Functional Outcome Following Treatment of Lower Grade Gliomas

Isabelle Rydén

Department of Clinical Neuroscience
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg

GÖTEBORGS UNIVERSITET
Gothenburg 2026

Cover illustration by ChatGPT, edited by Isabelle Rydén

© Isabelle Rydén 2026
isabelle.ryden@neuro.gu.se

ISBN 978-91-8115-647-8 (PRINT)
ISBN 978-91-8115-648-5 (PDF)

Printed in Borås, Sweden 2026
Printed by Stema Specialtryck AB

Dedicated to my late mother, Eva Rydén

Functional Outcome Following Treatment of Lower Grade Gliomas

Isabelle Rydén

Department of Clinical Neuroscience,
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Slow-growing gliomas most often affect individuals in midlife. These tumors are incurable, but multimodal treatment has improved survival. Consequences for patient functioning are less well understood. This thesis investigates functional outcomes after treatment, focusing on work, mental health, cognition, and quality of life, to improve knowledge and identify risk factors. The thesis is based on the following four studies:

Study I examines sick-leave patterns and return to work after first surgery using registry data. Patients with grade 2 gliomas and matched controls had similar sick-leave levels until months before surgery, then increasing in patients. After one year 52% worked and 63% at two years. Previous sick-leave, older age, lower functional status, and oncological treatment delayed return to work at one year. Female sex, comorbidity, and biopsy were associated with lower return to work at two years.

Study II investigates dispensed antiepileptic, antidepressant, and sedative medications after first surgery in patients with grade 2 gliomas. Antidepressants were usually initiated months after surgery, whereas sedatives and antiepileptics rose around diagnosis. Prior use and related diagnoses were the main predictors. Antidepressant use increased in recent years, and female patients had higher use than male patients and female controls.

Study III examines cognitive changes following treatment in a longitudinal two-center study of patients with *IDH*-mutated gliomas. Cognitive impairments were common before treatment, and individual declines were primarily observed in executive function, memory, and language. Older age and chemoradiotherapy emerged as risk factors.

Study IV addresses how cognitive functioning relates to quality of life at different stages of the disease trajectory. Reduced global HRQoL was common. Learning and memory were most relevant at diagnosis, language and executive functions at one year, while executive function was strongly associated in the long-term group.

In conclusion, treatment is associated with functional consequences and the findings underscore the need for systematic follow-up, early identification of patients at risk, and interventions to reduce negative long-term effects in these patients.
Keywords: *low-grade glioma, return to work, depression, anxiety, cognition, health related quality of life*

SAMMANFATTNING PÅ SVENSKA

Långsamtväxande gliom drabbar oftast personer mitt i livet. Tumörerna är obotliga, men ändringar i behandling har förbättrat överlevnaden. Konsekvenser för funktion och mående över tid är dock mindre kända. Denna avhandling undersöker utfall relaterade till funktion efter behandling, med fokus på arbete, psykisk hälsa, kognition och livskvalitet, för att förbättra kunskapen och identifiera negativa riskfaktorer.

Avhandlingen baseras på följande fyra delarbeten:

Delarbete I studerar sjukskrivningsmönster och arbetsåtergång upp till två år efter första operation med hjälp av registerdata. Patienter (WHO grad 2 gliom) och kontroller hade liknande sjukskrivningsgrad fram till månader före operation, därefter ökade den bland patienterna. Ett år efter operation arbetade 52%, och 63% arbetade efter två år. Tidigare sjukskrivning, högre ålder, lägre funktionsnivå och onkologisk behandling fördröjde arbetsåtergången vid ett år. Kvinnor, samsjuklighet och biopsi predicerade lägre återgång vid två år.

Delarbete II undersöker uttag av anti-epileptika, antidepressiva och lugnande läkemedel ett år före till ett år efter första operation för WHO grad 2 gliom. Patienter uppvisade högre läkemedelsuttag i samtliga kategorier. Antidepressiva initierades oftast månader efter kirurgi, medan lugnande och anti-epileptiska läkemedel ökade kring diagnos. Tidigare bruk och relaterad diagnos var den starkaste prediktorn för samtliga kategorier. Uttag av antidepressiva ökade på senare år och kvinnliga patienter hade högre uttag än manliga patienter och kvinnliga kontroller.

Delarbete III studerar kognitiva förändringar efter behandling i en longitudinell multicenterstudie av patienter med *IDH*-muterade gliom. Kognitiva nedsättningar var vanliga före behandling och individuella försämringar sågs framför allt avseende exekutiv funktion, minne och språk. Högre ålder och radiokemoterapi framkom som riskfaktorer.

Delarbete IV behandlar hur kognitiva funktioner relaterar till livskvalitet hos patienter vid olika tidpunkter i sjukdomsförloppet. Nedsatt global HRQoL var vanligt. Inlärning/minne var mest relevant vid diagnos, språk och exekutiva funktioner vid ett år, medan exekutiv funktion var viktigast i långtidsgruppen.

Behandling är förenat med funktionella konsekvenser och resultaten understryker behovet av systematisk uppföljning, tidig identifiering av riskgrupper och stödjande insatser för att minska negativa följdeffekter.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Rydén I**, Carstam L, Gulati S, Smits A, Sunnerhagen KS, Hellström P, Henriksson R, Bartek J Jr, Salvesen Ø, Jakola A S. *Return to work following diagnosis of low-grade glioma: A nationwide matched cohort study*. Neurology. 2020 Aug 18;95(7):e856-e866.

II. **Rydén I**, Thurin E, Carstam L, Smits A, Gulati S, Henriksson R, Salvesen Ø, Store Jakola A. *Psychotropic and anti-epileptic drug use, before and after surgery, among patients with low-grade glioma: a nationwide matched cohort study.* BMC Cancer. 2021 Mar 8;21(1):248. doi:10.1186/s12885-021-07939-w. Erratum in: BMC Cancer. 2022 Mar 31;22(1):350.

III. **Rydén I**, Latini F, Alberius Munkhammar Å, Hellström P, Neimantaite A, Harba D, Lycett A, Carstam L, Blomstrand M, Zetterling M, Smits A, Jakola A S. *Reliable cognitive changes the first year following guideline-based treatment of IDH-mutated gliomas: a longitudinal multicenter study* Neuro Oncol. 2025 Nov 9:noaf263.

IV. **Rydén I**, Buvarp D, Neimantaite A, Carstam L, Harba D, Weyhenmeyer L, Lycett A, Malmqvist S, Ozanne A, Elgeskog E, Corell A, Gómez Vecchio T, Smits A, Jakola A S. *Contribution of cognitive function and fatigue to health-related quality of life in patients with IDH-mutant gliomas – from diagnosis to long-term follow-up*. Manuscript

OTHER PUBLICATIONS

Other publications by the author, not included in the thesis.

- Dunås T, Leiss S, Corell A, Skoglund T, Dénes A, Carén H, Smits A, **Rydén I**, Jakola A. *Genetic Risk Factors for Poor Cognitive Outcome Following Brain Insult-A Systematic Review*. Brain Behav. 2026
- Jakola AS, **Rydén I**. *Targeting IDH mutation: another milestone, but not the finish line*. Lancet Oncol. 2025.
- Boele FW, Frances SM, Darlix A, Ducray F, Cartalat S, Guerdoux E, Tabouret E, Burger MC, **Rydén I**, Malmstrom A, Vauleon E, Kazda T, Renovanz M, Werner JM, Welsh L, Sanghera P, Dehais C, Desideri I, McBain C, Mehta S, Lord H, Jena R, Foweraker K, Ashkan K, Engelhardt J, Bourg V, Herrlinger U, McLean AL, Hertler C, Haldbo-Classen L, Dahlrot RH, Noel G, Durando X, Hrab I, Razis E, Weller M, Muhic A, Klein M. *Health-related quality of life and cognitive functioning in survivors of oligodendroglioma: an international cross-sectional investigation.* Neuro Oncol. 2025.
- Neimantaite A, Gómez Vecchio T, **Rydén I,** Harba D, Jakola AS, Smits A. *Mental fatigue and cognitive functioning in patients presenting with non-enhancing gliomas*. Acta Neurochir. 2025
- Boele F, Rosenlund L, Nordentoft S, Melhuish S, Nicklin E, **Rydén I**, Williamson A, Donders-Kamphuis M, Preusser M, Le Rhun E, Kiesel B, Minniti G, Furtner J, Dirven L, Taphoorn M, Galldiks N, Rudà R, Chalmers A, Short SC, Piil K. *Inequalities in access to neuro-oncology supportive care and rehabilitation: A survey of healthcare professionals' perspectives*. Neurooncol Pract. 2024
- Gómez Vecchio T, **Rydén, I**, Ozanne A, Blomstrand M, Carstam L, Smits A, Store Jakola A. *Global health status and fatigue score in IDH-mutant diffuse glioma grades 2 and 3 – A longitudinal population-based study from surgery to 12-month follow-up*. Neuro-Oncology Practice 2024.

- Heggebø LC, Borgen IMH, Rylander H, Kiserud C, Nordenmark TH, Hellebust TP, Evensen ME, Gustavsson M, Ramberg C, Sprauten M, Magelssen H, Blakstad H, Moorthy J, Andersson K, Raunert I, Henry T, Moe C, Granlund C, Goplen D, Brekke J, Johannessen TA, Solheim TS, Marienhagen K, Humberset Ø, Bergström P, Agrup M, Dahl L, Gubanski M, Gojon H, Brahme CJ, **Rydén I**, Jakola AS, Vik-Mo EO, Lie HC, Asphaug L, Hervani M, Kristensen I, Rueegg CS, Olsen IC, Ledal RJ, Degsell E, Werlenius K, Blomstrand M, Brandal P. *Investigating survival, quality of life and cognition in PROton versus photon therapy for IDH-mutated diffuse grade 2 and 3 GLIOmas (PRO-GLIO): a randomised controlled trial in Norway and Sweden.* BMJ Open. 2023
- Svenjeby C, Carstam L, Werlenius K, Bontell TO, **Rydén I**, Jacobsson J, Dénes A, Jakola AS, Corell A. *Changes in clinical management of diffuse IDH-mutated lower-grade gliomas: patterns of care in a 15-year period.* J Neurooncol. 2022
- **Rydén I,** Fernström E, Lannering B, Kalm M, Blomstrand M, Hellström P, Björk-Eriksson T, Jarfelt M. *Neuropsychological functioning in childhood cancer survivors following cranial radiotherapy - results from a long-term follow-up clinic.* Neurocase 2022
- Carstam L, **Rydén I**, S Jakola A J. *Seizures in patients with IDH-mutated lower grade gliomas.* J Neurooncol. 2022
- Gómez Vecchio T, Corell A, Buvarp D, **Rydén I**, Smits A, Jakola AS. *Classification of Adverse Events Following Surgery in Patients With Diffuse Lower-Grade Gliomas.* Front Oncol. 2021
- Thurin E, **Rydén I**, Skoglund T, Smits A, Gulati S, Hesselager G, Bartek Jr J., Henriksson R, Salvesen Ø, Store Jakola A. *Impact of meningioma surgery on use of antiepileptic, antidepressant and sedative drugs: A Swedish nationwide matched cohort study.* Cancer Med. 2021
- Buvarp D, **Rydén I**, S Sunnerhagen K, Olsson Bontell T, Gómez Vecchio T, Smits A, Store Jakola A. *Preoperative Patient-Reported Outcomes in Suspected Low-Grade Glioma: Markers of Disease Severity and*

Correlations with Molecular Subtypes. Journal of Clinical Medicine 2021

- Thurin E, Förander P, Bartek J Jr, Gulati S, **Rydén I**, Smits A, Hesselager G, Salvesen Ø, Jakola AS *Depression and ability to work after vestibular schwannoma surgery: a nationwide registry-based matched cohort study on antidepressants, sedatives, and sick leave*. Acta Neurochirurgica (Wien). 2021
- Carstam L, **Rydén I**, Gulati S, Rydenhag B, Henriksson R, Salvesen Ø, Smits A, S Jakola A. *Socioeconomic factors affect treatment delivery for patients with low grade glioma: a Swedish population-based study.* Journal of Neurooncology. 2020
- Stålhammar J, **Rydén I**, Nordlund A, Wallin A. *Boston Naming Test automatic credits inflate scores of nonaphasic mild dementia patients*. J Clin Exp Neuropsychol.

CONTENTS

Abstract v
Sammanfattning på svenska vii
List of papers viii
Other publications ix
Contents i
Abbreviations v
Definitions in short vii
1 Introduction 1
1.1 Case illustration 1
1.2 Epidemiology 2
1.3 Clinical presentation 3
1.3.1 Seizures 3
1.3.2 Tumor diagnostics 4
1.4 Glioma treatment 10
1.4.1 Surgery 10
1.4.2 Oncological treatment 11
1.5 Clinical outcome assessments 17
1.5.1 Patient-reported outcomes 17
1.5.2 Clinician-reported outcomes 18
1.5.3 Performance outcomes 18
1.6 Depression and anxiety 18
1.6.1 Prevalence 19
1.6.2 Fear of recurrance 20
1.6.3 Effects of medication 20
1.6.4 Related clinical factors 21
1.6.5 Quality of life 21
1.6.6 Risk of suicide 22
1.6.7 Treatment of depression and anxiety 22

1.7 Fatigue ... 23
1.7.1 Prevalence ... 24
1.7.1 Associated factors ... 24
1.7.2 Treating fatigue ... 25
1.8 Cognitive functions ... 29
1.8.1 Attention and processing speed ... 29
1.8.2 Working memory ... 29
1.8.3 Executive functions ... 31
1.8.4 Learning and memory ... 31
1.8.5 Language ... 32
1.8.6 Visuospatial functioning ... 33
1.8.1 Social cognition ... 34
1.9 Who, when, what? ... 35
1.10 Cognitive functioning across the disease trajectory ... 36
1.10.1 Cognition in the early phase ... 36
1.10.2 Cognition beyond the first year after treatment ... 37
1.10.3 Long-term cognitive outcome ... 38
1.11 Multifactorial influences on cognition ... 40
1.11.1 Tumor-related factors ... 40
1.11.2 Treatment-related factors ... 42
1.11.3 Seizures and medication ... 43
1.11.4 Fatigue, sleep and psychological factors ... 43
1.11.5 Demographic and genetic factors ... 43
1.11.6 Comorbidity and general health ... 44
1.12 Health-related quality of life ... 45
1.12.1 Cognition and HRQoL ... 45
1.12.2 Treatment, fatigue and HRQoL ... 46
1.12.3 Response shift ... 47
1.13 Returning to work ... 48
1.13.1 Factors related to RTW ... 49

2 Aim **50**
3 Patients and Methods **51**
3.1 Study design and participants 51
3.2 Data sources and registry linkage 52
3.2.1 The Swedish Brain Tumor Registry 52
3.2.2 Statistics Sweden 54
3.2.3 The National Board of Health and Welfare Registries 55
3.2.4 The Swedish Social Insurance Agency 56
3.3 Method for study I 58
3.3.1 Study population 58
3.3.2 Variables and outcomes 59
3.3.3 Statistical analyses 59
3.4 Method for study II 60
3.4.1 Study population 60
3.4.2 Variables and outcomes 60
3.4.3 Statistical analyses 61
3.5 Method for study III 62
3.5.1 Study population 62
3.5.2 Variables and outcomes 63
3.5.3 Reliable change index 69
3.5.4 Statistical analyses 69
3.5.5 Heatmap visualization of tumor location 70
3.6 Method for study IV 71
3.6.1 Study population 71
3.6.2 Variables and outcomes 73
3.6.3 Statistical analyses 74
4 Ethics **76**
5 Results **77**
5.1 Study I 77
5.1.1 Variables and outcomes 77

5.2 Study II 81
5.2.1 Variables and outcomes 81
5.3 Study III 85
5.3.1 Changes according to reliable change indices 85
5.3.2 Location heatmaps 87
5.4 Study IV 89
5.4.1 Cognition in relation to global HRQoL 89
5.4.2 Fatigue and symptoms of anxiety and depression 90
6 Discussion 92
6.1 Clinical context 92
6.2 Work participation (study I) 93
6.3 Medication use as a proxy for symptoms (study II) 94
6.4 Cognitive outcomes (Studies III–IV) 96
6.5 Onco-functional balance 97
7 Future perspectives 99
8 Acknowledgement 101
9 Use of generative AI 104
10 References 105

ABBREVIATIONS

AED	Anti-Epileptic Drug
BNT	Boston Naming Test
BVMT-R	Brief Visuospatial Memory Test revised
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/B
CNS	Central nervous system
CWIT	Color-Word Interference Test
D-KEFS	Delis-Kaplan Executive Function System
EORTC	European Organization of Research and Treatment of Cancer
HADS	Hospital anxiety and depression scale
HRQoL	Health Related Quality of Life
IDH	Isocitrate dehydrogenase
KPS	Karnofsky Performance Status
LGG	Low-grade glioma
LrGG	Lower-grade glioma
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
NBHW	National Board of Health and Welfare
OR	Odds ratio
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RCI	Reliable Change Index

RCT	Randomized Controlled Trial
RTW	Return to work
SBTR	Swedish Brain Tumor Registry
SCB	Statistics Sweden
SCR	Swedish Cancer Registry
SIA	Swedish Social Insurance Agency
TMT	Trail Making Test
TMZ	Temozolomide
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization

DEFINITIONS IN SHORT

1p/19q co-deletion	A combined loss of chromosomal arms 1p and 19q. A defining alteration of oligodendrogliomas in WHO 2021, always with concurrent *IDH* mutation
Fatigue	Fatigue is a sustained feeling of reduced energy and increased effort required for physical or mental activity, which is not sufficiently improved by rest.
IDH mutation	A genetic alteration in the isocitrate dehydrogenase genes (*IDH1* or *IDH2*), leading to abnormal production of the oncometabolite 2-hydroxyglutarate
Lower-grade gliomas	Diffuse gliomas classified as WHO grade 2–3 astrocytoma (*IDH*-mutant) or oligodendroglioma (*IDH*-mutant and 1p/19q-codeleted), characterized by slower growth and longer survival compared with high-grade gliomas.
Reliable Change Index	Statistical method for determining whether a change in a specific test score is considered a reliable change, meaning larger than expected compared to changes in a normative sample of healthy controls.
Return to work	Returning to work partially or full time (25-100%) after previous sick leave.

1 INTRODUCTION

1.1 CASE ILLUSTRATION

A married man in his late thirties, with two young children, worked full-time as an engineer at a mid-sized company. During a meeting, he began to feel strange and became unusually quiet. When it was his turn to speak, no words came out. Moments later, he lost consciousness as the episode progressed into a generalized epileptic seizure. The sudden event frightened his colleagues, who immediately called for an ambulance and notified his family. At the emergency department a computerized tomography (CT) scan revealed an abnormality in the brain and subsequent magnetic resonance imaging (MRI) indicated a slow-growing, malignant brain tumor. The man later underwent surgery and oncological treatment to delay disease progression.

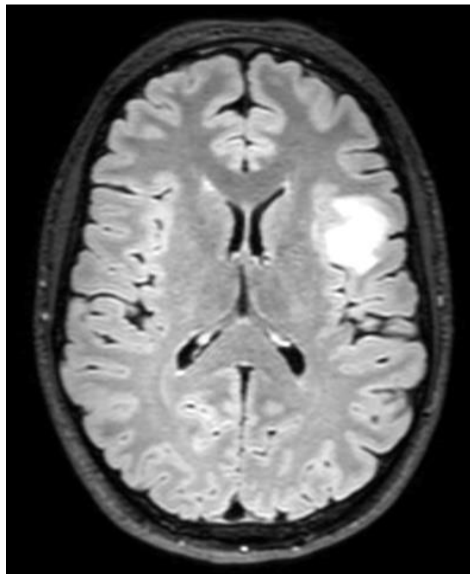

Figure 1. Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance image (MRI) demonstrating a hyperintense lesion in the left temporal lobe.

This previously healthy man was unexpectedly diagnosed with a lower-grade glioma (LrGG). What first appeared as an isolated event for him became the start of a major life transition for both him and his family.

This fictional case illustrates the typical presentation of a patient with a LrGG. The average age at diagnosis is approximately 35-40 years.(1) Survival ranges from approximately 5 to 20 years after diagnosis.(2) These patients often survive considerably longer after diagnosis than those with glioblastoma (GBM), yet they typically die at a younger age. The disease profoundly affects not only the patients, but also their children, partners, parents, friends, and colleagues. Preventing disease progression is a primary goal, but understanding and addressing patients' everyday functioning and psychological well-being are also of great importance.

By examining how the disease affects patients' lives and identifying factors associated with favorable or unfavorable outcomes, it is possible to intervene proactively with individualized treatment strategies. Identifying risk factors for not returning to work, severe depression or anxiety, cognitive decline, and poor quality of life (QoL) as well as factors that support recovery can help. Although studies on these aspects are increasing, few use a longitudinal design or include long-term survivors. Assessing both longitudinal change and long-term survival can deepen our understanding of individual trajectories and factors shaping them. Such knowledge is important for understanding how the disease influence patients' functioning and QoL over time.

1.2 EPIDEMIOLOGY

In Sweden, approximately 1300 adults are diagnosed each year with primary tumors affecting the central nervous system (CNS) of which 90% are located in the brain and 10% in the spinal cord.(1, 3-5) Tumor occurrence varies with age, with certain types appearing primarily in childhood and others more frequently in older adults.(6) There are more than one hundred recognized types of primary brain tumors, and gliomas

are the most common type accounting for roughly 40% of tumors in the CNS.(7)

IDH-wildtype GBM are most common in older adults and are also the most malignant and common type of glioma.(8, 9) The annual incidence is 3–4 per 100 000 inhabitants and GBM are approximately 60% more common in men than in women.(1, 10) Etiology remains largely unknown. Despite therapeutic advances, prognosis remains poor, particularly in elderly individuals with large tumor volumes and comorbidities, with median survival often less than one year.(11, 12) In contrast, *IDH*-mutant gliomas typically affect younger adults, most often in their 30s to 40s. *IDH*-mutant tumors account for around 12% of all gliomas.(13-15) The incidence is 0.5 - 0.8 per 100 000 per year.(1, 14-16). Median survival is approximately 5 - 10 years for *IDH*-mutant astrocytomas and over 15 years for grade 2 oligodendrogliomas, with some patients surviving considerably longer.

1.3 CLINICAL PRESENTATION

Symptoms in *IDH*-mutant gliomas are often subtle and may progress over several years. Owing to the slow tumor growth, neuroplasticity allows functional reorganization, which may preserve cognitive functions despite tumor progression.(17)

1.3.1 SEIZURES

Epileptic seizures are the most common initial symptom of *IDH*-mutant gliomas. Approximately 70–80% of patients present with a first-time seizure.(18, 19) These seizures are by definition focal, but the focal phase may be very short and therefore not always recognized by patients as epileptic activity. They may be recognized first when seizures spread to the contralateral hemisphere and progress to bilateral tonic–clonic seizures.(18)

1.3.2 TUMOR DIAGNOSTICS

1.3.2.1 DIAGNOSTIC PROCEDURES

Current brain tumor diagnostics combine clinical, radiological, and molecular approaches. Patients typically undergo neurological evaluation followed by radiological imaging. After surgery, definitive diagnosis is based on integrated histopathological and molecular assessment, combining morphology and molecular markers, reflecting the growing emphasis on molecular diagnostics in tumor classification in recent years.(20, 21)

A multidisciplinary team conference is standard practice in the management of suspected brain tumors. Specialists in neurology, neurosurgery, oncology, radiology, and pathology jointly review clinical findings, imaging, and molecular data to establish diagnosis and recommend optimal treatment strategies.(9)

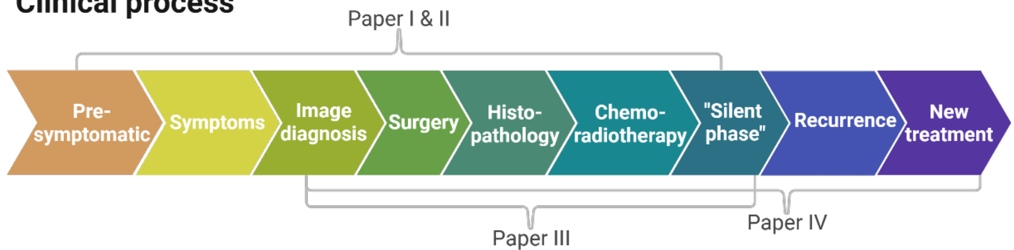

Figure 2. Typical clinical care process for patients with LrGG. Created in BioRender. Denes, A. (2026) https://BioRender.com/opv7lf2

1.3.2.2 ORIGIN AND CLASSIFICATION

Gliomas are tumors of neuroepithelial origin and are believed to arise from glial precursor cells or neural stem cells. The main subtypes include astrocytomas and oligodendrogliomas.(20, 22) Tumor malignancy is graded from 1 to 4 according to the World Health Organization (WHO) classification, where grade 1 represents a benign tumor and higher grades indicate greater malignancy.(20) Prognosis between tumor types varies widely and depends on multiple factors, including tumor biology.(1, 20)

1.3.2.3 THE NEW CLASSIFICATION

While gliomas were historically classified and graded based solely on histopathological features, recent advances have changed this framework. Building upon the WHO grading scale, the current WHO classification (2021) integrates histopathological and molecular features.(20) This change is driven by evidence that molecular markers critically influence tumor biology and outcome. Higher grades reflect greater biological aggressiveness and are characterized by elevated cellularity, nuclear atypia, mitotic activity, microvascular proliferation, and necrosis.

In *IDH*-mutant astrocytomas, grade 2 shows low nuclear atypia with low mitotic activity, while grade 3 is defined by increased atypia and mitotic activity. However, the distinction lacks strict numerical thresholds, allowing for some degree of subjectivity. Grade 4 is assigned in the presence of microvascular proliferation and/or necrosis. Oligodendrogliomas may demonstrate increased mitotic activity in grade 3 tumors, and the presence of microvascular proliferation and/or necrosis constitutes a criterion for CNS WHO grade 3 in this entity.

Figure 3 below presents a histopathological comparison of low-grade (LGG) and high-grade glioma (HGG) using representative hematoxylin and eosin stained sections. The LGG (left) is characterized by lower cellular density and mild nuclear atypia. In contrast, the HGG (right) demonstrates hypercellularity, pronounced nuclear pleomorphism and densely packed atypical cells reflecting greater biological aggressiveness.

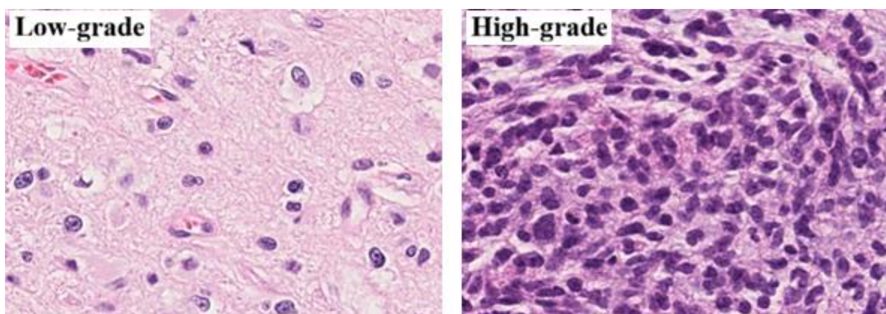

Figure 3.Histopathological comparison of a low-grade and high grade glioma.

According to the new classification, diffuse gliomas are still categorized into grades 2–4, but this grading has become somewhat less relevant.(23) Previously, WHO grade 2 (and sometimes also benign, grade 1) tumors were categorized as low-grade.(24) However, a key change in the adult-type diffuse gliomas has been the identification of mutations in the *isocitrate dehydrogenase* (*IDH*) gene, which defines a biological distinction between tumor types.(25) *IDH*-mutant gliomas are associated with a markedly better prognosis, whereas those lacking this mutation (*IDH*-wildtype) have a poor outcome and are now classified as GBM (WHO grade 4) if they harbor molecular features such as TERT promoter mutation, EGFR amplification, or combined chromosome 7 gain and chromosome 10 loss, even in the absence of histological grade 4 features.(20, 25)

An additional molecular marker that further refines classification and prognosis is the deletion of both chromosomal arms *1p* and *19q*. This co-deletion is associated with a favorable prognosis and, when occurring together with an *IDH* mutation, now defines oligodendrogliomas which are limited to CNS WHO grade 2 or 3. *IDH*-mutant tumors lacking this co-deletion are classified as *IDH*-mutant astrocytomas which may be graded as WHO grade 2-4. Another important marker in the classification is the homozygous deletion of the *cyclin-dependent kinase inhibitor* genes (*CDKN2A/B*), which is related to worse prognosis. When CDKN2A/B is homozygous deleted, the tumors are also classified as grade 4 astrocytoma regardless of histopathological features of relevance for grading.

