analysis of prospective clinical trials did not find improved OS neither from valproate nor from levetiracetam in patients with newly diagnosed GBM (152). Further studies on survival related to AEDs in glioma patients have been warranted (153).

1.3 Glioma and psychiatric comorbidity

1.3.1 Quality of life

Grade II glioma is mostly diagnosed in young adults aged 20-40 years (154). Cognitive and emotional functioning is often impaired in grade II glioma patients (155). During the six months following start of RT, 20% of the glioma patients developed a major depression (156). The risk for depression was higher with a previous history of depression and with functional impairment, and the depression often lasted for around three months (156). Health related quality of life (HRQOL) in grade II glioma patients has been reported to be poorer than in HGG patients (157,158) and healthy controls (159). Psychological deficits can be associated with the tumor and confrontation with the disease (160). Grade II glioma patients who underwent surgery showed a psychological maturation, commonly seen in cancer patients, while the patients with epilepsy had both lower life-satisfaction and psychological well-being (161). Patients with a stable grade II glioma reported similar HRQOL at six and twelve years after primary oncological treatment, except from physical functioning being worse at twelve years (162). Poor HRQOL has been related to age >40 years (163), male gender and lack of return to work (164).

1.3.2 Epilepsy and psychiatric comorbidity

Anxiety and depression are frequent comorbidities to epilepsy. For epilepsy in general, the prevalence has been estimated to 20% for anxiety and 23% for depression (165–167). Psychiatric comorbidity negatively affects QOL more than seizure frequency does (168). Poor QOL is better predicted from coexisting depression than from seizure frequency (169). Anxiety negatively influence the social functioning of patients with epilepsy (170). Adverse effects from AEDs impair the self-perceived health status of patients with epilepsy (171,172) and reduce QOL (173,174). One study found that higher level of self-perceived adverse effects from AEDs was associated with increased severity of anxiety and depression in patients with epilepsy (175). Further studies of psychiatric comorbidity in epilepsy should consider the underlying disease of the epilepsy (176), this being especially important for the patients with glioma.

1.3.3 Antiepileptic drugs with neuropsychiatric adverse effects

AAN reported that adverse effects from AEDs were both more frequent and severe in BTRE than in other persons using AEDs (130). This can partly be due to drug-drug interactions with chemotherapeutic agents. AEDs were reported to negatively influence QOL in patients with BTRE (177,178). Treatment with phenobarbital, vigabatrin, levetiracetam, felbamate or topiramate, and redrawal of carbamazepine, oxcarbazepine, valproate or lamotrigine, have been associated with depression (179). Levetiracetam causes depression, nervousness, hostility and anxiety in up to 10% of all treated patients (180,181). Risk factors for drug-treated anxiety and depression in patients with glioma had not been explored by any previous study.

2. Aims of the thesis

1. To determine the AED treatment patterns in a nationwide cohort of GBM patients. We hypothesized that over time, newer non-EIAEDs are increasingly preferred over older EIAEDs.

2. To investigate whether epilepsy or AED exposure worsen or improve OS in GBM patients. We hypothesized that epilepsy is not an individual favorable prognostic factor but that exposure to particular AEDs may be associated with improved OS.

3. To determine the temporary patterns of drug-treated epilepsy, pain, anxiety and depression related to a glioma diagnosis. We hypothesized that drug-treated epilepsy, pain, anxiety and depression can be symptoms of glioma.

4. To identify risk factors for drug-treated anxiety and depression after a glioma diagnosis. We hypothesized that some AEDs may be associated with drug-treated anxiety or depression.

5. To compare psychiatric medication prescribed and dispensed to glioma patients, with or without epilepsy, to the general population. We hypothesized that glioma patients receive more psychiatric medication than the general population.

6. To investigate SE in patients with grade II-IV glioma related to tumor grade and trigger factors. We hypothesized that SE is more frequent with grade II glioma than with HGG, and that SE can be triggered also by other factors than tumor growth.

7. To evaluate the treatment response and outcome after SE secondary to glioma. We hypothesized that SE with underlying tumor progression is more treatment refractory and has a worse outcome than SE with no tumor progression.

3. Material and methods

3.1 Material paper I-II

3.1.1 National registry data

Data from three national health registries, the Cancer registry of Norway (CRN), the Norwegian Prescription Database (NorPD) and the Norwegian Cause of Death Registry (CDR), were obtained for all patients diagnosed with glioma 2004-2010.

3.1.1.1 The Cancer Registry of Norway (CRN)

CRN was established in 1951 and contains information on all cases of verified or probable cancer. Reporting information on all cancer diagnoses to CRN is mandatory by Norwegian legislation. The data are collected from various sources as illustrated below (Figure 9). CRN data have been evaluated as near complete and to have satisfactory accuracy (182).

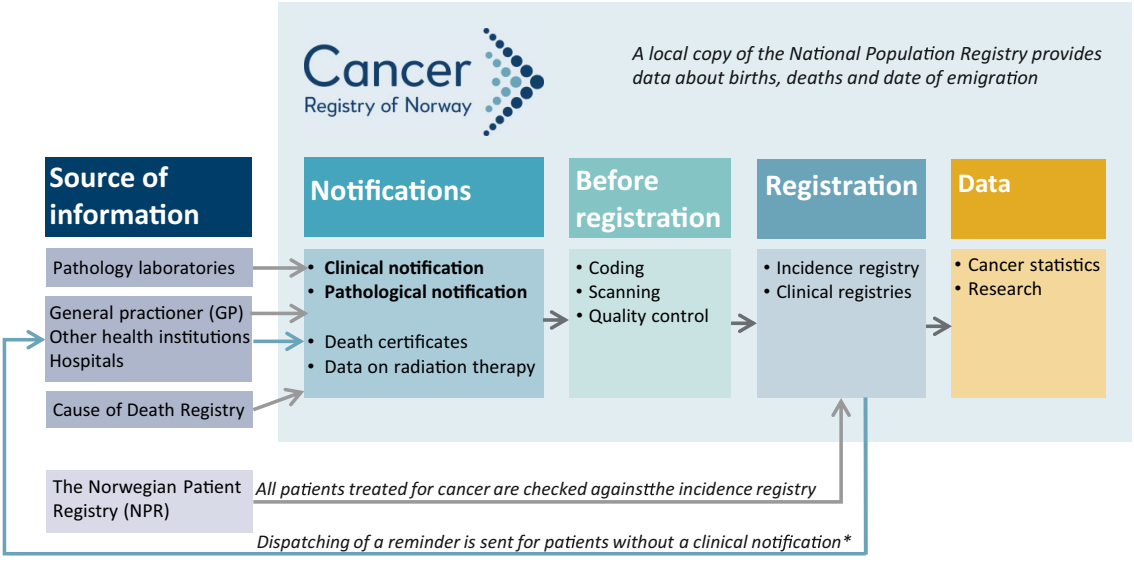


Figure 9 Sources of information and the process of cancer registration at CRN. Given with permission (183).

3.1.1.2 The Norwegian prescription database (NorPD)

NorPD registers information on all drugs that are prescribed and dispensed to individual patients treated in Norwegian ambulatory care (Figure 10, Figure 11). These registrations have been ongoing since the establishment on January 1, 2004 (184). Drugs are classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification (185). Also, NorPD reporting is mandatory by Norwegian legislation. For chronic diseases, reimbursement is given on certain diagnostic codes from the International Classification of Diseases (ICD-10) and the International Classification of Primary Care 2nd edition (ICPC-2).

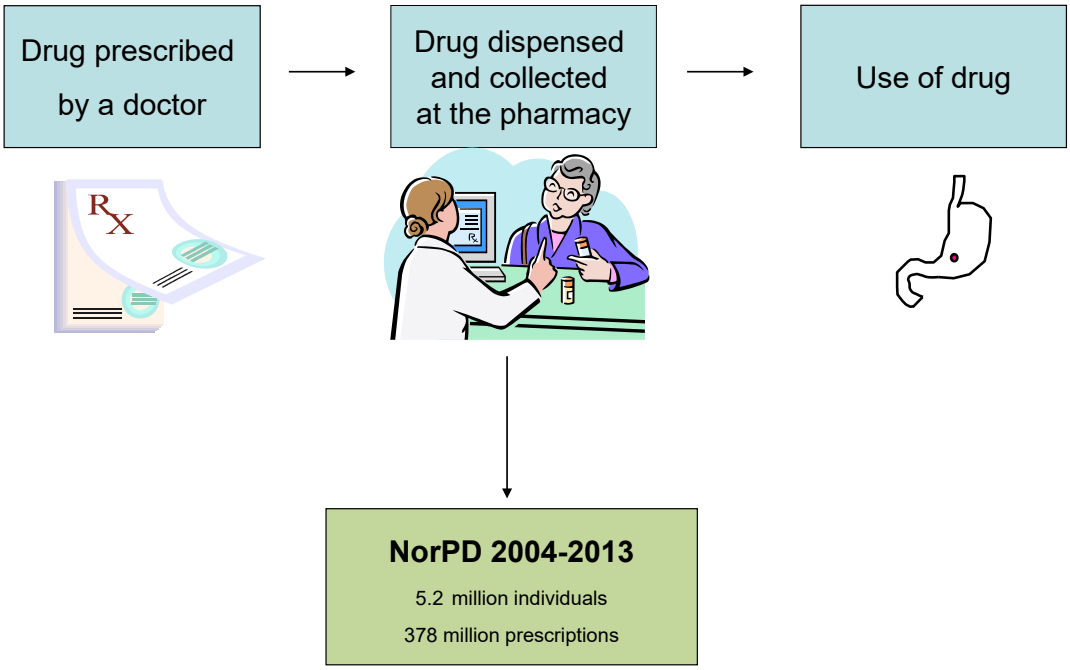


Figure 10 NorPD data collection. Modified with permission, including information provided by NorPD, NIPH.

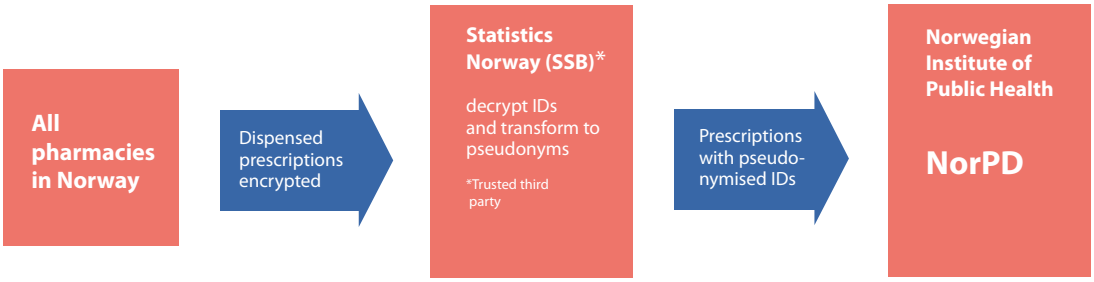


Figure 11 NorPD data flow. Given with permission (186).

3.1.1.3 The Norwegian Cause of Death Registry (CDR)

Statistics Norway maintained CDR data from the establishment of CDR in 1951 until January 1, 2014 when the responsibility was transferred to the Norwegian Institute of Public Health (NIPH). CDR contains causes of death for all persons registered as Norwegian residents at the time of death. All registered causes of death are coded according to ICD-10 as underlying cause of death and contributing causes of death. The reporting is mandatory for Norwegian doctors by the Norwegian Health Personnel Act. The information obtained from the death certificate is cross-linked to deaths in the Central Population Registry. If the death certificate is inadequate, additional information is retrieved as illustrated below (Figure 12).

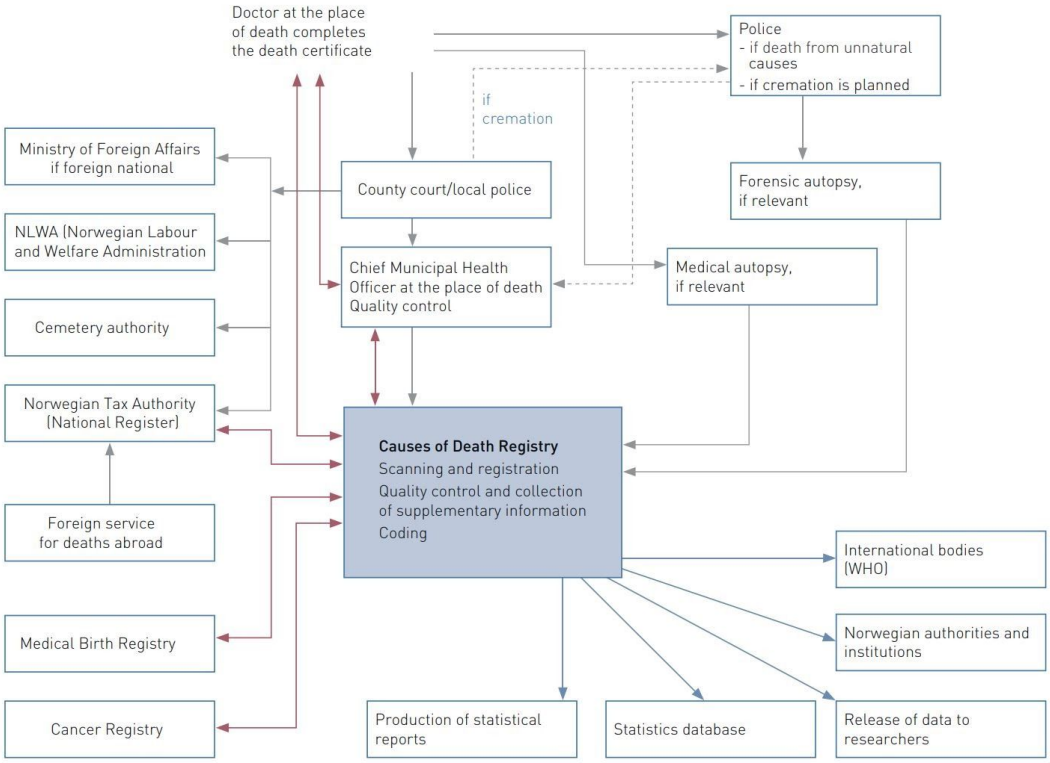


Figure 12 The reporting process for death certificates. Gray arrows indicate the information flow after a case of death. Red arrows indicate the feedback and quality control. Blue arrows indicate deliveries of data from CDR. Given with permission (187).

3.1.2 Linkage of data and follow-up

Since 1964, every Norwegian citizen has received a unique personal identification number (PIN). Data from the three national health registries described above were linked utilizing PIN (Figure

13). Because NorPD was established in 2004, we did not include patients diagnosed with glioma before 2004. The first three months of 2004 were excluded in paper I-II to ascertain that all drugs prescribed and dispensed to the study population were registered in NorPD. For paper II, data from CDR were included until December 31, 2011. For paper I-II, follow-up data from NorPD were included until October 31, 2013.

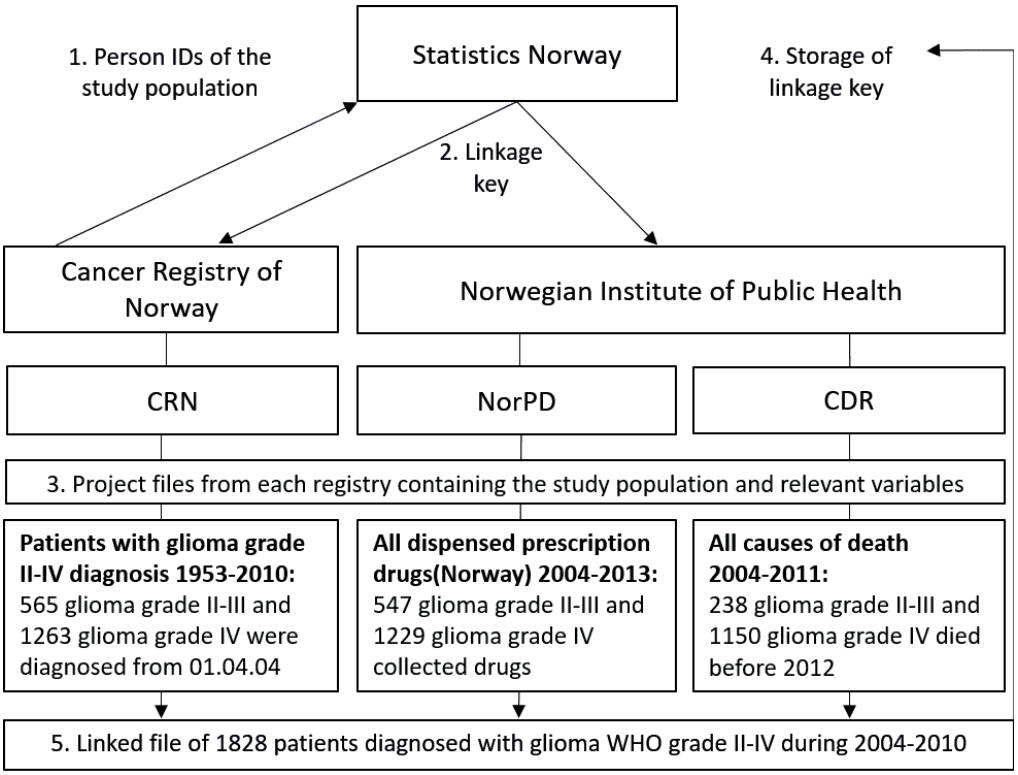


Figure 13 Flow chart of the data collection and linkage for paper I-II.

