# QUALITY OF CARE OF GLIOMA PATIENTS

EDITED BY: Marie-Therese Forster, Philip De Witt Hamer, Mirjam Renovanz and Shawn L. Hervey-Jumper

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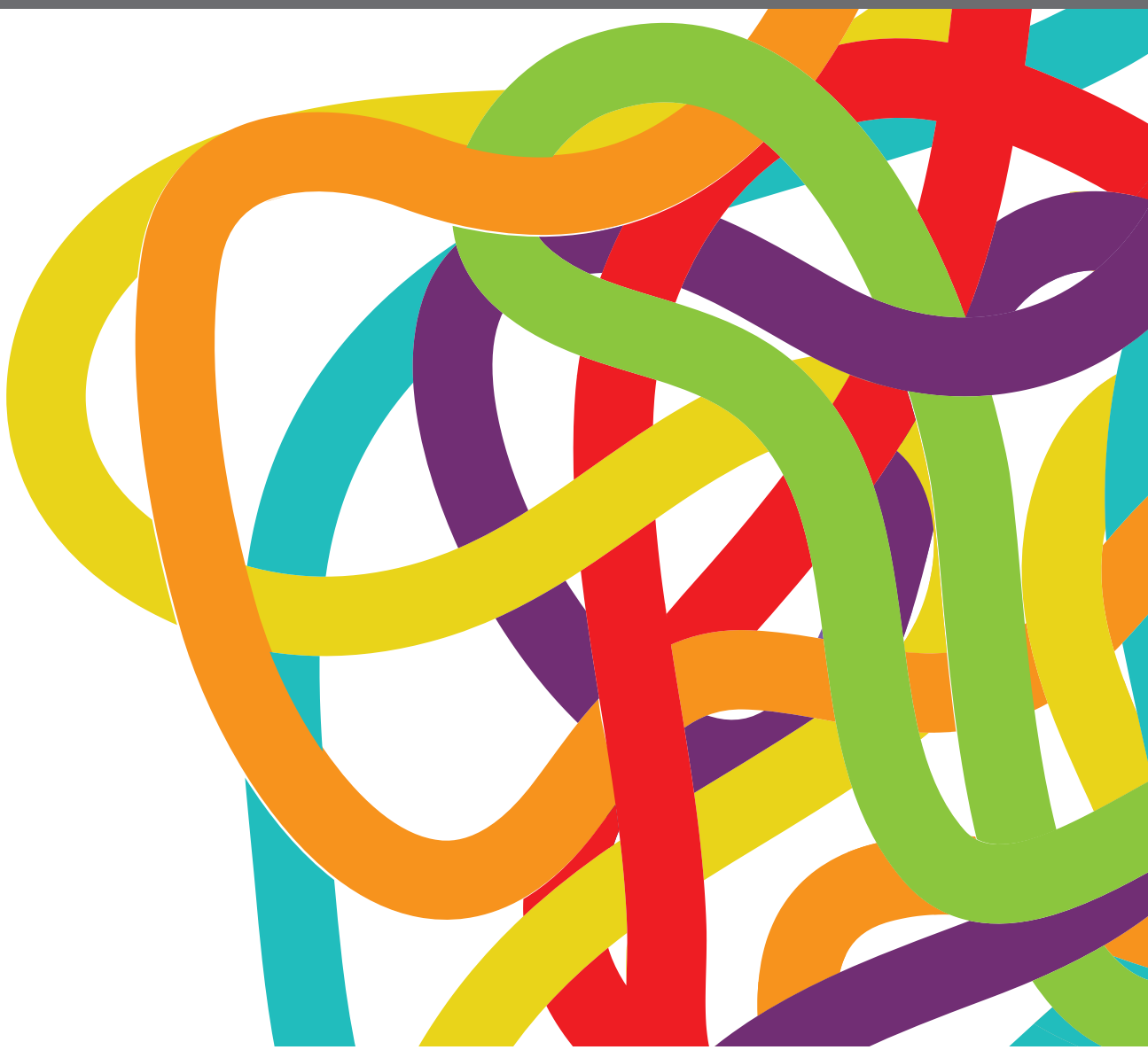

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# QUALITY OF CARE OF GLIOMA PATIENTS

Topic Editors:
**Marie-Therese Forster,** University Hospital Frankfurt, Germany
**Philip De Witt Hamer,** Amsterdam University Medical Center, Netherlands
**Mirjam Renovanz,** Universitätsmedizin Mainz
**Shawn L. Hervey-Jumper,** University of California, San Francisco, United States

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David D. Eisenstat,
Royal Children's Hospital, Australia

*CORRESPONDENCE
Marie-Therese Forster
Marie-Therese.Forster@med.uni-frankfurt.de

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# Editorial: Quality of care of glioma patients

Marie-Therese Forster[1]*, Philip De Witt Hamer[2], Shawn L. Hervey-Jumper[3] and Mirjam Renovanz[4]

[1]Department of Neurosurgery, University Hospital Frankfurt, Frankfurt, Germany, [2]Department of Neurosurgery, Neurosurgical Center Amsterdam, Amsterdam, Netherlands, [3]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, United States, [4]Department of Neurosurgery, University Hospital Tübingen, Tübingen, Germany

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**quality of care, glioma, quality of life, neurocognition, new technologies**

Editorial on the Research Topic
Quality of care of glioma patients

Over many decades, extent of tumor resection and overall survival were almost the sole parameters by which treatment success and quality of care of glioma patients had been measured. With the advent of new systemic therapy approaches and new imaging technologies, with the increasing understanding of brain connectivity and of molecular mechanisms of glioma disease, an individualized patient-centered therapy for glioma has evolved. Thus, today, many patients, especially patients with IDH-mutated gliomas with a more favorable prognosis, see themselves confronted with a chronic disease rather than with an end-of-life perspective immediately after tumor diagnosis.

As a consequence, quality of care of glioma patients has been brought into the focus, mainly encompassing high-quality and shared decision making (1), excellent performance, outcome measures and treatment accessibility (2). However, with regard to high-end techniques, complex quality and process management and the holistic approach toward patients considering their biopsychosocial situation, quality of care in this context still is defined to high-income countries. This applies even more for patients with brain tumors, for whom highest incidence rates have been found in countries with high sociodemographic index levels, reflecting the lack of accessibility of advanced and costly imaging technologies as well as advanced neurological and neurosurgical services in many areas of the world (3, 4). Moreover, due to population growth, aging as well as the environmental and socioeconomic situation of health care—including rising inflation and the shortage of qualified healthcare workers—the maintenance of quality of care of glioma patients will be challenging in the future.

Having all these healthcare system and healthcare service quality issues in mind, we aimed at gathering new insights into the current quality of care of glioma patients in this special Research Topic.

## Neurocognition and quality of life

A discussion on what quality of care means in lower-grade glioma patients has been provided by Taillandier et al., pointing out the importance of an "interactive patient-centered medicine." In their opinion article they elaborate on the limitations of randomized-controlled trials in neuro-oncology and argue in favor of well-conducted observational studies in order to understand the long-term evolution of glioma, with respect to neurocognitive and health-related quality of life (QoL) parameters instead of solely molecular markers.

Neurocognition and QoL is the topic of six publications in this article collection. Van Kessel et al. investigated whether glioma patients' preoperative neurocognitive performance had an impact on survival. They found that memory function added prognostic value in high-grade glioma patients (additionally to established pre-selected predictors), but not in patients with low-grade glioma. Dufner et al. pointed out the importance of assessing patients' psychosocial burden and mood disturbances during adjuvant tumor treatment, given the relation of depression and chemotherapy-induced nausea and vomiting. Two publications focused on the neurocognitive consequences of awake glioma surgery. Staub-Bartelt et al. found that planned awake surgery had no negative impact on the prevalence of distress, anxiety or depression in glioma patients. Reitz et al. observed not only a high number of patients experiencing anxiety and depression prior to awake surgery, but also clear improvements in this and all other neurocognitive domains at long-term postoperative follow-up. Moreover, all patients in their cohort were seizure-free after awake surgery, albeit under anti-convulsive medication in 81.5% of patients. Robe et al. equally addressed postoperative outcome concerning seizure-freedom in patients with low-grade glioma, and the benefits of early surgery in these patients. Thus, patients undergoing early surgery for low-grade glioma significantly later lost their ability to work after tumor diagnosis than patients who underwent tumor resection at least 6 months after diagnosis.

## Neurological function and frailty assessments

However, patients' pre- and post-operative neurological function, and thus, quality of life, clearly depends on glioma localization and invasion of eloquent regions. Thus, Coburger et al. reported on 83 patients with lower grade glioma (WHO grade II and III, according to the WHO 2016 classification) situated in regions involving motor and/or language function and observed permanent new postoperative deficits in 38.6% of their patients 3 months after surgery. They found that permanent new neurological deficits after surgery significantly correlated with preoperative neurological impairment and complete tumor resection.

While these authors did not address overall survival of their patients, another publication within this Research Topic, provided by Kasper et al., focusing on glioblastoma patients, found a clear association between patients' neurological function after surgery and overall survival. Similarly, Krenzlin et al. reported on a significant correlation of patients' frailty, assessed by The Geriatric eight health status screening tool (G8) and Groningen Frailty Index (GFI), and overall survival.

However, although QoL has increasingly been put into the focus of clinical trials of glioma patients, clinical assessment practice of patient-reported outcomes (PROs) still remains very heterogenous, as shown by Weiss Lucas et al. Investigating the use of PRO and neurocognition assessment practices throughout departments of surgical neuro-oncology in Germany, they observed that only a small majority of departments performed patient-centered screenings outside of clinical trials. As a consequence, the authors recommended a minimum number of PRO and neurocognitive assessments for routine clinical practice in their publication.

## Quality indicators and adverse events

While quality of care ultimately aims at excellent patient outcomes, quality of care highly depends on process quality. Besides defining quality indicators for quality of care assessments (5), detecting and reporting on adverse events and complications are therefore essential for continuously improving processes, and thus, improving the quality of care. Vecchio et al. addressed the issue of adverse events following surgery in lower-grade gliomas, using the Landriel–Ibanez classification (LIC) and the Therapy-Disability-Neurology (TDN) score, reporting on postoperative complications in 47.6% of their patients. Katzendobler et al. equally focused on severe adverse events; however, after stereotactic biopsies in 617 glioma patients, they only identified severe postoperative complications including complications requiring an intervention in 1.2% of cases. Moreover, they succeeded to establish an integrated diagnosis by stereotactic biopsy in 96.4% of their patients.

## Novel prognostic biomarkers

Regarding diagnosis and the prognostic value of gene expression profiling, Liu R. et al. reported on Guanine nucleotide-binding protein subunit gamma 12 (GNG12) as a novel biomarker, with high levels of GNG 12 expression representing an independent risk factor for poor prognosis in patients with glioma, regardless of the presence of IDH mutations or 1p/19q co-deletions.

## Uncommon co-morbidities and tumor presentations in adults with gliomas

The remaining two articles in this Research Topic focus on clinical themes with a relatively rare incidence in adults with glioma. El Rahal et al. retrospectively analyzed 1,800 glioblastoma patients of whom 2.1% had been treated for hydrocephalus by ventricular shunting. They observed symptomatic improvement in 95% of patients after shunting and the necessity of shunt revisions in 26% of patients, and concluded that hydrocephalus treatment in glioblastoma patients "might maintain patients' eligibility for crucial oncological therapy as well as quality of life."

Finally, Liu H. et al. provided an analysis of 1257 patients with optic pathway gliomas and revealed OS rates of 93% 10 years after tumor diagnosis with treatments including surgery, radiation and chemotherapy not resulting in better prognoses.

To summarize, this article collection includes remarkable publications on the quality of care of glioma patients and emphasizes again the multifaceted nature of the Research Topic. We thank all the authors, colleagues and the team of Frontiers who contributed to this work.

## Author contributions

M-TF: conceptualization. M-TF and MR: data interpretation and writing—original draft. M-TF, PDWH, SH-J, and MR: data acquisition and writing—review and editing. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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frontiers in Oncology

OPINION
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# What Does Quality of Care Mean in Lower-Grade Glioma Patients: A Precision Molecular-Based Management of the Tumor or an Individualized Medicine Centered on Patient's Choices?

*Luc Taillandier*[1,2], *Tiphaine Obara*[1,2] *and Hugues Duffau*[3,4]*

[1] Centre de Recherche en Automatique Nancy France - UMR 7039 - BioSiS Department, Faculty of Medicine, Université de Lorraine, Vandoeuvre-lès-Nancy, France, [2] Neurology Departement, Neurooncology Unit, CHRU, Nancy, France, [3] Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, Montpellier, France, [4] Team "Plasticity of Central Nervous System, Stem Cells and Glial Tumors", National Institute for Health and Medical Research (INSERM), U1191 Laboratory, Institute of Functional Genomics, University of Montpellier, Montpellier, France

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**Edited by:**
*Marie-Therese Forster, University Hospital Frankfurt, Germany*

**Reviewed by:**
*Joerg Tonn, LMU Munich University Hospital, Germany*

***Correspondence:**
*Hugues Duffau*
*h-duffau@chu-montpellier.fr*

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## INTRODUCTION

Neurooncology is a young specialty which initially dealt mostly with glioblastoma patients with a short overall survival (OS). Yet, recently the scope gradually expanded by taking care of lower-grade glioma (LGG) patients with a longer OS (1). Historically, these patients were managed with a "wait and see attitude" claiming "benignity" despite 6 to 7 years OS (2, 3). Therefore, quality of care was mainly based on physician's subjectivity and not on the natural history, leading to beliefs that early surgery was not adapted due to "normal neurological examination".

Twenty years later, it is now admitted that (i) beyond seizures, LGG patients suffer from cognitive and behavioral deficits at diagnosis even in incidental cases (4) (ii) this tumor will inescapably transform in higher grades, explaining the use of "lower-grade glioma" (mixing II/III) expression (5) (iii) early surgery is a main therapeutic factor (significant correlation between extent of resection and OS) (6, 7) (iv) early radiotherapy, at least given alone, is not associated with decreased mortality (6, 8). These changes resulted in a longer life expectancy now over 15 to 16 years (9–11).

Moreover, neurooncologists had to pay more attention to quality of life (QoL) for patients who must learn to live with a chronic neoplastic disease.

On the other hand, because LGG will systematically recur, further adapted treatments have to be administrated (12). However, heterogeneity of progression patterns (13) makes the prediction of timescales of proliferation, migration, and degeneration at the individual level impossible.

To provide more reliable prognostic factors, advances in molecular biology led to a new classification designed for more appropriate decisions (14). Surprisingly, although genetics was initially a tool to better dissociate types of LGG with distinct prognosis, molecular biology rapidly

became the first parameter in guidelines (15). Although useful, by taking mostly account of genetics criteria and extrapolating a correlation to specific OS based upon statistical analysis, there is a risk to neglect tumor-host interactions, patient's wishes, and long-term QoL.

Here, the main purpose is to redefine what "best quality of care" means by considering both tumor characteristics and patient's personal criteria. The ultimate goal is to give the choice of therapeutic orientation at each step thanks to honest although complex and time-consuming information highlighting oncofunctional balance and various strategies individually adapted over time in parallel with changes in tumor behavior and patient's expectations.

## TOWARD HEGEMONY OF PRECISION MEDICINE BASED ON GLIOMA MOLECULAR PROFILE: THE RISK TO IMPOSE A "UNIQUE SOLUTION"

Official guidelines, elaborated on EBM and mostly relying on randomized controlled trials (RCTs), were primarily designed to help physicians within a framework facilitating decision making and thus defining a "quality of care".

Particularly, progress allowed a refinement of the WHO classification increasingly based on genetic profiling (14, 16). This praiseworthy initiative gradually drifts toward more drastic molecular recommendations. Such a so-called precision EBM (17), glioma, and not patient-centered, is questionable. First, the 2016 classification (14) was built on few parameters (e.g., 1p19q, IDH, and MGMT status) too simplistic to capture complex glioma behavior and host interactions. Because improved knowledge will still take a considerable time, it is difficult to understand how "quality of care" can be determined on preliminary criteria. For example, IDH wild-type glioma were considered as molecular glioblastoma (15), whereas by integrating markers, such as TERT or EGFR, distinct groups exhibiting different prognosis (18–20) are now identified. Thus, many patients dogmatically receive and continue to receive RT-CT, whereas it would be more adapted to follow some of them by integrating parameters, such as growth rate (21, 22), and wonder about the multimodal heterogeneity. Similarly, because response rate to CT is statistically higher in oligodendrogliomas, it was peremptorily postulated that upfront, CT was not indicated in astrocytomas by neglecting that stabilization or shrinkage was nonetheless possible (23), thus opening the door to surgery which can have a major impact on prognosis. Thereby, tumor genetics represent an important but not exclusive part of the story (24).

These examples illustrate the drift in the utilization of EBM originally defined as "the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients" (25). Yet, the power of population-based observational studies based on real-life data collected in clinical routine was progressively denied for the benefit of exclusive RCTs. Nevertheless, they suffer from serious limitations (26, 27), first the inclusion of selected patients not reflecting the daily practice [e.g., young age in Stupp et al. trial (28)], or the fact that factors like extent of resection are overlooked (29), whereas a meta-analysis confirmed a strong correlation to OS (7) even after adjustment for molecular markers (6). Currently, a statistical result identified by RCTs is erected as a rigid law to be applied to each patient, without considering the inter-subject multimodal variability (30). If RCTs are the most convincing and effective strategy for answering a simple therapeutic question with measured short-term effects, they remain unsuitable to the current neuro-oncological issues. Indeed, the challenge in this era is rather to know what kind of patients will respond effectively to a therapeutic strategy and not to determine the best treatment among highly selected patients. Even if statistical tools as interaction tests used in RCTs design could give results of subgroup analyses, they remain insufficient because of a lack of statistical power and never allow conclusion. In fact, when the clinical questions and situations are not compatible with the use of RCTs, the importance of observational studies should be reconsidered. If they are conducted with a methodological rigor (long follow-up, sufficient size, few missing data) and analyzed with statistical tools limiting biases, they could provide reliable evidence and enable a better understanding of the long-term evolution. Besides, a Cochrane review (31) highlighted that the results of observational studies and RCTs are most often in agreement.

Third, EBM was not designed to validate a multistep strategy over years. Indeed, time-scales are different between the long life expectancy of patients and many RCTs with only a short follow-up which optionally use surrogates (such as progression-free survival [PFS] moreover often not accurately assessed) to demonstrate within the time allowed a significant difference regarding investigated parameters. This "reality of the moment" does not reflect long-term OS and QoL, e.g., early RT may have an impact on PFS but not on OS (8) while generating delayed and sometimes major cognitive deterioration (32, 33) not observed with too short a follow-up. It was the case in the RCT trial by Buckner et al. (29) within which (i) contrast enhancement was noted for approximately 50% of patients which is quite atypical for LGG (ii) surgical status is mainly represented by biopsies or partial surgeries in opposition to specialized teams practices mainly carrying out subtotal or total resections (iii) IDH status is only accessible in less than half of the cases and 1p19q in a quarter of them (iv) and cognitive analysis was only based on the MMSE (designed for dementia patients) with a longitudinal partial completion (**Table 1** for a critical review of RCTs).

Fourthly, whereas the quality of care relying on RCT depends on a reductionist panel of criteria, the selection of parameters "officially recognized" as decreed under the guise of EBM is questionable. For example, velocity expansion diameter is not incorporated in trials while it is an independent prognostic marker not correlated to molecular profile (45) and more reliable than 2007 WHO classification to predict OS (46, 47). Moreover, a main weakness of the 2016 WHO classification is

**TABLE 1 |** Main RCTs in medical neurooncology for LGGs: critical review of cognition and quality of life data.

| Reference | Authors conclusion | Cognition | Quality of Life |
|---|---|---|---|
| Klein M et al. Neuro-Oncology 2021;23:803–11 (34) | "Neuropsychological assessment was performed in 98 patients (53 RT, 46TMZ). At 12 months, compliance had dropped to 66%, restricting analyses to baseline, 6 months, and 12 months. At baseline, patients in either treatment arm did not differ in memory functioning, sex, age, or educational level. Over time, patients in both arms showed improvement in Immediate Recall ($P = 0.017$) and total number of words recalled (Total Recall; $P < 0.001$, albeit with delayed improvement in RT patients (group by time; $P = 0.011$). Memory functioning was not associated with RT gross, clinical, or planned target volumes. | Memory functioning was assessed using the Visual Verbal Learning Test (VVLT). 12 months compliance 66% **No data beyond one year** | See Reijneveld JC et al. Lancet Oncol. 2016;17:1533-42. (35) |
| Breen WG et al. Neuro Oncol.2020;22:830-37 (36) | *"Long-term follow-up indicates no benefit to high-dose over low-dose radiation for low-grade gliomas".* | "Cognitive function appeared to be stable after radiation as measured by MMSE" 187/203 MMSE at base line Completion <50% at all time points **Only MMSE** | **No data** |
| Dirven L, et al. Int J Radiat Oncol Biol Phys. 2019;104:90-100. (37) | *"The brain target volume receiving focal radiation therapy in fractions of 1.8 Gy to a total of 50.4 Gy did not appear to be independently associated with HRQoL in high-risk patients with low-grade glioma in the short term, as opposed to tumor progression".* | No data expect QLQ C30 BN 20 pre-selected "cognitive functioning" | QLQ-C30 and QLQ-BN20 4 preselected HRQoL scales (global health status, cognitive and social functioning, and fatigue) |
| Baumert BG, et al. Lancet Oncol. 2016;17:1521-32. (38) | *"Overall, there was no significant difference in progression-free survival in patients with low-grade glioma when treated with either radiotherapy alone or temozolomide chemotherapy alone. treatment choices".* | **Only MMSE** See Reijneveld JC **et al.** Lancet Oncol. 2016 (35) | EORTC QLQC30 + BN 20 See Reijneveld JC et al. Lancet Oncol. 2016 (35) |
| Reijneveld JC et al. Lancet Oncol. 2016;17:1533-42. (35) | *"The effect of temozolomide chemotherapy or radiotherapy on HRQOL or global cognitive functioning did not differ in patients with low-grade glioma".* | **Only MMSE** Completion 1 year •TMZ 74% •RT 67% 3 Years •TMZ 58% •RT 57% **No data after 3 years** | EORTC QLQC30 + BN 20 Completion 1 year •TMZ 68% •RT 59% 3 years •TMZ 50% •RT 54% **No data after 3 years** |
| Buckner JC et al N Engl J Med. 2016;374:1344-55 (29) | *"In a cohort of patients with grade 2 glioma who were younger than 40 years of age and had undergone subtotal tumor resection or who were 40 years of age or older, progression-free survival and overall survival were longer* | **Only MMSE** See Prabhu RS **et al.**, | **No data** |

*(Continued)*

**TABLE 1** | Continued

| Reference | Authors conclusion | Cognition | Quality of Life |
|---|---|---|---|
| | *among those who received combination chemotherapy in addition to radiation therapy than among those who received radiation therapy alone".* | 2014 (39) | |
| Prabhu RS et al. J Clin Oncol. 2014; 32:535–41 (39) | *"The MMSE is a relatively insensitive tool, and subtle changes in CF may have been missed. over RT alone for patients with low-grade glioma.* … *The addition of PCV chemotherapy to RT improves PFS without excessive CF detriment over RT alone for patients with low-grade glioma".* | **Only MMSE** Completion •55% 2 years •57% 3 years •44% 5 years **No data after 5 years** | – |
| Shaw EG et al. J Clin Oncol.2012;30:3065-70. (40) | *"PFS but not OS was improved for adult patients with LGG receiving RT + PCV versus RT alone. On post hoc analysis, for 2-year survivors, the addition of PCV to RT conferred a survival advantage, suggesting a delayed benefit for chemotherapy"* | **No data** | **No data** |
| van den Bent MJ, et al. EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. 2005;366:985-90. (8) | *"Early radiotherapy after surgery lengthens the period without progression but does not affect overall survival. Because quality of life was not studied, it is not known whether time to progression reflects clinical deterioration. Radiotherapy could be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored".* | ***"Quality of life was not studied"*** *"To investigate whether patients free from tumour progression had any neurological signs and symptoms, the neurological signs and symptoms at 1 year were analyzed in patients who were still progression-free at 2 years. The use of this subset ensures that the acute effects of treatment have subsided, and that patients who are already progressing at 1 year but have not yet been diagnosed with progression are excluded from the analysis. Post-hoc analysis found no differences between the two groups for cognitive deficit, focal deficit, performance status, and headache (data not shown)"* | |
| Brown PD, et al. Int J Radiat Oncol Biol Phys. 2004;59(1):117-25 (41) | *"The presence of an abnormal baseline MMSE score was a strong predictor of poorer progression-free and overall survival for patients with a low-grade glioma. The baseline MMSE should be considered in future prognostic scoring systems"* | **Only MMSE** | **No data** |
| Shaw E et al. J Clin Oncol. 2002;20:2267-76. (42) | *« This phase III prospective randomized trial of low- versus high-dose radiation therapy for adults with supratentorial low-grade astrocytoma, oligodendroglioma, and oligoastrocytoma found somewhat lower survival and slightly higher incidence of radiation necrosis in the high-dose RT arm. The most important prognostic factors for survival are histologic subtype, tumor size, and age. The study design of the ongoing intergroup trial in this population will be discussed.* | "Grade 3 to 5 radiation neurotoxicity (necrosis) was observed in seven patients, with one fatality in each treatment arm" See Brown PD et al., 2004 (41) | |
| Karim AB et al. Int J Radiat Oncol Biol Phys. 2002;52:316-24. (2) | *"Early postoperative conventional RT such as that used for this protocol appears to improve the time to progression or progression-free survival, but not overall survival, for patients with low-grade glioma".* | See van den Bent MJ 2005 (8) | See van den Bent MJ 2005 (8) |
| Kiebert GM et al.Eur J Cancer.1998;34:1902-9 (43) | *« A quality of life (QoL) questionnaire consisting of 47 items assessing a range of physical, psychological, social, and symptom domains was included in the trial to measure the impact of treatment over time. Patients who received high-dose radiotherapy tended to report lower levels of functioning and more symptom burden following completion of radiotherapy. These group differences were statistically significant for fatigue/malaise and insomnia immediately after radiotherapy and in leisure time and emotional functioning at 7-15 months after randomization. These findings suggest that for conventional radiotherapy for low-grade cerebral glioma, a schedule of 45 Gy in 5 weeks not only saves valuable resources, but also spares patients a prolonged treatment at no loss of clinical efficacy"* | | Since at the start of the study no well-validated, standardised QoL questionnaire was available for this population of patients, a questionnaire was constructed to meet the requirements of this study protocol. The questionnaire designed for this study was primarily adapted from a variety of sources including the Sickness Impact Pro®le (SIP), the Rand Corporation Health Insurance Study battery of questionnaires, the Center for Epidemiological Studies Depression Scale, and from previous questionnaires employed within the EORTC. A preliminary version of the questionnaire was pretested on a sample of patients at the Free University Hospital in Amsterdam, The Netherlands. The questionnaire consisted of 47 items assessing a range of physical, psychological, social, and symptom domains. Initial completion 82/345 pts. Completion à 36-60 months 61/143 |

*(Continued)*

**TABLE 1** | Continued

| Reference | Authors conclusion | Cognition | Quality of Life |
|---|---|---|---|
| Karim AB et al. Int J Radiat Oncol Biol Phys. 1996;36:549-56 (44) | *"The EORTC trial 22844 has not revealed the presence of radiotherapeutic dose-response for patients with LGG for the two dose levels investigated with this conventional setup, but objective prognostic parameters are recognized. The tumor size or T parameter as used in this study appears to be a very important factor".* | "The sequelae and the quality of life do not appear to be different in the two arms but will be reported separately later in another report" | |

arbitrarily to not consider intra-tumoral heterogeneity (19, 48, 49). Indeed, although areas of malignant transformation are frequently identified in the middle of LGG, especially after extensive surgery, they are not recognized as "foci of grade III/IV" within a grade II glioma but condition the final grading for the entire tumor. This oversimplification leads to a monolithic strategy, namely to administrate RT-CT, while efficient alternative exists, particularly to delay adjuvant treatments following maximal resection with a 95% survival rate at 5 years (50).

To sum up, due to a new orientation of EBM different from the Sackett et al. seminal concept (25) this "precision-medicine" risks to indirectly impose a "unique solution" based upon few molecular markers unable to reflect the complex glioma-host interactions. This simplistic inflexible attitude does not really represent the "informed consent" of the patient.

## THE ALTERATIVE WAY OF MULTIMODAL AND ADAPTIVE INDIVIDUAL DECISION MAKING AIMING TO ANTICIPATE THE STORY YEARS IN ADVANCE

Because LGG patients live one to two decades, neurooncologists should learn to anticipate functional considerations. Indeed, a major lack of "precision-medicine" in gliomas is to prioritize analysis of PFS and OS as first endpoints at the expense of QoL. However, if a patient is doing well, this means that he/she is still alive, while the reverse is not true. Therefore, QoL should be more systematically considered as the main endpoint since LGG patients should have an active life (30). Yet, physicians are usually content with a basic neurological examination optionally with a simplistic neuropsychological assessment (e.g. MMSE) and a performance scale score (15). Nonetheless, to enjoy an optimal lifestyle (social investment, sexuality, childbirth, work) preservation of higher-order cognitive, emotional, and behavioral functions is mandatory (12). Neurosurgeons developed intraoperative awake mapping and monitoring of conation, cognition, and personality, resulting in a connectome-based resection according to a real-time investigation of neural networks and taking account of neuroplasticity (51–53). This led to a decrease of morbidity with stabilization or even improvement of postoperative neuropsychological scores (4) and over 97% of return to employment (54). By contrast, these types of high-level parameters have never been reported in CT/RT randomized study.

Beyond the lack of cognitive or QoL parameters framing each treatment in RCTs for LGG, and criticisms concerning tools (MMSE or QoL questionnaires tailored for malignant rapidly evolving tumors), these criteria are nonetheless essential to elaborate new guidelines paving the way for "quality of care." Neuro-oncologists should ask the patient to define his/her own expectations and adjust the management accordingly (12, 33), e.g., awake surgery with identification of eloquent networks *à la carte* (55). Indeed, the patient must understand during the first meeting that therapeutic reserve is not inexhaustible. Typically, early RT may improve glioma control for years but entire re-irradiation is not possible at progression. This issue should be clearly explained to anticipate next stages. Moreover, because RT may induce delayed cognitive deteriorations, the onco-functional balance must be extensively discussed by tailoring a real patient-centered attitude (12, 56). The ultimate aim should be to use the good treatment(s) at the optimal moment(s) according not only to the tumor genetics but also other prognostic parameters and patient's expectations over time. Remarkably, recent series showed that applying this concept led to OS over 16 to 17 years while preserving the QoL for over one decade (10, 11).

## CONCLUSIONS

Beyond the fundamental opposition between precision medicine relying on molecular EBM and individualized multistep therapeutic approach adapted over years, "best quality of care" starts by giving the choice to the patient and family and by honestly detailing both philosophies. This approach of complexity is time-consuming and poorly suited to productionist practices of our care systems. It is, nevertheless, possible, independent of the socio-cultural level of each patient, and it represents the condition of a true interactive patient-centered medicine, far from a "unique solution" dogma.

The other risk of a single thought is to disempower the physicians who will not continue to actively discuss the best therapeutic option tailored to each patient but only passively apply a "standardized protocol". This could lead to an impoverishment of knowledge, failing to see the full picture if all alternatives are not critically considered anymore. The ultimate danger would be to end up with strategies exclusively dictated by processing of large databanks with pre-defined reductive parameters or to use artificial intelligence methods disconnected from clinical practice and real life: this may turn doctors into uncritical executing agents.

Therefore, official recommendations should only be a guide, and tumor boards should provide consultative proposals but not become too oppressive (particularly for medico-legal issues); otherwise, a rigid EBM might kill innovation, which is still essential because glioma patients cannot yet be cured.

In summary, although efforts have been made to excavate different molecular subtypes from the formerly not well-defined mix of gliomas LGG (57, 58), more refined instruments measuring QoL are still lacking. Overcoming the problem of an overbalance of molecular marker can only be counteracted by triggering high-quality multicentric studies focusing on imaging and QoL issues.

## AUTHOR CONTRIBUTIONS

LT and HD contributed to conception and design of the study. HD wrote the first draft of the manuscript. LT and TO wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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# Assessment Practice of Patient-Centered Outcomes in Surgical Neuro-Oncology: Survey-Based Recommendations for Clinical Routine

*Carolin Weiss Lucas*[1*†], *Mirjam Renovanz*[2,3†], *Johanna Jost*[4], *Michael Sabel*[5], *Dorothee Wiewrodt*[4†] *and Marion Rapp*[5†]

[1] Center of Neurosurgery, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany, [2] Department of Neurology & Interdisciplinary Neuro-Oncology, University Hospital Tuebingen, Tuebingen, Germany, [3] Department of Neurosurgery, University Hospital Tuebingen, Tuebingen, Germany, [4] Department of Neurosurgery, Muenster University Hospital, Muenster, Germany, [5] Department of Neurosurgery, Heinrich Heine University Hospital of Duesseldorf, Duesseldorf, Germany

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***Correspondence:**
*Carolin Weiss Lucas*
*carolin.weiss@uk-koeln.de*

[†]*These authors have contributed equally to this work*

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The psycho-oncological burden related to the diagnosis of an intracranial tumor is often accompanied by neurocognitive deficits and changes in character, overall affecting health-related quality of life (HRQoL) and activities of daily living. Regular administration of adequate screening tools is crucial to ensure a timely detection of needs for support and/or specific interventions. Although efforts have been made to assure the quality of neuro-oncological care, clinical assessment practice of patient-reported outcomes (PROs) remains overall heterogeneous, calling for a concise recommendation tailored to neuro-oncological patients. Therefore, this survey, promoted by the German Society of Neurosurgery, was conducted to evaluate the *status quo* of health care resources and PRO/neurocognition assessment practices throughout departments of surgical neuro-oncology in Germany. 72/127 (57%) of registered departments participated in the study, including 83% of all university hospital units. A second aim was to shed light on the impact of quality assurance strategies (i.e., department certification as part of an integrative neuro-oncology cancer center; CNOC) on the assessment practice, controlled for interacting structural factors, i.e., university hospital status (UH) and caseload. Despite an overall good to excellent availability of relevant health care structures (psycho-oncologist: 90%, palliative care unit: 97%, neuropsychology: 75%), a small majority of departments practice patient-centered screenings (psycho-oncological burden: 64%, HRQoL: 76%, neurocognition: 58%), however, much less frequently outside the framework of clinical trials. In this context, CNOC affiliation, representing a specific health care quality assurance process, was associated with significantly stronger PRO assessment practices regarding psycho-oncological burden, independent of UH status (common odds ratio=5.0, p=0.03). Nevertheless, PRO/neurocognitive assessment practice was not consistent even across CNOC. The overall most commonly used PRO/neurocognitive assessment tools were the Distress Thermometer (for psycho-

oncological burden; 64%), the EORTC QLQ-C30 combined with the EORTC QLQ-BN20 (for HRQoL; 52%) and the Mini-Mental Status Test (for neurocognition; 67%), followed by the Montreal Cognitive Assessment (MoCA; 33%). Accordingly, for routine clinical screening, the authors recommend the Distress Thermometer and the EORTC QLQ-C30 and QLQ-BN20, complemented by the MoCA as a comparatively sensitive yet basic neurocognitive test. This recommendation is intended to encourage more regular, adequate, and standardized routine assessments in neuro-oncological practice.

**Keywords: distress, burden, health-related quality of life (HRQL), patient-reported outcome (PRO), neurocognition, screening tools, brain tumor**

## INTRODUCTION

The diagnosis of an intracranial tumor confronts patients on the one hand with the burden of an oncological disease, but on the other hand also with neurocognitive deficits and changes in character, which overall affect health-related quality of life (HRQoL) and activities of daily living. Reliable patient-reported outcome measures (PROMs) can facilitate early recognition of psychosocial burden, depression, and anxiety and can lead to adequate support (1, 2). Accordingly, assessment and monitoring of neurocognitive function can play an important role in therapy and disease monitoring (3). Therefore, timely and closely followed patient-reported outcome (PRO) and performance-based assessments seem highly advisable to ensure a comprehensive neuro-oncological care, and have recently attracted increasing interest even beyond the context of clinical trials. However, to date there is no consensus regarding the best clinical and scientific practice of PRO and performance-based assessments in neuro-oncological patients.

Approximately 10 years ago, a standardized certification for neuro-oncology centers was implemented in Germany aiming at standardizing and improving patient care as comprehensively as possible. Since then, many positive developments have been observed in the field of neuro-oncology, driven by enhanced interdisciplinary cooperation. Despite all this, the sole requirement to date is to offer psycho-oncology counseling to at least 10% of brain tumor patients. Accordingly, clinical experience shows that the implemented standard operating procedures linked to certification have not yet reached a satisfactory level in terms of comprehensiveness and detail. For instance, adequate PROMs have not been included in official recommendations, and other important aspects, such as neurocognition, play a subordinate role, since no specifications are required. A fixed screening scheme to identify all types of related support needs would therefore be desirable as a standard operating procedure, even beyond the framework of certified neuro-oncology centers (CNOC; certified by the German Cancer Society [DKG]).

For this purpose and as a first step, we designed a survey, to describe the *status quo* of different assessment strategies applied throughout neuro-oncological units in CNOC and non-CNOC in Germany, also considering the university status as a potential confounder. Local organizational and health care structures are also considered to unravel interactions between existing structures as well as the clinical and scientific practice to evaluate psycho-oncological burden, HRQoL, and neurocognition in brain tumor patients. To conclude, this work provides a recommendation for a simple and little time-consuming assessment, based on the practical results of this survey and the literature.

## MATERIAL AND METHODS

### Study Design

The survey was designed by the authors on behalf of the neuro-oncological section of the German Society of Neurosurgery (DGNC) and was sent to all registered neurosurgical centers treating neuro-oncologic patients (i.e., n=127 centers) throughout Germany. The survey was conducted between November 2019 and April 2020. The heads of the neurosurgical departments or (if existing) of the specialized sub-units for neuro-oncological surgery were invited *via* electronic mail and/or telephone to participate in the survey. To ensure maximum survey response, multiple reminders were placed *via* electronic mail or phone calls to the departments' secretaries. If no response was received after at least six reminders, the department was excluded from the study. The survey contained 28 multiple- and single-choice questions divided into four sections, mainly covering the following points (for detailed overview, cf. translated survey in the supplement): (i) center organization (CNOC, university hospital [UH], specialized neuro-oncologic outpatient clinic, caseload); (ii) health care structure (psycho-oncology, neuropsychology, palliative care); (iii) HRQoL assessment (practice and tools); (iv) assessment of psycho-oncological burden, depression, and anxiety (practice and tools); (v) assessment of neurocognition (practice and tools).

### Statistical Analysis

Data were stratified by institutional academic level (two levels: UH; others) and by affiliation to a CNOC (two levels: affiliated; not affiliated) to investigate the association of institution type and certification on the health care structure as well as on the practice of PRO assessments.

Differences between groups (stratified by, e.g., CNOC affiliation) with respect to binary outcomes such as the existence of health care structures were analyzed using the Mantel Haenszel Chi-squared test with continuity correction, controlling for the respective confounding co-factor (e.g., UH). In case the Mantel Haenszel test was significant, Fisher's exact tests were calculated *post-hoc* for the respective subgroups.

For ordinal or continuous outcome variables, such as the time span between tumor diagnosis and first contact to palliative care, Wilcoxon's rank sum test with continuity correction was calculated. Associations between ordinal or continuous variables and binary variables (e.g., caseload and UH) were analyzed using point-biserial correlations. To control for the interfering effect of a second significant factor, partial correlations were additionally calculated when appropriate. Statistically significant differences are generally reported as exact p-values. Whenever appropriate, a false discovery rate (FDR) correction (4) was applied (referred to as FDR-corrected throughout the manuscript). The statistical analysis was performed using R (version 3.6.3; R Studio version 1.1.463).

# RESULTS

Out of 127 neurosurgical departments (including 36 UHs and 46 CNOCs), 72 departments (56.7%) participated. Four departments (3.1%) declined to participate; the remaining 51 departments did not respond despite being approached at least six times. 14 out of 16 German federal states returned the survey, with a certain overrepresentation of the districts North Rhine-Westphalia (21%) and Bavaria (15%).

## Center Organization

30 (42%) of the participating departments were part of UHs, as opposed to 37 (51%) university-affiliated teaching hospitals, and 5 (7%) district hospitals without university affiliation. 35 departments (49%) were part of CNOCs, and 60 departments (86%) declared to run a specialized neuro-oncologic outpatient clinic with a median caseload of 250 neuro-oncological consultations per year (range: 20-3000). This implies that this survey included 83% of all 36 German UHs running a neurosurgical unit and 76% of all 46 German CNOCs. Of note, there was a highly significant relationship between UH and CNOC status with most departments having the status of both (n=24/72) or neither UH nor CNOC (n=31/72; p<0.0001; **Table 1**).

For this reason, the use of the Mantel-Haenszel test was considered appropriate (cf. Statistical analysis). An overview of the caseloads specifically referring to primary brain tumors (referred to as "caseload" throughout the manuscript) is provided in **Table 2**. In our sample, the caseload showed a strong, significant correlation with UH (r=0.63; p<0.0001) which remains significant when controlling for the factor CNOC affiliation using a partial correlation approach (r=0.55; p<0.0001). In contrast, the moderate correlation of the caseload with the CNOC affiliation of the department (r=0.37; p=0.002) did not survive when controlled for the UH status (r=0.04; p=0.55).

Of interest, 28 (47%) of the participating departments replied to perform awake neurosurgery on a regular basis, ranging from 32% without to 62% with CNOC affiliation, irrespective of the UH status (Cochrane Mantel-Haenszel test: cOR=3.5, p=0.002) and caseload.

**TABLE 1** | Squared table of department affiliation to CNOC *versus* UH.

| Status | CNOC | No CNOC |
|---|---|---|
| University hospital | 24 | 6 |
| No university hospital | 11 | 31 |

*The chi-squared test shows a significant relationship between CNOC and UH status (p < 0.0001).*

## Health Care Structure

Except for departments without UH status nor CNOC affiliation (77%), psycho-oncology services were fully available in all other participating centers (**Table 2**), as reflected by a moderate, significant correlation of this care structure with caseload size (r=0.26; p=0.03). Across all centers, the availability of psycho-oncological support was higher for inpatients compared to outpatients (i.e., 78% *versus* 54%, respectively) and was mostly provided by psychologists (79%) and/or by medical staff (27%), and very rarely by pastors (1%).

Accordingly, inpatient palliative care was available in nearly all departments (97% overall), whereas the existence of outpatient palliative care services ranged from 43% to 71% (**Table 2**). In most centers, the respective services were provided by the hospitals and relatively rarely in collaboration with other institutions (psycho-oncology: 7%; palliative care: 15%, overall). The median time span between tumor diagnosis and first contact with palliative care was 39 weeks (i.e., 9 months), ranging from 1 to 87 weeks (i.e., 20 months), statistically unrelated to CNOC or UH status.

Overall, neuropsychological units/services existed in 75% of participating hospitals, ranging from 55% to 100% depending on department affiliation: there was a statistical trend towards better availability of neuropsychologists in UH (p=0.095) whereas the CNOC affiliation factor had no significant influence (**Table 2** and **Figure 1**). Accordingly, an utmost weak correlation was observed between neuropsychologist availability and caseload (r=0.21; p=0.09).

## Assessment of Psycho-Oncological Burden, Depression, and Anxiety

The assessment of psycho-oncological burden, depression, and anxiety is practiced in most of the participating departments (i.e., 64%), more commonly across CNOCs (p=0.03; **Table 3**), but independent of the caseload (r=0.17; p=0.16). However, this influence of CNOC affiliation on assessment practice was not significant after correcting for exclusively study-related practice, i.e., when considering only assessments outside the context of clinical trials (**Figure 2**). Overall, the majority of patients (median estimation 80%) is assessed in departments which reported to perform PROMs of psycho-oncological distress, depression, and anxiety. Relatively rarely (20%), the caregivers

**TABLE 2** | Caseload and health care structure.

| | Percentage | | | | | Statistical significance of stratifying factors | |
|---|---|---|---|---|---|---|---|
| | Overall | CNOC | | No CNOC | | Factor CNOC | Factor UH |
| | | UH (n=24) | No UH (n=6) | UH (n=11) | No UH (n=31) | (controlled for factor UH) | (controlled for factor CNOC) |
| **Primary brain tumor consultations per year*** | | | | | | | |
| <100 | **26%** | 4% | 30% | 0% | 52% | | |
| 100-199 | **39%** | 38% | 60% | 33% | 38% | | |
| 200-299 | **17%** | 25% | 10% | 33% | 10% | r=0.04; p=0.72 | r=0.55; p<0.0001 |
| ≥300 | **14%** | 33% | 0% | 33% | 0% | | |
| *[Reply rate]* | ***[96%]*** | *[100%]* | *[91%]* | *[100%]* | *[94%]* | | |
| **Health Care Structure**** | | | | | | | |
| Psycho-oncology | **90%** | 100% | 100% | 100% | 77% | $X^2$=1.63; p=.20; | $X^2$=0.55; p=.46; |
| *[Reply rate]* | ***[99%]*** | *[100%]* | *[100%]* | *[100%]* | *[97%]* | cOR=na | cOR=na |
| Palliative Care | | | | | | | |
| Inpatient | **97%** | 96% | 100% | 100% | 96% | $X^2$=0.01; p=.92; | $X^2$=0.04; p=.84; |
| *[Reply rate]* | ***[94%]*** | *[100%]* | *[91%]* | *[100%]* | *[90%]* | cOR=1.3 [0.02;79.0] | cOR=0.6 [0.01;36.6] |
| Outpatient | **57%** | 71% | 60% | 67% | 43% | $X^2$=0.32; p=.57; | $X^2$=0.73; p=.39; |
| *[Reply rate]* | ***[94%]*** | *[100%]* | *[91%]* | *[100%]* | *[90%]* | cOR=1.7 [0.5;5.3] | cOR=2.0 [0.5;5.3] |
| Neuropsychology | **75%** | 92% | 80% | 100% | 55% | $X^2$=0.48; p=.49 | $X^2$=2.79; p=.095; |
| *[Reply rate]* | ***[94%]*** | *[100%]* | *[91%]* | *[100%]* | *[94%]* | cOR=2.29 [0.51;10.21] | cOR=6.81 [1.02;45.59] |

*Significant differences regarding health care structures are highlighted (statistical trends in light blue). Statistical tests: *partial Pearson correlations; **Cochrane Mantel-Haenszel test. Percentages are also provided by subgroups, i.e., UHs (as opposed to non-university institutions) and CNOCs. Overall percentages [reply rates] are highlighted in bold.*

were included in distress assessments, irrespective of department affiliation and certification (**Table 3**); however, significantly associated with higher caseloads (r=0.46; p=0.02).