In fact, on a group level, a patient with a grade 3 oligodendroglioma has a better prognosis than a morphological grade 2 tumor lacking *IDH* mutation, but with GBM molecular features. Thus, tumors classified as “high grade” may, in biological and prognostic terms, represent a lower-grade disease. A substantial proportion, approximately 30–50%, of tumors that radiologically or histologically appear low-grade are in fact *IDH*-wildtype.(26)

In addition to *IDH* and *1p/19q* status, *alpha-thalassemia/mental retardation syndrome X-linked (ATRX)* is routinely assessed as a molecular marker in diffuse gliomas. In *IDH*-mutant tumors, *ATRX* mutation and *1p/19q* co-deletion are mutually exclusive, as *ATRX*-

mutant tumors lack the co-deletion.(27, 28) In contrast, *telomerase reverse transcriptase (TERT)* gene promoter mutations are strongly associated with *1p/19q* co-deletion in *IDH*-mutant tumors and therefore support a diagnosis of oligodendroglioma.(28, 29)

Apart from giving insight into the oncogenesis of diffuse gliomas, the molecular markers have led to an integrated classification system in which histopathology and molecular genetics are jointly required for accurate diagnosis and clinical management, replacing the earlier morphology-based grading approach.(20, 21) An overview of the molecular classification of adult-type diffuse gliomas according to the WHO 2021 classification is presented in Figure 4 below.

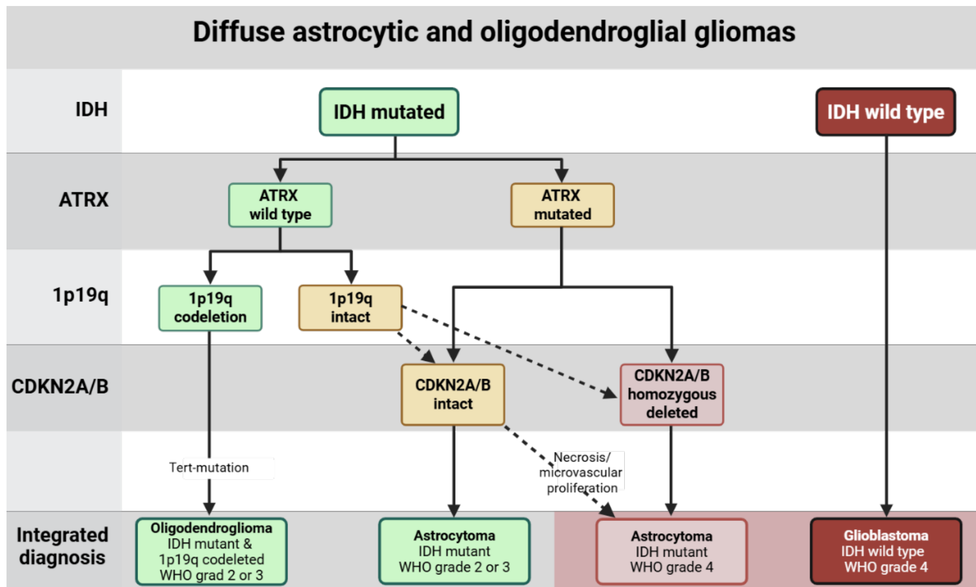

Figure 4. Overview of molecular classification of adult-type diffuse gliomas according to the WHO 2021 classification. Created in BioRender. Denes, A. (2026) https://BioRender.com/h95cgv5. Adapted from Carstam L., doctoral thesis, University of Gothenburg, 2023.(30)

1.3.2.4 RADIOLOGICAL METHODS AND DIAGNOSTIC FEATURES

When a patient seeks the emergency department, which is often the case after a first-time epileptic seizure, a computed tomography (CT) of the brain is frequently performed as a first step due to its widespread availability. If a tumor is suspected, a magnetic resonance imaging (MRI) should be performed for further evaluation, allowing for more precise characterization and surgical planning. MRI is the standard imaging modality for both the diagnostic evaluation and follow-up of gliomas.(9)

MAGNETIC RESONANCE IMAGING (MRI)

MRI is central to brain tumor diagnostics, measuring tissue-specific magnetic properties and enabling contrast to be tailored through different pulse sequences.(31) Standard imaging protocols for brain tumors typically include a combination of MRI sequences, such as T1-weighted images acquired before and after administration of gadolinium-based contrast, T2-weighted images, and fluid-attenuated inversion recovery (FLAIR) sequences, among others.

GBMs typically show contrast enhancement on T1-weighted images reflecting disruption of the blood–brain barrier, whereas LrGG often lack enhancement, although overlap exists.(32, 33) The T2-FLAIR mismatch sign is associated with *IDH*-mutant astrocytoma, particularly WHO grade 2–3, and it is defined by a homogeneously hyperintense T2 signal with a hypointense core on FLAIR sequences.(32, 34, 35)

Certain imaging features may suggest specific molecular or histopathological subtypes. Calcifications, typically seen as high-attenuation foci on CT or as distinct hypointense areas on MRI, especially on T2-weighted and susceptibility sequences, strongly suggest an oligodendroglioma.(36) Additional sequences such as diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), perfusion MRI, MR spectroscopy (MRS) and functional MRI (fMRI) may be used as complementary techniques when clinically indicated, available, and relevant to the diagnostic or therapeutic question.(36)

FLUOROETHYL-TYROSINE POSITRON EMISSION TOMOGRAPHY (FET-PET)

FET-PET is a nuclear medicine technique that uses a radioactive amino acid tracer to visualize tumor metabolism. Clinically, it has the potential to add information on tumor activity, particularly in difficult diagnostic situations such as differentiating progression from pseudoprogression and evaluating tumor malignancy.(37) It can also be used for biopsy targeting.(37) Findings should be interpreted cautiously, as uptake patterns are not fully specific and can be affected by treatment-related or biological factors, and considerable overlap in uptake values between tumor grades and even non-neoplastic lesions has been reported.(38) However, FET-PET for glioma recurrence have reported high pooled sensitivity of 0.86–0.92 and specificity of 0.83–0.85.(37)

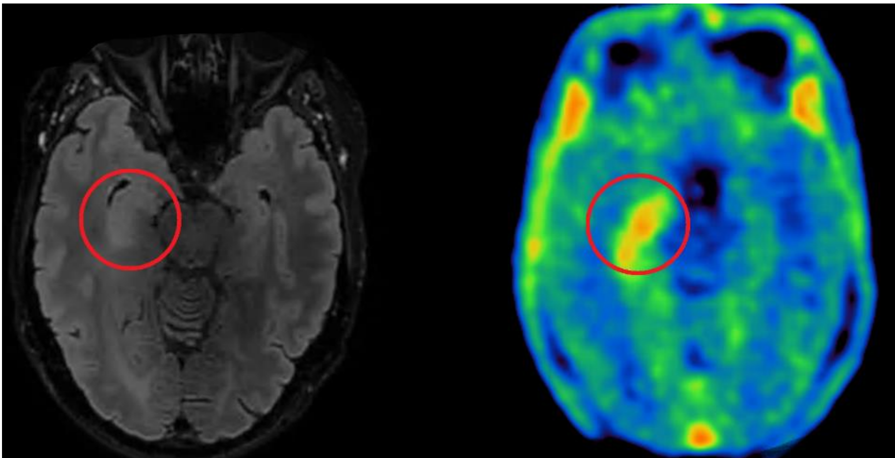

Figure 5. Illustration of MRI FLAIR (left) and FET PET (right) demonstrating a lesion in the right hippocampal region.

Figure 5 illustrates a lesion in the right hippocampal region. On MRI (left), the lesion appears as a FLAIR hyperintensity without contrast enhancement on T1-weighted imaging. On FET-PET (right), the same region demonstrates clearly increased tracer uptake (SUVmax 1.93; tumor-to-background ratio 2.1). This marked metabolic uptake raises a strong suspicion of malignancy beyond MRI findings. Histopathology later confirmed an *IDH*-wildtype astrocytoma, WHO grade 3, which corresponds biologically to GBM in current classification.

1.4 GLIOMA TREATMENT

1.4.1 SURGERY

According to both national and international guidelines, surgery is the first treatment option for malignant gliomas.(39, 40) Surgery is not curative, but larger extent of resection (EoR) is associated with better overall survival.(41, 42)

When a tumor causes increased intracranial pressure or obstructs cerebrospinal fluid flow, urgent surgical intervention may be required and can relieve the associated symptoms.(24) This is less common in slow growing tumors, such as *IDH*-mutant gliomas. When a tumor is detected and suspected to be slow growing, there is usually time to plan the surgical procedure. Radiological imaging provides information about the extent of the tumor and its proximity to structures important for specific functions. The goal of surgery is to achieve maximal safe resection, meaning to remove as much tumor tissue as possible while preserving neurological function.(42-45)

Diffuse LrGG are difficult to treat surgically because of their infiltrative growth pattern, and the difficulty in distinguishing tumor-infiltrated tissue from normal or edematous brain tissue.(17) In addition, these tumors are often situated within or near eloquent brain regions, meaning areas in which injury would result in significant functional impairment.(46) Intraoperative neurophysiological monitoring is frequently used to reduce the risk of permanent functional deficits.(47-50) When tumors are situated near eloquent areas that cannot be monitored while the patient is asleep, especially areas related to language functioning, awake surgery with functional mapping can be performed.(51-53) This may help the surgeon determine whether the resection risks damaging a specific function. During these procedures, the patient is awake for part of the surgery, and systematic electrical stimulation and functional testing are performed.(53)

When the risk of neurological impairment is considered too high, when the patient is unfit for surgery, or the tumor is too large or multifocal, a biopsy can be carried out instead.(39, 40) Biopsy provides tissue for

histopathological and molecular analysis and thereby guides subsequent oncological treatment.(39) Treatment and follow-up are based on the tumor's molecular profile and the histopathological appearance (the WHO classification), as well as the patient's condition and the tumor's anatomical location.(40)

1.4.2 ONCOLOGICAL TREATMENT

After surgery, further oncological treatment is determined based on the assessed risk of early tumor progression.(40) Current standard treatment for LrGG consists of external radiotherapy, and chemotherapy. Most patients receive some oncological treatment during their disease trajectory.

The timing and order of oncological treatments depend on several factors including: tumor grade, size, EoR, residual tumor, tumor crossing the midline, histological and molecular characteristics as well as the patient's functional status, neurological deficits, and presumed tolerance to therapy.(40, 54-57) Age above 40 years, has also been identified as a risk factor, although the relevance of the age cut-off has been debated.(24, 58, 59) Despite evidence from randomized trials that have significantly shaped the current practice, the optimal indications, timing, and choice of radiotherapy and chemotherapy regimens for different tumor subtypes remain to be clearly defined.(57, 58, 60-64) Current risk classification systems are largely based on data from non-molecular patient cohorts, that may not be directly applicable to patients with *IDH*-mutant gliomas.

The guidelines by the European Association of Neuro-Oncology (EANO) include recommendations for oncological treatment in patients with glioma. Patients considered to have a high risk of early tumor progression, such as those with subtotal resection, higher-grade tumors, or unfavorable molecular profiles, are generally offered chemoradiotherapy shortly after surgery. For patients with low-risk profiles an initial wait-and-scan strategy may be adopted to postpone potential long-term side effects associated with oncological treatment.(24, 55, 57)

1.4.2.1 RADIOTHERAPY

External radiotherapy is one of the central components of glioma treatment and is used either postoperatively or as a primary therapy in cases where surgery has not been feasible. At the cellular level, radiotherapy causes DNA damage, resulting in tumor cell death or reduced proliferation.(65) To minimize radiation-induced toxicity, focal radiotherapy is given in fractions for several weeks, and the total dose is kept as low as possible. For WHO grade 2 gliomas, standard doses typically range between 50.4 to 54 Gy, while doses around 60 Gy are used for higher-grade tumors.(57, 62, 66)

Guidelines for oncological treatment (EANO 2021)

- **Low-risk patients** include patients < 40 years of age, with complete resection and no neurological deficits. Active surveillance without immediate oncological treatment is recommended.
- **High-risk patients** include patients > 40 years of age, with incomplete resection, symptomatic disease, or evidence of progression. Recommended postoperative radiotherapy followed by chemotherapy.

(Weller et al., *Nat Rev Clin Oncol*, 2021)

PROTONS AND PHOTONS

Radiotherapy can be delivered using either photon or proton beams. Proton therapy represents a newer alternative to conventional photon irradiation and is theoretically associated with a more confined dose distribution, reducing the radiation exposure to surrounding normal brain tissue, as can be seen in figure 6.(67) However, current evidence does not clearly demonstrate the superiority of proton therapy over photon-based techniques.(67) Some studies suggest modality-specific toxicity patterns, with differing profiles, including a potential increase in focal radiation-induced injury with proton therapy.(68) Ongoing studies aim to clarify potential differences.(69)

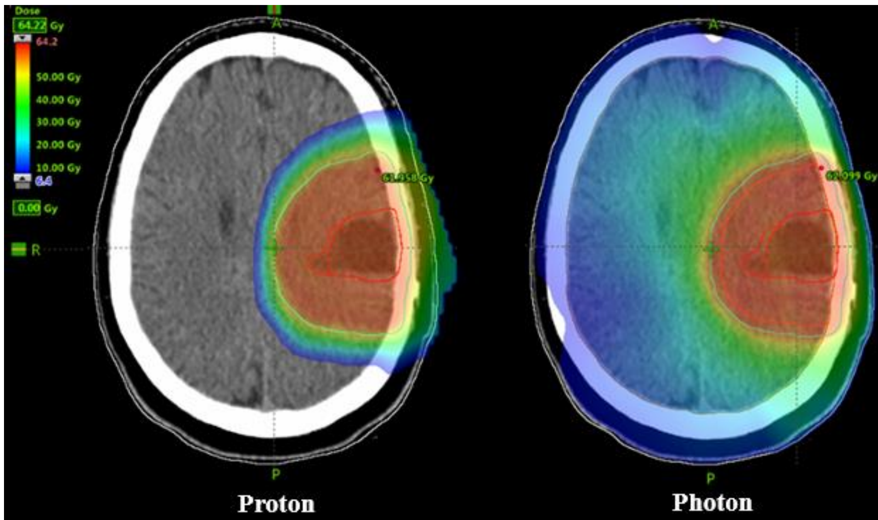

Figure 6. Comparison of dose distributions for proton (left) and photon (right) radiotherapy in a brain tumor case.

THE EVIDENCE OF RADIOTHERAPY

Clinical trials have been designed to assess the independent effect of radiotherapy in patients with glioma. The IWOT trial that was designed to compare early adjuvant radiotherapy and temozolomide to watchful waiting in patients with *IDH*-mutant astrocytoma was unfortunately terminated early.(70) Evidence from RCTs has nevertheless provided some important insights. A study comparing early (after first surgery) to delayed (after progression) radiotherapy in adults with non-molecularly classified WHO grade 2 gliomas showed that early treatment significantly prolonged progression-free survival (PFS) but not overall survival (OS), indicating that early radiotherapy delays tumor progression without extending survival, supporting a watchful waiting approach for selected patients to avoid potential long-term radiation effects.(63)

Another randomized trial compared radiotherapy with temozolomide monotherapy in high-risk grade 2 glioma. Results showed no difference in OS, although the number of events was still limited, and there was a trend favoring radiotherapy in *IDH*-mutant non-codeleted tumors

(corresponding to astrocytomas). In oligodendrogliomas, both treatments were considered effective with no one being superior. Since the study compared each treatment alone the effects on combined chemoradiotherapy were not assessed.(71)

While radiotherapy improves local tumor control, it can cause both acute and delayed side effects.(24, 72) Acute reactions such as fatigue, headache, and a feeling of cognitive slowing can be reversible, whereas delayed toxicities may develop months or years later and may be permanent. Such effects can include cognitive impairment, vascular damage, hormonal dysregulation, and in some cases radiation necrosis.(73-75) Late toxicity is related to radiation exposure of healthy brain tissue. The risk of late side effects is influenced by total radiation dose, fraction size, and the volume of brain tissue irradiated.(75, 76) Studies on long-term survivors indicate that radiotherapy may lead to measurable cognitive decline in some individuals, although findings are inconsistent across studies.(75, 76) Higher radiation doses have not shown survival benefit, supporting the current practice of moderate-dose regimens.(24)

1.4.2.2 CHEMOTHERAPY

Chemotherapy is a key component in the treatment of diffuse gliomas. It is often given together with radiotherapy, either concurrent (at the same time) or adjuvant (after radiotherapy).(60) In cases of tumor recurrence, chemotherapy can also be used as a separate treatment.(39, 40) The choice of regimen depends largely on the tumor's molecular profile, WHO grade, and prior treatments.

PCV

The PCV regimen includes the alkylating agents procarbazine and lomustine (CCNU) together with vincristine, which interferes with cell division.(77) The regimen combines both oral and intravenous agents given at fixed intervals within each cycle, followed by rest periods to allow bone marrow recovery. PCV is typically administered as six treatment cycles, each lasting approximately six weeks.

PCV has the strongest evidence supporting its efficacy in diffuse gliomas.(72, 78). In a randomized controlled trial (RCT) of patients with high-risk WHO grade 2 diffuse gliomas, radiotherapy alone was compared with radiotherapy plus adjuvant PCV chemotherapy, with long-term follow-up reported.(58) Radiotherapy plus PCV significantly improved both OS and PFS in these patients, compared to radiotherapy alone. The survival advantage was most pronounced in 1p/19q co-deleted oligodendrogliomas, but patients with *IDH*-mutant astrocytoma, also demonstrated improved outcomes. Patients with *IDH*-wildtype tumors did not show similar benefit.

Despite its proven survival benefit, PCV is associated with a relatively high incidence of adverse effects and requires close clinical monitoring.(24, 40) The most common adverse treatment effects are fatigue, nausea, and bone marrow suppression, which can lead to anemia or neutropenia and occasionally necessitate treatment interruptions.(40) Peripheral neuropathy related to vincristine and gastrointestinal intolerance caused by procarbazine are also frequent.(79) Dose reductions and premature discontinuation of therapy are not uncommon due to negative side-effects.(58, 80)

TEMOZOLOMIDE

Temozolomide (TMZ) is an established alkylating chemotherapeutic agent with oral administration and a generally more favorable tolerability profile than PCV.(71) TMZ is associated with fewer gastrointestinal and neurological side effects. It is often used in combination with radiotherapy or as monotherapy in selected cases.(39) It induces DNA damage through methylation, leading to tumor cell death.(77) Bone marrow suppression is a dose-limiting factor also for TMZ, but discontinuation due to such side-effects is less common.(24, 71, 81)

Clinical studies evaluating its efficacy om TMZ include a phase II single-arm trial comparing radiotherapy with concurrent and adjuvant temozolomide in patients with high-risk WHO grade 2 diffuse LGG, to historical controls.(82) They showed improved OS in patients treated with combined radiotherapy and TMZ. However, as all patients received both concurrent and adjuvant temozolomide, the individual contribution

of each component could not be determined, and molecular data was not available.(82) In addition, the recent randomized CATNON trial on grade 3 astrocytomas showed that radiotherapy with adjuvant TMZ significantly improved both OS and PFS in patients with *IDH*-mutant tumors, with a median OS of 12.5 years compared with 6 years without adjuvant temozolomide.(60) Concurrent TMZ treatment showed no additional benefit. (60)

To compare PCV and TMZ, the ongoing CODEL trial evaluates radiotherapy plus adjuvant PCV or TMZ, but only in patients with oligodendrogliomas.(83)

1.4.2.3 TARGETED THERAPIES

IDH INHIBITORS

IDH inhibitors have recently shown promising clinical results for patients with *IDH*-mutant gliomas. These agents represent a novel targeted therapeutic approach, but their availability remains limited and they are not yet accessible in Sweden.

The INDIGO trial has evaluated the *IDH* inhibitor vorasidenib in patients with WHO grade 2 *IDH*-mutant glioma following surgery but prior to oncological treatment.(84) The drug prolonged PFS, delayed the need for next intervention and reduced tumor growth rate. It was also well tolerated and showed a reduction of seizures in patients taking the drug.(84) Lately, neurocognitive functioning and QoL also showed to remain stable throughout the treatment.(85) The effects on OS is however still unknown, and since patients who received placebo where switched to receive the active drug, we will not be able to tell. It is also unknown how this treatment works in the longer run when patients receive other oncological treatments. Still, *IDH* inhibitors provide new hope for patients.

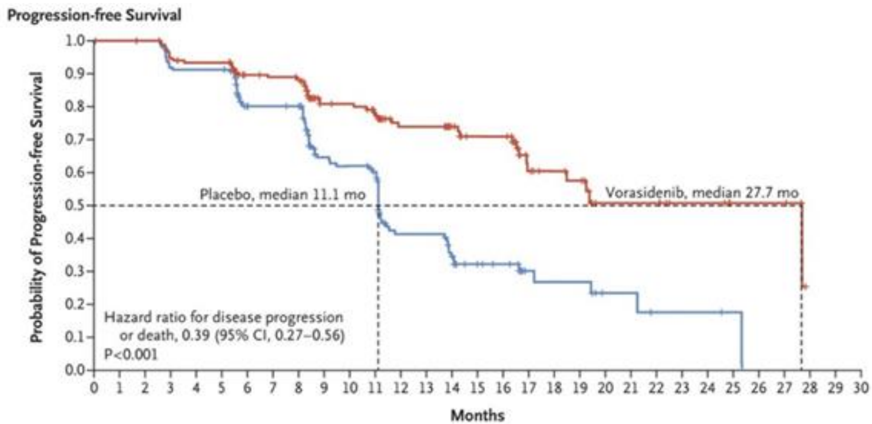

Figure 7. Kaplan–Meier plot of PFS in patients treated with vorasidenib versus placebo. The median time to progression or death is presented. Reproduced with permission from Mellinghoff IK et al., N Engl J Med 2023;389:589–601. Copyright Massachusetts Medical Society.

1.5 CLINICAL OUTCOME ASSESSMENTS

Clinical Outcome Assessments (COAs) are structured tools used in clinical research to measure patient outcomes. They may rely on patient reports, reports from clinicians, from observers, or can be performance-based tasks. They are used as study endpoints to demonstrate treatment benefit.(86) COAs capture how a patient feels or functions and should be viewed complementary rather than interchangeable measures.

1.5.1 PATIENT-REPORTED OUTCOMES

Patient-reported outcomes measures (PROMs) are self-administered assessments that capture the patient's perception and lived experience of functioning and symptoms, without interpretation by another person.(86) PROMs are subjective and may not always correlate closely with objective clinical or performance-based measures.(87) In this thesis, PROMs were used to evaluate depression, anxiety, mental fatigue, and overall QoL.

1.5.2 CLINICIAN-REPORTED OUTCOMES

Clinician-reported outcomes (ClinROs) are assessments based on observations and clinical judgments made by health-care professionals.(86) Similar to PROMS, they include evaluations of symptoms and functional abilities. In this thesis ClinROs included for example the assessment of Karnofsky Performance Status (KPS) as well as clinician-based grading of postoperative neurological deficits.

1.5.3 PERFORMANCE OUTCOMES

Performance outcomes (PerfOs) do not rely on subjective judgments. They are based on the patient's performance in structured tasks, where the result is quantified using standardized scoring methods.(86) These measures are commonly used in cognitive research and may vary substantially, from brief screening tools to comprehensive test batteries. In this thesis, performance outcomes were assessed using standardized neuropsychological testing to evaluate cognitive functioning.

1.6 DEPRESSION AND ANXIETY

A diagnosis of an incurable brain tumor confronts patients with fundamental concerns about life and death and commonly triggers a psychological crisis reaction. Although such reactions may diminish over time, monitoring of depressive symptoms and anxiety is important, as these symptoms may substantially reduce QoL and may worsen or develop into clinically significant psychiatric disorders.(88-90) Population-based studies have shown an elevated risk of depression following a cancer diagnosis, and anxiety is also more frequent among patients with cancer when compared with the general population.(91, 92)

1.6.1 PREVALENCE

Depression and anxiety are relatively common in patients with gliomas, but prevalence estimates are difficult to interpret due to substantial methodological heterogeneity across studies.(93, 94) Studies have employed different COAs, instruments, and cut-off values, which yield markedly different rates.(95-97) Study populations largely varies, ranging from mixed brain tumor cohorts to more specific subgroups such as LrGG or HGG, sometimes stratified by molecular status and sometimes not. Also, assessments have been conducted at different time points across the disease trajectory.

In the general population, the 12-month prevalence of major depressive disorder (MDD) is estimated to be around 10%.(98) A systematic review including 4089 patients with gliomas showed varying results depending on assessment method. The median prevalence of clinically diagnosed depression was approximately 15%. The use of self-report instruments, such as the Beck Depression Inventory (BDI), resulted in substantially higher estimates, around 39%.(90) One explanation to this discrepancy is that interviews allow contextual evaluation of symptoms and reduce misclassification of overlapping symptoms, such as fatigue.

In a narrative review focusing on adult patients with both HGG and LGG, van der Meer et al. found that prevalence of depressive symptoms varied substantially. Rates were approximately 41% with the Patient Health Questionnaire -9 (PHQ-9), compared with 16% when measured using the Hospital Anxiety and Depression Scale (HADS) depression subscale. When diagnosed by structured clinical interview, MDD was identified in approximately 14% of newly diagnosed patients with glioma.(99) Regarding anxiety, the same review reported that structured clinical interviews identified generalized anxiety disorder in approximately 6% of patients, whereas substantially higher prevalence rates were observed when using patient-reported outcome measures (PROMs).(95) Studies using the HADS anxiety subscale reported prevalence estimates ranging from 24% to 35%, and even higher rates were reported when other PROMs were used.(95, 96). It should be emphasized that structured diagnostic interviews based on DSM criteria are not equivalent to symptom screening with rating scales; PROMs identify elevated symptom levels rather than clinically confirmed

depressive or anxiety disorders.

Focusing specifically on LGG in an early phase of the disease, a prospective study included 149 adult patients with WHO grade 2 glioma, both patients with and without histologically verified diagnoses. Depressive and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Applying a relatively high cut-off of ≥11, 16% scored above the threshold for depression, and a similarly 16% for anxiety, while 21% scored above cut-off on at least one of the two subscales.(94) Symptoms are not limited to the early disease phase. In long-term follow-up of patients with LGG, 23% reported depressive symptoms more than two decades after diagnosis.(100)

1.6.2 FEAR OF RECURRANCE

Patients are monitored with MRI at regular intervals throughout their whole lives, and it is common for this follow-up to be accompanied by concern about tumor recurrence. This fear can be distressing and burdensome for the patient. Fear of cancer recurrence is described as worries and fear that the tumor may return or progress.(101-103) Mild reactions are generally regarded as a normal and understandable psychological response to a cancer diagnosis. However, if they become more severe, they may lead to clinically significant impairment, including avoidance behaviors and heightened sensitivity to bodily changes that are perceived as related to cancer.(102)

1.6.3 EFFECTS OF MEDICATION

As epileptic seizures are common in patients with glioma, many receive antiepileptic medication. Levetiracetam, lamotrigine and lacosamide are recommended options during oncological treatment due to low interaction potential.(39) Lamotrigine is not only used to treat epilepsy, but also as a mood stabilizer. Other antiepileptic drugs are known to have negative effects on mood. Perampanel is described to be related to aggressive behavior. Also, Levetiracetam that is frequently prescribed due to its generally favorable tolerability profile is associated with psychiatric adverse effects, most notably irritability, and less commonly depressive and anxiety symptoms.(95)

It is common for patients with LrGG to be treated with corticosteroids (e.g., betamethasone) in the initial phase. According to clinical routines, the treatment is typically initiated with a relatively high dose followed by a gradual postoperative tapering to discontinuation or to the lowest effective maintenance dose.(39) Corticosteroids may also be reintroduced later in the disease course if clinically indicated. Systemic corticosteroid therapy is associated with a range of adverse effects, including psychiatric manifestations such as mood changes. Clinically, some patients report increased energy or transient improvement in mood during high-dose treatment, whereas others may develop irritability or psychotic symptoms. Psychological distress may also emerge or intensify during dose tapering. In cases of significant psychiatric side effects, dose reduction or discontinuation is recommended. Sleep disturbances related to corticosteroid use are also well documented.(39)

1.6.4 RELATED CLINICAL FACTORS

Psychological health is influenced by multiple factors. In patients with glioma, affective symptoms may arise in the context of neurological deficits, oncological treatment, functional impairment, and psychosocial stressors. Among the most consistently identified factors associated with depression, in both brain tumor populations and in the general population, are prior depressive episodes or previous psychiatric treatment and female sex.(94, 95, 104-107) Reduced functional status has also been linked to depressive symptoms in several studies, although findings have not been entirely consistent.(90, 105) No consistent associations have been demonstrated between depression and age, marital status, tumor grade, EoR, tumor location or oncological treatment.(90, 97)

1.6.5 QUALITY OF LIFE

Several studies have related symptoms of depression to reduced health-related quality of life (HRQoL).(88, 89, 94) A prospective cohort study in patients with WHO grade 1-2 gliomas reported that depressive symptoms and reduced QoL were both common already at diagnosis.(108) Another study showed that depressive symptom severity was the strongest independent predictor of overall QoL.(88) In a study on patients with gliomas in the temporal lobe, symptoms of

depression were found to be strongly related to most aspects of HRQoL, explaining a substantial proportion of variance across domains.(89)

1.6.6 RISK OF SUICIDE

Persistent depressive and anxiety disorders represent clinically significant conditions that require recognition and appropriate management. If left untreated, symptoms may worsen over time.(109) In severe cases, depression may contribute to suicidal behavior. Suicide risk has been shown to be increased in patients with primary brain tumors, particularly during the first year after diagnosis.(110)

Patients with GBM had an approximately fourfold increased risk of suicide during the first year after diagnosis compared with the expected rate in the general population, whereas patients with non-GBM brain tumors had an approximately twofold increased risk during the same period.(110)

1.6.7 TREATMENT OF DEPRESSION AND ANXIETY

In Sweden, depression and anxiety in patients with glioma are generally managed according to standard psychiatric national treatment guidelines. For mild to moderate depression, psychological interventions such as cognitive behavioral therapy (CBT) are recommended, while antidepressant medication is indicated for moderate to severe cases.(111)

The evidence base for psychotherapy specifically in glioma patients remains limited, with few trials and studies including participants with formally diagnosed disorders of depression or anxiety. There are however interventions (randomized trials) in patients with brain tumors that have demonstrated reductions in psychiatric symptoms.(112, 113)

It is also common for patients to receive short-term anxiolytic or sleep-promoting medication, as well as antidepressant therapy.(114) The most commonly used pharmacological treatment consists of selective serotonin reuptake inhibitors (SSRIs), and in cases of insufficient response, serotonin–norepinephrine reuptake inhibitors (SNRIs) may be considered.(95) When prescribing such medication in this population,

careful consideration of potential interactions with ongoing oncological treatments and to monitor adverse effects. It is known that antidepressants, including SSRIs and SNRIs, may lower the seizure threshold and thereby increase seizure risk. This has also recently been demonstrated in a meta-analysis.(115) Although the absolute risk appears to be low, this is particularly relevant in patients with tumor-related epilepsy.