3.1.3 Study population paper I

The study population in paper I consisted of all patients registered in CRN with a valid PIN and diagnosis of WHO grade IV glioma between April 1, 2004 and December 31, 2010. There were 1263 patients with code 94403 or 94413 according to the International Agency for Research on Cancer (IARC) classification tool, International Classification of Diseases - Oncology, version 3 (ICD-O-3) (188).

3.1.4 Study population paper II

The study population in paper II consisted of all patients registered in CRN with a valid PIN and diagnosis of WHO grade II-IV glioma between April 1, 2004 and December 31, 2010. We defined glioma subgroups according to ICD-O-3 morphology codes and based on the 2007 WHO glioma classification (189). Among the patients with grade II, 81 had oligoastrocytoma (93823), 98 had oligodendroglioma (94503) and 231 had astrocytoma (94003, 94103, 94113, 94203 and 94243). Among the patients with grade III, 41 had anaplastic oligodendroglioma (94513) and 114 had anaplastic astrocytoma (94013). Of 1263 patients with GBM (94403 and 94413), 91% died before 2012. Among the 565 patients with grade II-III glioma, 42% died before 2012.

3.2 Material paper III

3.2.1 Prospective cohort study

The source population of the study population in paper III was a prospective clinical study of adult patients with WHO grade II–IV glioma and associated epilepsy in two Norwegian counties. The study was initiated in 2008 at Haukeland University Hospital, Bergen in Hordaland county and Førde Central Hospital in Sogn and Fjordane county. All eligible patients have been enrolled since 2009, and the study is still ongoing. Together, these counties had a population of 620 527 according to Statistics Norway on January 1, 2015. The inclusion criteria was ≥16 years of age when diagnosed with a verified grade II-IV glioma, and at least one epileptic seizure that was judged by the clinician to be related to the glioma disease. The criteria were that the epileptic seizure occurred within one year before the glioma diagnosis or later, and epilepsy with no other etiology than structural due to the glioma. Patients are followed clinically and radiologically from their first seizure until death. All relevant information regarding the glioma and the epilepsy from the medical records, descriptions of radiological images, EEGs, serum concentrations of AEDs and neurological examinations with regular intervals are included in the prospective study.

3.2.2 Study population paper III

The study population in paper III consisted of all patients in the prospective cohort (confer section 3.2.1) who had experienced at least one SE before December 10, 2014. These were five patients with grade II glioma, three patients with grade III glioma, and twelve patients with grade IV glioma. The 20 included patients had experienced a total of 31 SE.

3.3 Methods

3.3.1 Definitions

OS was defined as the time from glioma diagnosis till death. Reimbursement of drugs dispensed for chronic disease on a relevant diagnostic code was used as proxy for the diagnosis. Reimbursement of AEDs for epilepsy had the local reimbursement code 7 until 2008, and thereafter ICD code G40 and ICPC code N88. Anti-anxiety drugs for anxiety had the local reimbursement code 18 until 2008, and thereafter ICD code F4 and ICPC codes P74, P79 and P01. Antidepressants for depression had the local reimbursement code 18 until 2008, and thereafter ICD code F3 and ICPC codes P73, P76 and P03. We organized the data from NorPD according to ATC classification; AEDs (N03A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), analgesics (N02), non-steroid anti-inflammatory drugs (M01A), temozolomide (L01A X03), and systemic steroids (H02A).

In paper II, we used two consecutively dispensed prescriptions on a relevant reimbursement code for the specific diagnosis; AEDs for epilepsy, anxiolytics, hypnotics/sedatives and antidepressants for anxiety, and antidepressants for depression. In addition, reimbursement code -90 (ICD-10 and ICPC-2) for palliative care was included for anxiolytics and hypnotics/sedatives in the definition of anxiety, and for antidepressants in the definition of depression. Two consecutively dispensed prescriptions of analgesics, including all opioids and non-steroid anti-inflammatory drugs, were defined as chronic pain as no valid diagnostic reimbursement code for pain existed throughout the whole study period.

In paper III, SE was classified as “focal without consciousness impairment”, “focal with consciousness impairment” or “secondary generalized” because the classification was changing at the time, and these terms were in temporary use during our study (190). Our terms are similar to those finally chosen for the revised ILAE SE classification (111); “focal without impairment of consciousness”, “focal with impaired consciousness” and “focal onset evolving into bilateral

convulsive SE", but we did not further subclassify SE into "with prominent motor symptoms" or "without prominent motor symptoms". We adhered to the old SE definition of seizures lasting beyond 30 minutes (191), which has previously been recommended for study purposes (192). This definition was based on irreversible neuronal injury in baboons with seizures ≥82 minutes (193). Refractory status epilepticus (RSE) was defined as SE unresponsive to two AEDs and/or requiring anesthetic agents for seizure control (194). If the patient was treated with two different benzodiazepines as first line treatment, this was considered as the same AED. SE was categorized as onset symptom if the seizure occurred within 30 days prior to the glioma diagnosis. Previous seizures were defined as number of seizures the last month before SE. In paper III, we used the definitions LGG for grade II gliomas and HGG for grade III-IV gliomas. Tumor progression was defined as radiographic changes and clinical signs consistent with tumor progression within 30 days of the SE. Mortality was defined as death within 30 days after SE. Sequela was defined as a neurological deficit acquired during SE and documented in the medical record as persistent at the time of discharge from the hospital, or at the next control appointment at the hospital. Mild sequelae were defined as transient neurological deficits lasting <one month. Moderate sequelae were defined as neurological deficits that were still present >one month after SE. Major sequelae were defined as permanent neurological deficits which severely impaired the patient's functional ability.

3.3.2 Study variables

3.3.2.1 Independent variables

In paper I-II, we wanted to compare hazard rates with respect to a number of covariates x, also called independent variables. In paper I, the independent variables were:

- Age at GBM diagnosis in five age-groups: <20, 20–39, 40–59, 60–79 and ≥80 years
- Gender
- Extent of resection: None, biopsy, incomplete surgery or complete surgery
- No RT versus RT including gamma knife treatment of ten GBMs
- Comedication with TMZ or not
- Comedication with systemic corticosteroids or not
- AED treatment for epilepsy or not
- Exposure variables: Levetiracetam, valproate, carbamazepine, lamotrigine, oxcarbazepine and phenytoin. Few patients used other AEDs.

In paper II, the independent variables were:

- Age at GBM diagnosis in five age-groups: <20, 20–39, 40–59, 60–79 and ≥80 years
- Gender
- Grade III glioma versus grade II
- Tumor topography (ICD-O-3): Frontal lobe was the most frequent location; 189 (33%) of grade II-III glioma and 285 (23%) of grade IV
- Surgical treatment: No surgery, biopsy or tumor resection
- No RT versus RT including gamma knife treatment of ten GBMs
- Comedication with TMZ or not
- Comedication with systemic corticosteroids or not
- Analgesics, including all opioids and non-steroid anti-inflammatory drugs, or not
- AED treatment for epilepsy or not
- Exposure variables: Levetiracetam, valproate, carbamazepine, lamotrigine and oxcarbazepine. Few patients used other AEDs.

3.3.2.2 The date of glioma diagnosis

In paper I-II, the date of glioma diagnosis was the earliest date stated to CRN. The date was the radiological investigation in 19 patients with grade II-III glioma and 147 patients with grade IV, the tumor resection or biopsy in 544 patients with grade II-III and 1110 patients with grade IV and time of death in two patients with grade II-III and six patients with grade IV.

3.3.2.3 Outcomes

In paper I, OS was the outcome. In paper II, drug-treated anxiety and depression were the outcomes. Critical information related to both the exposure variables and the outcomes were missing in both studies, and there were high risks for unmeasured confounding (confer section 5.2.5.5). Causal relationships could thus not be determined.

3.3.3 Statistics

In addition to standard descriptive statistics, we applied the following statistical methods in paper I-II.

3.3.3.1 Kaplan-Meier method (paper I)

Kaplan-Meier method was an appropriate method for the survival analysis of paper I because we had access to exact censoring times (195,196). All patients had a validated date of death if they were not still alive, and the censoring was upon death or at the end of our study on October 31, 2013. Kaplan-Meier estimate for the probability of surviving until time t can be given by:

$$\hat{S}_t = \prod_{t_i \leq t} \left[1 - \frac{d_i}{n_i}\right]$$

Until the maximum time t, t_i is divided in n intervals t_1,..t_n according to the number of deaths that occurred (197). The number of deaths until point t_i is d_i, and n_i is the number of individuals at risk just before t_i. Each time an observation is censored, n_i is reduced by one.

3.3.3.2 Cox proportional hazards regression (paper I-II)

In paper I, we used Cox proportional hazard regression (Cox regression) to investigate whether six separate AEDs affected OS (198). A patient was registered as exposed to an AED from the date on which the first prescription was dispensed. No patient was registered as in treatment after death or end of study. The patients not using AEDs were the main comparison group. All analyses were adjusted for other AEDs and available prognostic factors. In paper II, we used Cox regression to identify risk factors for drug-treated anxiety and depression in patients with grade II-III or grade IV glioma. Cox regression can be expressed as:

$$h(t) = h_0(t) \cdot e^{\beta_1 x_1 + \beta_2 x_1 + .. \beta_n x_n}$$

The hazard as a function of time, is $h(t)$. The baseline hazard when all x=0, is $h_0(t)$. The independent variables are x_1,..x_n with the corresponding regression coefficients β_1,..β_n. The hazard rate (HR) is $\exp(\beta_n)$. The independent variables are multiplicatively related to $h_0(t)$, and HR is constant throughout the whole follow-up period, named the proportional hazard assumption.

3.3.3.3 Cumulative incidence (paper II)

We used the Aalen-Johansen estimator which is commonly used for estimating cumulative incidence (199). The cumulative incidence curves were used to illustrate the probability of drug-treated epilepsy, depression, anxiety and pain.

3.3.3.4 Standardized incidence ratio (SIR) (paper II)

We utilized SIR to compare drug use in the glioma cohort to drug use in the general population. Three specific ATC groups; anxiolytics (N05B), hypnotics or sedatives (N05C) and antidepressants (N06A), were compared. The glioma subgroups were divided into epilepsy or not. The comparison was matched on age and gender. The observed number in the glioma cohort with one dispensed prescription of a drug within the ATC group, independently of diagnostic codes, was divided by the estimated number in the general population. Poisson distribution was assumed when calculating 95% CI for SIR.

3.3.3.5 Multiple imputation (paper II)

Missing values in one or more of the variables in population-based registry datasets are frequent. Data may lack values from three different mechanisms; missing completely at random (MCAR) independent of the observed and unobserved data, missing not at random (MNAR) dependent on the unobserved data, or missing at random (MAR) independent of the unobserved data but conditioned on observed variables and/or outcomes in the dataset (200). Data on RT were absent for 90 patients with grade II-III glioma (16%) and 118 patients with grade IV (9%). In paper I, we used complete-subject analysis (201), but this approach assumes MCAR. In most registry-based datasets, MCAR is not the case (202), and to avoid bias, multiple imputation by chained equations is recommended (203). With MAR, we have relevant information for the data missing available in other variables in the dataset. To complete the missing RT, we replicated the dataset

multiple times replacing the missing data drawing the probable values from all available relevant information (204). All variables in Cox regressions in addition to survival indicator, survival time, year of glioma diagnosis, geographical region for the glioma diagnosis, the histological diagnosis (subgrouped into six categories of ICD-O-3), tumor topography (frontal, temporal, parietal, occipital, cerebellum/brain stem/spinal cord, overlapping lesions or unspecified), all contributed in predicting the missing values. Cox regression was performed on each new dataset estimating the outcome which were linked by "Rubin's rule" into a final multiple imputation estimate (200).

This approach was valid as RT data were considered to be MAR, and would also be valid if MCAR. When MNAR, there is not enough information in the dataset to reliably impute the missing values, and sensitivity analyses are preferred. Our dataset lacked information on surgical treatment for three patients with grade II-III glioma (0.5%) and ten patients with grade IV glioma (0.8%). This variable was not imputed because of low missing rate. It is recommended that the number of imputations is greater than the percentage of missing data (203). We made 20 imputations for the 16% missing RT status.

3.3.4 Data management

In paper I, IBM SPSS Statistics for Windows, version 22.0 and 23.0 (IBM, Corp., Armonk, NY, USA) was used for the linkage of data files, data cleaning and statistical analyses. In paper II, IBM SPSS Statistics for Windows, version 24.0 (IBM, Corp., Armonk, NY, USA) was used for the linkage of data files and data cleaning. In paper II, Stata version 14.0 – 15.1 (StataCorp LLC, Texas, USA) was used for statistical analyses. All tests were two-sided with a significance level of 5%. In paper III, IBM SPSS Statistics for Windows, version 22.0 and 23.0 (IBM, Corp., Armonk, NY, USA) was used for the statistical analyses.

3.4 Ethics

3.4.1 Ethical approval

Approval was obtained from The Regional Committee for Medical Research (REC West), reference 2011-02280 for paper I-II and references 2008/11243 and 2011/2137 for paper III. The use of data for paper I-II were also approved by CRN, NorPD and CDR.

3.4.2 Ethical considerations

NIPH collects data for several registries, and also stores and maintains the data. Storage of health information in the health registries of Norway is regulated by the Personal Health Data Filing System Act 2002 (205). For protection of the individual's right to privacy, access to data requires extensive applications, and is only granted when the application is considered in accordance with the aims defined by authoritative regulations. Anonymous data have no possibility of re-identification, are difficult to validate and lack the possibility of follow-up of individuals over time. Pseudonymous data have encrypted identity but each individual has a person-specific pseudonym, that enables follow-up of individuals. De-identified data are anonymized and the researchers do not access the serial number that was given to each individual in the data. A trusted third party has the serial number and may facilitate linkage of data.

The datasets for paper I-II were de-identified and the PINs were stored at Statistics Norway, not available to us. All datasets were appropriately stored on a protected institutional server and only available to the researchers involved in the project whom all adhered to the Norwegian Health Registry Law (206). The dataset for paper III was pseudonymous. Each individual's PIN and name were available to the researchers after written, informed consent from every participant. Each individual was assigned a number and PIN and name were stored separately from the dataset on a protected institutional research server, only accessible to K.M.K.-B. and A.M.S.

3.4.3 Ethical concerns

The data used in paper I-II were collected after requirements regulated by the Norwegian legislation based on “silent consent” from the whole Norwegian population. It is unlikely that an individual who do not wish to have their health information archived and accessed can get their data redrawn from all generated research datasets. This is an ethical concern of paper I-II. In paper III, all patients were informed when giving their written consent that they could redraw their consent at any time. No patient decided to redraw.

Strict rules behind the handling of applications may cause delay in national registry-based research projects during the period before data delivery. On the other hand, a handling process is necessary to ensure that information is only shared if accommodating the aims of each registry. Today, new systems for delivery of anonymous data are developed to simplify this process (207,208). Relevant information that is not routinely collected by the included national registries is missing in our datasets. Opportunities of linkage with data from additional registries were evaluated during the planning of each study to obtain as complete data as possible. However, each linkage is time-consuming and represents a risk for technical errors.