The most common PROM carried out to assess psycho-oncological burden, depression, and/or anxiety was by far the Distress Thermometer (DT; (5) 61% overall), followed by the Hospital Anxiety and Depression Scale (HADS; (6) 33% overall), the Beck Depression Inventory (BDI; (7, 8) 22% overall), and the Hornheider Screening Instrument (HIS; (9) 17% overall). The Basic Documentation for Psycho-Oncology [PO-Bado; (10)], which is an external assessment instrument, was used by four departments (i.e., 11% overall) in addition to at least one of the

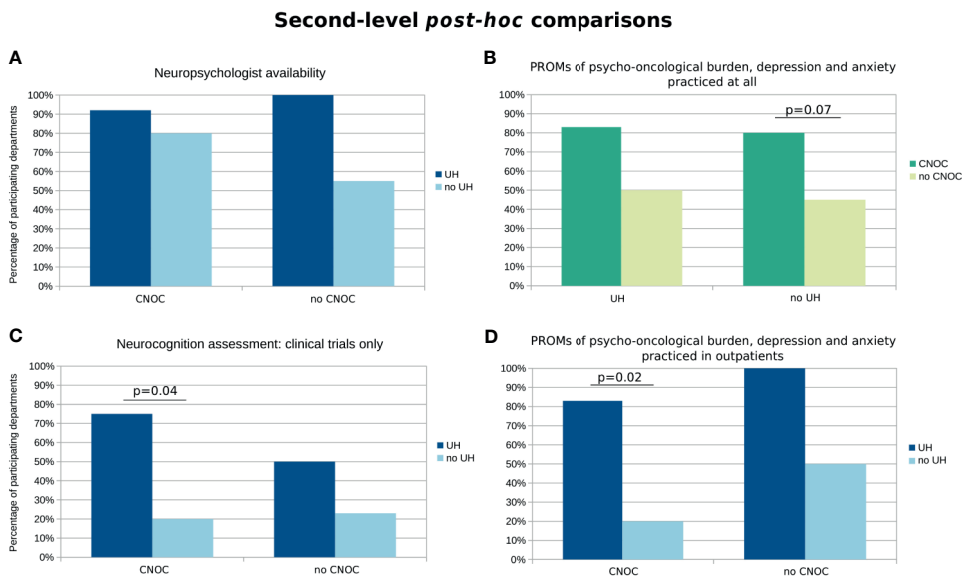


**FIGURE 1** | Second-level *post-hoc* comparisons of available health care structures and assessment practices influenced by quality assurance and institutional factors (i.e., either CNOC or UH affiliation as grouping factors). The y-axis represents the percentages of departments with **(A)** availability of the respective health care structures or **(B–D)** practice regarding the specific assessments. The selection of charts is based on statistically relevant group differences, at least on the level of a statistical trend ($p < 0.1$) according to the Cochrane Mantel-Haenszel test (cf. colored fields in **Tables 2** and **3**). Exact p-values according to post-hoc Fisher's Exact tests (FDR-corrected) are provided if $p < 0.1$.

**TABLE 3 |** Regularity and indications of PRO and neurocognitive assessments.

| | Percentage | | | | | Cochrane Mantel-Haenszel test | |
|---|---|---|---|---|---|---|---|
| | Overall | CNOC | | No CNOC | | Factor CNOC | Factor UH |
| | | UH (n=24) | No UH (n=6) | UH (n=11) | No UH (n=31) | (controlled for factor UH) | (controlled for factor CNOC) |
| **Psycho-oncological burden, depression, and anxiety** | | | | | | | |
| Assessments practiced | **64%** | 83% | 80% | 50% | 45% | $X^2$=4.96; p=.03; | $X^2$=0.10; p=.75; |
| *[Reply rate]* | ***[96%]*** | *[100%]* | *[91%]* | *[100%]* | *[94%]* | cOR=5.0[1.4;18.0] | cOR=1.2 [0.3;4.5] |
| Clinical trials only | **34%** | 45% | 13% | 100% | 15% | $X^2$=0.10; p=0.75; | $X^2$=6.09; p=0.14; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=1.2 [0.3;4.5] | cOR=11.0 [1.5;82.2] |
| Specific entities only | **7%** | 0% | 0% | 0% | 23% | $X^2$=0.01; p=0.92; | $X^2$=0.65; p=0.42; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=0 [nan;nan] | cOR=0 [nan;nan] |
| Caregiver included | **20%** | 30% | 0% | 0% | 23% | $X^2$=0.11; p=0.74; | $X^2$=0.30; p=0.58; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=0.7 [0.1;5.1] | cOR=3.0 [0.4;23.9] |
| Inpatients | **100%** | 100% | 100% | 100% | 100% | nan | nan |
| *[Relative reply rate]* | *[68%]* | *[75%]* | *[45%]* | *[17%]* | *[19%]* | | |
| Outpatients | **76%** | 83% | 20% | 100% | 50% | $X^2$=0.27; p=0.60; | $X^2$=5.21; p=0.02; |
| *[Relative reply rate]* | ***[68%]*** | *[75%]* | *[45%]* | *[17%]* | *[19%]* | cOR=0.2 [0.01;3.3] | cOR=23.3; [1.8;308.3] |
| **HRQoL** | | | | | | | |
| Assessments practiced | **76%** | 100% | 70% | 50% | 63% | $X^2$=2.63; p=0.11; | $X^2$=0.50; p=0.48; |
| *[Reply rate]* | ***[97%]*** | *[100%]* | *[91%]* | *[100%]* | *[97%]* | cOR=3.0 [0.8;11.0] | cOR=1.9 [0.5;7.4] |
| Clinical trials only | **55%** | 63% | 57% | 67% | 42% | $X^2$=0.01; p=0.91; | $X^2$=0.09; p=0.76; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=1.4 [0.3;5.8] | cOR=1.6 [0.4;6.5] |
| Specific entities only | **11%** | 21% | 0% | 33% | 0% | $X^2$=0.23; p=0.63; | $X^2$=1.12; p=0.29; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=0.5 [0.04;7.0] | cOR=inf. [nan;nan] |
| Inpatients | **93%** | 95% | 100% | 100% | 83% | $X^2$=0.01; p=0.91; | $X^2$=0.18; p=0.67; |
| *[Relative reply rate]* | ***[55%]*** | *[83%]* | *[14%]* | *[67%]* | *[32%]* | cOR=1.6 [0.004;509] | cOR=5.3 [0.01;2680] |
| Outpatients | **76%** | 80% | 0% | 100% | 67% | $X^2$=0.46; p=0.55; | $X^2$=1.2; p=0.3; |
| *[Relative reply rate]* | ***[55%]*** | *[83%]* | *[14%]* | *[67%]* | *[32%]* | cOR=0 [nan;nan] | cOR=inf. [nan;nan] |
| **Neurocognition** | | | | | | | |
| Assessments practiced | **58%** | 83% | 50% | 33% | 45% | $X^2$=1.82; p=0.18; | $X^2$=0.62; p=0.43; |
| *[Reply rate]* | ***[96%]*** | *[100%]* | *[91%]* | *[100%]* | *[94%]* | cOR=2.4 [0.8;7.5] | cOR=1.9 [0.6;5.8] |
| Clinical trials only | **50%** | 75% | 20% | 50% | 23% | $X^2$=0.1; p=0.7; | $X^2$=3.55; p=0.06; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=1.4 [0.2;9.0] | cOR=7.7 [1.2;47.6] |
| Specific entities only | **15%** | 15% | 20% | 0% | 15% | $X^2$=0.26; p=0.61; | $X^2$=0.38; p=0.60; |
| *[Relative reply rate]* | ***[100%]*** | *[100%]* | *[100%]* | *[100%]* | *[100%]* | cOR=2.0 [0.2;23.4] | cOR=0.5 [0.05;5.2] |

*Percentages of positive responses are provided by subgroups, i.e., UH and/or CNOC affiliation, along with the rate of replies to each question of the questionnaire (reply rate). Differences between groups (controlled for the alternative factor) are described according to Cochrane Mantel-Haenszel statistics. Results showing a statistical trend or significant association are highlighted (green: $p < 0.05$; blue: $p < 0.1$). In such cases, additional post-hoc tests (Fisher's exact tests) were calculated for the respective subgroups (cf. **Figure 1**). COR, common odds ratio (95 percent confidence intervals of true common odds ratios provided in brackets). Nan, not computable. Overall percentages [reply rates] are highlighted in bold.*

aforementioned PROMs (**Figure 3A**). When considering only the 22 departments which perform distress assessments (also) outside the context of clinical trials, the three most frequently used tools were the DT (64%), the HSI (23%), and the HADS (18%), followed by the BDI (14%) and the PO-Bado (9%).

Overall, the assessments were mostly performed by physicians (58%), followed by nurses (56%) and psycho-oncologists (28%), and rarely by students (9%) and case managers (5%) (**Figure 3B**). To account for the association between CNOC affiliation and assessment practice (in contrast to an utmost minimal association with UH), the descriptive data shown in **Figure 3** are stratified by CNOC.

## Health-Related Quality of Life Assessment

Although HRQoL assessment is practiced in the vast majority of departments (76%; **Table 2**), irrespective of their caseloads (r=0.18; p=0.15), the assessment is widely limited to clinical trials. Consequently, the percentage of centers with clinical routine practice in HRQoL assessment outside the context of studies reaches only 34%, statistically independent of their affiliations and caseload (**Figure 2**). Moreover, screening of brain tumor patients for HRQoL is generally irregular, even in departments that perform such screening (median 50% of patients, overall; see supplemental **Table S1**).

**Figure 4A** shows that the most commonly used HRQoL screening instrument was the 30-items quality of life questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) accompanied with its brain module (EORTC QLQ-BN20) (15), overall (52%) as well as in CNOC (64% *vs.* 31% no CNOCs). In contrast, outside CNOC departments, the Short Form Health 36 [SF-36; (16)] was mostly used (50% *versus* 29% in CNOCs; 36% overall). The shortened

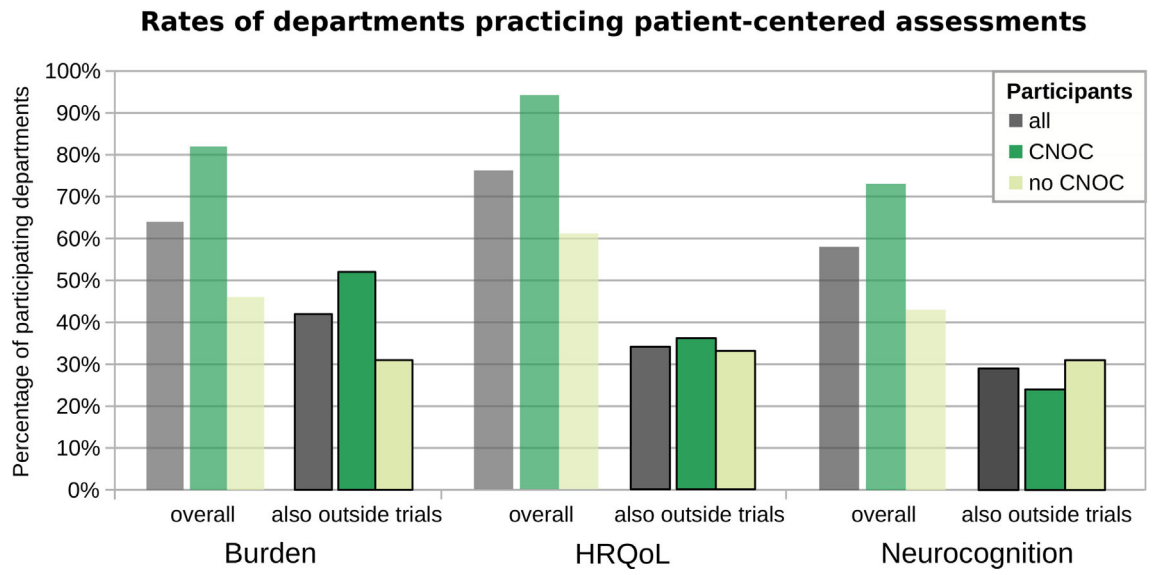


**FIGURE 2** | Assessment practice overall *versus* not exclusive to clinical trials. The y-axis represents the percentages of departments performing the respective assessment types, across all participating departments (grey) and grouped by CNOC (green) *versus* no CNOC (light green) status. Burden: psycho-oncological burden, depression, and anxiety.

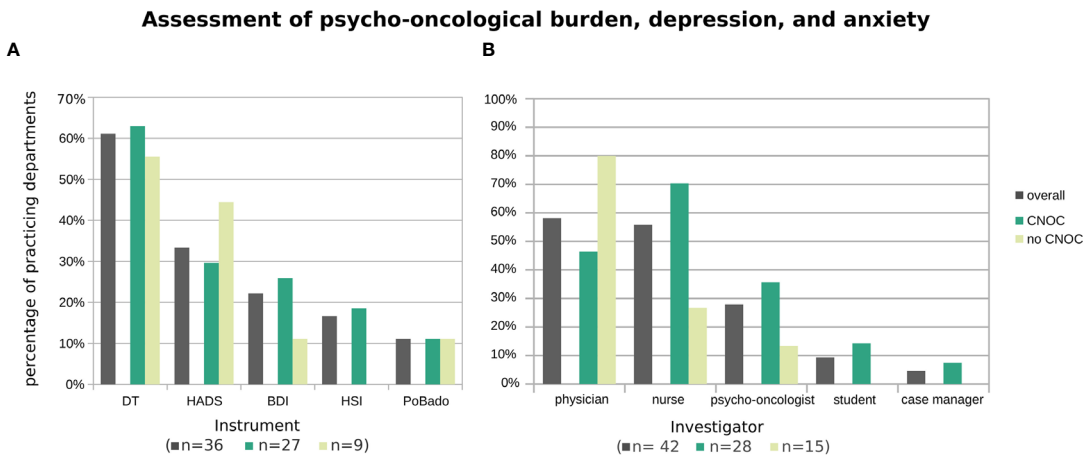


**FIGURE 3** | Applied psycho-oncological assessment instruments **(A)** and administering professionals **(B)**, overall and stratified by certification type of participating departments. Histograms are based on replies from *n* departments practicing assessment of psycho-oncological burden, depression, and anxiety (with *n* provided by subgroup in the x-axis label). Multiple instruments (or multiple types of professionals) were named by 39% (29%) of departments.

version of the SF-36 [i.e., SF-12; (17)] represented the third most frequent HRQoL assessment tool (24% overall; CNOCs: 18%; no CNOCs: 19%); further instruments were named by single centers (cf. **Figure 4** legend).

Additional analysis of the subset of 24 departments performing HRQoL assessments other than in the context of clinical trials revealed a similar but more diversified pattern (EORTC: 42%; SF-36: 26%; SF-12: 5%; others: 11%).

In line with the distress assessments, the HRQoL self-reports are again mostly obtained by physicians, followed by nurses; in contrast, case managers are only very rarely involved (**Figure 4B**).

## Neurocognitive Assessment

The overall rate of departments practicing neurocognitive assessments was 58% (**Table 2**), irrespective of the caseload. However, only 29% of participating departments (also) perform cognitive assessments unrelated to studies (statistically independent of center affiliation, certification, and caseload; **Figure 2**). Accordingly, the overall median percentage of brain

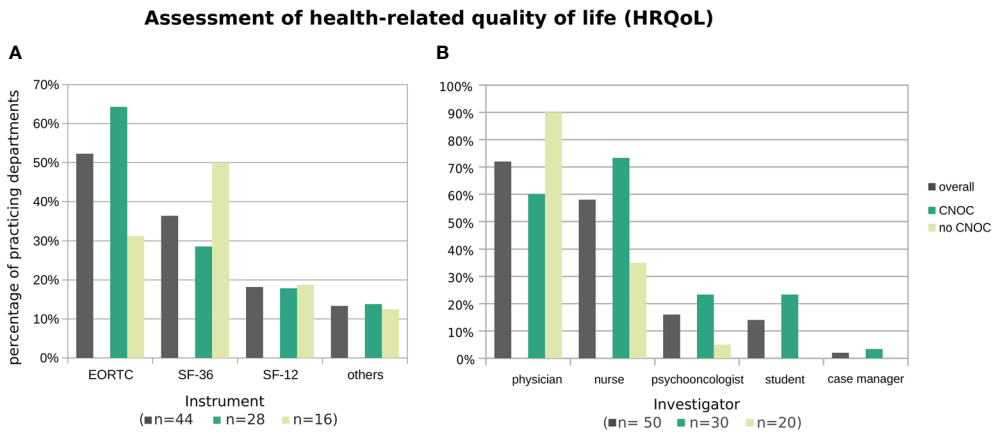


**FIGURE 4** | Practiced HRQoL assessment instruments **(A)** and administering professionals **(B)**, overall and stratified by CNOC affiliation. Histograms are based on replies from *n* departments practicing assessment of HRQoL (with *n* provided by subgroup in the x-axis label). Multiple instruments (or multiple types of professionals) were named by 27% (30%) of departments. Other instruments (all named once) were the Functional Assessment of Cancer Therapy [FACT; (11)], the 5-level EQ-5D version [EQ-5D-5L; (12)], the Hornheider Screening Instrument (HIS; (9) cf. Assessment of psycho-oncological burden, depression, and anxiety), the Barthel Index (13), the Aachen Life Quality Inventory [ALQI; (14)], and an unspecified instrument developed by the respective department.

tumor patients undergoing cognitive assessment in each department was low, i.e., 25% (with estimates ranging from 5% to 100%; cf. **Supplementary Table S1**), indicating that few centers follow regular clinical practice in this regard.

By far, the most commonly used screening instrument for neurocognitive functions was the mini mental status test (MMST) (18) (67% overall), particularly in centers without CNOC affiliation (**Figure 5A**). Accordingly, the MMST was practiced by seven out of nine (i.e., 78% of the) departments which practice neurocognitive assessment (also) beyond the exclusive context of clinical trials and answered this question.

The Montreal Cognitive Assessment [MoCA; (22)] represented the overall second most used neurocognitive test (33% overall) and reached the level of the MMST in CNOC (**Figure 5A**). When excluding the departments which practice neurocognitive assessments solely in clinical trials, the test was only named by one of the remaining nine centers.

Similar to the assessments of psycho-oncological burden, depression, and anxiety, as well as HRQoL, the tests were mostly performed by physicians. Nurses and neuropsychologists were also often included in the assessment, especially in CNOC (**Figure 5B**). Outside the context of clinical trials, the distribution was even between physicians and neuropsychologists (both 53%), followed by nurses (18%), whereas students played no role in collecting neurocognitive screening data (0%).

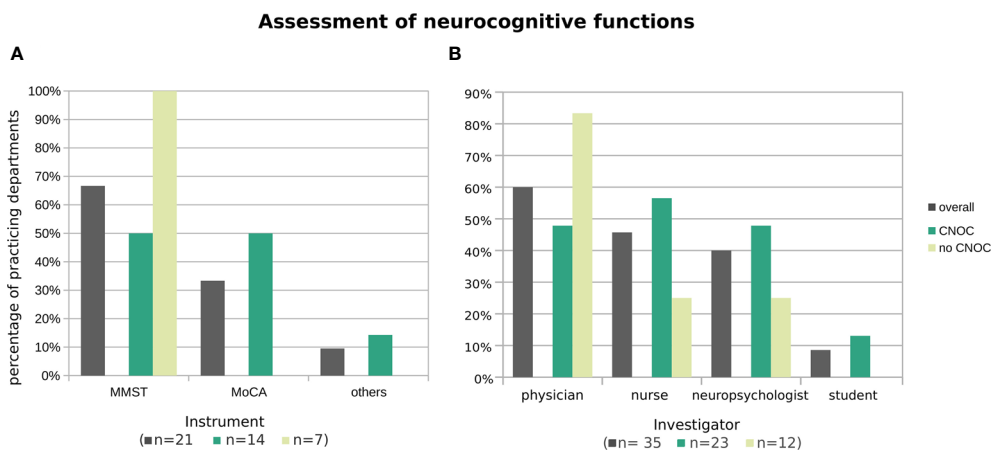


**FIGURE 5** | Practiced neurocognitive assessment instruments **(A)** and administering professionals **(B)**, overall and stratified by CNOC affiliation. Histograms are based on replies from *n* departments practicing assessment of neurocognitive functions (with *n* by subgroup in brackets in the x-axis label). Multiple instruments (or multiple types of professionals) were named by 10% (21%) of departments. Other instruments (each named once) were the dementia detection screening DemTect (19) and the screening battery of the NOA-19 study (20, 21), one naming of "others" was not further specified.

Regarding the time points of neurocognitive tests, the vast majority of the 35 centers practicing this assessment type investigate patients before (86%) and after (91%) surgery; 57% responded to conduct neurocognitive assessments during follow-up as well. Overall, 26% of the centers performing awake surgery include neurocognitive tests in the intraoperative setting (compared to 36% when considering only centers which practice neurocognitive screenings in clinical routine).

# DISCUSSION

This survey investigated available health care structures and PRO as well as neurocognitive assessment practice in German neurosurgical departments, depending on their UH status and CNOC affiliation as well as on their caseloads of primary brain tumor patients. To the best of the authors' knowledge, this is the first survey on this topic, providing a comprehensive overview due to the inclusion of the majority (57%) of the registered neurosurgical departments. Despite an overall good to excellent availability of relevant health care structures (i.e., referring to psycho-oncology, palliative care, and neuropsychology), the clinical routine assessment of relevant PROs, HRQoL assessment, and neurocognitive functions is limited, especially outside clinical trials. However, CNOC affiliation, representing a specific health care quality assurance process, was associated with significantly stronger PRO assessment practices regarding psycho-oncological burden, depression, and anxiety, independent of UH status.

## Assessment of Psycho-Oncological Burden and Adequate Support

Irrespective of tumor entity and prognosis, neuro-oncological patients are at risk for psychological comorbidities (23–25). A screening should be feasible within minutes and results have to be interpreted immediately in order to provide adequate support (26).

In line with our assumption from everyday clinical practice, psychosocial assessment was only carried out by a minority of participating departments outside clinical trials (42%). Although the majority of clinicians attach high importance to screening, its implementation in clinical routine is challenging (27), e.g., due to exhausted workload capacity of qualified staff. This applies particularly to screening instruments developed for cancer patients in general, which might be too complex and time-consuming for brain tumor patients, and thus difficult for them to manage. Even the application of seemingly quick and disease-specific self-report forms can bind significant staff resources, for instance, when patients need assistance in completing the form due to neurocognitive and/or other neurological deficits, or when the consecutive detection of needs requires further steps in patient management. On the other hand, the completion of screening forms by accompanying caregivers on behalf of patients reduces time expenditure for qualified medical personnel but leads to biased assessments. Compared to patients, it is even more difficult to address their relatives as well, reflected by only 20% of caregivers being included in distress assessments despite the generally heavy burden (28, 29). Although not yet widely used in clinical practice (and therefore not included in this survey), several established instruments are available to assess caregiver burden, e.g., the concise 12-items short form of the Zarit Burden Interview [ZBI] (30).

External factors such as certification requirements are leading to faster implementation of screening practice. This is underlined by the fact that psycho-oncological assessment was more common across CNOCs, where not only access to studies and specialized therapy is provided but also the required health care structures for patients are in place. However, implementing quality standards takes time. Looking at the past five years in the certification process, the numbers of initial psycho-oncological counselling have increased very slowly from 11.7% since 2015 (31) to 18.5% (32). Without the control of minimum requirements regarding the rate of patients to be psycho-oncologically assessed, the clinical assessment practice is prone to remain inconsistent.

The German psycho-oncology guideline recommends HADS-D, HSI, DT and PO-Bado, among others, as screening instruments. The BDI should not be regarded as a screening instrument for psycho-oncological distress/burden of disease. Nevertheless, it was indicated by 22% of participants and can be considered as a complementary and comparatively sensitive 21-items instrument to assess depression (as a disease to be medically treated with a considerable prevalence in brain tumor patients) (33). Since self-assessment might not be possible in every neuro-oncological patient, e.g., due to cognitive deficits, an external assessment by the physician can be helpful. If depression is suspected, this will be followed by a psycho-oncological consultation and specific diagnostics and, if necessary, therapy (cf. guideline unipolar depression of the Association of the Scientific Medical Societies in Germany [AWMF]) (34).

Regarding psycho-oncological screening instruments, the PO-Bado (11%) and the HSI (16%) were used rather rarely. The PO-Bado is an external assessment tool (10); hence, for the interpretation of its results, it should be considered that the physicians' estimations do not necessarily reflect the patients' perspectives (35). The HSI, a self-assessment screening instrument, as well as the PO-Bado, are widely used screening tools within Germany.

Both do not meet international quality criteria, which makes them rather unsuitable for international comparison.

The two most frequently used screening instruments were the HADS (33%) and the DT (61%). The HADS, an internationally well-established psycho-oncological screening instrument, refers exclusively to anxiety and depression, whereas the DT allows for the assessment of a much wider range of psychosocial problems and needs (36). Goebel and Mehdorn (37) validated the DT in brain tumor patients. Here, patients are considered to potentially carry a clinically relevant burden if the score is ≥ 6. In a previous work by Rapp et al. the relationship between HADS and DT was analyzed in more than 470 patients (26) resulting in the

recommendation to consult a psycho-oncologist if the DT score is ≥ 5 and emotional problems ≥ 2.

The predominant use of the DT – at least in surgical neuro-oncology in Germany – might not only mirror the broad international acceptance of its short answer option but be also due to its simple, easily administrable, and non-stigmatizing character. The importance of these characteristics should not be underestimated in respect of the considerable prevalence of cognitive deficits in the target population, which interferes with the completion of long and complex questionnaires (38, 39). To address the specific needs of brain tumor patients, Goebel et al. have recently developed an adapted version of the problem list of the DT [HEAT; (38)], focusing on a more disease-specific needs assessment. This test still needs to be validated but could become a highly valuable PROM for brain tumor patients in the future (cf. **Table 4**).

Currently, we recommend the DT as a psycho-oncological screening tool for brain tumor patients (**Table 4**).

## Health-Related Quality of Life Assessment

Serving as an independent predictor of therapy compliance and survival (44), HRQoL was the first PROM serving to evaluate new schemes of neuro-oncological therapy (45). In recent decades, its assessment has gained importance as an outcome measure of treatment response, far beyond the use as an endpoint in clinical trials (46, 47). In this regard, it is not surprising that this study showed a predominance of HRQoL assessment compared to other PROs evaluated (76% overall; up to 100% in CNOCs with UH status), although it also consumed relatively costly human resources (including 72% physicians and 58% nurses, overall). However, only 34% of participating departments practice HRQoL assessments outside clinical trials (independent of the institutional status). This demonstrates that the benefits of their use in improving clinical outcome prediction, complementing standard clinical outcomes, and detecting specific support needs are far from being exhausted. This finding might be influenced by (i) the lack of clear recommendations for HRQoL PROMs in current guidelines, (ii) the copyright protection of most common HRQoL PROMs making them less easily accessible, and (iii) logistic reasons related to the increased manpower required to ensure consequent assessment. In agreement with its predominance in European clinical trials, the EORTC QLQ-C30/BN-20 (15) was the most commonly used instrument (42%) in German centers, too. Notwithstanding its excellent quality in terms of internal consistency, content validity, and construct validity (48), as well as its validation for the specific group of neuro-oncological patients, this comparatively long 50-item questionnaire may be hard for patients to cope with, especially when being part of a comprehensive and repeated assessment based on multiple PROMs. This might be one reason why shorter HRQoL assessment tools (i.e., the 36-item SF-36 or its 12-item short form) (16, 17) were ranked second in frequency of use by the departments participating in this survey (SF-36: 26%; SF-12: 5%), especially by departments without CNOC affiliation, which are generally less influenced by specific requirements of clinical trials. Therefore, prospective studies and novel computerized concepts such as the computerized adaptive test version of the EORTC QLQ-C30 [EORTC CAT; (42, 43)] are highly appreciated. In the upcoming version, the authors intend to achieve a maximum PROM quality whilst reducing time needed to complete the questionnaires.

In summary, we presently recommend the EORTC QLQ-C30/BN-20 to assess quality of life in brain tumor patients (**Table 4**).

## Neurocognitive Assessment

The practice of neurocognitive assessment is rather limited (i.e., 58% overall; 29% outside clinical trials) and widely restricted to relatively simplistic dementia screening tools despite an apparently good overall availability of qualified investigators (e.g., almost 100% neuropsychologists, especially in UHs). Recent literature discussed brief cognitive screenings to be insensitive to important cognitive symptoms; thus, rendering them inadequate (49). The vast majority of departments assessing neurocognitive functions reported to use the well-known and easily administrable MMST, even more if outside the context of clinical studies. In contrast to its broad acceptance, the MMST, originally developed for dementia screening, demonstrates relatively low sensitivity regarding the detection of cognitive deficits in brain tumor patients (50). In comparison, another dementia screening test, i.e., the MoCA, which also allows for a relatively time-efficient and well standardized test administration, was reported to perform significantly better in neuro-oncological patients ($p<0.0001$) (51). This might explain why the MoCA is used relatively frequently in clinical trials, almost overtaking the MMST in departments with considerable study activity (i.e., CNOCs).

More sensitive but also more time-consuming and potentially burdensome, neurocognitive test batteries are apparently very rarely part of clinical assessments in German neurosurgical departments (2 centers, 3% overall), although nowadays generally recommended (52). This is noteworthy since cognitive deficits correlate strongly not only with HRQoL and activities of daily living (53) but also with tumor progression (54) and survival (55). Accordingly, timely detection of neurocognitive deficits using appropriate, sensitive screening instruments appears advisable to enable the responsible physicians to recommend adequate diagnostic, supportive, or therapeutic interventions. Here, a comprehensive but shortened neurocognitive testing instrument could help to improve assessment practice, and thus the detection of cognitive deficits and related support needs. It would need to be

**TABLE 4** | Recommendations for a basic, comprehensive assessment for brain tumor patients.

| Assessment type/topic | Basic (available) | Perspectives *[/complementary]* |
|---|---|---|
| Psycho-oncological burden | DT | Targeted assessment for neuro-oncological patients [based on (37)] |
| HRQoL | EORTC-QLQ-C30, BN20 | EORTC: Update BN-20 (40), *[EORTC item library (41)], [EORTC CAT (42, 43)]* |
| Neurocognition | MoCA | NOA-19 battery for glioblastoma (20, 21) |

*Along with our current recommendation, perspectives on promising future instruments are provided.*

tailored to the limited attention span and coping ability of (newly diagnosed) neuro-oncologic patients and sufficiently standardized to be administered by trained nurses or students. Such a neurocognitive test battery including five parallel versions is currently being evaluated for use in glioblastoma patients in the multicentric NOA-19 study (20, 21). The results will help to find an appropriate neurocognitive test strategy for brain tumor patients in the future.

For now, we recommend the MoCA as basic assessment tool for neurocognition (**Table 4**).

## Impact of Quality Assurance Strategies and Personnel Structure

The higher rate of psycho-oncological PRO assessments in the subgroup of CNOC departments demonstrates the potential of quality-assuring instruments to make a change in assessment practice, building the ground for the detection of support needs and subsequent initialization of supporting interventions. Therefore, the integration of further patient-centered outcome assessments into quality assurance strategies (such as standard-operating procedures, guidelines, or controlled certification requirements) seems advisable to achieve optimized health care standards in neuro-oncology also outside clinical studies. In this context, concrete recommendations regarding an ideal time frame for first contact to palliative care units might also be valuable, as early and regular contact with a palliative care team beginning within a few weeks after first tumor diagnosis has been shown to improve HRQoL, symptom burden, and mood in patients of other oncological entities (56, 57). Moreover, advanced care planning (ACP) is clearly appreciated by the vast majority of neuro-oncological patients and is highly dependent on the patient's general, psychological, and neurocognitive state still being adequate (58, 59). These and other points favoring an integrative palliative care approach argue for earlier involvement of palliative care teams than currently practiced in German departments of surgical neuro-oncology (with a median of 9 months, up to 20 months in our data set).

Another key finding of this work is the imbalance between existing health care structures and available instruments for assessing clinically clearly important PROs and neurocognition on the one hand, and the heterogeneous and incomplete clinical practice of such assessments on the other. As mentioned earlier, one reason for this might be the traditional dependency of PROM and neurocognitive assessments on highly qualified, high-cost personnel like physicians. Especially, the completion of traditional PROMs, i.e., self-report forms to be completed by patients, could be undertaken by less costly staff if appropriate training was to be provided. To which extent this model is transferrable to neurocognitive testing depends on the degree of standardization and the ease of administration of the tests used (which in our view are sufficiently high regarding, e.g., the MMST or the MoCA test).

## Strengths and Limitations

This survey, addressing all registered centers of surgical neuro-oncology in Germany to avoid selection bias, draws a rather comprehensive picture of the neuro-oncological PRO practices in the country. Even pursuing this inclusive approach, we achieved an excellent participation rate of 57% (n=72/127, including n=42 non-UHs) compared to recent surveys in the field of neuro-oncology which followed a similar inclusion strategy [e.g., 5%; n=362/7280; (60)]. Other surveys reporting response rates in the range of 36% (61) up to 75% (62) come with the limitation of addressing a highly selected group of centers [e.g., 28 centers across eleven European nations; (62)].

Despite this methodological strength, the survey is not fully representative due to (i) the missing centers, especially regarding non-UHs and non-CNOCs (selection bias), as well as (ii) missing values due to incomplete surveys/responses, and (iii) the at least potential subjectiveness/rater dependency of several survey items (since the data are based on information provided by medical consultants rather than on official/reliable statistics of the respective institutions). Moreover, (iv) the survey was addressed to neurosurgical units as one representative part of integrative neuro-oncological care centers. To provide a more comprehensive overview of assessment practices dependent on the stages of treatment/disease (and on the distinct disciplines involved) was beyond the scope of this work and will be subject to an upcoming survey.

In the present inquiry, the existence of certain institutional and medical structures was surveyed (e.g., presence of a neuropsychologist), whereas the extent to which this (personnel) structure is actively involved in the assessment of brain tumor patients was not. Moreover, it should be emphasized that the existence of health care structures and practice of assessments (to detect neurocognitive and psycho-oncological needs) do not *per se* lead to improved quality of care – unless followed by adequate interpretation of the outcomes and timely initiation of appropriate measures. The question of which resources and assessment tools, mediated by consecutive interventions/support, have a significant impact on health care quality was beyond the scope of this work and might be further addressed in a prospective study.

# CONCLUDING RECOMMENDATIONS

The *status quo* of PRO and neurocognition assessment in surgical neuro-oncology shows that despite existing care structures, even in CNOCs there are no consistent standard procedures. As a consequence, many patients and caregivers are left alone with their needs and burdens. Widespread adoption of screening tools is essential to implement regular PRO and neurocognitive assessments in clinical practice. Therefore, screening tools are best suited when they bridge the gap between high test quality and practical considerations: tests should be as familiar as possible to the hospital staff, little time-consuming, and easy to perform and to evaluate. With regard to the results of this survey and literature, we hope that our concise recommendation (provided in **Table 4**) will encourage more regular, appropriate and standardized routine assessments in neuro-oncological practice.

# DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

CW: conception and design, acquisition, analysis and interpretation of data, manuscript drafting and revision. MRe, DW, and MRa: conception and design, acquisition and interpretation of data, manuscript drafting and revision. JJ: acquisition and interpretation of data, manuscript drafting and revision. MS: conception and design, manuscript revision. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.702017/full#supplementary-material

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# Added Value of Cognition in the Prediction of Survival in Low and High Grade Glioma

*Emma van Kessel[1]*, Ewoud Schuit[2], Irene M. C. Huenges Wajer[1,3], Carla Ruis[1,3], Filip Y. F. L. De Vos[4], Joost J. C. Verhoeff[5], Tatjana Seute[1], Martine J. E. van Zandvoort[1,3†], Pierre A. Robe[1†] and Tom J. Snijders[1†]*

[1] University Medical Center Utrecht/UMC Utrecht Brain Center, Department of Neurology & Neurosurgery, Utrecht University, Utrecht, Netherlands, [2] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [3] Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, Netherlands, [4] University Medical Center Utrecht/UMC Utrecht Brain Center, Department of Medical Oncology, Utrecht University, Utrecht, Netherlands, [5] University Medical Center Utrecht/UMC Utrecht Brain Center, Department of Radiation Oncology, Utrecht University, Utrecht, Netherlands

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***Correspondence:**
*Emma van Kessel*
*e.vankessel-2@umcutrecht.nl*

*† These authors have contributed equally to this work and share senior authorship*

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**Background:** Diffuse gliomas, which are at WHO grade II-IV, are progressive primary brain tumors with great variability in prognosis. Our aim was to investigate whether pre-operative cognitive functioning is of added value in survival prediction in these patients.

**Methods:** In a retrospective cohort study of patients undergoing awake craniotomy between 2010 and 2019 we performed pre-operative neuropsychological assessments in five cognitive domains. Their added prognostic value on top of known prognostic factors was assessed in two patient groups [low- (LGG) and high-grade gliomas (HGG]). We compared Cox proportional hazards regression models with and without the cognitive domain by means of loglikelihood ratios tests (LRT), discriminative performance measures (by AUC), and risk classification [by Integrated Discrimination Index (IDI)].

**Results:** We included 109 LGG and 145 HGG patients with a median survival time of 1,490 and 511 days, respectively. The domain memory had a significant added prognostic value in HGG as indicated by an LRT ($p$-value = 0.018). The cumulative AUC for HGG with memory included was.78 ($SD$ = 0.017) and without cognition 0.77 ($SD$ = 0.018), IDI was 0.043 (0.000–0.102). In LGG none of the cognitive domains added prognostic value.

**Conclusions:** Our findings indicated that memory deficits, which were revealed with the neuropsychological examination, were of additional prognostic value in HGG to other well-known predictors of survival.

**Keywords: diffuse glioma, cognition, prediction models, added value, prognosis, survival**

## INTRODUCTION

Diffuse gliomas, which are at WHO grade II-IV, are progressive primary brain tumors with a variable, but generally poor prognosis, despite recent progress in treatment options. Until now, research yielded several important predictors of survival, including histomolecular classification, age, the extent of resection, preoperative tumor volume, and Karnofsky performance status (KPS)

for both high- and low-grade glioma (HGG and LGG, respectively) (1–4). Additionally, several prognostic factors for specific grades of tumors were reported. For low-grade glioma, the presence of neurologic deficits before surgery (not including epilepsy) and midline crossing are unfavorable predictors. For high-grade glioma, predictors include MGMT promoter methylation status and minimal mental state examination (MMSE) score (2, 5). These prognostic factors are important to personalize treatment and rehabilitation, and to stratify patients for clinical trials. Additionally, identification of certain, molecular or neurocognitive, prognostic markers, can lead to new insights into the pathophysiological mechanisms of diffuse glioma.

Cognitive deficits occur in all different grades of glioma (6, 7). In a recent study, we found these deficits to be independently, and possibly causally, related to survival in diffuse gliomas (8). However, if an independent or causal relationship is demonstrated between a determinant and outcome in such an etiological study, this does not necessarily mean that this variable is of added value to existing prediction models or known prognostic factors for the prediction of survival. Whereas the main goal in etiological research is to demonstrate relationships at a group level, prognostic research focuses on estimating the risk of future events for an individual patient. As such, investigations into the prognostic value of previously demonstrated causally related factors are sensible. In particular, to assess whether such factors have added value on top of existing prediction models or sets of known predictors.

To our knowledge, research in this field has been focused mainly on HGG and no data have been published about cognition as a predictor of survival for diffuse gliomas based on the WHO 2016-classification of Central Nervous System (CNS) tumors (9). In this work, we performed a retrospective cohort study to investigate the added prognostic value of cognitive functioning in treatment-naive patients with diffuse gliomas of all grades (II-IV), in addition to well-recognized predictors of survival in these patients.

# MATERIALS AND METHODS

## Design and Participants

We performed a single-center retrospective study in a cohort of treatment-naive diffuse glioma patients who underwent elaborate neuropsychological testing as part of their pre-operative work-up for awake brain surgery between January 2010 and July 2019 at the University Medical Center in Utrecht, The Netherlands (UMCU).

Inclusion criteria for this study were the presence of a diffuse glioma according to the criteria of WHO 2016 and a minimum age of 18 years. For tumors diagnosed before 2016, we used all available histological and molecular data (from immunohistochemical staining and targeted next-generation sequencing) from clinical practice to (re-)classify the tumor according to WHO 2016 criteria. Since a small sample (7.9%) (re-)classification was not possible based on the available molecular data, we labeled these as "missing values" and performed imputation later on.

Exclusion criteria were as follows:

(a) Any form of tumor-directed treatment, such as tumor reductive surgery, chemotherapy, and radiotherapy, before neuropsychological assessment. Having undergone a biopsy shortly before a planned resection was allowed. Symptom-directed treatments such as anti-epileptic drugs and dexamethasone were allowed as well.
(b) Incomplete neuropsychological assessment (due to emergency surgery or tumors merely located in the motor strip, for instance). Data were considered complete if more than 50% of tasks within one domain were performed.

Since the various glioma subtypes differ greatly in their biological behavior as well as their prognosis, it is possible that the effect of cognition, as well as other determinants, on survival also differs between WHO 2016 glioma subtypes. For this reason, we performed all analyses separately in HGG (Grade II/III Astrocytoma IDH-Wildtype, Glioblastoma IDH-mutated, and IDH-Wildtype) and LGG (Grade II/III Astrocytoma IDH-mutated, and Grade II/II Oligodendroglioma 1p19q-codeleted) patients.

The UMCU institutional ethical review board approved the study. The informed consent was not obtained for this observational study on data that were obtained as part of routine clinical care (protocol code METC 17/384 and 09-420).

## Neuropsychological Tests

In the study sample, we focused on neurocognitive functioning (NCF) scores for five predefined cognitive domains, namely, attention and executive functioning, memory, psychomotor speed, language, and visuospatial functioning. The neuropsychological instruments that were used as part of our routine clinical care are listed in **Table 1**. These tests are internationally widely used, standardized psychometric instruments for assessing neurocognitive deficits (although not specific for oncology patients) (10).

Neuropsychological tests often tap into more than one cognitive domain and classification into cognitive domains often varies in the literature. We made use of a predetermined test classification in accordance with previous studies and literature (**Table 1**) (23–25). The neuropsychological evaluation was conducted shortly (1–7 days) before the awake brain tumor surgery by an experienced clinical neuropsychologist (CR, MvZ, and IHW). Each neuropsychological test was scored according to standardized scoring criteria. For normative comparisons, the unadjusted scores were transformed into *Z*-scores based on the *M* and *SD* of control subjects derived from published norm data. Use of corticosteroids or anticonvulsants at the time of NPA did not serve as grounds for exclusion.

We measured NCF data at the individual patient level, which means that we counted the number of individual patients with an impaired performance per domain. A patient was considered impaired in a given domain if the patient performed below −2 *SD* on any of the administered (sub) tests within that domain, in accordance with previous studies and based on clinical practice

**TABLE 1 |** Neuropsychological tasks per domain.

| **Attention & Executive Functioning** |
|---|
| Wechsler Adult Intelligence Scale (WAIS) Digit Span Forward[a] |
| Trail Making Test (TMT) Switching ratio (TMTB/TMTA)[b] |
| Phonologic Fluency[c] |
| Stroop/Delis Kaplan Executive Function System (DKEFS) inhibition ratio[d] |
| Wechsler Adult Intelligence Scale (WAIS_IV) Digit Span Backward |
| **Memory** |
| RAVLT-Dutch Version immediate, delay, recognition[e] |
| Rey-Osterieth Complex Figure Test (ROCF) delay[f] |
| Semantic Fluency[g] |
| **Visuospatial functioning** |
| Judgment of Line Orientation (JULO)[h] |
| ROCF Copy |
| **Psychomotor Speed** |
| Stroop/DKEFS I |
| Stroop/DKEFS II |
| TMTA |
| **Language** |
| Boston Naming Test[i] |
| Token Test[j] |

[a] *Wechsler Adult Intelligence Scale Third Edition Digit Span [WAIS-III] (11), Wechsler Adult Intelligence Scale Fourth Edition Digit Span [WAIS-IV] (12).*
[b] *Trail Making Test [TMT] (13).*
[c] *Phonologic Verbal Fluency Test [Lexical Fluency] (14, 15).*
[d] *Delis-Kaplan Executive Function System [DKEFS] (16).*
[e] *15 Words Test [15WT] (17).*
[f] *Rey-Osterieth Complex Figure Test [ROCF] (18, 19).*
[g] *Semantic Verbal Fluency Test [Semantic Fluency] (14).*
[h] *Judgment of Line Orientation [JULO] (20).*
[i] *Boston Naming Task [BNT] (21).*
[j] *Token Test [TT] (22).*

(7). We used a threshold of −1.5 *SD* for cognitive deficits in each domain because of the lower frequencies of impairments in LGG. This was an epidemiological choice to increase the variability in the determinant, however, this more liberal threshold was still clinically relevant and was used in several previous studies before (6).

## Data Collection

At our center, all neuropsychological data are prospectively collected. We extracted data on patient characteristics from the electronic patient file for all diffuse glioma patients undergoing awake surgery between 2010 and 2019. Data included sex, age at surgical resection, survival time and status, integrated ('layered') histomolecular diagnosis based on WHO 2016 classification, extent of resection, $O^6$-methylguanine-DNA methyltransferase (MGMT)-methylation status of the tumor, Karnofsky Performance Scale score (KPS), preoperative tumor volume, and neurologic deficits or epileptic seizures at presentation (5, 26). Volumes were measured in 3D with the use of Osirix Lite version 9.5.2: by Pixmeo R version 4.0.3: by RStudio PBC on T2-/fluid-attenuated inversion recovery (FLAIR)-weighted MRI scans and the volume was defined as the whole area of hyperintensity. This represented the total lesion volume, including tumor infiltration and edema. Volumes were measured by a neuro-oncological neurosurgeon and a junior clinical scientist under the supervision of the same neurosurgeon. Since this parameter was independent of enhancement (and thereby grade) of the lesion, it formed a widely usable representation of the extent of brain volume that was potentially hampered in its function by the tumor in any way (27). The extent of resection was based on the surgical report from the electronic patient file and classified into three different categories, which were biopsy or debulking (1–78%), 79–90%, and 91–100% of macroscopically complete ("gross total") tumor-resection. According to literature, this classification has the highest clinical relevance (28–30). In cases where percentages of resection were not reported, we did not calculate percentages based on the report, but classified "gross total" as 91–100%, "subtotal or incomplete" as 79–90%, and "partially or only small part could be removed" as "1–78%".

Survival time was defined as the period between the first respective neurosurgery and the date of death from cancer or any other cause or censored at the date of last follow-up (March 1, 2020).

## Statistical Analyses

We established, for all different cognitive domains, the additional value to a model with well-recognized predictors of survival per patient group (see below).

Analyses were performed with R version 4.0.3. First, we assessed missing data and whether data were missing completely at random (MCAR) by means of an MCAR table in which patients without missing values was compared with patients with one or more missing values. In order to avoid bias and a decrease in power due to missing data, we imputed missing values by means of multiple imputations (10 imputation sets). The imputation model included all new and existing predictors as well as the outcome. Results were pooled across imputation sets using Rubin's Rules (31).

We analyzed baseline characteristics with descriptive statistics. Univariable analysis was performed to assess the (unadjusted or crude) association of the five cognitive domains of interest and all other determinants with survival, by univariable Cox proportional hazard (CPH) models.

### Model Preparation: Schoenfeld, Df-Beta Residuals, and Collinearity

The Cox model assumes that survival curves of two strata follow hazard functions that are proportional over time. This proportional hazard (PH) assumption was checked for all determinants with log-minus-log plots and by Schoenfeld residuals. Scaled Schoenfeld residuals helped to decide whether the proportional hazards assumption holds, in addition to the log-minus-log plots.