Data from the Glioma Outcomes Project demonstrated a marked discrepancy between patient-reported depressive symptoms (PROMs) and physician-recognized depression (ClinROs), with substantially higher rates reported by patients. This discordance was most pronounced in the early postoperative period but remained significant at six months after surgery, suggesting possible under-recognition and under-treatment of depressive symptoms in this population.(116)

1.7 FATIGUE

Fatigue is a common and disabling symptom both in patients with neurological disorders and in patients with cancer.(117, 118) Fatigue, together with cognitive deficits, and emotional distress have been identified as some of the most burdensome and functionally limiting symptoms in glioma.(119) Cancer-related fatigue is particularly frequent close to treatment, but can occur at any stage of the disease and may persist long after completion of treatment.(118)

Fatigue is a multidimensional construct encompassing physical, cognitive, and activity-related components.(117, 120) Regardless of subtype, fatigue is characterized by tiredness, weakness, and lack of energy. Unlike normal tiredness, it is typically disproportionate to activity level and not fully relieved by rest. (118) Fatigue may involve both physical exhaustion and mental fatigue, such as reduced concentration, slowed thinking, and increased effort during cognitive tasks. It can manifest as difficulties in initiating or sustaining physical or mental activities, reflecting reduced endurance rather than simple sleepiness.

1.7.1 PREVALENCE

In a systematic review of fatigue in adults with WHO grade 1 and 2 gliomas, fatigue was common in all phases of the disease.(120) Prevalence ranged from 39–77%, depending on assessment method and timing of evaluation. Fatigue was assessed using a variety of PROMs, and studies did not consistently distinguish between different aspects of fatigue, such as physical and mental fatigue in the reporting. Most results reflected overall fatigue rather than clearly separated subtypes.

A recent study highlighted the importance of distinguishing between mental and physical fatigue by examining these in 148 patients with diffuse grade 2–3 gliomas who were in a stable disease phase.(121) Severe mental fatigue was reported by 38% of patients, and 22% reported physical fatigue, with only partial overlap between the two. Mental fatigue was associated with anxiety, depressive symptoms, and impaired divided attention, whereas physical fatigue was related to depressive symptoms and larger tumor volume.

Similar patterns of high prevalence have been reported in glioma cohorts. In a prospective study of 112 patients with diffuse glioma, high fatigue was seen in 45% preoperatively and in 42% one month postoperatively. Changes were also frequently seen (38% improved and 39% worsened) underscoring that fatigue varies over time.(122) Still, preoperative fatigue has been shown to predict postoperative fatigue.(123)

Long-term data further demonstrate the persistent impact of fatigue. In a large longitudinal study of patients with LGG fatigue remained significantly elevated postoperatively compared to a normative population at most time points up to more than ten years after surgery. Fatigue showed the strongest relationship with reduced global HRQoL.(124)

1.7.1 ASSOCIATED FACTORS

In a study examining associations of fatigue in patients with glioma, it appeared to be more strongly related to PROMs and physical functioning than demographical, tumor- or treatment-related

characteristics, such as tumor grade, histological subtype, *IDH*-status and oncological treatment.(123)

Associations between severe mental fatigue and poorer performance on objective cognitive tests have also been demonstrated, and affected patients were more likely to have reduced working hours or be unemployed.(120) Similarly, Boele et al. (2014) emphasized that fatigue and cognitive deficits may substantially impair occupational functioning and social participation.(119)

1.7.2 TREATING FATIGUE

Studies have explored interventions aimed at reducing fatigue, with accumulating evidence suggesting that symptom improvement is achievable.

NON-PHARMACOLOGICAL INTERVENTIONS

In a recently published RCT of patients with stable diffuse glioma and severe fatigue, CBT was shown to significantly improve fatigue severity.(125) The intervention targeted fatigue-maintaining thoughts and behaviors, including patterns related to sleep, activity, and coping. It combined therapist sessions with individualized online modules and email support. After 12 weeks, 68% of patients in the intervention group were no longer severely fatigued compared to 24% in the control group. The intervention also improved anxiety and HRQoL. As can be seen in figure 8, both the CIS (checklist individual strength) and FSS (Fatigue severity scale) questionnaires on fatigue yielded clear results of the effect on fatigue.

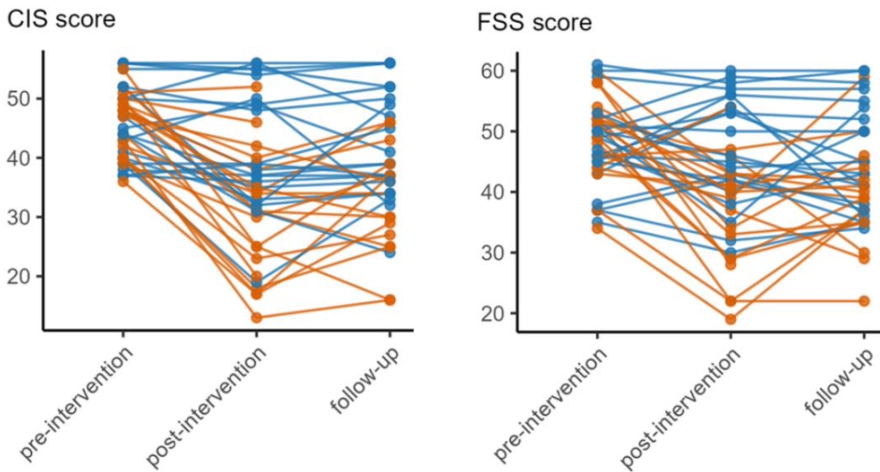

Figure 8. Longitudinal line plots for primary endpoint (CIS score) and a secondary fatigue endpoint (FSS score). Patients were assessed pre- and post-intervention (2 weeks) and at 12 weeks follow-up. Each dot represents one patient. ***Orange*** *= intervention group,* ***blue*** *= control group. Abbreviations: CIS Score = checklist individual strength score in fatigue, FSS = fatigue severity scale. Adapted from Gortner et al., 2025, licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).*

Variations of physical exercise have been investigated in several studies as an intervention for fatigue in patients with brain tumors. In an RCT 64 patients with WHO grade 2–4 glioma received either a six week supervised rehabilitation intervention (n = 32) or usual rehabilitation care (n = 32).(126) The intervention consisted of structured physical therapy and when indicated occupational therapy sessions. The control group received usual rehabilitation care consisting of referral to municipal or outpatient services or no rehabilitation. At six-week follow-up, the intervention group showed a significantly reduced fatigue compared to controls.

In a another RCT pilot study, clinically stable patients with WHO grade 2-3 glioma were allocated to a six month, home-based, remotely supervised aerobic exercise program or to a waiting-list control group.(127) At follow-up, the exercise group showed indicated improvements in physical fatigue and reduced activity compared to controls, while no clear differences were observed in the other fatigue domains.

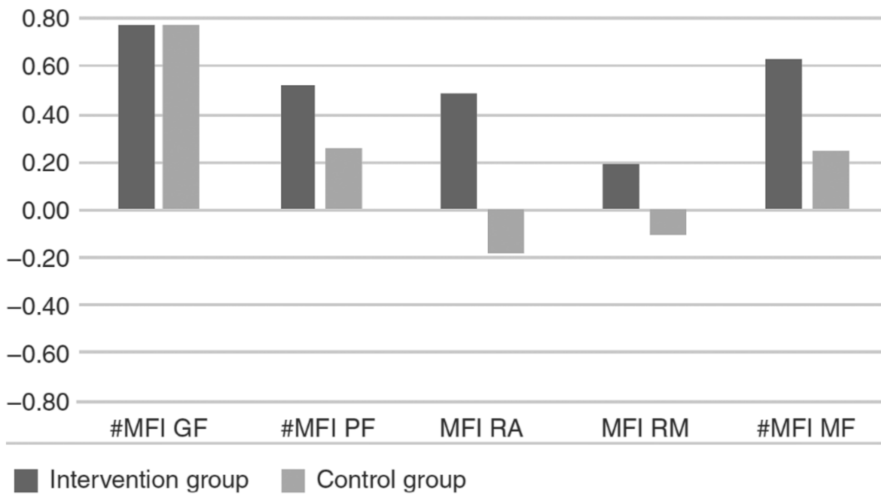

Figure 9. Within-group median changes in Z scores. Adapted from Gehring et al., 2020, licensed under CC BY-NC 4.0.(127) Abbreviations: MFI = Mental Fatigue Inventory, GF = General fatigue, PF = Physical fatigue, RA = Reduced activity, RM = Reduced motivation, MF = Mental fatigue.

In contrast, another RCT of similar sample size, but on HGG, showed no beneficial effect on fatigue. Instead, fatigue increased in both active exercise groups (endurance and strength training), while it decreased in the control condition.(128)

PHARMACOLOGICAL INTERVENTIONS

Psychostimulants are drugs that enhance alertness, attention, and energy levels by increasing CNS activity.(129) Different pharmacological agents have been investigated as potential treatments for fatigue across multiple clinical populations, including various cancer cohorts.(130) The most frequently studied agents in this context are methylphenidate, dextroamphetamine, and modafinil.(129, 130)

In a multicenter double-blind RCT phase III trial including more than 600 cancer patients undergoing chemotherapy, modafinil was compared with placebo for treatment of fatigue.(131) Overall, modafinil showed no significant reduction in fatigue compared to placebo. However,

patients with severe fatigue at baseline demonstrated a statistically significant improvement with modafinil, whereas no benefit was observed in those with mild or moderate fatigue.

Studies have also been conducted specifically in patients with brain tumors. A randomized but not placebo-controlled trial on the efficacy of modafinil and methylphenidate in patients with brain tumors demonstrated that both medications were associated with reduced fatigue with no significant differences between treatment groups. (132) More than 40% of patients showed a clinically meaningful improvement based on minimal important difference criteria. In another phase III, double-blind, RCT of patients with primary or metastatic brain tumors receiving radiotherapy, fatigue was one of the primary outcomes.(133) No differences in fatigue were observed between the methylphenidate and placebo groups at any time point, including up to 12 weeks after completion of radiotherapy, and fatigue levels remained largely unchanged over time.

The evidence for the treatment of fatigue remains limited, and in Sweden central stimulants are typically not used in clinical practice. Central stimulants may also lower the seizure threshold.(134, 135) Although the overall risk appears low, caution advised in clinical practice, in patients with a seizure risk.(135)

1.8 COGNITIVE FUNCTIONS

Cognitive functioning encompasses several domains. Although these domains are here described separately for clarity, they are overlapping and interact dynamically.

1.8.1 ATTENTION AND PROCESSING SPEED

Encoding of information requires adequate attention and a sufficient level of processing speed, as attentional capacity and cognitive efficiency determine how effectively incoming information can be registered and processed further.(136) Attention reflects the ability to sustain focus over time (sustained attention), select relevant stimuli while inhibiting distractions (selective attention), and manage multiple demands simultaneously (divided attention).(137)

Processing speed describes how rapidly a cognitive tasks is completed and is typically reflected in timed neuropsychological measures.(137) Because attention and processing speed depend on large-scale network efficiency rather than highly localized cortical regions, they are especially vulnerable to structural disconnection and white-matter changes.(136, 138, 139)

Impairment in attention and processing speed may manifest as reduced vigilance, increased distractibility, slowed mental operations, or difficulty managing multiple tasks.(137) In neuropsychological assessment, attention is typically evaluated using tasks measuring sustained, selective, and divided attention, whereas processing speed is assessed through timed tasks requiring rapid and accurate responses.

1.8.2 WORKING MEMORY

Building on attention, working memory refers to the capacity to temporary store and manipulate information. It depends on the ability to sustain attention as information must first be held in mind before it can be actively manipulated.(137) Working memory underlies other functions such as executive control and supports goal-directed behavior in situations requiring simultaneous processing and storage of

information. Deficits may present as problems with for example maintaining relevant material under cognitive load.(120) The most widely recognized and extensively established theoretical framework of working memory is Baddeley's multi-component model of working memory.

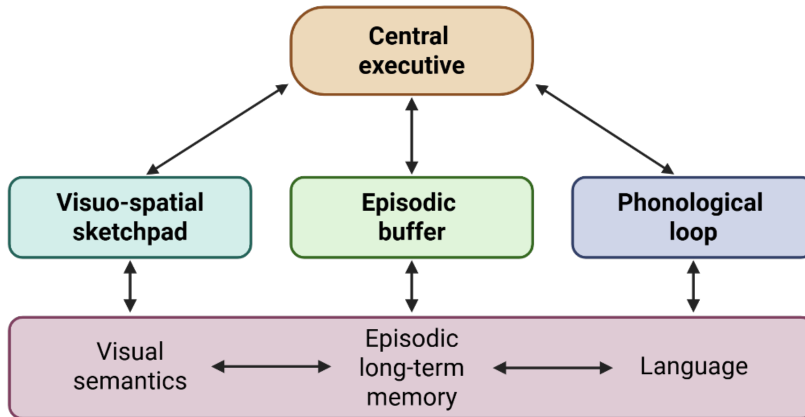

Figure 10. The multi-component model of working memory presented by Baddeley, 2000. Created in BioRender. Denes, A. (2026) https://BioRender.com/xa4os46

Baddeley's model explains working memory as a system of interacting components. The central executive represents the core component of the model. It is an attentional control system that guides attention, coordinates and regulates the sub-systems. The phonological loop specializes in short-term storage and maintenance of verbal and auditory information. It includes a temporary phonological store and a rehearsal process that keeps verbal information active. The visuospatial sketchpad is responsible for the temporary storage and manipulation of visual and spatial information. Like the phonological loop, it functions as a domain-specific subsystem.(140) The episodic buffer works as a temporary storage that merges information from the phonological loop, the visuospatial sketchpad, and long-term memory into unified, multimodal representations where information can be combined and consciously accessed.(141) Given its role in actively maintaining and manipulating goal-relevant information, working memory is often considered an executive function.(142)

1.8.3 EXECUTIVE FUNCTIONS

Executive functions represent higher-order control processes that regulate and coordinate other cognitive domains. Common executive functions include inhibition, cognitive flexibility, planning, monitoring, and also updating of working memory.(137) While working memory maintains and manipulates information, other executive functions determine how it is selected, updated, and used in line with goals.(120)

Inhibitory control refers to the ability to inhibit automatic responses and regulate behavior in accordance with goal-directed intentions.(143) The response inhibition and interference control enables individuals to resist distractions and suppress competing stimuli in order to maintain goal-relevant focus.(142) Updating involves actively monitoring and revising working memory contents by replacing no longer relevant information with goal-relevant material.(144) Cognitive flexibility reflects the ability to switch between tasks, rules, and to adjust behavior when circumstances or demands change.(143) The shifting builds upon inhibitory control and working memory, as it requires suppressing previously relevant rules and activating new.(142) These executive functions are related yet separable, reflecting both shared and distinct aspects of executive control.(144) Executive functions rely on distributed large-scale networks rather than isolated brain regions. Frontoparietal control systems are central for working memory, inhibition, and cognitive flexibility.(142, 143)

Because executive functions integrate and modulate other cognitive domains, impairment may amplify deficits in memory, attention, and language. Executive dysfunction can therefore limit independent, goal-directed behavior and consequently disrupt everyday and occupational functioning.(137)

1.8.4 LEARNING AND MEMORY

Learning and memory refer to encoding, consolidation, storage, and retrieval of information. Encoding is the registration and transformation of information into a memory trace and depends on the hippocampal formation to establish new declarative memories. During encoding, the hippocampus links distributed cortical representations into an integrated

memory representation. Consolidation is the process through which new memories are gradually stabilized. Storage means they are kept long-term in the brain and become less dependent on the hippocampus.(145) Retrieval involves accessing and bringing stored information back into awareness.

As described, these processes rely on partially distinct but interacting systems. Episodic memory, particularly verbal episodic memory, depends critically on hippocampal and parahippocampal regions and their interaction with lateral temporal and frontal areas.(145) Working memory, supports the temporary maintenance and manipulation of information during encoding and retrieval and is related but distinct from long-term memory systems.(140)

Impairment in learning and memory may manifest in different patterns depending on the underlying mechanism. In neuropsychological testing, repeated learning trials are used to measure how well someone learns and how quickly they improve over time.(137, 145) Reduced improvement across trials suggests encoding difficulties, and loss of information over time suggests difficulties with storage. Problems with retrieval can also be observed despite preserved storage.(136, 145)

1.8.5 LANGUAGE

Language enables communication through speech and writing and includes comprehension, production, reading, and writing.(137) Although these modalities differ, they rely on shared central linguistic processes. In clinical assessment, language is typically evaluated through confrontation naming, verbal fluency, comprehension, and repetition tasks. Naming and fluency tasks assess lexical retrieval, while fluency measures additionally require controlled search and executive processes, making them sensitive to both temporal and frontal dysfunction.(137) The type of language difficulty may help localize the underlying dysfunction. For example, word retrieval problems may suggest temporal involvement, whereas reduced verbal phonemic fluency can indicate frontal lobe dysfunction.(136)

The core language network supports both language comprehension and production across spoken and written modalities. It operates as an

integrated system specialized in processing linguistic structure and meaning.(146) Within this distributed frontotemporal network, partially specialized pathways can be identified. Syntactic (grammatical) processing relies predominantly on left-lateralized temporo-frontal connections, whereas semantic processing (the meaning of words) involves broader connections and is less strictly lateralized to the left hemisphere.(147) Models of the language network further distinguish between two main pathways, the dorsal and ventral streams:

- The dorsal stream comprises the arcuate fasciculus and superior longitudinal fasciculus, which connect posterior temporal and inferior frontal regions and are central to phonological processing and auditory–motor integration.(148)

- The ventral stream involves pathways such as the inferior fronto-occipital fasciculus and uncinate fasciculus, supporting semantic processing and lexical access.(148)

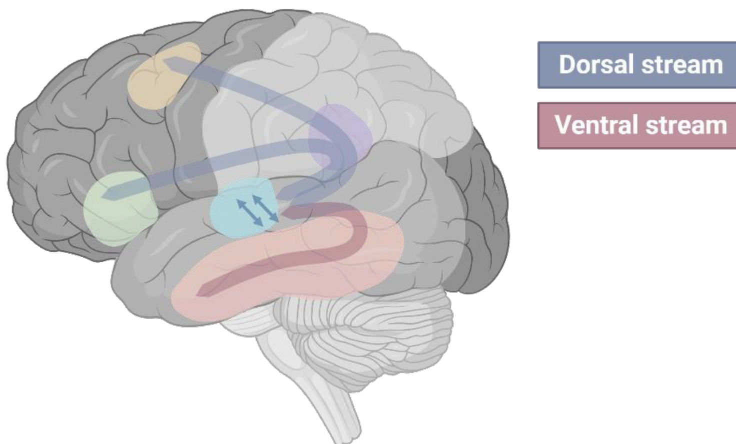

Figure 11. Conceptual model based on Chang et al. 2015.(149) Created in BioRender. Denes, A. (2026) https://BioRender.com/poidki4

1.8.6 VISUOSPATIAL FUNCTIONING

Visuospatial and constructional abilities are primarily linked to the parietal lobe and posterior parts of the brain.(137, 150) These functions allow us to perceive and interpret spatial relationships, such as how

objects are positioned in relation to one another.(150) They help us judge distance, direction, and orientation, and to mentally represent and process visual information.(137, 150) In clinical assessment, visuospatial functioning is commonly evaluated using figure copying tasks, block construction tasks, and visual organization measures. Constructional abilities refer to the capacity to organize and reproduce shapes and patterns, for example when drawing a figure or assembling objects. This requires coordination between visual perception and motor function.(137)

Neuroanatomically, the dorsal visual stream plays a central role in spatial processing and visuomotor integration.(150) The right parietal lobe is known to be important for spatial attention and organization, and damages can lead to e.g. hemispatial neglect. The left parietal lobe is more often associated with praxis and sequential tasks, and damages can lead to e.g. apraxia.(137, 150)

1.8.1 SOCIAL COGNITION

Social cognition refers to the mental abilities that help us understand and respond to other people in everyday life. It involves recognizing emotions in others, understanding what someone else might be thinking or intending (often referred to as theory of mind), and being able to take another person's perspective. It also includes empathy, which means understanding and sharing another person's feelings, and social judgment, which involves knowing what is appropriate to say or do in different situations.

In practical terms, social cognition enables individuals to recognize subtle social cues, such as detecting humor or identifying emotional states that are not explicitly expressed. It also supports the ability to adjust behavior according to contextual demands, for example by modifying conduct across different social environments. These capacities are essential for maintaining interpersonal relationships and functioning effectively in social contexts. As social cognition was not included in the thesis, only a brief overview is provided on the subject.

1.9 WHO, WHEN, WHAT?

Apparent discrepancies in reported symptoms or cognitive outcomes may reflect differences in study design rather than true variation in patient functioning. When comparing findings across studies, neglecting key differences can lead to misleading interpretations. To interpret results meaningfully, three fundamental dimensions must be considered: who is included, when are patients assessed, and what is measured?

The characteristics of the included patients are central to the interpretation of cognitive findings. Studies vary considerably in their inclusion criteria; some focus exclusively on incidentally discovered tumors, others on specific tumor grades or molecular subtypes whereas others comprise mixed populations. Certain cohorts have been restricted to patients who were employed or undergoing specific treatments, such as awake surgery or particular radiotherapy regimens with defined inclusion criteria, which may introduce selection bias. Given that cognitive outcome is influenced by multiple factors, differences in patient selection may largely affect reported results. Factors influencing cognitive functioning are discussed in more detail in Section 1.11.

The timing of assessment shapes outcomes. Cognitive performance may vary depending on whether patients are evaluated early or late in the disease trajectory, during active treatment, in a stable phase, or in the presence of comorbid conditions. Methodological decisions are important, for example to determine what is considered an impairment. Results depend on whether studies use brief screening tools, self-reported measures, or comprehensive objective neuropsychological assessments, and whether analyses focus on group averages or individual performance.

1.10 COGNITIVE FUNCTIONING ACROSS THE DISEASE TRAJECTORY

Cognitive impairment is frequently seen in patients with glioma, also those with slower growth.(151) Reported prevalence varies substantially across studies, ranging from approximately 19% to 83% in LrGG populations.(136, 152) As previously described, this wide variation reflects the methodological heterogeneity across studies. Despite variability in prevalence estimates, certain cognitive domains are more often affected. Impairments in attention, executive functioning, processing speed, and memory have repeatedly been described.(136, 151, 153-155) LrGG often give rise to subtle and gradually evolving cognitive impairments that may not be evident at a routine examination but can be identified through neuropsychological assessment.(155)

1.10.1 COGNITION IN THE EARLY PHASE

Cognitive impairment in patients with LrGG can be observed even before treatment initiation. In a longitudinal study of selected patients selected for awake surgery, 55.4% had at least one impaired test score preoperatively (defined as <-1.645 SD below the mean). At three months postoperatively, cognitive decline (decrease of >1 SD) was most frequently observed in semantic fluency (23%) and phonemic fluency (20%) but was also reported in other executive-demanding tasks, including the Stroop test and the Trail Making Test (TMT), as well as in measures of social cognition. However, the majority of patients remained stable according to this definition.(52)

The first postoperative year can be a dynamic period for cognitive change, as many patients undergo multimodal treatment during this time, including surgery, radiotherapy, chemotherapy, and receive medications (e.g. anti seizure medication), all of which may influence cognitive functioning. In a prospective study of patients with *IDH*-mutant LrGG selected for radiotherapy, 34% showed impairment in at least one domain (domain composite Z-score <-1.5), and 10% had impairments in multiple domains.(156)

Studies evaluating PROMs on cognitive function before and after surgery suggest that cognitive trajectories vary considerably between individuals, while remaining relatively stable at group level.(157) Similar patterns of group-level stability has been seen alongside cognitive decline at the individual level also when using neuropsychological testing, indicating that average scores can mask individual deterioration.(158)

1.10.2 COGNITION BEYOND THE FIRST YEAR AFTER TREATMENT

A meta-analysis of cognitive outcomes in adult patients with glioma suggested that in comparisons conducted at least one year after treatment, patients performed worse than controls or normative populations on several neuropsychological tests. Tests showing moderate impairments included semantic fluency, digit span backward, Stroop interference tasks, and TMT B.(159)

Evidence from individual studies provide insight into cognitive trajectories during this period. In a large study on patients with LGG, cognition was assessed using the cognitive screening instrument Mini-Mental State Examination (MMSE) before radiotherapy and at follow-up after treatment. The results showed overall stability several years after treatment. Among patients without tumor progression, approximately 8% showed a decline at one year and approximately 5% at later follow-ups.(160) However, the MMSE captures cognitive functioning only at a superficial level, and cognitive testing was not performed before surgical treatment. A subgroup (n=20) of patients from the same RCT was actually evaluated using a more extensive neuropsychological test battery, and similarly found generally stable cognitive performance during follow-up.(161) Paired comparisons did not show any significant decline in cognitive performance over time. However, the study was likely underpowered to detect subtle changes, and the authors also discussed possible practice effects.

Other studies using neuropsychological test batteries provide further evidence into cognitive changes during this period. Hendriks and colleagues examined tumor location and cognitive changes following surgery in patients with gliomas WHO grade 1–3.(138) Cognitive

function was assessed before surgery and again after one year. Cognitive changes were relatively common: 17% of the patients showed improvement in at least one cognitive domain, while 25% showed decline in one domain and 17% declined in several domains. The domains most often affected were attention and information processing speed. Interestingly, more pronounced cognitive decline was associated with tumors and resections in the right hemisphere, particularly in perisylvian and orbitofrontal regions. This was important because the test battery covered several different cognitive domains. However, it should also be noted that only 59 patients were included, molecular data was not available and practice effects were not accounted for (they used $\Delta z>1.5$ as a cut-off for change).

1.10.3 LONG-TERM COGNITIVE OUTCOME

Long-term cognitive outcomes in patients with LrGG have been examined in some studies, most often with cross-sectional design.

In a cross-sectional study of patients with LGG (n=195) using extensive neuropsychological testing 1–22 years after diagnosis, patients performed significantly worse than healthy controls across several cognitive domains, including psychomotor speed, memory, attention, and executive functioning.(87) Impairment was defined as performance at least 2 SD below the mean. Deficits were not restricted to a single domain but tended to be more global. Approximately one third of patients had major cognitive impairment, defined as four or more deviating test scores. Disease duration was examined in regression analyses but was not significantly associated with cognitive functioning.

Another study on 237 long-term survivors of oligodendrogliomas showed that cognitive difficulties can persist many years after diagnosis. Patients were assessed with a mean of 10 years (range 5-28) after diagnosis.(162) More than half reported clinically relevant cognitive problems based on PROMs. Objective neuropsychological testing in the same cohort showed impairment (defined as $z<-1.5$) rates of 18% in processing speed and 46% in delayed episodic verbal memory.

In a smaller study of 63 patients with *IDH*-mutant gliomas, neuropsychological assessment was performed a median of 7 years postoperative (range 3–28 years).(73) Cognitive impairment, defined as $z \leq -1.5$ on two tests in different domains, was observed in 48% of patients, while 63% showed impairment on at least one test. Impairments were seen across multiple domains, particularly in delayed episodic verbal memory (40%), executive functioning (TMT B, 33%), and processing speed (Coding 18%, TMT A, 19%). Cognitive impairment was associated with higher tumor grade, longer disease duration, older age at testing, and prior treatment with radiotherapy or chemotherapy.

1.11 MULTIFACTORIAL INFLUENCES ON COGNITION

Cognitive functioning in LrGG should be understood as the result of multiple interacting influences rather than as a direct and isolated consequence of tumor presence. Tumor-related, anti-tumor treatment, biological, psychological, and contextual factors all contribute to cognitive outcome.