4. Summary of results

4.1 Overview of results

4.1.1 Paper I

In paper I, we described OS in a nationwide cohort of patients diagnosed with GBM in Norway 2004-2010 (Figure 14).

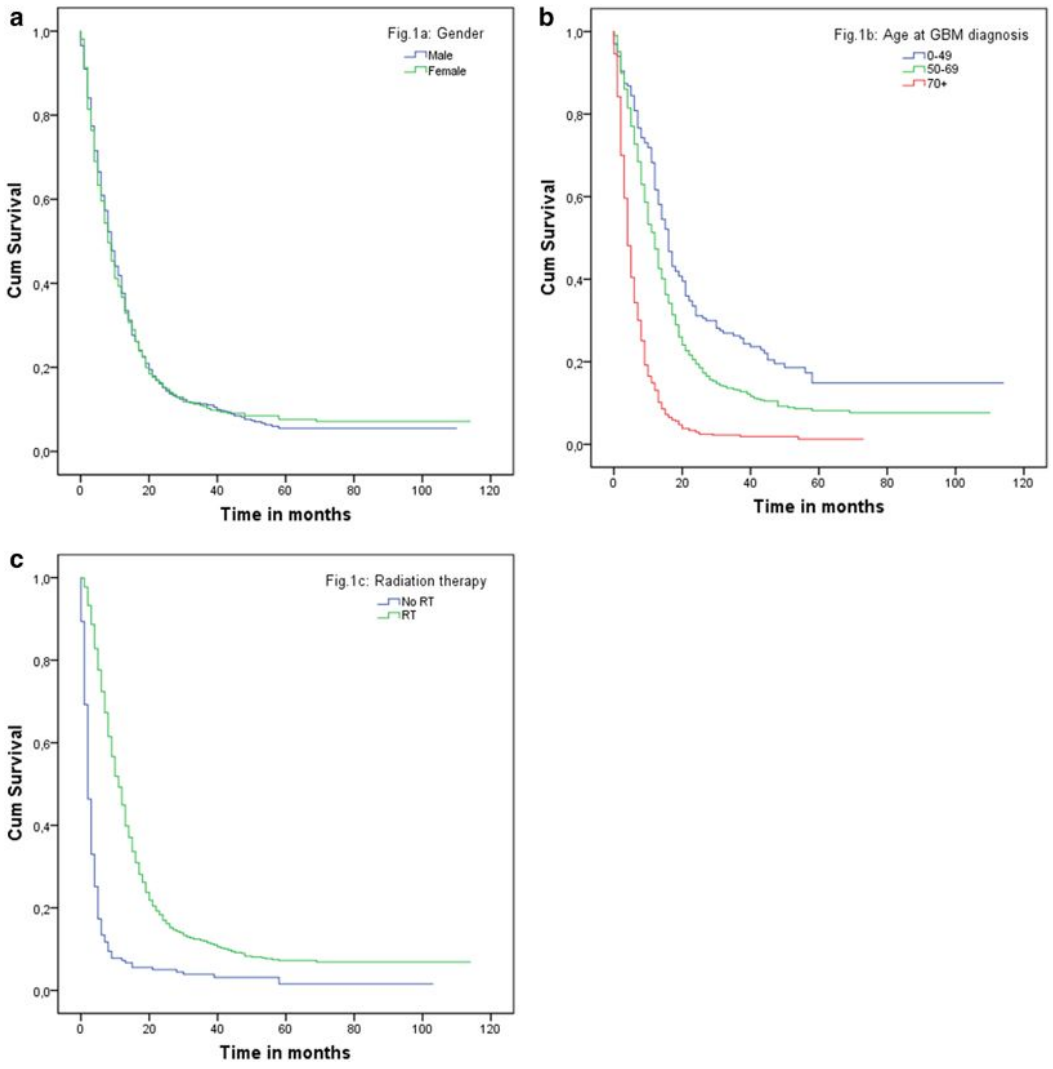


Figure 14 Kaplan–Meier plots with cumulative proportion of patients still alive on the y-axis and OS in months on the x-axis. OS was compared for the subgroups of **a** gender **b** age at GBM diagnosis and **c** no RT or RT.

Patients diagnosed during the earlier inclusion period were mostly treated with EIAEDs while levetiracetam became the preferred AED with time. There was no survival benefit neither from drug-treated epilepsy, nor from exposure to any of the most commonly used AEDs (Figure 15).

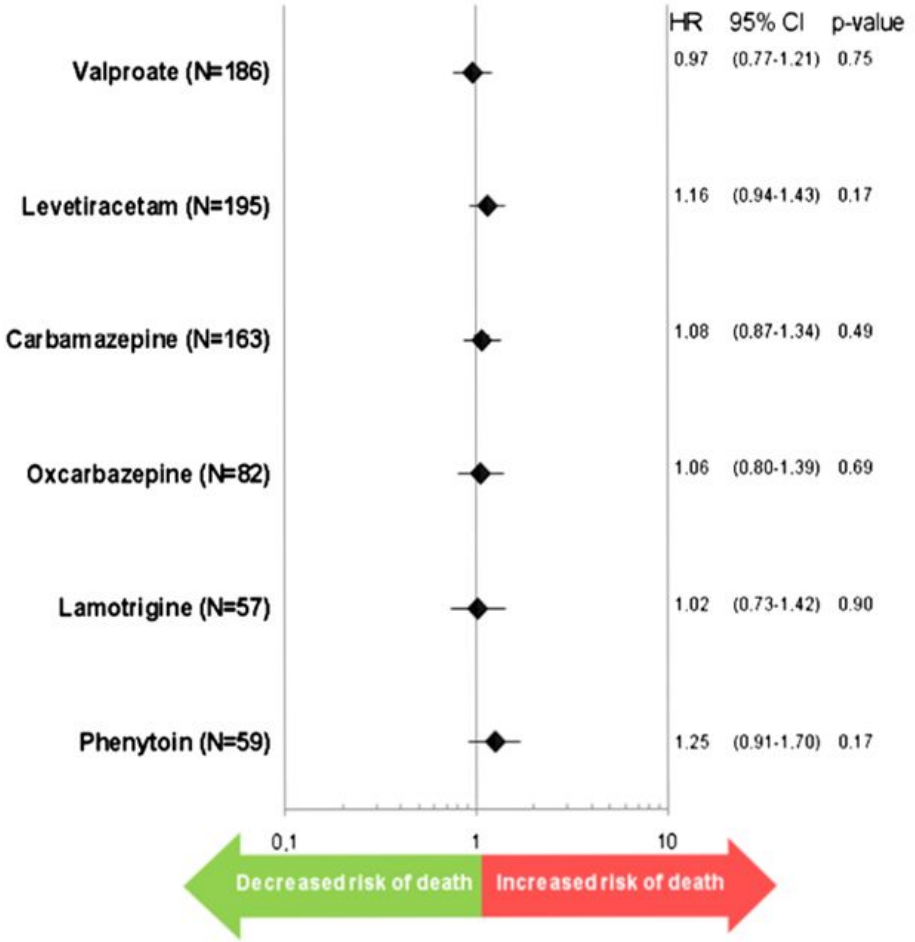


Figure 15 Forest plot illustrating the risk of death for GBM patients exposed to AEDs compared to non-exposed patients. The Cox regression was adjusted for gender, age at GBM diagnosis, extent of tumor resection, RT or not, epilepsy or not, TMZ or not and systemic corticosteroids or not.

4.1.2 Paper II

Drug-treated depression and pain increased from one year before the glioma diagnosis, drug-treated epilepsy increased sharply at the time of glioma diagnosis, and drug-treated anxiety started to increase from time of glioma diagnosis (Figure 16).

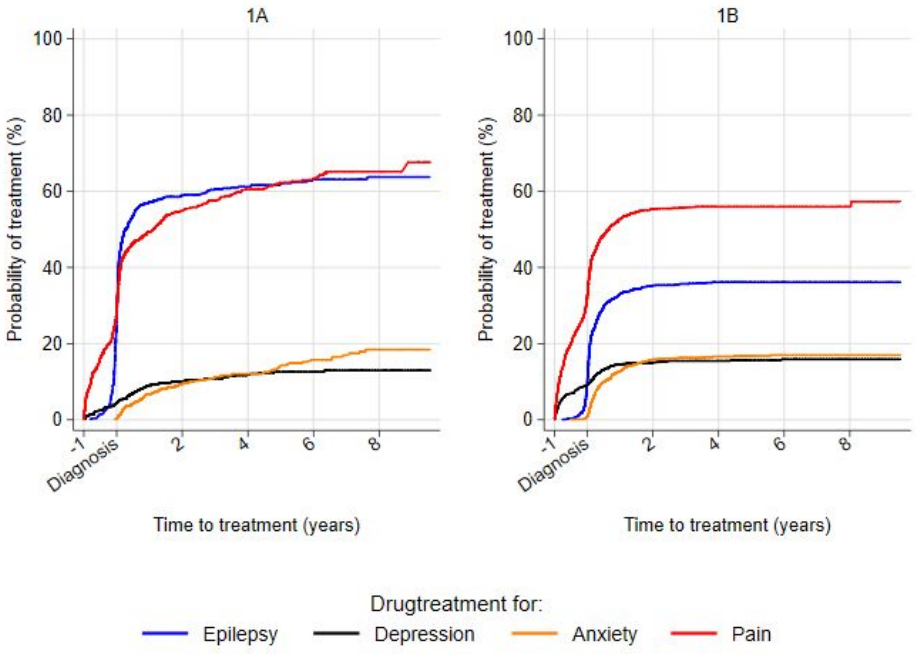


Figure 16 The probability of drug-treated epilepsy, depression, anxiety and pain related to time from one year before **A** grade II–III glioma diagnosis and **B** grade IV glioma diagnosis.

Grade II-III glioma patients exposed to levetiracetam had an increased risk for drug-treated anxiety compared to the non-exposed; HR 2.8 (95% CI 1.7-4.9) (Figure 17). Female gender was a risk factor for drug-treated anxiety (Table 2, paper II), but not during the first to years after a grade II-III glioma diagnosis (Online Resource 1, paper II). Treatment with TMZ or systemic corticosteroids increased the risk for drug-treated anxiety in patients with grade II-IV glioma.

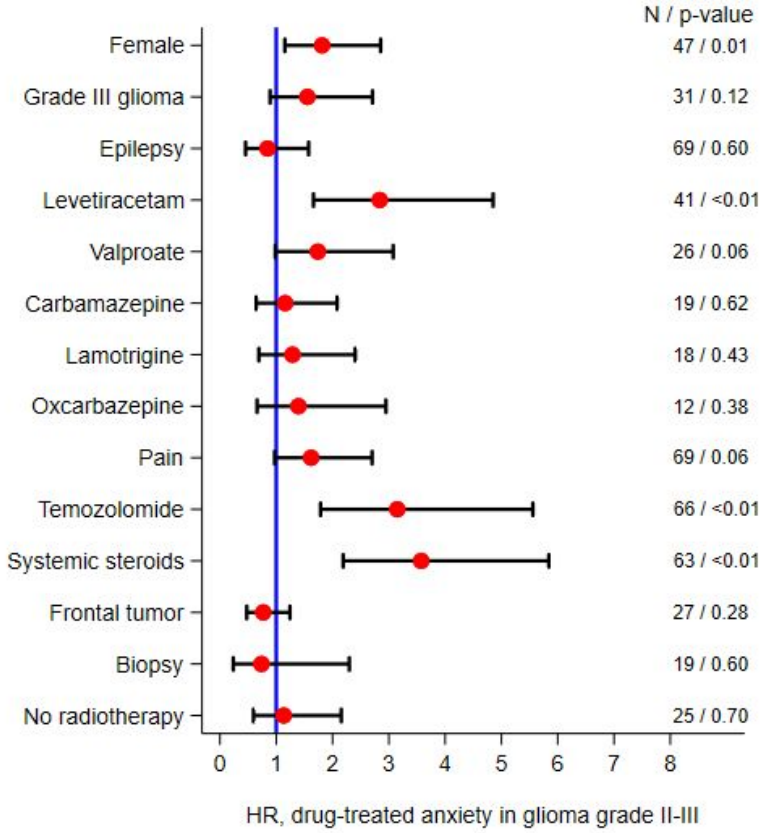


Figure 17 Forest plot of results from the risk factor analysis for drug-treated anxiety in patients with grade II-III glioma. HR <1 indicates decreased risk and HR >1 indicates increased risk for drug-treated anxiety. In addition to 95% CI, the number of patients with drug-treated anxiety within each subgroup and p-value for HR is given. In total, 86 of the 565 patients with grade II-III glioma had drug-treated anxiety.

Fewer among the patients with grade II-III glioma and epilepsy than among the corresponding group in the general population were registered with a dispensed prescription of antidepressants (Table 4, paper II).

4.1.3 Paper III

In paper III, we described the clinical course of SE in patients with grade II-IV glioma. The tumor was parietal, frontal or frontoparietal in 14/20 patients (Figure 18).

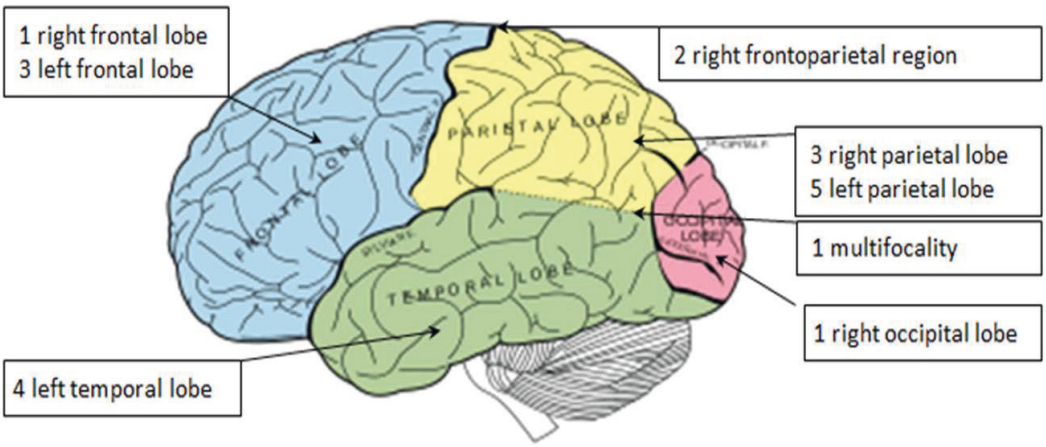


Figure 18 Tumor location for the gliomas of the 20 patients in paper III.

Three times as many patients with HGG than LGG experienced SE. There were four times as many males as females with SE. In half of all SE, the epileptic seizures had bilateral hemispheric involvement (Figure 19).

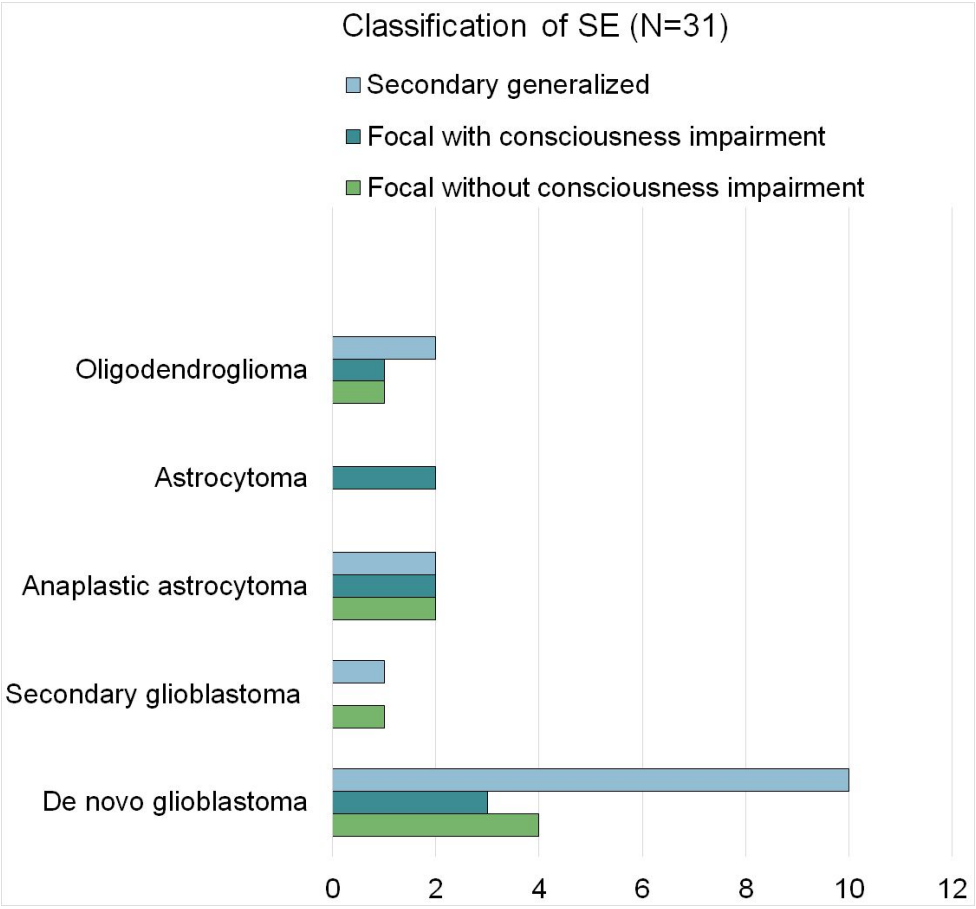


Figure 19 Seizure type for 31 SE and the histological subgroup of the glioma.