We calculated Df Beta residuals to decide which cases were (too) influential in estimating the model parameters. We performed sensitivity analyses by excluding "influential" patients and checked why these patients were of such great influence.

Before performing survival analyses, we tested for multicollinearity between the determinants KPS and all cognitive domains by Pearson correlation coefficients.

**TABLE 2 |** Baseline characteristics.

| Determinant | LGG** | HGG** | *p*-value |
|---|---|---|---|
| | **Median [IQR]** | **Median [IQR]** | |
| Total number of patients | 109 | 145 | |
| Tumor-volume ($cm^3$) | 48.71 [20.71–75.04] | 71.14 [28.00–134.50] | <0.001* |
| Age at first surgery | 400 [34.00–500] | 600 [54.00–67.00] | <0.001* |
| Survival in days | 1,490 [694–2554] | 5100 [269.00, 774.00] | <0.001* |
| | **N (%)** | **N (%)** | |
| **WHO2016** | | | |
| Grade II/III Astrocytoma IDH-M | 62 (56.6) | - | NA |
| Grade II/III Oligodendroglioma 1p19q deletion | 47 (43.4) | - | NA |
| Grade II/III Astrocytoma IDH-WT | - | 15 (10.0) | NA |
| Glioblastoma IDH-M | - | 10 (7.2) | NA |
| Glioblastoma IDH-WT | - | 120 (82.8) | NA |
| Cognitive impairments | | | |
| Executive functioning and attention (−2) | 15 (13.7) | 53 (36.8) | <0.001* |
| Memory (−2) | 4 (4.0) | 55 (37.5) | <0.001* |
| Psychomotor speed (−2) | 10 (9.0) | 45 (30.7) | <0.001* |
| Visuospatial functioning (−2) | 9 (8.6) | 34 (23.1) | 0.010* |
| Language (−2) | 4 (4.0) | 32 (21.8) | <0.001* |
| Executive functioning and attention (−1.5) | 34 (31.3) | 83 (57.0) | <0.001* |
| Memory (−1.5) | 22 (20.0) | 86 (58.8) | <0.001* |
| Psychomotor speed (−1.5) | 15 (14.1) | 58 (39.9) | <0.001* |
| Visuospatial functioning (−1.5) | 15 (14.1) | 54 (37.2) | 0.001* |
| Language (−1.5) | 10 (9.3) | 51 (35.3) | <0.001* |
| **Extent of resection** | | | <0.001* |
| 1–78 % | 63 (57.5) | 35 (23.9) | |
| 79–90 % | 23 (21.4) | 39 (26.5) | |
| 91–100 % | 23 (21.1) | 72 (49.6) | |
| Midline crossing | 36 (33.4) | 60 (41.4) | 0.403 |
| MGMT-methylation | NA | 72 (49.4) | NA |
| Neurologic deficits at presentation | 71 (65.5) | 112 (76.9) | 0.071 |
| Karnofsky performance score (≥70) | 105 (96.8) | 126 (86.6) | 0.015* |
| Seizures at presentation | 79 (72.6) | 77 (53.3) | 0.004* |
| Sex (female) | 39 (35.5) | 50 (34.7) | 0.957 |
| **Location (measured on T2 FLAIR)** | | | |
| Frontal | 87 (79.9) | 107 (73.6) | 0.340 |
| Temporal | 45 (41.3) | 83 (57.3) | 0.020* |
| Parietal | 31 (28.5) | 82 (56.1) | <0.001* |
| Occipital | 9 (8.3) | 32 (21.9) | 0.010* |
| **Hemisphere** | | | 0.075 |
| Left | 63 (58.0) | 101 (69.4) | |
| Right | 39 (35.9) | 36 (24.8) | |
| Both | 5 (5.2) | 8 (5.8) | |

*P-value refers to the difference between HGG and LGG. IQR, interquartile range; LGG, low grade glioma; HGG, high grade glioma *p < 0.05 (threshold significant value). **Low grade regarding to WHO 2016 criteria. Grade II/III Astrocytoma IDH-mutated, Grade II/III Oligodendroglioma 1p19q deletion. High-grade: Grade II/III Astrocytoma IDH-Wildtype, Glioblastoma IDH-mutated and IDH-Wildtype. Variables do not always add up to the total number of patients, because the average of 10 imputation sets has been taken.*

Furthermore, the potential non-linearity of the association between continuous predictors and the outcome was assessed using restricted cubic splines.

## Determining the Additional Prognostic Value

We determined the added prognostic value for all five different cognitive domains. There were several performance

measures available for quantifying the added value of predictive variables (32).

We calculated added prognostic values by comparing different measures of goodness of fit and predictive performance of the models with and without cognitive functioning included as a predictor. In both HGG and LGG patients, we used a "baseline model" with known predictors from literature and without the inclusion of cognition. These parameters differed for both patient groups (1, 3). We adhered quite strictly to the prognostic factors that are already used as such in models in the literature. Thereafter, we added each one of the cognitive domains to the model separately: resulting in five models per patient group. For all these models, we used multivariable cox-proportional hazard (CPH) regression analyses. The following measures were compared between the baseline model and the five cognitive domain extended models: loglikelihood [formally tested using a likelihood ratio test (LRT)], Akaike's and Bayesian information criterium (AIC and BIC), discriminative performance (by Harrell's c-statistic, Gönen en Heller's k c-statistic and Chambles C/Cumulative AUC), and risk classification [by Integrated Discrimination Index (IDI)]. All these measures were calculated in ten different imputation sets and results were pooled across sets.

# RESULTS

## Patient Characteristics

We made use of an existing cohort as described in an earlier study (8), and extended this cohort with 57 patients operated in between 2017 and 2019. In total 254 eligible patients underwent awake surgery between 2010 and 2019. We included 109 LGG and 145 HGG patients with a median survival time of 1,490 and 511 days, respectively. Descriptive characteristics (after multiple imputations with ten imputation sets) are presented in **Table 2**. As expected, most of our determinants significantly differed between HGG and LGG. These results supported the choice for stratified analysis according to tumor grade.

For the domains executive functioning and memory, 2% of data was missing. Visuospatial functioning had the highest percentage of missing values of all cognitive domains with 14.2%. In the extent of resection, 15.7% of values were missing, while 20% of values in midline-crossing (only for LGG) and 33.7% of MGMT-status (only for HGG). All the other variables had missing values between 1–6.3%. **Supplementary Table 1** shows that patients without and with one or more missing values differed in terms of baseline characteristics, meaning data were not MCAR. Therefore, missing data were accounted for using multiple imputations.

## Neuropsychological Data and Survival

Cognitive impairments ($Z$-values $\leq -2$) in HGG, were most common for the domain memory and executive functioning (37.5 and 36.8%, respectively). In LGG, wherein we used thresholds of $-1.5$ $SD$, deficits were 31.3% for executive functioning and 20% for domain memory.

The univariable survival analyses for all five cognitive domains and other variables are shown in **Supplementary Table 2** (stratified by grade). We did not find collinearity between KPS and cognition.

## Hazard Assumptions, Influential Cases, and Functional Form of Prognostic Factors

The PH assumption was checked for all determinants with log-minus-log plots and by Schoenfeld residuals and was found to hold for all variables.

We calculated Df-beta residuals to estimate for each patient by how much the β estimate for each prognostic factor would change if that patient was deleted from our database. In HGG patients

**TABLE 3 |** Mean added prognostic value for each cognitive domain in high-grade glioma.

| Cognitive domain (Z-value−2 or lower) | No cognition included in model | Memory | Executive functioning | Psychomotor speed | Visuospatial functioning | Language |
|---|---|---|---|---|---|---|
| **Risk classification** | | | | | | |
| 1. IDI | ***NA*** | 0.043 | 0.003 | 0.001 | (−0.011–0.030) | (−0.004–0.029) |
| (95% CI) | | (0.000–0.102) | (−0.015–0.047) | (−0.004–0.026) | | |
| 2. NRI | ***NA*** | 0.301 | 0.158 | 0.034 | 0.090 | 0.040 |
| (continuous) (95% CI) | | (−0.035–0.477) | (−0.139–0.340) | (−0.204–0.235) | (−0.241–0.289) | (−0.211–0.266) |
| **Discrimination** | | | | | | |
| 1. Harrell's c-statistic (SD) | 0.72 (0.013) | 0.73 (0.011) | 0.72 (0.015) | 0.72 (0.013) | 0.71 (0.014) | 0.72 (0.013) |
| 2. Gönen and Heller's c-statistic (SD) | 0.71 (0.015) | 0.72 (0.014) | 0.71 (0.016) | 0.71 (0.014) | 0.71 (0.015) | 0.72 (0.014) |
| 3. Cumulative AUC (Chambles C) (SD) | 0.77 (0.018) | 0.78 (0.017) | 0.77 (0.020) | 0.77 (0.018) | 0.77 (0.018) | 0.77 (0.018) |
| AIC | 882.06 | 877.80 | 880.89 | 882.99 | 883.26 | 882.71 |
| BIC | 906.56 | 905.03 | 908.12 | 910.22 | 910.49 | 909.94 |
| **LL and LLR test** | −4303 (df = 9) | −428.90 (df = 10) | −430.44 (df = 10) | −431.49 (df = 10) | −431.63 (df = 10) | −431.34 (df=10) |
| LL with df | ***NA*** | 5.638 | 1.902 | 0.464 | 0.401 | 0.936 |
| $Chi^2$ | | 0.018 | 0.171 | 0.497 | 0.527 | 0.334 |
| *p*-value | | | | | | |

**LLR test is cognition model vs. no cognition included in model, based on pooled chi-square (over 10 imputation sets). LL, loglikelihood; LLR, loglikelihood ratio; IDI, integrated discrimination index; NRI, net reclassification index; AIC, akaike information criterion; BIC, bayesion information criterion; AUC, area under the curve; df, degrees of freedom.*

**TABLE 4 |** Mean added prognostic value for each cognitive domain in low-grade glioma.

| Cognitive domain (Z-value−2 or lower) | No cognition included in model | Memory | Executive functioning | Psychomotor speed | Visuospatial functioning | Language |
|---|---|---|---|---|---|---|
| **Risk classification** | | | | | | |
| 1. IDI | ***NA*** | 0.063 | 0.027 | 0.047 | 0.013 | 0.002 |
| (95% CI) | | (−0.012–0.201) | (−0.029–0.196) | (−0.007–0.174) | (−0.018–0.108) | (−0.009–0.152) |
| 2. NRI (continuous) | ***NA*** | 0.359 | 0.185 | 0.149 | −0.049 | 0.068 |
| (95% CI) | | (−0.178–0.637) | (−0.366–0.582) | (−0.236–0.590) | (−0.422–0.456) | (−0.535–0.484) |
| **Discrimination** | | | | | | |
| 1. Harrell's c-statistic (SD) | 0.85 (0.022) | 0.87 (0.015) | 0.86 (0.026) | 0.87 (0.017) | 0.85 (0.023) | 0.85 (0.022) |
| 2. Gönen and Hellers c-statistic (SD) | 0.82 (0.016) | 0.83 (0.014) | 0.84 (0.024) | 0.82 (0.018) | 0.82 (0.016) | 0.83 (0.017) |
| 3. Cumulative AUC (Chambles C) (SD) | 0.86 (0.019) | 0.89 (0.015) | 0.88 (0.025) | 0.88 (0.019) | 0.88 (0.021) | 0.87 (0.020) |
| AIC | 110.27 | 109.19 | 109.19 | 109.31 | 111.50 | 111.63 |
| BIC | 115.88 | 115.60 | 115.61 | 115.72 | 117.92 | 118.05 |
| **LL and LLR test** | −48.13 (df = 7) | −46.59 (df = 8) | −46.60 (df = 8) | −46.65 (df = 8) | −47.75 (df = 8) | −47.82 (df = 8) |
| LL with df | ***NA*** | 2.338 | 1.997 | 2.456 | 0.610 | 0.388 |
| $Chi^2$ | | 0.127 | 0.160 | 0.118 | 0.435 | 0.534 |
| *p*-value | | | | | | |

**LLR test is cognition model vs. no cognition included in model, based on pooled chi-square (over 10 imputation sets). LL, loglikelihood; LLR, loglikelihood ratio; IDI, integrated discrimination index; NRI, net reclassification index; AIC, akaike information criterion; BIC, bayesion information criterion; AUC, area under the curve; df, degrees of freedom.*

there were no influential cases. For LGG we found two influential patients (with change in B-coefficients > 0.5). We checked why these patients were of such great influence. Both patients died early while having prognostic favorable determinants (1p19q deletion, extent of resection >91%, no cognitive impairments). We decided not to exclude these patients, because of the risk for a data-driven model.

Because of a non-linear relation between pre-operative tumor volume and survival in HGG patients and age and survival in LGG patients, we changed the functional form of these variables. "Tumor volume" was log-transformed to "log tumor volume" (in HGG models) and "Age in years" was squared to (Age-42.3) (2), with 42.3 being the mean age in our study population. We had to exclude KPS in the LGG models because of the lack of variability (almost all patients had KPS of 70 or higher). In both patient groups, we merged the "biopsy" and "1–78% resection" categories in the "extent of resection" predictor, because of low frequencies in the "biopsy" category.

## Added Values and Multivariable Models

The results of added value assessments for all different cognitive domains in both patient groups are shown in **Tables 3**, **4**. Only the cognitive domain memory showed significant prognostic value in addition to the established, pre-selected predictors in HGG patients. Loglikelihood of the model without cognition showed a value of −4303 (df = 9) vs. −428.9 (df = 10) for the model with memory included (likelihood ratio test *p*-value = 0.018). The cumulative AUC for HGG with memory included was 0.78 (*SD* = 0.017) and without cognition 0.77 (*SD* = 0.018). Integrated discrimination index (IDI) was 0.043 (0.000–0.102).

The multivariable model with memory included is presented in **Table 5**. Impairments in memory showed a significant association with survival [hazard ratio = 1.71 (*p*-value = 0.018; CI; 1.1–2.63)] in presence of the pre-selected predictors age at presentation, the extent of resection, neurologic deficits, epileptic seizures, KPS, WHO-2016 classification, and pre-operative tumor volume. In **Figure 1**, cumulative survival curves for this model are shown, stratified by memory performance.

In LGG, none of the cognitive domains was of added prognostic value, the results of the model without cognition included are shown in **Supplementary Table 3**.

# DISCUSSION

The goal of this study was to investigate the prognostic value of cognitive functioning in treatment-naive patients with diffuse gliomas (low grade and high grade), in addition to well-recognized predictors of survival in these patients. In the multivariable Cox-regression model with HGG, the cognitive domain memory had significant prognostic value when added to a model which included molecular subtype, MGMT-methylation, the extent of resection, age at diagnosis, KPS, seizures at presentation, and tumor volume. In other words, the prognosis of a patient could be predicted more precisely if memory deficits are included as a predictor in prognostic models for overall survival in HGG. In LGG, we did not find the additional value of any of the five cognitive domains.

In earlier work, we already showed that cognitive deficits are independently associated with survival (8). However, the focus of this recently published study was etiologic, rather than prognostic. This means that the main goal was to demonstrate the independent, and possibly causal, the relationship between cognitive deficits and survival at a group level. This was in contrast with the aim of this study, which was prognostic and took place at an individual level with the aim of estimating the risk for an individual patient. Following from these two

**TABLE 5 |** Multivariable cox-regression model with memory included in high-grade glioma.

| Variable | HR | Lower 95% CI | Upper 95% CI | Estimate B | Std-Error (SE) | *p*-value |
|---|---|---|---|---|---|---|
| **Memory** | 1.706 | 1.104 | 2.635 | 0.534 | 0.222 | 0.018** |
| **Extent of resection** | | | | | | |
| (1–80%=ref) | | | | | | |
| 81–90 % | 0.517 | 0.265 | 011 | −0.659 | 0.342 | 0.061* |
| 91–100 % | 0.557 | 0.302 | 029 | −0.585 | 0.313 | 0.070* |
| **WHO−2016** | | | | | | |
| Grade II/III–WT=ref | 092 | 0.281 | 4.240 | 0.088 | 0.692 | 0.899 |
| Grade IV IDH-Mut | 3.169 | 002 | 10.029 | 1.154 | 0.588 | 0.057* |
| Grade IV IDH-WT | | | | | | |
| **Seizures at presentation** | 050 | 0.611 | 1.804 | 0.049 | 0.276 | 0.860 |
| **MGMT/methylation** | 0.491 | 0.274 | 0.878 | −0.712 | 0.297 | 0.024** |
| **KPS (1–69=ref)** | 0.501 | 0.239 | 049 | −0.692 | 0.377 | 0.077* |
| **70–100** | | | | | | |
| **LogVolume** | 039 | 0.820 | 1.318 | 0.038 | 0.121 | 0.753 |
| **Age at presentation** | 046 | 021 | 070 | 0.045 | 0.012 | 0.0003** |

*HR, Hazard ratio. *p-value < 0.1 **p-value < 0.05. Ref, reference category.*

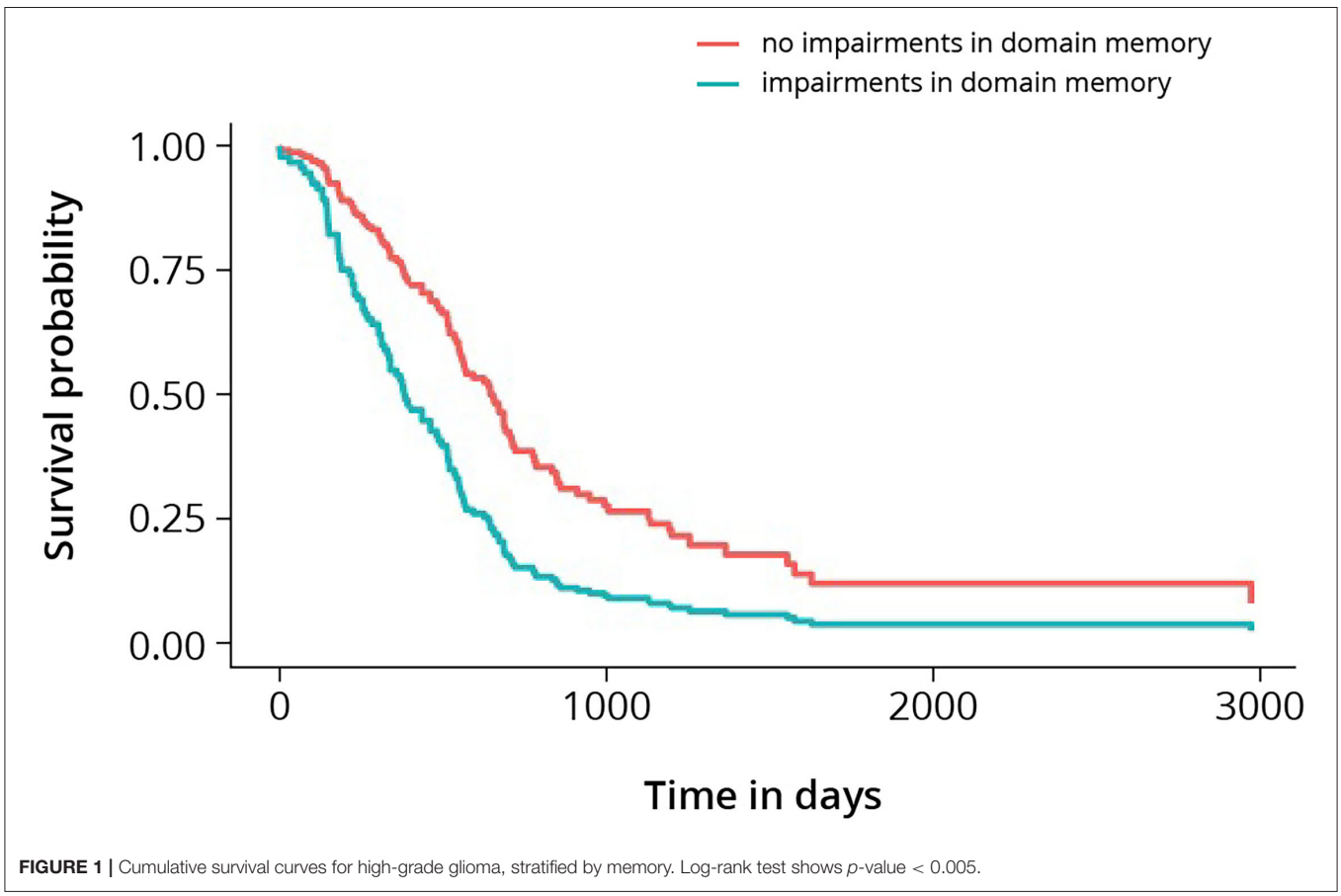


**FIGURE 1 |** Cumulative survival curves for high-grade glioma, stratified by memory. Log-rank test shows *p*-value < 0.005.

distinct yet related study designs, it was a logical step to take the findings from the previous etiological study and investigate the added prognostic value of these previously identified factors in the current prognostic study, for their predictive value at the individual level. As a consequence of the difference in focus, we performed different types of

statistical analyses in both studies. Additionally, we included different determinants in the models than in the etiologic study. For the present study, all possible predictors were extracted from prediction models previously published in the literature. Finally, in this current study, we conducted separate analyses in two different study subpopulations (LGG and HGG).

As a result of differences in analyses, we found noticeable differences in results as well. We did not find executive functioning to be of significant added value in prediction models. Apparently, executive functioning has an insufficient predictive value at the individual patient level. According to the literature, our results were domain-specific and memory was more strongly correlated with survival than other cognitive domains in HGG (7, 8). Hypothetically, memory is more vulnerable to the effects of the structural nuance of the infiltrative tumor and metabolic changes in the tumor environment (33–35). Cognitive functioning in this domain may be hampered before more structural changes occur and therefore may reflect the aggressiveness of the tumor in a more sensitive way than MRI. In LGG we did not find additional prognostic value of any of the five cognitive domains. However, the predictive performance of the model without cognition included was already high (Harrell's c-statistic = 0.85), which makes it more difficult to demonstrate the added value of a predictor. This is also known as a "ceiling effect". If a model already predicts the data almost perfectly, the chance becomes smaller that makes new variables in your model add significant value.

A second explanation can be that cognitive impairments are less common in LGG and as a consequence the lower threshold used to define 'impairment' in LGG. These factors, combined with the low number of events in this subgroup, cause insufficient power to establish a relationship between survival and cognition. A third explanation for the difference in the added value of cognition between subgroups is that various glioma subtypes differ greatly in their biological behavior as well as their prognosis. Possibly, the effect of cognition – and interaction with underlying pathophysiological mechanisms of the tumor – differs between WHO 2016 glioma subtypes.

We included variables for the HGG prediction models based on the most validated and recently published nomograms. We used most elements from the nomogram of Gorlia et al. but used WHO2016 classification instead of WHO2007 for tumor grade and histomolecular classification (2). Additionally, we focused on domain-specific neuropsychological assessment instead of Mini-Mental State Examination (MMSE) as a measure for cognitive functioning. We confirmed the published prognostic value of extensive cognitive testing, age at presentation, and MGMT-methylation status. At a more liberal threshold ($p \leq 0.1$) as is admitted in prognostic research; WHO2016 classification, KPS, and extent of resection were of predictive value as well. The fact that the extent of resection was not significantly correlated, stresses the need to assess this extent or resection with volumetric methods rather than surgical reports.

We found that 53.3% of HGG patients, while 72.6% LGG, presented with seizures as their first symptom. Presentation with seizures has traditionally been identified as an independent positive prognostic factor (26, 36). The observed prognostic effect might result from distinct biological features of epileptogenic tumors (26). Our study did not find a presentation with seizures to be a statistically significant prognostic factor ($P = 0.86$). However, the strong prognostic effect has been demonstrated particularly in GBM, IDH-WT tumors, and our subgroup of HGG included grade IV IDH-mutated tumors as well (26). We did not remove the variable 'epilepsy at presentation' from the final model as we prespecified the variables we wanted to include, to avoid data-driven results and overfitting of our model (37). Tumor size has been described in the literature as an important prognostic factor as well, independent of tumor grade. We did not find tumor size to be a statistically prognostic factor in our model ($p = 0.753$). A possible explanation for this could be the way tumor volume was measured (based on a very liberal FLAIR volume which could have underestimated the relation with survival). Additionally, in literature tumor size is an independent prognostic factor of tumor grade, but the grade is based on WHO-2007 classification (1, 2). Hypothetically, WHO-2016 predicts survival better than WHO2007 classification and therefore tumor size becomes redundant in our model (38). Again, because described in the literature as a well-known prognostic factor, we kept this factor in our model.

For the model of LGG, we included variables based on different nomograms to be as complete as possible (1, 3, 5). The recently published nomogram for LGG patient survival by Gittleman et al. included tumor grade, molecular subtype, KPS, age at diagnosis, and sex. In the well-known prediction model of Gorlia et al. presence of neurologic deficits and tumor size are also included. Midline crossing, age at presentation, and WHO2016 classification were significant predictors in our multivariable model. Unfortunately, we had to exclude KPS from our model, because the frequencies of patients with KPS $\leq$ 70 were too low. The presence of neurologic deficits was frequent at presentation (65.6%) but did not correlate to survival in our model; neither did the extent of resection and sex. This may be related to the composition of our study population and difference with other study populations, wherein non-awake operated patients were included too. In earlier work, we described the differences between awake and non-awake operated patients (7). In general, patients in our cohort were relatively young and had good performance status. Also, the proportion of oligodendrogliomas was higher. Furthermore, the reason why we did not find a relation between the extent of resection and survival may also be related to the fact that we based the degree of resection on the surgical report. The variability of this factor might be less reproducible in this way. Another possibility is that extent of resection is already influenced by cognitive monitoring during operation, which could have reduced the prognostic value of this determinant.

Rather than measuring cognitive changes postoperatively, pre-operative cognitive functioning was used to determine

the impact of cognition on survival. Cognitive functioning at baseline represents the unbiased effects of the tumor on the underlying brain networks best, as cognitive functioning during follow-up can be influenced by surgical procedure and postoperative treatment as well. From a practical point of view, informing patients about their prognosis is most valuable in the earliest stages of the disease, when treatment choices have yet to be made. For the same reason, we did not include post-operative treatment in any of our models; post-operative treatment is not known at the moment of diagnosis yet. Since WHO-2016 diagnosis and extent of resection are included in the model, it is applicable during the early postoperative timeframe, when the medical team discusses the results from histological analysis with a patient. Prognostic data are most useful at this time, for patient counseling and as an aid for patients and physicians in therapeutic decision-making.

Our study has several strengths. In other studies, cognitive testing often consisted of MMSE or other cognitive screening tools instead of extensive domain-specific testing (2, 39, 40). We used comprehensive methods to establish the added value of cognitive functioning, based on the most recent recommendations (32). Further strengths of our study are the relatively large HGG sample size, the standardized NCF testing prior to surgical resection, the conservative cut-off value of *Z*-values for cognitive impairments (which adds further to the robustness of our findings), and the significant proportion of patients with tumor involvement of the right hemisphere, as opposed to many cognition-aimed studies in glioma, with an overrepresentation of left hemisphere-tumors.

Limitations of our study should also be mentioned. At our center, NCF was routinely performed in patients undergoing awake surgery, which carries the risk of selection bias. As published before (7), these patients may have different characteristics than those undergoing biopsy or standard resection. In addition, the percentage of LGG patients is higher in the group of awake surgery patients than in the total glioma population (7). However, since we included all consecutive patients that underwent awake surgery, regardless of their cognitive performance or their outcome (survival), we feel that our analyses offer a valid description of the relation between cognitive performance and survival, without selection bias and without compromising the internal validity of our study. Still, it is possible that this selection of patients has influenced the generalizability (external validity) of our results.

Another factor that could have led to selection bias is the selective loss to follow-up of patients who had insufficient neuropsychological data to perform analyses on. The reason for having insufficient data was often emergency surgery in case of rapid clinical decline. This could have led to exclusion of patients with cognitive impairments and worse clinical performance and therefore we possibly underestimated the relation between cognitive functioning and survival. Finally, we decided to group tasks on their conceptual background ("domain") to enhance power; analyses per task would add up to an undesirable number of analyses and could potentially obscure findings for the overarching cognitive domain. The question of which cognitive concept (or domain) is best represented by a specific task is always complicated since intrinsically more than one concept is tapped in any task. However, neuropsychologists do share common ground in the categorization of tasks across domains, and we grouped tasks according to such shared insights (24, 25). Finally, due to missing data, we had to use multiple imputation methods. However, missing data were considered to be 'missing at random' and cognitive domains had low frequencies of missing data. Lastly, we used advanced imputation methods with multiple imputation sets, which minimizes the risk of bias due to missing data, and data between these different sets did not differ significantly.

## CONCLUSION

Our findings supported the hypothesis that the pre-operative presence of memory deficits, as measured with detailed neuropsychological assessment (NPA), was of additional prognostic value in high-grade glioma when added to other well-known predictors of overall survival. This finding was domain-specific and was not found in low-grade glioma.

Ultimately, parts of the NPA could be implemented in prognostic models for glioma patients. In the full, extensive form, neuropsychological testing may not be practical to implement in prediction models, so a shorter NPA should first have to be developed, containing those tests with the highest predictive value.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (or Ethics Committee) of University Medical Center of Utrecht (protocol code METC 17/384 and 09-420 on 2nd of august 2018). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

EvK and TJS: Conceptualization and supervision. EvK, IHW, CR, FDV, JV, TS, and MvZ: Data curation. EvK and ES: Formal analysis. PR: Funding acquisition and investigation. EvK,

ES, and TJS: Methodology. EvK: Writing–original draft. ES, IHW, CR, FDV, JV, TS, MvZ, PR, and TJS: Writing–review and editing. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

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# Frailty in Glioblastoma Is Independent From Chronological Age

*Harald Krenzlin[1]*, Dragan Jankovic[1], Christoph Alberter[1], Darius Kalasauskas[1], Christiane Westphalen[2], Florian Ringel[1] and Naureen Keric[1]*

*[1] Department of Neurosurgery, University Hospital Mainz, Mainz, Germany, [2] Department of Geriatrics, University Hospital Mainz, Mainz, Germany*

**Objective:** Treatment of glioblastoma in elderly patients is particularly challenging due to their general condition and comorbidities. Treatment decisions are often based on chronological age. Frailty screening tests promise an assessment tool to stratify geriatric patients and identify those at risk for an unfavorable outcome. This study aims to evaluate the impact of age and frailty on the surgical outcome and overall survival in geriatric patients with glioblastoma.

**Methods:** Data acquisition was conducted as a single-center retrospective analysis. From January 1st 2015, and December 31st 2019, 104 glioblastoma patients over 70 years of age were included in our study. Demographic data, tumor size, Karnofsky Performance Score (KPS), and Eastern Cooperative Oncology Group Performance Status (ECOG), as well as treatment modalities, were assessed. The Geriatric 8 health status screening tool (G8) and Groningen Frailty Index (GFI) were compiled pre-and postoperatively.

**Results:** The mean patient age was 76.86 ± 4.11 years. Forty-nine (47%) patients were female, 55 (53%) male. Sixty-seven patients underwent microsurgical tumor resection, 37 received tumor biopsy alone. Mean G8 on admission was 12.4 ± 2.0, mean GFI 5.0 ± 2.5. In our cohort, frailty was independent of patient age, tumor size, or localization. Frailty, defined by G8 and GFI, is associated with shorter overall survival (G8: $p = 0.0035$; GFI: $p = 0.0136$) and higher numbers of surgical complications (G8: $p = 0.0326$; GFI: $p = 0.0388$). Frailer patients are more likely to receive best supportive care ($p = 0.004$). Nevertheless, frailty did not affect adjuvant treatment decision-making toward either single-use of chemo- or radiation therapy, stratified treatment, or concomitant therapy. The surgical decision on the extent of resection was not based on pre-operative frailty.

**Conclusion:** In our study, frailty is a predictor of poorer surgical outcomes, post-operative complications, and impaired overall survival independent of chronological age. Frailty screening tests offer an additional assessment tool to stratify geriatric patients with glioblastoma and identify those at risk for a detrimental outcome and thus should be implemented in therapeutic decision making.

**Keywords: glioblastoma, frailty, Groningen Frailty Index, G8, geriatric patients**

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****Correspondence:***
*Harald Krenzlin*
*Harald.Krenzlin@unimedizin-mainz.de*

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## INTRODUCTION

Glioblastoma is the most common primary malignant brain tumor in adults with a dismal prognosis (1). Population studies have shown that survival declines with increasing age while the incidence increases, especially among the elderly over 70 years (2, 3). As of today, no unanimous definition of when a patient is defined as an "elderly" exists. The WHO propagates an age limit of 60–65 years, although the prevalence of age-defining symptoms such as loss of hearing, impaired vision, sleeplessness, incontinence, and physical and mental deterioration start to increase in patients 70–75 years (4). Given the poor overall prognosis, frequent coexisting conditions, and an increased risk of toxic effects from chemo- and radiotherapy on the aging brain, glioblastoma management in patients 65 years or older is exceedingly complex (5). Progress has been limited for decades, as clinical trials traditionally used upper age limits excluding elderly patients (6). Older patients with glioblastoma have been underrepresented in clinical trials, as the average age of participants is 55 years compared to 65 years in population-based studies (3). Recently, randomized data for the treatment of elderly patients with glioblastoma has been provided by trials conducted by the Scandinavian Neuro Oncology Network, the Neuro oncology Working Group of the German Cancer Society (NOA), as well as the Canadian Cancer Trials Group (CCTG) and the European Organization for Research and Treatment of Cancer (EORTC) (6–8). Evidence supports maximal safe surgical resection, the superiority of the concurrent radio-chemotherapy compared to TMZ or radiotherapy alone, and equivalency of short-course radiotherapy compared to longer treatments (8, 9). These studies establish a new paradigm for treating elderly patients over 65 years. Nevertheless, across-the-board treatment decisions based on chronological age are no longer feasible in the context of individualized medicine. Old age alone is not associated with increased perioperative complication rates, such as infections, prolonged intensive care treatment, and slower recovery (10). A growing body of evidence suggests that frailty is a more appropriate predictor of surgical outcome, post-operative complications, and impaired overall survival than chronological age (11). Although frailty screening tests offer assessment tools to stratify geriatric patients and identify those at risk for a detrimental outcome, they are not commonly used in informing surgical decisions (12).

This study aims to evaluate the impact of age and frailty measured using the Groningen Frailty Index (GFI) and the G8 questionnaire on the surgical outcome and long-term survival in geriatric patients with glioblastoma.

## PATIENTS AND METHODS

### Patients

All patients over the age of 70 with newly diagnosed glioblastoma treated at our hospital between January 1st 2015, and December 31st 2019, were included in our study. Baseline characteristics, including age, sex, functional neurological status at admission and discharge, as well as radiological and molecular tumor features, were recorded. The Karnofsky performance score (KPS), the ECOG (Eastern Cooperative Oncology Group) performance status, the Groningen frailty index, and the G8 Questionnaire were used to evaluate geriatric patients according to their frailty and functional status. All patients either received stereotactic biopsy or tumor resection. Early (<72 h) post-operative magnetic resonance imaging (MRI) was used to determine the extent of resection. Complete resection of the contrast-enhancing tumor was deemed gross-total resection (GTR). Progression free survival (PFS) and overall survival (OS) measured in weeks were defined from surgery until radiological progression or death, respectively. During institutional interdisciplinary tumor board meetings, treatment decisions concerning the surgical procedure and adjuvant treatment were made prior to and after surgery.

### The Groningen Frailty Index and the G8 Questionnaire

The GFI is a 15-item questionnaire with a score range from zero to fifteen. Four principal dimensions, physical, cognitive, social, and psychological, are assessed. A score of four or greater is considered as a cut-off point for frailty (13). The G8 questionnaire is a screening tool for comprehensive geriatric assessment (CGA) in elderly oncological patients. It consists of seven questions plus age. The cut-off value for identifying frailty in cancer patients with the G8 questionnaire has been previously determined as 12.5 (AUC of 0.87 (95% CI: 0.81–0.92; SE 0.03) (14, 15) (**Supplementary Materials 1, 2**).

### Statistics

Data analysis was performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY). Unpaired categorical and binary variables were analyzed in contingency tables using Fisher's exact test. The Mann–Whitney U-test was chosen to compare continuous variables as the data were mainly not normally distributed. OS was analyzed by the Kaplan–Meier method using Gehan–Breslow–Wilcoxon test. The hazard ratio was calculated using the Mantel-Haenszel test. Results with $p < 0.05$ were considered statistically significant. Finally, a backward stepwise method was used to construct a multivariate logistic regression model to validate age, ECOG, KPS, G8, GFI, MGMT, and resection as predictors of PFS and OS.

### Ethical Approval

Data acquisition and analysis were performed anonymously and were approved by the Ethics Committees of the medical association of Rhineland Palatinate, Germany. According to the local laws, no informed consent is necessary for such kind of retrospective analysis.

## RESULTS

### Baseline Characteristics

Between January 1st 2015 and December 31st 2019, 104 consecutive patients aged 70 years or older with newly diagnosed Glioblastoma were treated at our department. Of all patients, 49 were female, 55 male. The patient's age ranged from 70 to 89 years (76.60 ± 4.41). Between all patients, median pre-operative

**TABLE 1 |** Baseline demographics and clinical characteristics.

| | Entire cohort ($n = 104$) | Not frail patients ($n = 36$) | Frail patients ($n = 68$) |
|---|---|---|---|
| **Gender** Female | 49 (47%) | 13 (12.5%; ns) | 36 (34.5%; ns) |
| Male | 55 (53%) | 23 (22%; ns) | 32 (31%; ns) |
| **Age** (+SD) | 76.60 ± 4.41 | 76.69 ± 4.66 (ns) | 76.42 ± 3.945 (ns) |
| **Tumor size** | 35.43 ± 18.90 | 30.00 ± 14.17 (ns) | 38.30 ± 20.49 (ns) |
| **ECOG** Admission | 1.77 ± 0.99 | 1.25 ± 0.87 (ns) | 2.04 ± 0.94 (ns) |
| Discharge | 2.15 ± 1.12 | 1.47 ± 0.99 (****) | 2.51 ± 1.00 (****) |
| **KPS** Admission | 70.7 ± 13.5 | 78.1 ± 10.6 (ns) | 66.8 ± 13.3 (ns) |
| Discharge | 85.44 ± 0.23 | 94.44 ± 0.23 (ns) | 80.6 ± 0.39 (ns) |
| **MGMT** Methylated | 46 (44%; ns) | 16 (44%; ns) | 30 (44%; ns) |
| Unmethylated | 58 (56%; ns) | 20 (56%; ns) | 38 (56%; ns) |
| **Resection** GTR | 66 (63.5%; ns) | 28 (80%; ns) | 38 (56.7%; ns) |
| PR/Biopsy | 36 (34.6%; ns) | 7 (20%; ns) | 29 (43.3%; ns) |
| **Radiation** Definitive | 24 (27%; ns) | 12 (42%; ns) | 12 (20%; ns) |
| Concomitant | 17 (19%; ns) | 9 (32%; ns) | 8 (13%; ns) |
| **Chemotherapy** | 20 (22%; ns) | 5 (18%; ns) | 15 (25%; ns) |
| **Best supportive care** | 28 (31%; ns) | 2 (7%; ns) | 26 (43%; ns) |

*ns, not significant; **** $p < 0.001$.*

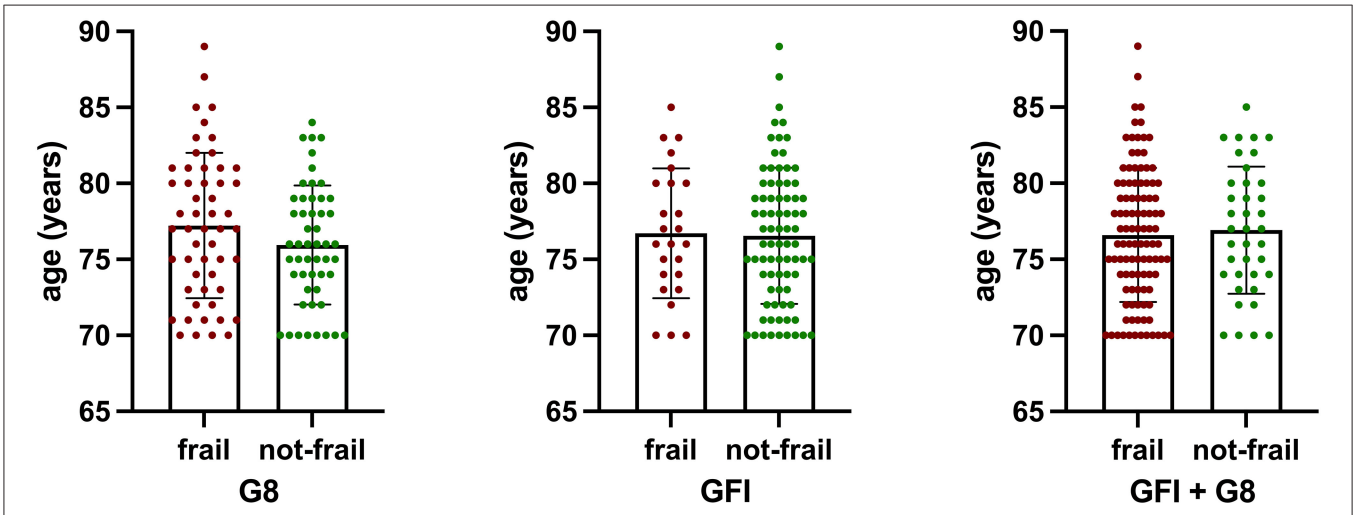


**FIGURE 1 |** There was no statistically significant difference in age of patients defined as frail by either metric (G8, $p = 0.1379$; GFI, $p = 0.8729$) or a combination of both (G8 + GFI, $p = 0.6940$).

KPS was 70 (range 30–100), mean ECOG was two (range 0–4). At the time of discharge, the mean KPS was 85 (range 30–100), mean ECOG was two (range 0–4). On admission, geriatric patients with glioblastoma had a median GFI of five (range 1–11) and a median G8 score of 12 (6–15). According to GFI, 43 (41.34%) geriatric patients with glioblastoma showed no signs of frailty, 51 (49.04%) according to the G8 Questionnaire. Tumors most frequently involved the temporal lobe (39.4%), followed by the frontal (25.9%), parietal (18.3%), and occipital (3.8%) lobe, and deeper regions (12.5%). In 14 patients (13.5%), the tumor

involved both hemispheres. Biopsy was performed in 36 patients (35.6%), GTR in 45 (43.3%) and STR in 22 (21.2%). Methylation of the MGMT promotor was detected in 46 patients (44.23%). All tumors were IDH 1/2 wild-type. Median OS was 29 weeks (95% CI 22.9–35.8) (**Table 1**).

## Frailty Is Independent of Chronological Age and Concomitant Comorbidities

Patients defined as frail by the G8 score had a mean age of 77.2 ± 4.8 years; those defined as not-frail were 75.9 ± 3.9 years ($p$ = 0.1379). According to GFI, frailer patients were 76.7 ± 4.3 years old, compared to 76.6 ± 4.5 years ($p$ = 0.8729). Frail patients, according to either metric, were 76.6 ± 4.4 years of age, those not-frail 76.9 ± 4.2 ($p$ = 0.6940) (**Figure 1**). The mean CCI of patients defined as frail was 7.906 ± 1.061 (G8, $p$ = 0.9088) and 7.905 ± 0.982 (GFI) ($p$ = 0.9486). All patients had a CCI of six and higher.

## Frailty Is Associated With Shortened Overall Survival

According to the G8 score, 53 patients were defined as frail, compared to 61 using the GFI and 69 using a combination of both scales. Geriatric patients with glioblastoma defined as frail according to the G8 questionnaire had a median OS of 7.7 ± 10.1 months. In comparison, not-frail patients had a median OS of 13.4 ± 14.3 months ($p$ = 0.0216). Patients defined as frail according to the GFI had a median OS of 6.7 ± 8.1 months. Those defined as not-frail had a median OS of 12.3 ± 13.0 months ($p$ = 0.0167). Patients defined by both metrics as frail had a median OS of 7.1 ± 7.8 compared to 14.3 ± 13.7 months in those defined as not-frail ($p$ = 0.0025) (**Figure 2**). Survival analysis revealed a statistically significant shorter survival in frail patients with glioblastoma according to the G8 questionnaire (HR = 1.743, 95% CI 1.121–2.711, $p$ = 0.0136) as well as the GFI (HR = 1.672, 95% CI 1.087–2.570, $p$ = 0.0035) and those patients classified as frail with either G8 or GFI (HR = 2.272, 95% CI 1.448–3.563, $p$ = 0.0004) (**Figure 2**).

## Frailty and Post-operative Morbidity

Geriatric patients had a higher likelihood of developing post-surgical complications if identified as frail using the G8 (OR = 3.6795, 95% CI 1.1143–12.1502, $p$ = 0.0326), the GFI (OR = 4.0, 95% CI 1.0741–14.8961, $p$ = 0.0388), or the combination of both (OR = 3.913, 95% CI 1.0515–14.5620, $p$ = 0.0419). Pre-operative ECOG or KPS was similar in both groups. However, post-operative ECOG status (GFI: $p < 0.0001$; G8: $p < 0.0001$) and KPS (GFI: $p < 0.0001$; G8: $p < 0.0001$) was significantly worse in frail patients using either of the two scales (**Figure 3**). No difference was found between patients defined as frail/not frail by G8 or GFI.

## Treatment Data

There was no statistically significant difference in the number (cases) of resections performed in patients stratified as not frail (75.00%) and in those defined as frail (58.73%). While tumor resection led to improved PFS in patients defined as frail compared to biopsy alone ($p$ = 0.0069), it was only associated with improved overall survival in patients defined as not frail ($p$ = 0.0017) (**Figure 4**). No statistically significant differences in OS were found between either frail or not frail patients treated with chemotherapy or radiation alone compared to a combination of both.

## Multivariate Analysis

A multivariate logistic regression analysis was conducted to identify independent predictors of OS in geriatric patients with glioblastoma. ECOG three ($p$ = 0.028, OR = 2.520, 95% CI 1.106–5.741), radiotherapy ($p$ = 0.026, OR = 2.219, 95% CI 1.1–4.47) and frailty detected by GFI ($p$ = 0.017, OR = 0.895, 95% CI 0.818–0.980) were significant and independent predictors of OS. Age ($p$ = 0.855, OR = 1.043, 95% CI 0.667–1.628), KPS ($p$ = 0.320, OR = 0.530, 95% CI 0.131–2.142), MGMT methylation ($p$ = 0.888, OR = 0.969, 95% CI 0.628–1.495) and extent of resection (GTR: $p$ = 0.599, OR = 0.822, 95% CI 0.551–1.411; PR: $p$ = 0.555, OR = 1.2, 95% CI 0.654–2.201) were no independent predictors of OS in geriatric patients with glioblastoma.

# DISCUSSION

Demographic changes with an increased life expectancy led to a rapidly growing geriatric population. As high-grade gliomas are the most common central nervous system malignancy and are mostly diagnosed at a median age of 64 years, the incidence increases with growing life expectancy (2, 3). At the same time, the treatment of glioblastoma in elderly patients is particularly challenging due to their general condition and comorbidities (16). As of today, clinical data in geriatric patients with glioblastoma is scarce. Here, we evaluated patients over 70 years of age with newly diagnosed glioblastoma for the influence of age and prevalent frailty on surgical outcome and overall survival.