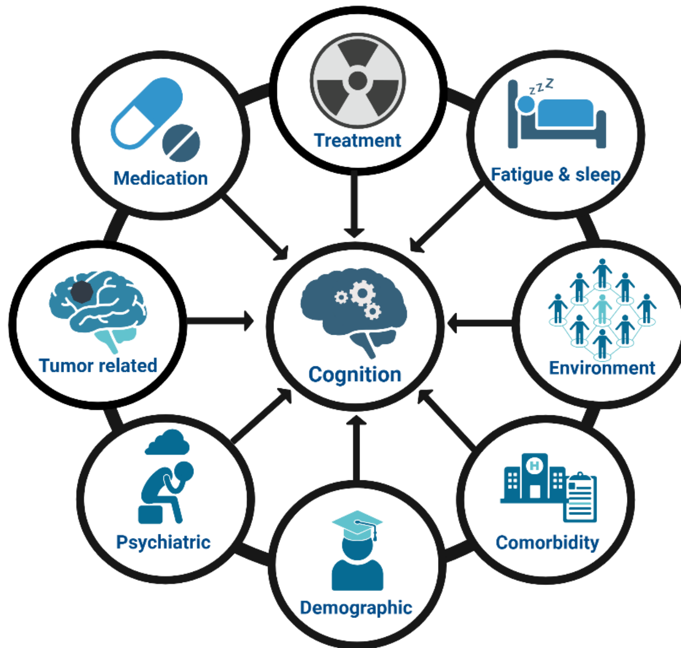

Figure 12. Factors influencing cognitive functioning in patients with lower-grade gliomas. Inspired by Weyer-Jamora et al. Neurooncol Pract, 2020. Created in BioRender. Denes, A. (2026) https://BioRender.com/hkidaos

1.11.1 TUMOR-RELATED FACTORS

Even when structural imaging shows a relatively small lesion without clear mass effect, microscopic infiltration and altered connectivity may still affect cognitive processing efficiency.(17) LrGG are diffuse, infiltrative and can disrupt large-scale neural networks. (136, 163, 164)

The anatomical location of the tumor determines which cognitive domains are at greatest risk of impairment.(149, 165) As previously described, the left hemisphere is typically responsible for language functions.(46) Within this hemisphere, language is mainly associated with frontotemporal regions, while learning and memory are mainly linked to medial temporal structures. Other eloquent functions include motor and somatosensory functions, which are associated with the frontal and parietal regions, respectively.(145, 147) In addition, visual abilities are linked to occipital regions, while visuospatial functions are associated with parietal regions, particularly in the right hemisphere.(164)

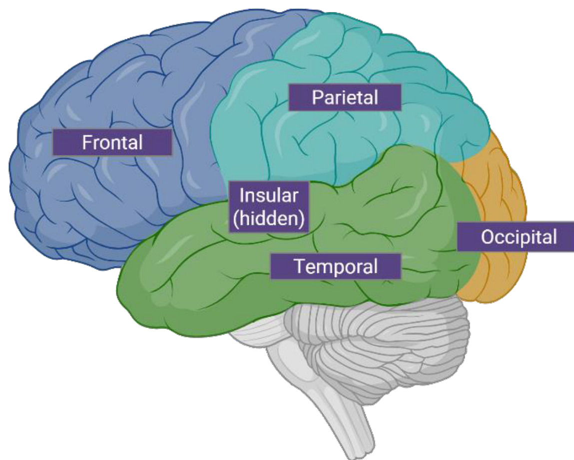

Figure 13. Sagittal view of the lobes of the brain. Created in BioRender. Denes, A. (2026) https://BioRender.com/jc87nnt

Cognitive deficits cannot be fully explained by traditional anatomical location.(136, 155, 166) Over time, the view of tumor localization has increasingly shifted toward a network-based perspective, in which disruption of functional white matter networks gives rise to clinical symptoms.(166) This has also been described in relation to cognitive functions in chapter 1.7.

The extent of cognitive impairment may depend on lesion momentum, reflecting how quickly and widely the tumor grows and spreads into surrounding brain tissue.(151) Lesion momentum is considered to influence the brain's capacity for plastic reorganization, thereby affecting how and when symptoms emerge.(17, 151, 166) *IDH*-mutant

gliomas, which typically are slow growing, have been associated with less pronounced cognitive impairment, possibly reflecting a greater opportunity for functional plasticity.(136, 151, 164, 167)

Molecular subtype has emerged as an additional factor of relevance.(136, 149, 151, 168) *IDH*-wildtype tumors have been associated with poorer neurocognitive performance compared to *IDH*-mutant tumors prior to treatment, suggesting that tumor biology influences cognitive function.(151, 169) Structural and functional connectivity studies indicate that *IDH*-wildtype tumors may demonstrate more invasive growth patterns, lesion momentum and greater disruption of large-scale networks.(170, 171)

1.11.2 TREATMENT-RELATED FACTORS

Surgical resection, radiotherapy, and chemotherapy may all affect cognitive function. Resection in eloquent or network-critical regions may lead to transient or lasting deficits. For oncological treatment, it has been difficult to study chemotherapy in isolation, but it is believed that it may contribute to decline through effects on neurogenesis and network integrity.(172) Radiotherapy has shown mixed results regarding cognitive adverse effects, where time since treatment and choice of assessment instrument partly influence the findings.(75, 173) In a Cochrane review from 2019, it is stated that it “may increase the risk of neurocognitive side effects in the long term” for patients with a good prognosis.(75) Another review further reported that factors such as fraction dose and total radiation dose may influence the magnitude of cognitive effects observed after radiotherapy.(173) The adverse effects are thought to be associated with treatment-induced white matter damage and microvascular alterations.

Several studies have identified impairments specifically in processing speed, memory, and executive functioning.(76, 87, 173) Some studies have shown radiotherapy to be associated with delayed cognitive decline several years after treatment.(174, 175) A long-term follow-up study on patients with LGG showed that patients who received radiotherapy (without chemotherapy) had cognitive declines while those receiving no adjuvant treatment showed cognitive declines only in the group receiving radiotherapy indicating that this treatment is related to

negative cognitive outcome.(76)

1.11.3 SEIZURES AND MEDICATION

Epileptic seizures are very common in patients with LrGG and may independently affect cognitive functioning. In addition, antiepileptic drugs and corticosteroids can influence attention, processing speed, and memory, and antiepileptic drug use has been linked to poorer cognitive performance.(87) Sedative effects, mood changes, and reduced alertness may contribute to subjective and objective cognitive inefficiency.(155) Thus, cognitive impairment may reflect not only tumor and treatment effects, but also pharmacological burden.

1.11.4 FATIGUE, SLEEP AND PSYCHOLOGICAL FACTORS

Mental fatigue is highly prevalent in patients with LrGG and has been shown to correlate with reduced cognitive performance and employment status.(120) Fatigue can make problems with attention and executive functions more noticeable by making tasks feel more effortful and make it harder to stay focused and mentally engaged over time. Sleep disturbance can further worsen fatigue by increasing overall tiredness and reducing mental alertness. Fatigue is discussed in more detail in section 1.7.

Symptoms of depression and anxiety are frequently reported in brain tumor populations and may independently affect concentration, memory, and motivation.(105, 176) Psychological distress may also alter subjective perception of cognitive functioning.(89) Distinguishing primary cognitive impairment from affective contributions is therefore important. Psychological factors are presented more in section 1.6.

1.11.5 DEMOGRAPHIC AND GENETIC FACTORS

Age has been examined as a potential determinant of cognitive outcome in glioma populations. Several studies report associations between increasing age and poorer neurocognitive performance; however, findings are not entirely consistent across cohorts, and the magnitude

and independence of this effect vary.(73, 136, 177) Educational level and cognitive reserve may modulate the resilience.

APOE, particularly the ε4 allele, has been suggested to influence cognitive functioning, as associations have been observed in other clinical populations, and in a cohort of patients with brain tumors.(178, 179) However, most studies have not demonstrated comparable findings.(180)

1.11.6 COMORBIDITY AND GENERAL HEALTH

Vascular risk factors, such as hypertension and cerebral small vessel disease, together with diabetes and comorbid neurological or neurodegenerative conditions including dementia, are well-established contributors to cognitive impairment in the general population. (181, 182) Through reduced cognitive reserve and increased cerebral vulnerability, these factors may also influence cognitive functioning in patients with LrGG. Also psychiatric comorbidities such as depression has been related to reduced cognitive performance in the general population.(183) Comparable relationships have been observed in patients with brain tumors.(184)

1.12 HEALTH-RELATED QUALITY OF LIFE

HRQoL is a multidimensional construct that includes physical, cognitive, emotional and social functioning.(86) In patients with LrGG, HRQoL has emerged as a key outcome alongside survival and several studies have reported impaired HRQoL across multiple domains.(119, 176, 185, 186) A review reported substantial differences between studies in HRQoL measures, timing of assessments, and treatment variables examined, making comparisons between findings challenging.(186)

In a large cross-sectional study by Aaronson et al., on patients with LGG (without molecular classification) were assessed an average of 5.6 years after diagnosis.(185) Compared with norms from the general population, patients reported problems across several domains of HRQoL, including role functioning (physical and emotional), general health perceptions, vitality, social functioning, and mental health. Another more recent large longitudinal study reported similar findings, with poorer cognitive, emotional, and social functioning in patients with LGG compared to controls. In addition, fatigue was common in this cohort. Role functioning, social functioning, and fatigue were strongly related to global health status/quality of life (QoL).(124)

An important consideration is that deterioration in HRQoL may occur at the individual level even when group-level averages appear stable. An example of has been shown in a longitudinal study of patients with *IDH*-mutant LrGG, where deterioration beyond minimal clinically important difference was observed at the individual level despite stable group-level means, with worsening in fatigue in 33% of patients and in global health status in 24%.(187)

1.12.1 COGNITION AND HRQOL

In the previously mentioned study by Aaronson et al., PROMs were used to report on cognitive complaints. They found that particularly forgetfulness (27%) and concentration difficulties (26%) were commonly reported.(185) Poorer HRQoL was associated with a greater epilepsy burden and with a higher number of objectively assessed cognitive deficits.(185) However, the study did not specify which

individual cognitive tests or domains accounted for this association.

Using data from the same cohort of patients, Boele et al. further examined the relationship between objective cognitive functioning and HRQoL.(188) The analysis showed that poorer cognitive performance was associated with worse disease-specific and generic HRQoL. In particular, lower performance in executive functioning, processing speed, working memory, and information processing was related with poorer mental health and overall HRQoL.

1.12.2 TREATMENT, FATIGUE AND HRQOL

Treatment factors and diagnosis may also influence HRQoL in patients with glioma.(186) In the systematic review treatment was one of the most examined factors. Some studies reported associations between oncological treatment and lower HRQoL, while others did not find such relationships. The extent to which radiotherapy independently influences HRQoL remains difficult to determine because several things occur at the same time, such as disease progression and treatment-related factors.

In a longitudinal cohort of patients undergoing primary glioma surgery, deterioration in HRQoL between one and six months postoperatively was associated with HGG subtype, comorbidities, and lower resection grades.(189) However, this association may partly reflect the overall worse health status and prognosis in more aggressive disease. In another cohort assessing HRQoL after surgery for LrGG, several HRQoL domains declined during the first months after surgery. These changes were only weakly associated with surgical variables, including EoR.(190)

Fatigue frequently co-occurs with other symptoms such as cognitive deficits and depression, contributing to an overall symptom burden that can negatively affect patients' QoL.(119) In a large cohort of patients with stable disease several years after diagnosis, worse functioning and greater symptom load were associated with poorer generic and disease-specific HRQoL.(188)

In another, more recent longitudinal population-based study, fatigue and

global HRQoL were among the domains most frequently changing at the individual level in patients with LrGG, and deterioration in fatigue often occurred alongside worsening HRQoL.(187) Fatigue has previously been described more in detail in section. 1.7.

1.12.3 RESPONSE SHIFT

When interpreting longitudinal HRQoL data, the possibility of response shift should be considered. Response shift refers to a process in which patients recalibrate their internal standards or reprioritize life domains when evaluating HRQoL after illness or treatment.(191) In cancer populations, this adaptation may lead patients to report stable or improved HRQoL over time despite persistent symptoms or functional limitations.

Evidence from glioma populations remains limited. In a prospective study assessing HRQoL before and after glioma surgery, no overall response shift was observed at the group level, but it was identified in patients whose HRQoL changed.(192) In these patients, retrospective reassessment of baseline HRQoL showed that patients who improved tended to rate their previous health as better than originally reported, while those who deteriorated tended to rate it as worse. This process reduced the apparent magnitude of HRQoL change between baseline and follow-up.

1.13 RETURNING TO WORK

Returning to work (RTW) constitutes an important marker of functional recovery and societal reintegration after treatment.(193) For patients with LrGG, who are often adults in the midst of their working lives, maintaining participation in professional life can be important for the feeling of independence, social integration and well-being.

In a systematic review on RTW after surgery for LGG, rates varied largely.(193) Across the included studies, the timing varied considerably, ranging from 15 days to 22 months after surgery. The proportion of patients employed at the time of diagnosis varied between studies. The review included studies in which patients with LGG were part of the cohort, meaning that some studies included only a small number of such patients.(193, 194)

Among the larger studies including only patients with LGG, RTW rates of up to 94% during follow-up were reported. This was in patients undergoing surgery for tumors located in eloquent areas and using intraoperative mapping, all WHO grade 2 gliomas (pre-molecular classification).(195) In a later study from the same group, where molecular data was available (16% *IDH*-wildtype tumors), 83% had RTW within one year after surgery.(52) In another, cross-sectional study conducted at a median of 8 years after diagnosis 73 patients with WHO grade 2 tumors (88% *IDH*-mutant) were included.(196) Of those employed at diagnosis (n=61) 52% were working at follow-up. These findings should be interpreted with some caution given the relatively low response rate of 57%.

RTW often involves adjustments in the work situation, such as modified workload and tasks, reduced working hours and changes in employment position, affecting approximately one-third to one-half of patients.(194, 196-198) However, work adjustments have also been reported in more than one-third of cases during the year preceding diagnosis.(199). An interview study including patients with different types of cancer reported similar experiences, highlighting workplace support and RTW as a way to regain normality. Financial pressures were also described as a common driver for RTW, while patients often reported receiving little

guidance from the healthcare regarding work-related issues.(200)

1.13.1 FACTORS RELATED TO RTW

Several studies have examined predictors of RTW following treatment. One important factor is epilepsy. Given the high prevalence of epilepsy in this patient group and associated driving restrictions, typically lasting one year and considerably longer for professional drivers, may affect the ability to RTW.(201)

Other studies have identified sociodemographic factors. Older age and lower functional status have been related to poorer RTW in several studies.(194, 196, 202) Female sex has also been linked to lower rates of RTW in some studies.(196, 203) Occupational characteristics such as being employed prior to surgery and having a white-collar occupation, typically involving less physically demanding work, have been associated with a higher likelihood of RTW.(194, 202, 203)

Clinical and treatment-related factors have also been studied. In a mixed glioma cohort, sole breadwinner status, smaller tumor volume, and better preoperative memory performance were significantly associated with the probability of RTW.(203) Surgical factors have also been investigated. A greater EoR has been reported to be significantly related to RTW in some cohorts.(204, 205) There are also studies indicating that the use of intraoperative mapping or awake surgery may improve outcome and RTW.(197, 205, 206) However, in a recent multicenter cohort, one center with substantially lower use of awake surgery demonstrated comparable RTW rates and even higher EoR, suggesting that EoR may be a more important determinant than surgical approach.

Postoperative oncological treatment may also influence RTW, as patients may need to participate in ongoing treatment and experience side effects that can affect their RTW.(194, 207) Fatigue is a key factor influencing RTW and often requires adjustments in working hours, workload, or job tasks.(120, 194, 197, 202) Cognitive functioning has also been related to RTW, with impairments in domains such as processing speed, language, and sustained attention reported to negatively affect the capacity to perform work-related tasks.(196, 208)

2 AIM

The overall purpose was to investigate functional outcomes following standard treatment of lower-grade glioma.

1. To study patterns of sick leave and explored predictors for return to work (RTW) in patients with low-grade glioma in Sweden, compared to a matched control group. We hypothesized that RTW would be gradual and influenced by multiple factors.

2. To investigate temporal patterns of the use of psychotropic, and anti-epileptic drugs in patients with low-grade glioma around time for diagnosis compared to a matched control group. In addition, the aim was to explore predictors for drug use. We hypothesized that drug use would increase around the time of tumor discovery and remain significantly elevated in patients compared to controls over time.

3. To outline cognitive trajectories from pre-operatively to one year post-operatively, in patients with *IDH*-mutant gliomas receiving guideline-based treatment. In addition, the aim was to explore predictors of cognitive declines. We hypothesized that patients would show measurable cognitive declines over the first year, and that clinical and treatment-related factors would predict such decline.

4. To identify how different aspects of cognitive functioning relate to patients' global HRQoL at different stages of the disease, in patients with *IDH*-mutant gliomas. We hypothesized that specific cognitive impairments would be associated with reduced global HRQoL, and that the relative importance of domains would vary across disease stages.

3 PATIENTS AND METHODS

3.1 STUDY DESIGN AND PARTICIPANTS

All studies included in this thesis were observational cohort studies based on nationwide registry data or prospective clinical cohorts. Study I and II were retrospective registry-based matched cohort studies, using controls from the general population for comparison. Study III was a prospective longitudinal multicenter study, in which patients were assessed before and one year after treatment. Study IV was a cross-sectional study using data from several time points during the disease trajectory. Table 1 presents an overview of the included studies.

All included patients were diagnosed in Sweden with a diffuse glioma verified by histopathology. For paper I and II, patients were classified according to the 2007 WHO classification of tumors of the CNS and for paper III and IV patients were classified according to the 2021 WHO classification.(20)

Table 1. Overview of the included studies.

Title	Study type	Status	N	Classification
I. Return to work following diagnosis of low-grade Glioma: A nationwide matched cohort study	Retrospective registry-based study	Published in Neurology 2020	Patients n = 381, Controls n =1900	Oligodendroglioma, astrocytoma or oligoastrocytoma WHO 2007 Grade 2
II. Psychotropic and anti-epileptic drug use, before and after surgery, among patients with low-grade glioma: a nation-wide matched cohort study.	Retrospective registry-based study	Published in BMC Cancer 2021	Patients n = 485, Controls n = 2412	Same as study I
III. Reliable cognitive changes the first year following guideline-based treatment of *IDH*-mutated gliomas: a longitudinal multicenter study	Prospective cohort study	Published in Neuro-Oncology 2025	Patients n =127, Controls n = 88	*IDH*-mutated astrocytoma or *IDH*-mutated Grade 2-4 & 1p/19q co-deleted oligodendroglioma grade 2-3 WHO 2021
IV. Contribution of cognitive function and fatigue to HRQoL in patients with *IDH*-mutant gliomas - from diagnosis to long-term follow-up	Cross sectional study	Submitted	Patients n = 82-107	Same as study III

3.2 DATA SOURCES AND REGISTRY LINKAGE

In Sweden, each resident is assigned a unique personal identification number, which enables linkage between various national registries. These registries contain both non-medical information, as well as health-related and disease-specific data. This infrastructure allows large-scale, population-based research and facilitates the inclusion of matched control cohorts.

This approach was used in Study I and II, where data from multiple national sources were combined through individual-level linkage. Patients were identified by the Swedish Brain Tumor Registry (SBTR) and their recorded diagnoses. Patients receiving a pathological diagnosis of grade 2 astrocytoma, oligoastrocytoma or oligodendroglioma (WHO 2007) between 2005 and 2015 were included.(209) Patients had to be at least 18 years of age at their first surgery. Information was transferred from the SBTR to Statistics Sweden (SCB), which added information from their registry and created a matched control group. SCB also produced an encrypted key code that they held. SCB received linked data from the Swedish Social Insurance Agency (SIA) and two registries from the National Board of Health and Welfare (NBHW). Data was then delivered in coded form to Sahlgrenska University Hospital for analysis.

3.2.1 THE SWEDISH BRAIN TUMOR REGISTRY

The Swedish brain tumor registry (SBTR) is a national quality registry covering all six neurosurgical units in Sweden. It includes adult patients (≥18 years) diagnosed with primary brain tumors and provides detailed information on demographics, preoperative symptoms, imaging findings, tumor size and location, surgical approach, histopathology, postoperative treatment, and short-term complications. As no other neurosurgical departments than those represented in the SBTR perform brain tumor surgery in Sweden, the SBTR represents nearly all surgically treated brain tumor cases nationwide.

Data are reported to the SBTR by using standardized forms. Reporting coverage has generally been high. For our population-based analyses,

regions and years with a minimum of 80% registration rate were included. To ensure completeness, registry data were cross-checked against the compulsory National Cancer Registry. During the study period (2005–2015), regions that did not meet this threshold were excluded for specific years. As a result, data collected between 2005 and 2011 from one center and between 2005 and 2008 from another were excluded. Based on patient records from nearby years, the estimated number of patients lost during these periods was approximately 165. In total 547 patients were extracted from the SBTR. Data was accessed October 21, 2016. Demographics and clinical characteristics, tumor-related and treatment related variables were retrieved from the SBTR. Definitions of the variables are presented in Table 2 below.

Table 2. Definition of variables.

Category	Definition
Index date	Date of surgery according to the SBTR. Controls were assigned the same index date as their corresponding patients.
Index year	Year of surgery according to the SBTR. Controls were assigned the same index year as their corresponding cases.
Sex	Biological sex.
Age	Age at diagnosis.
WHO performance status	Patient’s level of functional ability, ranging from fully active (0) to disabled, confined to bed (4).
Tumor laterality	Defined as left, right or bilateral.
Tumor size	Tumor size according to the largest diameter were separated into three categories: <4 cm, 4–6 cm, and >6 cm.
Days from imaging to surgery	Number of days from the first imaging indicating a well-founded suspicion of a tumor to the first surgical intervention.
Surgical procedure	Either a biopsy or resective surgery.
New deficit after surgery	New neurological deficit (dysphasia, paresis/plegia, cranial nerve or cognitive deficit) persisting >30 after surgery.
Reoperation	Reoperation due to complication
Radiotherapy	Treatment with radiotherapy. Yes/no according to SBTR. This variable was combined with data from the NPR (see below)
Chemotherapy	Treatment with chemotherapy. Yes/no according to SBTR. This variable was combined with data from the NPR and the NPrP (see below)

3.2.2 STATISTICS SWEDEN

SCB is the national authority responsible for compiling and coordinating official statistics in Sweden. The agency maintains comprehensive registers containing demographic and socioeconomic data for all residents. For study I and II, data were obtained from several national registers held by SCB: the Register of the total population (RTB), the Longitudinal database for integration studies (STATIV) and the Income and taxation register (IoT).

Variables retrieved from SCB registers:

- **Register of the Total Population (RTB):**
  Controls: sex, year of birth
- **Longitudinal Database for Integration Studies (STATIV):**
  Patients and controls: Highest attained education (according to SUN2000).
- **Income and Taxation Register (IoT):**
  Patients and controls: disposable income and total income earned for patients and controls.

Table 3. Definition of variables

Category	Definition
Educational level	Educational attainment categorized according to the Swedish nomenclature for education (SUN2000) and grouped into primary/secondary education (grades 1–4) and higher education (grades 5–7).
Income	Disposable income and total income earned.

Control individuals were selected from RTB, with five controls matched to each patient by year of birth, sex, educational level, and municipality of residence at the turn of the year preceding diagnosis. Each control individual was used only once. Due to limited availability of suitable matches, the control cohort was incomplete for some cases, resulting in 12 fewer controls than expected. In total, 2412 controls were extracted from SCB.

3.2.3 THE NATIONAL BOARD OF HEALTH AND WELFARE REGISTRIES

3.2.3.1 THE NATIONAL PATIENT REGISTRY

The national patient registry (NPR) includes all hospital admissions and specialist outpatient visits in Sweden since 2001. Reporting is mandatory and nationwide coverage exceeds 99%. Each record includes admission and discharge dates, and diagnoses are coded according to the International Classification of Diseases (ICD-10), and procedural codes. Data from the NPR were used to define comorbidities and previous medical history. Comorbidity burden was quantified using the Elixhauser Comorbidity Index, excluding conditions directly related to the brain tumor disease.(210)

3.2.3.2 NATIONAL PRESCRIPTION REGISTRY

Established in July 2005, the National prescription registry (NPrP) contains comprehensive data on all prescribed medications dispensed at Swedish pharmacies, with mandatory reporting from all providers. Each entry includes the Anatomical Therapeutic Chemical (ATC) classification code, quantity dispensed, and date of dispensing. Drug use was defined as at least one dispensed prescription within 90 days for antiepileptic and antidepressant medications, or within 30 days for sedatives, reflecting the typical prescription intervals for these drugs.

Table 4. Description of variables from the NPR and NPrP

Category	Definition
Anti-epileptic drug use	Purchase of any drug in ATC class N03A (antiepileptics), excluding those mainly used for pain: N03AX12 (Gabapentin) and N03AX16 (Pregabalin).
Antidepressant use	Purchase of any drug in ATC class N06A (antidepressants).
Sedative use	Purchase of any drug in ATC classes N05B (anxiolytics) or N05C (hypnotics and sedatives), excluding N05CD08 since it is commonly used to treat seizures.

History of seizure	A purchase of anti-epileptic drugs (ATC N03A, excluding N03AX12 and N03AX16), or a diagnosis according to ICD-10 code G40 (epilepsy), or a registration of seizure as a symptom in the SBTR within one year prior to the index date.
History of depression	A purchase of antidepressants (ATC N06A), or a diagnosis according to any of the following ICD-10 codes: F20.4, F31.3–F31.5, F32, F33.0–F33.3, F34, F41.2, F43.2 within one year prior to the index date.
Anxiety and/or sleeping difficulties	A purchase of drugs in ATC classes N05B or N05C (except N05CD08) and/or a diagnosis according to any of the following ICD-10 codes: G47, F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42.0, F42.1, F42.2, F42.8, F42.9.
Comorbidity	Elixhauser Comorbidity Index according to standard definitions. The conditions G40, G41 (Status epilepticus), R56 (Convulsions), R47 (Dysphasia/aphasia), and C70–C72 (Malignant tumor in the CNS) were removed from the index due to possible association with diagnosis of LGG. Cases and controls were assigned a score from 0 to 30 based on comorbid categories present or not and reported as 0, 1, 2, or ≥3. The ICD-10 data used to classify comorbidity was taken from the NPR during the year prior to index date.
Radiotherapy	Administration of radiotherapy (RT) according to the NPR, or a registration of RT in the SBTR.
Chemotherapy	Administration of chemotherapy according to the NPR or prescription for chemotherapy (ATC: L01) according to the NPrP. after index date or registration of chemotherapy in the SBTR.

3.2.4 THE SWEDISH SOCIAL INSURANCE AGENCY

The Swedish social insurance agency (SIA) is a Swedish government agency responsible for administering financial support in cases of illness. In Sweden, employers cover sick leave for the first two weeks, after which SIA provides sickness benefits. This register was used in Study I to determine RTW status at one and two years after surgery. Data from the year preceding diagnosis were also included to examine patterns before tumor detection.

Variables retrieved from the SIA:

- Time periods with received compensation (including the first two weeks being paid by the employer)
- Type of compensation (temporary or permanent).
- Degree of work incapacity (25%, 50%, 75%, 100%)

Table 5. Descriptions of variables from the SIA

Category	Definition
Return to work	Considered to have taken place once compensation payments ended; the return was not necessarily full.
Previous sick-leave	Net days absent prior to index date (per 10 days). A composite measure defined by multiplying the number of compensated days by the level of compensation, yielding an annual value ranging from 0 to 365; in the event of death, patients were classified as not working (100% absence from work)

3.3 METHOD FOR STUDY I

3.3.1 STUDY POPULATION

In total, 547 patients were identified in the SBTR. Individuals over 60 were excluded as many in this age group are near retirement and may decide not to RTW for reasons unrelated to their disease or treatment. In addition, patients that did not receive sick-leave compensation at the day of their surgery were excluded. For the one-year analysis, this rendered a group of 381 patients and 1900 matched controls (five missing matches). For the two-year analyses, an additional 38 patients (and their respective controls) were excluded since they were diagnosed in 2015 and did not have two-year follow-up data available at the time. Hence 343 patients were included in the two-year analyses. Figure 14 displays a flow chart of the inclusion of patients.

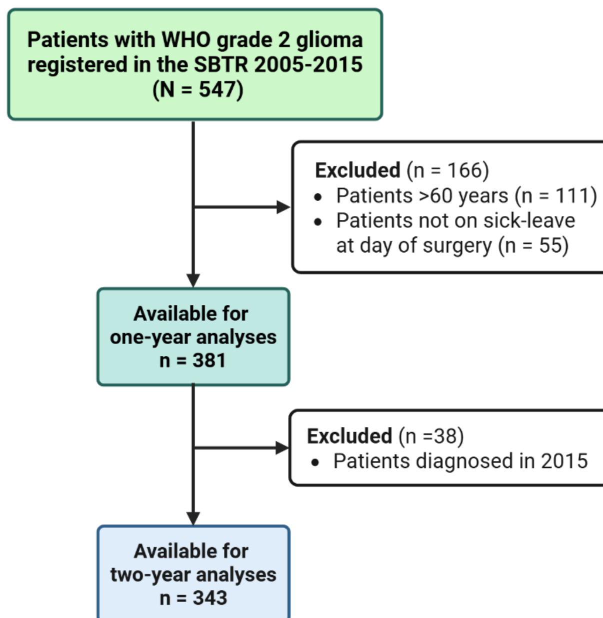

Figure 14. Flow chart of patient inclusion

3.3.2 VARIABLES AND OUTCOMES

RTW at one year, and at two years after surgery respectively were used as outcome variables in regression analyses. RTW was defined as no longer receiving full sick-leave compensation (see table 5). The following covariates were used as potential predictors of RTW: index year, sex, age, WHO performance status, tumor size, educational level, income, history of seizure, history of depression, comorbidity and previous sick-leave. See tables 2-5 for descriptions of each variable. Sensitivity analyses were performed for one and two years respectively. These were done to investigate the influence on other, postoperative and treatment-related variables. Variables comprised tumor laterality, surgical procedure, radiotherapy, chemotherapy, reoperation, and new deficit after surgery. These variables are presented in table 2.