Half of all SE were related to glioma debut or tumor progression. Within the other half, trigger factors such as oncological treatment or changes in AED regimen could be identified. One SE self-terminated, 15 SE were treated successfully with first line treatment, seven SE responded to second line treatment and eight were RSE. With underlying tumor progression, SE was not more treatment refractory but more often followed by major sequelae or death.

5. Discussion

5.2 Methodological considerations

5.2.1 Study design

The two main study designs are experimental and observational. To investigate possible predictive factors for a specified outcome, an experimental study with randomization is preferred. RCTs are time- and cost-consuming. Patients who do not meet the strict inclusion criteria of RCTs are excluded leading to a study population that is different from clinical practice. RCTs to address our research questions would be challenging, especially because of the time-consuming inclusion. When a randomized design is not possible, a population-based observational study is an alternative. Data collected by the Nordic health registries are unselected, nationwide, hold high quality, and are suitable for research purposes (184,209–211). PIN allows reliable data linkage between registries. Correlation, case-control, cross-sectional and cohort studies all have observational study designs. In our opinion, the relationships between the exposures and the outcomes of our papers were better suited to be explored in cohort studies. Paper I-II were nationwide registry-based observational cohort studies, and paper III was a clinical observational cohort study. The time of which the data are collected categorizes cohort studies as prospective or retrospective (212). All the data for paper I-III were prospectively collected. For paper I-II, the study aims were retrospectively defined.

5.2.2 Advantages and disadvantages of cohort studies

Cohort studies that compare individuals who have taken a specific drug with those who have not taken the drug may be affected by “confounding by indication” meaning that the individuals who met the medical indication of the drug differ from the group who did not in terms of disease severity or other risk factors. In addition to “confounding by indication”, the main weakness of

paper I-II was the lack of detailed clinical information which increases the risk of unmeasured confounding with mixing of the effects. We improved both the extent of information available and the level of details by linkage of data from different registries. Still, important data for the research questions were absent, making the results less reliable. Main strengths of paper I-II were the relatively large sample size and minimal selection bias. For paper III, the main weakness was the lack of statistical power due to the small sample size. The main strength of paper III was the detailed, individual information obtained through the clinical follow-up of patients.

5.2.3 Study variables

5.2.3.1 Independent variables

The independent variables, also called the explanatory variables, were not based on results from univariate analyses but chosen based on our clinical judgement of the relevance for each paper. We decided upon this approach because selection of independent variables based on univariate analyses may introduce bias. Extent of tumor resection is important for OS and had four categories in paper I but was considered to be of less importance for drug-treated anxiety and depression, and had three categories in paper II.

The exposure variables in paper I-II were the most commonly used AEDs in each cohort. Topiramate was considered but not included because there were too few exposed patients for a meaningful statistical analysis. For the same reason, phenytoin was not included as exposure variable in paper II. Three sets of sensitivity analyses were performed for each Cox regression in paper II but none of these altered the results. These were analyses without multiple imputation of RT, analyses with age as continuous variable and analyses with exclusion of the highest age group. The categorized age variable was kept to display non-linear effects from age as some risks can be exponentially increasing with increasing age. We evaluated the intervals of the age-groups as appropriate for our study population.

5.2.4 Random errors and precision

5.2.4.1 Type I and type II error

In paper I, type I error would be to reject the null hypothesis of no difference between AEDs regarding effect on OS, conditioned that the null hypothesis is true. A theoretical consequence could be AED choice in GBM patients being based upon an erroneously reported beneficial survival effect despite a less favorable adverse effect profile for this drug. In paper I, type II error would be present if there was a true difference in OS between AEDs. A theoretical consequence could be patients missing out on a possible prolonged survival. Increase in sample size reduces the probability of type I and type II error because of a smaller standard error (=standard deviation/√sample size). A collaborative study including data from the national health registries of all the Nordic countries would provide a larger sample size than in paper I-II. An extended collaboration with a higher number of hospitals covering larger geographical areas, for instance most or all Norwegian counties, would provide a larger sample size than in paper III. Also, a prolonged enrollment period would increase sample sizes. Significance level of 5% with two-sided p-values is also used in similar studies. A lower significance level would have reduced the risk for type I error but increased the risk for type II error.

5.2.4.2 Power

Power is the probability of rejecting a false null hypothesis. A power level of 80% is usually required for experimental studies. We could not influence the sample sizes of our cohorts. For paper II we performed power calculations before the statistical analyses to assess whether grade II-III and grade IV glioma could be analysed as separate groups. The power calculations were

made with the sampsi command in Stata and measured the lowest detectable difference in outcome between the most commonly used AED (levetiracetam) and each of the other included AEDs. Based on our clinical judgement, we decided that the use of subgroups was valid if the lower detectable difference in outcome was ≤20% for most comparisons (Table 5).

Outcome	The Lowest detectable difference in outcome with ≥80% power.	
Anxiety	Grade II-III glioma	Grade IV glioma
Oxcarbazepine	21.5%	15.7%
Carbamazepine	17.8%	14.0%
Lamotrigine	17.5%	17.7%
Valproate	15.8%	11.9%
Depression	Grade II-III glioma	Grade IV glioma
Oxcarbazepine	19.5%	17.1%
Carbamazepine	16.3%	15.1%
Lamotrigine	16.0%	19.7%
Valproate	14.5%	12.6%

Table 5 The lowest detectable difference in outcome between exposure to levetiracetam and exposure to each of the other included AEDs, with ≥80% power.

In paper I-II, we accessed information on the defined daily dosage (DDD) for each drug. DDD is the average dosage for an adult on the main indication of the drug. Dose of AED is often not included in studies of AED exposure related to GBM survival (152). Subdivision of variables into many subgroups may impair the statistical power as the reference group becomes too small, leading to reduced reliability of the estimation. We were interested in including DDD in Cox regressions but did not access enough data to reliably evaluate effects from AED dosage in small

subgroups. Neuropsychiatric adverse effects from AEDs in patients with BTRE were reported to be dose-independent (213).

5.2.5 Systematic error and validity

5.2.5.1 Accuracy

The closeness of results to the truth is called accuracy, which depends on precision and validity (201). The relatively large sample sizes in paper I-II increased our results` accuracy. The main problem with an observational study design is the lack of randomizing exposures, mixing the exposures effect with that of the confounders (confer section 5.2.5.5) and other systematic errors (201). When evaluating if the associations found are real, validity is important. Validity includes generalization to the source population (internal validity), to the target population (external validity), and whether the variables used are representative (concept validity) (214).

5.2.5.2 Validity

The study populations of paper I-II are representative for the entire Norwegian population due to the nationwide inclusion of patients in the health registries with minimal selection bias. That no patients were lost to follow-up, strengthens the external validity of all papers. The study population of paper III is representative for the adult population of the two Western Norwegian counties. It can be questioned whether the inhabitants of Hordaland and Sogn and Fjordane are completely representative for the entire adult Norwegian population. Norwegian counties have unequal mortality and life expectancy due to differences in socioeconomic factors such as educational level (215). Also, the palliative cancer care differs between Norwegian counties (216). Such differences reduce the external validity of paper III. A comparison between the source population of paper III and paper I-II could indicate whether county differences are

evident among patients with glioma. However, paper III only reflects the patients with epilepsy and the comparison would only be valid for this subgroup. A patient does not always receive medical treatment in their county of residence. For this reason, we did not especially compare data for patients from different counties in paper I-II. Our study populations resemble the populations of the other Nordic countries as socioeconomic factors including educational level, health care system and ethnicity are comparable. Regarding oncological treatment, our study population is comparable to countries that adhere to the European Association of Neuro-Oncology (EANO) guideline on the treatment of glioma (45). Differences in ethnicity reduces the external validity towards the more distantly located European countries, and gaps in mortality and life expectancy reduce the external validity to populations of low-income countries.

The concept validity of paper I-II depends on whether the treatment with AEDs for epilepsy is representative for the diagnosis of epilepsy. ILAE defines tumor-related epilepsy as a history of at least one epileptic seizure due to the presence of an enduring alteration in the brain (217). The etiology of glioma-associated epilepsy is classified as structural (101). In Norway, a patient with a single seizure due to structural etiology is treated with AEDs, while AEDs are not given prophylactically to a glioma patient who never had a seizure. One dispensed prescription of AED for epilepsy is thus a valid proxy for glioma-associated epilepsy. In our cohort, there were 526 GBM patients (41.6%) with one dispensed prescription on an epilepsy code and 463 GBM patients (37%) with two consecutively dispensed prescriptions on an epilepsy code. Anxiety and depression that were never treated with drugs were not registered in our data, and thus not included in the outcomes of paper II. Symptoms of anxiety and depression are not always communicated to the doctor. Some patients diagnosed with anxiety and/or depression receive psychological treatment instead of drugs. The Norwegian patient registry contains information on patients treated in the specialist health care but lacks data from the primary health care, and such data were therefore not added.

5.2.5.3 Selection bias

In paper I-II, we included patients with specific morphology codes and did not exclude patients based on other criteria. The ICD-O-3 code for gliomatosis cerebri (93813) was not included in paper II similar to most epidemiological reports on glioma (218).

In paper II, we excluded the patients diagnosed during 2004 in SIR analyses to secure at least one year of follow-up in NorPD before the glioma diagnosis. This did not affect the SIR estimates as the comparison group in the general population was recruited from the corresponding period.

Susceptibility bias is an exposed group having an increased risk for the outcome due to factors related to the exposure. There is a possibility that valproate or lamotrigine were preferred AEDs in patients with bipolar disease or depression, and that patients using these AEDs more often received drug treatment for anxiety and depression. For the study population of paper II, we examined valproate and lamotrigine prescriptions for diagnostic codes other than epilepsy, and there were too few cases to assess this further in statistical analyses. Among all 1828 glioma patients, ten used lamotrigine and 13 used valproate on reimbursement code for depression.

In paper III, the study population did not include permanent nursing home inhabitants with glioma who had never been referred to a neurologist. SE that occurred in included patients after transfer to a nursing home was only registered if the patient was admitted to the hospital or if the nursing home contacted the hospital for medical advice. The clinical signs of a seizure can be subtle and misdiagnosed as neurological decline due to the tumor or other conditions. Especially, focal non-motor seizures are often not acknowledged, and NCSE may not be recognized as SE due to the lack of prominent motor symptoms.

5.2.5.3.1 Loss to follow-up

In paper I-III, no included patient emigrated or otherwise left the study during follow-up. Attrition bias is when study participants are lost to follow-up and the initial and ending study populations are different. This is avoided in population-based register studies with complete

exposure and outcome data (219). In paper III, patients transferred to nursing homes could have been lost to follow-up but the study population was small, and we could obtain detailed information on all included patients.

5.2.5.3.2 Missing data

In paper I, «unknown» in the treatment variables surgical treatment and RT was categorized as missing and not included in the analyses. The missing percentage of RT was higher for grade II-III, and multiple imputation was applied (confer section 3.3.3.5).

5.2.5.4 Information bias

Non-differential information bias is present if the variables are equally misclassified for the exposed and non-exposed individuals and/or with or without the outcome, and differential if unequally misclassified. Non-differential misclassification cannot explain an association between exposure and outcome, but can decline a true association. Differential misclassification can overestimate or underestimate the true values. The registrations in paper I-II were initially provided by the diagnosing and/or treating institution through reports from clinicians and pathologists. Incorrect diagnoses in these reports was a potential source for non-differential misclassification. Duplicate records for patients treated at several institutions and all other data were controlled by CRN employees. The main strength of NorPD is the complete individual information obtained from all Norwegian pharmacies on all dispensed prescription drugs. Currently, there is no way to obtain individual data on the drug use of patients in hospitals and nursing homes. Elderly and palliative patients who lived at home or in service apartments had their drug use individually registered but a patient transferred directly from the hospital to a nursing home could theoretically be included in the study population but fail to be included in the epilepsy subgroup if AEDs were never dispensed from a pharmacy, and possibly also fail to be registered with paper II outcomes, causing differential misclassification. This is more relevant for grade IV glioma as patients with lower grade glioma rarely spend their total disease course in

hospitals and nursing homes. Among patients with grade II-III glioma, 15.2% were registered with drug-treated anxiety and 11.5% with drug-treated depression. Among patients with grade IV, 16.3% were registered with drug-treated anxiety and 10.2% with drug-treated depression.

RT with concomitant TMZ followed by adjuvant TMZ became standard therapy in 2005, which is less than a year after the initial patient enrollment for paper I-II, and we chose not to have a separate group for adjuvant TMZ alone. In a previous report on Norwegian GBM patients, concomitant TMZ with adjuvant TMZ and adjuvant TMZ alone did not yield different OS (220). The number of TMZ cycles was difficult to ascertain from NorPD, and TMZ was dichotomized into exposure or no exposure without dosage information. Adjuvant TMZ is often given at home and it is unlikely that patients transferred directly to nursing homes received TMZ as patients who spend >50% of their daytime in bed, have severe cognitive impairment and/or live in a nursing home usually do not receive TMZ.

Incident seizures before SE in non-hospitalized patients was impossible to validate, and could be affected by recall or reporting bias. Information on trigger factors and administered SE treatment were controlled against scanned medication lists and all available reports in the medical records and were less likely to be biased. In two SE, the seizure semiology was described in the medical record by clinicians at departments other than the Departments of Neurology at Haukeland University Hospital or Central Hospital, Sogn and Fjordane county. In both cases, the attending neurologist at Haukeland University Hospital was contacted during SE and upon this consultation, the attending neurologist also documented relevant information including the seizure semiology in the patient's medical record.

5.2.5.4.1 Dependency (paper III)

In paper III, 31 SE were included in the descriptives of the study population. Only the first SE was included in statistical analyses if there were two or more SE in the same patient, as the recurrent episodes were considered not to represent independent observations.

5.2.5.4.2 Immortal time bias (paper I-II)

The patients were grouped according to drug exposure based on treatment changes that occurred during the follow-up. Time between start of follow-up and the first relevant drug prescription must be registered as untreated time to avoid immortal time bias (221,222). Cox regressions in paper I-II had time-dependent variables for all drug treatments. In this way, patients classified as drug-exposed were classified as unexposed from the start of follow-up until the date of their first dispensed prescription. If not adjusted for, this period becomes immortal person-time during which the patient is predetermined to survive. Several observational cohort studies that reported drugs to reduce mortality were affected by this bias as immortal person-time was misclassified as drug-exposed time, or the patients who did not survive long enough to receive the drug represented the control group in the study (223–225).

5.2.5.5 Confounding

Confusion of effects due to a variable that cause or correlate with both the exposure and the outcome is termed confounding (Figure 20).

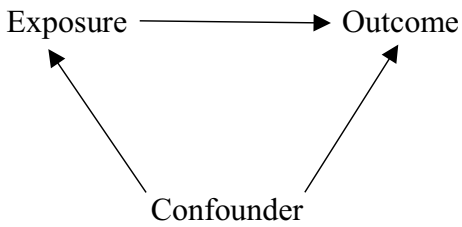


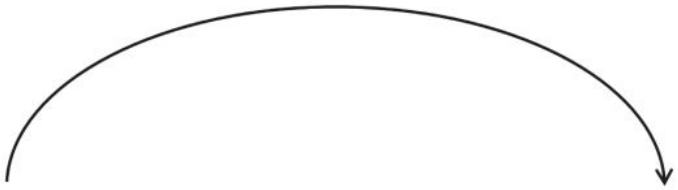
Figure 20 Causal relations between confounder, exposure and outcome.