Currently, most treatment decisions are based on chronological age (17). The landmark study of Stupp et al. showed a benefit of radiotherapy plus temozolomide followed by adjuvant temozolomide to treat glioblastoma (18). However, only patients younger than 70 years were included in this trial. The addition of temozolomide has been shown to be less effective in patients between 65 and 70 years (19). Underrepresentation of elderly patients in clinical cancer trials leads to heterogeneous data on treatment effectiveness, as well as inconsistent and highly subjective treatment decision-making in this ever-growing group of patients. Older patients are often treated less aggressively due to a perceived lack of physical resilience in response to post-operative complications and treatment toxicity (20, 21). Our cohort reflects this circumstance as only a fraction has been treated concomitantly, while most received either adjuvant radiation or chemotherapy alone. The influence of the extent of resection on overall survival is still a matter of debate. The EORTC 26,062 trial showed the patients with tumor resection had significantly longer survival than those with biopsy only (8). Similar findings were reported in a randomized trial in patients older than 65 (22). The small number of patients severely hampered the clinical

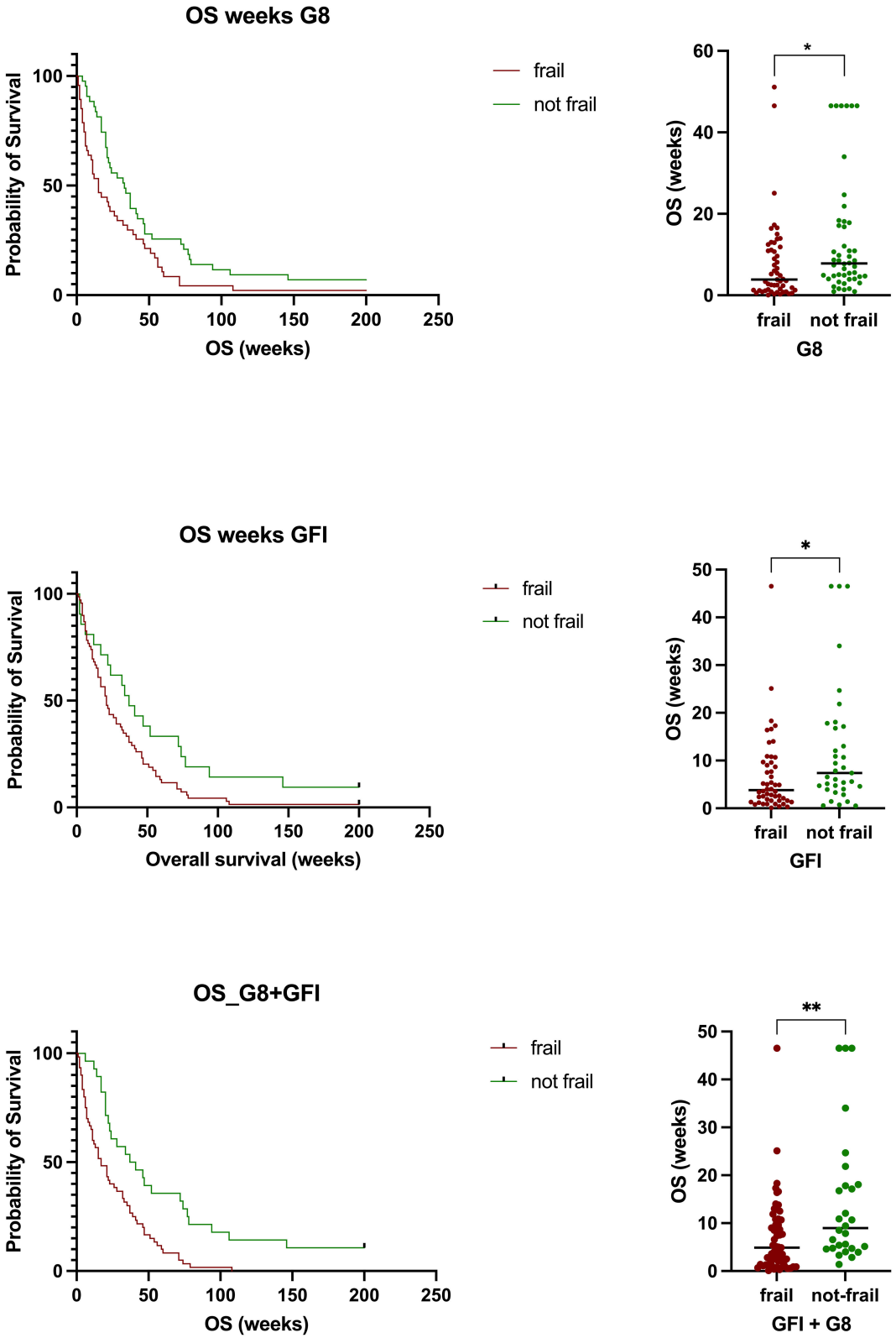


**FIGURE 2 |** Patients defined as frail by either scale or a combination of both had a statistically significant shorter overall survival compared to those defined as not frail (G8, $p = 0.0216$; GFI, $p = 0.0167$) or a combination of both (G8 + GFI, $p = 0.0025$).

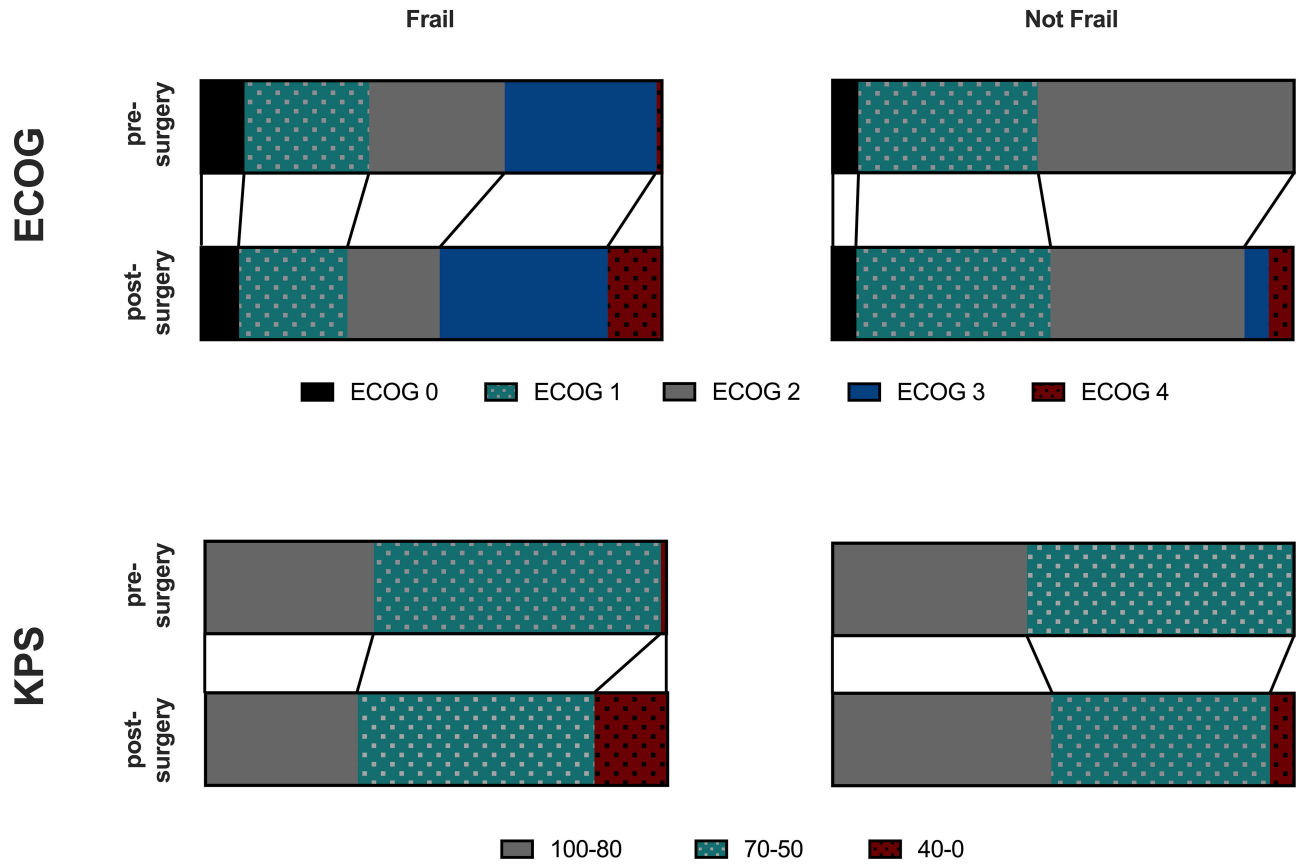


**FIGURE 3 |** ECOG or KPS was similar in frail and not frail Patients. Those defined as frail had a higher likelihood of developing postsurgical complications and post-operative ECOG status was significantly worse in frail patients using either of the two scales using the G8 ($p < 0.0001$), GFI ($p < 0.0001$) or a combination of both ($p < 0.0001$).

implication. Our study adds proof to this observation as we found that OS improved in patients receiving tumor resection compared to biopsy taking independent from preexisting frailty. As expected, patients undergoing resection had a higher likelihood of an improved neurological outcome, while those receiving biopsy alone remained unchanged or deteriorated.

Patients' frailty and comorbidity burden have recently emerged as predictors of morbidity and mortality in various types of cancer in older patients (14). This observation falls in line with the results of our study where patients identified as frail using either the G8 questionnaire, the GFI, or a combination of both have a significantly reduced overall survival. As patients over 70 years of age are underrepresented in clinical trials, there is even less data on the impact of chronological age in geriatric patients with different glioblastoma (6). Our data suggest that this void might be overcome by adding frailty as an additional marker to stratify older patients for those with favorable or unfavorable outcome as frailty is associated with the occurrence of surgical complications and shortened OS. In the present study, frailty has been assessed using the G8 and the GFI. Both instruments are capable of separating older patients with cancer according to their preexisting frailty. The G8 is supposed to offer a better sensitivity with less specificity compared to the GFI (14). Consequently, the combination of both scales provided the best results in identifying frailty in older patients with glioblastoma in our patients. Subsequently, increased frailty resulted in a significantly higher probability of poorer survival. In our highly selective cohort of patients, including only geriatric patients older than 70, chronological age was no longer a predictor of morbidity or overall survival in a multivariate analysis. This finding might argue in favor of a more stratified treatment approach as age alone might not suffice for informed decision-making in geriatric patients with glioblastoma. In our elderly patient collective, ECOG and KPS were no striking predictors of an individual outcome but improved after tumor resection, if the patient was not frail. Individual frailty and comorbidity burden might identify those patients with sufficient resilience for more intense treatment protocols and thus longer OS.

Modified treatment regimens have been proposed to minimize treatment-associated toxicity and adverse events in elderly patients with glioblastoma. Short course radiotherapy (34Gy for two weeks) proved to be as effective as standard radiotherapy

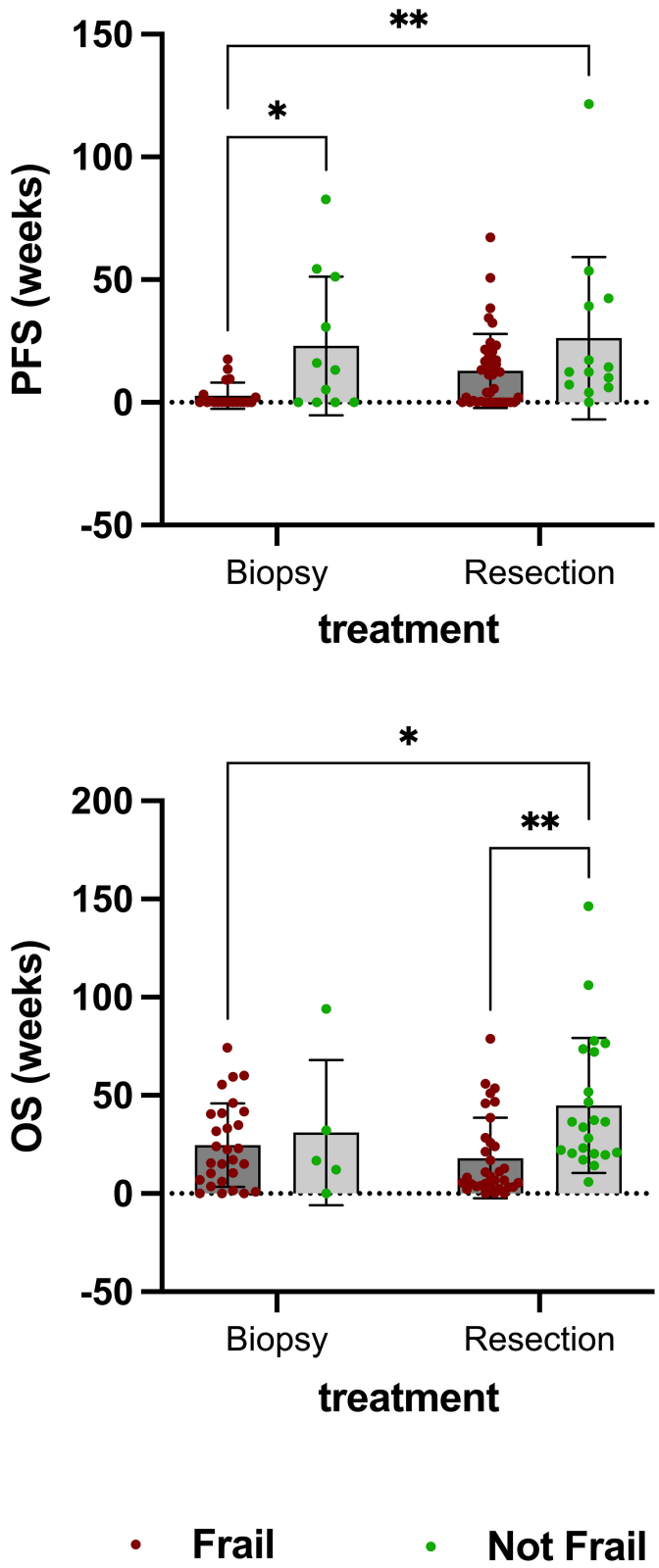


**FIGURE 4 |** There was no statistically significant difference in the number (cases) of resections performed in patients stratified as not frail (75.00%) and in those defined as frail (58.73%). While tumor resection led to improved PFS in patients defined as frail compared to biopsy alone ($p = 0.0069$), it was only associated with improved overall survival in patients defined as not frail ($p = 0.0017$).

(60Gy for 6 weeks) in patients older than 70 years (23). There is also evidence that temozolomide alone might be more efficient than radiotherapy in patients with methylation of the O6-methylguanine–DNA methyltransferase (MGMT) gene promotor region in the elderly (23). The combination of temozolomide and short-course radiotherapy resulted in a more prolonged survival than short-course radiotherapy alone in a large clinical trial funded by the Canadian Cancer Society Research Institute (8). Our data argues the same way as a combined treatment showed a tendency to prolonged PFS and OS without being statistically significant. As expected, frail patients seem to benefit less from adjuvant treatment, compared to those classified as not frail. Fittingly, best supportive care showed a similar PFS and OS in frail patients compared to all other treatment regiments. Applying a multivariate analysis, radiotherapy emerged as an independent predictor of OS in our patient cohort. However, the MGMT-promotor methylation and MGMT stratified treatment showed an inclination to prolonged OS without reaching statistically significance in our cohort.

However, there are several important limitations to our study. Due to a limited and heterogeneous group of patients, the influence of different therapeutic regiments on PFS and mOS might have been underestimated. Further bias might arise from involuntarily accounting for poor general health and signs of frailty during the process of treatment decision making. Rretrospective data collection and a lack of randomization are important limitation the generalizability of our study. To account for these shortcomings, future prospective studies with an increased number of patients and data acquisition sites might be capable to establish frailty not only as an important influence on PFS/mOS, but as an independent outcome predictor and parameter in the treatment of not only geriatric patients with glioblastoma.

## CONCLUSION

In our study, frailty is associated with a shortened overall survival in geriatric patients with glioblastoma. Thus, frailty screening is an essential and telling addition to clinical and demographical patient evaluation offering the possibility to improve the selection of suitable patients for different treatment strategies. Additionally, frailty screening provides insightful information to ameliorate counseling those patients and their families.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

HK, DJ, CW, and NK contributed to conception and design of the study. CA and DJ organized the database. HK and DK performed the statistical analysis. HK wrote the first draft of the manuscript. FR and NK supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.777120/full#supplementary-material

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# The Prognostic Value of NANO Scale Assessment in IDH-Wild-Type Glioblastoma Patients

*Johannes Kasper[1]*, Tim Wende[1], Michael Karl Fehrenbach[1], Florian Wilhelmy[1], Katja Jähne[1], Clara Frydrychowicz[2], Gordian Prasse[3], Jürgen Meixensberger[1] and Felix Arlt[1]*

*[1] Department of Neurosurgery, University Hospital Leipzig, Leipzig, Germany, [2] Division of Neuropathology, University Hospital Leipzig, Leipzig, Germany, [3] Institute of Neuroradiology, University Hospital Leipzig, Leipzig, Germany*

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***Correspondence:**
*Johannes Kasper*
*johannes.kasper@medizin.uni-leipzig.de*
*orcid.org/0000-0003-2122-2676*

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*Kasper J, Wende T, Fehrenbach MK, Wilhelmy F, Jähne K, Frydrychowicz C, Prasse G, Meixensberger J and Arlt F (2021) The Prognostic Value of NANO Scale Assessment in IDH-Wild-Type Glioblastoma Patients. Front. Oncol. 11:790458. doi: 10.3389/fonc.2021.790458*

**Background:** IDH-wild-type glioblastoma (GBM) is the most frequent brain-derived malignancy. Despite intense research efforts, it is still associated with a very poor prognosis. Several parameters were identified as prognostic, including general physical performance. In neuro-oncology (NO), special emphasis is put on focal deficits and cognitive (dys-)function. The Neurologic Assessment in Neuro-Oncology (NANO) scale was proposed in order to standardize the assessment of neurological performance in NO. This study evaluated whether NANO scale assessment provides prognostic information in a standardized collective of GBM patients.

**Methods:** The records of all GBM patients treated between 2014 and 2019 at our facility were retrospectively screened. Inclusion criteria were age over 18 years, at least 3 months postoperative follow-up, and preoperative and postoperative cranial magnetic resonance imaging. The NANO scale was assessed pre- and postoperatively as well as at 3 months follow-up. Univariate and multivariate survival analyses were carried to investigate the prognostic value.

**Results:** One hundred and thirty-one patients were included. In univariate analysis, poor postoperative neurological performance (HR 1.13, $p = 0.004$), poor neurological performance at 3 months postsurgery (HR 1.37, $p < 0.001$), and neurological deterioration during follow-up (HR 1.38, $p < 0.001$), all assessed *via* the NANO scale, were associated with shorter survival. In multivariate analysis including other prognostic factors such as the extent of resection, adjuvant treatment regimen, or age, NANO scale assessment at 3 months postoperative follow-up was independently associated with survival prediction (HR 1.36, $p < 0.001$). The optimal NANO scale cutoff for patient stratification was 3.5 points.

**Conclusion:** Neurological performance assessment employing the NANO scale might provide prognostic information in patients suffering from GBM.

**Keywords: GBM, glioblastoma, neuro-oncology, neurological performance, NANO scale**

## INTRODUCTION

IDH-wild-type glioblastoma (GBM) is the most common brain-derived malignancy. Due to its high mitotic activity, neoangiogenesis, and highly infiltrative behavior, it is classified as WHO grade four (1). GBM accounts for 14.5% of all primary brain tumors and is more commonly diagnosed in men. Moreover, the median age at first diagnosis is 65 years and the 12-month survival is poor with around 42.8% (2). Standard therapy includes maximum safe resection and adjuvant radiochemotherapy up to 60.0 Gy with concomitant temozolomide, followed by 6 cycles of temozolomide alone (3, 4). Several parameters were identified as influential on patient survival, including tumor location (5), extent of resection (6), age at date of diagnosis (7), O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (8), and clinical performance (4). Here, the Karnofsky Performance Score (KPS) is commonly used to assess the overall physical status as well as to monitor possible tumor progression *via* a decrease of clinical performance (9, 10). Moreover, poor or worsened overall neurological performance (11–14) and isolated motor or language deficits might be associated with decreased overall survival (15, 16). In order to address this rising evidence and to standardize the evaluation of neurological performance, the Neurologic Assessment in Neuro-Oncology (NANO) scale was created (17). It was shown to predict overall survival in GBM patients more precisely than comparable performance scales (18, 19). However, previous works are limited by inconsistent therapy regimen within the investigated patient cohorts. Hence, this study was designed to evaluate the independent, prognostic value of neurological performance assessed *via* the NANO scale at different points of follow-up when the abovementioned clinical and radiological factors are considered within a standardized GBM patient collective.

## METHODS

### Patient Selection and Treatment

Data collection and analysis were approved by the Ethical Committee of the Medical Faculty, University of Leipzig (No. 144/08-ek). The database of Leipzig University Hospital was searched for all patients with new diagnosis of IDH-wild-type glioblastoma between 2014 and 2019. Inclusion criteria were age over 18 years, at least 3 months postoperative follow-up, and preoperative and postoperative cranial magnetic resonance imaging within 72 h after surgery. Due to the selection criteria, patients with an overall survival less than 3 months or further therapy at another facility were excluded. All cases were discussed in a weekly, interdisciplinary tumor board and therapy regimen was determined based on current EANO guidelines for glioma therapy (20, 21).

### Clinical, Pathological, and Radiological Assessment

Medical records were analyzed for age at date of diagnosis, sex, and adjuvant therapy regimen. The date of diagnosis was set as the date of surgery after neuropathological proof of glioblastoma. Histopathological diagnosis and immunohistochemical status were extracted from neuropathology reports. IDH-mutation status and MGMT promoter methylation of all GBM samples were determined using immunohistochemistry and pyrosequencing or nucleic acid amplification followed by pyrosequencing. According to Quillien et al., the MGMT promoter methylation status was dichotomized into positive (≥12%), negative (<12%), or unknown (22).

Overall survival (OS) was defined as the time between the date of neurosurgery and the date of death. The date of death, if not provided by our hospital database, was collected from the Leipzig Cancer Registry. Dates were assessed on May 31, 2021. If death did not occur by then or if patients were lost to follow-up, the date of last contact to our department was integrated into statistical analysis as censored value.

Tumor location and extent of resection (EOR) were retrospectively determined revising perioperative MRI T1 sequences with and without contrast. Volumetric assessment was manually carried out employing the iPlan Cranial software (version 3.0.5, Brainlab AG, Munich, Germany). If a needle biopsy was performed, EOR was set as 0%.

### Assessment of Neurological Performance Status

All patients appointed to our department are examined based on a standardized procedure including general symptoms, cranial nerve status, sensorimotor deficits, and other focal symptoms, such as aphasia or behavior. Findings are routinely documented within a physician report template. The NANO scale was then retrospectively assessed from physician reports at the time of hospital admission, at the time of discharge, and 3 months postsurgery employing the NANO scale as proposed by Nayak et al. (17). Gait, strength, ataxia of upper extremities, sensation, visual fields, facial strength, language, level of consciousness, and behavior sum up to a maximum of 23 points. High-scale values represent impaired neurological performances. NANO scale changes were calculated by subtracting preoperative scale values from postoperative values (NANO difference 1 or time point 1) or postoperative values from values assessed at 3 months postoperative follow-up (NANO difference 2 or time point 2). NANO scale differences below or equal to 0 represent a stable or improved neurological performance and vice versa. In case of missing data, the corresponding neurological deficit was defined as absent and set as 0 points within NANO scale calculation.

### Statistical Analysis

Statistical analysis was carried out using SPSS statistics software version 24.0.0.2 (IBM, Armonk, NY, USA). First, the assessed parameters were applied as continuous variables and analyzed

**Abbreviations:** 95 CI, 95% confidence interval; AUC, area under the curve; EOR, extent of resection; GBM, IDH-wild-type glioblastoma; HR, hazard ratio; MGMT, O6-methylguanine-DNA methyltransferase; NANO, Neurological Assessment in Neuro-Oncology; NO, neuro-oncology; RCx, radiochemotherapy; Rx, radiotherapy; ROC, receiver operator characteristic.

*via* univariate Cox regression. Time-dependent receiver operator characteristic (ROC) analysis was then performed for NANO scale values with *p*-values below 0.2 from Cox regression, and the optimal cutoff point was defined as the value that maximizes the Youden's index (parameter value for which sensitivity + specificity − 1 is maximal). After NANO scale values were dichotomized according to cutoff values, a second univariate analysis was carried out employing the Kaplan–Meier estimate. Finally, all continuous variables with *p*-values below 0.2 in univariate Cox regression were utilized for a multivariate analysis *via* proportional hazard Cox regression in order to investigate independent statistical relevance. Non-parametric parameters were compared with Mann–Whitney *U* test.

Survival rates from Kaplan–Meier analysis are given with standard deviation, and statistical significance was calculated *via* log-rank testing. Hazard ratios (HR) are provided with 95% confidence intervals (95 CI). *p*-values below 0.05 were considered statistically significant.

# RESULTS

## Patient Cohort

Baseline data are presented in **Table 1**. Within the study period, 227 patients were newly diagnosed with IDH-wild-type GBM and 131 met the inclusion criteria for the study (a flowchart is shown in **Supplementary Figure 1**). Concerning average age and sex ratio, the cohort is comparable to larger studies (2). The average preoperative NANO scale value was 3.3 ± 2.5 and slightly increased up to 3.8 ± 2.7 at 3 months postsurgery, but statistical significance was not reached ($p = 0.09$ by Mann–Whitney *U* test).

**TABLE 1** | Baseline data.

| No. of patients | | 131 |
|---|---|---|
| Sex | Male | 88 (67.2) |
| | Female | 43 (32.8) |
| Average age (years) | | 65.8 ± 10.2 |
| Tumor location | Frontal | 32 (24.4) |
| | Temporal | 37 (28.2) |
| | Parietal | 26 (19.8) |
| | Occipital | 8 (6.0) |
| | Multilocular | 27 (20.6) |
| | Brainstem | 1 (0.8) |
| Average extent of resection (%) | | 81.5 ± 29.8 |
| MGMT status | Positive | 60 (45.8) |
| | Negative | 67 (51.1) |
| | Unknown | 4 (3.1) |
| Average NANO | Preoperative | 3.3 ± 2.5 |
| | Postoperative | 3.6 ± 2.6 |
| | At 3 months postsurgery | 3.8 ± 2.7 |
| Adjuvant therapy | RCx | 111 (84.7) |
| | Rx | 17 (13.0) |
| | w/o | 3 (2.3) |
| 12-month survival (%) | | 63.9 ± 4.4 |

*Averages are presented with standard deviation. Percentages of absolute counts are shown in brackets.*
*MGMT, O6-methylguanine-DNA methyltransferase; NANO, Neurological Assessment in Neuro-Oncology; RCx, radiochemotherapy; Rx, radiotherapy.*

## NANO Scale Assessment and Overall Survival (Univariate and Multivariate Analyses)

In univariate Cox regression (see **Supplementary Table 1**), low patient age (HR 1.03, $p = 0.028$), high extent of resection (HR 0.87, $p < 0.001$), adjuvant radiochemotherapy (HR 0.27, $p < 0.001$), positive MGMT promoter methylation status (HR 0.46, $p = 0.002$), and tumor location (HR 0.42, $p = 0.001$) were significantly associated with prolonged survival. Also, a low postoperative NANO scale value (HR 1.13, $p = 0.004$), low NANO scale values at 3 months postsurgery (HR 1.37, $p < 0.001$), and the difference of NANO scale values after 3 months postoperative follow-up and postoperatively (NANO time point 2, HR 1.38, $p < 0.001$) had a significant influence on overall survival. Preoperative NANO values and the difference of post- and preoperative NANO scale values were not associated with patient survival.

A further analysis *via* ROC and Youden's index calculation revealed 3.5 scale points as the optimal cutoff for both postoperative NANO scale values (AUC 0.706) and NANO scale values at 3 months postoperative follow-up (AUC 0.827). For NANO time point 2, the cutoff was set at 0, with values ≤0 representing stable or increased neurological performance and values >0 representing decreased neurological performance, respectively. Corresponding data were hence dichotomized and employed into Kaplan–Meier analysis, presented in **Figure 1**. Here, patients with NANO scale values below 3.5 points at 3 months postoperative follow-up (12-month survival 85.0 ± 4.4% *vs.* 38.7 ± 6.9%, $p < 0.001$) as well as patients with stable or increased neurological performance (12-month survival 76.2 ± 4.4% *vs.* 23.1 ± 8.6%, $p < 0.001$) had a significantly prolonged overall survival. Postoperative NANO scale assessment was associated with prolonged survival but did not reach significance (12-month survival 77.1 ± 5.0% *vs.* 47.1 ± 7.3%, $p = 0.056$).

Finally, a multivariate Cox regression (**Table 2**) revealed that the extent of resection, adjuvant therapy regimen, MGMT promoter methylation status, and NANO scale assessment at 3 months postoperative follow-up (HR 1.36, $p < 0.001$) were independently associated with increased overall survival.

# DISCUSSION

In this retrospective study with 131 IDH-wild-type glioblastoma patients, neurological performance, assessed using the NANO scale, was significantly associated with overall survival in univariate analysis (postoperative, at 3 months postoperative follow-up) and in multivariate survival prediction (at 3 months postoperative follow-up). The optimal NANO scale cutoff for cohort stratification in our series was defined with ROC analysis at 3.5 points. Moreover, patients with NANO scale progression (worsened neurological performance) at 3 months postsurgery suffered from significant shorter OS compared with the corresponding subgroup. It is important to note that due to inclusion criteria (only patients with more than 3 months postoperative follow-up), our cohort mainly consists of "good performers," reflected by prolonged survival when compared

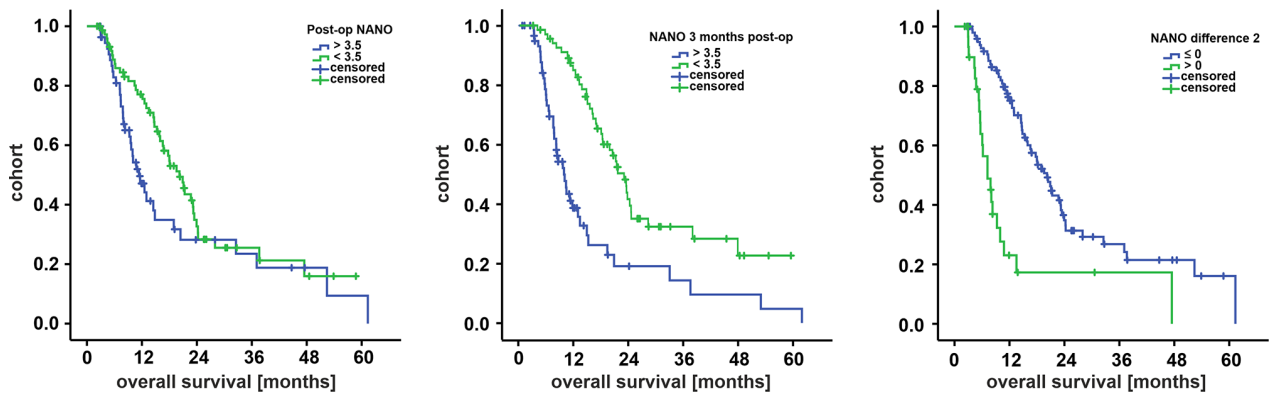


**FIGURE 1** | Survival curves for subcohorts by Kaplan–Meier analysis for postoperative NANO scale (left), NANO scale at 3 months follow-up (middle), and NANO scale difference of postoperative values and values at 3 months follow-up (right). Cutoffs for the first two diagrams were determined *via* ROC analysis. NANO difference 2 was dichotomized in stable/increased (≤0) or worsened (>0) neurological performance at 3 months follow-up compared with postoperative values. NANO, Neurologic Assessment in Neuro-Oncology.

with larger studies. The issue is discussed in detail in the succeeding paragraphs.

The influence of general fitness on the prognosis of cancer patients is universally accepted. KPS and the Eastern Co-operative Oncology Group score/WHO performance scale are universally employed to evaluate the general functional status and are recognized for cancer treatment stratification, including glioma treatment guidelines (21, 23). Commonly, cancer-associated cachexia, chemotherapy toxicity and cancer-associated organ dysfunction are the main causes for an impaired general status. The toxicity of temozolomide is relatively low when compared with other anticancer drugs with thrombocytopenia, neutropenia, fatigue, nausea, and vomiting as the main adverse effects (24, 25). Concerning patients suffering from high-grade glioma on the other hand, neurological deterioration, including focal deficits and cognitive impairment, is pivotal for general performance (26). A decreased preoperative (27, 28) or postoperative (12) neurological performance was shown to be associated with poor prognosis in GBM patients; especially, (newly acquired) aphasia and motoric deficits were found to impair overall survival (15, 29). Moreover, a postoperative decrease of neurological performance has been shown to abrogate the beneficial survival effects gained through an increased extent of GBM resection (11, 13).

**TABLE 2** | Multivariate Cox regression.

| | HR | 95 CI | *p*-value |
|---|---|---|---|
| Age | 1.0 | 0.97–1.02 | 0.87 |
| Extent of resection | 0.91 | 0.88–0.99 | *0.03* |
| Location | 0.61 | 0.33–1.12 | 0.11 |
| Adjuvant therapy | 0.45 | 0.24–0.85 | *0.01* |
| MGMT status | 0.54 | 0.33–0.88 | *0.01* |
| NANO preoperative | 1.0 | 0.89–1.09 | 0.81 |
| NANO postoperative | 0.91 | 0.78–1.05 | 0.19 |
| NANO at 3 months | 1.36 | 1.19–1.57 | *<0.001* |
| NANO difference 2[a] | 1.39 | 0.67–2.91 | 0.38 |

*95 CI, 95% confidence interval; MGMT, O6-methylguanine-DNA methyltransferase; NANO, Neurological Assessment in Neuro-Oncology.*

[a]*Difference of NANO scale values at 3 months follow-up and postoperatively.*

*Statistical significance is emphasized in italicized values.*

All the abovementioned studies employed a non-standardized evaluation of neurological deficits, so the NANO scale was created to objectify clinical assessment in neuro-oncology (17). For glioblastoma patients and in compliance with our results, it was previously shown that NANO scale assessment is significantly associated with patient survival in multivariate survival prediction (19) and might predict overall survival or tumor recurrence more specifically when compared with KPS or ECOG (18). However, there are several limitations to both studies. First, Ung et al. did not evaluate additional clinical and radiological parameters such as the extent of resection, adjuvant radiochemotherapy regimen, or patient age. A NANO scale cutoff is not provided. Second, Lee et al. included patients outside the Stupp regimen defining the present first-line therapy algorithm for glioblastoma. The calculated NANO scale cutoff was 7 points, probably due to an overall reduced neurological performance at initial screening when compared with our data (7.3 ± 3.8 *vs.* 3.3 ± 2.5 in our cohort). Last, both groups did not screen for IDH-mutations and the number of eligible patients did not exceed 80 in either study. In comparison, our data are derived from a larger, homogeneous collective, screened for clinical, radiological, and molecular parameters that are considered essential by current glioma therapy guidelines and classification of CNS tumors (1, 21). This allowed a more coherent interpretation of results and might represent a more reliable database for further projects evaluating the feasibility and prognostic value of neurological performance assessment *via* the NANO scale.

Our study is limited by well-known factors inherent to all retrospective analyses. Selection bias cannot be fully ruled out, especially as all patients with less than 3 months postoperative follow-up are excluded by selection criteria. The time frame was set based on the clinical routine at our center and to allow monitoring neurological performance *via* NANO scale assessment. After receiving the histopathological diagnosis of GBM, patients are directly admitted to adjuvant therapy, followed by 4 to 6 weeks of neurorehabilitation, or vice versa. Hence, the first readmission

appointment to our outpatient clinic for initiating maintenance chemotherapy is averagely set 3 months after surgery. Naturally, patients with an extreme short survival period or the wish for palliative care are not recognized by the presented data (55 patients within the study period, see **Supplementary Figure 1**), explaining the prolonged 12-month survival rate shown in **Table 1** when compared with epidemiological analyses (2). This also might have led to a false-negative non-significance of NANO time point 1 (difference of postoperative and preoperative NANO scale values) as patients with an initial extremely poor clinical performance were likely to be ruled out by the study design. Neuro-oncologists should be aware of this especially vulnerable group of patients that is commonly ruled out in projects evaluating new treatment options.

## CONCLUSION

Monitoring neurological performance *via* the NANO scale might provide prognostic information independently from other well-established clinical, radiological, or pathological factors. Special attention should be paid when worsened neurological performance occurs at the first outpatient appointment after radiochemotherapy and neurorehabilitation. Prospective and multicenter data are needed to further investigate NANO scale assessment in glioblastoma patients, also including a comparison to other performance scales such as KPS or ECOG.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Medical Faculty, University of Leipzig. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

Conceptualization: FA, JK, and JM. Data curation: JK, GP, and CF. Formal analysis: JK, MF, TW, and FW. Methodology: JK, MF, TW, and FW. Project administration: JM and FA. Software: GP. Supervision: KJ, FA, and JM. Validation: JM, FA, and KJ. Writing—original draft: JK. Writing—review and editing: all authors. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.790458/full#supplementary-material

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# Classification of Adverse Events Following Surgery in Patients With Diffuse Lower-Grade Gliomas

*Tomás Gómez Vecchio*[1*], *Alba Corell*[1,2], *Dongni Buvarp*[2], *Isabelle Rydén*[1], *Anja Smits*[1,3] *and Asgeir S. Jakola*[1,2]

[1] Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2] Department of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden, [3] Department of Neuroscience, Uppsala University, Uppsala, Sweden

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***Correspondence:**
Tomás Gómez Vecchio
tomas.gomez.vecchio@gu.se

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**Background:** Recently, the Therapy-Disability-Neurology (TDN) was introduced as a multidimensional reporting system to detect adverse events in neurosurgery. The aim of this study was to compare the novel TDN score with the Landriel–Ibanez classification (LIC) grade in a large cohort of patients with diffuse lower-grade glioma (dLGG). Since the TDN score lacks validation against patient-reported outcomes, we described health-related quality of life (HRQoL) change in relation to TDN scores in a subset of patients.

**Methods:** We screened adult patients with a surgically treated dLGG World Health Organization (WHO) grade 2 and 3 between 2010 and 2020. Up until 2017, it consists of a retrospective cohort ($n$ = 158). From 2017 and onwards, HRQoL was registered using EuroQoL-5-dimension, three levels of response (EQ-5D 3L) questionnaire at baseline and 3 months follow-up, in a prospectively recruited cohort ($n$ = 102). Both the LIC grade and TDN score were used to classify adverse events.

**Results:** In total, 231 patients were included. In 110/231 (47.6%) of the surgical procedures, a postoperative complication was registered. When comparing the TDN score to LIC grades, only a minor shift towards complications of higher order could be observed. EQ-5D 3L was reported for 45 patients. Patients with complications related to surgery had pre- to postoperative changes in EQ-5D 3L index values ($n$ = 27; mean 0.03, 95% CI –0.06 to 0.11) that were comparable to patients without complications ($n$ = 18; mean –0.06, 95% CI –0.21 to 0.08). In contrast, patients with new-onset neurological deficit had a deterioration in HRQoL at follow-up, with a mean change in the EQ-5D 3L index value of 0.11 ($n$ = 13, 95% CI 0.0 to 0.22) compared to –0.06 ($n$ = 32, 95% CI –0.15 to 0.03) for all other patients.

**Conclusions:** In patients with dLGG, TDN scores compared to the standard LIC tend to capture more adverse events of higher order. There was no clear relation between TDN

severity and HRQoL. However, new-onset neurological deficit caused impairment in HRQoL. For the TDN score to better align with patient-reported outcomes, more emphasis on neurological deficit and function should be considered.

**Keywords: glioma grade 2, glioma grade 3, neurosurgery, postoperative complications, classification, health-related quality of life, patient-centered care**

## INTRODUCTION

A standardized reporting system for adverse events has been much wanted in neurosurgery. The Clavien–Dindo (1) and its adaptation the Landriel–Ibanez classification (LIC) (2) systems have been more commonly used in recent literature. Both scales classify adverse events relying on the therapy used to treat the complication. Such classifications were criticized since the kind of treatment required by a specific complication may not always correlate with the patient's health status at discharge and follow-up (3). This is especially true for new neurological deficits following neurosurgery that are typically left untreated, hence being classified as a mild complication. Recently, the Therapy-Disability-Neurology (TDN) score was proposed and suggested to better capture the neurological aspects of complications (4). In TDN, adverse events are graded in relation to the therapy, disability, and neurological deficits that are involved. This system uses Clavien–Dindo and LIC as fundaments, but also adds function with the modified Rankin Scale (mRS) and neurological deficit to the classification.

The novel TDN score was initially validated against Karnofsky performance status scale (KPS). This can be criticized since mRS and KPS have similar prognostic value (5), besides being both a clinical reported outcome. A better calibration, or at least a valid supplementation, may be to add patient-reported outcome measures (PROMs) to the TDN. Multidimensional PROMs such as health-related quality of life (HRQoL) are useful to determine patients' needs in a broader setting with a patient-centered approach. It has been shown that in addition to the mRS, PROMs may play an important role in the assessment of health status in clinical practice (6, 7).

Still, TDN is a promising multidimensional and patient-centered approach to the classification of the severity of adverse events in neurosurgery. A standardized reporting system would allow for monitoring and comparison, where the goal of benchmarking and transparency would ultimately improve the quality of care for patients undergoing surgery. However, more studies are needed to evaluate the differences between the traditional reporting and the TDN score. Of particular interest in this respect are the questions how often the inclusion of mRS and neurological deficits significantly changes the classification and how the complication grades relate to PROMs.

In this study, we aimed to compare the novel TDN score with the LIC grade in a large cohort of patients with diffuse lower-grade glioma (dLGG), to establish the relationship between these two measures. In a subset of patients, we explored the relation between the abovementioned scales (LIC grade and TDN score) and HRQoL following neurosurgical management.

## MATERIALS AND METHODS

### Recruitment

All patients were recruited at our neurosurgical department, which covers a population of approximately 1.7 million inhabitants in a system with referrals based on area of residence. The department manages all patients requiring a neurosurgical procedure due to an intracranial lesion in the region of Västra Götaland, Sweden.

Data were derived from two cohort studies, one retrospective and one prospectively recruited (**Figure 1**). The *retrospective* cohort was obtained using the electronical health records (EHR), pathology database, and operation logs. Patients were ≥18 years old with histopathological verified supratentorial dLGG classified according to the 2007 World Health Organization (WHO) classification of tumors of the central nervous system (8) and graded as grade 2 or 3. Patients who underwent biopsy or tumor resection during the period January 2010 through December 2016 were identified.

The *prospectively recruited* cohort consists of patients ≥18 years old with radiologically suspected dLGG based on MRI scan(s). These patients underwent biopsy or tumor resection during the period January 2017 through December 2020. As part of pre-operative work-up and approximately 3 months postoperatively, these patients were invited to provide quality-of-life measurement in terms of EQ-5D 3L. Subsequently, only patients with dLGG classified according to the WHO 2016 classification (9) as grade 2 or grade 3 were selected for the study.

### Assessment of Molecular Status

Immunohistochemistry staining for *isocitrate dehydrogenase* 1 R132H (*IDH*) mutant protein was performed as the initial step in assessment of *IDH* mutation. Negative immunohistochemistry analyses were subsequently tested with next-generation sequencing to detect rarer *IDH* mutations (10). Codeletion of chromosomal arms 1p and 19q was evaluated with fluorescence *in situ* hybridization, multiplex ligation-dependent probe amplification or evaluation from methylation arrays as reported previously (11). A minority of the retrospective material was not evaluated according to WHO 2016 due to lack of tissue and therefore excluded from the study. The 2021 fifth edition of the WHO Classification of the Tumors of the Central Nervous System (WHO 2021) was not available during the design of the study. As a result, all remaining material, including *IDH* wild-type dLGG where the majority show clinical features of glioblastoma and are currently assessed as glioblastoma according to WHO 2021, was classified according to WHO 2016 for this study (12).

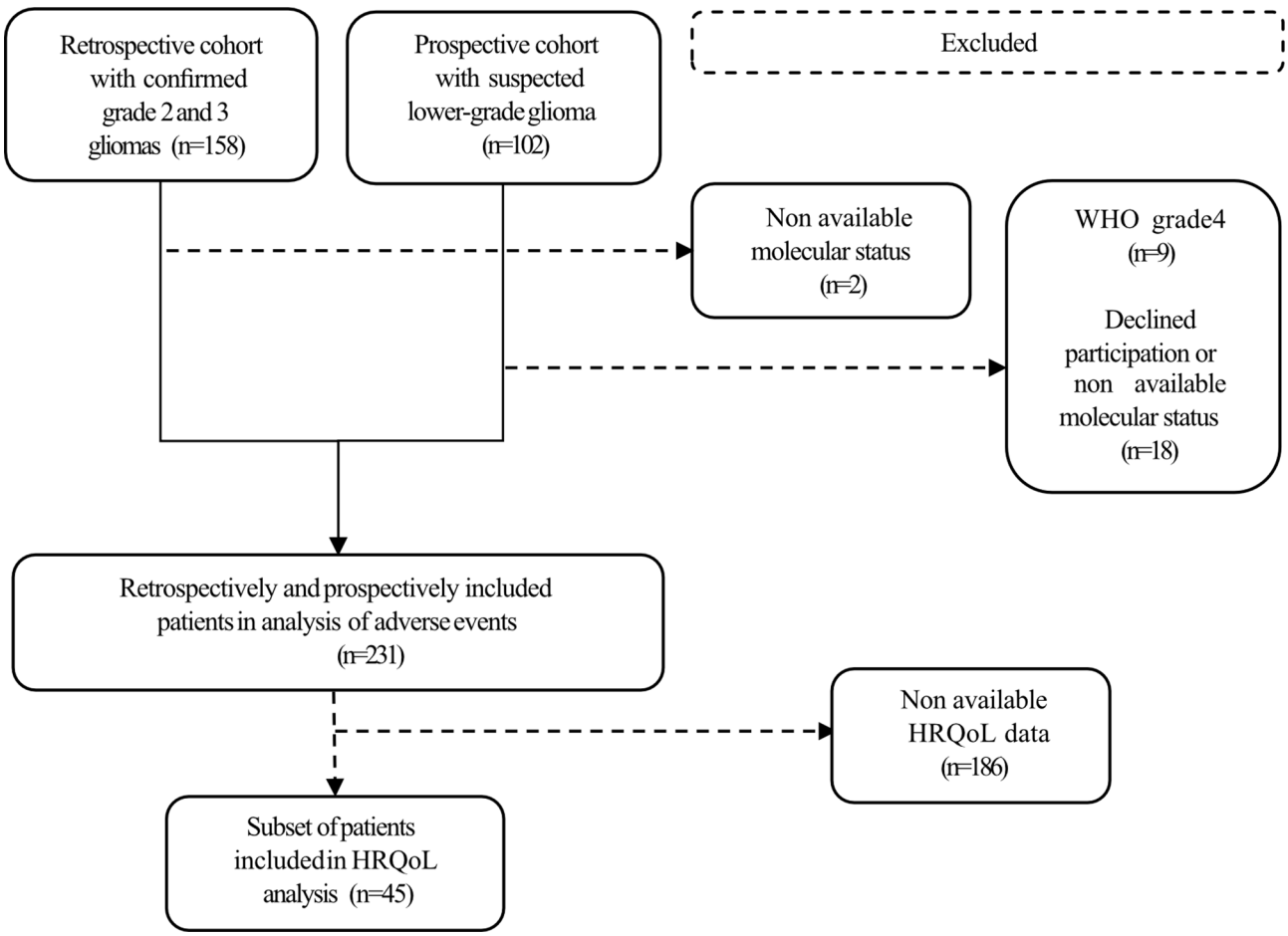


**FIGURE 1** | Flow chart of included cases.

## Measures

KPS is an ordinal scale designed to measure levels of patient activity and medical requirements. Patients are classified into 11 categories from 100 (no evidence of disease) to 0 (dead) (5, 13). KPS at admission was retrospectively scored based on data extracted from EHR. The mRS was originally designed for stroke patients; it focuses on patient disabilities, and patients are classified on 7 categories from 0 (no symptoms) to 6 (dead) (5, 14). For all patients, the mRS was retrospectively estimated from the EHR at follow-up visit (1–3 months postoperative) by clinicians (AJ and DB). To assess whether mRS was affected by surgical complications in patients registering adverse events, mRS at follow-up was qualitatively and retrospectively estimated from EHR.