In addition to the dichotomous RTW outcome, temporal patterns of work participation were examined. For each day from 365 days prior to index date until 365 days after index date (and up to two years for the extended analysis), individual compensation status was categorized as no compensation, partial compensation (25-75%), or full compensation (100%). Deceased patients were classified separately. Daily proportions of patients and controls within each category were calculated at group level and used for graphical visualization.

3.3.3 STATISTICAL ANALYSES

Data were imported into myQOL (Oracle). Data on sick leave were processed using Python version 2.7 (Python Software Foundation). R Statistical software version 3.1 was used to perform statistical analyses. Univariable and multivariable logistic regression models were used to identify predictors of RTW. Statistical significance was set at p-value <.05 (a two-sided) for all tests. For the sensitivity analyses, predictors with a p-value <.15 in the univariable models, were included in the multivariable models using forward selection. These models also included postoperative and treatment-related variables. Model performance was evaluated with C-statistics. Continuous variables were reported as medians with interquartile ranges and compared using the Mann–Whitney U test. Categorical variables were reported as counts and proportions comparing cases and controls using Fisher's exact test.

3.4 METHOD FOR STUDY II

3.4.1 STUDY POPULATION

The same registry framework was used as in Study I. Of the 547 patients initially identified, 58 patients diagnosed before October 1, 2006 were excluded due to incomplete NPrR coverage (established in July 2005, with a three-month run-in period). In addition, patients who had emigrated (n=4) were excluded. In total, 485 patients and their corresponding controls were included.

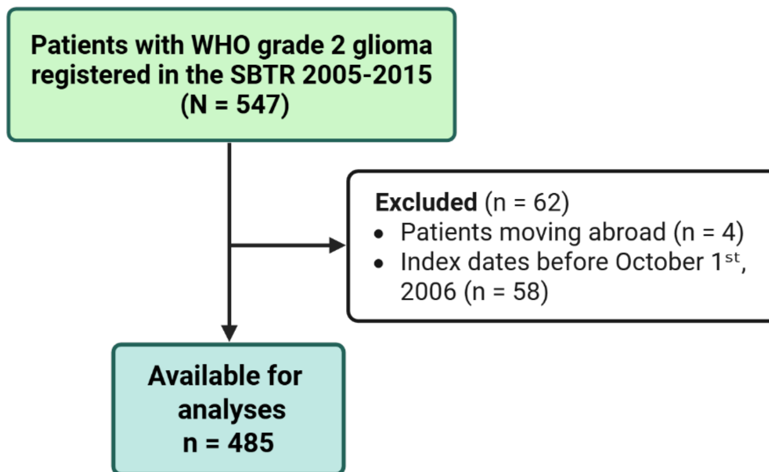

Figure 15. Flow chart of patient inclusion

3.4.2 VARIABLES AND OUTCOMES

The outcomes for this study were the use of antiepileptic, antidepressant, and sedative medications respectively. Definitions of these variables are described in table 4. Each patient's medication history was traced from one year prior to one year after the surgery. A one-year period before the index date was used to define medical history variables. The following covariates were used as potential predictors of RTW: index year, sex, age, WHO performance status, tumor size, educational level, income, history of depression, use of antidepressant preoperatively,

history of anxiety and/or sleeping difficulties, use of sedatives preoperatively, history of seizure, use of anti-epileptic drugs preoperatively. Definitions of the variables are presented in table 2-4.

3.4.3 STATISTICAL ANALYSES

Data from the registries were imported into a MySQL (Oracle) database. Drug dispensations were analyzed for each individual based on date and ATC codes using Python. Statistical analyses were performed in R (version 3.1) and SPSS (version 25.0).

For each calendar day from one year before to one year after the index date, individuals were classified as current users or non-users within each drug category based on predefined exposure windows (90 days for antidepressants and antiepileptics, and 30 days for sedatives). The daily proportion of patients and controls classified as users within each drug category was calculated relative to the total number of individuals in each group and illustrated graphically with 95% confidence intervals. Continuous variables were summarized as medians with interquartile ranges and compared using the Mann–Whitney U test, while categorical variables were expressed as counts and proportions and compared using Fisher's exact test.

To identify predictors of drug use one year after surgery, univariable and multivariable logistic regression analyses were performed separately for antidepressants, sedatives, and anti-epileptic drugs. Only patients alive one year after index date were included in the regression analyses.

Sensitivity analyses were conducted in which diagnoses and dispensed medications were entered separately in the regression models to assess the robustness of the exposure definitions. All tests were two-sided, and a p-value $<.05$ was considered statistically significant.

3.5 METHOD FOR STUDY III

3.5.1 STUDY POPULATION

3.5.1.1 PATIENTS

Between January 2016 and May 2024, patients were prospectively recruited from two Swedish university hospitals covering population-based regions in Sweden: Sahlgrenska University Hospital in Gothenburg and Uppsala University Hospital in Uppsala. Eligible participants were identified through multidisciplinary neuro-oncology conferences at each site.

Adult patients (≥18 years) with MRI features indicative of a diffuse LrGG, typically a hyperintense lesion on T2-FLAIR without significant contrast enhancement, were invited to participate and underwent preoperative neuropsychological assessment. Eligibility required that patients were scheduled for resective surgery or biopsy.

Patients with a histopathologically verified *IDH*-mutant astrocytoma or oligodendroglioma were assessed again approximately 12 months following surgery and were included in the final analyses. All participants received written and oral study information and provided written informed consent.

3.5.1.2 CONTROLS

A separate comparison group was established to enable calculation of reliable change indices (RCIs) and to account for expected variation and learning effects between repeated assessments. The control sample consisted of cognitively healthy adults recruited from the community. Recruitment was carried out through advertisements in public settings and professional networks. Controls were selected to approximate the patient cohort in terms of age, sex distribution, and educational level. All control participants underwent neuropsychological testing at two time points corresponding to the patient assessment schedule. All controls completed a brief health screening prior to inclusion. Written informed consent was obtained from all participants.

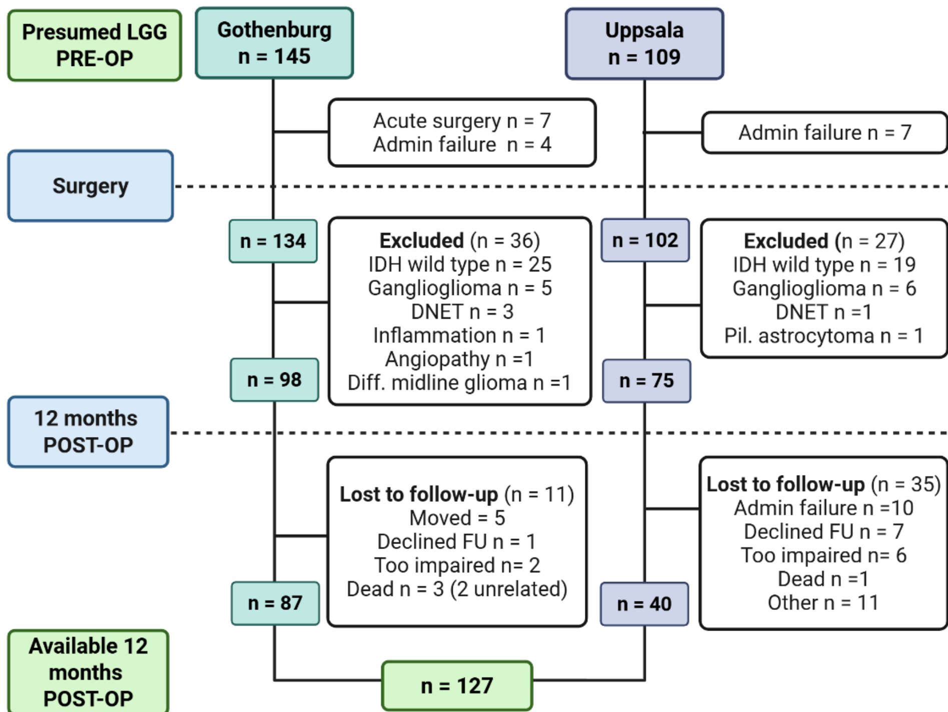

Figure 16. Flow chart of patient inclusion

3.5.2 VARIABLES AND OUTCOMES

3.5.2.1 CLINICAL VARIABLES

Clinical data on demographic, treatment-related, and tumor-specific variables were collected from electronic health records. Tumor volume was quantified using semi-automated segmentation of T2-FLAIR MRI scans acquired preoperatively and during the early postoperative period (within 72 hours of surgery). Functional status was documented using the Karnofsky Performance Status (KPS) scale at baseline and at follow-up. Deficits that remained present more than three months after surgery were classified as permanent.

Details regarding oncological treatment were recorded, including type of radiotherapy (proton or photon), prescribed total dose and fractionation, as well as chemotherapy regimen. During the first postoperative year, no cases of radiological progression were identified.

3.5.2.2 HOSPITAL ANXIETY AND DEPRESSION SCALE

Symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire developed for use in medical populations.(211) HADS was completed prior to the neuropsychological assessment. This was the only self-report instrument administered at both centers and therefore the sole patient-reported measure included in the analyses. HADS comprises 14 items divided into two subscales assessing anxiety (HADS-A) and depression (HADS-D). Each item is rated on a 0–3 scale, yielding subscale scores ranging from 0 to 21, with higher scores indicating greater symptom severity. During the assessment visit, responses were reviewed, and any ambiguities or missing items were clarified through structured follow-up questions.

Results from HADS-A and HADS-D were presented separately. In line with previous validation studies, a cut-off score of ≥8 on either subscale was used to indicate clinically relevant symptoms of anxiety or depression.(212, 213)

3.5.2.3 NEUROPSYCHOLOGICAL ASSESSMENT

Minor differences in the neuropsychological test batteries were present between centers. As the majority of patients were recruited from the Gothenburg site, measures administered at this center were prioritized when test versions were not directly comparable. Neuropsychological evaluations were conducted in person.

BRIEF VISUOSPATIAL MEMORY TEST–REVISED

The Brief Visuospatial Memory Test – Revised (BVMT-R) assesses visuospatial learning and memory by requiring participants to reproduce a set of geometric figures after brief exposure across multiple learning trials. Performance is evaluated for immediate recall, learning rate, and

delayed recall, providing indices of visual memory acquisition and retention.(214) Total learning and delayed recall was used as variables.

REY AUDITORY VERBAL LEARNING TEST

The Rey Auditory Verbal Learning Test (RAVLT) is a validated measure of verbal learning and memory.(215-217) It involves presentation of a 15-word list across five consecutive learning trials, each followed by immediate free recall. Performance across trials reflects learning capacity and acquisition rate. After a delay, a free recall trial is administered providing a measure of delayed verbal memory. The sum of learning trials and score on the delayed recall were used as variables.(218)

TRAIL MAKING TEST

The Trail Making Test (TMT) measures visual scanning, attention, processing speed, and executive functioning. In Part A, participants are required to connect numbered circles in ascending order as quickly as possible, primarily assessing visual scanning, sustained attention, and psychomotor speed. Part B increases task demands by requiring alternation between numbers and letters in sequence (1–A–2–B, etc.), thereby measuring cognitive flexibility. The task is to be performed as quickly and accurately as possible and has demonstrated established validity in assessing attention and executive functions.(219, 220) Time to finish part A and B respectively were used as variables.

REY COMPLEX FIGURE

The Rey Complex Figure Test (RCFT) is a reliable test to assess visuo-constructive abilities through a complex figure copy task, followed by a visuospatial memory task through immediate and delayed recall conditions.(221) For the studies in this thesis, only the copying part was assessed. This part reflects visuo-perceptual organization and places executive demands on the ability to plan the drawing strategy and monitor and correct performance when needed.

BOSTON NAMING TEST

The Boston Naming Test (BNT) measures confrontational naming ability by requiring participants to verbally identify drawings of objects with increasing difficulty. The test indexes word retrieval and language function and can also reflect semantic knowledge. A Swedish translation of the Boston Naming Test has been psychometrically evaluated and shown to be suitable for use in Swedish-speaking populations.(222) Number of correct words were used as variable.

DELIS–KAPLAN EXECUTIVE FUNCTION SYSTEM

The Delis-Kaplan Executive Function System (D-KEFS) is a comprehensive and validated neuropsychological assessment battery developed to examine different components of executive functioning.(223, 224) It includes a series of tasks targeting abilities such as cognitive control, flexibility, inhibition, and verbal production, and is structured to help distinguish higher-order executive processes from more basic cognitive skills such as processing speed and language abilities.(225)

D-KEFS VERBAL FLUENCY

The Verbal Fluency test is designed to assess different aspects of verbal production and executive control. In the phonemic fluency condition, participants are asked to generate as many unique words as possible beginning with each of three specified letters within a fixed time limit, with proper nouns and numbers excluded. This condition places demands on lexical retrieval, initiation, and self-monitoring. The semantic fluency condition requires word generation within predefined semantic categories; in the present study, only the animal category was used. The outcome variables were the total number of correct responses in the phonemic and semantic fluency conditions.(222)

D-KEFS COLOR WORD INTERFERENCE TEST

The Color–Word Interference Test (CWIT) is a timed task assessing processing speed and executive control across four conditions of increasing difficulty. Condition 1 (Color Naming) and Condition 2

(Word Reading) primarily measure basic processing speed and automatic responding. Condition 3 (Inhibition) introduces response conflict by requiring participants to name the ink color of incongruent color words, thereby assessing inhibitory control. Condition 4 (Inhibition/Switching) further increases task demands by requiring alternation between response rules, providing a measure of cognitive flexibility under conditions of interference. In the present study, completion time for each condition was used as the outcome measure.(226)

WECHSLER ADULT INTELLIGENCE SCALE - FOURTH EDITION (WAIS-IV)

The WAIS-IV is a widely used, individually administered cognitive assessment for adults that examines several key aspects of intellectual functioning. It consists of a set of structured subtests targeting domains such as working memory, processing speed, verbal abilities, and perceptual reasoning, enabling a multidimensional evaluation of cognitive performance.(227-229)

WAIS IV DIGIT SPAN

The Digit Span task involves oral presentation of number sequences of increasing length. Participants first repeat the digits in the same order (Forward span), assessing attention span, and then repeat the digits in reverse order (Backward span), which place greater demands on working memory. A third condition, Sequencing, requires reordering the digits into ascending numerical order assessing mental manipulation; however, this condition was not administered in the present study. Performance was indexed by the maximum number of digits correctly recalled in the Forward and Backward conditions. For patients from the Uppsala cohort, another version of the Digit span (The RBANS - Repeatable Battery for the Assessment of Neuropsychological Status) was used.(230)

WAIS IV CODING

The Coding subtest assesses processing speed, visuomotor coordination, and sustained attention by requiring participants to copy symbols paired with numbers as quickly and accurately as possible according to a key, within a two-minute time limit. The variable used was the number of correctly copied items.

Significant changes in test performance according to RCI were analyzed (see description of the method above). The tests where patients showed the most declines (>20%) were analyzed using regression univariable and multivariable logistic regression models, with reliable cognitive decline coded as a dichotomous outcome (decline yes/no). In addition, analyses were also performed per cognitive domain. Because of the risk of problems with mass significance, only seven predictors were chosen. Predictors were selected per category and presumed relevance. The variables presented in table 6 below were included as predictors.

Table 6. Definitions of demographic, functional, tumor-, and treatment-related variables

Variable	Definition
Age	Age at the pre-operative assessment.
KPS pre-operative	Karnofsky performance status pre-operatively.
Tumor size	Tumor size in milliliters.
1p/19q co-deletion	1p/19q co-deletion defined as the combined loss of chromosomal arms 1p and 19q, a defining molecular feature of oligodendroglioma.
High grade	Grade 2 defined low-grade, and grade 3 and 4 defined high grade.
HADS >8 p preop	A score >8 in either subscale indicative of problematic levels of anxiety and/or depression.
Chemoradiotherapy	Treatment with combined chemotherapy and radiotherapy.

3.5.3 RELIABLE CHANGE INDEX

RCI evaluates whether an observed change in an individual's test score is greater than what can be attributed to practice effects, measurement error or normal fluctuations. The approach incorporates test–retest reliability, baseline performance, and variability derived from a control group assessed at comparable time points. By using control group means and dispersion measures, the method adjusts for systematic gains related to test familiarity and accounts for regression toward the mean. This allows identification of individual changes that are unlikely to reflect chance variation.

The adjusted, regression-based RCI, corresponding to Model 10 described by Maassen, Bossema, and Brand, 2009.(231)

$$AdjRCI_{srb} = \frac{D_i - \overline{D}_C + [1-(S_Y / S_X)](X_i - \overline{X}_C)}{\sqrt{(S_X^2 + S_Y^2)(1-r_{XY})}}$$

- D_i = The average difference in a test variable among patients calculated as the result at 12 months minus the result at 0 months (post - pre)
- $\overline{D}_C$ = The average difference in a test variable among controls (post–pre)
- S_Y = Standard deviation and S_Y^2 the variance of controls at 12 months
- S_X = Standard deviation and S_X^2 the variance of controls at 0 months
- X_i = The individuals test score at 0 months
- $\overline{X}_C$ = The average test score in controls at 0 months
- r_{XY} = The product-moment correlation coefficient for the relationship between the controls' scores at 0 and 12 months

3.5.4 STATISTICAL ANALYSES

Statistical analyses were performed using SPSS (version 28.0). All tests were two-sided and a p-value $<.05$ was considered statistically significant. Demographic, tumor-related, and treatment-related variables were summarized using descriptive statistics. Raw

neuropsychological test scores were transformed into standardized z-scores based on published normative data.

To evaluate within-patient change between baseline and one-year follow-up, paired statistical tests were applied depending on distributional assumptions. Proportions of impairment were compared using Fisher's exact test. Reliable cognitive decline was defined according to the RCI methodology described above.

Univariable and multivariable logistic regression analyses were conducted to examine predictors of reliable cognitive decline. Tests showing declines in more than 20% of patients were entered into regression models. Domain-level analyses were performed using averaged RCI scores within each domain. Predictors were selected based on predefined clinical relevance and limited to seven variables to reduce the risk of overfitting.

3.5.5 HEATMAP VISUALIZATION OF TUMOR LOCATION

To explore spatial patterns of tumor distribution in relation to reliable cognitive decline, preoperative tumor segmentations were transformed to standardized anatomical space. Registered tumor masks were visually inspected to ensure alignment accuracy. For each test showing the highest proportion of reliable decline, tumor masks from patients with and without significant decline were aggregated separately to generate group-wise overlap maps. Color intensity reflected the degree of spatial overlap within each subgroup. Visualization procedures were performed using standard neuroimaging software and custom scripts.

3.6 METHOD FOR STUDY IV

3.6.1 STUDY POPULATION

Patients were included according to the same diagnostic criteria as in study III. However, only patients from the Gothenburg site were included as self-assessments were not available from Uppsala. Patients were included from the longitudinal cohort. For the present study, inclusion required only a single assessment, meaning that participants had completed neuropsychological testing and a quality-of-life questionnaire at least at one of four time points. Additionally, patients diagnosed before the start of the longitudinal study in 2017, with substantially longer follow-up times (up to 21 years) were also invited to participate. This resulted in four partly overlapping groups: pre-operative, three months, one year, and at least five years postoperative. Patient flow and attrition are shown in the figure on the next page. Patients were included between February 2017 and December 2025.

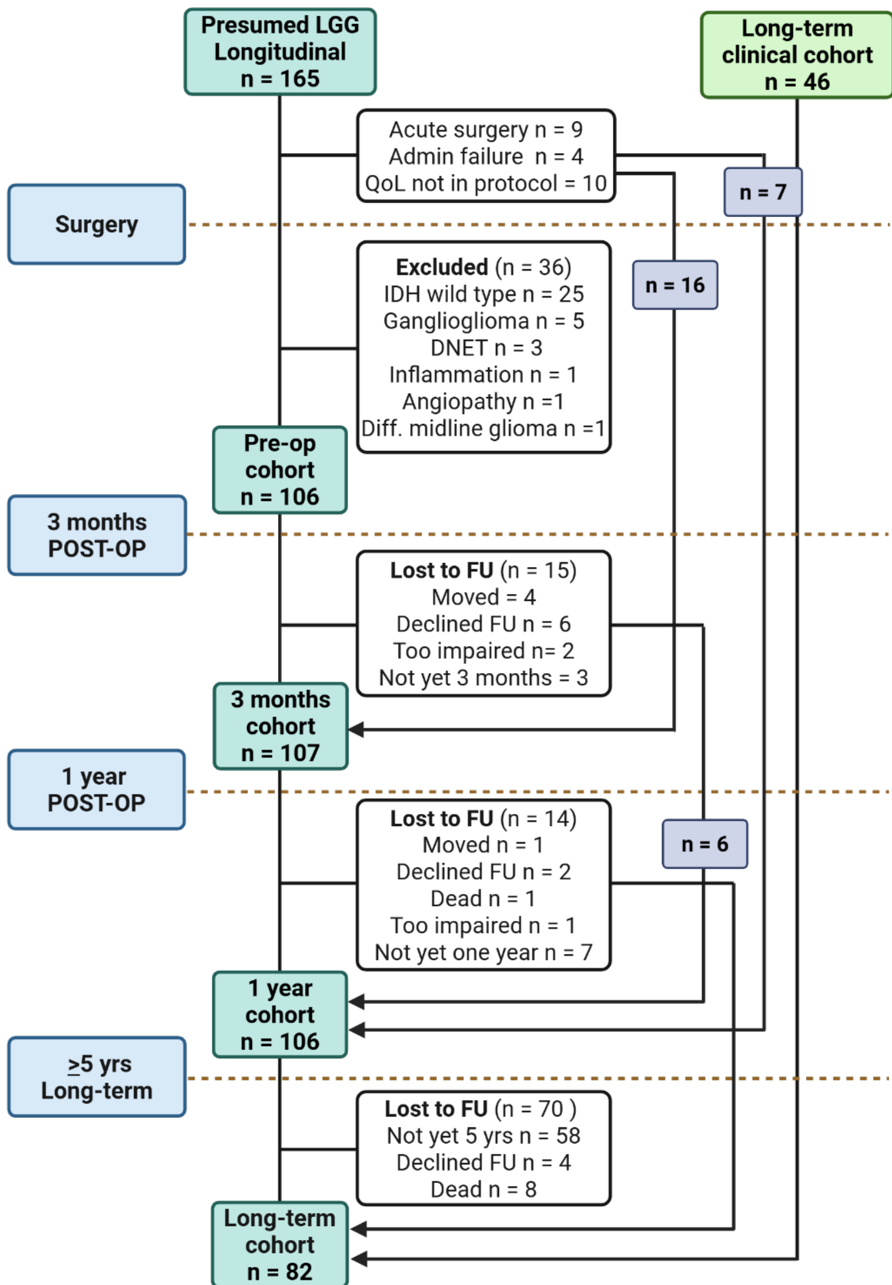

Figure 17. Flow chart of patient inclusion

3.6.2 VARIABLES AND OUTCOMES

3.6.2.1 CLINICAL VARIABLES

Clinical data were assessed as described in study III.

3.6.2.2 NEUROPSYCHOLOGICAL VARIABLES

All neuropsychological assessments were administered in person at each time points by a trained clinical neuropsychologist. The test battery was identical to that described in Study III. As in Study III, raw scores were converted into standardized z-scores using published normative data.

Impairments in neuropsychological test outcomes were defined as performance ≤−1.5 SD relative to the normative mean.(177, 232) At the individual level, domains were classified dichotomously as impaired or not. Impairment was present if either two tests within a domain were ≤−1.5 SD or one test was ≤−2.0 SD below the normative mean, in accordance with the recommendations of the International Cognition and Cancer Task Force (ICCTF).(233)

3.6.2.3 SELF-ASSESSMENTS

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), version 3. Scale scores were calculated and linearly transformed to a 0–100 metric in accordance with the EORTC scoring manual.(234)

The primary outcome was the Global health status/QoL scale (Global HRQoL), based on two items evaluating overall health and overall quality of life during the preceding week, each rated from 1 (very poor) to 7 (excellent). Higher scores indicate higher experienced global HRQoL.(234) Missing data were handled according to the EORTC scoring guidelines.(234) The QLQ-C30 has demonstrated established validity and reliability in oncology populations.(235, 236).

MENTAL FATIGUE ASSESSMENTS

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20), a validated 20-item self-report questionnaire comprising five subscales: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity.(237) Each subscale yields a score based on four items rated on a five-point Likert scale, with higher scores reflecting greater fatigue severity.(237)

A total fatigue score (range 20–100) was derived by summing all 20 items of the MFI-20. This overall score was entered in the regression analyses as an indicator of global fatigue severity. Domain scores were calculated when at least half of the items within a domain were completed; missing responses were replaced using the individual's mean for the remaining items in that domain.

DEPRESSION AND ANXIETY

Symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS), following the same procedures as described in Study III.

3.6.3 STATISTICAL ANALYSES

All statistical analyses were conducted using SPSS (version 28.0). Statistical significance was defined as a two-sided p-value $<.05$. Descriptive statistics were used to summarize demographic and clinical characteristics.

To examine the relationship between cognitive functioning and global HRQoL, separate hierarchical linear regression analyses were performed for each time point, with global HRQoL entered as the dependent variable. Demographic variables were included in the first block, followed by cognitive domains language, learning/memory, executive functioning, attention, visuospatial/perceptual functioning, and speed in the second block. The additional contribution of cognitive variables was evaluated by examining changes in explained variance (ΔR^2), calculated based on unadjusted R^2 values.

Comparisons between patients with and without cognitive impairment were performed using independent group analyses. To assess the influence of patient-reported symptoms, additional regression models were fitted including fatigue and symptoms of anxiety/depression. In order to further explore the impact of fatigue, analyses were repeated in a subgroup defined by higher levels of fatigue. Assumptions for regression modelling were examined prior to analysis.

4 ETHICS

Ethical permits:

- Dnr. 702-16 (main application for Study I and II), T789-17 Covering the use of data on psychotropic drugs, and data from the National Patient Registry and, T180-17 approval for merging data from registries and, all approved by the Regional Ethical Review Committee.

- Dnr. 1067-16 (main application for Study III) and T1068-17 covering the use of healthy controls, and T688-18 covering the inclusion of patients with grade WHO grade 3. T181-17 covering the use of identifiable data. All approved by the Regional Ethical Review Committee.

- Dnr. 2015/210 covering the collection and analysis of neuropsychological and clinical data in patients from Uppsala. Approved by the Regional Ethical Review Committee.

- Dnr. 2022-06310-02 (Study III and IV) for inclusion of all patients with *IDH*-mutation. Approved by the Swedish Ethical Review Authority.

- Dnr. 2021-03313 covering the long-term follow-up of patients (part of Study IV), approved by the Swedish Ethical Review Authority.

For Study I and II informed consent was waived by the ethical committee. In the recruiting process (Study III and IV), all patients are carefully informed about the study and given time to consider their participation. Participation was voluntary and all patients signed a consent form. Withdrawal is possible at any time. Patients are given information on how to contact the PI.

5 RESULTS

5.1 STUDY I

Return to work following diagnosis of low-grade glioma: a nationwide matched cohort study

Result summary
Patients and controls showed similar work (approximately 90 %) until the last months before surgery. One year after surgery, 52% of patients had returned to work (RTW), increasing to 63 % at two years. Negative predictors for RTW were previous sick leave, lower functional level, and adjuvant treatment at one year, and with lower functional level, female sex, comorbidity, and biopsy (no resective surgery) at two years.

5.1.1 VARIABLES AND OUTCOMES

5.1.1.1 TEMPORAL TRENDS IN WORKING RATES

Work participation was comparable between patients and matched controls one year before surgery, with 88% of patients and 91% of controls working. Among controls, employment rates remained stable throughout the entire observation period. In contrast, patients with low-grade glioma demonstrated a distinct preoperative decline in work participation, driven by increasing sick leave. Sick leave among patients became apparent between six and three months prior to surgery, followed by an exponential rise during the final three months. These temporal changes in work participation are illustrated in figure 18.