To handle confounding in paper I-II, we used the available information on possible confounders in a multivariate statistical method to estimate the variable of interest. We did not use sensitivity analyses based on an external sample (226) or instrumental variable methods (227) as our sample sizes were not sufficient for such analyses. Possible confounding from lack of data is called residual confounding (228). There was no available information in the national health registries on MGMT promoter methylation, IDHmut, time interval to surgery, time interval to tumor progression, neurological and cognitive functioning, AED serum levels, frequency of epileptic seizures, comorbidities, social status or educational level.

5.2.5.6 Colliding bias

If a mediator is adjusted for while there are unmeasured variables that cause both the mediator and the outcome, colliding bias arises. Genetic predisposition for psychiatric disease is an important risk factor for both anxiety and depression. Surrogate measures could be first degree relatives with psychiatric disease or psychiatric history unrelated to the glioma, but such information was not available in our study. Sensitivity analyses identified drug-treated depression as a mediator for drug-treated anxiety as the results were affected when patients treated with antidepressants for depression were excluded. The results in paper II would have been affected by

colliding bias if the mediator was adjusted for in Cox regression (Figure 21). The identified mediator was thus not included in the analyses to preserve the effect that we aimed to measure.



Genetic predisposition for psychiatric disease→Drug-treated depression→Drug-treated anxiety
(unmeasured variable) (mediator) (outcome)

Figure 21 In paper II, colliding bias was avoided in Cox regression by not adjusting for the mediator.

5.2.6 Causality (paper II)

We cannot determine to what degree anxiety was caused by glioma growth, a psychological reaction to the glioma diagnosis, or adverse effects from levetiracetam. Neither glioma nor epilepsy are necessary factors for anxiety, but the burden of a glioma diagnosis and possibly the frequency of epileptic seizures, are susceptible to increase the risk. One third of newly diagnosed glioma patients experience persistent distress until six months after the primary oncological treatment (229). This distress is especially associated with younger age, major depressive disorder and functional impairment (229). Fatigue is a frequently reported cause of distress which has been associated with AED treatment (229). A deterministic approach to causation would be to conclude that adverse effects from levetiracetam represent the increased risk for drug-treated anxiety in the patients who were exposed to levetiracetam. However, in this study, a probabilistic approach to causation is more correct. We believe that in addition to the glioma and having epilepsy both being strongly associated with anxiety, the risk is influenced by individual genetic predisposition for anxiety, history of psychiatric disease, comorbidities, previous life experiences, personality traits, behavioral patterns for dealing with life crises, educational level,

socioeconomic status, concept of disease, awareness of disease state, tumor symptom burden, tumor progressions, and unknown factors that affect the vulnerability for developing anxiety. As we did not adjust for all possible influencing factors, our results cannot determine any causal mechanisms for anxiety in glioma patients.

5.2.7 Statistical methods (paper II)

We used SIR to compare the drug use in the glioma cohort to the drug use in the general population. All information on drug prescriptions for the glioma cohort and the general population were from NorPD, ensuring equal quality of data. However, the glioma cohort was probably different regarding comorbidity and frequency of contact with health care personnel. The comparison was considered as a rough estimate of the drug use, and does not accommodate that a patient with glioma usually has a shorter survival than a person without a glioma. We also compared glioma subgroups by estimating cumulative incidence curves, which considers the competing risks of death, but which does not adjust for covariates. To adjust for confounding factors, we estimated Cox regressions. The cause-specific HR is considered to be a valid measure of the association between an exposure and an outcome in the presence of competing risks (230). Combining the various analyses, we believe that the current results give new insights and increase our understanding of the risk factors for and the psychiatric drug-treatment that patients with glioma are exposed to.

5.1 General discussion of main results

5.1.1 Paper I

There was a shift from EIAEDs to non-EIAED levetiracetam in our cohort, following the trend for epilepsy in general (231). Reasons for preference of non-EIAEDs can be to avoid drug-drug interactions and to reduce adverse effects. Exposure to the six most commonly used AEDs in our cohort did not improve OS. A systematic review and meta-analysis of the effect from valproate on OS in GBM patients identified 967 records on the initial search criteria of which 35 full-text articles were screened, but only seven retrospective cohort studies fulfilled the selection criteria (232). Paper I in this thesis, and one of the other six studies, gained the maximum quality score of 9 after the Newcastle-Ottawa Scale (NOS) (Supplementary material, (232)). The factors assessed were whether the cohort was representative, selection of the non-exposed, cohort ascertainment of exposure, outcome of interest, comparability of cohort, assessment of outcome, adequate duration of follow-up, and adequate follow-up of cohort. Three studies reported Cox regression with beneficial OS in the subgroup treated with valproate. Kerkhof et al. included patients on valproate combined with TMZ (6). As TMZ is usually a part of the primary GBM treatment, that study was less likely to be affected by immortal time bias. Weller et al. did not report whether the variables for drug treatment included in their analyses were adjusted for time on treatment (146). Redjal et al. did not adjust for the length of valproate treatment but included dosage and found an association between higher valproate dosage and more favorable survival (233). The number of patients in each AED group was limited in all papers. Younger age at diagnosis and oncological treatment, but also unifocality of tumor and secondary tumor genesis are beneficial prognostic factors for GBM survival that should be adjusted for in survival analyses (234). For the seven studies included in the meta-analysis all together, OS was beneficial in the subgroup treated with valproate (HR 0.71, 95% CI 0.56-0.91, $p<0.01$). However, asymmetry in the funnel plot for HR from all included studies indicated publication bias (Figure 22). For this reason, Lu et al. applied a trim-and-fill method that estimates the number and outcomes of missing studies. After adjusting the meta-analysis by incorporating the theoretically missing studies, OS was no longer beneficial in the subgroup treated with valproate (HR=0.80, 95%CI 0.62-1.05, $p=0.09$) (232).

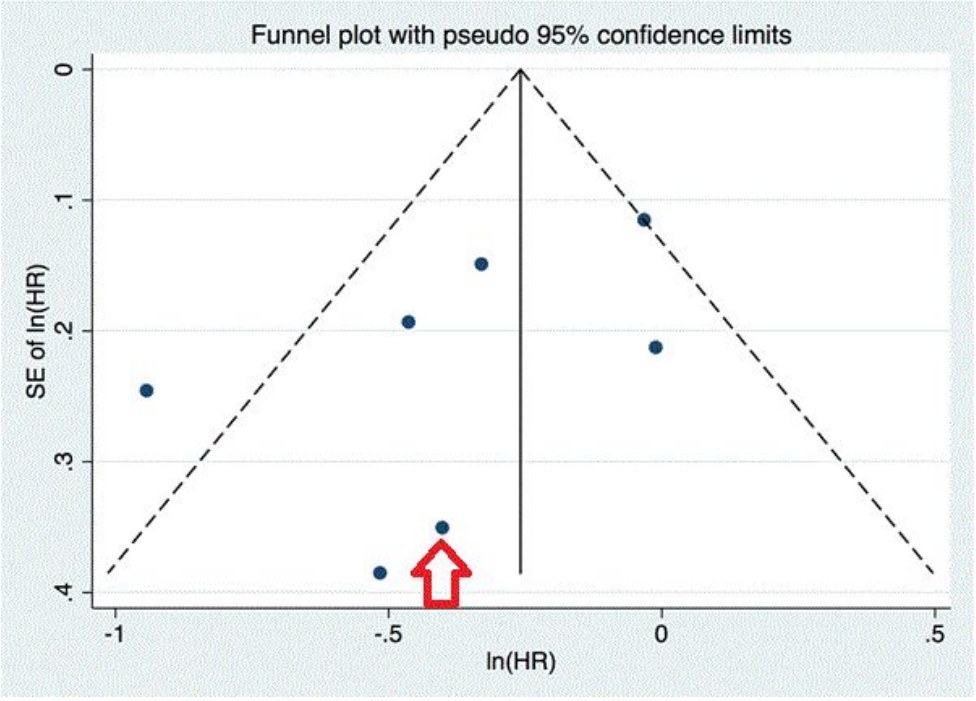


Figure 22 Funnel plot for HR indicating publication bias. Each study is represented by a point located at the logarithm of each respective HR against its standard error (SE). Our study had ln(HR)= -0.03 and SE of ln(HR)= 0.35 (red arrow). Given with permission (232).

Neither separate analyses for patients exposed or never exposed to TMZ, nor sensitivity analyses of subgroups exposed to only one of the six AEDs during the total follow-up, altered our results. Due to the limited number of patients, we could not rule out completely whether more specific subgroups, such as young patients receiving maximal oncological treatment, had a small survival benefit from particular AEDs. A limitation of our survival estimation was the lack of information on MGMT promoter methylation, IDHmut and KPS. Our study should also preferably have included information on sequential use of AEDs, total doses of individual AEDs, effect on epileptic seizures and AED serum levels. A collaborative multicenter clinical trial organized through European Organisation for Research and Treatment of Cancer (EORCT) (235) could provide enough patients to be able to conclude regarding impact on OS from particular AEDs in

subgroups of GBM patients. The length of a survival benefit is of uttermost importance. If the survival benefit is <one month, the clinical implication is modest, and calls for an assessment of the potential benefit weighed against the risk for adverse effects which may reduce QOL. A proven survival benefit of >three months in a well-defined subgroup would support a change into this AED.

We could not confirm the previously reported survival benefit from having epilepsy, in accordance with our research hypothesis. Toledo et al. reported that in a retrospective study of 134 patients >14 years of age diagnosed with GBM 2008-2012, patients who presented with seizures had HR 1.93 (1.21-3.07) for longer survival compared to patients without seizures at presentation (p=0.006), but two years later in a prospective study enrolling patients ≥18 years of age diagnosed with GBM 2012-2014, multivariate analysis including the available prognostic variables found age <60 years as the only independent predictor of longer survival (105,236). Cardona et al. reported that GBM patients with <five seizures in six months had median OS 17.3 months (95% CI 4.79-29.0) compared to 11.8 months (95% CI 3.7-19.9) with >five seizures in six months (p=0.046), but as this was assessed in univariate analysis only without further multivariate analysis, the result is not reliable (237). If tumors presenting with epileptic seizures are more extensively resected than tumors not presenting with seizures, this could represent a confounder leading to the beneficial survival. We did not access information on whether the decision on completeness of surgery was made intraoperatively or postoperatively based on control MRI. Also, we did not include tumor location, tumor volume or KPS in our analyses, and cannot determine whether these factors biased our results. Frontal and temporal tumors could lead to a favorable OS compared to tumors with less resectable locations. Cardona et al. categorized the tumor as “multicentricity yes/no” and “infiltration of the corpus callosum yes/no” without further information, while Toledo et al. and Berendsen et al. based their tumor location on the preoperative MRI (236–238). Complete resection in glioma, and particularly in GBM, is based upon macroscopic evaluations, and a subtotal resection is the best possible outcome in most patients. In our study, 68% of GBMs were categorized with “complete surgery”, but this number is probably too high or rather represent subtotal resections. Other studies reported that 59-66% of

GBMs were completely resected (105,236,237). Berendsen et al. reported that 66% received debulking surgery, and that the group with epilepsy included 10% more patients with surgery and 10% less patients with biopsy compared to the non-epilepsy group (238). If not adjusted for in statistical analyses, such differences could overestimate a survival benefit in the group with epilepsy. In a retrospective multivariate analysis of 443 GBM patients, having epileptic seizures but no other symptoms before surgery was associated with beneficial survival, HR 0.54 (95% CI 0.37-0.75) compared to GBM patients not presenting with seizures or presenting with seizures and additional preoperative symptoms ($p< 0.001$) (239). MRI is readily available to the general practitioners in Norway, and brain tumors may be diagnosed earlier also without epileptic seizures, reducing confounding from earlier treatment due to seizures. A meta-analysis of six retrospective studies found that GBM patients presenting with seizures survived longer than GBM patients without seizures, also regardless of other symptoms (240). However, in addition to an earlier glioma diagnosis and younger age at diagnosis, both of which are prognostically favorable, epilepsy at presentation is associated with favorable histological origin, IDHmut, smaller tumor size, higher KPS, more extensive resection and maximum oncological treatment (77,89,238,241).

The increased incidence of GBM in Norway 2004-2010 is supported by an increased incidence of GBM in England across all ages during 1995-2015 (32). According to the CBTRUS statistical report, there was an annual increase in the US incidence for all gliomas of 0.8% (95% CI 0.4-1.3) during 2000-2007, followed by a decrease during 2007-2015 of -0.6% (95% CI -1.0-(-0.2)) (21). There was an annual increase in incidence for GBM of 1.0% (95% CI 0.1-1.8) during 2000-2005, but stable during 2005-2015 (21). The increase in GBM incidence confirmed by paper I can be explained by an aging population, and by the increasing availability of MRI and improved neuroimaging techniques for detecting tumors. The decrease in incidence of grade II glioma confirmed by paper II can be explained by reduced autopsy frequency, especially among the elderly, causing an under-reporting of these diagnoses compared to previous years (242).

GBM patients in our cohort treated with systemic corticosteroids had unfavorable OS. Dexamethasone acts anti-proliferative in GBM and has been suggested to decrease genotoxicity from RT and chemotherapy (243). A retrospective analysis of 113 GBM patients linked impaired OS and progression free survival (PFS) to dexamethasone-induced leukocytosis, which was especially found in elderly patients, and was associated with reduced CD15+ granulocytic and CD3+ lymphocytic tumor infiltration (244). The shift from EIAEDs to non-EIAEDs in our cohort could be relevant for the impaired OS in patients treated with systemic corticosteroids. Systemic corticosteroids are 3A4 enzyme-inducers which influence serum levels of EIAEDs. Corticosteroid plasma T1/2 can be reduced to 50% by EIAEDs (82). Effect from corticosteroids on OS in patients concurrently treated with EIAEDs compared to non-EIAEDs was not assessed in paper I. Adverse effects from corticosteroids are often dose-dependent (245). Corticosteroids` detrimental effects on survival is difficult to determine regarding dose-dependency because of possible confounding factors. Corticosteroids were retrospectively found to reduce survival in three independent GBM patient cohorts adjusted for age at diagnosis, performance status (KPS or WHO), initial treatment and extent of resection (243). In those cohorts, a higher steroid dose was prognostically worse in patients treated with RT alone than in patients who also received TMZ. Alternative drugs treating cerebral edema in GBM are needed. Anti-vascular endothelial growth factor agents are not the first line treatment for cerebral edema because of adverse effects and the financial costs. Steroid therapy is thus still recommended, but in as low dosage and for as short time as possible.

5.1.2 Paper II

Drug-treated anxiety increasing from glioma diagnosis could be related to the psychological reaction after being diagnosed. In patients with glioma grade II-III, levetiracetam exposure was a proven risk factor for drug-treated anxiety. AEDs with negative psychotropic effects, such as levetiracetam, topiramate, zonisamide and felbamate, are in general not recommended for

patients with symptoms of anxiety (246). Benzodiazepines are not recommended and can lead to problems related to dependency and long-term tolerance (246). On the contrary, pregabalin have anxiety reducing effects, and lacosamide does not worsen anxiety (247,248). In a study from general practice, carbamazepine and lamotrigine reduced the risk for psychiatric symptoms in monotherapy, and carbamazepine reduced the risk for anxiety (HR 0.77, 95% CI 0.63-0.95) and depression (HR 0.81, 95% CI 0.69-0.96) (231). A systematic review concluded that published studies on the efficacy and safety of levetiracetam in patients with brain tumors until December 2015 were all at high risk of bias (249). Treatment recommendations for glioma-associated epilepsy lack high-quality evidence, but there is consensus to avoid EIAEDs because of potential drug-drug interactions with chemotherapy (179). Levetiracetam has generally been regarded as well tolerated, but is associated with dose-independent psychotropic effects (250) and behavioral disturbances (251). Several studies have reported levetiracetam to cause neuropsychiatric and behavioral adverse events more frequently than other AEDs (213,252). In patients with epilepsy, the relative risk (RR) for anxiety as adverse event was estimated to 8.65 (99% CI 0.19-395.33) for levetiracetam compared to placebo (181). Patients with BTRE had odds ratio (OR) 7.94 (95% CI 1.68–37.56, $p<0.01$) for neuropsychiatric adverse events from levetiracetam compared to other AEDs, and OR 20.00 (95% CI not given, $p<0.05$) for anxiety (213). Based on the efficacy, lack of drug-drug interactions, easy titrating scheme and equivalent intravenous dosage, levetiracetam is still the recommended first line AED for BTRE, explaining the increased use of levetiracetam (77,82,179,249).