Adverse events related to post-operative complications were evaluated using the LIC. LIC focuses on general postoperative morbidity using a four-grade severity scale based on the therapy administered to treat a postoperative adverse event within 30 days of surgery; it also considers whether the complication is medical or surgical (2). Complications were recorded based on EHR.

Neurological deficit and any information concerning seizures and seizure control was routinely assessed at admission, discharge, and follow-up at the neurosurgical department. Also based on EHR, neurological deficits recorded included motor, language, cognitive, and visual domains. Any post-operative new or worsened neurological deficit, including transient or suspected ones like the supplementary motor area syndrome, was registered. A deficit was considered permanent if deterioration compared to baseline was still present at 3 months, even if significant recovery had occurred.

Anatomical magnetic resonance imaging (MRI) T2-weighted image (T2) or fluid-attenuated inversion-recovery (FLAIR) sequences were used to assess tumor volume using software 3D Slicer (15) according to our previously reported method (16). Multifocal lesions were classified according to the largest tumor. Main tumor location and presumed eloquent brain areas were routinely identified as part of the preoperative work, and both were recorded based on EHR. Location taxonomy followed the anatomical lobe mainly involved by the lesion. Presumed eloquent brain areas were identified following the areas listed

in the University of California San Francisco classification system (17).

TDN grades were calculated following the TDN criteria (4), here referred to as TDN scores. Adverse events were ordered in relation to the therapy, disability, and neurological deficits they involved. Therapy was evaluated using the LIC; Disability was assessed with the mRS at follow-up (mRS was not considered for TDN classification if it was affected by documented tumor progression); Neurological deficit was assessed using a binary definition for any new or worsened neurological deficit following surgery. According to TDN criteria, the dimensions of Disability and Neurology were only considered for TDN scoring when their deterioration resulted from the adverse event (**Figure 2**).

HRQoL was measured with EuroQoL-5-dimension, three levels of response (EQ-5D 3L) questionnaire (18). Patients completed the EQ-5D 3L at the time of first visit to the outpatient clinic and at follow-up approximately 3 months postoperatively. EQ5D 3L was only available in parts of the prospective cohort. The results of EQ-5D 3L questionnaire were transferred to a utility index ranging from −0.594 to 1 (19), where higher scores indicated better quality of life. A minimal clinical important difference (MCID) of ±0.14, previously reported in patients undergoing glioma surgery, was used for this study (20). Change in EQ-5D3L index value was calculated subtracting the follow-up value from the preoperative value. Negative values (postoperative better than preoperative) indicated improvement; positive values indicated a decline.

## Statistical Analysis

All analyses were carried out in IBM SPSS version 28 (IBM Corp., Armonk, NY, US). Central tendencies for descriptive statistics are

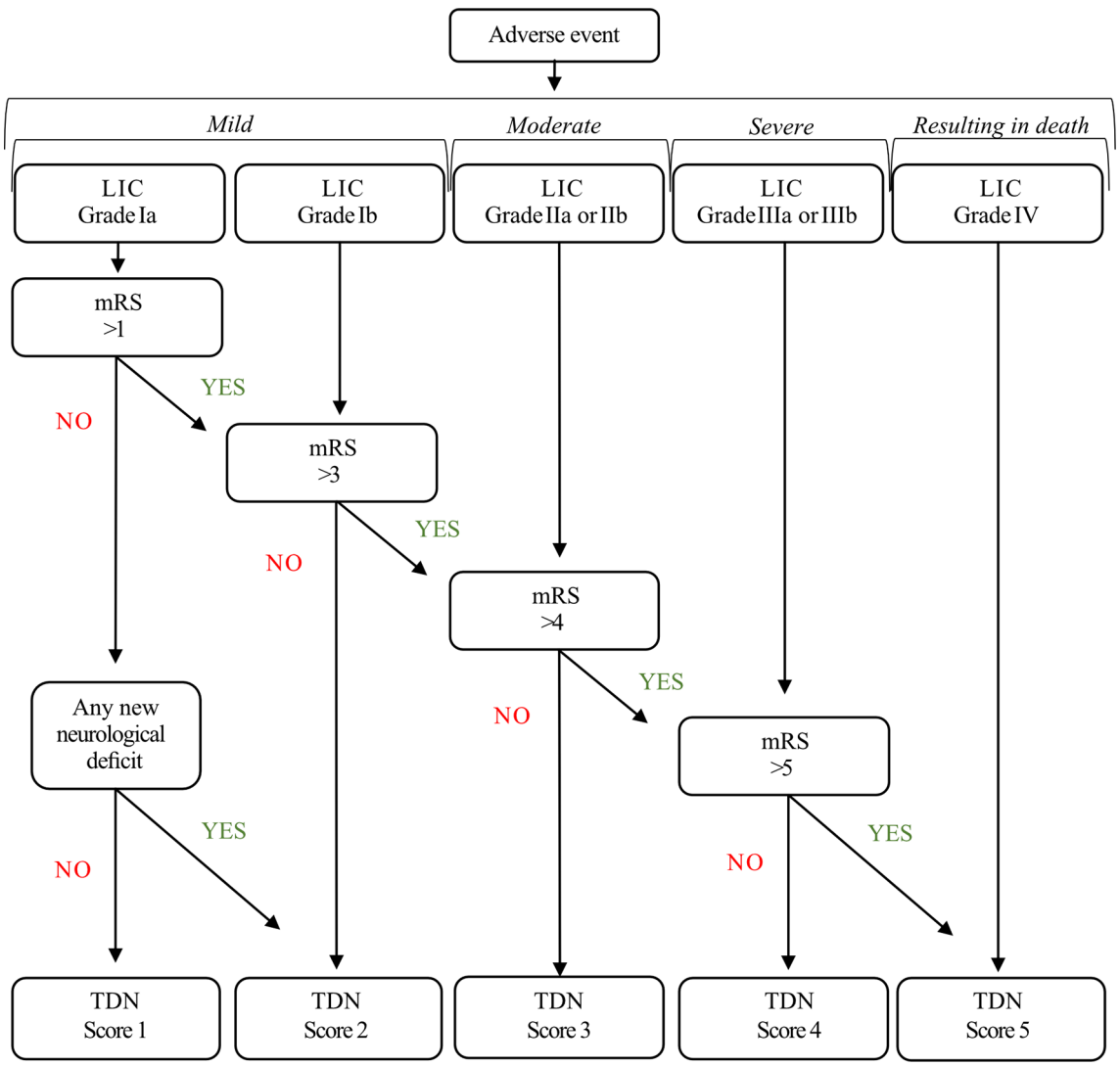


**FIGURE 2** | TDN algorithm.

presented with either percentages, means with standard deviation (SD) or 95% confidence intervals (CI), or medians with first and third quartile (Q1, Q3). Statistical significance level was set to $p < 0.05$. All tests were 2 sided. Comparisons between groups were conducted with unpaired *t*-test, Mann–Whitney *U* test, Pearson $\chi^2$, or Fisher's exact test as appropriate. Collinearity was assessed with Pearson correlation, ANOVA, and Cramer test between covariables, covariables and factors, and between factors, respectively. Collinearity between variables was set to values higher than 0.80 for Pearson's eta, 0.64 for ANOVA's eta squared, and 0.80 for Cramer's V. Multivariable logistic regression was used with complications related to surgery as response. Age, sex, preoperative KPS, epilepsy, neurological deficits at admission (motor, cognitive, visual, and language), type of neurological intervention, tumor classification, main tumor location, tumor volume, and preoperative eloquence were used as dependent variables. Additional Sankey diagram, bar plots, and box plots were generated using Python programming language version 3.8.3 (Python Software Foundation, Delaware, US).

# RESULTS

## Patient Characteristics

A total of 260 patients were screened for inclusion. Two patients in the retrospective cohort were excluded due to lack of tissue. From the prospectively recruited cohort, 27 patients were excluded because final histopathological diagnosis was other than dLGG grade 2 or grade 3, or because patients declined to participate in the study (**Figure 1**).

A total of 231 patients were included in the study. The mean age at surgery was 48.3 years (SD 14.5), and 134 patients (58.0%) were males. There were 69 patients (29.9%) with oligodendrogliomas, 75 (32.5%) with astrocytoma *IDH*-mutant, and 87 (37.6%) with astrocytoma *IDH* wild type. The distribution of grade showed that 119 patients (51.5%) had tumors of WHO grade 2 and 112 patients (48.5%) of WHO grade 3. Within 3 months of surgery, a total of 46/231 patients (19.9%) started chemotherapy only (either temozolomide or procarbazine-lomustine-vincristine), and 52/231 patients (22.5%) had started radiotherapy only, and 61/231 patients (26.4%) had started both chemotherapy and radiotherapy.

At admission, 157 patients (68%) reported a history of seizures. From surgery to the 3 months follow-up, five of these patients (2.2% of total cohort) had worsening of seizures. During the same period, three patients (1.3%) had first-onset seizures. All worsened and first-onset seizures occurring withing 30 days of surgery were scored according to LIC grading. The proportion of any neurological deterioration post-operatively was 89/231 (38.5%). Deficit in more than one function occurred in 36/231 patients (15.6%). Also, out of 89 patients with deficits, 40 patients (44.9%) had complete recovery at 3 months postoperatively. A detailed list of patient characteristics and clinical variables is provided in **Table 1**.

## Patient Characteristics and Adverse Events Related to Surgery

Regarding surgical outcomes, 121/231 patients (52.4%) did not present with any postoperative complications and consequently received a TDN score of 0. The remaining 110 patients with complications related to surgery were scored according to TDN criteria. In 10 out of 110 patients (9.1%) with complications, mRS measurements could not be considered for TDN scoring. Five of these ten patients had notable deterioration in mRS at follow-up due to tumor progression, which is therefore unrelated to complications following glioma surgery. For the remaining five patients, mRS was missing due to loss of follow-up. A comparison between TDN score and LIC grade results is provided in **Table 2** and **Figure 3**.

Patient characteristics and clinical variables in cases with and without complications related to surgery are shown in **Table 3**. Of the included variables, only preoperative cognitive deficit and type of surgery were found to be significantly differently distributed among groups of patients with and without complications. Patients with complications more often had cognitive impairment prior to surgery than patients without complications (23.6% versus 10.7%, $p = 0.01$) and more often

**TABLE 1** | Patient characteristics and clinical variables (*N* = 231).

| Variable | Study sample |
|---|---|
| Age at surgery, mean (SD) | 48.3 (14.5) |
| Female, *n* (%) | 97 (42.0) |
| KPS[1] at admission, median (Q1, Q3) | 90 (80, 90) |
| WHO 2016 classification, *n* (%) | |
| Oligodendroglioma, WHO grade 2 | 36 (15.6) |
| Oligodendroglioma, WHO grade 3 | 33 (14.3) |
| Diffuse astrocytoma, IDH-mutant, WHO grade 2 | 36 (15.6) |
| Astrocytoma, IDH-mutant, WHO grade 3 | 39 (16.9) |
| Diffuse astrocytic glioma, IDH-wildtype, WHO grade 2 | 47 (20.3) |
| Diffuse astrocytic glioma, IDH-wildtype, WHO grade 3 | 40 (17.3) |
| Seizure, *n* (%) | 157 (68.0) |
| Neurological deficit at admission, *n* (%) | |
| Motor | 28 (12.1) |
| Cognitive | 39 (16.9) |
| Visual | 12 (5.2) |
| Language | 28 (12.1) |
| Any neurological deficit | 76 (32.9) |
| Type of neurosurgical intervention, *n* (%) | |
| Tumor resection | 184 (79.7) |
| Seizure[2], *n* (%) | 8 (3.5) |
| New neurological deficit [3], *n* (%) | |
| Motor | 49 (21.2) |
| Cognitive | 22 (9.5) |
| Visual | 17 (7.4) |
| Language | 45 (19.5) |
| Any new neurological deficit | 89 (38.5) |
| *Transient deficit* | *40 (17.3)* |
| *Permanent deficit* | *49 (21.2)* |
| Deficits in more than one domain | 36 (15.6) |

[1]*Karnofsky Performance Status Scale.*
[2]*New or worsened. Neither prophylactic or therapeutic use of anti-epileptic drugs were recorded for the study.*
[3]*New neurological deficits were defined as new or worsened from surgery to the 3-month follow-up.*

**TABLE 2** | Comparison between LIC grade and TDN score (*N* = 231).

| Variable | Cohort (*n* = 231) | Variable | Cohort (*n* = 231) |
|---|---|---|---|
| LIC[1], *No* (%) | | TDN[2], *No* (%) | |
| No complications, | 121 (52.4) | No complications, | 121 (52.4) |
| Grade Ia | 69 (29.9) | Score 1 | 1 (0.4) |
| *Ia surgical//medical* | *66//3* | | |
| Grade Ib | 25 (10.8) | Score 2 | 89 (38.5) |
| *Ib surgical//medical* | *15//10* | | |
| Grade IIa | 3 (1.3) | | |
| *IIa surgical//medical* | *2//1* | Score 3 | 18 (7.8) |
| Grade IIb | 11 (4.8) | | |
| *IIb surgical//medical* | *10//1* | | |
| Grade IIIa | 2 (0.9) | Score 4 | 2 (0.9) |
| *III surgical//medical* | *1//1* | | |
| Grade IIIb | - | | |
| Grade IV | - | Score 5 | - |
| Type of complication, *No* (%) | | | |
| Medical | 16 (6.9) | | |
| Surgical | 94 (40.7) | | |

[1] *Landriel–Ibanez classification.*
[2] *Therapy-Disability-Neurology.*

underwent tumor resection than tumor biopsy as primary surgery strategy (90% versus 70.2%, $p < 0.001$ see **Table 3**).

A multivariable logistic regression was performed to ascertain the effects of age, sex, preoperative KPS, epilepsy, neurological deficits at admission, type of neurological intervention, tumor classification, main tumor location, tumor volume, and preoperative eloquence on the likelihood that complications arise following glioma surgery. Of these, cognitive impairment at admission, surgical resection, and tumors located in eloquent regions were associated with an increased likelihood of complications following glioma surgery (respectively $p = 0.01$, $p \leq 0.001$, and $p = 0.01$, see **Supplementary Table 1**).

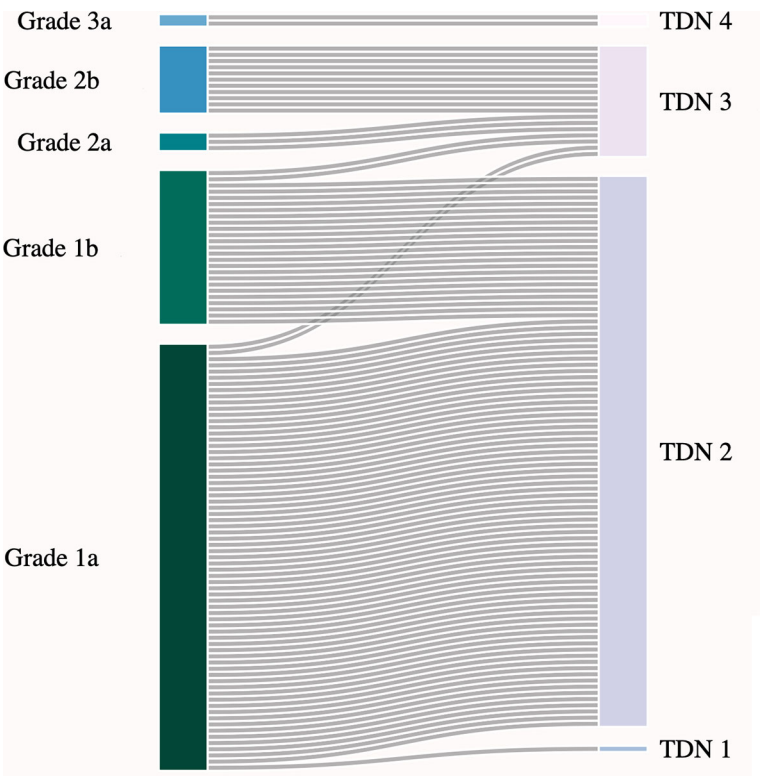


**FIGURE 3** | Comparison between LIC grade and TDN score (*N* = 110).

**TABLE 3 |** Patient characteristics and clinical variables in patients with and patients without complications related to surgery (*N* = 231).

| Variable | No Complications (*n* = 121) | TDN[1] (1 to 5) (*n* = 110) | *p*-value[2] |
|---|---|---|---|
| Age at surgery, mean (SD) | 48.5 (14.5) | 48.2 (14.6) | 0.87 |
| Female, *n* (%) | 52 (43.0) | 45 (40.9) | 0.79 |
| KPS[3] at admission, median (Q1, Q3) | 90 (70, 90) | 90 (80, 90) | 0.99 |
| WHO 2016 classification, *n* (%) | | | |
| Oligodendroglioma, WHO grade 2 | 18 (14.9) | 18 (16.4) | 0.86 |
| Oligodendroglioma, WHO grade 3 | 17 (14.0) | 16 (14.5) | 1.00 |
| Diffuse astrocytoma, IDH-mutant, WHO grade 2 | 17 (14.0) | 19 (17.3) | 0.59 |
| Astrocytoma, IDH-mutant, WHO grade 3 | 19 (15.7) | 20 (18.2) | 0.73 |
| Diffuse astrocytic glioma, IDH-wildtype, WHO grade 2 | 30 (24.8) | 17 (15.5) | 0.10 |
| Diffuse astrocytic glioma, IDH-wildtype, WHO grade 3 | 20 (16.5) | 20 (18.2) | 0.86 |
| Epilepsy, *n* (%) | 80 (66.1) | 77 (70.0) | 0.57 |
| Neurological deficit at admission, *n* (%) | | | |
| Motor | 19 (15.7) | 9 (8.2) | 0.11 |
| Cognitive | 13 (10.7) | 26 (23.6) | 0.01 |
| Visual | 8 (6.6) | 4 (3.6) | 0.38 |
| Language | 11 (9.1) | 17 (15.5) | 0.16 |
| Any neurological deficit excluding seizures | 38 (31.4) | 38 (34.5) | 0.68 |
| Type of neurosurgical intervention, *n* (%) | | | |
| Tumor resection | 85 (70.2) | 99 (90.0) | <0.001 |
| Main tumor location, *n* (%) | | | |
| Frontal | 61 (50.4) | 58 (52.7) | 0.79 |
| Temporal | 34 (28.1) | 32 (29.1) | 0.89 |
| Parietal | 11 (9.1) | 10 (9.1) | 1.00 |
| Occipital | 1 (0.8) | 1 (0.9) | 1.00 |
| Insular | 11 (9.1) | 7 (6.4) | 0.47 |
| Basal ganglia | 3 (2.5) | 2 (1.8) | 1.00 |
| Tumor located in eloquent regions (UCSF[4]) | 79 (65.3) | 78 (71.6) | 0.32 |
| Tumor volume[5], median (Q1, Q3) | 55.1 (27.6, 133.5) | 54.8 (28.1, 97.8) | 0.60 |
| *Change in EQ-5L 3D index value, n (%)* | *n = 18* | *n = 27* | |
| *MCID[6] change in EQ-5D 3L index value - IMPROVED* | *5 (27.8)* | *4 (14.8)* | *0.45* |
| *MCID change in EQ-5D 3L index value - UNCHANGED* | *10 (55.6)* | *18 (66.7)* | *0.54* |
| *MCID change in EQ-5D 3L index value - WORSENED* | *3 (16.7)* | *5 (18.5)* | *1.00* |

[1] *Therapy-Disability-Neurology.*
[2] *Statistical significance level was set to p < 0.05. All tests are 2 sided. Comparisons between groups were conducted with unpaired t-test, Mann–Whitney U-test or Fisher's exact test as appropriate.*
[3] *Karnofsky Performance Status Scale.*
[4] *University of California San Francisco classification system.*
[5] *Volume in cubic millimeters. One missing case due to unavailable MRI.*
[6] *Minimum clinical important difference.*

## Neurological Deficit in Patients Experiencing Adverse Events Related to Surgery

In 110 patients experiencing adverse events, a total of 133 new or worsened neurological deficits were found. Of the 110 patients experiencing adverse events, 21 patients (19.1%) did not present with new or worsened neurological deficit. On average, patients scoring TDN 2 experienced more neurological deficits (112 deficits in 89 patients) and more often postoperative neurological deficit only (51/89 patients, 57%) than patients with TDN higher than 2 (21 deficits in 20 patients; and 7/20 patients, 35% respectively). A detailed list of neurological deficits in groups of patients by TDN score is shown in **Table 4**.

## Postoperative Health-Related Quality of Life

EQ-5D 3L was reported for 45 patients. The patients experiencing complications related to surgery had similar pre- to postoperative change in EQ-5D 3L index values (*n* = 27; mean 0.03; 95% CI −0.06 to 0.11) compared to patients without complications (*n* = 18; mean −0.06; 95% CI −0.21 to 0.08). Although subgroups were small, there was no apparent difference in change in EQ-5D 3L index values for TDN scores 3–5 (*n* = 3; mean 0.04; 95% CI −0.12 to 0.21) compared to TDN scores 1–2 (*n* = 24; mean 0.02; 95% CI −0.07 to 0.12). Changes in EQ-5D 3L index value in subgroups of patients based on TDN scores are shown in **Table 5** and **Figure 4**.

In patients grouped by the presence of neurological deficit at follow-up, patients without new or worsened neurological deficit at follow-up had better HRQoL change with mean −0.08 change in pre- to post-operative EQ-5D 3L index value (*n* = 21; 95% CI −0.20 to 0.05) compared to patients experiencing any new or worsened neurological deficit (*n* = 24; mean 0.05; 95% CI −0.04 to 0.13). Changes in EQ-5D 3L index value in patients grouped by presence of neurological deficit at follow-up are shown in **Table 6** and **Figure 5**.

Patients with new-onset neurological deficit(s) at follow-up had worse HRQoL change, with mean 0.11 change in pre- to postoperative EQ-5D 3L index value (*n* = 13; 95% CI 0.0 to 0.22)

**TABLE 4 |** Neurological deficits at admission and follow-up in patients by TDN score (*N* = 231).

| Variable | TDN[1] 0 *n* = 121 | TDN 1 *n* = 1 | TDN 2 *n* = 89 | TDN 3 *n* = 18 | TDN 4 *n* = 2 | TDN 5 *n* = 0 |
|---|---|---|---|---|---|---|
| New neurological deficit[2], *n* (%) | | | | | | |
| Motor | – | – | 41 (46) | 7 (39) | 1 (50) | – |
| Cognitive | – | – | 19 (21) | 2 (11) | 1 (50) | – |
| Visual | – | – | 14 (16) | 3 (17) | – | – |
| Language | – | – | 38 (43) | 6 (33) | 1 (50) | – |
| *Patients with any new or worsened ND[3]* | - | - | *77 (87)* | *10 (56)* | *2 (100)* | - |
| *Patients with postoperative ND only* | - | - | *51 (57)* | *6 (33)* | *1 (50)* | - |
| *Patients with permanent ND* | - | - | *40 (45)* | *7 (39)* | *2 (100)* | - |

[1] *Therapy-Disability-Neurology.*
[2] *New neurological deficits were defined as new or worsened (transient/permanent) from surgery to the 3-month follow-up.*
[3] *Neurological deficits.*

**TABLE 5 |** Change in the EQ-5D 3L index value in subgroups of patients based on TDN scores (*N* = 45).

| Cohort (*n* = 45) | Change in EQ-5D 3L index value |
|---|---|
| Total sample; mean (95% CI) | –0.01 (–0.09 to 0.07) |
| TDN[1]; mean (95% CI) | |
| No complications related to surgery (Score 0), *n* = 18 | –0.06 (–0.21 to 0.08) |
| TDN scores 1 to 5; mean (95% CI), *n* = 27 | 0.03 (–0.06 to 0.11) |
| *"Mild" complications (TDN 1 and 2), n = 24* | *0.02 (–0.07 to 0.12)* |
| *"More than mild" complication (TDN 3 to 5), n = 3* | *0.04 (–0.12 to 0.21)* |

[1] *Therapy-Disability-Neurology.*

compared to other patients (*n* = 32; mean −0.06; 95% CI −0.15 to 0.03). Changes in EQ-5D 3L index value in patients grouped by change in neurological deficit from admission to follow-up are shown in **Table 7** and **Figure 6**.

Patients undergoing any adjuvant treatment within 3 months of surgery showed a similar change in EQ-5D 3L index values mean −0.06 (*n* = 28, CI −0.17 to 0.06). Despite small subgroups, no major trend was seen with the different adjuvant treatment (*n* = 11, mean −0.05, CI −0.23 to 0.14 for patients undergoing chemotherapy only; *n* = 8, mean −0.19, CI −0.45 to 0.07 for patients undergoing radiotherapy only; and *n* = 9, mean 0.05, CI −0.09 to 0.19 for patients undergoing chemotherapy and radiotherapy). The patients without any adjuvant treatment within 3 months of surgery had comparable results (*n* = 17, mean 0.07, CI 0.00 to 0.13).

## DISCUSSION

Comparing the TDN score to LIC in our population-based cohort of dLGG, we observed a slight shift from mild complications towards complications of higher order. This shift represented the "severity" of the complication that was expressed in either new neurological deficits or new functional deficits. This finding demonstrates the capacity of the TDN score to multidimensionally report the functional consequences and severity of postoperative complications related to dLGG surgery. Regarding HRQoL, no important clinical differences, measured as EQ-5D 3L index values, were found between patients with and patients without complications related to surgery. Although acknowledging that subgroups were small, we conclude that

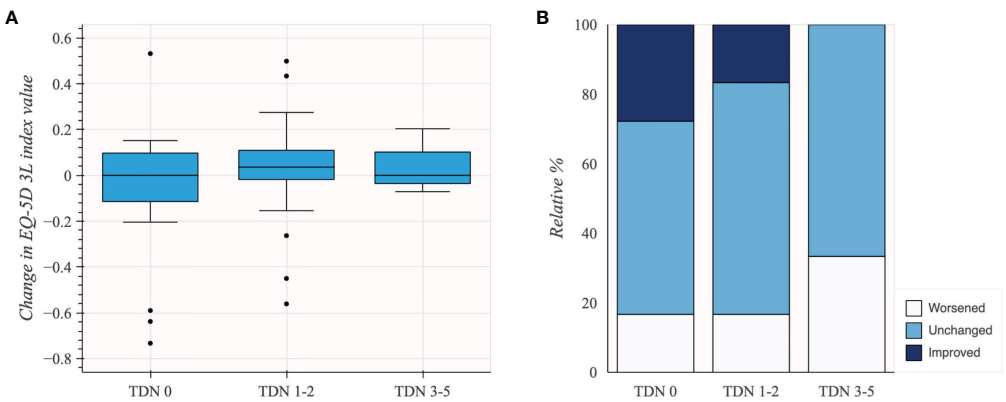


**FIGURE 4** | Change in the EQ-5D 3L index value in subgroups of patients based on TDN scores (*N* = 45). **(A)** Box plot illustrating distribution of change in EQ-5D 3L index values. **(B)** Stacked bar plot illustrating change in EQ-5D 3L based on MCID.

**TABLE 6 |** Change in the EQ-5D 3L index value in patients grouped by presence of neurological deficit at follow-up (*N* = 45).

| Cohort (*n* = 45) | Change in EQ-5D 3L index value |
|---|---|
| Patients by presence of neurological deficit; mean (95% CI) | |
| *Any new or worsened neurological deficit*[1], *n = 24* | 0.05 (–0.04 to 0.13) |
| *None new or worsened neurological deficit at follow-up, n = 21* | –0.08 (–0.20 to 0.05) |

[1] *Including transient or permanent neurological deficits from surgery to the 3-month follow-up.*

there was no apparent difference in HRQoL change among subgroups of patients with complications of different order.

When compared side by side, only a small fraction of patients experiencing mild complications according to LIC received TDN scores higher than 2 due to impairment in mRS scores. Although the majority of patients with dLGG undergoing surgery did not have a marked reduction in functional capacity as measured by mRS, and consequently little effect on results at the group level, it demonstrates that TDN is capable of identifying such patients. Furthermore, most complications initially classified as Grade 1a in LIC were classified as TDN score 2 due to the presence of various neurological deficits postoperatively, showing that the TDN scoring system is clearly capturing the neurological consequences of surgery. Nevertheless, the diversity of neurological deficits at follow-up is not further differentiated by the TDN scoring system. Overall, when compared to LIC, the trajectories marked by TDN classification, although useful, do not introduce substantial changes into the classification of complications related to surgery in our cohort of patients with dLGG.

Acknowledging limitations of the HRQoL subset size, our data suggest that changes in HRQoL reflect changes in neurological function related to aspects of patient's daily activities that are not addressed by the TDN score. Given the small sample size, we only used the EQ-5D 3L index value. An analysis of all EQ-5D 3L dimensions or use of a more fine-tuned instrument in a larger cohort may certainly better reflect neurological function than the EQ-5D 3L index value alone. It was previously demonstrated that new neurological deficits can have major undesirable effects on HRQoL (21). Nevertheless, we found that patients with new or worsened neurological deficits and patients with postoperative neurological deficit only were mostly classified as TDN 2. We also found that these patients had generally a decline in HRQoL. We suggest that TDN may be too insensitive to changes in neurological function related to aspects of patient's daily activities that are important to patients, and perhaps more important than many of the non-neurological complications. Despite small numbers, one nuance in our preliminary data suggests that the presence of postoperative neurological deficit alone might not be as relevant from a patient's perspective as an unexpected decline in neurological status from admission to follow-up.

Considering the relative short period of time from radiological diagnosis to 3 months follow-up, it would be interesting to explore how this trend in HRQoL evolves in the medium and long term. This would be especially important in patients with oligodendroglioma or *IDH*-mutated astrocytoma where a more indolent course of disease is expected. However, in that case, attention should be also given to the so-called response shift phenomena. It has been reported that a response shift seems to reduce the effects of HRQoL changes in patients with glioma (22). Thus, this is a potential source of unexpected findings and a potential limitation for anchoring outcomes with HRQoL in the longer term. Despite unclear patterns in the short term, the effect of adjuvant treatment on HRQoL change should also be considered in future research.

Some limitations raised by the authors of the TDN classification system are its inability to differentiate between

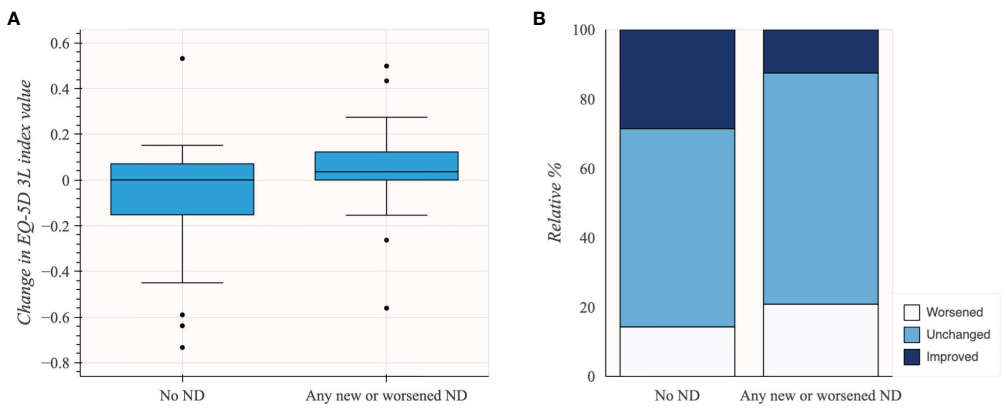


**FIGURE 5 |** Change in EQ-5D 3L index value in patients grouped by the presence of neurological deficit (ND) at follow-up (*N* = 45). **(A)** Box plot illustrating distribution of change in EQ-5D 3L index values. **(B)** Stacked bar plot illustrating change using MCID groups.

**TABLE 7 |** Change in the EQ-5D 3L index value in patients grouped by change in neurological deficit from admission to follow-up (*N* = 45).

| Cohort (*n* = 45) | Change in EQ-5D 3L index value |
|---|---|
| Patients by change neurological deficit[1]; mean (95% CI) | |
| *Patients with new postoperative neurological deficit only, n = 13* | 0.11 (0.00 to 0.22) |
| All other patients, *n* = 32 | –0.06 (–0.15 to 0.03) |
| *Patients with new post- and with preoperative neurological deficit, n = 11* | *–0.03 (–0.15 to 0.09)* |
| *Patients without new post- and without preoperative neurological deficit, n = 13* | *–0.05 (–0.20 to 0.10)* |
| *Patients without new post- and with preoperative neurological deficit, n = 8* | *–0.12 (–0.37 to 0.13)* |

[1]*New neurological deficits were defined as new or worsened (transient/permanent) from surgery to the 3-month follow-up.*

adverse events and failure to cure, and the lack of account for surgical complexity (4). In our study, including some patients with an unfavorable prognosis, we strictly limited the recording of adverse events and follow-up to 1 and 3 months, respectively, to reduce the risk of upgrading complications due to the natural course of the disease or due to the documented side effects (e.g., thrombocytopenia and leukopenia) related to adjuvant treatment. Thus, we can appreciate the importance of time-point measurement tailored towards particular diagnostic groups. A 3-month time interval was shown to be sufficient for recovery from transient deficits following surgery in patients with dLGG (23). However, in patients with a notable deterioration in mRS at follow-up due to tumor progression, mRS measurements could not be used for TDN scoring. Furthermore, in order to avoid too much "thresholding" of own results (with a significant portion of data based on retrospective data), any new or worsened postoperative neurological deficit was carefully recorded. Being cautious not to select deficits considered more important by the clinical team than the patient, or remove expected ones, we were interested in keeping the patient perspective (24). Thus, our study presents a comprehensive, although retrospective, view on the clinical burden related to surgery that patients with dLGG experience.

In neurosurgery, multidimensional PROMs measuring different aspects of HRQoL have shown slight to moderate agreement with traditional clinical scales including KPS and mRS (21, 25, 26). Patient- and surgeon-reported outcomes detect different aspects of the patients' health status that are relevant for clinical practice, with the potential to enhance individually tailored patient care (27). We believe that the weight of neurological deficit and function within the TDN score should be further explored to reflect the burden of adverse event as experienced by patients, if the intention of TDN indeed is a more holistic adverse event classification. In case the TDN fails to capture the importance of new or worsened neurological deficit (s) and impaired functional status, we would advocate continuing to report these outcomes separately and not hidden within the TDN grade. Further research on HRQoL trajectories in relation to specific complications is needed.

## STRENGTHS AND LIMITATIONS

The demographics of the study cohort together with the variables associated with presence of complications following glioma surgery were comparable with previous reports on patients with dLGG (28–32), indicating that our results hold high external validity. There are, however, limitations inherent to the retrospective design of our study. Although the inclusion of patients and a portion of the data was prospectively collected, mRS was not included in the collection template. Thus, mRS was supplemented in retrospect. At our institution, clinical routine comprising the period 2017–2020 included the screening of patients by neuropsychological testing. Therefore, a bias towards detecting more cognitive deficits in the prospectively recruited cohort may be present both pre- and postoperatively.

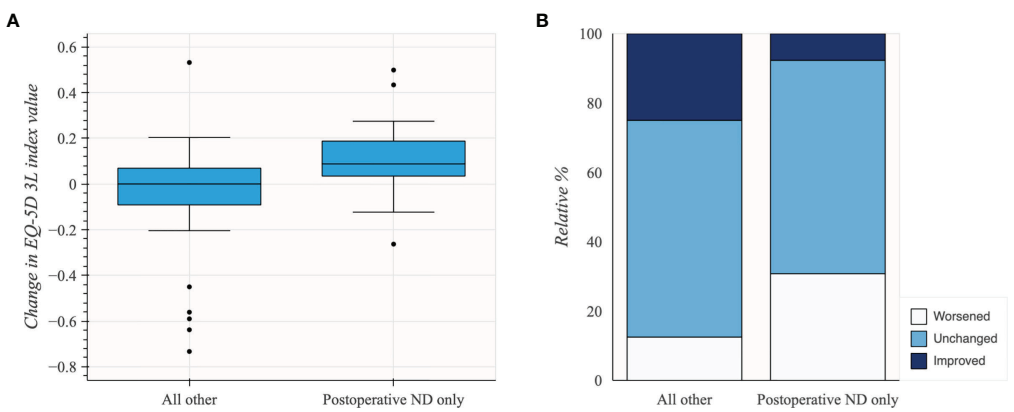


**FIGURE 6** | Change in the EQ-5D 3L index value in patients grouped by change in neurological deficit (ND) from admission to follow-up (*N* = 45). **(A)** Box plot illustrating distribution of change in EQ-5D 3L index values. **(B)** Stacked bar plot illustrating change using MCID groups.

The inclusion of HRQoL enabled us to explore the impact of negative outcomes as reported by patients. However, the limited sample size for HRQoL data did not allow us to perform statistical analyses on the relation between TDN score and EQ-5D 3L. Thus, data exploration in smaller but clinically relevant subgroups was not possible. The EQ-5D 3L index value is known for being prone in particular to the ceiling effect (20). Indeed, there was a significant ceiling effect in our cohort, where the best possible EQ-5D 3L index value at admission was scored by 18% of our patients. In contrast, there was no floor effect for the EQ-5D 3L index value.

## CONCLUSIONS

TDN score compared to LIC tends to modestly capture more adverse events of higher order, by putting new emphasis on the functional and neurological outcome. Classification with TDN seems intuitive and adequate to be used in future studies. We suggest that future work on TDN score, with further validation against PROM, should explore if the neurological and functional consequences should be weighed differently.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr. 1067-16). Informed written consent was obtained for all prospectively included patients. The committee waived the need of written consent for the retrospective cohort. The study was conducted in accordance with the Declaration of Helsinki.

## AUTHOR CONTRIBUTIONS

All authors participated equally in the initial design and final reviewing of the manuscript. TV contributed to the planning of the study, data curation, data analysis, and drafting of the manuscript, including design of figures and tables, and revising and submission of manuscript. AC contributed by recruiting patients, reviewing the manuscript, and approval of the final manuscript. DB contributed by mRS assessment, reviewing the manuscript, and approval of the final manuscript. IR contributed by HRQoL measurement, reviewing the manuscript, and approval of the final manuscript. AS contributed by reviewing the manuscript and approval of the final manuscript. AJ contributed by planning the study, recruiting patients, reviewing the manuscript, and approval of the final manuscript. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.792878/full#supplementary-material

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ORIGINAL RESEARCH
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# Impact of Anticipated Awake Surgery on Psychooncological Distress in Brain Tumor Patients

*Franziska Staub-Bartelt*, Oliver Radtke, Daniel Hänggi, Michael Sabel and Marion Rapp*

*Department of Neurosurgery, University Hospital Duesseldorf, Duesseldorf, Germany*

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**Edited by:**
*Shawn L. Hervey-Jumper, University of California, San Francisco, United States*

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*Markus Klimek, Erasmus Medical Center, Netherlands*

***Correspondence:**
*Franziska Staub-Bartelt*
*franziska.staub-bartelt@med.uni-duesseldorf.de*

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**Background:** Brain tumor patients present high rates of distress, anxiety, and depression, in particular perioperatively. For resection of eloquent located cerebral lesions, awake surgery is the gold standard surgical method for the preservation of speech and motor function, which might be accompanied by increased psychological distress. The aim of the present study was to analyze if patients who are undergoing awake craniotomy suffer from increased prevalence or higher scores in distress, anxiety, or depression.

**Methods:** Patients, who were electively admitted for brain tumor surgery at our neurooncological department, were perioperatively screened regarding distress, anxiety, and quality of life using three established self-assessment instruments (Hospital Anxiety and Depression Scale, distress thermometer, and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30-BN20). Screening results were correlated regarding operation technique (awake vs. general anesthesia). Retrospective statistical analyses for nominal variables were conducted using chi-square test. Metric variables were analyzed using the Kruskal–Wallis test, the Mann–Whitney U-test, and independent-samples t-tests.

**Results:** Data from 54 patients (26 male and 28 female) aged 29 to 82 years were available for statistical analyses. A total of 37 patients received primary resection and 17 recurrent tumor resection. Awake surgery was performed in 35 patients. There was no significant difference in awake versus non-awake surgery patients regarding prevalence (of distress ($p = 0.465$), anxiety ($p = 0.223$), or depression ($p = 0.882$). Furthermore, awake surgery had no significant influence on distress thermometer score ($p = 0.668$), anxiety score ($p = 0.682$), or depression score ($p = 0.630$) as well as future uncertainty ($p = 0.436$) or global health status ($p = 0.943$). Additionally, analyses revealed that primary or recurrent surgery also did not have any significant influence on the prevalence or scoring of the evaluated items.

**Conclusion:** Analyses of our cohort's data suggest that planned awake surgery might not have a negative impact on patients concerning the prevalence and severity of manifestation of distress, anxiety, or depression in psychooncological screening. Patients undergoing recurrent surgery tend to demonstrate increased distress, although results were not significant.

**Keywords: awake surgery, psychooncological distress, glioblastoma, brain tumor, HADS, EORT C QLQ-C30**

## INTRODUCTION

Cancer patients are at high risk of suffering increased levels of distress, anxiety, and depression. A study regarding the prevalence of distress in patients with different types of cancer reported an overall prevalence of distress of about 35% (1). When focusing on neurooncological patients, prevalence of distress is reported to be even higher with ranges of between 38% and 52% (2, 3). According to previous studies, approximately one-fourth of cancer patients also suffer from depression or depressive symptoms (4). In brain tumor patients, the prevalence of depression is reported to be approximately 21% and generally assumed to be higher than in patients with different cancers (4, 5). Further analyses underlined that in correlation to increased levels of distress, anxiety, and depression, brain tumor patients additionally show a reduction of quality of life (QoL) (6, 7), finally resulting in decreased overall survival. Studies reported that psychological distress is associated with increased cancer mortality (8) and significantly worse outcomes in cancer patients with brain tumors, especially in patients with high-grade glioma (9–12). Longitudinal analyses regarding distress in neurooncological patients underlined increased distress especially perioperatively during hospitalization (13). Therefore, in particular, perioperative screening to facilitate a timely additional psychooncological support seems to be crucial.

The aim of surgery in neurooncological patients is a maximal aggressive tumor resection without causing permanent neurological deficits. In order to achieve this goal, the operation techniques were significantly improved by using neuronavigation, fluorescence-guided surgery, and intraoperative neuromonitoring during the last decade. Especially awake surgery in patients with eloquent located lesions has been proven to maximize the extent of resection leading to an improved outcome while decreasing risks for new postoperative neurological deficits (14–16). But less is known if this anticipated operation technique causes additional distress for neurooncological patients.

Therefore, the present study aimed to answer the question of whether the anticipation of awake surgery has an additional negative impact on distress, anxiety, depression, and QoL status in neurooncological patients in the preoperative phase as compared with patients undergoing surgery under general anesthesia (GA).

## PATIENTS AND METHODS

In this retrospective single-center analysis (screening period January 2019 to September 2020), we investigated the perioperative impact of anticipation of awake surgery regarding psychooncological distress of brain tumor patients. The study was approved by the local ethics committee (Study Number 4087). Reporting of this study was according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (**Supplementary Material**).

### Patients

Inclusion criteria for the present analysis were 1) patients age >18 years with the diagnosis of a brain tumor 2) who were electively admitted for tumor surgery at our neurooncological department with 3) a complete preoperative data set of distress and QoL assessment. Due to the retrospective study design, assessment questionnaires were filled out quite heterogeneously with partially missing data. In order to avoid interference of analyses by an indifferent amount of data for each single screening parameter, we defined that only patients with a complete psychooncological screening assessment were eligible for inclusion. Patients with missing data in any of the below-described screening items were excluded, finally leading to exclusion of 74.65% of the patients. Screening assessment comprising all screening items will be described further below.

For further analysis, patients were divided regarding their resection modality (awake vs. GA) (**Figure 1**). Secondly, analyses concerning the impact of primary or recurrent surgery were performed.

Detailed epidemiological information including clinical data of both groups is summarized in **Table 1**.

### Screening Assessments

Screening was performed as tablet-based self-assessment after short instruction by our medical staff. All patients were screened 1–2 days preoperatively during hospitalization with the following instruments.

#### National Comprehensive Cancer Network, Distress Thermometer

As a routine screening instrument for distress in cancer patients, the distress thermometer (DT) was firstly published in 1999 by the National Comprehensive Cancer Network (NCCN). The DT is now part of the NCCN guidelines and an easy-to-administer self-reporting tool with a rating scale ranging from 0 (no distress) to 10 (extreme distress). According to the NCCN guidelines, we defined a DT score of 5 or above as indicating distress. The DT also contains a list of 40 symptoms representing practical, family,

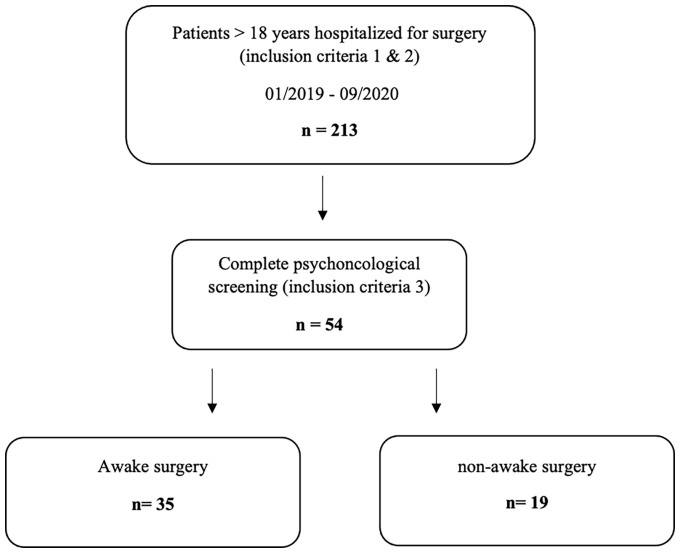


**FIGURE 1** | Flowchart describing patient selection.

emotional, spiritual–religious, and physical concerns. In our setting, we only used the visual scale, and the symptom list was excluded.