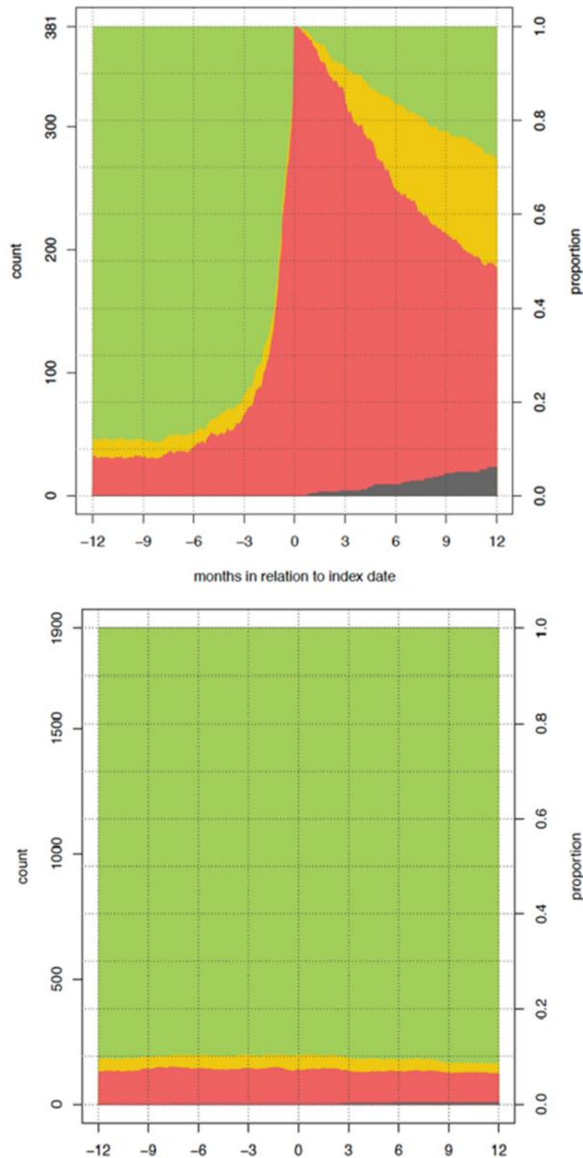

Figure 18. Sick leave compensation in patients (upper) vs. controls (lower) from one year before until one year after primary surgery. ***Green*** *= no compensation,* ***yellow*** *= partial compensation,* ***red*** *= full compensation. The dark gray stack at the bottom represents deceased patients. Reproduced from Rydén et al.,2020,(238) licensed under CC BY 4.0.*

After surgery, patients showed a gradual and incomplete RTW during the first postoperative year. At one year after surgery, 52% of patients had RTW, of whom 28% were working full-time. Work participation also continued to improve during the second year. At two years postoperatively, 63% of patients were working, with 45% working full-time. Despite this improvement, work participation among patients remained considerably lower than that observed in matched controls, who maintained stable working rates throughout the whole two-year period.

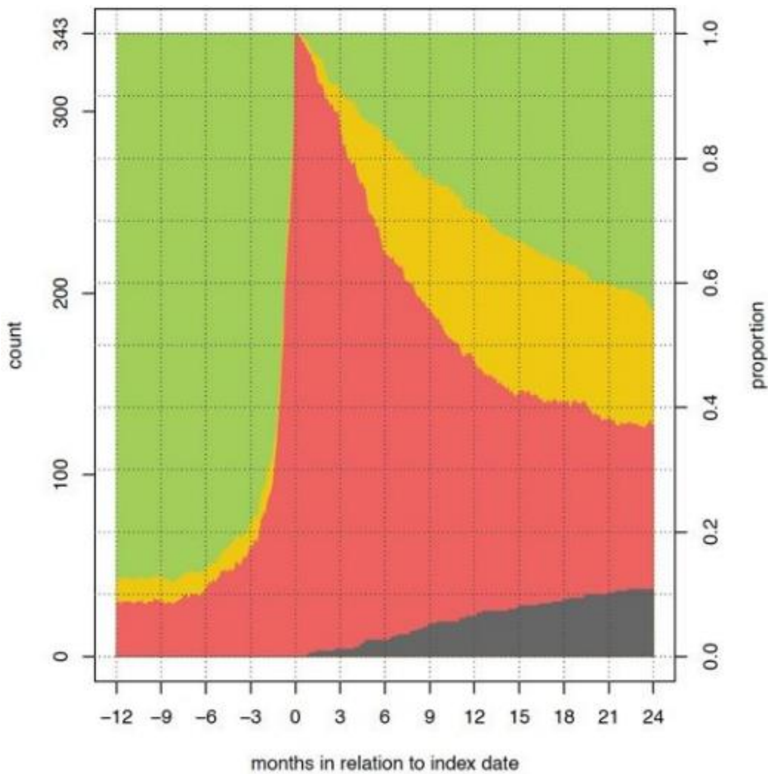

Figure 19. Sick leave compensation in patients vs. controls from one year before until two years after surgery of surgery. ***Green*** *= no compensation,* ***yellow*** *= partial compensation,* ***red*** *= full compensation. The dark gray stack at the bottom represents deceased patients. Reproduced from Rydén et al., 2020, (238)licensed under the CC BY 4.0.*

5.1.1.2 MULTIVARIABLE LOGISTIC REGRESSION

In the multivariable model for RTW at one year postoperatively, previous sick leave, older age, earlier index year, and lower preoperative functional level were independently associated with reduced RTW. In a sensitivity analysis based on forward selection, female sex replaced index year, while the other associations remained unchanged. In a further sensitivity analysis including additional variables (laterality, re-operation, new deficit, type of surgery, chemotherapy, radiotherapy), oncological treatment during the first postoperative year was independently linked to lower RTW.

In the corresponding multivariable model for RTW at two years, lower functional level, female sex, older age, and previous sick leave were independently associated with reduced RTW. In the sensitivity analysis using forward selection, comorbidity replaced age as a significant factor. In the analysis including more variables, biopsy, compared to resective surgery, was also independently associated with lower RTW at two years. Oncological treatment was not significant at this time point.

5.2 STUDY II

Psychotropic and anti-epileptic drug use, before and after surgery, among patients with low-grade glioma: a nationwide matched cohort study.

Result summary
Anti-epileptic drugs (AEDs)
Patients' use of AEDs was 4x increased one year before surgery and stabilized around 60% at one year postoperatively. used AEDs. History of seizures and preoperative use were significant predictors for use at one year.

Sedatives
Sedative use increased sharply around surgery, peaked at 25% and stabilized at 10% at one year (3x more than controls). Many of the patients using sedatives had a history of anxiety or sleep problems. Previous use or related diagnosis were significant predictors

Antidepressants
Similar numbers before surgery but increased postoperatively up to 12% at one year being 2x compared to controls. Previous depression or use of antidepressants, female sex and diagnosis within later years were significant predictors.

5.2.1 VARIABLES AND OUTCOMES

5.2.1.1 ANTI-EPILEPTIC DRUGS

During the year preceding surgery, patients with low-grade glioma had a higher prevalence of anti-epileptic drug (AED) use compared with matched controls. Among patients, AED use increased over the preoperative period, with the most pronounced increase observed during the months immediately preceding surgery. AED use reached its highest level shortly after surgery and remained elevated throughout the first postoperative year, whereas use among controls remained low and stable across the entire observation period. Temporal patterns of AED use in patients and controls are presented in figure 20 below.

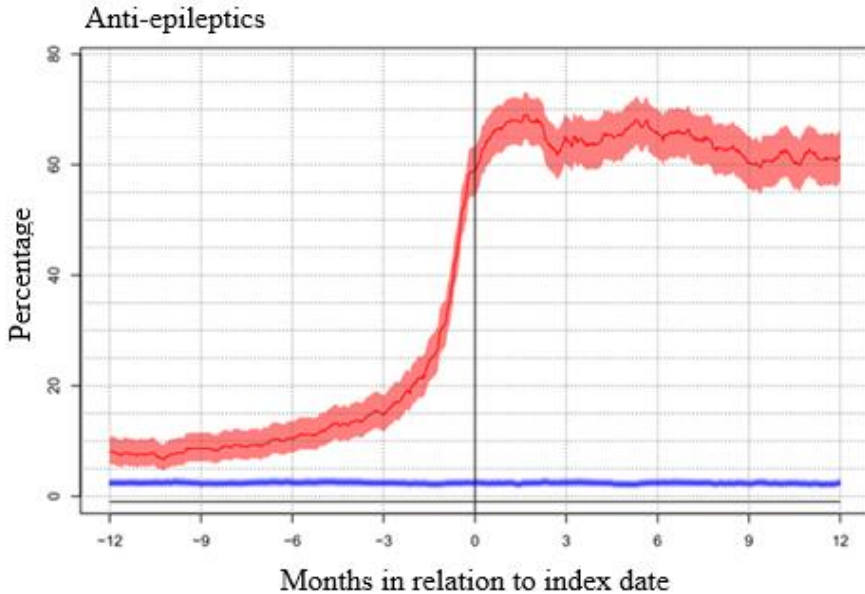

*Figure 20. Proportion of patients with LGG (**red**) (95% CI) versus controls (**blue**) with a use of anti-epileptics from one year before to one year after index date.*

In multivariable logistic regression analyses of AED use one year after surgery, history of seizure and preoperative AED use were independently associated with AED use at one year. No significant associations were observed for age, sex, tumor-related variables, or treatment-related factors in the adjusted model.

5.2.1.2 SEDATIVES

During the year preceding surgery, dispensing of sedatives did not differ significantly between patients and matched controls. In patients, sedative use increased in the period immediately surrounding surgery, with the highest prevalence observed shortly after the index date. Following this perioperative peak, sedative use declined during the subsequent months. At one year after surgery, sedative use among patients remained higher than among controls, whereas dispensing rates in the control group were low and stable throughout the entire observation period. Temporal patterns of sedative use in patients and controls are presented in figure 21 below.

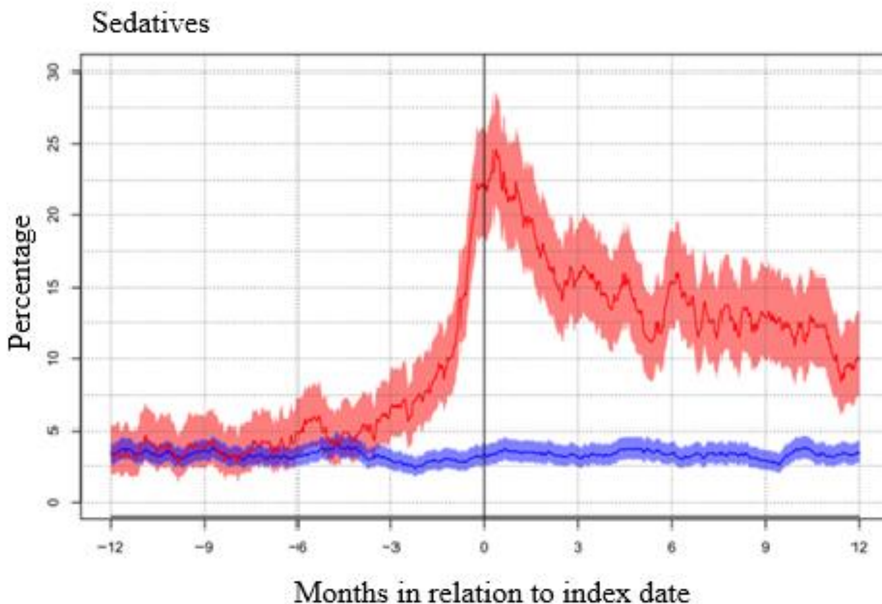

*Figure 21. Proportion of patients with LGG (**red**) (95% CI) versus controls (**blue**) with a use of sedatives from one year before to one year after index date.*

In multivariable logistic regression analyses of sedative use one year after surgery, a history of anxiety and/or sleeping difficulties was independently associated with continued sedative use. No significant associations were observed for age, sex, tumor-related variables, or treatment-related factors in the adjusted model.

5.2.1.3 ANTIDEPRESSANTS

For antidepressants patients did not differ from controls preoperatively. Antidepressant use increased more gradually after surgery and reached a stable level for several months postoperatively. At one year after surgery, patients had higher dispensing rates of all three drug categories compared with controls. The temporal distribution of drug use is shown in figure 22.

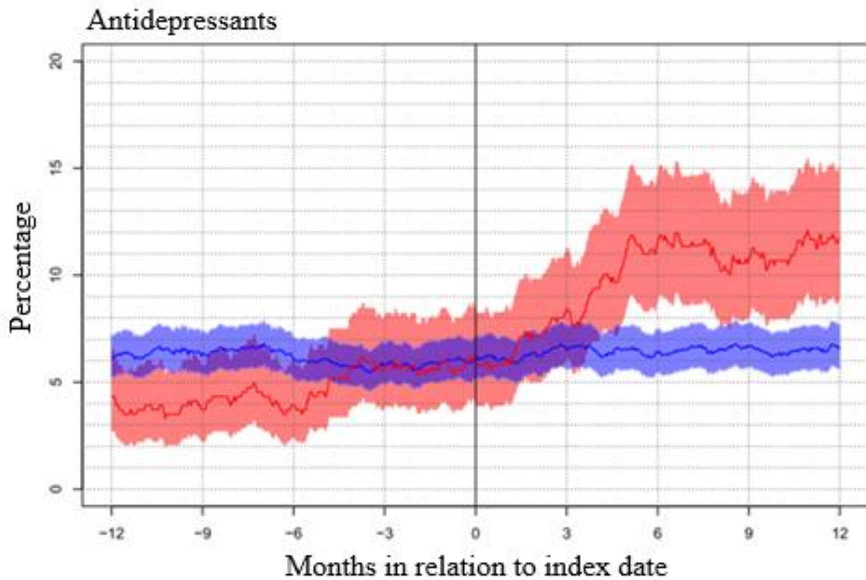

*Figure 22. Proportion of patients with LGG (**red**) (95% CI) versus controls (**blue**) with a use of anti-depressants from one year before to one year after index date.*

In multivariable logistic regression analyses for antidepressant use, a prior history of depression emerged as the most robust predictor of postoperative treatment. Female sex and later index year were also independently associated with a higher likelihood of antidepressant use.

5.3 STUDY III

Reliable cognitive changes the first year following guideline-based treatment of IDH mutated gliomas: a longitudinal multicenter study.

Result summary
Reliable cognitive decline one year after surgery was observed in 14–24 % of patients, depending on cognitive domain. Declines were most common in executive functioning, learning/memory, and language. Older age and chemoradiotherapy were the main predictors of decline.

5.3.1 CHANGES ACCORDING TO RELIABLE CHANGE INDICES

RCI:s were calculated to account for measurement error and practice effects. The proportions of patients showing reliable decline, unchanged performance, or improvement for each individual test are presented in figure 23.

The proportion of reliable decline varied across tests. The highest decline rate was observed for CWIT 4 (32.4%). Decline rates above 20% were also seen for CWIT 1, RAVLT learning, RAVLT delayed recall, BNT, Phonemic Fluency, and TMT B. Small proportions of decline were observed for Digit Span forward, Digit Span backward, and TMT A. Improvements were present in a minority of patients across tests and were generally less frequent than declines. The highest proportions of improvement were observed for TMT B and Digit Symbol Coding.

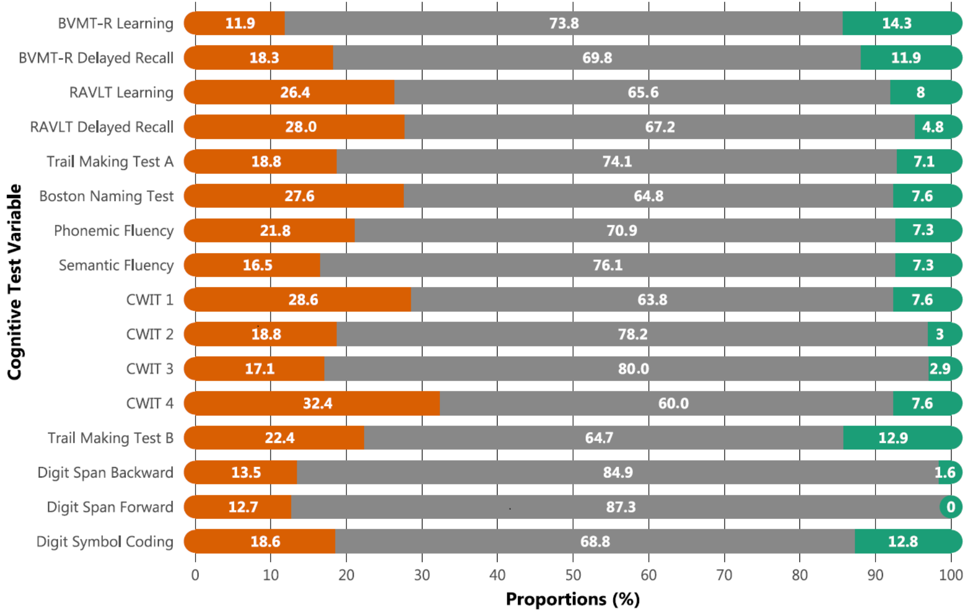

Figure 23. Proportion of patients showing reliably changed results in each test variable based on Reliable Change Indices (RCI). Adapted from Rydén et al. 2025.(239) Abbreviations: BVMTR = Brief Visuospatial Memory Test – Revised; CWIT = Color Word Interference Test; RAVLT = Rey Auditory Verbal Learning Test.

Table 7. Logistic regression models for identifying predictors for cognitive decline according to reliable change indices (significant predictors shown only).

Covariate	Univariable OR (95% CI)	*p*-value	Multivariable, OR (95% CI)	*p*-value
Rey Auditory Verbal Learning Test, delayed recall				
Age	1.04 (1.00 – 1.08)	0.049*	1.05 (1.00 – 1.09)	0.045*
Color Word Interference Test 1				
Age	1.04 (1.00 – 1.08)	0.043*	1.04 (1.00 – 1.09)	0.033*
High grade	2.65 (1.14 – 6.14)	0.023*	2.71 (0.70 – 7-55)	0.057
Chemoradiotherapy	3.97 (1.08 – 14.6)	0.038*	6.05 (1.32 – 27.80)	0.021*
Color Word Interference Test 4				
Age	1.06 (1.02 – 1.10)	0.003*	1.08 (1.03 – 1.13)	0.002*
KPS pre-operative	0.95 (0.91 – 1.00)	0.040*	0.99 (0.93 – 1.05)	0.632
High grade	2.59 (1.12 – 5.97)	0.025*	2.64 (0.98 – 7.13)	0.056
Chemoradiotherapy	4.58 (1.25 – 16.81)	0.022*	5.60 (1.16 – 26.99)	0.032*

* = $p<.05$

5.3.2 LOCATION HEATMAPS

In the heatmaps illustrating tumor distribution for patients with and without reliable cognitive decline showed lateralized patterns for the tests with the highest decline rates. For the test demonstrating the greatest proportion of decline, tumor overlap was predominantly left-sided among patients with cognitive deterioration. In contrast, patients without reliable decline more frequently exhibited tumor distribution in the contralateral hemisphere. Similar lateralized tendencies were observed in the corresponding domain-level heatmaps although spatial patterns varied between cognitive domains. Domain-level heatmaps are presented in figure 24.

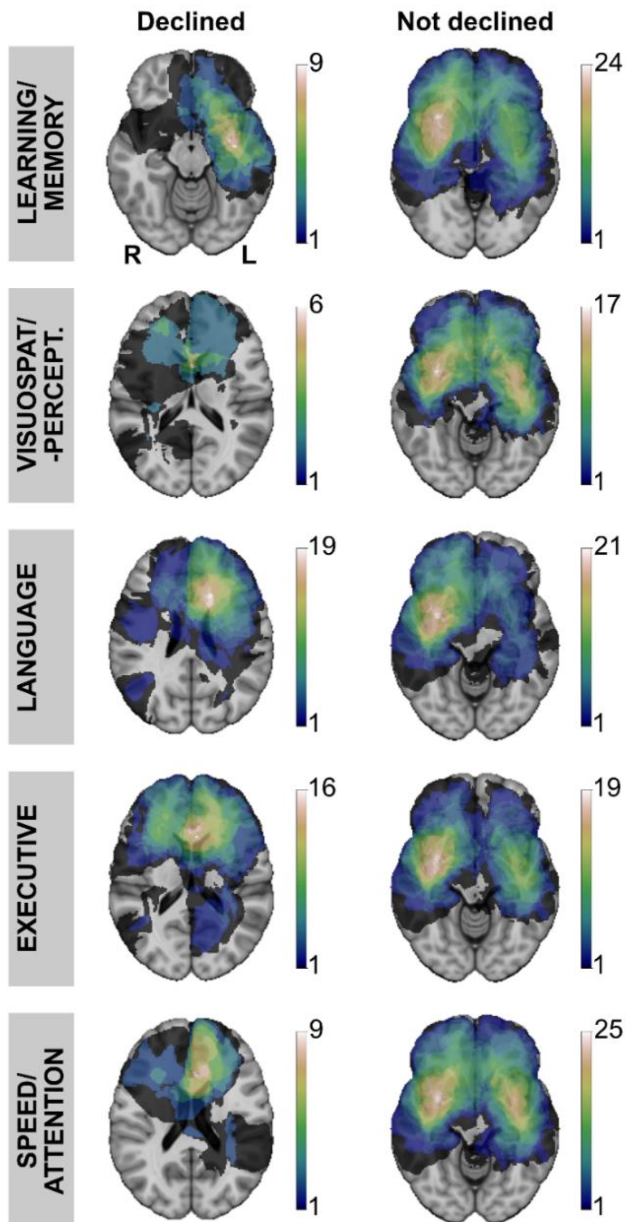

Figure 24. Domain-specific heatmaps illustrating tumor distribution in patients with versus without significant cognitive decline.

5.4 STUDY IV

Contribution of cognitive function and fatigue to health-related quality of life in patients with IDH-mutant gliomas – from diagnosis to long-term follow-up

Result summary
Cognitive domains were differentially associated with HRQoL across time points. Preoperatively, learning and memory were most closely related to global HRQoL. At one year, language and executive functioning were the domains most clearly linked to HRQoL. In the long-term cohort, executive functioning showed the most consistent relationship with global HRQoL, explaining a substantial proportion of variance beyond age and sex. Fatigue was consistently closely related to global HRQoL across time points.

5.4.1 COGNITION IN RELATION TO GLOBAL HRQOL

Hierarchical regression analyses were conducted separately at each assessment time point. Preoperatively, demographic variables did not significantly explain variance in global HRQoL. When cognitive domains were added, the model improved significantly (p<.001) with learning and being the only domain significantly associated with global HRQoL (p<.001). The speed domain was not included due to insufficient cases. Cognitive analyses were not conducted at the three-month follow-up, as several domains had insufficient data; two were not assessed due to the shorter test protocol, and others did not meet regression assumption.

At one year postoperatively, age (p<.05) was significantly associated with global HRQoL, although demographic variables accounted for only a small proportion of variance. Adding cognitive domains further improved the model (p<.01). Language (p<.05) and executive functioning (p<.01) were the domains most clearly related to HRQoL. As in the preoperative model, the speed domain did not meet inclusion criteria.

In the long-term cohort, age ($p<.01$) was again a significant predictor. The addition of cognitive domains resulted in a clear improvement of the model ($p<.001$) and executive functioning ($p<.001$) was the only domain consistently related to global HRQoL. Cognitive domain analyses were not performed at the three-month follow-up due to insufficient data and unmet regression assumptions.

5.4.1.1 ANY PRESENT COGNITIVE IMPAIRMENT

Group comparisons using the dichotomous variable representing the presence of at least one impaired cognitive domain showed consistent differences in global HRQoL. Patients meeting this criterion had lower global HRQoL at baseline ($p=.002$), one year ($p=.002$), and long-term follow-up ($p<.001$).

5.4.2 FATIGUE AND SYMPTOMS OF ANXIETY AND DEPRESSION

Sensitivity analyses were conducted to examine the contribution of patient-reported fatigue and symptoms of anxiety and depression. After adding fatigue (MFI total score) and HADS to models after including demographic variables, the explained variance increased markedly across time points, with additional explained variance ranging from 0.49–0.67, all $p<.001$. Fatigue was consistently strongly associated with global HRQoL, whereas symptoms of anxiety and depression showed weaker and less consistent relations.

Following adjustment for fatigue and anxiety/depression, cognitive domains were not significantly related to global HRQoL at the preoperative or one-year assessments. However, in the long-term cohort, executive dysfunction remained significantly associated with global HRQoL.

Further analyses restricted to patients with higher fatigue burden, based on a median split of the total fatigue score, showed a similar pattern of results. At the preoperative assessment, learning and memory remained significantly associated with global HRQoL, and language additionally emerged as a significant predictor in this subgroup. At one year and at

long-term follow-up, executive dysfunction was the only cognitive domain that remained independently associated with global HRQoL. Overall, stratification by fatigue did not substantially change the pattern of associations.

6 DISCUSSION

As survival has improved in patients with LrGG, the focus on functional outcomes has increased. Traditional endpoints such as survival remain central, but they do not fully reflect how patients manage in everyday life. Patients are often diagnosed at a stage of life characterized by high demands from work and family life, and many patients are long-term survivors. This makes issues such as RTW, cognitive functioning, fatigue, and QoL highly relevant. These are also common concerns in clinical practice, for both patients and clinicians.

This thesis contributes by examining different aspects of functioning, health, and QoL. In sum, although not without limitations, the approaches used here provide complementary insight into functional outcomes that are not captured by traditional endpoints. Given the limited number of patients at individual centers, further work in this area will likely require larger collaborative efforts, both nationally and internationally, to improve understanding of patient functioning in LrGG.

6.1 CLINICAL CONTEXT

Current management of LrGG typically involves a combination of surgery, radiotherapy, and chemotherapy. Treatment strategies are based on clinical guidelines but also involve individual decisions regarding timing and suitability of treatment for the patient. With more knowledge, it becomes possible to better tailor both treatment and patient support to the individual.

Questions related to work are common in clinical consultations. As shown in this thesis, work participation is influenced by several factors. Knowledge of these may support more informed expectations regarding RTW and has already also been used as a basis for discussions with patients about likely outcomes in our clinical practice.

Patients commonly develop epilepsy, and may experience anxiety and depression, which can require medical treatment. Medication use may reflect aspects of symptom burden, although it does not fully capture

patients' experiences. Also, cognitive functioning is relevant for many aspects of everyday functioning. Even mild impairments may affect the ability to manage complex tasks, particularly in cognitively demanding situations. Overall, the management of LrGG includes not only tumor-directed treatment, but also consideration of its effects on function and daily life where this thesis has contributed with new data.

6.2 WORK PARTICIPATION (STUDY I)

The findings in this study show that sick leave begins close to the time of imaging diagnosis. Prior to this period, patients and controls showed similar proportions of individuals working, indicating that symptoms were not yet sufficiently pronounced to lead to absence from work.

After surgery, work participation increased gradually, but many patients had still not RTW at one and two years of follow-up. A large proportion of patients were unable to work during oncological treatment, which is expected, but many had also not RTW after this treatment had been completed, when RTW might otherwise be anticipated. In other patients, such as those with breast cancer, a similar pattern of absence during treatment is seen, but RTW is generally higher, with more than 80% of patients returning within the first 12–18 months according to a larger study.(240) For patients treated with stem cell transplantation for hematological malignancies, RTW has been shown to be more prolonged, with around 50–70% returning within the first year.(241)

When compared with other conditions affecting the brain, RTW also appears to be delayed, similar to what is observed in our patients. In stroke, a study showed that 49% RTW at one year and 60% at two years, which is comparable to our findings of 52% at one year and 63% at two years.(242) In traumatic brain injury, RTW also appears to be delayed and varies over time depending on injury severity and follow-up period.(243) One possible explanation is that treatment-related effects may contribute to a longer recovery period, particularly as treatments affecting the brain can lead to cognitive difficulties, fatigue, and other neurological symptoms that influence the ability to meet the demands of work. Longer follow-up is necessary to understand how factors such as treatment influence RTW over time.

In our study, several factors were associated with a lower chance of RTW, including older age, poorer functional status, and previous sick leave. Similar factors have been reported in other conditions, where female sex, higher age, and lower physical function have been linked to reduced RTW.(241-243) Previous sick leave has also been identified as a relevant factor in patients with stroke, where prior absence was associated with lower RTW.(244) RTW is influenced by societal and structural factors, including the extent to which sick leave is socially accepted and economically supported. In welfare systems like the one in Sweden, with more generous compensation and stronger social acceptance of sickness absence, remaining on sick leave may be more feasible, which should be considered when interpreting RTW outcomes across different contexts.

6.3 MEDICATION USE AS A PROXY FOR SYMPTOMS (STUDY II)

In our registry-based study on patients with grade 2 glioma, use of medication was used as an indirect indicator of symptoms such as epilepsy, depression, and anxiety that required treatment. The observed changes in medication use around the time of diagnosis and treatment reflect how different symptoms present during the disease course.

Use of AEDs, now often referred to as anti-seizure medications, and sedatives increased around the time of diagnosis, while antidepressant use remained similar to controls at index and increased later during follow-up. This pattern suggests that seizure-related symptoms and acute psychological distress are more prominent around diagnosis, whereas depressive symptoms may become more apparent later in the disease course.

The sustained use of AED over time is expected, as seizure prevention is a central aspect of clinical management in patients with glioma. Even after tumor resection, there remains a risk of seizures, and treatment is therefore often continued. This approach may also be influenced by practical considerations, such as driving regulations requiring a

prolonged period of seizure freedom, which may affect both clinical decisions and patient preferences.