Female gender was a risk factor for anxiety from two years after a grade II-III glioma diagnosis. AEDs are often initiated during the first two years, and gender differences in adverse effects from AEDs can thus not explain the increased risk for drug-treated anxiety in females. State anxiety, trait anxiety and depression are more frequent in females than in males with primary brain tumors (253,254). We did not find any gender difference in risk for drug-treated depression, which is in accordance with other reports on depression after a glioma diagnosis (255). Information on psychiatric medication prescribed earlier than one year before the glioma diagnosis would be complicated to implement in our analyses because NorPD lacks all drug records before 2004. In a retrospective study of 1173 patients with epilepsy who received a first prescription of

levetiracetam, 14.1% experienced a psychiatric symptom or disorder within the following two years and OR was increased for female gender (1.41, 95% CI 0.99-2.01), and a pre-exposure history of depression (2.20, 95% CI 1.49-3.24), anxiety (1.74, 95%CI 1.11-2.72), social deprivation (1.15, 95% CI 1.01-1.31) and recreational drug use (2.02, 95% CI 1.20-3.37) (256).

We analysed grade IV glioma patients separately following the latest classification (1). Status for molecular markers was not available in CRN. A previous study based on CRN data employed IDH proxy groups, of which grade II-III glioma represented IDH1mut and grade IV glioma represented IDH1wt (27), but we already had this subdivision. We could not prove any difference in drug-treated anxiety or depression between patients with grade II and grade III glioma. In a questionnaire survey, grade IV glioma patients less frequently reported anxiety than grade I-II glioma patients (OR 0.36, 95% CI 0.20-0.64), while there was only a trend for less anxiety reported by grade III glioma patients compared to grade I-II patients, but this study neither adjusted for neurocognitive impairment from cancer disease and treatment, nor for awareness of disease state or disease-related mortality, which are likely to have affected the expression of neuropsychiatric symptoms (254). Only 31% of brain tumor patients with anxiety and 26% with depression are treated pharmacologically (254). Our results are therefore not directly comparable to studies with symptom-based definitions of anxiety and depression.

Coexistence of anxiety and epilepsy has been related to the amygdala and the hippocampus (257). Gyrus cinguli regulates the amygdala and can influence ictal anxiety (258). Coexistence of anxiety and epilepsy has also been linked to the serotonin transmission as serotonin receptor-binding is reduced both in patients with anxiety and in patients with epilepsy (259,260). Coexistence of anxiety and epilepsy in glioma patients is probably related to other mechanisms than pathology in limbic structures and reduced serotonin receptor-binding (confer section 1.2.1). If epilepsy could explain the increased risk for drug-treated anxiety in levetiracetam treated patients, this would have been “confounding by indication” (261). We believe that this was not the case in our study as the epilepsy proxy did not increase the risk for drug-treated anxiety.

Our data had a specific variable for chemotherapy, but according to CRN this variable was of poor quality (communication 2017). CRN is currently (2019-2020) improving the quality of chemotherapy variables, but updated information was not available for our study. The oncological treatment followed the European guidelines at the time. These guidelines were updated by EANO in 2017 (45). RT as primary treatment and tumor progression treatment given within one year after the initial glioma diagnosis were included in all Cox regressions. Surgery was coded as primary surgery or surgery for tumor recurrence. We did not access information on RT for later tumor progressions. TMZ and systemic corticosteroids were risk factors for drug-treated anxiety. Patients treated with TMZ and corticosteroids might have a higher glioma grade than patients without these therapies. However, grade III glioma patients did not have increased risk for drug-treated anxiety compared to grade II glioma patients in our cohort.

Pain and depression treated from one year before and until the glioma diagnosis probably represented symptomatic treatment of an unacknowledged glioma. Headache is frequent with glioma and 27% of the patients experience such pain during the disease course, 31% in the diagnostic phase, and increasingly with glioma grade from 22% of grade II up to 38% of grade IV glioma patients (262). That pain increased the risk for drug-treated anxiety and depression may be explained by complex clusters of symptoms affecting each other (263).

Epilepsy was associated with decreased risk for drug-treated depression in patients with grade IV glioma. Mood-stabilizing effects from AEDs may be one explanation as some AEDs are beneficial for depressive moods, such as lamotrigine, carbamazepine, oxcarbazepine and valproate (264). An explanation for discrepancies between our glioma subgroups may be that patients with grade IV glioma differ from patients with grade II-III glioma regarding higher age at diagnosis, more rapid tumor growth with clinical deterioration and shorter life expectancy. These factors may influence psychological reactions, communication of depressive symptoms, and treatment with antidepressants. Considering the burden of disease, we expected the use of antidepressants to be higher among patients with glioma and epilepsy than in the general population. We therefore interpreted the result of fewer patients with dispensed prescription of antidepressants among patients with glioma grade II-III and epilepsy as possible undertreatment.

Reports on proconvulsive effects from antidepressants, and drug-drug interactions between AEDs and antidepressants that can decrease seizure thresholds may have created a resistance among doctors towards treating depression in epilepsy patients even though these reports have been contradicted (265). There is not scientific evidence for restraining the treatment with newer antidepressants in patients with epilepsy. Serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline reuptake inhibitors (SNRI) and noradrenergic and specific serotonergic antidepressants are all considered not to cause seizures when used in therapeutic doses (266). Patients with epilepsy and depression have been reported with a greater seizure burden than those without depression (267). Depression treatment has been associated with a greater seizure burden, indicating that severity of depression is associated with severity of epilepsy (268). Chronic use of SSRI in a kindling model in rats enhanced epileptogenesis but this has not been proven in humans (269). A meta-analysis revealed that HGG patients with depression have reduced survival (270). In an American study, the annual suicide mortality rate in people with epilepsy was 22% higher than in the general population (271). In our cohort, suffocation or hanging was the cause of death in 1.44% of all grade II glioma patients and 2.20% of the grade II glioma patients with epilepsy. Suffocation or hanging represented 0.51% of all death causes in the total Norwegian population during the same period (272).

The follow-up of a patient with glioma and epilepsy may differ from that of a patient with glioma without epilepsy. In most hospitals, patients with glioma-associated epilepsy are followed by a neurologist in addition to an oncologist. A patient's personal perception of the medical care they receive may affect the level of anxiety and depression. If this was the case for our patients, frequent pre-scheduled specialist consultations could have prevented or reduced symptoms of anxiety and depression. Theoretically, if neurologists referred depressed glioma patients with epilepsy to psychological treatment instead of initiating pharmacological treatment, this might have affected the extent of psychiatric medication dispensed to these patients. From clinical experience, referral of patients with glioma and epilepsy to psychological treatment is not a common routine in neurological practice, supporting that our result more likely represents undertreatment of depression in this subgroup.

5.1.3 Paper III

The gliomas were mostly located in the frontal and parietal regions, as in previous studies of tumor-related SE (112,273). Cortical grade II gliomas have a higher risk of presenting with epileptic seizures than gliomas involving midline structures (89), especially frontal lobe gliomas (274). Of our patients, 12/20 (60%) had tumor location in the left hemisphere, similar to 16/26 patients (62%) in a later cohort of glioma patients with associated SE (275). Grade II gliomas in the left premotor area have been associated with increased risk of focal to bilateral seizures (276).

Despite the shorter survival and the lower risk of epilepsy compared to grade II glioma, most patients in our cohort had HGG (4). This is supported by other studies in which HGG was more prone to SE than grade II glioma (112,273,275,277–279). Biological factors, such as breakdown of the blood-brain barrier, cortical edema, necrosis, hemorrhage and hemosiderin deposits, may contribute to the development into SE. Hypoxia and acidosis caused by large edemas from aggressive tumors damage glial cells. Focal disruption of the blood–brain barrier, an acidic environment and changes in ionic concentrations across cell membranes reduce the seizure threshold by increasing neuronal excitability, and even possibly by lowering AED levels (69,280). There is no evidence of corticosteroids increasing the severity of seizures with development into SE. On the contrary, corticosteroids is used in the treatment of encephalopathic epilepsy syndromes (281). Our cohort was too small to subdivide according to the specific histology and molecular marker status, but the presence of 1p19q co-deletion was used to classify tumors as oligodendrogliomas. Additional molecular subtypes were available for less than half of the patients.

The gender difference was much larger than expected. Gliomas are more common in males than in females, recently attributed to larger intracranial volume (29). Only two other studies of brain tumor-related SE reported the male proportion of included patients; 23/35 (66%) and 15/26 (58%)

(275,277). The age-adjusted annual incidence of SE in adults within the area of the University Hospital Marburg, Germany 1997-1999 was 13.7/100,000 for females and 26.1/100,000 for males (282). The age and sex-adjusted incidence of non-hypoxic SE in Salzburg, Austria during 2011-2015 was 12.8/100,000 for females and 23.4/100,000 for males aged 18-59 years (283). On the contrary, the incidence was 89.6/100,000 for females and 67.6/100,000 for males aged >60 years, and 77.6% of all NCSE were in females (283). Our cohort had a median age 55 years compared to 69 years in the Salzburg cohort. We suspect that NCSE was underdiagnosed in our study as it is especially difficult to distinguish NCSE from general neurological decline in brain tumor patients. In the main treating Neurological department of our cohort, in total 48 NCSE from all causes in 39 adults were registered between 2004-2009, and these were 17 females and 22 males (284). The higher incidence of SE in males than in females has previously been explained by a higher risk of cerebrovascular disease, brain trauma and CNS infection (285). Differences due to influence from sex steroid hormones on seizure threshold is complicated by estrogens acting proconvulsant and progesterone acting anticonvulsant (286). In Switzerland, the risk for recurrence of SE in adults was borderline more frequent in females (HR 1.6, 95% CI 0.97-2.65, p=0.06) (287).

SE evolved to both cerebral hemispheres in 15/31 SE (48%), which is similar to 17/35 SE (49%) reported for SE in patients with neoplasms (277). Previous studies of brain tumor-related SE did not report the seizure semiology (112,273,279), or focal seizures amounted the majority (288). We used the 30 minutes definition of SE, which is often used in studies with prognostic evaluations, to be able to compare results to previous studies. This definition does not reflect the new ILAE definition for focal SE with impaired consciousness (111). The duration was >one hour to five hours in 13/31 SE (42%). Focal without or with impaired consciousness SE more often persisted >five hours than focal onset evolving into bilateral convulsive SE. The duration of SE was not reported in most comparable studies. A systematic review and meta-analysis found a shorter mean duration of brain tumor-related SE compared to SE from other causes; 152.9 minutes versus 174.1 minutes (289).

SE was debut symptom in 7/31 SE (23%) and due to tumor progression in 8/31 SE (26%). This is similar to previously reported 10/35 SE (29%) as debut symptom and 8/35 SE (23%) due to tumor progression (277). In the other studies, glioma-associated SE was more frequently related to tumor growth than in our cohort; 2/10 and 14/26 SE (54%) as debut symptom in addition to 4/10 and 12/26 SE (46%) due to tumor progression (112,275). SE can induce a transient increase in signal intensity and contrast enhancement on MRI which may erroneously be interpreted as caused by tumor progression. In paper III, all cases of radiological tumor progression were confirmed by clinical progression, which should distinguish between contrast enhancement caused by SE alone or by the tumor. SE was triggered by the primary oncological treatment in 4/31 (13%), which is comparable to previously reported 4/35 (11%) and 2/10 (112,277).

Recurrent SE occurred in 7/20 (35%), which we consider to be substantial. This rate is similar to the recurrence rate of 32% for SE from all causes, of which 14% of all the recurrent SE were due to a brain tumor (287). Our rate is higher than previously reported 2/10 with recurrent SE evaluated at eleven months after glioma diagnosis (112). One of the three patients who died within 30 days of SE in our cohort had recurrent SE. One patient died within three months after SE without any signs of tumor progression. The 30 days mortality rate calculated for first SE episodes for our total cohort was 3/20 (15%). The 30 days mortality rate for the patients with HGG was 3/15 (20%), which is comparable to previously reported 3/11 (27%) for HGG (277). No patient with grade II glioma died within 30 days, also in accordance with that study (277). Short-term mortality for brain tumor-related SE was reported to be higher than for SE from all causes (17% versus 11%, RR 1.53, 95% CI 1.24-1.90) (289). Also, 30 days mortality for NCSE in cancer patients was 28% while overall mortality for NCSE from all causes was 6.3-18% (284,290,291).

SE due to tumor progression was associated with major sequelae or death within three months, explained by the tumor growth. We could not determine or quantify contributions from SE to the increased morbidity and mortality of tumor progressions due to the small sample size. NCSE has

been considered to negatively affect the clinical course of patients with brain tumors leading to a worse outcome (279). Long-term morbidity was 33.3% for brain tumor-related SE (292), compared to 15.2% for SE from other causes (289). No previous study analysed treatment response, morbidity and mortality of SE secondary to brain tumor for subgroups with or without tumor progression. A recent cohort study found a worsening of the clinical condition in 10/26 (38%) and death in 1/26 (4%) after glioma-associated SE (275). Their lower rate of sequelae is probably related to the SE definition of 5 minutes used in that study, and the treatment response was good with only 12% RSE despite a larger proportion of SE caused by tumor progression (275). A difference between these two cohorts was that more of our patients had tumor location involving the frontal lobe, which is associated with treatment refractoriness (273). Refractoriness to SE treatment is also associated with longer SE duration and worse prognosis (293). In our cohort, all patients with SE due to tumor progression had HGG, specifically one had grade III glioma and seven had grade IV glioma. The rate of 26% RSE in our cohort is higher than 18% reported for brain tumor-related SE (294) and 11% reported for SE in patients with neoplasms (277). Due to the small sample size we could not use Cox regression and determine risk factors for treatment refractoriness. The RSE rate in our cohort is in the lower range of previously reported 23-43% for SE from all causes (284,295–298), indicating that glioma-associated SE is not especially treatment refractory.

6. Main conclusions

1. There has been a shift in the AED treatment of GBM patients from EIAEDs to the non-EIAED levetiracetam.

2. Neither AED treatment for epilepsy nor exposure to any of the six most commonly used AEDs in our GBM cohort were proven to affect OS.

3. Drug-treated pain and depression increased already before the glioma diagnosis, epilepsy increased during time of diagnosis, and drug-treated anxiety increased firstly from the glioma diagnosis.

4. In patients with grade II-III glioma, exposure to levetiracetam was associated with drug-treated anxiety. We recommend that clinicians assess for symptoms of anxiety before initiating levetiracetam in these patients.

5. Fewer received antidepressants among the patients with grade II-III glioma and epilepsy than among the corresponding group in the general population. We interpret this discrepancy as possible undertreatment of depression in this particular subgroup.

6. Three times as many patients with HGG than grade II glioma had SE. SE was caused by tumor growth, either as debut symptom or as tumor progression, in one half of all episodes.

7. SE in glioma patients responded well to standard treatment. Underlying tumor progression was not associated with SE treatment refractoriness but with major sequelae or death. We recommend that SE is treated aggressively in all glioma patients.

7. Clinical implications and future aims

The overarching goal of the three papers and this thesis was to improve our knowledge on drug treatment of epilepsy in patients with grade II-IV glioma. Paper I reassures the clinician to choose AED based on the aim of superior antiepileptic effect with a minimum of adverse effects, as for other patients with epilepsy. Paper II calls for an assessment of anxiety and depression symptoms before and during the antiepileptic drug treatment of glioma-associated epilepsy. We recommend that AEDs are adjusted accordingly to prevent worsening of psychiatric symptoms. Implementing routines for diagnosing and treating anxiety and depression in glioma patients is likely to improve these patients` QOL. A future aim is for CRN to register clinical data on patients with CNS cancer through patient questionnaires including epileptic seizure frequency, psychiatric symptoms and QOL. CRN has already applied for financial support to establish a quality register for CNS cancer. We also encourage CRN to include information on molecular markers and tumor progressions to improve future studies of glioma.