### Hospital Anxiety and Depression Scale

Firstly published in 1983, the Hospital Anxiety and Depression Scale (HADS) was originally designed to assess the psychological state of physically ill patients. Meanwhile, it has been established as an effective screening tool for the assessment of anxiety and depression. The 14-item self-report questionnaire consists of 7 items used to identify anxiety (HADS-A) and 7 items for depression (HADS-D), with each item having a 4-point (0–3) Likert-type scale. The maximum score on each subscale is 21 points. A cutoff score of >8 is assumed to be optimal concerning sensitivity and specificity in defining anxiety disorders in patients (17, 18).

**TABLE 1** | Descriptive epidemiologic data of patient cohort.

| | Awake (n = 35) | Non-awake (GA) (n = 19) |
|---|---|---|
| Age (years) | | |
| Mean | 55 [SEM ± 2.9] | 59 [SEM ± 2.8] |
| Range | 29–81 | 40–83 |
| Gender | | |
| Female | 21 | 7 |
| Male | 14 | 12 |
| Diagnosis | | |
| Glioblastoma (WHO IV) | 18 | 13 |
| Anaplastic oligodendroglioma (WHO III) | 2 | 0 |
| Anaplastic astrocytoma (WHO III) | 3 | 1 |
| Diffuse glioma (WHO II) | 2 | 0 |
| Astrocytoma IDH mutant (WHO II) | 5 | 0 |
| Cerebral metastases | 4 | 2 |
| Cerebral lymphoma | 0 | 3 |
| Ganglioglioma (WHO I) | 1 | |
| ECOG pre-op | | |
| Mean | 0.8 [SEM ± 0.1] | 1.0 [SEM ± 0.2] |
| ECOG post-op | | |
| Mean | 0.9 [SEM ± 0.2] | 1.2 [SEM ± 0.2] |
| Primary surgery | 25 | 12 |
| Recurrent surgery | 10 | 7 |

*GA, general anesthesia; ECOG, Eastern Cooperative Oncology Group.*

### Health-Related Quality of Life Assessment

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30-BN20 is a disease-specific questionnaire developed by the EORTC to assess the QoL of cancer patients. The EORTC QLQ-C30 consists of a 4-point scale containing four function scales, three symptom scales, and six single-item scales as well as two 7-point scales: the global health status and the QoL. The QLQ-BN20 is an additional module for brain tumor patients, consisting of 20 questions specifically assessing brain tumor-related symptoms. Distress screening results were correlated with the following items: global health status, QoL, and future uncertainty (7, 19). The threshold for the global health and QoL score was ≤4 and for emotional function, cognitive function, and future uncertainty ≥2.75, scored according to the recommended scoring manual of the EORTC.

## Indication for Awake Surgery and Preparation Protocol

For eloquent (cortically and/or subcortically) located tumors (evaluated in preoperative MRI scans), awake surgery with intraoperative monitoring was planned to preserve functionality. In patients with suspected language affecting lesions or for specific motoric testing, awake surgery was indicated in order to perform adequate intraoperative monitoring of function (14, 20). Speech monitoring was performed using 60-Hz stimulation,

and motor stimulation was performed using high-frequency monopolar stimulation.

Independently from localization, patients with severe preoperative speech disorders were excluded from the awake surgery group.

All patients in the awake group underwent baseline testing 1 day prior to surgery, with the same tests used intraoperatively. Additionally, the intraoperative setting of awake surgery was practiced with the patients in order to prepare patients for the upcoming procedure.

In patients with a suspected malignant brain tumor, 5-aminolevulinic acid (5-ALA) was administered orally 3–4 h prior to surgery. 5-ALA leads to the accumulation of fluorescent porphyrins in malignant cells and helps intraoperatively with the identification of tumor tissue leading to the increased extent of resection and increased progression-free survival in patients with malignant glioma (21, 22).

## Statistical Analyses

Obtained results were statistically analyzed by using the chi-square test for nominal variables. Metric variables were analyzed using the Kruskal–Wallis test, the Mann–Whitney U-test, and independent-samples t-tests. Statistical analyses were conducted using IBM SPSS Statistics Version 26 (IBM Corporation, USA). Statistical cutoff stated as p-value was set at 0.05.

# RESULTS

Fifty-four out of 213 patients were eligible for inclusion in the final analysis (**Figure 1**). Of the patients, 26 were male and 28 female, with mean age of 56.04 [ ± 2.1 SEM]. A total of 37 patients (68.52%) received first tumor resection, and 17 (31.48%) were hospitalized due to recurrent surgery. Out of 54, 35 patients were undergoing awake surgery (64.81%), as intraoperative speech and motoric testing were required for enabling safe resection due to eloquent localization of the lesion. In the recurrent patient group, there was one case where surgical procedures had changed (primary surgery, non-awake; recurrent surgery, awake surgery). Sixteen patients underwent recurrent surgery following the same surgical strategy compared with primary surgery. The subgroups' mean time between primary and recurrent surgery was 2.9 years [ ± 0.54 SEM].

Preoperative mean Eastern Cooperative Oncology Group (ECOG) Performance Status was 0.9 [ ± 0.1 SEM] and postoperative 1 [ ± 0.1 SEM]. Neither of the included patients reported a psychiatric diagnosis in medical history.

## Screening Results

Independent from the screening instruments, in the awake patient cohort, 22 patients were indicated to suffer from increased distress (62.86%). In comparison, 10 out of 19 patients who were undergoing surgery under GA complained about distress (52.63%). The prevalence of distress ($p = 0.465$) did not significantly differ between both cohorts. Furthermore, six patients of the awake patient cohort indicated increased anxiety (17.14%) and five depression (14.29%). Also, six patients (31.58%) in the GA cohort (n = 10/19) reported anxiety and three depression (15.79%). Therefore, again, the prevalence of anxiety ($p = 0.223$) and depression ($p = 0.882$) did not differ significantly between patients who were undergoing awake surgery and patients undergoing surgery under GA.

The main results are presented regarding the different screening instruments.

### Distress Thermometer

Regarding results of the DT assessment, the mean score in the awake surgery patient cohort was 5.69 [ ± 0.50 SEM], compared with 6.26 [ ± 0.66 SEM] for patients undergoing surgery under GA. Statistical analyses revealed no significant difference in the scoring of DT in both cohorts ($p = 0.668$, **Figure 2A**).

Regarding the impact of recurrent surgery, there was no significant influence, although patients undergoing recurrent surgery tended to demonstrate increased distress more often (recurrent 76.47% vs. primary 51.35%, **Figure 2B**).

### Hospital Anxiety and Depression Scale

Scoring of anxiety and depression items showed a mean score of 6.14 [ ± 0.75 SEM] for anxiety and 5.23 [ ± 0.72 SEM] for depression score in the awake group. In comparison, the mean score in the GA group was 7.16 [ ± 1.29 SEM] for anxiety and 5.89 [ ± 0.99 SEM] for depression. Neither of both results reached significance (anxiety awake vs. GA $p = 0.682$; depression $p = 0.630$, **Figures 3A, B**).

Comparable with the DT results, although recurrent surgery had no significant influence on the prevalence or scoring of both parameters, patients with recurrent surgery tend to demonstrate higher scores for anxiety and depression.

### Quality of Life

Concerning analyses of global health status and future uncertainty from the EORTC brain module, awake surgery did not have any significant influence on scores of future uncertainty ($p = 0.436$) or global health status ($p = 0.943$, **Figures 4A, B**).

Again, there was no significant impact on those parameters concerning recurrent surgery; however, a decreased global health status was observed in the recurrent surgery patient cohort.

### Psychooncological Support

At hospitalization, all patients were asked if they wish to get psychooncological support perioperatively. Fifteen patients (27.78%) accepted additional support. Regarding different patient groups awake vs. GA and recurrent vs. primary surgery, there was no difference ($p > 0.05$).

# DISCUSSION

For eloquent located tumors, awake surgery is the gold standard treatment option to obtain maximal safe resection. But less is known about the potential negative impact that this additional pressure may have on neurooncological patients who are already at high risk for increased distress, anxiety, and depression.

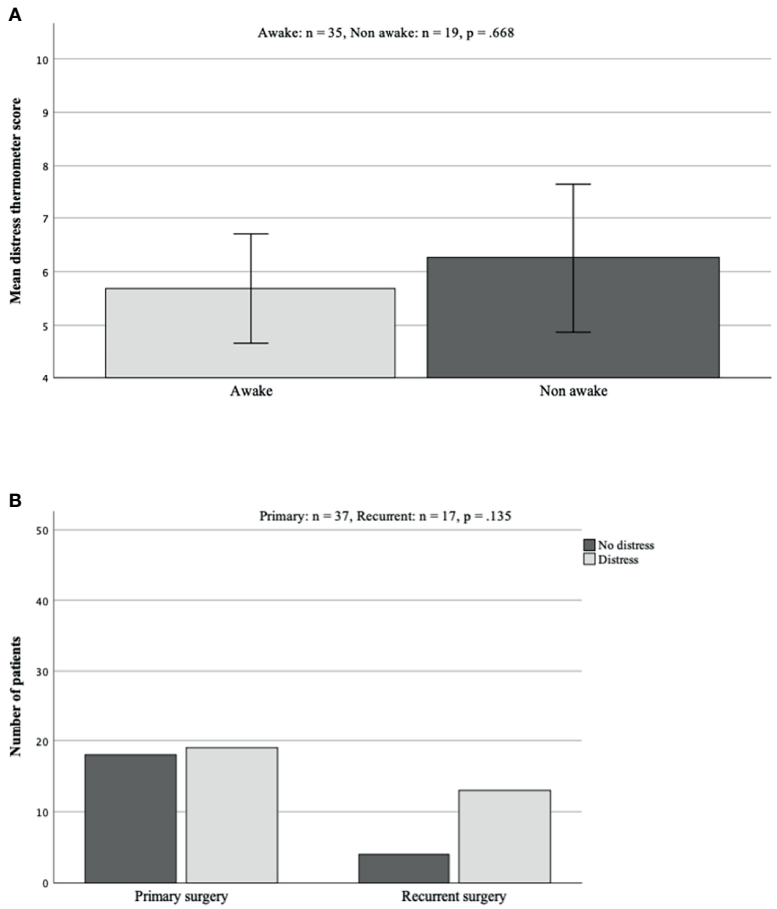


**FIGURE 2** | **(A, B)** Mean scoring in DT in group comparison. There were no significant differences seen between both patient groups (**A**; p = 0.668). Concerning comparison of reported distress in either primary or recurrent surgery, although not statistically significant, patients undergoing recurrent surgery reported distress more often **(B)**. DT, distress thermometer.

We aimed to include various essential psychooncological testing parameters in order to obtain a comprehensive overview of the preoperative psychological status of patients when undergoing awake surgery compared with undergoing surgery under GA. Our data reflect that patients undergoing awake surgery for cerebral lesions do not demonstrate distress, anxiety, or depression more often than patients who are undergoing surgery under GA in the preoperative phase. Furthermore, our analysis also clearly underlines the additional impact of recurrent surgery regarding increased distress.

There are only a few data regarding the psychooncological impact of anticipated awake surgery. Ruis et al. analyzed 70 patients using the HADS, and they reported a mean anxiety scale of 6.1 points, comparable with our data. In this analysis, particularly younger patients and women were identified with higher anxiety scores (23). However, they did not compare results with patients undergoing surgery under GA. Our 2013 research group performed a postoperative survey of brain tumor patients who received awake surgery. Most patients stated that they would undergo awake surgery at any time again. A thoroughly pre-op preparation was the most important to support the patients in this situation (24). Different studies underlined that detailed preparation of a well-selected patient cohort is essential to prevent stress disorders and negative psychological aftereffects (25, 26). In this context, Santini and colleagues firstly reported psychological profiling for candidates of awake surgery under the use of psychological questionnaires, neuropsychological testing of language, neurocognition, and intraoperative interviews (27).

At our department, patients undergo a preoperative psychooncological screening as described before; furthermore, a simulation of the awake situation 1 day before scheduled surgery is performed, and all intraoperative performance tasks are explained and practiced with the patient.

Besides careful patient selection and preparation, participation in the decision making and anticipated active role throughout surgery and therefore active role in a positive surgery outcome might contribute to the fact that awake surgery does not have a negative influence on the patients (28). Additionally, contrary to our preoperative screening results, published reports

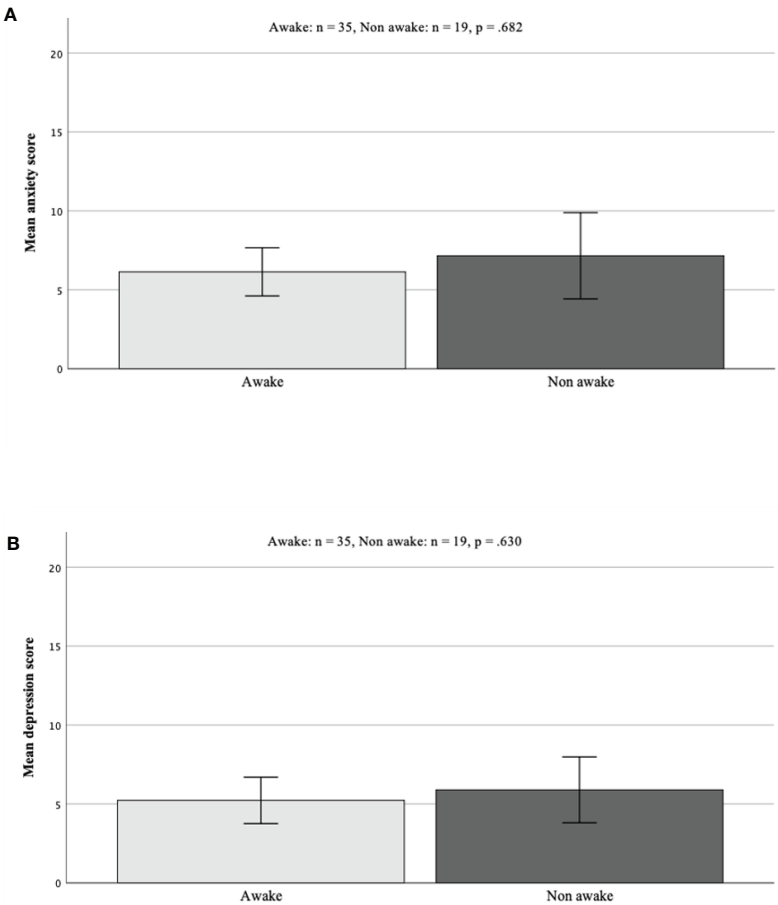


**FIGURE 3** | **(A, B)** Group comparison of scores in HADS screening. Results did not differ significantly [awake vs. GA anxiety scores p = 0.682 **(A)**; depression scores p = 0.630 **(B)**]. HADS, Hospital Anxiety and Depression Scale; GA, general anesthesia.

of postoperative screening results of patients undergoing awake craniotomy also revealed no major negative impact of awake surgery on patients. Goebel et al. described pre- and postoperative HADS anxiety and depression scores of 25 patients undergoing awake surgery combined with intraoperative MRI, and only 1 patient showed negative reaction to surgery protocol postoperatively (29). In line with that, Danks et al. reported no major consequences like post-traumatic stress disorders after awake surgery (29, 30).

Although not significant, independent from the assessment instrument, here, patients undergoing recurrent surgery presented increased scores for distress, anxiety, and depression. In the literature, there are some data about distress in the course of neurooncological diseases. There seem to be specific time points, where increased distress was observed, especially during hospitalization as well as at the time point of tumor recurrence (31). This might be due to various general apprehensions when being diagnosed with recurrent cancer. In our cohort additionally, a worse subjective global health status at recurrence was revealed, and that might have also contributed to the increase of psychooncological screening scores.

However, along with positive results from our study, we also have to state major limitations of our data analyses with an arguable small cohort due to our restrictive inclusion criteria. We only included patients with full data sets during preoperative psychooncological testing in order to generate comparability in all analyzed categories. That led to exclusion of approximately 75% of the screened patients. Furthermore, the size of both patient groups quite differed in numbers and might have led to some bias in the analysis.

Nevertheless, to our knowledge, this is the first analysis of a comprehensive psychooncological screening in patients undergoing brain tumor surgery under either awake or non-awake surgery. Hence, our data are of high importance, as awake surgery offers a full range of intraoperative monitoring of speech and motor function for the surgeon, which is essential in patients with brain tumors of some locations. According to previous research perioperative psychooncological distress, anxiety and depression can have a negative influence on the outcome and the patients'

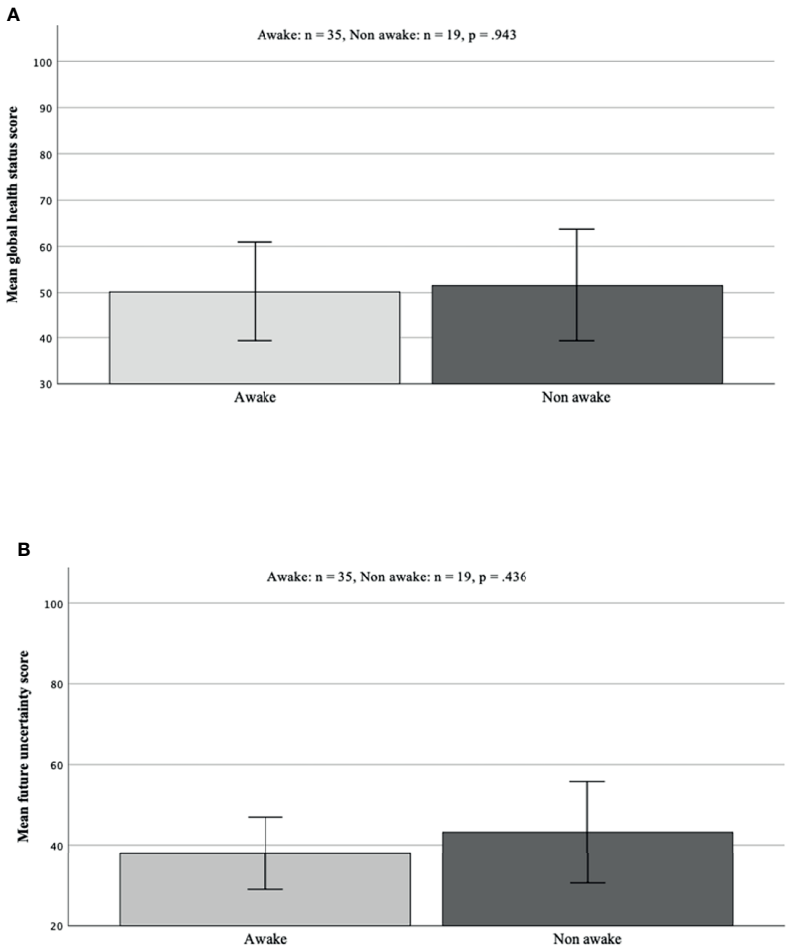


**FIGURE 4** | **(A, B)** Analysis of differences in future uncertainty and global health status taken from *EORTC QLQ-BN20* quality of life questionnaire. There was no significant difference in mean scores in both analysed items [global health status p = 0.943 **(A)** future uncertainty p = 0.436 **(B)**]. EORTC, European Organisation for Research and Treatment of Cancer.

subjective perception of global health care status, which is quite the opposite of the treatment intention. Therefore, an indication for awake surgery has to be questioned for every single patient. But our data show that with detailed preparation and close monitoring of the patients, awake surgery does not have any negative influence on patients, and we can expect our patients to go through this procedure without harming them. On the contrary, the positive effects of a possible increased extent of resection and that accompanying increased overall survival predominate.

## CONCLUSION

Our data demonstrate that anticipation of awake surgery represents no significant impact for increased distress, anxiety, or depression preoperatively. Surgeons can expect their patients to undergo awake surgery without increasing psychooncological distress. If expected localization of cerebral lesion includes eloquent areas, awake surgery is recommended in order to increase the safety of the patient.

Even if the results were not significant, our data clearly illustrate that patients undergoing recurrent surgery tend to demonstrate increased distress; in this special situation, early contact with professional psychooncologists is recommended.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the correspondent author on reasonable request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the medical faculty of the

University of Düsseldorf (Study Number 4087). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MR designed and directed the project. FS-B analyzed the data and wrote the paper. OR analyzed the data. DH and MS provided critical feedback and helped shape the research and manuscript. All authors discussed the results and commented on the manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.795247/full#supplementary-material

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# Hydrocephalus Shunting in Supratentorial Glioblastoma: Functional Outcomes and Management

*Amir El Rahal*[1,2*], *Debora Cipriani*[1], *Christian Fung*[1], *Marc Hohenhaus*[1], *Lukas Sveikata*[3,4], *Jakob Straehle*[1], *Mukesch Johannes Shah*[1], *Henrik Dieter Heiland*[1], *Jürgen Beck*[1] *and Oliver Schnell*[1]

[1] *Department of Neurosurgery, Medical Center - University of Freiburg, Freiburg im Breisgau, Germany,* [2] *Department of Neurosurgery, Department of Clinical Neurosciences, Geneva University Hospitals, Faculty of Medicine, Geneva, Switzerland,* [3] *J.P. Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States,* [4] *Division of Neurology, Department of Clinical Neurosciences, Geneva University Hospitals, Geneva, Switzerland*

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**Edited by:**
*Marie-Therese Forster, University Hospital Frankfurt, Germany*

**Reviewed by:**
*Tom Flannery, Queen's University Belfast, United Kingdom*
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***Correspondence:**
*Amir El Rahal*
*amir.elrahal@uniklinik-freiburg.de*

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**Background:** Glioblastoma is the most common and the most challenging to treat adult primary central nervous system tumor. Although modern management strategies modestly improved the overall survival, the prognosis remains dismal associated with poor life quality and the clinical course often dotted by treatment side effects and cognitive decline. Functional deterioration might be caused by obstructive or communicating hydrocephalus but due to poor overall prognosis surgical treatment options are often limited and its optimal management strategies remain elusive. We aimed to investigate risk factors, treatment options and outcomes for tumor-associated hydrocephalus in a contemporary 10 years cohort of glioblastoma patients.

**Methods:** We reviewed electronic health records of 1800 glioblastoma patients operated at the Department of Neurosurgery, Medical Center – University of Freiburg from 2009 to 2019. Demographics, clinical characteristics and radiological features were analyzed. Univariate analysis for nominal variables was performed either by Fisher's exact test or Chi-square test, as appropriate.

**Results:** We identified 39 glioblastoma patients with symptomatic communicating hydrocephalus treated by ventricular shunting (incidence 2.1%). Opening of the ventricular system during a previous tumor resection was associated with symptomatic hydrocephalus ($p<0.05$). There was also a trend toward location (frontal and temporal) and larger tumor volume. Number of craniotomies before shunting was not considered as a risk factor. Shunting improved hydrocephalus symptoms in 95% of the patients and Karnofsky Performance Score (KPS) could be restored after shunting. Of note, 75% of the patients had a post-shunting oncological treatment such as radiotherapy or chemotherapy, most prevalently chemotherapy. Infection (7.7%) and over- or under

drainage (17.9%) were the most common complications requiring shunt revision in ten patients (25.6%), No peritoneal metastasis was found. The median overall survival (OS) was 385 days and the median post shunting survival was 135 days.

**Conclusion:** Ventricular system opening was identified as a risk factor for communicating hydrocephalus in glioblastoma patients. Although glioblastoma treatment remains challenging, shunting improved hydrocephalus-related functional status and may be considered even in a palliative setting for symptom relief.

**Keywords: glioblastoma, hydrocephalus, shunt, risk factors, quality of life, outcome, overall survival, KPS = karnofsky performance scale**

## INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant central nervous system (CNS) tumor. GBM accounts for 48.6% of CNS tumors with an estimated incidence of 3.23 per 100'000 persons per year (1). Modern treatment strategies have improved overall prognosis; however, clinical course is often marked by significant treatment side effects, functional or cognitive decline. The current standard of care is maximal safe resection of the contrast-enhancing tumor followed by adjuvant radiotherapy and temozolomide chemotherapy (2). The overall survival rate for GBM patients improved from 3.3 months up to a median of 15 months in the past 30 years (3–8).

Moreover, tumor progression or complications occurring during the disease's course can lead to neurologic deterioration such as hemiparesis, aphasia, cognitive decline, or gait disturbance, reflected by a reduction in the Karnofsky performance status (KPS) (9). Thus, despite increased life expectancy GBM patients often experience poor quality of life during the course of the disease (1, 3, 4, 7, 8).

Communicating hydrocephalus (CH) is a common complication during GBM course and can be readily detected in the presence of ventriculomegaly. However, often CH presents in an insidious fashion presenting with subacute cognitive decline, gait disturbance, or incontinence, overshadowed by prominent GBM-related symptoms or deficits. In addition, ventriculomegaly is challenging to identify in the context of treatment-associated cerebromalacia (10–12). The pathophysiology underlying GBM-related CH remains elusive with possible mechanistic explanations including cerebrospinal liquid circulation impairment due to ventricular opening, multiple surgical interventions, leptomeningeal metastases, and impaired CSF resorption due to radiotherapy-induced fibrosis, as well as tumor location (9, 11–15). Moreover, it remains unclear which symptoms are most likely to improve after shunting of glioblastoma patients and what would be the best time point to intervene in this situation. Our study aimed to investigate the risk factors, treatment options and functional outcomes for tumor-associated hydrocephalus and post-shunting oncological therapy in a contemporary 10 years cohort of GBM patients.

**Abbreviations:** GBM, Glioblastoma multiforme; KPS, Karnofsky performance score; CNS, Central nervous system; OS, Overall survival; MR, Magnetic resonance; GTR, Gross total resection.

## MATERIAL AND METHODS

### Patient Data Acquisition

We retrospectively reviewed all GBM patients treated at the Department of Neurosurgery, Medical Center – University of Freiburg from January 2009 to December 2019 following the STROBE statement and guidelines (16). Out of 1800 glioblastoma patients in total, we identified 39 patients presenting a communicating hydrocephalus. Inclusion criteria were: 1) Histologically confirmed GBM and available molecular profiling 2) Suspected symptomatic hydrocephalus, 3) age of 18 years or older, 4) at least one previously attempted complete resection, 5) available pre- and post-operative MRI within 72 hours and for follow-up. All cases were treated by ventriculo-peritoneal (VP) or ventriculo-atrial (VA) shunting.

Clinical data were extracted from electronic medical records. We collected the following clinical variables: 1) pre-operative KPS 6-12 weeks before surgery and at admission, 2) KPS 6-12 weeks after shunting, 3) date of last follow-up, 4) death date.

We collected the following tumor- and surgery-related variables: location, tumor volume ($cm^3$), ventricular opening during previous tumor surgery and leptomeningeal spreading.

Written informed consent was obtained from all patients. Ethical approval was obtained from the local ethics committee (Freiburg ethic commission N: 21-1272). Demographics and clinical characteristics are presented in **Table 1**. Four patients with obstructive hydrocephalus or a loss of follow-up were excluded from the study.

### Histopathological and Molecular Analysis

Diagnosis of GBM was based on the 2016 WHO Classification of Tumors of the Central Nervous System (17). Specimens were analyzed using the standard protocol at the Institute of Neuropathology, Medical Center-University of Freiburg as described in previous publications (17–19). IDH mutations were detected by immunohistochemistry (IHC). In patients <65 years old, next-generation sequencing of IDH1 and IDH-2 was performed to confirm negative staining results. MGMT promoter methylation status was performed using methylation-specific PCR.

### Hydrocephalus Ascertainment

Communicating hydrocephalus was suspected in the setting of emergent ventricular enlargement and associated clinical

**TABLE 1** | Patient's demographics and admission parameters.

| Patient Demographics | N = 39 | % |
|---|---|---|
| Gender | | |
| Female | 13 | 33.3 |
| Male | 26 | 66.6 |
| Age in years | | |
| Median (IQR) | 56.1 (46.5.7-62.8) | |
| GSC at admission | | |
| Median (IQR) | 14 (13-15) | |
| Hydrocephalus-related symptoms | | |
| Gait disturbance | 36 | 92.3 |
| Headache | 33 | 84.6 |
| Cognitive decline | 28 | 71.8 |
| Incontinence | 13 | 33.3 |
| Motor deficit | 12 | 30.7 |
| Hakim's Triad | 10 | 25.6 |
| MGMT – Promoter status methylation | | |
| Non methylated | 20 | 51.3 |
| Methylated | 5 | 12.8 |
| NA | 14 | 35.9 |

*Males were predominant in our cohort, and the median age was 56.1 years. Gait disturbance is the most prevalent symptom and Hakim's triad is present in approximately 25% of patients on admission. IQR, Interquartile range; MGMT, Promoter status methylation; NA, Not available.*

symptoms. Hydrocephalus-associated clinical symptoms were collected: headache, cognitive decline, gait disturbance, or urinary incontinence. The latter three symptoms comprising the Hakim's triad (20). We calculated the Evans's ratio based on the preoperative MRI or CT (21). In brief, Evan's index is the ratio of the maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull at the same level. Evan's index of >0.3 was indicative of hydrocephalus. A lumbar tap test was routinely performed to evaluate post-tap clinical improvement When hydrocephalus was diagnosed, a shunt was placed with a MiniNav 10® valve or proGav 2.0® by Miethke valve and occasionally other type of valves (Dual Switch 5/30® or Dual Switch 10/30® by Miethke) either by a ventriculo-peritoneal (VP) or ventriculo-atrial (VA) shunt procedure.

## MR Imaging Acquisition

MRI acquisition was realized on 1.5 or 3.0 Tesla whole body system. Anatomical imaging used for resection analysis consisted of 3D T1-weighted sequences before and after contrast application. Patients usually received a preoperative and postoperative MRI within 48-72h and every 3 consecutive months. Gross total resection was defined as removal of more than 95% of the contrast-enhancing tumor (22). Tumor progression was defined according to the RANO-criteria (23). An emphasis was placed on the following factors: leptomeningeal tumor spreading, ventricular wall enhancement, and tumor location. The volumetric segmentation of the tumor was performed using the Elements software proposed by BrainLAB®. Tumor volume was measured in cm3.

## Oncological Treatment

Patients were treated according to the standard of care protocol by Stupp et al. in 2005 (2). In brief, patients underwent gross total resection of contrast-enhancing tumor, adjuvant radiotherapy and temozolomide chemotherapy. In some cases, patients received alternative chemotherapeutic treatments (lomustine), antiangiogenic therapy with bevacizumab, or radiotherapy alone. Intraoperative chemotherapeutics such as BCNU (Carmustine) wafers were not administered to any of the 39 patients.

## Study Endpoints

The primary endpoint was the clinical and functional outcome of patients benefiting from shunting for a communicating hydrocephalus. For this purpose, we measured the KPS and collected variables related to clinical symptoms and parameters.

The secondary endpoints were 1) the clinical symptoms experienced, 2) overall survival in GBM shunted patients, and 3) the median postoperative survival time after the shunt placement.

## Statistical Analysis

Statistical analysis was performed using R software [version R 4.0.4] through the studio interface Version 1.4.1106. Univariate analysis for nominal variables was performed either by Fisher's exact test or Chi-square test, as appropriate. Results are reported as odds ratio with 95% confidence intervals and 2-sided p values. The statistical differences were considered significant at a $p<0.05$. Bonferroni correction was used to account for type I error when conducting multiple analyses on the same dependent variable. Kaplan-Meier analysis was used to estimate the survival distributions. Patients' loss of follow-up were censored at the recorded date of last contact or consultation.

## Illustrative Case

We illustrate in **Figure 1** the case of a 50 years old woman known for non-structural epilepsy since her childhood treated with Carbamazepine. She presented with new symptoms including hallucinations, headaches, and fatigue. She consulted at the neurosurgical department and an MRI showed a left temporal contrast-enhancing tumor. The first resection was performed the same month with a gross total resection (GTR) and no contrast-enhancing residual lesions were seen on the postoperative MRI. The histopathological analysis revealed a glioblastoma WHO IV, IDH wildtype with unmethylated MGMT promoter. Radiochemotherapy according to the Stupp protocol was introduced without complications (2).

After 8 months she developed a tumor recurrence. A second surgery with GTR was achieved and the temporal horn was opened during the procedure. One month later she presented new symptoms with acute drowsiness (GCS 12 on admission), gait disturbance, cognitive decline, and incontinence compatible with the Hakim's triad. The MRI revealed a ventriculomegaly with Evan's Ratio of >1. A lumbar puncture revealed a high level of protein >1.5g/l and the patient improved clinically after the lumbar puncture A VP shunt was implemented with a Miethke MiniNav 10® valve. The patient improved clinically with resolving symptoms and an increase in KPS from 40 to 50 post-operatively. This strategy allowed the patient to maintain her quality of life and successfully receive chemotherapeutic

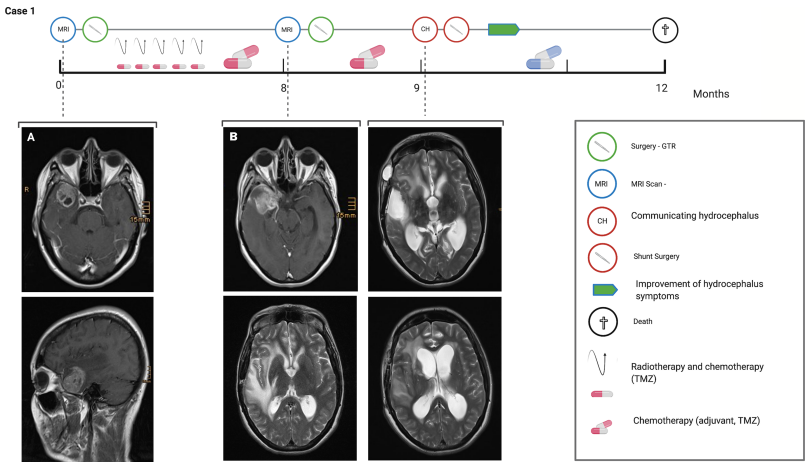


**FIGURE 1** | Illustrative case of a 50 y/o woman with a right temporal GBM WHO grade IV, IDH wildtype and unmethylated MGMT promoter. Eight months after the first resection, the patient presented a recurrence with a second surgery performed and a repeated GTR achieved. One month later patient presented clinically and radiological a communicating hydrocephalus requiring shunt. Unfortunately, the patient died after 12 months. Created with Biorender.

treatment due to an improved functional status. Despite the treatment, the patient died three months later.

# RESULTS

## Patient Characteristics

Thirty-nine patients were treated surgically for a supratentorial glioblastoma multiforme WHO grade IV and benefited from a shunt for communicating hydrocephalus (CH) at the Medical Center-University of Freiburg between 2009 and 2019. The median age was 56.1 years (IQR 46.5. - 62.8), 66,6% were male and 33% were female (**Figure 2**). The mean time between the first tumor resection to shunt placement was 187 days (IQR 45.5 – 176.5). Among 25 patients with measurements of the MGMT methylation status, we found the methylation to be present in 5 patients (12.8%) and absent in 20 patients (51.2%) (**Table 1**).

## Treatment

A gross total resection was attempted in all patients. Most patients underwent a single surgery before shunt placement 17/39 (43.5%), 14 patients underwent two resections (35.9%), and 8 patients had three or four resections (20.5%). Chemotherapy was given in 37 (95%). Among patients treated with chemotherapy, all were treated with temozolomide. In addition to temozolomide, six patients (15%) were treated with bevacizumab before shunt treatment. No patients benefited from intracavity BCNU wafers. Radiotherapy was also performed in 37 (95%) patients. One patient had an early glioblastoma recurrence before any adjuvant treatment could be started, and

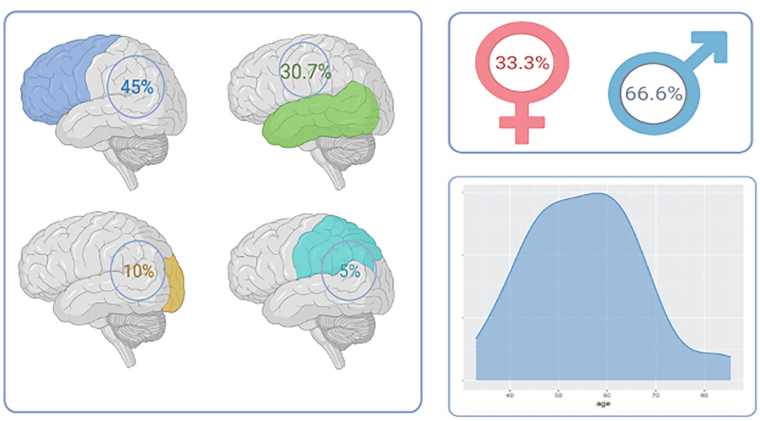


**FIGURE 2** | Tumor location and patient demographics in GBM-related hydrocephalus cohort. Left panel: Tumor location showing a predominance of GBM in the frontal lobe followed by temporal tumors. Right upper panel: sex distribution. Right lower: age distribution.

one was lost to follow-up. Of note, 75% of the patients had a post-shunting oncological treatment such as radiotherapy or chemotherapy, most prevalently chemotherapy.

## Diagnostics Features of Patients With Communicating Hydrocephalus

Symptoms preceding the clinical or radiological diagnostic of hydrocephalus were gait disturbance in 35 (90%), headaches in 33 (85%), cognitive decline in 28 (72%). Only 10 (25.6%) presented with the typical Hakim's triad. Median GCS on admission was 14 (IQR 13-15). Nine (23%) patients presented acute drowsiness related to hydrocephalus.

Eighteen (46%) patients received a lumbar tap test where 20-40 ml were withdrawn which resulted in a transient improvement of symptoms in all patients. CSF protein concentration levels were only analyzed in half of the cases and therefore couldn't be interpreted. Regarding the post resection compilations, seven (18%) patients had a CSF leak (18%), six patients had a postoperative complication such as meningitis in 3 patients and 3 suffered from a postoperative hemorrhage (6.6%).

## Radiological Characteristics

The frontal lobe tumor location was present in 45% followed by the temporal lobe in 30.7%, occipital lobe in 10%, and parietal lobe in 5%. In 12.5% of the cases, a cortico-subcortical tumor invading the deep structures was diagnosed. Thirty-two (82%) patients received a gross-total resection, 4 patients had between 70-90% of the tumor resected and 4 less than 50% of the tumor resection (**Figure 2**).

Evans' index of > 0.3 as mentioned above, considered as positive and was found in 20 patients out of 39 at diagnosis (51%) with no statistical correlation as an independent risk factor ($p>0.05$).

## Treatment for CSF Diversion

All patients received a VP shunt in the first intention. A differential non-adjustable pressure valve (Miethke MiniNAV 10) was implanted in 25 (64%), an adjustable valve (Miethke proGAV) in 9 (23%), and other valves in 5 patients (usually Dual Switch 5/30® and Dual Switch 10/30®).

## Shunt Implantation Outcomes

Ten patients (26%) with implanted shunts required a revision surgery. Among patients requiring a revision, in three patients (30%) it was due to an early (<30 days) and seven (70%) due to a late shunt complication (**Table 2**). In the early complication group, two had an infection and one an early shunt malfunction. In the late complication group, there was one case of infection and six cases of valve malfunction (over- or under drainage). No peritoneal metastases were found in the whole cohort.

**TABLE 2** | Shunt complications requiring revision surgery.

| Shunt complications requiring revision surgery | N = 10 | 25.6% |
|---|---|---|
| **Infection** | **3** | **7.7%** |
| • Early < 30 days | 2 | |
| • Late >30 days | 1 | |
| **Malfunction** | **7** | **17.9%** |
| • Early < 30 days | 1 | |
| • Late >30 days | 6 | |

*In toto 10 patients required a revision surgery with "3 infection and 7 shunt dysfunctions" representing respectively the bold values in column 1 and column 2.*

## Risk Factors for HC in Glioma Patients

Ventricular system opening was associated with hydrocephalus Chi square test $p<0.05$). The number of craniotomies, tumor volume or localization were not associated with hydrocephalus. Leptomeningeal enhancement was found in 8 (20.5%) patients and was not associated with hydrocephalus.

## Postoperative Clinical Performance and GBM Survival

Thirty-seven (95%) patients had a symptomatic improvement after shunting. Of the other two patients, one died shortly after shunting and the second one was lost to follow up. The median of the last documented KPS during neuro-oncological routine follow-up before shunting was 50 (IQR 30-65). However, immediately before shunting, a dip was observed revealing a median of 40 (IQR 30-50). Finally, the median KPS post-op (6-12 weeks) was 50 (IQR 40-60) again. Therefore, no statistical difference was found when comparing the KPS 6-12 before and KPS 6-12 weeks after surgery but the acute deterioration before shunting was indicated led to a dip in the KPS of patients reflecting their general status (**Figure 3**).

The OS after GBM diagnosis was 385 days (IQR 311-724) (**Figure 4**). The median shunt to death survival was 130 days (IQR 54.75-322) (**Figure 5**).

# DISCUSSION

Modern treatment concepts have significantly improved the overall prognosis for glioblastoma patients during the past three decades (3–8). However, this gain in life expectancy did not lead to the same extent of improvement in quality of life in these patients (24–26). Therefore, a paradigm shift towards focusing on factors contributing to improvement, maintenance or decline of quality of life might be necessary in order to help our patients benefit from novel therapies and multi-modal management.

The incidence of post-operative communicating hydrocephalus has been estimated to range between 2 and 10% consistent with our findings of 2.1% (9–11, 13–15, 27, 28). The mechanisms responsible for communicating hydrocephalus in the context of glioblastoma surgery are not entirely understood and few studies have addressed this underrecognized issue. The usually presumed mechanism is leptomeningeal tumor cell dissemination that impairs CSF absorption, proteinic precipitation, or fibrosis of arachnoid granulations due to radiation. Therefore hydrocephalus management is still a matter of debate in glioblastoma patients (10–14, 29, 30) and the decision-making process needs a personalized approach. With one of the biggest series in literature (10–14, 27, 29, 30), we provide evidence that although shunting may

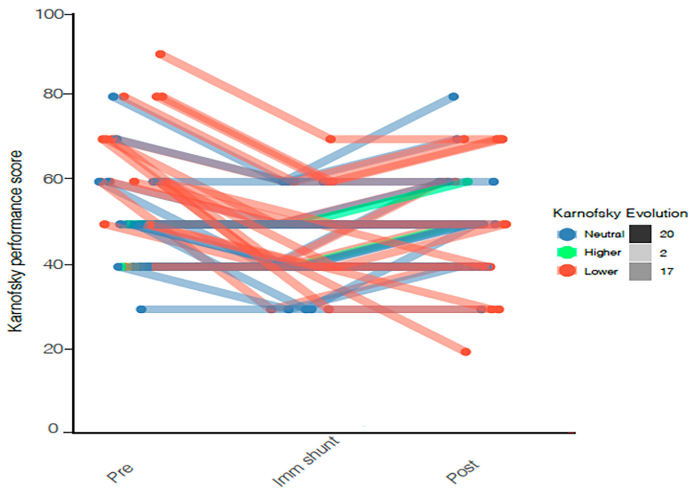


**FIGURE 3** | KPS before, immediately before shunting, and after shunting is represented by a Line plot showing individual KPS. Progression in the KPS is colored in green, a decline in red and stability in blue. Median KPS before and after surgery is 50 with no statistical difference.

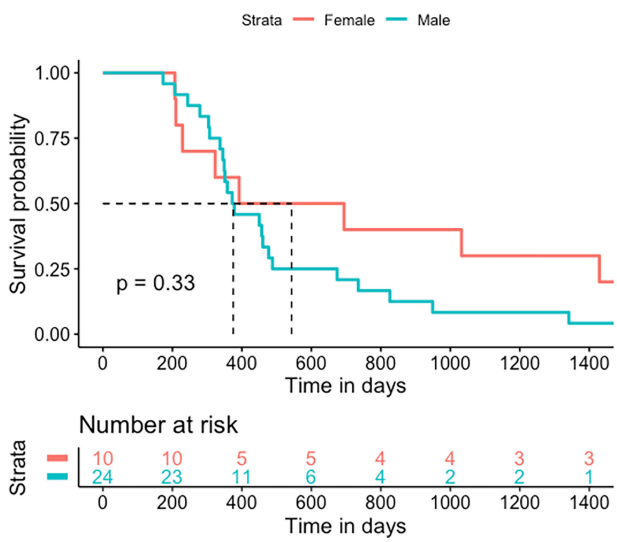


**FIGURE 4** | Kaplan-Meier statistics for the overall survival of GBS patients treated for hydrocephalus. Median OS was 385 days (IQR 311-724).

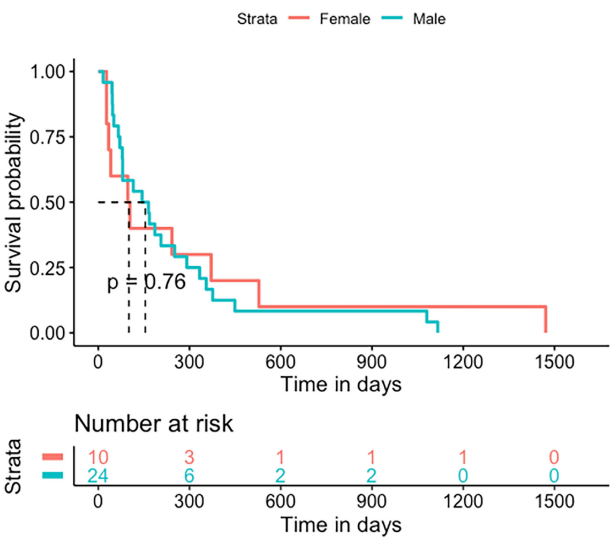


**FIGURE 5** | Kaplan-Meier statistics for post-shunt survival. Shunt to death median survival was 130 days (IQR 54.75-322).

not prolong overall survival, it may help improve symptoms and functional performance of patients. This is illustrated by maintained KPS after shunting reflecting stability in the daily quality of life of patients.

Glioblastoma patients usually develop cognitive decline due to tumor progression, radiation-induced brain atrophy, CSF tumor dissemination, seizures, or even general condition alteration (31–34). CSF disturbance might be a contributing factor of clinical deterioration and treatment by VP or VA shunt can reverse or stabilize the general condition of patients, as shown in our cohort.

Improvement of symptoms after shunting was reported to vary between 61% and 100% (9, 12, 13, 29, 30, 35). With a 95% improvement rate after shunting our findings align with these previous reports. Interestingly, we observed two different aspects regarding the general condition of patients. First, there was a dip in the KPS just before shunting, returning to baseline after shunting. Second, more than 75% of the patients could benefit from chemotherapy and radiotherapy post-shunting. We demonstrate that the hydrocephalus-related clinical decline was reversed by shunting and helped maintain patients' clinical condition. We can also assume that shunting may prevent further clinical deterioration by halting the hydrocephalus symptomatology progression. Thus, we conclude that shunt placement should not be delayed since there might be a threshold beyond which some of

the symptoms may not be fully reversible. Furthermore, worse functional status precludes oncological treatment and might shorten the overall survival. We continue to need better preoperative screening and indicators to determine which patients will benefit from shunting. Strategy implicating new management like infusion test might be a useful tool in the future (36, 37).

Historically, one of the major concern of shunt implantation in glioblastoma patients is the risk of peritoneal metastasis (32, 38–41). However, it is now well established that spread by shunts is a rare albeit potential serious complication in high-grade gliomas. However, in our study, no patients presented with peritoneal metastasis. This confirms the hypothesis that peritoneal metastasis is a rare complication and might not be a major obstacle for hydrocephalus treatment in GBM.