Medication does not necessarily reflect whether a patient has depression or not but indicates a need for treatment and thus indirectly suggests the presence of clinically relevant symptoms. It is also possible that medication-based measures underestimate the true prevalence of depressive symptoms, since not all receive treatment.

Use of antidepressants was similar to controls at index date (approximately 6%). In Study III, we also saw that 15% of patients scored above cut-off for depression. This proportion are in line with those presented in a prospective study in an early disease phase including patients with both low- and high-grade gliomas, where approximately 13–14% were diagnosed with MDD based on structured clinical interviews.(99) However, in that study, only a minority of patients used antidepressants, indicating that not all patients with clinically relevant depression are treated pharmacologically. We also found that the increase in use of antidepressant increased months after surgery, suggesting a delay between symptom onset and initiation of treatment. In clinical practice, antidepressants are associated with improvements in both depressive and anxiety symptoms but are typically used long term and prescribed when symptoms are long-lived. We founds that sedative use increased around the index date to about 25% followed by a rapid decline, consistent their short-term indication and number of patients with high anxiety scores close to the index date (27% in study III). About the time when sedative declined was also about the time when use of antidepressants increased.

In our study, previous use of medication and related diagnoses were the strongest predictors of continued use across all drug categories. For AEDs, a history of seizures or epilepsy was the main predictor, although most patients were new users reflecting the onset of tumor-related epilepsy requiring treatment. For antidepressants and sedatives, prior psychiatric symptoms or medication use were most strongly associated with subsequent treatment. Women were more likely to use antidepressants than men, which was also observed for controls.(245) These findings suggest that medication use largely reflects ongoing or

pre-existing symptom burden rather than being driven solely by tumor-related factors.

6.4 COGNITIVE OUTCOMES (STUDIES III–IV)

The study on changes in cognitive functioning during the first postoperative year provides insight into different factors affecting specific cognitive domains. Preoperative cognitive performance is typically related to postoperative functioning and may reflect differences in cognitive reserve, defined as the ability to maintain function despite disease- and treatment-related burden. This highlights the value of baseline assessment, both for describing initial status, and for understanding changes over time.

During the first postoperative year, reliable declines were most prominent in executive functions, as well as memory and language domains. Given the results from Study IV, memory and language impairments appeared to be particularly relevant for Global HRQoL in earlier phases. These types of difficulties are more easily noticeable to both the patient and others. Executive functioning on the other hand did not seem to affect Global HRQoL in the early phase, but as demands become more prominent over time when patients attempt to resume more complex activities such as work, these functions seem more important. Executive functions are involved in planning, flexibility, multitasking, and the ability to manage complex everyday demands. These functions can possibly be central for being able to successfully work, live an independent life, and participate in social activities. They may also be less noticeable and therefore not always easy for employers or family members to understand and adjust to compared to more apparent ones such as memory or language difficulties. In line with this, our results from Study IV showed that executive function was both the most frequently affected domain and the one showing the strongest association with Global HRQoL, both at one year and in the long-term cohort.

At the group level, only one test showed a significant change between pre- and postoperative assessments, indicating limited average differences over time. In contrast, when examining the proportion of

patients classified as impaired, a clearer increase in deficits was observed across multiple tests postoperatively. This suggests that group-level comparisons, which reflect average change, may mask clinically relevant deterioration in subgroups of patients, as improvements in some individuals may offset decline in others.

The use of RCI further enabled identification of within-individual changes while accounting for practice effects. This allowed detection of declines even within the normal range, including in tests with substantial practice effects, such as certain verbal measures, where improvement from repeated testing might otherwise conceal deterioration. Some patients may experience measurable decline while remaining within the normal range, whereas others with smaller numerical changes may experience significant functional limitations due to high cognitive demands in daily life.

At the same time, these findings should be interpreted with caution. Although RCI captures statistically reliable change, it does not necessarily imply clinical significance, and the functional impact depends on individual circumstances such as occupational demands and available compensatory strategies. Moreover, practice effects may differ between groups; while healthy individuals typically show learning effects over repeated testing, patients may exhibit attenuated gains due to underlying impairments, which could in turn influence the magnitude and interpretation of observed change.

6.5 ONCO-FUNCTIONAL BALANCE

Treatment of LrGG involves balancing oncological control against preservation of neurological and cognitive function. Multimodal treatment may improve tumor control and prolong survival but may also be associated with measurable cognitive changes and functional consequences.

In Study III, chemoradiotherapy was associated with an increased risk of cognitive decline in selected domains. Older age also emerged as a predictor. Although causality cannot be established, these findings are in line with concerns about adverse treatment-related effects on

cognition. At the same time, these associations should be interpreted with caution, as patients with more aggressive tumors also receive more aggressive treatment approach, reflecting confounding by indication.

The variability in cognitive outcomes is complicated. Patients with seemingly similar characteristics and treatments may experience different trajectories, suggesting that individual factors influence how treatment and disease burden translate into functional outcome. Cognitive outcome may be understood as a balance between cumulative burden and individual capacity. When this capacity is maintained, function may be preserved; when exceeded, cognitive decline may occur. This may help explain why outcomes are difficult to predict based on clinical factors alone.

Potentially, decisions regarding timing of treatment may also be guided by individual factors, including cognitive decline after surgery. In patients with relatively good prognosis, delaying further treatment may preserve function but could mean a risk of tumor progression, whereas earlier or more intensive treatment may improve disease control at the potential expense of irreversible cognitive symptoms. The optimal balance likely varies between patients and depends on tumor biology and individual vulnerability.

Fatigue also appears to be a major and clinically relevant problem in this patient group, and its development may be difficult to predict. Even when objective cognitive decline is modest, fatigue may substantially affect everyday functioning and perceived QoL. Given its strong association with global HRQoL, fatigue represents an additional factor to consider in the balance between treatment and functional outcome, as it may significantly influence patients’ ability to manage daily activities.

7 FUTURE PERSPECTIVES

This thesis provides insight into the functional consequences of current multimodal standard treatment for LrGG. As survival improves and treatment strategies evolve, it is increasingly important to understand not only how long patients live, but also how they live with the disease. The findings of this thesis show that treatment can affect work participation, medication related to mental health and epilepsy, cognitive functioning, and QoL. These findings support the continued inclusion of functional outcomes alongside traditional outcomes such as PFS and OS.

With the introduction of new treatments, such as *IDH* inhibitors and other targeted therapies, the functional consequences of treatment will need careful evaluation. As these treatments are introduced into clinical practice, they may also alter the functional risk profile of LrGG, for example by delaying or modifying exposure to radiotherapy or by introducing new patterns of treatment-related effects. Future studies should examine patient functioning and well-being over time, and how these outcomes relate to different treatment strategies, both during and after treatment. Our results on cognitive functioning prior to the introduction of *IDH* inhibitors may provide a basis for comparison when evaluating the impact of newer treatments on cognition.

The results of this thesis underline the need for continued longitudinal research in LrGG. We observed that following changes over time from each patient's baseline may provide different insights compared with cross-sectional assessments that only examine the proportion of patients with abnormal test results at a single time point. As patients with LrGG live longer, long-term follow-up has become increasingly important. Research has advanced our understanding of the consequences of treatment in both the short and long term, but the subject remains complex and long-term outcomes remain insufficiently understood. A recommended approach would be to follow patients over longer periods of time to better distinguish temporary treatment effects from more persistent changes in cognition and HRQoL. Our aim is therefore to continue following patients and controls in our longitudinal cohort in order to better understand long-term trajectories and the relationship

between treatment, symptoms, and functional outcomes. Improved tools for predicting both oncological and functional outcomes may help identify patients at higher risk of cognitive decline, reduced work participation, or reduced QoL, allowing earlier and more individualized support.

Following patients over time is important, but the ultimate goal is to improve patients’ everyday lives and well-being. An important area for future research, and perhaps even more for clinical implementation, is improved rehabilitation. This includes both increasing access to rehabilitation and ensuring that patients receive the most appropriate type of support.

Many patients experience fatigue, cognitive difficulties, or problems with RTW after treatment. Rehabilitation strategies should therefore be individualized and focused on the most common challenges experienced by patients and should be available throughout the disease trajectory. Future intervention studies could focus on cognitive rehabilitation, fatigue management, psychological support, and work-directed interventions to determine which approaches are most effective and for which patients. Early identification of vulnerable patients may allow preventive support rather than reactive management.

Since LrGGs are rare tumors, the number of patients at each center is limited. Increased collaboration between centers, both within Sweden and internationally, will therefore be important to increase sample sizes and improve the comparability and generalizability of studies in this field. Further standardization of cognitive tests and outcome definitions may facilitate comparisons across studies, while still allowing flexibility to account for tumor location and individual variability in recovery. Integration of molecular data with functional outcomes may also help identify patient groups at higher risk of cognitive decline or reduced work participation.

8 ACKNOWLEDGEMENT

First and foremost, I wish to thank my main supervisor, **Asgeir Store Jakola** who has an exceptional ability to navigate new and complex topics. Thank you for your generosity, support and brilliant guidance throughout the years. You are a true inspiration and a great co-worker.

To my co-supervisor **Per Hellström,** for your genuine kindness and belief in me. You inspired me both to become a neuropsychologist and to take the leap into doctoral studies, and I'm sincerely thankful for that. Thank you for all our in-depth discussions, your help, and your friendship – even if I'll never forgive you for moving away from us.

To my co-supervisor, **Anja Smits,** thank you for always encouraging me at every step of this journey. I truly appreciate all our conversations and your valuable input. Thank you for always making time for discussion whether it was about science, patients, or books.

To my co-supervisor, **Katarina Stibrant Sunnerhagen**, thank you for how inclusive and welcoming you were from the very beginning of this journey, and for giving me valuable input. Your strong advocacy for rehabilitation has been an inspiration.

I would also like to extend my sincere thanks to the **Sahlgrenska Academy** at **University of Gothenburg**, the **Department of Clinical Neuroscience** at the **Institute of Neuroscience and Physiology**.

To all members of the **Brain Tumor Research Group**. In particular, I want to acknowledge **Anna Dénes**, **Louise Carstam, Alice Neimantaite, Anneli Ozanne, Tomás Gomez Vecchio,** and **Erik Thurin,** for great collaboration, helpful advice, and for always making me feel welcome at the office. To all students helping out during the years, with special thanks to: **Lotta Weyhenmeyer, Dima Harba,** and **Andrew Lycett.**

To my current and former colleagues at the **Neurology Department,** thank you for your care about both patients and neuropsychologists, and for sharing your knowledge. A special thanks the neuropsychologists

Magnus Segerström, Sofia Ljunggren, Annika Renck Ljunggren, Nora Balogh and **Sanna Pääaho,** thank you for your special humor, support, and understanding. To the great psychologists and neuropsychologists **Fredrik Juhlin, Josefine Mellqvist, Timothy Hadarsson Bodin**, **Linn Weick** and **Kajsa Asklöf**. And to my newer colleagues, **Anders Hellenäs-Silano** and **Jenny Lisshammar**, whom I look forward to future collaboration.

To the head of our department, **Urban Wåhlander**, thank you for your trust and for enabling me to engage in research alongside my clinical duties.

To my colleagues and friends in the clinical **brain tumor team**. You all understand what it is like working with these patients and you are amazing at providing the help they need. Special thanks to our contact nurses **Alicia Hellgren, Cecilia Skoglund** and **Christina Charling**. Thank you for sharing your warmth, humor and knowledge.

I would also like to express my sincere gratitude to **my friends** for their support and encouragement throughout this journey. Special thanks to **Sofie Ahlin**, you are the strongest and most amazing friend of all times. To **Johanna Eriksson** for your ways of providing perspective and true friendship. To **Sanna Pääaho** (again) it is amazing to have such a great friend and co-worker. You and me, Judy Hopps – through chats, laughs, and moments of clarity.

To the most important people in my life, my children, **Evert** and **Edvard**, who fill my life with meaning, perspective and love. Thank you for helping me appreciate what truly matters. To my favorite teen, **Alva** - thank you for all the love, laughter, and conversations we've shared. I love you all so much!

To my beloved father, **Ingvar Rydén**, you are a rock. Your loyalty and constant willingness to help, whether it be with childcare or a comforting hug or giving advice, have always been a source of strength for me. Your steady presence and unwavering support mean the world.

To my brothers, **Henric Rydén** and **Fredrik Rydén**, I feel like you

understand my way of thinking better than anyone. Henric, my twin doctor, you are my best supporter and friend. Fredrik, even though we live far apart, you are always in my heart.

To **Katarina Andersson** for being the teacher I needed and encouraging me to try to reach higher.

I want to express my sincere gratitude to all patients and controls for taking their time to participate in the studies. And for the funding supporting my research: **ALF**, **Amlövs stiftelse, Insamlingsstiftelsen för neurologisk forskning, Anna-Lisa och Bror Björnssons stiftelse.**

9 USE OF GENERATIVE AI

ChatGPT (version 5.2, OpenAI) was used to assist with language editing in this thesis. All generated text was reviewed and modified where required to ensure accuracy and consistency

10 REFERENCES

1. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol. 2019;21(Suppl 5):v1-v100.
2. Lassman AB, Hoang-Xuan K, Polley MC, Brandes AA, Cairncross JG, Kros JM, et al. Joint Final Report of EORTC 26951 and RTOG 9402: Phase III Trials With Procarbazine, Lomustine, and Vincristine Chemotherapy for Anaplastic Oligodendroglial Tumors. J Clin Oncol. 2022;40(23):2539-45.
3. Bauchet L, Rigau V, Mathon B, Darlix A. Epidemiological analysis of adult-type diffuse lower-grade gliomas and incidence and prevalence estimates of diffuse IDH-mutant gliomas in France. Neurochirurgie. 2025;71(3):101627.
4. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, et al. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the the Danish Neuro-Oncology Registry. J Neurooncol. 2017;135(3):571-9.
5. Weidl D, Capper D, Onken J, Liu I, Glaser D, Orben F, et al. Epidemiology of WHO grade 2 and grade 3 gliomas from 2009 to 2021 in Germany. J Neurooncol. 2025;174(2):391-400.
6. Miller KD, Ostrom QT, Kruchko C, Patil N, Tihan T, Cioffi G, et al. Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin. 2021;71(5):381-406.
7. Socialstyrelsen. Statistik för cancer: Socialstyrelsen; 2025 [Available from: https://sdb.socialstyrelsen.se/if_can/val.aspx.
8. Colopi A, Fuda S, Santi S, Onorato A, Cesarini V, Salvati M, et al. Impact of age and gender on glioblastoma onset, progression, and management. Mech Ageing Dev. 2023;211:111801.
9. samverkan Rci. Nationellt vårdprogram tumörer i hjärna, ryggmärg och dess hinnor. Stockholm; 2025.
10. Jovanovich N, Habib A, Chilukuri A, Hameed NUF, Deng H, Shanahan R, et al. Sex-specific molecular differences in glioblastoma: assessing the clinical significance of genetic variants. Front Oncol. 2023;13:1340386.
11. Schaff LR, Mellinghoff IK. Glioblastoma and Other Primary Brain Malignancies in Adults: A Review. Jama. 2023;329(7):574-87.
12. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma

multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001;95(2):190-8.
13. Miller JJ, Gonzalez Castro LN, McBrayer S, Weller M, Cloughesy T, Portnow J, et al. Isocitrate dehydrogenase (IDH) mutant gliomas: A Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. Neuro Oncol. 2023;25(1):4-25.
14. Iorgulescu JB, Sun C, Neff C, Cioffi G, Gutierrez C, Kruchko C, et al. Molecular biomarker-defined brain tumors: Epidemiology, validity, and completeness in the United States. Neuro Oncol. 2022;24(11):1989-2000.
15. Mandonnet E, Delattre JY, Tanguy ML, Swanson KR, Carpentier AF, Duffau H, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol. 2003;53(4):524-8.
16. Ohgaki H, Kleihues P. Epidemiology and etiology of gliomas. Acta Neuropathol. 2005;109(1):93-108.
17. Duffau H. Diffuse low-grade gliomas and neuroplasticity. Diagn Interv Imaging. 2014;95(10):945-55.
18. Rudà R, Bello L, Duffau H, Soffietti R. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro Oncol. 2012;14 Suppl 4(Suppl 4):iv55-64.
19. Carstam L, Rydén I, Jakola AS. Seizures in patients with IDH-mutated lower grade gliomas. J Neurooncol. 2022;160(2):403-11.
20. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51.
21. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-20.
22. Venkatesh H, Monje M. Neuronal Activity in Ontogeny and Oncology. Trends Cancer. 2017;3(2):89-112.
23. Carstam L, Corell A, Smits A, Dénes A, Barchéus H, Modin K, et al. WHO Grade Loses Its Prognostic Value in Molecularly Defined Diffuse Lower-Grade Gliomas. Front Oncol. 2021;11:803975.
24. van den Bent MJ, Geurts M, French PJ, Smits M, Capper D, Bromberg JEC, et al. Primary brain tumours in adults. Lancet. 2023;402(10412):1564-79.
25. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765-73.
26. Milano MT, Chan MD, Minniti G, Hattangadi-Gluth JA, Redmond KJ, Soltys SG. The IMPACT of Molecular Grading of Gliomas on

Contemporary Clinical Practice. Int J Radiat Oncol Biol Phys. 2020;107(5):859-62.
27. Mair MJ, Geurts M, van den Bent MJ, Berghoff AS. A basic review on systemic treatment options in WHO grade II-III gliomas. Cancer Treat Rev. 2021;92:102124.
28. Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR, Cooper LA, et al. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med. 2015;372(26):2481-98.
29. Modrek AS, Golub D, Khan T, Bready D, Prado J, Bowman C, et al. Low-Grade Astrocytoma Mutations in IDH1, P53, and ATRX Cooperate to Block Differentiation of Human Neural Stem Cells via Repression of SOX2. Cell Rep. 2017;21(5):1267-80.
30. Carstam L. On the Surgical Management of Diffuse Low-Grade Gliomas in Adults. Göteborg: University of Gothenburg; 2023.
31. Lauterbur PC. Image formation by induced local interactions. Examples employing nuclear magnetic resonance. 1973. Clin Orthop Relat Res. 1989(244):3-6.
32. Smits M, van den Bent MJ. Imaging Correlates of Adult Glioma Genotypes. Radiology. 2017;284(2):316-31.
33. Pallud J, Capelle L, Taillandier L, Fontaine D, Mandonnet E, Guillevin R, et al. Prognostic significance of imaging contrast enhancement for WHO grade II gliomas. Neuro Oncol. 2009;11(2):176-82.
34. Corell A, Ferreyra Vega S, Hoefling N, Carstam L, Smits A, Olsson Bontell T, et al. The clinical significance of the T2-FLAIR mismatch sign in grade II and III gliomas: a population-based study. BMC Cancer. 2020;20(1):450.
35. Patel SH, Poisson LM, Brat DJ, Zhou Y, Cooper L, Snuderl M, et al. T2-FLAIR Mismatch, an Imaging Biomarker for IDH and 1p/19q Status in Lower-grade Gliomas: A TCGA/TCIA Project. Clin Cancer Res. 2017;23(20):6078-85.
36. Smits M. Imaging of oligodendroglioma. Br J Radiol. 2016;89(1060):20150857.
37. Tang C, Ruan R, Xiong Z. Comparison between [18F]FET PET/MRI and [18F]FET PET/CT in the diagnosis of glioma recurrence: a systematic review and meta-analysis. Clinical and Translational Imaging. 2023;11(5):479-91.
38. Näslund O, Smits A, Förander P, Laesser M, Bartek J, Jr., Gempt J, et al. Amino acid tracers in PET imaging of diffuse low-grade gliomas: a systematic review of preoperative applications. Acta Neurochir (Wien). 2018;160(7):1451-60.
39. Nationellt vårdprogram – Tumörer i hjärna och ryggmärg. Stockholm; 2023.

40. Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170-86.
41. Jakola AS, Skjulsvik AJ, Myrmel KS, Sjåvik K, Unsgård G, Torp SH, et al. Surgical resection versus watchful waiting in low-grade gliomas. Ann Oncol. 2017;28(8):1942-8.
42. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery. 2008;62(4):753-64; discussion 264-6.
43. Duffau H, Mandonnet E. The "onco-functional balance" in surgery for diffuse low-grade glioma: integrating the extent of resection with quality of life. Acta Neurochir (Wien). 2013;155(6):951-7.
44. Duffau H. The challenge to remove diffuse low-grade gliomas while preserving brain functions. Acta Neurochir (Wien). 2012;154(4):569-74.
45. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. J Neurooncol. 2016;130(2):269-82.
46. Duffau H, Capelle L. Preferential brain locations of low-grade gliomas. Cancer. 2004;100(12):2622-6.
47. Trevisi G, Barbone P, Treglia G, Mattoli MV, Mangiola A. Reliability of intraoperative ultrasound in detecting tumor residual after brain diffuse glioma surgery: a systematic review and meta-analysis. Neurosurg Rev. 2020;43(5):1221-33.
48. Stepp H, Stummer W. 5-ALA in the management of malignant glioma. Lasers Surg Med. 2018;50(5):399-419.
49. Saito T, Muragaki Y, Maruyama T, Tamura M, Nitta M, Okada Y. Intraoperative functional mapping and monitoring during glioma surgery. Neurol Med Chir (Tokyo). 2015;55(1):1-13.
50. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012;30(20):2559-65.
51. Freyschlag CF, Duffau H. Awake brain mapping of cortex and subcortical pathways in brain tumor surgery. J Neurosurg Sci. 2014;58(4):199-213.
52. Lemaitre AL, Herbet G, Ng S, Moritz-Gasser S, Duffau H. Cognitive preservation following awake mapping-based neurosurgery for low-grade gliomas: A longitudinal, within-patient design study. Neuro Oncol. 2022;24(5):781-93.
53. Gogos AJ, Young JS, Morshed RA, Hervey-Jumper SL, Berger MS. Awake glioma surgery: technical evolution and nuances. J Neurooncol. 2020;147(3):515-24.
54. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol. 2002;20(8):2076-84.

55. Halasz LM, Attia A, Bradfield L, Brat DJ, Kirkpatrick JP, Laack NN, et al. Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2022;12(5):370-86.
56. Horbinski C, Berger T, Packer RJ, Wen PY. Clinical implications of the 2021 edition of the WHO classification of central nervous system tumours. Nat Rev Neurol. 2022;18(9):515-29.
57. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys. 1996;36(3):549-56.
58. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. N Engl J Med. 2016;374(14):1344-55.
59. Kessler T, Schrimpf D, Doerner L, Hai L, Kaulen LD, Ito J, et al. Prognostic Markers of DNA Methylation and Next-Generation Sequencing in Progressive Glioblastoma from the EORTC-26101 Trial. Clin Cancer Res. 2023;29(19):3892-900.
60. van den Bent MJ, Ghisai SA, Wick W, Sanson M, Brandes AA, Clement PM, et al. Concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): final and exploratory analyses of a randomised, open-label, phase 3 trial. Lancet Oncol. 2026;27(1):45-56.
61. Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol. 2012;30(25):3065-70.
62. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol. 2002;20(9):2267-76.
63. van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005;366(9490):985-90.
64. Prabhu RS, Won M, Shaw EG, Hu C, Brachman DG, Buckner JC, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. J Clin Oncol. 2014;32(6):535-41.

65. Lomax ME, Folkes LK, O'Neill P. Biological consequences of radiation-induced DNA damage: relevance to radiotherapy. Clin Oncol (R Coll Radiol). 2013;25(10):578-85.
66. Breen WG, Anderson SK, Carrero XW, Brown PD, Ballman KV, O'Neill BP, et al. Final report from Intergroup NCCTG 86-72-51 (Alliance): a phase III randomized clinical trial of high-dose versus low-dose radiation for adult low-grade glioma. Neuro Oncol. 2020;22(6):830-7.
67. Goliot N, Mohssine S, Stefan D, Leclerc A, Emery E, Riverain J, et al. Proton therapy for adult-type diffuse glioma: A systematic review. Crit Rev Oncol Hematol. 2024;204:104501.
68. Winter SF, Gardner MM, Karschnia P, Vaios EJ, Grassberger C, Bussière MR, et al. Unique brain injury patterns after proton vs photon radiotherapy for WHO grade 2-3 gliomas. Oncologist. 2024;29(12):e1748-e61.
69. Heggebø LC, Borgen IMH, Rylander H, Kiserud C, Nordenmark TH, Hellebust TP, et al. Investigating survival, quality of life and cognition in PROton versus photon therapy for IDH-mutated diffuse grade 2 and 3 GLIOmas (PRO-GLIO): a randomised controlled trial in Norway and Sweden. BMJ Open. 2023;13(3):e070071.
70. Cancer EOfRaTo. IDH-mutated 1p/19q intact lower-grade glioma following resection: Wait Or Treat?

IWOT (EORTC 1635-BTG). European Organisation for Research and Treatment of Cancer (EORTC); 2020.
71. Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2016;17(11):1521-32.
72. Bell EH, Zhang P, Shaw EG, Buckner JC, Barger GR, Bullard DE, et al. Comprehensive Genomic Analysis in NRG Oncology/RTOG 9802: A Phase III Trial of Radiation Versus Radiation Plus Procarbazine, Lomustine (CCNU), and Vincristine in High-Risk Low-Grade Glioma. J Clin Oncol. 2020;38(29):3407-17.
73. Lanman TA, Gross H, Faria CM, Miller JJ, Cahill DP, Shih HA, et al. Factors associated with cognitive impairment in long-term IDH-mutant glioma survivors. J Neurooncol. 2025.
74. Ahmad H, Martin D, Patel SH, Donahue J, Lopes B, Purow B, et al. Oligodendroglioma confers higher risk of radiation necrosis. J Neurooncol. 2019;145(2):309-19.
75. Lawrie TA, Gillespie D, Dowswell T, Evans J, Erridge S, Vale L, et al. Long-term neurocognitive and other side effects of radiotherapy, with

or without chemotherapy, for glioma. Cochrane Database Syst Rev. 2019;8(8):Cd013047.
76. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol. 2009;8(9):810-8.
77. Fu D, Calvo JA, Samson LD. Balancing repair and tolerance of DNA damage caused by alkylating agents. Nat Rev Cancer. 2012;12(2):104-20.
78. Lassman AB, Hoang-Xuan K, Polley M-YC, Brandes AA, Cairncross JG, Kros JM, et al. Joint Final Report of EORTC 26951 and RTOG 9402: Phase III Trials With Procarbazine, Lomustine, and Vincristine Chemotherapy for Anaplastic Oligodendroglial Tumors. J Clin Oncol. 2022;40(23):2539-45.
79. Irfan N, Samuel E, Rafi Ranjha F, Waheed A, Abu Bakar M, Usman S, et al. Toxicity Profile of Procarbazine Lomustine and Vincristine Chemotherapy in Low-Grade Glioma - Retrospective Review. Cureus. 2020;12(10):e11070.
80. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31(3):337-43.
81. Kaloshi G, Benouaich-Amiel A, Diakite F, Taillibert S, Lejeune J, Laigle-Donadey F, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. Neurology. 2007;68(21):1831-6.
82. Fisher BJ, Pugh SL, Macdonald DR, Chakravatri A, Lesser GJ, Fox S, et al. Phase 2 Study of a Temozolomide-Based Chemoradiation Therapy Regimen for High-Risk, Low-Grade Gliomas: Long-Term Results of Radiation Therapy Oncology Group 0424. Int J Radiat Oncol Biol Phys. 2020;107(4):720-5.
83. Group NS. Improvement of Functional Outcome for Patients With Newly Diagnosed Grade 2 or 3 Glioma With Co-deletion of 1p/19q – IMPROVE CODEL: the NOA-18 Trial. Bethesda, Maryland, USA: National Library of Medicine (US); 2022. Report No.: NCT05331521.
84. Mellinghoff IK, van den Bent MJ, Blumenthal DT, Touat M, Peters KB, Clarke J, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023;389(7):589-601.
85. Cloughesy TF, van den Bent MJ, Touat M, Blumenthal DT, Peters KB, Ellingson BM, et al. Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a

randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2025;26(12):1665-75.
86. Walton MK, Powers JH, 3rd, Hobart J, Patrick D, Marquis P, Vamvakas S, et al. Clinical Outcome Assessments: Conceptual Foundation-Report of the ISPOR Clinical Outcomes Assessment - Emerging Good Practices for Outcomes Research Task Force. Value Health. 2015;18(6):741-52.
87. Klein M, Heimans JJ, Aaronson NK, van der Ploeg HM, Grit J, Muller M, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. Lancet. 2002;360(9343):1361-8.
88. Pelletier G, Verhoef MJ, Khatri N, Hagen N. Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues. J Neurooncol. 2002;57(1):41-9.
89. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. Psychooncology. 2017;26(5):617-24.
90. Rooney AG, Carson A, Grant R. Depression in cerebral glioma patients: a systematic review of observational studies. J Natl Cancer Inst. 2011;103(1):61-76.
91. Dalton SO, Laursen TM, Ross L, Mortensen PB, Johansen C. Risk for hospitalization with depression after a cancer diagnosis: a nationwide, population-based study of cancer patients in Denmark from 1973 to 2003. J Clin Oncol. 2009;27(9):1440-5.
92. Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. Psychother Psychosom. 2015;84(2):72-81.
93. Chang SM, Parney IF, McDermott M, Barker FG, 2nd, Schmidt MH, Huang W, et al. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg. 2003;98(6):1175-81.
94. Ley A, Kamp M, von Sass C, Hänggi D, Sabel M, Rapp M. Psychooncological distress in low-grade glioma patients-a monocentric study. Acta Neurochir (Wien). 2022;164(3):713-22.
95. van der Meer PB, Dirven L, Hertler C, Boele FW, Batalla A, Walbert T, et al. Depression and anxiety in glioma patients. Neurooncol Pract. 2023;10(4):335-43.
96. Ford E, Catt S, Chalmers A, Fallowfield L. Systematic review of supportive care needs in patients with primary malignant brain tumors. Neuro Oncol. 2012;14(4):392-404.