The propensity for SE in patients with HGG in paper III raises the question whether epilepsy secondary to HGG and grade II glioma require different treatment approaches. Whether regulating mechanisms of seizure termination differ between glioma subgroups would be interesting to explore in experimental studies. While glioma-associated epilepsy is known to be especially treatment refractory, glioma-associated SE was not more treatment refractory than reported for SE from other causes. We strongly recommend that any glioma patient is equally aggressively treated for SE as a patient without brain tumor to shorten the duration of SE and reduce sequelae. Patient enrollment for the prospective clinical study of patients with grade II-IV glioma and associated epilepsy is ongoing. Extending the inclusion to other hospitals in Norway and abroad will increase the sample size and enable statistical analyses of subgroups.

The association between exposure to levetiracetam and drug-treated anxiety in grade II-III glioma patients, and no proven survival benefit for GBM patients from any of the investigated AEDs, support the consideration of newer non-EIAEDs when treating glioma-associated epilepsy. Brivaracetam has a similar mechanism of action as levetiracetam and was reported to be generally well tolerated as adjunctive treatment for focal epileptic seizures in adults (299). Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels and was reported as generally well tolerated when given as adjunctive therapy to adult glioma patients (300,301). The AMPA receptor antagonist perampanel is used for focal epileptic seizures (302,303), and a RCT for glioma patients is planned (304). In vitro studies showed possible anti-tumor effects on glioma cells from brivaracetam and lacosamide (305), and reduced GBM cell proliferation and altered gene expressions with less glutamate release from perampanel (306). Future aims are to determine which AED is the most efficacious for glioma-associated epilepsy with a minimum of adverse effects, and to clarify whether any of the new, approved AEDs actually provide any clinically relevant prolonged survival for subgroups of glioma patients.

8. Errata

1. In paper I, Table 1, age at diagnosis should have been 0-29 instead of 1-29. Of the 23 patients, two patients were diagnosed with GBM the same year (one in July and one in December) as their year of birth.
2. There are discrepancies in the subgroups of surgery in paper I and paper II due to different selections of CRN codes. The statistical analyses included the correct number of patients for the defined categories of "extent of resection" in each paper. Paper I included 155 patients with "no surgery", twelve with "biopsy", 154 with "incomplete resection" including one with resection of tumor progression, 932 with "complete resection" and ten with "unknown". These terms should have been referred in the section "statistical analyses" of paper I. In the result section of paper I, stricter selections of CRN codes were chosen when presenting 137 patients with "incomplete surgery" and 859 patients with "complete surgery". In paper II, Table 1, the category "biopsy" for glioma grade IV included twelve patients with "biopsy" and 153 patients with "incomplete resection". The one patient with resection of tumor progression was classified as "incomplete resection" in paper I and as "tumor resection" in paper II. We should have kept the term "incomplete resection" instead of "biopsy" when reducing the number of categories for surgery in paper II.
3. In paper III, Table 2, the category for previous seizures termed "no seizures the last month before SE" could have been divided into two separate categories; One for 7/31 "SE leading to glioma diagnosis not preceded by any seizure the last month before SE" and one for 13/31 "later SE not preceded by any seizure the last month before SE".

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Papers I-III

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Status epilepticus secondary to glioma

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ABSTRACT

Purpose: Epilepsy is common in glioma patients, but clinical data on the course of status epilepticus (SE) in this group are sparse. The aim of this study was to investigate the relationship of SE to tumor grading, seizure semiology, trigger factors, treatment response, recurrence and outcome of SE in patients with glioma.
Methods: Adult patients with SE and glioma WHO grade II–IV were identified from a prospective clinical study at two neurological departments. We identified 31 SE in 20 patients during a period of 7 years.
Results: SE was more frequent in patients with high-grade glioma. Half of the seizures were secondary generalized. Patients with a clinical and radiological stable glioma had SE as often as patients with untreated tumor or tumor in progression. The majority of patients had a well-controlled epilepsy prior to SE. SE responded well to first and second line treatment. Patients with SE and tumor progression were not more refractory to treatment than patients without progression.
Conclusion: SE secondary to glioma responded well to treatment and should be treated aggressively regardless of the oncological prognosis. Seizures during tumor progression were not more treatment refractory than SE in patients with stable glioma disease.

1. Introduction

Brain tumor related epilepsy is an important aspect of the burden of disease for patients with glioma and often pose a therapeutic challenge. The risk of epileptic seizures is 70–90% for patients with low grade glioma (LGG) and 30–60% for patients with high grade glioma (HGG) [1–5]. In this study, we explored status epilepticus (SE) in a prospective patient database with glioma and epilepsy. SE is a life-threatening medical emergency in which seizure activity continues for a prolonged period of time, or where seizures recur before full clinical recovery from the preceding seizure [6,7]. The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have proposed a new definition of SE: Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. It is a condition which can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures [8]. SE is often operationally defined as ≥5 min of continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness [9]. If inadequately treated and lasting beyond 30 min, which is the older definition of SE, this condition can result in permanent pathophysiological changes [6,10]. Thus, SE requires immediate treatment, often in an intensive care unit (ICU). Brain tumor is the cause of SE in 3–12% of adult cases [11–14]. Previous studies on SE in glioma patients [15–18] have been retrospective, of small sample size and including tumors of various histologies.

The aim of our study was to investigate SE in a prospective material of adult patients with verified glioma. We investigated the relationship of SE to tumor grading, seizure semiology, trigger factors and treatment response, in addition to recurrence and outcome. Our research is important to gain a better understanding of this challenging epileptic condition in a patient group with complicating underlying tumor.

Abbreviations: AEDs, antiepileptic drugs; GBM, glioblastoma; HGG, high grade glioma; LGG, low grade glioma; RSE, refractory status epilepticus; SE, status epilepticus.

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2. Material and methods

Patients with SE and glioma were identified from a prospective clinical study of adult patients with verified glioma WHO grade II–IV and one or more epileptic seizures during the course of disease. The study has been ongoing since 2008 with inclusion of all eligible patients at the only two neurological departments in two counties of western Norway (Haukeland University Hospital in Bergen, Hordaland County and Central Hospital, Sogn and Fjordane County) since 2009. These two counties have a population of 620,527 (Statistics Norway 01.01.15). The glioma patients are followed clinically and radiologically from their first seizure until death. Neurological, oncological and paraclinical data are collected every 6 months and at other admittances to the hospitals. By 10.12.2014, 20 patients had been registered with SE, once or on several occasions. These 20 glioma patients had in total 31 SE. We adhered to the old definition of SE as seizures lasting beyond 30 min, as this is regarded as the threshold for neurological damage. We evaluated the medical records, prehospital information, blood analyses, cerebral CT and MRI, EEG and follow-up data of all patients. For descriptive purposes, all 31 status episodes were included. In patients with multiple SE episodes, only the first episode was included in the statistical analyses, to avoid the bias of repeated measurements in one subject. The study was approved by Regional Committees for Medical Research Ethics (REK 2008/11243) and all patients gave a written consent.

3. Theory/calculation

3.1. Definitions

SE was defined as either 30 min of continuous seizure activity or two or more sequential seizures without recovery of full consciousness between the seizures [19]. Although the definition was recently modified, we adhered to this version which is often used in evaluating prognosis and has been used throughout the study period [8,20]. Seizures were classified as focal SE without consciousness impairment, focal SE with consciousness impairment or secondary generalized SE. Refractory status epilepticus (RSE) was defined as SE unresponsive to two AEDs and/or requiring anesthetic agents for seizure control [21,22]. If the patient was treated with two different benzodiazepines as first line treatment, this was considered as the same AED.

The patients were grouped according to histological diagnosis at onset of disease, or, in case of malignant transformation, according to the most recent histological diagnosis. The LGG group includes astrocytoma and oligodendroglioma of WHO grade II. HGG includes anaplastic astrocytoma (WHO grade III) and glioblastoma (GBM) (WHO grade IV) [23]. SE was categorized as onset symptom if the seizure unfolded within 30 days prior to glioma diagnosis. Progression was defined as radiographic changes and clinical signs consistent with tumor progression within 30 days of the SE. Mortality was defined as death within 30 days after the SE. Sequela was defined as a neurological deficit acquired during the SE and documented in the medical record as persistent at time of discharge, or at the next control appointment at the hospital. Mild sequelae were defined as transient neurological deficits lasting less than 1 month. Moderate sequelae were defined as neurological deficits that were still present more than 1 month after SE. Major sequelae were defined as permanent neurological deficits which severely impaired functional ability.

3.2. Statistical methods

Statistical analyses were carried out in IBM SPSS Statistics for Windows, versions 22.0 and 23.0 (Armonk, NY: IBM Corp). Background variables were compared using cross-tables with Fisher's exact test of independence. Two-sided P values ≤ 0.05 were interpreted as statistically significant dependence of variables.

4. Results

4.1. Patient and tumor characteristics

We identified 31 SE in 20 patients (Table 1). Five patients had LGG and 15 had HGG. Two of the HGG were transformed from previous LGG. The glioma was localized in the left hemisphere in 60%. Four tumors had a frontal location, ten were localized in the parietal lobe or frontoparietal region, four were temporal lobe tumors, one was occipital and one multilobal.

4.2. SE characteristics

The SE was secondary generalized in 15/31 (48%), focal with consciousness impairment in eight (26%) and focal without consciousness impairment in eight (26%) (Fig. 1). Repeated SE was seen in seven of the 20 patients. Six of them had HGG, including two patients with four SE each. The single LGG patient had oligodendroglioma with SE as onset symptom and a second SE several years later, at a time with no AED use.

The duration of SE varied from 30 min to 4 days (Table 2). The focal seizures more often persisted longer than 5 h than the secondary generalized seizures ($P = 0.01$). In patients where SE led to initial glioma diagnosis (seven SE) or diagnosis of progression (eight SE), we regarded the tumor as the main SE trigger factor. In the other 16 SE, the tumor was stable and other possible trigger factors were identified, as ongoing radiotherapy with or without concomitant chemotherapy (four), intercurrent disease (one) or changes in AED regimen (two). Most SE occurred in a setting of well-controlled epilepsy with no or few seizures the last month (Table 2). Four SE occurred in patients with no prophylactic AED treatment, in addition to the seven SE which heralded glioma diagnosis. Of the 20 SE in patients taking prophylactic AEDs, only six were during polytherapy. Two patients had serum AED levels below and one patient above the reference areas at SE.

First line treatment was sufficient to terminate the seizures in 15/31 SE (48%) and second line treatment was needed in 7/31 (23%) (Table 2). Eight cases were RSE; additional levetiracetam and/or valproate were needed in six SE and general anesthesia with

Table 1
Characteristics of patients ($n = 20$).

Gender	Frequency
Male	16
Female	4
Tumor histology	
Oligodendroglioma	3
Astrocytoma	2
Anaplastic astrocytoma	3
Glioblastoma	12
Number of SE	
1 SE	13
2 SE	5
3 SE	0
4 SE	2
Age at glioma diagnosis	Years
Median	55
Minimum	24
Maximum	95

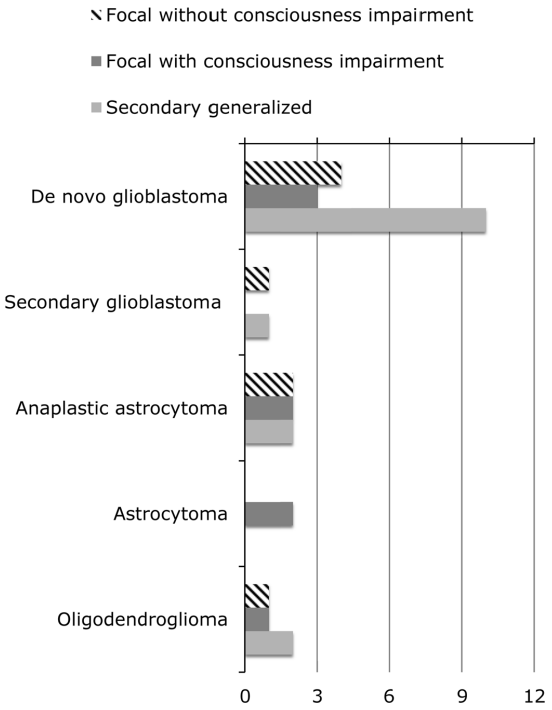

Fig. 1. Classification of SE semiology ($n = 31$).

propofol in two. Of the recurrent SE, four were treated successfully with first line treatment, three needed second line treatment and four were RSE. Considering only the first SE in every patient, 16/20 (80%) responded to first or second line treatment. None of the first SE episodes required general anesthesia. SE in patients with tumor progression was not proven to be statistically significant more treatment refractory ($P = 1.00$).

4.3. Outcome after SE

Sequelae in terms of new neurological deficits were present after 6/20 first SE (30%), one patient with tumor progression and five patients without tumor progression. Mild sequelae were aphasia and diminished hand motility. Moderate sequelae were exacerbation of hemiparesis, aphasia and impaired balance. Major sequelae were severe exacerbation of hemiparesis, dysarthria and impaired consciousness. Patients with SE and tumor progression had a worse outcome after SE (major sequelae or death within 3 months after SE) ($P = 0.01$).

At the end of this study, 16 patients were dead (Table 3). Mean and median time from glioma diagnosis to death were 28.5 months and 20 months (minimum 3, maximum 152). Follow-up from glioma diagnosis to end of study for the four survivors were 12–52 months. No patient died during SE or earlier than 3 weeks after SE. Six patients died within 3 months after SE, of which two were de novo GBM with recurrent SE. One of these patients died 2 months after her second SE and the other patient died 21 days after his fourth SE. Death within 3 months occurred in 0% of LGG and 40% of HGG. Additionally, two of the six patients died within 30 days of SE; one had transformed GBM and one anaplastic astrocytoma, which gave a 30 days' mortality rate of 0% for LGG and 20% for HGG.

Table 2
Status epilepticus (SE) characteristics ($n = 31$).

Semiology	Frequency
Focal without consciousness impairment	8
Focal with consciousness impairment	8
Secondary generalized	15
Duration of SE	
30 min	2
>30 min–1 h	6
>1–5 h	13
>5–24 h	4
>24 h–5 days	6
Previous seizures	
No seizure the last month before SE	20
1–2 seizures	8
3–4 seizures	1
>4 seizures	0
Unknown	2
Treatment	
None	1
Diazepam and/or midazolam	15
Diazepam and/or midazolam + phosphenytoin	7
Refractory[a]	8
Sequelae or death unrelated to progression[b]	
No	13
Mild	2
Moderate	4
Major	3
Death within 3 months	1
Sequelae and/or death related to progression[b]	
No	3
Mild	0
Moderate	0
Major	1
Death within 3 months	5

[a] Refractory SE was defined as the need of more medication than first and second line treatment.
[b] Sequela was defined as a neurological deficit acquired at time of SE and persistent at hospital discharge or at the next control appointment.

5. Discussion

The majority of SE occurred in HGG patients. This is surprising as the survival time is shorter in HGG and seizures are more frequent in LGG than in HGG. Advances in oncological therapy may affect the prevalence of seizures in glioma. Temozolomide has prolonged the survival time for GBM patients and may thus

Table 3
Outcome stratified by histological features.