The Karnofsky performance score is a well-established score that is simple to use and has been validated in the functional evaluation of oncological patients (42). Nevertheless, limitations were noted regarding its adequacy for quality of life evaluation (43, 44). New scores were developed, such as the NANO score, which promises better accuracy in estimating neurologic function and, therefore, life expectancy, but still needs to be validated regarding the quality of life (45). Whether shunting positively influences overall survival or whether this leads to an improvement in QoL would need to be validated in a prospective study. In fact, we neither have a control group nor a structured QoL questionnaire due to the retrospective nature of our study.

The delicate balance between a shunting procedure to relieve symptoms and the overall survival in glioblastoma has to be considered in the context of an optimal neuro-oncological treatment. The surgical complication rate in our series was acceptable with ten patients requiring revision surgery (25%) of whom three patients (7.7%) had an early complication (<30 days) and seven (17.9%) a late complication. Interestingly, no major complications were encountered. This is in line with the findings of Castro et al. where 29% of complications were reported without any major complication (30). Roth et al. reported in 2008 a rate of complication of 50% with a rate of 33% of infections and major events such as coma or death in 12.5% (12). This is also in line with rates previously reported by Giordan et al. in a recent review regarding shunting in idiopathic normal pressure hydrocephalus (46). As a matter of fact, the revision rate reported in this meta-analysis is about 18% regarding a shunt malfunction, similar to our dysfunction revision rate of 17.9% (46). Life expectancy was not affected by shunt revision in our cohort. Therefore, we conclude that shunting complication risk should not be a reason to defer shunting. Patients with acute clinical decline without radiological findings of tumor progression and with signs or symptoms of hydrocephalus should be considered for a shunt placement. In most cases, shunt placement led to a reversal of the acute deterioration presented by an acute dip on the KPS.

### Limitations and Strengths

Although, our work is based on retrospective analysis, it provides data supporting an important feature in GBM patients which is quality of life and palliative support. Compared to other studies our cohort included only CH in GBM and this limits biases caused by mixed hydrocephalus etiology. Our cohort is one of the biggest published recently even if limited by the small number of patients allowing limited analysis of risk factors of CH in the context of a GBM.

## CONCLUSION

Treatment of hydrocephalus in the context of a glioblastoma is challenging but improves symptoms in most patients and may therefore be considered in routine care and in a palliative setting for relief of symptoms. The benefit of symptomatic improvement is higher than the complication and morbidity rate linked to shunting. We conclude that early detection of CH might maintain patients' eligibility for crucial oncological therapy as well as quality of life. Novel strategies are warranted to improve the early detection of glioblastoma-related hydrocephalus.

## DATA AVAILABILITY STATEMENT

Datasets are available from the corresponding author or the senior author on reasonable request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical committee Freiburg im Breisgau. (Freiburg ethic commission N: 21-1272). informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

AER and OS contributed to conception and design of the study. AER, DC, MH, HH, and JS organized the database. AER and HH performed the statistical analysis. AER and OS wrote the first draft of the manuscript. CF wrote sections of the manuscript. LS, MHS and JB provided substantial corrections to the final manuscript. All authors contributed to the article and approved the submitted version.

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# Epidemiology and Survival of Patients With Optic Pathway Gliomas: A Population-Based Analysis

*Huanbing Liu†, Yong Chen†, Xiaowei Qin†, Zheng Jin, Yining Jiang and Yubo Wang**

*Department of Neurosurgery, First Affiliated Hospital of Jilin University, Changchun, China*

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***Correspondence:**
*Yubo Wang*
*wangyubo@jlu.edu.cn*

*†These authors have contributed equally to this work*

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**Background:** We aimed to analyze the epidemiology and outcomes of pediatric patients and adult patients with optic pathway gliomas in the United States using a population-based method.

**Methods:** Data for patients with optic pathway gliomas diagnosed between 2000 and 2018 were extracted from the SEER database. We divided the patients into a pediatric group and an adult group. Descriptive analyses were conducted to analyze demographic and clinical characteristics and treatment. We used the chi-square test to evaluate differences between pediatric and adult patients with optic pathway gliomas. The possible prognostic indicators were analyzed by Kaplan–Meier curves and Cox proportional hazards models.

**Results:** Optic pathway gliomas represented 86.6% of all lesions originating from the optic pathway. In total, 1257 cases of optic pathway gliomas were included in our study. Pediatric patients accounted for 83.7% in this cohort, and most of the patients were diagnosed at 1-4 years old. Chemotherapy was chosen most often for pediatric patients, but radiation therapy was chosen most often for adult patients. Pilocytic astrocytoma accounted for 59.1% of pediatric patients and 37.5% of adult patients. The overall survival (OS) rates were 94.8% 5 years after diagnosis and 93.0% 10 years after diagnosis. Survival analysis showed that surgery, radiation and chemotherapy did not help patients obtain a better prognosis. Overall, pediatric patients had a better prognosis.

**Conclusion:** Optic pathway gliomas are relatively rare lesions with good prognosis. They mostly affect children, and pilocytic astrocytoma is the most common histological diagnosis. Highly individualized treatment is essential for such patients.

**Keywords: epidemiology, survival, SEER program, CNS disease, optic pathway glioma**

## INTRODUCTION

Gliomas account for almost 30% of all primary brain tumors and are responsible for the majority of deaths from primary brain tumors (1). Optic pathway gliomas (OPGs), also known as optic nerve gliomas, are relatively rare lesions that comprise 1% of all intracranial tumors and 3–5% of all pediatric brain tumors (2, 3). OPGs are believed to be the most common tumor of the optic nerve, and they are confined to the structures of the visual pathway (2, 4, 5). The Surveillance, Epidemiology, and End Results (SEER) Program is a clinical database funded by the National Cancer Institute (NCI) that was created to collect cancer incidence, prevalence, and survival data in the United States, covering approximately 35% of the United States population (6). We conducted this population-based study to analyze the epidemiology and outcome of patients with OPGs using data from the SEER program.

## METHOD

### Detailed Clinical Data Extraction

The SEER database is available to the public for research purposes, and no ethics committee approval or informed consent was required to perform this analysis. Patients diagnosed with glioma originating from the optic pathway (C73.0-optic nerve) from 2000 to 2018 were included. The term glioma was defined by setting the variable "Histology recode - broad groupings" as "9380-9489: gliomas". SEER*Stat (Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.3.9) was used to extract detailed patient data from SEER Research Plus Data, 18 Registries (November 2020 submission) (7).

### Variables and Population Analysis

Demographic and clinical variables included age at diagnosis (0-19 years and older than 19 years), sex (male, female), race (white, other), laterality (left, right, bilateral and unknown), behavior code (benign and borderline, malignant), surgery (yes, none/unknown), radiation therapy (yes, none/unknown), chemotherapy (yes, none/unknown), survival months and vital status (alive, dead). First, we analyzed the distribution of patients by age at diagnosis. Second, we divided the patients into pediatric and adult groups and evaluated the differences in demographic and clinical characteristics and treatment between pediatric and adult patients with OPGs by the chi-square test, and statistical significance was set to $p<0.05$. Third, we analyzed the differences in treatment patterns between the two groups. Fourth, we analyzed the distribution of patients by pathology type, and pathology type was recorded according to the code "Histology recode - Brain groupings". Only patients with available histology were included to make the results more accurate.

### Survival Analysis

Survival to 5 and 10 years after diagnosis was calculated using the Kaplan–Meier method. The log-rank test and univariate Cox proportional hazard models were performed to estimate possible independent prognostic factors associated with overall survival (OS) in patients with OPGs, and statistical significance was set to $p<0.05$. OS was defined as the time from diagnosis to death from any cause. All the data were analyzed using SPSS Statistics, Version 25 (IBM SPSS Statistics for Windows, Version 25 Armonk, NY: IBM Corp). Survival analysis was first conducted for the entire cohort. To make the sample more homogeneous, survival analysis was performed for pediatric patients and adult patients separately.

## RESULTS

### Population Analysis

In total, 1451 cases of primary lesions originating from the optic nerve were indexed between 2000 and 2018, and 1257 cases were identified as gliomas, which represented 86.6% of all patients with lesions originating from the optic nerve. Pediatric patients (≤19 years old) accounted for 83.7% of the cohort, and most of the patients were diagnosed at 1-4 years old (**Figure 1**). There

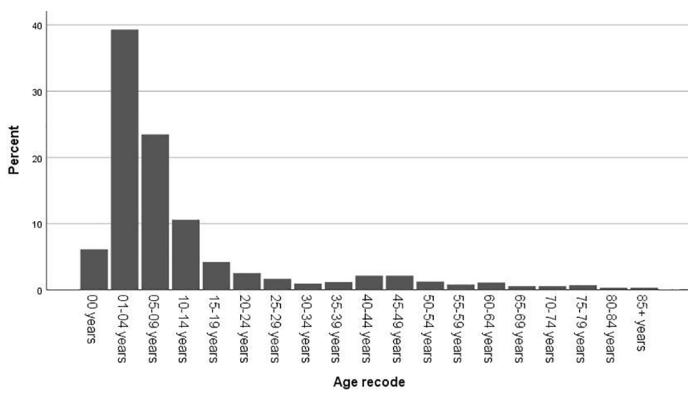


**FIGURE 1** | Distribution of the patients by age at diagnosis.

were 662 female patients (52.7%) and 595 male patients (47.3%), and white patients accounted for approximately 82.8% (n=1041) of all patients. Overall, 43.4% of the tumors (n=89) originated from the left side in adult patients, and 41.6% of the tumors (n=438) were bilateral or unknown in pediatric patients. There was a statistically significant difference between the pediatric and adult populations in laterality and treatment options (**Table 1**). A total of 63.1% of the patients (n=793) chose observation for treatment. Except for observation, pediatric patients mostly chose chemotherapy, and adult patients mostly chose radiation therapy (**Table 2**). We analyzed the pathology type of the patients with available histology, and 283 cases were included (80 adults and 203 pediatric patients). Pilocytic astrocytoma accounted for 53.0% of the patients with available histology (59.1% for pediatric patients and 37.5% for adult patients). Overall, 17.5% of the adult patients were diagnosed with glioblastoma, and no pediatric patients were diagnosed with glioblastoma (**Table 3**).

## Survival Analysis

The OS rates were 94.8% 5 years after diagnosis and 93.0% 10 years after diagnosis. The OS of the whole cohort is shown in **Figure 2A**, as determined by a Kaplan–Meier curve. The results of the log-rank test indicated that pediatric patients had better OS than adult patients (**Figure 2B**). The results for the log-rank tests and univariate Cox proportional hazard models for the whole cohort showed that sex, race, laterality and behavior code did not statistically significantly influence OS. Meanwhile, we found that treatments, including surgery, radiation and chemotherapy, did not result in better prognoses. Then, we analyzed the pediatric patients and adult patients separately to avoid heterogeneity, but the results were unchanged. The results of the log-rank test are presented in **Table 4**, and the results of the univariate Cox proportional hazard models, including the hazard ratios (HRs) and 95% confidence intervals (CIs), are presented in **Table 5**.

# DISCUSSION

OPGs are relatively rare and mostly affect children (8). Several systematic reviews have been reported (5, 9), but population-based studies of OPGs have seldom been described. The SEER database provides a sufficient amount of publicly available information for research purposes, enabling us to conduct this population-based analysis to better understand OPGs. To ensure that sufficient information was included, we chose the latest database and set the period as 2000-2018.

In our study, we found that more than 80% of the patients were diagnosed before 20 years of age. However, the oldest patient was 101 years old, and OPGs can be diagnosed at any age. Survival analysis showed that age at diagnosis was an independent prognostic factor, and pediatric patients had a better prognosis than adult patients. The predominance of white patients was also noted, as in other reports (10). It has been reported that 85% of OPGs are located in the optic nerves and/or chiasm, and 15% are located in the optic tracts and radiation (11). In addition, chiasmatic/hypothalamic tumor sites have been reported as risk factors for long-term visual deterioration (12). We could not obtain information on whether the OPGs originated from the optic nerve, chiasm or optic tracts. Therefore, we analyzed laterality instead, and we found that 41.6% of the tumors in the pediatric group did not originate from the left or right. We deduced that these tumors originated from the chiasm. In addition, the influence of laterality was not significant in the survival analysis; further

**TABLE 1** | Demographic and clinical characteristics of patients with optic pathway gliomas.

| Variables | Adult | Pediatric | Total | P value |
|---|---|---|---|---|
| **Sex** | | | | 0.091 |
| Female | 119(58.0%) | 543(51.6%) | 662(52.7%) | |
| Male | 86(42.0%) | 509(48.4%) | 595(47.3%) | |
| **Race** | | | | 0.334 |
| White | 165(80.5%) | 876(83.3%) | 1041(82.8%) | |
| Others | 40(19.5%) | 176(16.7%) | 216(17.2%) | |
| **Laterality** | | | | <0.001 |
| Right | 89(43.4%) | 313(29.8%) | 402(32.0%) | |
| Left | 63(30.7%) | 301(28.6%) | 364(29.0%) | |
| Biliteral and unknown | 53(25.9%) | 438(41.6%) | 491(39.1%) | |
| **Behavior code** | | | | 0.461 |
| Benign and borderline | 14(6.8%) | 88(8.4%) | 102(8.1%) | |
| Malignant | 191(93.2%) | 964(91.6%) | 1155(91.9%) | |
| **Surgery** | | | | <0.001 |
| Yes | 40(19.5%) | 111(10.6%) | 151(12.0%) | |
| None/Unknown | 165(80.5%) | 941(89.4%) | 1106(88.0%) | |
| **Radiation** | | | | <0.001 |
| Yes | 76(37.1%) | 19(1.8%) | 95(7.6%) | |
| None/Unknown | 129(62.9%) | 1033(98.2%) | 1162(92.4%) | |
| **Chemotherapy** | | | | <0.001 |
| Yes | 30(14.6%) | 298(28.3%) | 328(26.1%) | |
| None/Unknown | 175(85.4%) | 754(71.7%) | 929(73.9%) | |

**TABLE 2 |** Analysis of treatment patterns chosen by patients with optic pathway gliomas.

| Treatment | Adult | Pediatric | Total |
|---|---|---|---|
| Chemotherapy | 8(3.9) | 237(22.5) | 245(19.5) |
| Chemotherapy and Radiation | 13(6.3) | 4(0.4) | 17(1.4) |
| Observation | 101(49.3) | 692(65.8) | 793(63.1) |
| Radiation | 43(21.0) | 8(0.8) | 51(4.1) |
| Surgery | 19(9.3) | 51(4.8) | 70(5.6) |
| Surgery and Chemotherapy | 1(0.5) | 53(5.0) | 54(4.3) |
| Surgery and Radiation | 12(5.9) | 3(0.3) | 15(1.2) |
| Surgery+Radiation+Chemotherapy | 8(3.9) | 4(0.4) | 12(1.0) |
| Total | 205(100.0) | 1052(100.0) | 1257(100.0) |

**TABLE 3 |** The distribution of the patients with histology records.

| Histology recode | Adult | Pediatric | Total |
|---|---|---|---|
| Anaplastic astrocytoma | 7(8.8) | 1(0.5) | 8(2.8) |
| Astrocytoma, NOS | 10(12.5) | 13(6.4) | 23(8.1) |
| Benign and malignant neuronal/glial, neuronal and mixed | 0 | 1(0.5) | 1(0.4) |
| Diffuse astrocytoma (protoplasma, fibrillary) | 0 | 1(0.5) | 1(0.4) |
| Embryonal/primitive/medulloblastoma | 0 | 1(0.5) | 1(0.4) |
| Ependymoma/anaplastic ependymoma | 1(1.3) | 0 | 1(0.4) |
| Glioblastoma | 14(17.5) | 0 | 14(4.9) |
| Glioma, NOS | 18(22.5) | 64(31.5) | 82(29.0) |
| Mixed glioma | 0 | 2(1.0) | 2(0.7) |
| Pilocytic astrocytoma | 30(37.5) | 120(59.1) | 150(53.0) |
| Total | 80(100.0) | 203(100.0) | 283(100.0) |

high-quality studies are needed to address the potential role of laterality at the time of OPG presentation on OS.

Although most of these tumors were pilocytic astrocytomas, we also found that some of the OPGs were glioblastomas, accounting for 17.5% of the adult patients with available histology. Because only 22.5% of the diagnoses were confirmed by available histology, we did not include pathology type in the survival analysis. In 2020, Kinori et al. (13) reported that children with neurofibromatosis type 1 (NF-1)-associated OPGs who had a normal initial exam had excellent long-term visual function. Pediatric patients with sporadic OPGs, however, have been reported to have significant long-term visual impairment (14). A systematic review from Opocher et al. (5) showed that solid evidence is needed to prove whether NF-1 is an independent prognostic factor. Unfortunately, information on NF-1 was not included in the SEER program; thus, we could not conduct such an analysis. However, our survival analysis results showed that pediatric patients have better OS than their adult counterparts.

The treatment for OPGs remains controversial (9, 15, 16). According to a previous report, observation is suggested for

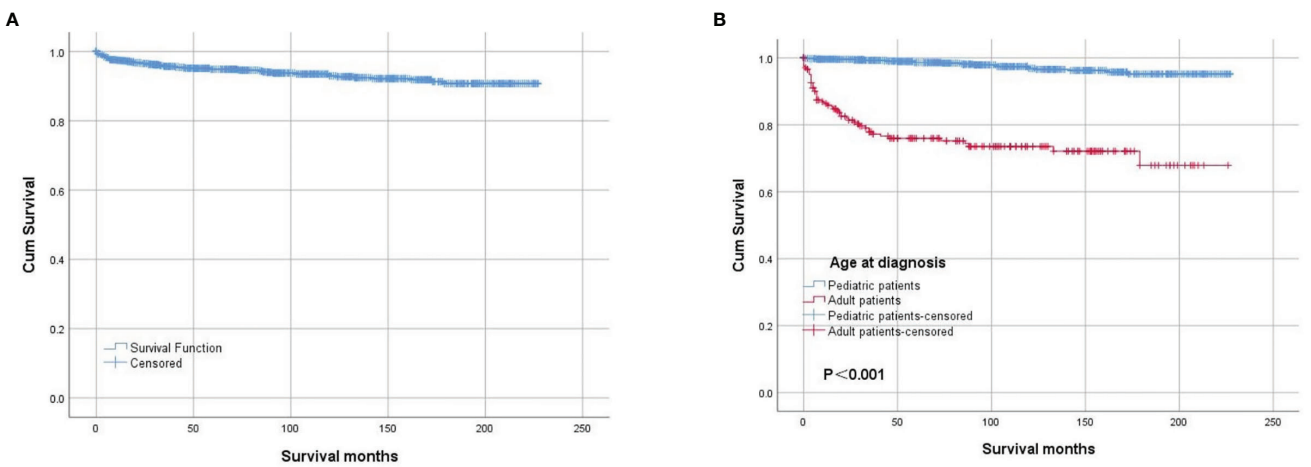


**FIGURE 2** | Kaplan–Meier survival analysis: **(A)** The overall survival for the whole cohort. The survival analysis of patients classified based on age at diagnosis **(B)**.

**TABLE 4 |** The results of the log-rank test.

| Variables | Adult | Pediatric | Total |
|---|---|---|---|
| **Age at diagnosis** (years) | | | <0.001 |
| 0-19 | | | |
| >19 | | | |
| **Sex** | 0.191 | 0.814 | 0.814 |
| Female | | | |
| Male | | | |
| **Race** | 0.931 | 0.461 | 0.517 |
| White | | | |
| Others | | | |
| **Laterality** | 0.654 | 0.688 | 0.779 |
| Right | | | |
| Left | | | |
| Biliteral and unknown | | | |
| **Behavior code** | 0.931 | 0.903 | 0.375 |
| Benign and borderline | | | |
| Malignant | | | |
| **Surgery** | 0.081 | <0.001 | <0.001 |
| Yes | | | |
| None/Unknown | | | |
| **Radiation** | <0.001 | <0.001 | <0.001 |
| Yes | | | |
| None/Unknown | | | |
| **Chemotherapy** | <0.001 | 0.068 | 0.013 |
| Yes | | | |
| None/Unknown | | | |

**TABLE 5 |** The results of the univariate Cox regression analysis.

| Variables | Adult | | Pediatric | | Total | |
|---|---|---|---|---|---|---|
| | HR(95%CI) | P value | HR(95%CI) | P value | HR(95%CI) | P value |
| **Age at diagnosis** (years) | | | | | | |
| 0-19 | | | | | 0.082(0.050-0.134) | <0.001 |
| >19 | | | | | Reference | |
| **Sex** | | | | | | |
| Female | Reference | | Reference | | Reference | |
| Male | 1.443(0.829-2.513) | 0.195 | 0.908(0.407-2.028) | 0.814 | 1.056(0.669-1.666) | 0.815 |
| **Race** | | | | | | |
| White | Reference | | Reference | | Reference | |
| Others | 1.032(0.501-2.125) | 0.932 | 1.445(0.539-3.874) | 0.464 | 1.212(0.677-2.169) | 0.518 |
| **Laterality** | | | | | | |
| Right | 0.935(0.461-1.896) | 0.853 | 0.709(0.253-1.988) | 0.513 | 1.147(0.651-2.021) | 0.635 |
| Left | 0.743(0.376-1.468) | 0.393 | 0.685(0.245-1.920) | 0.472 | 1.208(0.700-2.087) | 0.497 |
| Biliteral and unknown | Reference | | Reference | | Reference | |
| **Behavior code** | | | | | | |
| Benign and borderline | Reference | | Reference | | Reference | |
| Malignant | 3.162(0.436-22.915) | 0.255 | 0.882(0.118-6.608) | 0.903 | 1.870(0.458-7.644) | 0.383 |
| **Surgery** | | | | | | |
| Yes | 1.704(0.927-3.133) | 0.086 | 5.515(2.463-12.348) | <0.001 | 3.495(2.165-5.642) | <0.001 |
| None/Unknown | Reference | | Reference | | Reference | |
| **Radiation** | | | | | | |
| Yes | 2.743(1.555-4.836) | <0.001 | 7.142(2.430-20.985) | <0.001 | 11.219(7.099-17.729) | <0.001 |
| None/Unknown | Reference | | Reference | | Reference | |
| **Chemotherapy** | | | | | | |
| Yes | 5.436(3.010-9.816) | <0.001 | 2.075(0.931-4.627) | 0.074 | 1.788(1.123-2.845) | 0.014 |
| None/Unknown | Reference | | Reference | | Reference | |

patients with neurofibromatosis type 1 (NF-1) or nonprogressive gliomas. When pronounced proptosis and blindness are present or a mass effect or hydrocephalus is observed, surgery is usually considered appropriate (15, 16). Our results show that most (63.1%) of the treatment regimens were no/unknown because the codes for radiation and chemotherapy in the SEER database did not distinguish between "no" and "unknown" treatment. However, the surgery codes showed that only 14 of the 1257

cases (1.1%) were unknown. Therefore, we speculate that observation is recommended for most patients. The survival analysis revealed that the patients who underwent surgery had a worse prognosis. We speculate that the patients had larger tumors or more serious visual damage; thus, although surgery was conducted, the prognosis was not better than that of their counterparts.

Because radiation-related complications, including endocrinopathy, vasculopathy, and cognitive decline, occur in young children, radiation therapy has been gradually abandoned for pediatric patients with OPGs, and chemotherapy has been increasingly adopted (17). Our result of the treatment analysis was coincident with previous reports, but the patients who received chemotherapy also had a worse prognosis. Moreno et al. (9) conducted a systematic review in 2010 and found that treatment with chemotherapy does not improve the resulting vision in the majority of children with OPGs. However, indication bias may exist in our study. Perhaps the worse survival of patients with treatment is due to the severity of the tumor itself and not the treatment. We agree that the treatment of OPGs requires a multidisciplinary approach in which all treatment options are implemented in a highly individualized manner (18).

Except for possible bias and inaccurate data, we have to consider other limitations of our analysis. First, information about tumor progression and ophthalmologic examinations, such as visual acuity and visual field, was limited and is very important for patients with OPGs. Second, the SEER program provided limited information about the genetics of central nervous system tumors, and NF-1 is believed to be associated with the survival of patients with OPGs (19). Third, detailed information about surgery, radiation and chemotherapy was limited, and our results of the survival analysis therefore could not explain the specific condition of individual patients. Despite these limitations, this population-based study can provide helpful information and a better understanding of the epidemiology and survival of patients with OPGs.

## CONCLUSION

OPGs are relatively rare lesions, representing 86.6% of all patients with lesions originating from the optic pathway. They mostly affect children, and pilocytic astrocytoma is the most common histological diagnosis. In our cohort, the prognosis was good, and the OS rate at 10 years after diagnosis was 93.0%. Observation is recommended for most patients. Based on the SEER data, surgery, radiation and chemotherapy showed no evidence of improving OS. Highly individualized treatment is essential for patients with OPGs.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

YW: Conceptualization, methodology, and writing—reviewing and editing. ZJ, YJ, and YW: Data curation, software, and validation. HL, YC, XQ, and YW: Writing—original draft preparation. Writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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# The Emesis Trial: Depressive Glioma Patients Are More Affected by Chemotherapy-Induced Nausea and Vomiting

*Vera Dufner[1*†], Almuth Friederike Kessler[1†], Larissa Just[2], Peter Hau[3], Elisabeth Bumes[3], Hendrik Johannes Pels[4], Oliver Martin Grauer[5], Bettina Wiese[6], Mario Löhr[1], Karin Jordan[7] and Herwig Strik[8]*

[1] Department of Neurosurgery, University Hospital Würzburg, Würzburg, Germany, [2] Department of Neurology, University Medical Center, Marburg, Germany, [3] Wilhelm Sander Neuroonkologische Therapieeinheit, Universitätsklinikum Regensburg, Regensburg, Germany, [4] Krankenhaus der Barmherzigen Brüder, Regensburg, Germany, [5] Department of Neurology, University Medical Center Muenster, Muenster, Germany, [6] Department of Hematology, University Medical Center, Heidelberg, Germany, [7] Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany, [8] Department of Neurology, Sozialstiftung Bamberg, Bamberg, Germany

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**Edited by:**
*Marie-Therese Forster, University Hospital Frankfurt, Germany*

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***Correspondence:**
*Vera Dufner*
*Dufner_V@ukw.de*

[†]*These authors share first authorship*

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**Purpose:** Glioma patients face a limited life expectancy and at the same time, they suffer from afflicting symptoms and undesired effects of tumor treatment. Apart from bone marrow suppression, standard chemotherapy with temozolomide causes nausea, emesis and loss of appetite. In this pilot study, we investigated how chemotherapy-induced nausea and vomiting (CINV) affects the patients' levels of depression and their quality of life.

**Methods:** In this prospective observational multicentre study ($n = 87$), nausea, emesis and loss of appetite were evaluated with an expanded MASCC questionnaire, covering 10 days during the first and the second cycle of chemotherapy. Quality of life was assessed with the EORTC QLQ-C30 and BN 20 questionnaire and levels of depression with the PHQ-9 inventory before and after the first and second cycle of chemotherapy.

**Results:** CINV affected a minor part of patients. If present, it reached its maximum at day 3 and decreased to baseline level not before day 8. Levels of depression increased significantly after the first cycle of chemotherapy, but decreased during the further course of treatment. Patients with higher levels of depression were more severely affected by CINV and showed a lower quality of life through all time-points.

**Conclusion:** We conclude that symptoms of depression should be perceived in advance and treated in order to avoid more severe side effects of tumor treatment. Additionally, in affected patients, delayed nausea was most prominent, pointing toward an activation of the $NK_1$ receptor. We conclude that long acting antiemetics are necessary to treat temozolomide-induced nausea.

**Keywords: glioblastoma, chemotherapy, depression, nausea and emesis, quality of life**

## INTRODUCTION

Brain tumors are among the most aggressive neoplasms. Glioblastoma, the malignant glioma with the worst prognosis, is associated with a median survival time of 16–18 months and a 5 year survival rate of 6 % for male and 9 % for female patients (1). Standard treatment includes bulk surgery, if possible, followed by radiotherapy combined with concomitant and adjuvant chemotherapy with temozolomide (TMZ). TMZ is an orally available alkylating agent administered concomitantly during radiotherapy at 75 mg/m²/d followed by six adjuvant cycles at 150–200 mg/m² of body surface on day 1–5 of a 28 day cycle. Common side effects are bone marrow suppression and, in rare cases, liver toxicity with elevated transaminases (2), skin erythema, alopecia and others. Close monitoring of neutrophils, lymphocyte and thrombocyte count and transaminases on a weekly basis and dose reduction, if required, is crucial.

The most common non-hematological side-effects are nausea, emesis and loss of appetite. At the standard dose of 150–200 mg/m$^2$, TMZ is considered to be moderately emetogenic, which means that 30–90 % of patients would experience nausea, emesis and loss of appetite during treatment without appropriate emetogenic prophylaxis.

Chemotherapy-induced nausea and vomiting (CINV) can occur as an acute or delayed reaction. Acute nausea and vomiting occur within 24 h after application of chemotherapy, usually with a peak at 5–6 h. Nausea is induced via the peripheral 5-hydroxytryptophan receptor 3 (5-HT$_3$) (3). Delayed nausea occurs from 24 to 120 h and is activated through a central pathway, mainly activated through the neurokinin-1 (NK$_1$) receptor. Anticipatory nausea is a conditioned response starting already before application of chemotherapy in expectancy of nausea, i.e., when the chemotherapy infusion comes in sight.

The most important breakthrough in antiemetic treatment took place in 1992 when ondansetron was launched as the first 5-HT$_3$ antagonist in the market. A second important member of this class of agents is granisetron. With a median half-life of approximately 4 h (ondansetron) and 10 h (granisetron), both substances are useful to treat acute, but not delayed nausea. Prophylactic antiemetic treatment with steroids is usually not applied in brain tumor patients since patients are often heavily pretreated with corticosteroids to reduce peritumoral edema and rapid tapering is desired. In addition, several publications suggest tumor-promoting effects of corticosteroids (4, 5).

The usual antiemetic treatment in patients with glioma receiving TMZ consists of a 5-HT$_3$ antagonist like ondansetron or granisetron, approximately 1 h before chemotherapy. However, clinical experience shows that about one third of patients suffer from severe nausea and emesis despite antiemetic treatment, affecting the patients' health-related quality of life (HRQoL). A recent randomized phase-II trial showed that combination of aprepitant plus ondansetron may increase acute anti-emetic response on day 1 and may have benefits regarding CINV's effect on HRQoL (6).

In addition to treatment burden, patients with gliomas develop depression during the first six months after diagnosis in about 15–20 % of cases (7) and up to 30 % of brain tumor patients suffer from clinically relevant depression (assessed at any time during the course of disease) (8). Depression is associated with reduced physical function, cognitive impairment and HRQoL reduction (7, 9). HRQoL is impaired in patients with high grade gliomas as compared to healthy controls, and similar results were found in patients with other types of solid cancer, e.g., NSCLC (10). Patients treated with TMZ experience no worsening but rather a slight improvement of HRQoL as compared to their baseline pretreatment assessment (11). Adding TMZ after radiotherapy has no negative implications on HRQoL (2, 12). Nonetheless, treatment associated side-effects like CINV may seriously affect patients' HRQoL. Accordingly, one of the most common fears of patients from chemotherapy is nausea (13).

In the study presented here, we investigated the level and time course of nausea, emesis and loss of appetite in patients with malignant brain tumors during their first two cycles of chemotherapy with TMZ. In addition, we asked for the patients' HRQoL and levels of depression prior to chemotherapy and after the first and second cycle of chemotherapy. Our aim was to determine whether there is an interaction between CINV and patients' levels of depression and HRQoL at any of the given time-points.

## METHODS

### Study Population

In this prospective, observational, multicentre study, we investigated patients suffering from primary or recurrent malignant glioma receiving chemotherapy in six hospitals in Germany specialized in treatment of glioma patients (University Hospitals Marburg, Münster, Regensburg, Würzburg as well as DIAKOVERE Henriettenstift Hannover and Hospital Barmherzige Brüder Regensburg) in between 2012 and 2016. All 87 patients were included consecutively. Permission of the local ethics committee was obtained (08/13, 26.02.2013), and all patients gave informed consent to participate. Main inclusion criteria were age older than 18 years, qualification for legal acts and a primary or recurrent glioma requiring chemotherapy during the adjuvant phase of the treatment. HRQoL and levels of depression were assessed at least 1 week prior to chemotherapy (t0) and at least 1 week after the first (t1) and second (t2) cycle of chemotherapy. The level and time course of nausea, emesis and loss of appetite were asked for during the first two cycles of chemotherapy with TMZ (c0, c1). This study was conducted following the STROBE guidelines for observational studies.

### Questionnaires

Patients' baseline characteristics (sex, age, Karnofsky Performance Status (KPS), WHO-grade (low: WHO grade I+II, high: WHO grade III+IV), chemotherapeutic agent and dosage and concomitant antiemetic therapy) were assessed by a questionnaire designed for this study's purpose.

The validated MASCC questionnaire was used to evaluate nausea, emesis and loss of appetite. It scales nausea from 0 to 10 with 0 meaning no nausea at all, frequency of emesis and

loss of appetite (on a dichotome scale with yes/no) on a daily basis (14). We expanded the original MASCC questionnaire from 5 to 10 days in order to additionally cover the five days after the last application of TMZ, which is given day 1–5 in cycles of 28 days (**Supplement 2**). Timepoints of evaluation were 1 day prior to chemotherapy as baseline, on the first day of chemotherapy (before and after application) and day 2–10 during c1 and c2. Patients were asked to indicate their level of nausea on a numeric rating scale to visualize the extent of nausea.

The PHQ-9 is an established tool to evaluate depression by patient self-report (15) and is validated for glioma patients (16). PHQ-9 is sensitive for intra-patient changes (17) and consists of nine questions, ranging on a scale from 0 to 3 with a maximum of 27 points. Results can be subclassified in five groups (no symptoms: 0–4 points, minimal symptoms: 5–9 points, minor depression: 10–14 points, moderate major depression: 15–19 points, severe major depression: 20–27 points).

In this study, levels of depression were evaluated prior to the first cycle of chemotherapy (t0), after completion of the first cycle of therapy (t1) and after completion of the second cycle of therapy (t2).

In order to identify changes in patients' HRQoL, we asked patients to fill in the EORTC QLQ-C30 and Modul QLQ-BN20 questionnaires at t0, t1 and t2. The EORTC QLQ-C30 consists of 30 questions, which can be subclassified in 15 categories (global health, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) (18, 19). Answers are ranging on a scale from 0 to 4 (except global health item: 0–7). The EORTC QLQ-BN20 was designed to measure HRQoL particularly in glioma patients (20). Answers range on a scale from 0 to 4 which are subclassified in 11 brain tumor specific categories (future uncertainty, visual disorder, motor dysfunction, communication deficit, headache, seizures, fatigue, rash, alopecia, weakness of legs, and loss of bladder control).

**TABLE 1 |** Patients'characteristics, $n = 87$, chemotherapy and concomitant antiemetic therapy in cycle 1 (c1) and cycle 2 (c2), TMZ, Temozolomide; CCNU, Lomustine.

| **Characteristics** | |
|---|---|
| **Age** | **Mean (Min–Max)** |
| | 53.78 (25–84) |
| **Sex** | **F/M (%)** |
| | 39 (44.8) / 48 (55.2) |
| **Karnofsky-status** | **MEAN (MIN-MAX)** |
| | 83.91 (40–100) |
| **WHO-diagnosis** | ***N* (%)** |
| Pilocytic astrocytoma | 1 (1.1) |
| Ganglioglioma | 1 (1.1) |
| Diffuse astrocytoma | 2 (2.3) |
| Oligoastrocytoma | 6 (6.9) |
| Oligodendroglioma | 11 (12.6) |
| Anaplastic astrocytoma | 16 (18.4) |
| Glioblastoma | 50 (57.5) |
| **WHO-grade** | |
| I | 1 (1.1) |
| II | 12 (13.8) |
| III | 24 (27.6) |
| IV | 50 (57.5) |
| **Chemotherapy C1** | |
| TMZ | 81 (93.1) |
| CCNU + TMZ | 6 (6.9) |
| **Chemotherapy C2** | |
| TMZ | 70 (80.5) |
| CCNU + TMZ | 5 (5.7) |
| Lost to follow-up | 12 (13.8) |
| **Antiemetic therapy C1** | |
| Ondansetrone | 46 (52.8) |
| Granisetrone | 13 (14.9) |
| Palonosetrone | 6 (6.9) |
| Metoclopramide | 1 (1.1) |
| Alizaprid | 20 (23) |
| Dronabinol | 1 (1.1) |
| **Antiemetic therapy C2** | |
| Ondansetrone | 39 (44.8) |
| Granisetrone | 9 (10.3) |
| Palonosetrone | 13 (14.9) |
| Mcp | 1 (1.1) |
| Alizaprid | 12 (13.8) |
| Dronabinol | 1 (1.1) |
| Lost to follow-up | 12 (13.8) |
| **History of nausea** | |
| Motion sickness | 12 (13.8) |
| Pregnancy sickness | 5 (5.7) |
| Food intolerance | 8 (9.2) |
| Drug intolerance | 4 (4.6) |
| Others | 67 (77) |

## Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Worldwide, Chicago, IL, USA). For patients' characteristics, descriptive statistics were performed. For EORTC QLQ-C30 and QLQ-BN20, scores for each subcategory and overall scores were calculated via linear transformation using the official EORTC QLQ-C30 Scoring Manual (21, 22). Patients with missing data were included if more than 50 % of questions per item were completed. Missing single items, items with <50 % of given information and missing questionnaires were not taken into account. For PHQ-9, overall points achieved were summed up and summarized into the five given subcategories described above. Mean values for nausea, emesis and loss of appetite (MASCC) were calculated for each time point during the first two cycles of chemotherapy. Data was examined for Gaussian distribution by Kolmogorov-Smirnov testing. We performed the student's *t*-test in equally distributed data and the Wilcoxon test in non-equally distributed data to evaluate significant effects. Effect size was calculated by Pearson's correlation coefficient *r*. Data were regarded as significant if $\alpha < 0.05$.

# RESULTS

## Study Population

In this prospective multicenter study, we included 87 patients suffering from primary or recurrent glioma from six different institutions [University Hospital of Marburg, $n = 33$ (37.9 %); University Hospital of Münster, $n = 4$ (4.6 %); University Hospital of Regensburg, $n = 26$ (29.9 %); University Hospital of Würzburg, $n = 15$ (17.2 %); DIAKOVERE Henriettenstift Hannover, $n = 1$ (1.1 %) and Regensburg Barmherzige Brüder, $n = 8$ (9.2 %)]. Drop-out rates are displayed in the **Supplements 1, 2**. The mean age was 53.78 years (25–84 years), and 39 female and 48 male patients participated. Most patients suffered from glioblastoma ($n = 50$, 57.5 %), other entities included in this study were pilocytic astrocytoma, ganglioglioma, diffuse astrocytoma, oligoastrocytoma, oligodendroglioma and anaplastic astrocytoma. Most patients received TMZ as a single chemotherapeutic agent in c1 ($n = 81$, 93.1 %) and c2 ($n = 70$, 80.5 %), a minor part of the patients received a combination of Lomustine (CCNU) and TMZ [$n = 6$ (6.9 %) in c1]; $n = 5$ (5.7 % in c2). Serotonine receptor antagonists were the most prevalent antiemetic prophylaxis during c1 (ondansetrone $n = 46$, 52.8 %; granisetrone $n = 13$, 14.9 %; palonosetrone $n = 6$, 6.9 %) and c2 (ondansetrone $n = 39$, 44.8 %; granisetrone $n = 9$, 10.3 %; palonosetrone $n = 13$, 14.9 %) (**Table 1**).

## Gastrointestinal Symptoms

During c1, we spotted an increase of nausea directly after the application of the chemotherapeutical agent using the MASCC questionnaire (**Figure 1A**). Symptoms remained constantly high until day 7. The CINV associated symptoms lasted ∼2 days longer than chemotherapy was applied. Similarly, emesis increased directly after application and took 5 days to return to baseline levels (**Figure 1B**). During c1, patients gradually lost their appetite with a minimum of appetite at day 5 and did not completely recover until day 10 (**Figure 1C**). During c2, nausea slowly increased with a maximum at day 6 (**Figure 1A**). In contrast to c1, emesis most often developed not before day 2 of chemotherapy and was back to baseline levels by day 4 (**Figure 1B**). Appetite, on the contrary, hit its minimum at day 4 during c2 and was not back to former levels at day 10 (**Figure 1C**). Exact frequencies of nausea, emesis and loss of appetite at the respective days of chemotherapy during c1 and c2 are provided in **Table 2**.

In order to investigate if the choice of chemotherapeutic regimen had any impact on nausea, emesis or loss of appetite, we performed a subanalysis in patients who received TMZ only (c1: $n = 81$, c2: $n = 70$) or TMZ + CCNU (c1: $n = 6$, c2: $n = 5$). The chemotherapeutic regimen had no significant effect on nausea (c1: $p = 0.607$, c2: $p = 0.514$), emesis (c1: $p = 0.471$, c2: $p = 0.412$) or loss of appetite (c1: $p = 0.471$, c2: $p = 0.207$).

The extent of CINV (nausea c1: $p = 0.969$, c2: $p = 0.614$; emesis c1: $p = 0.260$, c2: $p = 0.863$; loss of appetite c1: 0.368, c2: 0.716) was not significantly significantly different in patients with low ($n = 13$) or high grade ($n = 74$) tumors during c1 nor c2.

A poorer general condition as assessed with the KPS ($\leq$70) was not significantly associated with nausea (c1: $p = 0.969$, c2: $p = 0.614$), emesis (c1: $p = 0.260$, c2: $p = 0.863$) or loss of appetite (c1: $p = 0.368$, c2: $p = 0.716$), as compared with patients with a KPS $> 70$ at c1 or c2.

## Depression

Prior to chemotherapy, the mean baseline PHQ-9 score was 6.79 (0–22). At t1, it increased to 8.25 (0–25), but dropped to 7.13 (0–27) at t2 (**Figure 2**). In total, mean PHQ-9 scores indicated minimal depressive symptoms. However, single patients with moderate or severe major depression could be identified after chemotherapy (**Table 3**). The mean PHQ-9 was significantly higher at t1 as compared to the level prior to chemotherapy, with an effect size $r$ of 0.35 ($p = 0.003$). By contrast, at t2, levels of depression were not significantly different from the scores at t0 ($p = 0.341$) (**Figure 2**). Patient drop-out is summarized in **Supplement 1**.

We performed a subanalysis to investigate if the chemotherapeutic regimen (TMZ or CCNU + TMZ) would have any impact on depression in c1 (TMZ: $n = 81$, TMZ + CCNU: $n = 6$) or c2 (TMZ: $n = 70$, TMZ + CCNU: $n = 5$). No significant effect on the PHQ-9 score was found at t0 (c1: $p = 0.648$, c2: $p = 0.503$), t1 (c1: $p = 0.158$, c2: $p = 0.308$) or t2 (c1: $p = 0.629$, c2: $p = 0.629$).

Patients with low grade gliomas ($n = 13$) had a significant higher likelihood of a higher PHQ-9 score at t1 ($p = 0.010$) and t2 ($p = 0.041$) as compared with patients with high grade glioma ($n = 74$). There was no significant difference to the baseline values at t0 ($p = 0.133$). Patients with a lower KPS ($\leq 70$) had a significantly higher PHQ-9 score at t1 ($p = 0.010$) and t2 ($p = 0.041$) as compared to patients with a KPS of $>$70. At baseline assessment at t0, however, no significant difference of PHQ-9 was found ($p = 0.133$).

Patients with higher levels of depression at t0 showed a significantly higher likelihood of developing nausea ($p = 0.00$) and emesis ($p = 0.023$) during c1. Similarly, patients with higher levels of depression at t1 also had a significantly higher incidence of emesis ($p = 0.00$) and loss of appetite ($p = 0.03$) during c2. Vice versa, patients experiencing nausea ($p = 0.00$) or emesis ($p = 0.002$) during c1 showed significantly elevated levels of depression at t1. This was also found to be true for patients' levels of depression at t2, if they experienced nausea ($p = 0.027$) and emesis ($p = 0.00$) during c2.

## Quality of Life

Patients' HRQoL assessment with the QLQ-C30 questionnaire showed a significant drop in the mean of the global health item with an effect size r of 0.22 ($p = 0.044$) and physical function with an effect size r of 0.22 ($p = 0.044$) at t1. Fatigue ($p = 0.002$) and nausea ($p = 0.009$) increased at t1 with effect sizes r of 0.34 and 0.29, respectively. Global health was also reduced at t2 with an effect size r of 0.24 (p =0.029), as well as nausea with an effect size r of 0.28 ($p = 0.01$). The other items of the QLQ-C30 questionnaire showed no significant changes in t1 or t2. The QLQ-BN20 questionnaire showed a significant increase of the weakness of legs item at t1 with an effect size r of 0.027 ($p = 0.014$). At t2 loss of hair worsened significantly with an

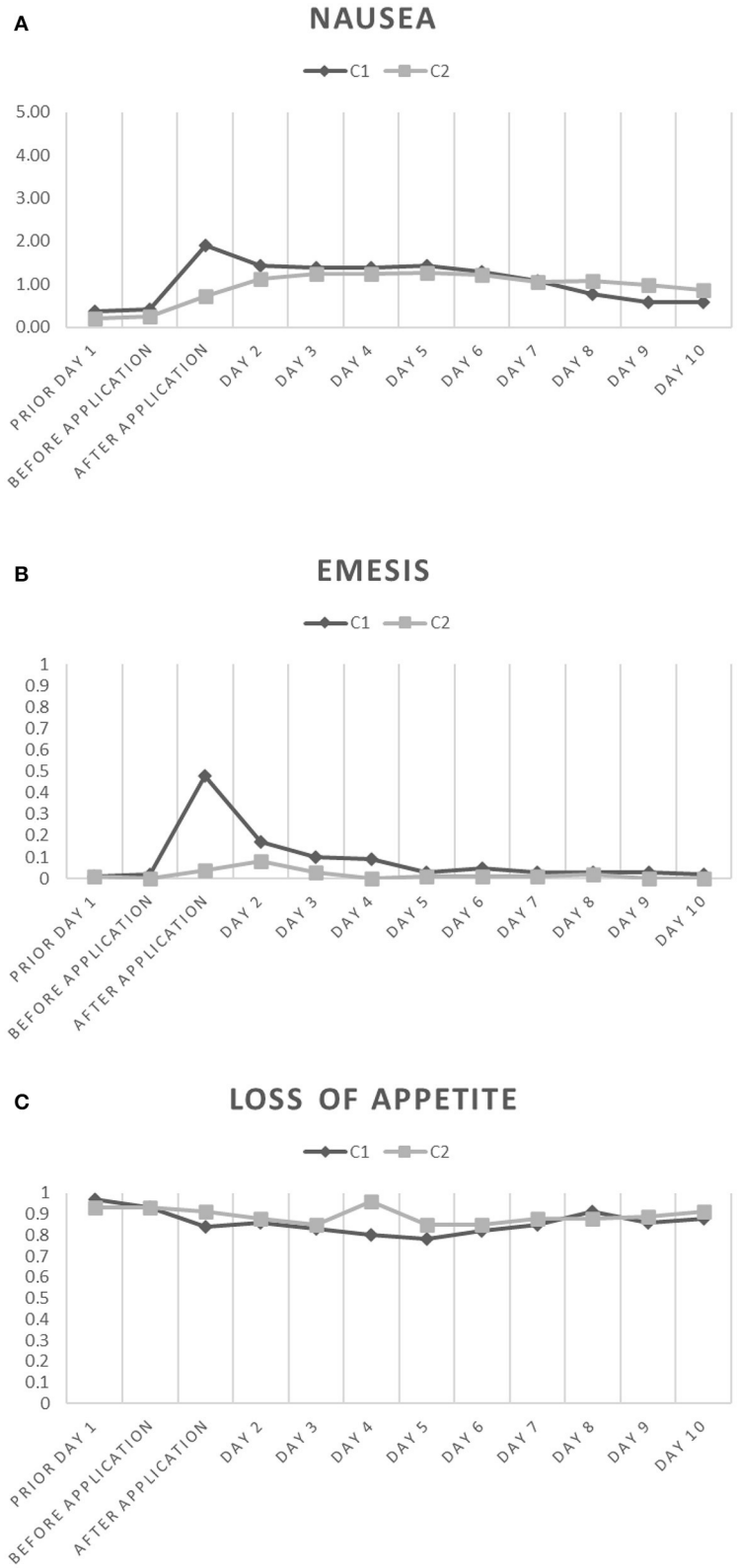


**FIGURE 1 |** Mean of nausea **(A)**, emesis **(B)** and loss of appetite **(C)** during the first 10 days of the c1 (black rhombus) and c2 (gray square) of chemotherapy. Respective days during the course of chemotherapy are displayed on the x-axis. The median MASCC is shown on the *y*-axis (nausea: 0–10; emesis: frequency per day; loss of appetite: 0: not at all, 1: loss of appetite).