97. Huang J, Zeng C, Xiao J, Zhao D, Tang H, Wu H, et al. Association between depression and brain tumor: a systematic review and meta-analysis. Oncotarget. 2017;8(55):94932-43.
98. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. JAMA Psychiatry. 2018;75(4):336-46.
99. Rooney AG, McNamara S, Mackinnon M, Fraser M, Rampling R, Carson A, et al. The frequency, longitudinal course, clinical associations, and causes of emotional distress during primary treatment of cerebral glioma. Neuro Oncol. 2013;15(5):635-43.
100. Boele FW, den Otter PWM, Reijneveld JC, de Witt Hamer PC, van Thuijl HF, Lorenz LMC, et al. Long-term wellbeing and neurocognitive functioning of diffuse low-grade glioma patients and their caregivers: A longitudinal study spanning two decades. Neuro Oncol. 2023;25(2):351-64.
101. Humphris GM, Watson E, Sharpe M, Ozakinci G. Unidimensional scales for fears of cancer recurrence and their psychometric properties: the FCR4 and FCR7. Health Qual Life Outcomes. 2018;16(1):30.
102. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer. 2016;24(8):3265-8.
103. Sun H, Yang Y, Zhang J, Liu T, Wang H, Garg S, et al. Fear of cancer recurrence, anxiety and depressive symptoms in adolescent and young adult cancer patients. Neuropsychiatr Dis Treat. 2019;15:857-65.
104. Farzaneh R, Malek A, Mirzaei F, Amiri S, Salehpour F, Meshkini A, et al. Evaluation of comorbid psychiatric disorders in patients with primary brain tumors before and after surgery. Neurology, Psychiatry and Brain Research. 2020;36:8-13.
105. Rooney AG, McNamara S, Mackinnon M, Fraser M, Rampling R, Carson A, et al. Frequency, clinical associations, and longitudinal course of major depressive disorder in adults with cerebral glioma. J Clin Oncol. 2011;29(32):4307-12.
106. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. Front Neuroendocrinol. 2014;35(3):320-30.
107. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004(420):55-64.
108. Mainio A, Hakko H, Niemelä A, Koivukangas J, Räsänen P. Depression and functional outcome in patients with brain tumors: a population-based 1-year follow-up study. J Neurosurg. 2005;103(5):841-7.

109. Ghio L, Gotelli S, Marcenaro M, Amore M, Natta W. Duration of untreated illness and outcomes in unipolar depression: a systematic review and meta-analysis. J Affect Disord. 2014;152-154:45-51.
110. Saad AM, Elmatboly AM, Gad MM, Al-Husseini MJ, Jazieh KA, Alzuabi MA, et al. Association of Brain Cancer With Risk of Suicide. JAMA Netw Open. 2020;3(5):e203862.
111. Socialstyrelsen. Nationella riktlinjer för vård vid depression och ångestsyndrom – Stöd för styrning och ledning. Stockholm; 2017 2026-02-27.
112. Ownsworth T, Chambers S, Damborg E, Casey L, Walker DG, Shum DH. Evaluation of the making sense of brain tumor program: a randomized controlled trial of a home-based psychosocial intervention. Psychooncology. 2015;24(5):540-7.
113. Zhao YH, Xu Y. Effect of Comprehensive Nursing Based on Cognitive Behavior on Psychological Function of Glioma Patients. Neuropsychiatr Dis Treat. 2021;17:777-85.
114. Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R. Novel and emerging treatments for major depression. Lancet. 2023;401(10371):141-53.
115. Yang W, Jia YH, Jiang HY, Li AJ. Antidepressant use and the risk of seizure: a meta-analysis of observational studies. Eur J Clin Pharmacol. 2024;80(2):175-83.
116. Litofsky NS, Farace E, Anderson F, Jr., Meyers CA, Huang W, Laws ER, Jr. Depression in patients with high-grade glioma: results of the Glioma Outcomes Project. Neurosurgery. 2004;54(2):358-66; discussion 66-7.
117. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet. 2004;363(9413):978-88.
118. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet. 2003;362(9384):640-50.
119. Boele FW, Klein M, Reijneveld JC, Verdonck-de Leeuw IM, Heimans JJ. Symptom management and quality of life in glioma patients. CNS Oncol. 2014;3(1):37-47.
120. van Coevorden-van Loon EMP, Heijenbrok-Kal MH, Horemans HLD, Boere R, de Bat R, Vincent A, et al. The relationship between mental fatigue, cognitive functioning, and employment status in patients with low-grade glioma: a cross-sectional single-center study. Disabil Rehabil. 2022;44(24):7413-9.
121. Siebenga FF, Rakers SE, Gelmers F, van der Weide HL, Kramer MCA, van der Hoorn A, et al. Distinguishing Mental From Physical Fatigue in Patients With Low-Grade Glioma. Psychooncology. 2025;34(10):e70289.

122. Schei S, Solheim O, Jakola AS, Sagberg LM. Perioperative fatigue in patients with diffuse glioma. J Neurooncol. 2020;147(1):97-107.
123. Röttgering JG, Belgers V, De Witt Hamer PC, Knoop H, Douw L, Klein M. Toward unraveling the correlates of fatigue in glioma. Neurooncol Adv. 2022;4(1):vdac169.
124. Teng KX, Price B, Joshi S, Alukaidey L, Shehab A, Mansour K, et al. Life after surgical resection of a low-grade glioma: A prospective cross-sectional study evaluating health-related quality of life. J Clin Neurosci. 2021;88:259-67.
125. Gorter M, Röttgering JG, Belgers V, Blom MEC, Thomassen B, De Witt Hamer PC, et al. Bayesian Adaptive Randomized Trial of Blended Cognitive Behavioral Therapy for Severe Fatigue in Stable Diffuse Glioma. Neuro Oncol. 2025.
126. Hansen A, Pedersen CB, Jarden JO, Beier D, Minet LR, Søgaard K. Effectiveness of Physical Therapy- and Occupational Therapy-Based Rehabilitation in People Who Have Glioma and Are Undergoing Active Anticancer Treatment: Single-Blind, Randomized Controlled Trial. Phys Ther. 2020;100(3):564-74.
127. Gehring K, Stuiver MM, Visser E, Kloek C, van den Bent M, Hanse M, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. Neuro Oncol. 2020;22(1):103-15.
128. Eisenhut L, Sadeghi-Bahmani D, Gerber M, Saemann A, Staub L, Brand S, et al. Effects of two types of exercise training on psychological well-being, sleep and physical fitness in patients with high-grade glioma (WHO III and IV). J Psychiatr Res. 2022;151:354-64.
129. Breitbart W, Alici Y. Psychostimulants for cancer-related fatigue. J Natl Compr Canc Netw. 2010;8(8):933-42.
130. Yennurajalingam S, Bruera E. Review of clinical trials of pharmacologic interventions for cancer-related fatigue: focus on psychostimulants and steroids. Cancer J. 2014;20(5):319-24.
131. Jean-Pierre P, Morrow GR, Roscoe JA, Heckler C, Mohile S, Janelsins M, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. Cancer. 2010;116(14):3513-20.
132. Gehring K, Patwardhan SY, Collins R, Groves MD, Etzel CJ, Meyers CA, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. J Neurooncol. 2012;107(1):165-74.

133. Butler JM, Jr., Case LD, Atkins J, Frizzell B, Sanders G, Griffin P, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. Int J Radiat Oncol Biol Phys. 2007;69(5):1496-501.
134. Eaton C, Yong K, Walter V, Mbizvo GK, Rhodes S, Chin RF. Stimulant and non-stimulant drug therapy for people with attention deficit hyperactivity disorder and epilepsy. Cochrane Database Syst Rev. 2022;7(7):Cd013136.
135. Zagnoni PG, Albano C. Psychostimulants and epilepsy. Epilepsia. 2002;43 Suppl 2:28-31.
136. Kirkman MA, Hunn BHM, Thomas MSC, Tolmie AK. Influences on cognitive outcomes in adult patients with gliomas: A systematic review. Front Oncol. 2022;12:943600.
137. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological Assessment. 5th ed. Oxford: Oxford University Press; 2012.
138. Hendriks EJ, Habets EJJ, Taphoorn MJB, Douw L, Zwinderman AH, Vandertop WP, et al. Linking late cognitive outcome with glioma surgery location using resection cavity maps. Hum Brain Mapp. 2018;39(5):2064-74.
139. Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. Br J Cancer. 2004;90(9):1691-6.
140. Baddeley AD. Is working memory still working? Am Psychol. 2001;56(11):851-64.
141. Baddeley A. The episodic buffer: a new component of working memory? Trends Cogn Sci. 2000;4(11):417-23.
142. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68.
143. Uddin LQ. Cognitive and behavioural flexibility: neural mechanisms and clinical considerations. Nat Rev Neurosci. 2021;22(3):167-79.
144. Miyake A, Friedman NP. The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. Curr Dir Psychol Sci. 2012;21(1):8-14.
145. Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A. 1996;93(24):13515-22.
146. Fedorenko E, Ivanova AA, Regev TI. The language network as a natural kind within the broader landscape of the human brain. Nat Rev Neurosci. 2024;25(5):289-312.

147. Friederici AD. The brain basis of language processing: from structure to function. Physiol Rev. 2011;91(4):1357-92.
148. Saur D, Kreher BW, Schnell S, Kümmerer D, Kellmeyer P, Vry MS, et al. Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A. 2008;105(46):18035-40.
149. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. J Neurosurg. 2015;122(2):250-61.
150. Kravitz DJ, Saleem KS, Baker CI, Mishkin M. A new neural framework for visuospatial processing. Nat Rev Neurosci. 2011;12(4):217-30.
151. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. Neuro Oncol. 2016;18(12):1656-63.
152. van Loon EM, Heijenbrok-Kal MH, van Loon WS, van den Bent MJ, Vincent AJ, de Koning I, et al. Assessment methods and prevalence of cognitive dysfunction in patients with low-grade glioma: A systematic review. J Rehabil Med. 2015;47(6):481-8.
153. Boone M, Roussel M, Chauffert B, Le Gars D, Godefroy O. Prevalence and profile of cognitive impairment in adult glioma: a sensitivity analysis. J Neurooncol. 2016;129(1):123-30.
154. Ng JCH, See AAQ, Ang TY, Tan LYR, Ang BT, King NKK. Effects of surgery on neurocognitive function in patients with glioma: a meta-analysis of immediate post-operative and long-term follow-up neurocognitive outcomes. J Neurooncol. 2019;141(1):167-82.
155. Weyer-Jamora C, Brie MS, Luks TL, Smith EM, Braunstein SE, Villanueva-Meyer JE, et al. Cognitive impact of lower-grade gliomas and strategies for rehabilitation. Neurooncol Pract. 2021;8(2):117-28.
156. van der Weide HL, Buunk AM, Siebenga FF, Langendijk JA, Bannink-Gawryszuk A, Bosma I, et al. Neurocognitive function in lower grade glioma patients selected for proton radiotherapy: real-world data from a prospective cohort study. J Neurooncol. 2025;173(1):147-56.
157. Schei S, Solheim O, Salvesen Ø, Hjermstad MJ, Bouget D, Sagberg LM. Pretreatment patient-reported cognitive function in patients with diffuse glioma. Acta Neurochir (Wien). 2022;164(3):703-11.
158. Barberis M, Poisson I, Facque V, Letrange S, Prevost-Tarabon C, Houdart E, et al. Group-level stability but individual variability of neurocognitive status after awake resections of right frontal IDH-mutated glioma. Sci Rep. 2022;12(1):6126.
159. De Roeck L, Gillebert CR, van Aert RCM, Vanmeenen A, Klein M, Taphoorn MJB, et al. Cognitive outcomes after multimodal treatment in adult glioma patients: A meta-analysis. Neuro Oncol. 2023;25(8):1395-414.

160. Brown PD, Buckner JC, O'Fallon JR, Iturria NL, Brown CA, O'Neill BP, et al. Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the folstein mini-mental state examination. J Clin Oncol. 2003;21(13):2519-24.
161. Laack NN, Brown PD, Ivnik RJ, Furth AF, Ballman KV, Hammack JE, et al. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. Int J Radiat Oncol Biol Phys. 2005;63(4):1175-83.
162. Boele FW, Frances SM, Darlix A, Ducray F, Cartalat S, Guerdoux E, et al. Health-related quality of life and cognitive functioning in survivors of oligodendroglioma: an international cross-sectional investigation. Neuro Oncol. 2025.
163. Derks J, Kulik S, Wesseling P, Numan T, Hillebrand A, van Dellen E, et al. Understanding cognitive functioning in glioma patients: The relevance of IDH-mutation status and functional connectivity. Brain Behav. 2019;9(4):e01204.
164. Morshed RA, Young JS, Kroliczek AA, Berger MS, Brang D, Hervey-Jumper SL. A Neurosurgeon's Guide to Cognitive Dysfunction in Adult Glioma. Neurosurgery. 2021;89(1):1-10.
165. Stuss DT. Functions of the frontal lobes: relation to executive functions. J Int Neuropsychol Soc. 2011;17(5):759-65.
166. Douw L, Reijneveld JC, Mandal AS. Multiscale network perspectives on glioma: from tumour biology to symptoms, survival and treatment. Nature Reviews Neurology. 2026;22(2):73-89.
167. Bunevicius A, Miller J, Parsons M. Isocitrate Dehydrogenase, Patient-Reported Outcomes, and Cognitive Functioning of Glioma Patients: a Systematic Review. Curr Oncol Rep. 2020;22(12):120.
168. Landers-Wouters M, Brouwers B, Rutten GJ, Butterbrod E. Differences in Executive Functioning Between Patients with IDH1-Mutant Oligodendroglioma and Astrocytoma Before and After Surgery. Cancers (Basel). 2026;18(1).
169. van Kessel E, Snijders TJ, Baumfalk AE, Ruis C, van Baarsen KM, Broekman ML, et al. Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study. J Neurooncol. 2020;146(1):97-109.
170. Kesler SR, Noll K, Cahill DP, Rao G, Wefel JS. The effect of IDH1 mutation on the structural connectome in malignant astrocytoma. J Neurooncol. 2017;131(3):565-74.
171. Price SJ, Allinson K, Liu H, Boonzaier NR, Yan JL, Lupson VC, et al. Less Invasive Phenotype Found in Isocitrate Dehydrogenase-mutated Glioblastomas than in Isocitrate Dehydrogenase Wild-Type

Glioblastomas: A Diffusion-Tensor Imaging Study. Radiology. 2017;283(1):215-21.
172. Wefel JS, Schagen SB. Chemotherapy-related cognitive dysfunction. Curr Neurol Neurosci Rep. 2012;12(3):267-75.
173. Koutsarnakis C, Neromyliotis E, Komaitis S, Mazarakis N, O'Hara DJ, Stranjalis G, et al. Effects of brain radiotherapy on cognitive performance in adult low-grade glioma patients: A systematic review. Radiother Oncol. 2021;160:202-11.
174. Torres IJ, Mundt AJ, Sweeney PJ, Llanes-Macy S, Dunaway L, Castillo M, et al. A longitudinal neuropsychological study of partial brain radiation in adults with brain tumors. Neurology. 2003;60(7):1113-8.
175. Armstrong CL, Hunter JV, Ledakis GE, Cohen B, Tallent EM, Goldstein BH, et al. Late cognitive and radiographic changes related to radiotherapy: initial prospective findings. Neurology. 2002;59(1):40-8.
176. Taphoorn MJ, Sizoo EM, Bottomley A. Review on quality of life issues in patients with primary brain tumors. Oncologist. 2010;15(6):618-26.
177. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. Neuro-Oncology. 2015;17(4):580-7.
178. Correa DD, Satagopan J, Baser RE, Cheung K, Richards E, Lin M, et al. APOE polymorphisms and cognitive functions in patients with brain tumors. Neurology. 2014;83(4):320-7.
179. Dunås T, Leiss S, Corell A, Skoglund T, Dénes A, Carén H, et al. Genetic Risk Factors for Poor Cognitive Outcome Following Brain Insult-A Systematic Review. Brain Behav. 2026;16(1):e71173.
180. Butterbrod E, Sitskoorn M, Bakker M, Jakobs B, Fleischeuer R, Roijers J, et al. The APOE ε4 allele in relation to pre- and postsurgical cognitive functioning of patients with primary brain tumors. Eur J Neurol. 2021;28(5):1665-76.
181. Smith JR, Pike JR, Gottesman RF, Knopman DS, Lutsey PL, Palta P, et al. Contribution of Modifiable Midlife and Late-Life Vascular Risk Factors to Incident Dementia. JAMA Neurol. 2025;82(7):644-54.
182. Filler J, Georgakis MK, Dichgans M. Risk factors for cognitive impairment and dementia after stroke: a systematic review and meta-analysis. Lancet Healthy Longev. 2024;5(1):e31-e44.
183. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med. 2014;44(10):2029-40.

184. Anderson SI, Taylor R, Whittle IR. Mood disorders in patients after treatment for primary intracranial tumours. Br J Neurosurg. 1999;13(5):480-5.
185. Aaronson NK, Taphoorn MJ, Heimans JJ, Postma TJ, Gundy CM, Beute GN, et al. Compromised health-related quality of life in patients with low-grade glioma. J Clin Oncol. 2011;29(33):4430-5.
186. Rimmer B, Bolnykh I, Dutton L, Lewis J, Burns R, Gallagher P, et al. Health-related quality of life in adults with low-grade gliomas: a systematic review. Qual Life Res. 2023;32(3):625-51.
187. Gómez Vecchio T, Rydén I, Ozanne A, Blomstrand M, Carstam L, Smits A, et al. Global health status and fatigue score in isocitrate dehydrogenase-mutant diffuse glioma grades 2 and 3: A longitudinal population-based study from surgery to 12-month follow-up. Neurooncol Pract. 2024;11(3):347-57.
188. Boele FW, Zant M, Heine EC, Aaronson NK, Taphoorn MJ, Reijneveld JC, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. Neurooncol Pract. 2014;1(2):40-6.
189. Drewes C, Sagberg LM, Jakola AS, Solheim O. Perioperative and Postoperative Quality of Life in Patients with Glioma-A Longitudinal Cohort Study. World Neurosurg. 2018;117:e465-e74.
190. Svedung Wettervik T, Ersson M, Latini F, Ryttlefors M, Zetterling M. Patient-reported quality of life in grade 2 and 3 gliomas after surgery, can we do more? Clin Neurol Neurosurg. 2022;214:107175.
191. Ilie G, Bradfield J, Moodie L, Lawen T, Ilie A, Lawen Z, et al. The Role of Response-Shift in Studies Assessing Quality of Life Outcomes Among Cancer Patients: A Systematic Review. Front Oncol. 2019;9:783.
192. Jakola AS, Solheim O, Gulati S, Sagberg LM. Is there a response shift in generic health-related quality of life 6 months after glioma surgery? Acta Neurochir (Wien). 2017;159(2):377-84.
193. Pascual JSG, Duffau H. The need to consider return to work as a main outcome in patients undergoing surgery for diffuse low-grade glioma: a systematic review. Acta Neurochir (Wien). 2022;164(10):2789-809.
194. Schiavolin S, Mariniello A, Broggi M, Acerbi F, Schiariti M, Franzini A, et al. Characteristics of Patients Returning to Work After Brain Tumor Surgery. Front Hum Neurosci. 2020;14:609080.
195. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Taillandier L, et al. Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. J Neurosurg. 2003;98(4):764-78.

196. van Loon EMP, Ernens W, Heijenbrok-Kal MH, Horemans HLD, Ribbers GM, van den Bent MJ. Long-term employment status and the association with fatigue in patients with grade II glioma. J Rehabil Med. 2021;53(5):jrm00198.
197. Leroy HA, Strachowksi O, Tuleasca C, Vannod-Michel Q, Le Rhun E, Derre B, et al. Microsurgical resection of fronto-temporo-insular gliomas in the non-dominant hemisphere, under general anesthesia using adjunct intraoperative MRI and no cortical and subcortical mapping: a series of 20 consecutive patients. Sci Rep. 2021;11(1):6994.
198. Nicklin E, Phang I, Short SC, Hoogendoorn P, Boele FW. Patient and caregiver return to work after a primary brain tumor. Neurooncol Pract. 2023;10(6):565-75.
199. Smits A, Zetterling M, Lundin M, Melin B, Fahlström M, Grabowska A, et al. Neurological Impairment Linked with Cortico-Subcortical Infiltration of Diffuse Low-Grade Gliomas at Initial Diagnosis Supports Early Brain Plasticity. Front Neurol. 2015;6:137.
200. Kennedy F, Haslam C, Munir F, Pryce J. Returning to work following cancer: a qualitative exploratory study into the experience of returning to work following cancer. Eur J Cancer Care (Engl). 2007;16(1):17-25.
201. Pallud J, McKhann GM. Diffuse Low-Grade Glioma-Related Epilepsy. Neurosurg Clin N Am. 2019;30(1):43-54.
202. Senft C, Behrens M, Lortz I, Wenger K, Filipski K, Seifert V, et al. The ability to return to work: a patient-centered outcome parameter following glioma surgery. J Neurooncol. 2020;149(3):403-11.
203. Yoshida A, Motomura K, Natsume A, Chalise L, Iijima K, Hara D, et al. Preoperative predictive factors affecting return to work in patients with gliomas undergoing awake brain mapping. J Neurooncol. 2020;146(1):195-205.
204. Muto J, Dezamis E, Rigaux-Viode O, Peeters S, Roux A, Zanello M, et al. Functional-Based Resection Does Not Worsen Quality of Life in Patients with a Diffuse Low-Grade Glioma Involving Eloquent Brain Regions: A Prospective Cohort Study. World Neurosurg. 2018;113:e200-e12.
205. Pallud J, Dezamis E. Functional and oncological outcomes following awake surgical resection using intraoperative cortico-subcortical functional mapping for supratentorial gliomas located in eloquent areas. Neurochirurgie. 2017;63(3):208-18.
206. Duffau H. Awake Mapping With Transopercular Approach in Right Insular-Centered Low-Grade Gliomas Improves Neurological Outcomes and Return to Work. Neurosurgery. 2022;91(1):182-90.
207. Lima GLO, Dezamis E, Corns R, Rigaux-Viode O, Moritz-Gasser S, Roux A, et al. Surgical resection of incidental diffuse gliomas

involving eloquent brain areas. Rationale, functional, epileptological and oncological outcomes. Neurochirurgie. 2017;63(3):250-8.
208. Moritz-Gasser S, Herbet G, Maldonado IL, Duffau H. Lexical access speed is significantly correlated with the return to professional activities after awake surgery for low-grade gliomas. J Neurooncol. 2012;107(3):633-41.
209. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114(2):97-109.
210. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36(1):8-27.
211. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
212. Wu Y, Levis B, Sun Y, He C, Krishnan A, Neupane D, et al. Accuracy of the Hospital Anxiety and Depression Scale Depression subscale (HADS-D) to screen for major depression: systematic review and individual participant data meta-analysis. Bmj. 2021;373:n972.
213. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
214. Benedict R. Brief visuospatial memory test - revised: Professional manual Lutz, FL: Psychological Assessment Resources, Inc; 1997.
215. Magalhães SS, Malloy-Diniz L, Hamdan A. Validity convergent and reliability test-retest of the rey auditory verbal learning test. Clinical Neuropsychiatry. 2012;9:129-37.
216. Loring DW, Saurman JL, John SE, Bowden SC, Lah JJ, Goldstein FC. The Rey Auditory Verbal Learning Test: Cross-validation of Mayo Normative Studies (MNS) demographically corrected norms with confidence interval estimates. J Int Neuropsychol Soc. 2023;29(4):397-405.
217. Weitzner DS, Pugh EA, Calamia M, Roye S. Examining the factor structure of the Rey auditory verbal learning test in individuals across the life span. J Clin Exp Neuropsychol. 2020;42(4):406-14.
218. Stricker NH, Christianson TJ, Lundt ES, Alden EC, Machulda MM, Fields JA, et al. Mayo Normative Studies: Regression-Based Normative Data for the Auditory Verbal Learning Test for Ages 30-91 Years and the Importance of Adjusting for Sex. J Int Neuropsychol Soc. 2021;27(3):211-26.
219. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol. 2004;19(2):203-14.
220. Sánchez-Cubillo I, Periáñez JA, Adrover-Roig D, Rodríguez-Sánchez JM, Ríos-Lago M, Tirapu J, et al. Construct validity of the Trail

Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J Int Neuropsychol Soc. 2009;15(3):438-50.
221. Meyers JE, Meyers, Kelly R. Rey Complex Figure Test and Recognition Trial: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1995.
222. Tallberg IM, Ivachova E, Jones Tinghag K, Ostberg P. Swedish norms for word fluency tests: FAS, animals and verbs. Scand J Psychol. 2008;49(5):479-85.
223. Delis DC, Kramer JH, Kaplan E, Holdnack J. Reliability and validity of the Delis-Kaplan Executive Function System: an update. J Int Neuropsychol Soc. 2004;10(2):301-3.
224. Latzman RD, Markon KE. The factor structure and age-related factorial invariance of the Delis-Kaplan Executive Function System (D-KEFS). Assessment. 2010;17(2):172-84.
225. Delis DC, Kaplan, E., & Kramer, J. H. Delis-Kaplan Executive Function System (D–KEFS): APA PsycTests; 2001.
226. Espenes J, Lorentzen IM, Eliassen IV, Hessen E, Waterloo K, Timón-Reina S, et al. Regression-based normative data for the D-KEFS Color-Word Interference Test in Norwegian adults ages 20-85. Clin Neuropsychol. 2024;38(5):1227-55.
227. Wechsler D. WAIS-IV. Manual del 1 – svensk version. Stockholm, Sweden 2011.
228. Wechsler D. WAIS-IV Administration and Scoring Manual. 4 ed. San Antonio, TX: Pearson; 2008.
229. Nelson JM, Canivez GL, Watkins MW. Structural and incremental validity of the Wechsler Adult Intelligence Scale-Fourth Edition with a clinical sample. Psychol Assess. 2013;25(2):618-30.
230. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998;20(3):310-9.
231. Maassen GH, Bossema E, Brand N. Reliable change and practice effects: outcomes of various indices compared. J Clin Exp Neuropsychol. 2009;31(3):339-52.
232. Karunamuni R, Tringale KR, Burkeen J, Tibbs MD, Huynh-Le MP, Bahrami N, et al. Multi-domain neurocognitive classification of primary brain tumor patients prior to radiotherapy on a prospective clinical trial. J Neurooncol. 2020;146(1):131-8.
233. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011;12(7):703-8.

234. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001.
235. Kaasa S, Bjordal K, Aaronson N, Moum T, Wist E, Hagen S, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. European journal of cancer. 1995;31(13-14):2260-3.
236. Smets E, Garssen B, Cull A, De Haes J. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. British journal of cancer. 1996;73(2):241-5.
237. Smets E, Garssen B, Bonke Bd, De Haes J. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of psychosomatic research. 1995;39(3):315-25.
238. Rydén I, Carstam L, Gulati S, Smits A, Sunnerhagen KS, Hellström P, et al. Return to work following diagnosis of low-grade glioma: A nationwide matched cohort study. Neurology. 2020;95(7):e856-e66.
239. Rydén I, Latini F, Munkhammar Å A, Hellström P, Neimantaite A, Lycett A, et al. Reliable cognitive changes the first year following guideline-based treatment of IDH mutated gliomas: a longitudinal multicenter study. Neuro Oncol. 2025.
240. Bouknight RR, Bradley CJ, Luo Z. Correlates of return to work for breast cancer survivors. J Clin Oncol. 2006;24(3):345-53.
241. Kirchhoff AC, Leisenring W, Syrjala KL. Prospective predictors of return to work in the 5 years after hematopoietic cell transplantation. J Cancer Surviv. 2010;4(1):33-44.
242. Palstam A, Westerlind E, Persson HC, Sunnerhagen KS. Work-related predictors for return to work after stroke. Acta Neurol Scand. 2019;139(4):382-8.
243. Odgaard L, Pedersen AR, Poulsen I, Johnsen SP, Nielsen JF. Return to work predictors after traumatic brain injury in a welfare state. Acta Neurol Scand. 2018;137(1):44-50.
244. Westerlind E, Abzhandadze T, Rafsten L, Persson HC, Sunnerhagen KS. Very early cognitive screening and return to work after stroke. Top Stroke Rehabil. 2019;26(8):602-7.
245. Bacigalupe A, Martín U, Triolo F, Sjöberg L, Sterner TR, Dekhtyar S, et al. Is the diagnosis and treatment of depression gender-biased? Evidence from a population-based aging cohort in Sweden. Int J Equity Health. 2024;23(1):252.