Tumor histology	Number	Time from glioma diagnosis	Time from first SE
		Median (months)	Median (months)
Time until death ($n = 16$)			
Oligodendroglioma	1	152	152
Astrocytoma	1	27	27
Anaplastic astrocytoma	2	8.5	7.5
Glioblastoma	12	20	6
Follow-up of survivors ($n = 4$)			
Oligodendroglioma	2	51	46
Astrocytoma	1	12	12
Anaplastic astrocytoma	1	13	13
Glioblastoma	0		

increase the incidence of epilepsy in this group. The pathophysiology of epilepsy in LGG and HGG is different, as the slow growth in LGG allows for development of functional changes whereas the rapid growth in HGG leads to distortion of cortical tissue and edema [24,25]. Even though single or recurrent seizures are more common in LGG, the risk of tumor associated SE appears to be directly proportional to tumor grade [26]. HGG is fivefold as common as LGG in Europe [27] but as epilepsy was the major inclusion criterion, LGG constitutes as many as half of the patients in our database. Nevertheless, we found that 75% of first SE was in HGG, compared to 44% in a previous study [16]. Rosati et al. found a lower frequency of epilepsy in de novo GBM than in secondary GBM, supporting the hypothesis that the mechanisms of seizure in slow-growing and fast-growing tumors are different [24]. Aggressive tumors with insufficient blood supply cause intratumoral hypoxia and acidosis that may extend to surrounding tissue and cause glial swelling and damage leading to risk of seizures [28]. Two of our patients had secondary GBM. Other factors may also explain the higher frequency of SE in HGG. Chemotherapy may affect AED levels [29], and although seizure control usually improves by radiotherapy, some patients have seizures due to acute radiation encephalopathy. The four patients with SE related to oncological treatment were all GBM. Corticosteroids decrease susceptibility to seizures in laboratory studies [30], and are used liberally as anti-edema therapy in HGG. Dose tapering may increase susceptibility to seizures, also due to increased edema, although no studies investigate this issue. Most HGG in our study were treated with dexamethasone.

In half of the SE, the semiology was secondary generalized seizures. Most previous studies of SE in glioma have not defined seizure type [18] or only included particular seizure types [15,17], thus making a general comparison of semiology with these studies challenging. Brain tumors have earlier been regarded as having the propensity to cause focal SE rather than secondary generalized SE [31]. However, the majority of brain tumor patients with SE in an Italian study [16] also suffered secondary generalized SE, similar to our results. For SE in general, secondary generalized seizures are reported to be observed in 19–66% of patients [32]. The recurrence rate was 35%, which is roughly comparable with a recent estimate not limited to tumor patients of 32% [33].

The glioma was most often located in the parietal lobe. Parietal tumors are easier to operate, with improved survival and thereby longer possibility for developing SE. Another reason for our finding can be that the risk of epileptic seizures is substantial in tumors of the parietal lobes [34,35].

Four times as many males than females were affected by SE, which cannot be explained by the modest gender difference in glioma. SE in general is more common among men, which has been explained by the higher male frequency of cerebrovascular disease [36]. However, our findings in a tumor population suggest that gender differences in epileptogenicity or other factors might be important.

More than 70% of the SE in this study was controlled by first or second line treatment, of which 75% had a well-controlled seizure situation prior to SE. About one fourth were treatment refractory, which is toward the lower margin of estimations reported for SE with other etiology than tumor [12]. Refractory SE has been estimated to 23–43% in different studies and is associated with high morbidity and mortality [37–40]. SE associated with tumor progression was not less treatment responsive but had worse outcome, which could be due to SE, the tumor progression or both. Thus, evaluating outcome measures with respect to SE are uncertain in this subgroup. However, we hypothesize that SE in the context of tumor progression might exacerbate the neurological decline. We found a similar 30 days' mortality rate for HGG with SE as a previous study, 20% vs 18% [16]. Tumor progression was known in all cases that led to death within 3 months of SE except one. As SE is a medical emergency and progression may be unknown at the time of hospital admittance, we propose that all SE in glioma are treated aggressively until tumor status is clarified. In a setting of acknowledged tumor progression and RSE, the clinician may decide to withhold therapy requiring ICU – however, our data show that third line treatment is unnecessary in most cases. In addition, for palliative and psychological reasons, it is highly important to avoid SE in the terminal phase, and we suggest that effective SE therapy should not be withheld in any patient with clinical SE and glioma.

There were no losses to follow-up. Non-convulsive SE might be underdiagnosed in patients with marked consciousness impairment within the last weeks of life and dying at home or in nursing homes. The two neurological departments participating in the study covers the complete population in a defined geographical cohort. This material therefore has minimal selection bias, reflecting the total population of patients with a glioma and SE, recorded prospectively during 7 years.

6. Conclusion

Our results show that SE should be treated as aggressively in glioma patients as in patients with no tumor. The response to treatment was good and general anesthesia seldom required. SE arose in patients with clinically and radiologically stable disease as often as in patients with untreated tumor or tumor in progression. Patients with SE triggered by tumor progression were not more refractory to treatment than patients with a stable glioma.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

The authors received no funding for this study. None of the authors has any conflict of interest to disclose.

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Supplementary material, paper II

Online Resource 1-5

Online Resource 1 Examination of potential risk factors [a] for anxiety in patients with glioma grade II-III and grade IV the first two years after glioma diagnosis

Glioma II-III	**N=28**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	11	39	2.39	1.04	5.50	0.04
Carbamazepine	5	18	1.48	0.62	3.53	0.38
Oxcarbazepine	2	7	0.31	0.04	2.34	0.25
Valproate	5	18	1.55	0.65	3.66	0.32
Lamotrigine	2	7	1.30	0.47	3.60	0.61
Grade III glioma	17	61	1.68	0.83	3.39	0.15
Epilepsy	19	68	1.21	0.53	2.75	0.65
No surgery	0	0	0.31	0.03	3.05	0.32
Biopsy	5	18	0.95	0.46	1.99	0.90
No radiotherapy	3	11	1.48	0.58	3.81	0.41
Temozolomide	23	82	6.54	2.61	16.35	<0.01
Systemic steroids	20	71	2.92	1.49	5.73	<0.01
Pain	22	79	1.55	0.81	2.97	0.19
Frontal tumor	6	21	0.68	0.33	1.38	0.28
Female	16	57	1.50	0.81	2.77	0.20
Age <20	2	7	2.14	0.65	7.03	0.21
Age 20-39	9	32	0.86	0.41	1.80	0.69
Age 40-59	9	32	Reference			
Age 60-79	6	21	1.10	0.48	2.52	0.82
Age 80+	2	7	27.93	4.73	164.76	<0.01
Glioma IV	**N=144**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	37	26	1.47	0.85	2.54	0.17
Carbamazepine	8	6	1.16	0.60	2.21	0.66

Oxcarbazepine	12	8	1.14	0.57	2.29	0.71
Valproate	25	17	0.66	0.36	1.19	0.17
Lamotrigine	8	6	1.63	0.78	3.39	0.19
Epilepsy	75	52	0.95	0.61	1.47	0.82
No surgery	6	4	0.77	0.30	1.93	0.57
Biopsy	20	14	1.49	0.97	2.28	0.07
No radiotherapy	9	6	1.29	0.65	2.59	0.47
Temozolomide	116	81	1.88	1.23	2.87	<0.01
Systemic steroids	99	69	1.55	1.14	2.10	<0.01
Pain	113	78	2.13	1.55	2.92	<0.01
Frontal tumor	35	24	0.93	0.66	1.31	0.66
Female	76	53	1.50	1.13	2.00	<0.01
Age <20	1	1	0.65	0.16	2.67	0.55
Age 20-39	4	3	0.50	0.23	1.09	0.08
Age 40-59	63	44	1.07	0.78	1.46	0.68
Age 60-79	67	47	Reference			
Age 80+	9	6	1.33	0.61	2.87	0.47

[a]HR=Hazard ratios. CI=Confidence intervals. Age in years

Online Resource 2 Examination of potential risk factors [a] for depression in patients with glioma grade II-III and grade IV the first two years after glioma diagnosis

Glioma II-III	**N=39**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	13	33	1.33	0.37	4.72	0.66
Carbamazepine	5	13	0.83	0.23	2.92	0.77
Oxcarbazepine	3	8	1.63	0.46	5.85	0.45
Valproate	11	28	1.84	0.69	4.85	0.22
Lamotrigine	6	15	0.55	0.12	2.48	0.43
Grade III glioma	10	26	0.84	0.38	1.85	0.66
Epilepsy	25	64	0.55	0.25	1.22	0.14
No surgery	3	8	1.37	0.43	4.37	0.59
Biopsy	4	10	0.72	0.29	1.77	0.47
No radiotherapy	12	31	0.84	0.37	1.88	0.67
Temozolomide	20	51	0.77	0.35	1.69	0.51
Systemic steroids	22	56	0.98	0.50	1.94	0.96
Pain	34	87	3.65	1.88	7.08	<0.01
Frontal tumor	13	33	0.88	0.47	1.64	0.69
Female	18	46	1.29	0.72	2.32	0.39
Age <20	0	0	0.00	0.00	0.00	0.00
Age 20-39	10	26	0.80	0.41	1.53	0.49
Age 40-59	19	49	Reference			
Age 60-79	9	23	0.95	0.43	2.11	0.90
Age 80+	1	3	1.62	0.20	13.37	0.65
Glioma IV	**N=109**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	17	16	0.93	0.34	2.55	0.88
Carbamazepine	9	8	0.71	0.21	2.40	0.58

Oxcarbazepine	9	8	1.32	0.44	3.98	0.63
Valproate	12	11	0.48	0.16	1.46	0.20
Lamotrigine	4	4	0.83	0.19	3.62	0.81
Epilepsy	43	39	0.54	0.28	1.04	0.07
No surgery	6	6	0.95	0.37	2.41	0.91
Biopsy	17	16	1.72	1.04	2.85	0.04
No radiotherapy	6	6	0.87	0.38	2.03	0.75
Temozolomide	77	71	0.90	0.57	1.43	0.67
Systemic steroids	72	66	1.19	0.82	1.73	0.36
Pain	70	64	1.50	1.03	2.20	0.04
Frontal tumor	16	15	0.55	0.33	0.91	0.02
Female	57	52	1.38	0.96	1.98	0.08
Age <20	1	1	0.54	0.07	3.93	0.54
Age 20-39	5	5	1.10	0.46	2.60	0.83
Age 40-59	41	38	1.23	0.82	1.84	0.32
Age 60-79	53	49	Reference			
Age 80+	9	8	1.26	0.59	2.73	0.55

[a]HR=Hazard ratios. CI=Confidence intervals. Age in years

Online Resource 3 Medication during the year prior to the glioma diagnosis (N observed), compared to the total Norwegian population (N expected) [a]

[a]SIR=Standardized incidence ratios. CI=Confidence intervals

Medication	Glioma grade	Strata	N observed	N expected	SIR	95% CI	
Anxiolytics		**All**	311	139	2.24	2.00	2.50
	II-III	**Epilepsy**	15	1	12.76	7.69	21.17
		No epilepsy	67	29	2.30	1.81	2.93
	IV	**Epilepsy**	8	2	5.02	2.51	10.04
		No epilepsy	221	107	2.06	1.81	2.36
Hypnotics		**All**	370	185	2.00	1.81	2.21
and sedatives	**II-III**	**Epilepsy**	9	2	5.30	2.76	10.18
		No epilepsy	75	35	2.15	1.72	2.70
	IV	**Epilepsy**	2	2	0.81	0.20	3.24
		No epilepsy	284	146	1.94	1.73	2.18
		All	172	128	1.35	1.16	1.56
Antidepressants	**II-III**	**Epilepsy**	1	2	0.55	0.08	3.92
		No epilepsy	32	31	1.05	0.74	1.48
	IV	**Epilepsy**	5	1	3.72	1.55	8.94
		No epilepsy	134	94	1.42	1.20	1.69

Online Resource 4 Examination of potential risk factors [a] for anxiety in patients with glioma grade II-III and grade IV without depression

Glioma II-III	**N=59**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	32	54	4.30	2.27	8.14	<0.01
Carbamazepine	15	25	1.49	0.77	2.89	0.24
Oxcarbazepine	8	14	0.99	0.36	2.67	0.98
Valproate	19	32	2.28	1.19	4.38	0.01
Lamotrigine	13	22	1.60	0.77	3.34	0.21
Grade III glioma	25	42	1.94	1.00	3.78	0.05
Epilepsy	49	83	0.83	0.38	1.81	0.64
No surgery	0					
Biopsy	16	27	1.29	0.70	2.40	0.41
No radiotherapy	16	27	1.38	0.63	3.01	0.42
Temozolomide	50	85	5.59	2.60	12.04	<0.01
Systemic steroids	46	78	4.29	2.29	8.01	<0.01
Pain	47	80	1.14	0.63	2.06	0.67
Frontal tumor	21	36	1.13	0.63	2.01	0.68
Female	29	49	1.44	0.83	2.49	0.19
Age <20	7	12	2.66	1.04	6.82	0.04
Age 20-39	16	27	0.71	0.37	1.36	0.30
Age 40-59	26	44	Reference			
Age 60-79	9	15	0.77	0.35	1.71	0.53
Age 80+	1	2	27.60	2.93	260.12	<0.01
Glioma IV	**N=163**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	40	25	1.58	0.91	2.74	0.10
Carbamazepine	14	9	1.21	0.63	2.32	0.58
Oxcarbazepine	10	6	0.98	0.46	2.11	0.96
Valproate	30	18	0.60	0.33	1.11	0.11
Lamotrigine	15	9	1.83	0.90	3.73	0.10
Epilepsy	89	55	1.07	0.68	1.70	0.76

No surgery	5	3	0.65	0.24	1.79	0.40
Biopsy	18	11	1.17	0.70	1.93	0.55
No radiotherapy	9	6	1.44	0.69	3.01	0.34
Temozolomide	137	84	1.84	1.15	2.95	<0.01
Systemic steroids	118	72	1.73	1.24	2.42	<0.01
Pain	130	80	2.12	1.50	2.99	<0.01
Frontal tumor	44	27	1.17	0.83	1.67	0.37
Female	77	47	1.38	1.01	1.89	0.04
Age <20	2	1	0.76	0.18	3.13	0.70
Age 20-39	8	5	0.49	0.23	1.03	0.06
Age 40-59	69	42	0.90	0.64	1.27	0.57
Age 60-79	76	47	Reference			
Age 80+	8	5	1.47	0.65	3.34	0.36

[a]HR=Hazard ratios. CI=Confidence intervals. Age in years

Online Resource 5 Examination of potential risk factors [a] for depression in patients with glioma grade II-III and grade IV without anxiety

Glioma II-III	**N=38**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	14	37	2.57	0.86	7.69	0.09
Carbamazepine	7	18	1.35	0.43	4.28	0.61
Oxcarbazepine	2	5	0.61	0.07	5.04	0.65
Valproate	10	26	4.52	1.59	12.82	<0.01
Lamotrigine	9	24	3.67	1.20	11.19	0.02
Grade III glioma	8	21	0.85	0.34	2.11	0.73
Epilepsy	21	55	0.20	0.07	0.57	<0.01
No surgery	3	8	1.74	0.45	6.66	0.42
Biopsy	4	11	0.72	0.24	2.16	0.56
No radiotherapy	12	32	0.68	0.25	1.86	0.45
Temozolomide	18	47	0.38	0.15	0.94	0.04
Systemic steroids	23	61	2.27	1.06	4.86	0.03
Pain	30	79	3.70	1.67	8.22	<0.01
Frontal tumor	17	45	1.39	0.70	2.76	0.35
Female	14	37	0.75	0.38	1.49	0.41
Age <20	0	0				
Age 20-39	15	39	1.07	0.50	2.32	0.85
Age 40-59	14	37	Reference			
Age 60-79	9	24	1.39	0.59	3.28	0.45
Age 80+	0	0				
Glioma IV	**N=86**	**%**	**HR**	**95% CI**		**P-value**
Levetiracetam	9	10	0.98	0.28	3.47	0.97
Carbamazepine	10	12	2.24	0.81	6.17	0.12
Oxcarbazepine	5	6	0.62	0.08	4.85	0.65
Valproate	13	15	1.59	0.57	4.44	0.37
Lamotrigine	5	6	2.62	0.73	9.39	0.14

Epilepsy	33	38	0.31	0.13	0.71	0.01
No surgery	5	6	0.95	0.34	2.68	0.92
Biopsy	13	15	1.59	0.86	2.93	0.14
No radiotherapy	5	6	0.81	0.30	2.20	0.68
Temozolomide	58	67	0.85	0.49	1.45	0.55
Systemic steroids	60	70	1.33	0.85	2.07	0.21
Pain	50	58	1.14	0.73	1.79	0.56
Frontal tumor	13	15	0.59	0.32	1.07	0.08
Female	39	45	1.20	0.78	1.85	0.40
Age <20	1	1	0.70	0.09	5.12	0.72
Age 20-39	3	3	0.63	0.19	2.08	0.45
Age 40-59	31	36	1.02	0.63	1.65	0.94
Age 60-79	43	50	Reference			
Age 80+	8	9	1.50	0.65	3.46	0.34

[a]HR=Hazard ratios. CI=Confidence intervals. Age in years

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