**TABLE 2 |** Frequencies of symptoms of nausea, emesis and loss of appetite during c1 and c2 in %.

| Cycle 1 (%) | D-1 | D 1* | D 1# | D 2 | D 3 | D 4 | D 5 | D 6 | D 7 | D 8 | D 9 | D 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No nausea | 90.8 | 87.4 | 62.1 | 62.1 | 63.2 | 65.5 | 63.2 | 64.4 | 70.1 | 76.6 | 84.1 | 84.1 |
| Any nausea | 9.2 | 12.6 | 37.9 | 37.9 | 36.8 | 34.5 | 36.8 | 35.6 | 29.9 | 23,4 | 15.9 | 15.9 |
| No emesis | 98.9 | 97.7 | 86.2 | 93.1 | 94.3 | 95.4 | 96.6 | 95.4 | 96.9 | 96.9 | 96.9 | 98.4 |
| Any emesis | 1.1 | 2.3 | 13.8 | 6.9 | 5.7 | 4.6 | 3.4 | 4.6 | 3.1 | 3.1 | 3.1 | 1.6 |
| No loss of appetite | 94.4 | 91.0 | 82.0 | 84.3 | 80.9 | 78.7 | 76.4 | 79.8 | 83.1 | 66.3 | 62.9 | 64.0 |
| Loss of appetite | 5.6 | 9.0 | 18.0 | 15.7 | 19.1 | 21.3 | 23.6 | 20.2 | 16.9 | 33.7 | 37.1 | 36.0 |

*D-1 means day prior to chemotherapy application. D1* day 1 prior to application of chemotherapy and D1# day 1 after application of chemotherapy.*

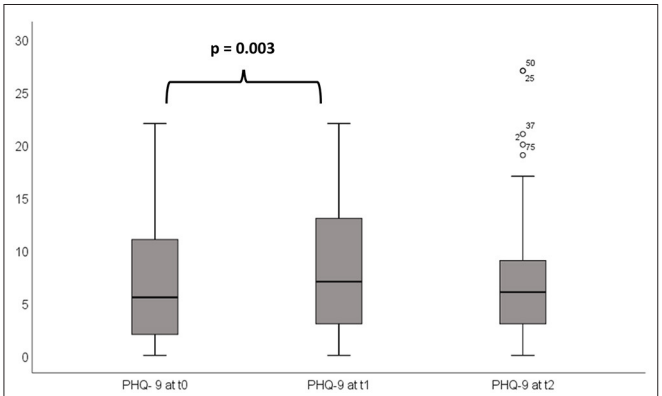


**FIGURE 2 |** PHQ-9 prior to (t0) and after the first (t1) and second (t2) cycle of chemotherapy: The mean PHQ-9 at t1 is significantly ($p = 0.003$) higher than mean PHQ-9 at t0 indicating a higher burden of depression at t1. No significant difference was found in PHQ-9 at t1 and t2.

**TABLE 3 |** Classification of PHQ-9 symptoms, the absolute and relative number of patients and the severity of their symptoms respectively at t0, t1 and t2.

| | | | t0, $n = 73$ *N* (%) | t1, $n = 77$ *N* (%) | t2, $n = 67$ *N* (%) |
|---|---|---|---|---|---|
| No symptoms | 0–4 | 0 | 29 (39.7) | 26 (33.8) | 29 (43.3) |
| Minimal symptoms | 5–9 | 1 | 24 (32.9) | 25 (32.5) | 22 (32.8) |
| Minor depression | 10–14 | 2 | 13 (17.8) | 13 (16.9) | 8 (11.9) |
| Moderate major depression | 15–19 | 3 | 5 (6.8) | 9 (11.7) | 4 (6.0) |
| Severe major depression | 20–27 | 4 | 2 (2.7) | 4 (5.2) | 4 (6.0) |

effect size $r$ of 0.26 ($p = 0.018$). No other items of the QLQ-BN20 questionnaire showed significant effects at t1 or t2. Patient drop-out is summarized in **Supplement 1**.

Patients whose PHQ-9 levels reached a score above 15 were defined as moderately or severely depressed and analyzed in a separate HRQoL subanalysis. In contrast to patients with a PHQ-9 score lower than 15 during all time-points of observation (t0, t1, t2), patients with signs of major depression showed a significant impairment in their HRQoL concerning global health, physical function, role function, social function, future uncertainty and fatigue during all time points of measurement (**Table 4**). Chemotherapy-induced nausea was not significantly different between the two groups, whereas loss of appetite was significantly more frequent in patients with higher levels of depression at t1 and t2 (**Table 4**).

In order to analyze the impact of general condition, our patient series was divided in a group with a lower ($\leq$70, $n = 20$) and higher (>70, $n = 62$) KPS. We performed a HRQoL subanalysis comparing these two groups. Patients with a lower KPS showed a significant impairment in HRQoL concerning global health, physical functioning, role functioning, social functioning, future uncertainty, motor dysfunction and weakness of legs compared to patients with a KPS > 70 at all time-points of observation (t0, t1, t2). Neither nausea nor loss of appetite were significantly different in the two groups (**Table 5**).

## DISCUSSION

To our knowledge, this is the first prospective multicenter study assessing glioma patients under the following conditions: a defined 10-day period before, during and after application of chemotherapy and its effects on HRQoL and levels of depression.

In order to measure nausea, emesis and loss of appetite, we applied the expanded MASCC questionnaire, modified with a numeric rating scale and assessed nausea, emesis and loss of appetite for 10 consecutive days, during the c1 and c2 of chemotherapy. Overall, the burden of CINV symptoms was moderate. Interestingly, the application of TMZ during day 1–5 in both c1 and c2 appeared to cause delayed and prolonged nausea, emesis and loss of appetite. In view of the significant delay of nausea and emesis observed in this study, we speculate that a relevant activation of the NK1 pathway takes place, supported by several clinical trials reducing nausea by combining a NK1 receptor antagonist with a 5 $HT_3$ antagonist setron (23–25). Shorter acting antiemetics should therefore be substituted with longer acting substances like palonosetron, or through the addition of a NK1 receptor antagonist like aprepitant, rolaprepitant or the fix combination of netupitant and palonosetron (26, 27). We also observed a tendential decrease of emesis in c2, possibly as a consequence of an adjustment in antiemetic prophylaxis after c1, e.g., increase in palonosetron intake (**Table 1**). As higher levels of nausea and emesis exhibit significant intercorrelations with depressive

**TABLE 4 |** Comparison of the mean of the items of the EORTC QLQ-C30 and QLQ-BN20 questionnaire at t0 prior to chemotherapy and after the first (t1) and second cycle of chemotherapy (t2) in patients with a PHQ-9 score of <15 and ≥15.

| Questionnaire/item | t0 | | | t1 | | | t2 | | |
|---|---|---|---|---|---|---|---|---|---|
| | PHQ-9 < 15 | PHQ-9 ≥ 15 | *p* | PHQ-9 < 15 | PHQ-9 ≥ 15 | *p* | PHQ-9 < 15 | PHQ-9 ≥ 15 | *p* |
| **QLQ-C30** | | | | | | | | | |
| Global health | 57.82 | 42.19 | **0.013** | 54.27 | 28.65 | **0.012** | 57.85 | 41.67 | **0.026** |
| Physical functioning | 73.52 | 38.65 | **0.001** | 71.49 | 33.33 | **0.005** | 71 | 41.33 | **0.006** |
| Role functioning | 59.58 | 22.92 | **0.00** | 56 | 12.22 | **0.001** | 58.22 | 27.38 | **0.03** |
| Emotional functioning | 67.9 | 46.88 | 0.239 | 62.2 | 38.02 | 0.084 | 62.78 | 45 | **0.026** |
| Cognitive functioning | 67.9 | 47.92 | **0.011** | 65.45 | 37.5 | 0.060 | 65.28 | 45.56 | **0.033** |
| Social functioning | 59.26 | 33.33 | **0.002** | 57.52 | 24 | **0.004** | 58.33 | 31.11 | **0.007** |
| Fatigue | 44.86 | 80.56 | **0.011** | 50.47 | 85.42 | **0.000** | 46.88 | 80.74 | **0.001** |
| Nausea | 8.85 | 18.75 | 0.111 | 16.06 | 29.17 | 0.164 | 11.81 | 16.67 | 0.218 |
| Pain | 14.2 | 35.42 | 0.139 | 14.63 | 35.56 | 0.181 | 11.87 | 26.67 | 0.438 |
| Dyspnea | 15.23 | 33.33 | 0.385 | 15.64 | 35.56 | **0.029** | 16.44 | 31.11 | 0.096 |
| Insomnia | 26.34 | 50 | **0.033** | 33.33 | 43.75 | 0.143 | 21.46 | 42.22 | **0.046** |
| Appetite loss | 20.16 | 33.33 | 0.140 | 26.75 | 52.08 | **0.002** | 21.3 | 37.78 | **0.02** |
| Constipation | 20.16 | 31.25 | **0.013** | 25.2 | 31.25 | 0.081 | 27.31 | 28.89 | 0.395 |
| Diarrhea | 8.64 | 14.58 | 0.755 | 11 | 31.25 | 0.468 | 8.33 | 20 | 0.901 |
| Financial difficulties | 24.17 | 33.33 | 0.170 | 24.4 | 20.83 | **0.023** | 26.85 | 40 | **0.039** |
| **QLQ-BN20** | | | | | | | | | |
| Future uncertainty | 47.81 | 62.5 | 0.074 | 46.44 | 66.84 | **0.017** | 44.95 | 60.56 | **0.024** |
| Visual disorder | 12.92 | 22.92 | 0.052 | 13.14 | 23.61 | 0.175 | 12.21 | 18.52 | 0.381 |
| Motor dysfunction | 19.9 | 39.58 | 0.126 | 20 | 39.24 | 0.235 | 18.94 | 28.15 | 0.204 |
| Communication deficit | 21.46 | 25.69 | 0.509 | 18.1 | 21.53 | 0.233 | 18.31 | 22.96 | 0.438 |
| Headache | 21.67 | 39.58 | 0.222 | 22 | 39.58 | 0.127 | 22 | 40 | 0.052 |
| Seizures | 8.33 | 2.08 | 0.733 | 6.91 | 12.5 | 0.205 | 3.76 | 0 | 0.353 |
| Fatigue | 47.26 | 79.17 | **0.003** | 52.03 | 85.42 | **0.003** | 44.6 | 75.56 | **0.005** |
| Rash | 24.05 | 41.67 | 0.357 | 24.4 | 35.42 | 0.803 | 25.35 | 31.11 | 0.960 |
| Alopecia | 30 | 29.17 | 0.733 | 28.8 | 20.83 | 0.362 | 18.31 | 11.11 | 0.644 |
| Weakness of legs | 23.75 | 56.25 | **0.038** | 8.94 | 58.33 | 0.745 | 27.7 | 40 | 0.370 |
| Loss of bladder control | 7.5 | 16.67 | 0.950 | 29.67 | 16.67 | 0.571 | 7.98 | 0 | 0.527 |

*P-values are provided for each time-point and each item; significant p-values are highlighted.*

symptoms and HRQoL, constant monitoring and treatment of gastrointestinal side effects would be crucial.

While the PHQ-9 score prior to chemotherapy indicated only minimal symptoms of depression in most patients, PHQ-9 scores of 15 or higher in single patients pointed toward moderate to severe pre-existing symptoms of depression in a specific subpopulation. After completion of c1, levels of depression increased significantly. Chemotherapy effects such as nausea and emesis or myelosuppression and infections, but also the fear of these symptoms may enhance the psychosocial burden of patients and lead to a higher level of psychological stress (28, 29). After completion of c2, however, levels of depression decreased. This may point toward a reduced level of stress once the treatments have become routine.

Interestingly, we observed that not only was the extent of gastrointestinal symptoms associated with a significantly higher level of depression after the respective cycle of chemotherapy, but also vice versa—patients with higher baseline levels of depression experienced significantly more severe nausea, emesis or loss of appetite. We presume that treatment-resistant or anticipatory nausea during chemotherapy may be psychosomatic to a relevant extent (30, 31).

The QLQ-C30 and QLQ-BN20 questionnaire assessed prior to and after c1 and c2 indicated fatigue and loss of hair, which may not necessarily have been caused by chemotherapy alone, but possibly resulted also from previous radiotherapy (32–34). Interestingly, the QLQ-C30 questionnaire showed a significant increase of nausea at t1 and t2, respectively, thus supporting results from the MASCC questionnaire. Global health dropped significantly at t1 and t2. Patients with signs of depressive mood, as indicated by a PHQ-9 score of 15 or higher, showed more severe effects through decreased HRQoL than non-depressed patients. Global health, physical function, role function, social function, future uncertainty and fatigue were already significantly impaired prior to chemotherapy in depressed patients. In the further course of disease, these executing aspects of the patients' lives deteriorated more markedly than in non-depressed patients. By contrast, emotional functioning, dyspnea, appetite loss,

**TABLE 5 |** Comparison of the mean of the items of the EORTC QLQ-C30 and QLQ-BN20 questionnaire at t0 prior to chemotherapy and after the first (t1) and second cycle of chemotherapy (t2) in patients with a KPS of ≤70 and >70.

| Questionnaire/item | t0 | | | t1 | | | t2 | | |
|---|---|---|---|---|---|---|---|---|---|
| | KPS ≤ 70 | KPS >70 | *p* | KPS ≤ 70 | KPS >70 | *p* | KPS ≤ 70 | KPS >70 | *p* |
| **QLQ-C30** | | | | | | | | | |
| Global health | 47.92 | 61.01 | **0.012** | 39.58 | 59.00 | **0.002** | 45.83 | 60.91 | **0.034** |
| Physical functioning | 52.25 | 80.49 | **<0.0** | 48.57 | 79.25 | **<0.0** | 49.78 | 76.44 | **0.009** |
| Role functioning | 41.23 | 65.30 | **0.013** | 35.09 | 62.37 | **0.005** | 37.18 | 62.93 | **0.022** |
| Emotional functioning | 54.03 | 65.03 | 0.166 | 49.17 | 66.40 | **0.006** | 44.44 | 67.59 | **0.004** |
| Cognitive functioning | 63.33 | 69.40 | 0.330 | 58.33 | 67.74 | 0.158 | 51.11 | 69.01 | **0.018** |
| Social functioning | 45.83 | 63.66 | **0.048** | 40.00 | 63.17 | **0.006** | 41.11 | 62.87 | **0.019** |
| Fatigue | 58.33 | 40.44 | **0.027** | 66.67 | 44.99 | **0.004** | 56.30 | 44.44 | 0.131 |
| Nausea | 15.00 | 6.83 | 0.093 | 18.33 | 15.32 | 0.449 | 7.78 | 12.87 | 0.712 |
| Pain | 26.67 | 10.11 | 0.10 | 21.43 | 12.30 | 0.106 | 13.33 | 11.49 | 0.759 |
| Dyspnea | 26.67 | 11.48 | **0.039** | 21.67 | 13.66 | 0.181 | 26.67 | 13.79 | **0.050** |
| Insomnia | 28.33 | 25.69 | 0.680 | 26.99 | 29.57 | 0.634 | 17.78 | 22.41 | 0.470 |
| Appetite loss | 26.67 | 18.03 | 0.241 | 38.60 | 23.12 | 0.099 | 22.22 | 21.05 | 0.812 |
| Constipation | 30.00 | 16.94 | 0.172 | 26.67 | 24.73 | 0.981 | 26.67 | 27.49 | 0.685 |
| Diarrhea | 6.67 | 9.29 | 0.899 | 3.33 | 13.44 | 0.095 | 2.22 | 9.94 | 0.405 |
| Financial difficulties | 21.67 | 25.00 | 0.894 | 30.00 | 22.58 | 0.251 | 28.89 | 26.31 | 0.661 |
| **QLQ-BN20** | | | | | | | | | |
| Future uncertainty | 61.25 | 43.33 | **0.013** | 64.15 | 40.37 | **0.001** | 65.56 | 39.43 | **0.003** |
| Visual disorder | 18.33 | 11.11 | 0.066 | 21.16 | 10.38 | **0.020** | 21.48 | 9.72 | **0.036** |
| Motor dysfunction | 36.11 | 14.44 | **<0.00** | 35.45 | 14.66 | **<0.00** | 35.56 | 14.48 | **0.011** |
| Communication deficit | 25.83 | 20.00 | 0.508 | 22.22 | 16.67 | 0.578 | 27.41 | 15.87 | 0.079 |
| Headache | 36.67 | 16.67 | **0.015** | 23.81 | 21.31 | 0.685 | 31.11 | 19.05 | 0.111 |
| Seizures | 13.33 | 6.67 | 0.100 | 7.94 | 6.56 | 0.216 | 6.67 | 2.98 | 0.430 |
| Fatigue | 54.39 | 45.00 | 0.315 | 71.43 | 45.36 | **0.002** | 57.78 | 41.07 | 0.730 |
| Rash | 31.67 | 21.47 | 0.307 | 22.22 | 25.13 | 0.568 | 22.22 | 26.19 | 0.858 |
| Alopecia | 48.33 | 23.73 | **0.014** | 41.27 | 24.44 | 0.118 | 28.89 | 15.48 | 0.272 |
| Weakness of legs | 51.67 | 14.44 | **<0.00** | 55.56 | 20.77 | **<0.00** | 51.11 | 21.43 | **0.006** |
| Loss of bladder control | 15.00 | 5.00 | 0.195 | 14.29 | 7.10 | 0.188 | 8.89 | 7.74 | 0.713 |

*P-values are provided for each time-point and each item; significant p-values are highlighted.*

headaches and financial difficulties were significantly impaired only during chemotherapy at either t1 or t2. This subanalysis should be interpreted with care as there were less patients represented in the group of a PHQ-9 score of 15 or higher (at t0 $n = 7$, at t1 $n = 13$, at t2 $n = 8$) compared to the group with lower depression scores (at t0 $n = 66$, at t1 $n = 64$, at t2 $n = 59$) and the two subgroup are not equally distributed.

Due to its design, the results obtained in this pilot study should be interpreted with some caution. At first, the study is not adequately powered for the quantity of HRQoL parameters assessed with the EORTC QLQ-C30 and QLQ-BN20. Second, we investigated a series of primary and recurrent glioma of different WHO grading treated at different hospitals with inhomogeneous chemotherapy and antiemetic medication representing the daily practice of outpatient care. While most patients received TMZ alone, some patients were treated additionally with lomustine. Third, we neither assessed the general toxicity nor tolerability of chemotherapy. General side-effects of therapy might have had interactions with depression, CINV and HRQol. Even though we documented baseline depression, CINV and HRQoL scores, we did not interview the patients about preexisting psychiatric disorders. In addition, we cannot provide information on the consecutive development of depression, CINV or HRQoL beyond the first two courses of chemotherapy. Although these factors may have influenced the severity of nausea, emesis and loss of appetite, the mode of evaluation established in this study appears to be adequate and the observations on duration of gastrointestinal side effects, intercorrelation with depressive symptoms and effect on HRQoL seems to be robust enough to draw initial conclusions.

Taken together, we observed a relevant interaction between gastrointestinal side effects of chemotherapy and depressive symptoms. Neither KPS, WHO grading nor chemotherapeutical regimen did influence CINV symptoms significantly. CINV may be underestimated in glioma patients, may last longer than anticipated, and appears to be aggravated by pre-existing depressive symptoms, severely affecting the HRQoL of the affected patients. During treatment, CINV should be asked for

thoroughly and treated with effective, long-lasting antiemetics not only to reduce gastrointestinal symptoms, but also to prevent depressive mood and impairment of HRQoL.

Moreover, HRQoL was impaired after initiation of chemotherapy, especially in patients suffering from pre-existing depressive mood. According to the standard within German certified oncological centers, we consider it important to introduce regular screening of the extent of psychosocial burden and depressive symptoms during the course of disease. Early detection and treatment of depression may probably not only stabilize the patient's mood, but also prevent deterioration of gastrointestinal symptoms and HRQoL.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the respective Ethik-Kommission der Medizinischen Fakultät. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

Study conception and design were prepared by HS, LJ, and KJ, and consented with all co-authors. Material preparation was performed by AK, PH, HP, OG, BW, ML, KJ, and HS. Data collection was coordinated by HS and LJ. Statistical analysis was performed by VD. The manuscript was prepared by VD, HS, and AK, and commented by all authors. All authors read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

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# Eloquent Lower Grade Gliomas, a Highly Vulnerable Cohort: Assessment of Patients' Functional Outcome After Surgery Based on the LoG-Glio Registry

*Jan Coburger[1]*, Julia Onken[2], Stefan Rueckriegel[3], Christian von der Brelie[4], Minou Nadji-Ohl[5], Marie-Therese Forster[6], Rüdiger Gerlach[7], Meike Unteroberdörster[2], Constantin Roder[8], Katja Kniese[9], Stefan Schommer[5], Dietrich Rothenbacher[10], Gabriele Nagel[10], Christian Rainer Wirtz[1], Ralf-Ingo Ernestus[3], Arya Nabavi[9], Marcos Tatagiba[8], Marcus Czabanka[6], Oliver Ganslandt[5], Veit Rohde[4], Mario Löhr[3], Peter Vajkoczy[2] and Andrej Pala[1]*

[1] Department of Neurosurgery, University of Ulm, Günzburg, Germany, [2] Department of Neurosurgery, Charité - University of Berlin, Berlin, Germany, [3] Department of Neurosurgery, University of Würzburg, Würzburg, Germany, [4] Department of Neurosurgery, University of Göttingen, Göttingen, Germany, [5] Department of Neurosurgery, Katharinenhospital Stuttgart, Stuttgart, Germany, [6] Department of Neurosurgery, University of Frankfurt, Frankfurt am Main, Germany, [7] Department of Neurosurgery, Helios Hospital Erfurt, Erfurt, Germany, [8] Department of Neurosurgery, University of Tübingen, Tübingen, Germany, [9] Department of Neurosurgery, KRH Klinikum Region Hannover, Hannover, Germany, [10] Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany*

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***Correspondence:**
*Jan Coburger*
*jan.coburger@uni-ulm.de*

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Majority of lower grade glioma (LGG) are located eloquently rendering surgical resection challenging. Aim of our study was to assess rate of permanent deficits and its predisposing risk factors. We retrieved 83 patients harboring an eloquently located LGGs from the prospective LoG-Glio Database. Patients without surgery or incomplete postoperative data were excluded. Sign rank test, explorative correlations by Spearman ρ and multivariable regression for new postoperative deficits were calculated. Eloquent region involved predominantly motor (45%) and language (40%). At first follow up after 3 months permanent neuro-logical deficits (NDs) were noted in 39%. Mild deficits remained in 29% and severe deficits in 10%. Complete tumor removal (CTR) was successfully in 62% of intended cases. Postoperative and 3-month follow up National Institute of Health Stroke Score (NIHSS) showed significantly lower values than preoperatively ($p<0.001$). 38% cases showed a decreased NIHSS at 3-month, while occurrence was only 14% at 9-12-month follow up. 6/7 patients with mild aphasia recovered after 9-12 months, while motor deficits present at 3-month follow up were persistent in majority of patients. Eastern oncology group functional status (ECOG) significantly decreased by surgery ($p < 0.001$) in 31% of cases. Between 3-month and 9-12-months follow up no significant improvement was seen. In the multivariable model CTR ($p=0.019$, OR 31.9), and ECOG>0 ($p=0.021$, OR 8.5) were independent predictors for permanent postoperative deficit according to NIHSS at 3-month according to multivariable regression model. Patients harboring eloquently located LGG are highly vulnerable for permanent deficits. Almost one third of

patients have a permanent reduction of their functional status based on ECOG. Risk of an extended resection has to be balanced with the respective oncological benefit. Especially, patients with impaired pre-operative status are at risk for new permanent deficits. There is a relevant improvement of neurological symptoms in the first year after surgery, especially for patients with slight aphasia.

**Keywords: LGG, neurological deficit, awake surgery, iMRI = intraoperative MRI, iUS = intraoperative ultrasound, intraoperative monitoring (IOM), eloquent area tumours, eloquent area surgery**

# INTRODUCTION

Lower grade gliomas (LGG) are typically infiltrative and diffuse growing lesions, commonly involving eloquent regions (1–3). Although, slow progressing, they recur unavoidably and undergo malignant transformation (4). Despite better understanding of molecular patterns resulting in the new classification based on isocitrat dehydrogenase (IDH) mutation, surgery remains the main first line treatment (5, 6). A complete fluid-attenuation inversion recovery (FLAIR) or T2 based resection mostly allows for a longer progression free survival and may decrease rate of malignant transformation (7). Gross total resection or even supramaximal resection became an important goal for surgical treatment (1, 8–13). Nevertheless, the aggressive resection might result unintentionally to inferior quality of life (QoL) and compromise daily routines in both private and working spheres (14, 15). This holds true especially for eloquent lesions. Although, there are multicenter retrospective studies suggesting that a volumetric increase of extent of resection leads to an increased survival (5, 16). A deterioration of patients' functional status apart from reduced QoL might lead to an exclusion from adjuvant treatment resulting in suboptimal outcome (17). Apart from counterbalancing of maximal safe resection and avoidance of neurological and cognitive deterioration, surgeons have to choose from a wide armamentarium of surgical tools various intraoperative imaging devices or mapping techniques at hand (10, 18, 19).

Currently, there are no randomized controlled trials (RCT) or controlled clinical trials (CCT) available on which to base clinical decision making (20). Informed consent is often based on surgeon's individual experience (20). Incidence of neurological deficits in eloquent location like insular gliomas is often based on retrospective single center data and can thus be underestimated (21). The aim of our study was to evaluate the outcome of patients with eloquently located LGG based on prospective non-selected data from the Log-Glio registry.

# MATERIALS AND METHODS

## Study Design and Patient Selection

Patients included in the study were prospectively selected from the Log-Glio Registery (clinicaltrials.gov NCT02686229) of patients between November 2016 and May 2021. Primary selection criteria for the registry are patients with a suspected diagnosis of LGG, based upon initial MRI scans. Further inclusion criteria were age over 18 years and signed informed consent. The LoG-Glio registry is a German based multi-center prospective registry with ongoing follow up every 6 month. Currently 13 centers are participating in the registry. Nine centers took part in the current assessment. The detailed study protocol has been described in detail in our earlier publication (22). For the current study only patients with a final histopathological diagnosis of astrocytoma and oligodendroglioma World Health Organization (WHO) grade II and III according to 2016 classification were selected.

Ethical approval was received by the ethic committee of the University of Ulm (Ethikkommission Ulm, No. 201/15). Study was performed in accordance with the Declaration of Helsinki.

## Patient and Tumor Characteristics

Basic demographic data were extracted from the registry. Follow up as evaluated in this study was performed routinely at 3 months after surgery. Motor, speech and visual cortex as well as basal ganglia were considered as eloquent regions based on Brodman anatomical localization. Furthermore, hippocampus, gyrus cinguli and corpus callosum were defined as eloquent regions as well. Mild postoperative neurological deficit was defined as the decrease of 1 grade according to British Medical Research Council or a new or slightly more pronounced aphasia (1 point on National Institute of Health Stroke Score (NIHSS) sub-scale for language). Severe deficit was defined either as worsening of more than 1 grade or severe aphasia (more than 1 point on NIHSS for language). Surgical complications within the first 3 months after surgery apart from neurological deficits were evaluated separately.

As part of the typical treatment regime in Germany in all centers physiotherapy, speech therapy and neuropsychological therapy is offered to all patients during their in hospital stay. Patients suffering from neurological deficits will be offered an in-patient neurological rehabilitation at their discretion. When radiotherapy is recommended, neurological rehabilitation is usually postponed until end of radiotherapy.

## Statistical Analysis

A descriptive assessment was done for demographic data. As part of the explorative assessment we correlated the typical clinical factors calculating Spearman's ρ (rho) [WHO grade, histology, type of surgical approach, tumor location, awake surgery, sex, recurrent surgery, delay of surgery of more than 3 months after primary diagnosis, use of intraoperative magnetic resonance imaging (iMRI) or intraoperative ultrasound imaging (iUS)].

Correlations were used exploratively thus, it was not corrected for multiple testing.

Chi Square test with Fischer's exact test was used for binary comparisons. Sign test with Fisher's exact test was used for related samples. Kruskal-Wallis test was used to test for differences of neurological deficits by center.

We used a binary multivariable regression model to assess influence on presence of a new neurological deficits based on NIHSS at 3-month follow up. Selection of variables included in the model was hypothesis driven and based on previous literature. Variables included in the regression model were type of surgery, recurrent surgery, awake surgery, IDH mutation status, preoperative neurological deficit, preoperative Eastern oncology group functional status (ECOG), use of iMRI, use of iUS, use of intraoperative monitoring (IOM), time to surgery > 3 months, adjuvant treatment and WHO grade. 63 cases entered the multivariable model. 23 were excluded due to missing values in one of the variables. Statistical significance level was set asa two-sided $p<0.05$. We used SPSS 28.0. (IBM) for calculations.

# RESULTS

## Patients Characteristics

According to the above mentioned criteria 83 patients with complete data sets were selected for the further analysis. Basic demographic data are summarized in **Table 1**. The most common function at risk was motor function (44.6%, n=37) followed by speech (39.8%, n=33). The most common presenting symptoms were seizures (N=47, 56.6%). 54 patients (68.4%) had no restricts in ECOG performance status (0). ECOG status of 1 was found in 5 patients (6.7%). Astrocytomas were more common than oligodendrogliomas. (56.6%, n=47 vs. 42.7% n=35, **Table 1**). 57 of 71 patients with primary surgery (80.3%) had surgery within the first 3 months after primary diagnosis. Median time to surgery was 0 months, and maximum time to surgery was 81 months.

## Characteristics of Surgical Resection

Awake surgery was performed in 19 cases (22.9%) and recurrent surgery was done in 10 cases (11.5%). iMRI was performed in 35 patients (42.2%), while iUS was used in 22 surgeries (26.5%). Intraoperative neuromonitoring (IoM) was applied in 66 cases (79.5%).

## Surgical Complications

Surgical complications apart from new neurological deficits were noted in 14 (16.9%) patients. They are summarized in **Table 2**. Ischemic complications resulted in permanent neurological deficits in four of five cases. All patient had a visible preoperative contact of larger vessels with the tumor. Three patients had insular lesions, one patient a lesion in basal ganglia and one patient suffered from a bifrontal tumor.

## New Neurological Deficits

Considering new neurological impairment directly after surgery, 43 (51.8%) patients showed no neurological worsening, while 27 (32.5%) patients had mild new neurological deficit. The remaining 13 (15.7%) patients had a severe postoperative neurological deficit. Four of these patients suffered from ischemic lesions and one patient had a hemorrhage. Patients

**TABLE 1** | Patients´ and treatment characteristics.

| Variable | N (%) |
|---|---|
| **Female sex** | 37 (44.6) |
| **Age >60 years** | 14 (16.1) |
| **Oligodendroglioma vs. astrocytoma** | 35 (42.7) |
| **Isocitrat dehydrogenase (IDH) wildtype** | 12 (13.8) |
| **World Health Organisation (WHO) grade III** | 24 (27.6) |
| **O-6-Methylguanin-DNA-Methyltransferase (MGMT) unmethylated** | 12 (14.5) |
| **Tumor location** | |
| Frontal | 43 (51.8) |
| Parietal | 16 (19.3) |
| Temporal | 15 (18.1) |
| Occipital | 1 (1.2) |
| Other | 8 (9.6) |
| **Hemisphere** | |
| Left | 46 (55.4) |
| Right | 36 (43.4) |
| Both | 1 (1.2) |
| **Presenting symptoms** | |
| Seizure | 47 (56.6) |
| Headache | 7 (8.4) |
| Neurological deficit | 4 (4.8) |
| Incidental | 9 (10.8) |
| Others | 16 (19.3) |
| **Preoperative decreased Eastern oncology group score (ECOG) > 0** | 25 (28.7) |
| **Preoperative deficits according to National Institute of Health Stroke Score (NIHSS) >0** | 11 (12.6) |
| **Timing of surgery > 3 months *(italic only primary surgeries)*** | 22 (27.2), *14 (19.7)* |
| **Recurrent surgery** | 10 (11.5) |
| **Awake surgery** | 19 (21.8) |
| **Intraoperative monitoring or mapping (IoM)** | 66 (75.9) |
| **Intraoperative ultrasound** | 22 (25.3) |
| **Intraoperative magnetic resonance imaging (MRI)** | 35 (40.2) |
| **Type of surgery** | |
| Stereotactic biopsy | 8 (9.2) |
| Open biopsy | 3 (3.4) |
| Intended subtotal resection | 30 (34.5) |
| Intended complete tumor resection (CTR) | 42 (48.3) |
| **Complete tumor resection based on radiological criteria (CTR)** | 26 (29.9) |
| **Adjuvant treatment** | |
| None (wait and scan) | 26 (29.9) |
| Chemotherapy (CT) | 4 (4.6) |
| Radiotherapy (RT) | 10 (11.5) |
| Consecutive CT & RT | 17 (19.5) |
| Combined CT & RT | 25 (28.7) |

**TABLE 2** | Surgical complications (CSF – cerebrospinal fluid).

| Complications | N (83) |
|---|---|
| Infection | 2.4% (2) |
| CSF Leakage | 1.2% (1) |
| Meningitis | 1.2% (1) |
| Ischemic lesion | 6.0% (5) |
| Hemorrhage | 3.6% (3) |
| Others | 2.4& (2) |

with mild deficits showed an improvement in 14 (52%) patients, it remained stable in 11 (41%) patients. and decreased in 2 (7%) patients. The differences were significant in Sign test (p=0.004). In patients with severe new deficits, 7 (53.8%) patients improved all others retained severe deficits. These differences were significant as well p=0.016.

At first follow up after 3 months, permanent new postoperative neurological deficits were noted in 32 (38.6%) patients. Mild deficits remained in 24 (28.9%) patients and severe deficits in 8(9.6%). patients.

At first follow up after 3 month NIHSS was decreased in 27 patients compared to preoperative values (37.5%) representing an objective prevalence of new permanent deficits. Concerning NIHSS score, both postoperative and follow up NIHSS showed significantly lower values (p<0.001), while postoperative and follow up NIHSS showed no statistical difference (p=0.213). Comparing preoperative and 1st follow up NIHSS, an improvement was seen only in 5/71 (7%) patients, 27(56%) patients remained stable and 27 (38%) decreased after surgery.

Second follow up between 9 -12 months after surgery was available in 19 of 27 (70%) patients with neurological deterioration after surgery according to NIHSS. We found a significant difference of NIHSS from 3 months follow up to 9-12 months follow up (p<0.001). From 1st to 2nd follow up 13 of 19 (68%) patients improved in NIHSS. Twelve of those showed no deficits according to NIHSS. Patients with permanent deficits at 9-12 months (7) had motor deficits in 6 of 7 (86%) cases. Only one patient with a motor deficit showed an improvement of NIHSS. Six of seven (86%) patients with a mild aphasia (1 point in NIHSS) at 3-month follow up recovered until 9-12-month follow up.

We searched for center effects on change of NIHSS between preoperative score and follow up score using Kruskal-Wallis test and found no significant differences (p=0.966).

## Functional Outcome Based on ECOG Performance Status

Overall performance status of the patients as documented in ECOG also reflect the above mentioned findings for neurological deficits: At first follow up, ECOG decreased in 22(31%) patients compared to pre-OP. ECOG before surgery was significantly higher if compared to postoperative and follow up ECOG (p<0.001 and p=0.022 respectively). The difference between postoperative and follow up ECOG did not reach statistical difference (p=0.089). Detailed overview is depicted in **Table 3**. Increased NIHSS at follow up correlated significantly with increase ECOG (p=0.003, ρ 0.352). On the other hand, 15 of 41 (36.7%) patients with a normal NIHSS had a decreased ECOG. **Figure 1** shows a histogram comparing ECOG and NIHSS results. Follow up for ECOG between 9-12 months was available in 51 (62%) patients. We assessed all patients, not only patients with decreased ECOG after surgery since a deterioration is also possible following adjuvant treatment. From 1st to 2nd follow up 10 (21%) patients improved, 4 (9%) patients declined and 33 (70%) remained stable. There was no significant difference of 1st to 2nd follow up in ECOG (p=0.180).

## Extent of Resection

Complete tumor resection (CTR) was intended in 42 (50.6%). patients. Subtotal resection was planned in 30 (36.1%), cases, extended biopsy in 3 (3.6%) patients and stereotactic biopsy in 8 (9.6%) patients. After surgery assumed CTR by surgeon was noted in 38.6% (n=32) and radiologically confirmed in 31.3% (n=26), so that CTR was successfully in 61.9% of intended cases (N=26/42). When a CTR was intended it was achieved using iMRI in 16 of 22 (73%) patients and, using ultrasound only in one of 8 (12%) patients. iMRI showed a significant correlation with CTR (p=0.010, ρ -0.292) when assessed in all cases. iMRI was used more often when a CTR was intended (22/35, 63%). It was also used for intended STR in 11 of 35 (31%) patients and in open biopsies two of 35 (6%) patients.

After CTR patients had a significantly higher rate of decreased NIHSS at follow up (50% vs.26% p= 0.036 Chi-Square test). **Figure 2** shows a bar chart comparing prevalence of decreased NIHSS at follow up compared to preoperative scores for CTR.

## Influencing Factors on New Permanent Neurological Deficits at 3-Month Follow Up

Presence of a decreased NIHSS score at follow up compared to preoperative data correlated significantly with elevated NIHSS before surgery (p=0.031 ρ –.255), awake surgery (p=0.044,

**TABLE 3** | The Eastern Cooperative Oncology Group (ECOG) and National Institute for Stroke Scale (NIHSS) before surgery, at discharge and during follow up.

| ECOG | Before surgery (N=79) | At discharge (N=79) | 3-month follow up (N=75) | 9-12-month follow up (N=51) |
|---|---|---|---|---|
| 0 | 68.4% (54) | 40.5% (32) | 54.7% (41) | 41.0% (34) |
| 1 | 26.2% (21) | 41.8% (33) | 28.7% (29) | 16.9% (14) |
| 2 | 3.6% (3) | 15.2% (12) | 5.3% (4) | 3.6% (3) |
| 3 | 1.2% (1) | 2.5% (2) | 0 | 0 |
| 4 | 0 | 0 | 1.2% n (1) | 0 |
| 5 | 0 | 0 | 0 | 0 |
| **NIHSS** | **Before surgery (N=75)** | **At discharge (N=69)** | **3-month follow up (N=77)** | **9-12-month follow up (N=51)** |
| 0 | 85.3% (64) | 50.7% (35) | 54.5% (42) | 86.3% (0) |
| 1 | 6.7% (5) | 26.1% (18) | 24.7% (19) | 5.9% (3) |
| 2 | 6.7% (5) | 5.8% (4) | 11.7% (9) | 2.0% (1) |
| 3 | 0 | 7.2% (5) | 0 | 2.0% (1) |
| 4 | 1.3% (1) | 1.4% (1) | 3.9% (3) | 3.9% (2) |
| >4 | 0 | 8.8% (6) | 5.2% (4) | 0 |

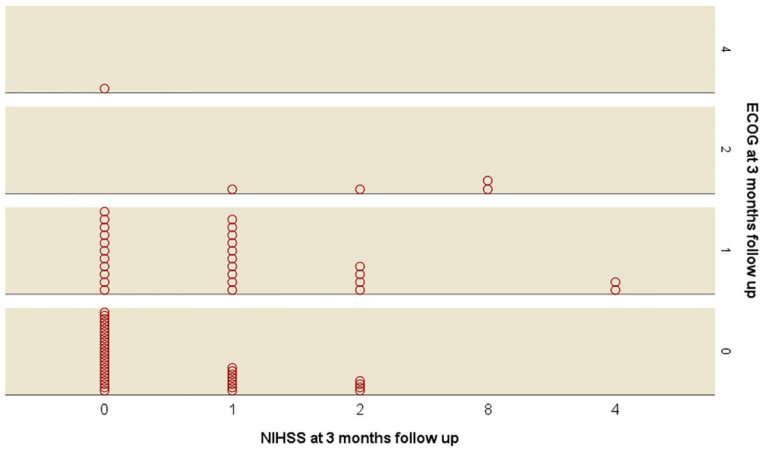


**FIGURE 1** | Histogram comparing Eastern Oncology Group (ECOG) score and National institute of health score (NIHSS).

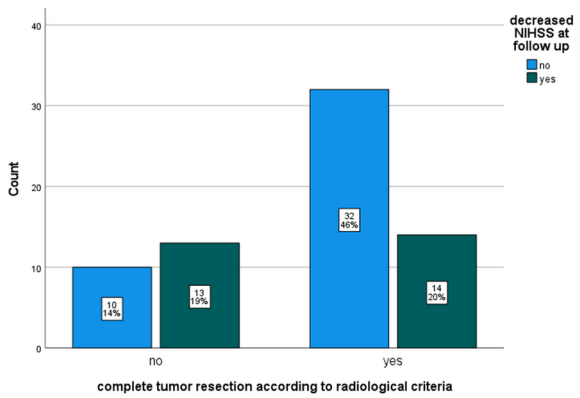


**FIGURE 2** | Bar chart comparing proportions of decreased National institute of health score (NIHSS) at 3-month follow up compared to preoperative scores by complete tumor resection (CTR) according to radiological criteria.

ρ.238), CTR based on radiological imaging (p=0.037, ρ -.252) No significant correlation was found for patient's age, WHO grade, IDH mutation, type of surgery (stereotactic biopsy (STX) as indicator), tumor location (insular as indicator), recurrent surgery, intraoperative monitoring, intraoperative ultrasound, intraoperative MRI, adjuvant treatment and sex. In patients with primary surgery (n=73) time to surgery > 3 month significantly correlated with decreased NIHSS at follow up (p=0.047, ρ -.255).

We performed a binary multivariable logistic regression for permanent neurological deficits as shown in **Table 4**. CTR (p=0.019, odds ratio (OR) 31.9) and ECOG>0 (p=0.021, OR 11.2) showed a significant influence on new permanent neurological deficits based on NIHSS. Awake surgery showed a tendency towards a significant influence (p=0.060, OR 8.5). IDH mutation, WHO grade, tumor location, IOM, iMRI, iUS, age, type of surgery, adjuvant treatment, time to surgery > 3 months and preoperatively decreased NIHSS showed no significant difference. We also calculated the binary regression model for cases with primary surgery only, because of the interaction of recurrent surgery and time to surgery. We found no relevant differences in the calculation.

## Subgroup Assessment

### Awake Surgery

Based on our finding we further assessed the subgroup of the 19 (22%) patients with awake surgery: rate of preoperative deficits was lower compared to the other patients' (5% vs. 16%), while rate of insular involvement was slightly higher (11% vs. 8%). No impairment of preoperative ECOG was found less often in awake operated patients (58% vs. 67%). Rate of intended CTR was similar to asleep operated patients (47% vs. 52%).

### Surgery > 3 Months After Primary Diagnosis

In patients who underwent surgery later than 3 months after the primary diagnosis, WHO grade II was more common (n=13, 93% vs. 38, 67%). They had slightly more often preoperative deficits in NIHSS (3, 21% vs. 7, 14%) and less often an impaired ECOG (>0) (3, 21% vs. 20, 37%). Majority (7, 54% vs. 7, 12%) of the delayed surgeries were accidental findings. Rate of epileptic seizures as presenting symptoms was lower in patients who underwent surgery after 3 months (5, 39% vs. 36, 63%). Distribution of tumor location as well as functional involvement were relatively similar (e.g. language 43% vs. 42%).

### Stereotactic Biopsy

One of eight (13%) patient after STX had a decrease of NIHSS at follow up. All others had no new neurological deficits. This is the lowest rate compared to all other surgical approaches (open biopsy 1/3, 33%; intended subtotal resection 10/29, 35%; intended complete tumor resection 15/34, 44%). Patients after STX were slightly older than after other types of surgery: 3/5 (38%) vs. 12/75 (16%) were >60 years old. The preoperative ECOG >0 was lower in these patients, too (3/8 (38%) vs. 22/75

**TABLE 4 |** Multivariable binary logistic regression for presence of new permanent neurological deficits at 3 months follow-up after surgery according to National Institute of Health Score.

| | B | S.E. | Wald | df | Sig. | Odds Ratio (OR) | 95% C.I. for odds ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| IDH mutation positive | ,381 | 1,475 | ,067 | 1 | ,796 | 1,46 | ,081 | 26,361 |
| WHO grade III | ,422 | 1,095 | ,149 | 1 | ,700 | 1,53 | ,178 | 13,045 |
| Tumor location (frontal indicator) | | | 1,979 | 4 | ,740 | | | |
| Parietal (1) | -1,678 | 1,269 | 1,749 | 1 | ,186 | ,19 | ,016 | 2,245 |
| Temporal (2) | -,419 | 1,134 | ,136 | 1 | ,712 | ,66 | ,071 | 6,075 |
| Insula (3) | -20,514 | 40192,970 | ,000 | 1 | 1,000 | ,000 | ,000 | . |
| Basal ganglia (4) | -,106 | 1,687 | ,004 | 1 | ,950 | ,90 | ,033 | 24,514 |
| Recurrent surgery | ,972 | 1,536 | ,400 | 1 | ,527 | 2,64 | ,130 | 53,612 |
| Awake surgery | 2,141 | 1,140 | 3,525 | 1 | ,060 | 8,51 | ,910 | 79,534 |
| Intraoperative monitoring | -,372 | 1,705 | ,048 | 1 | ,827 | ,69 | ,024 | 19,497 |
| Intraoperative ultrasound | 1,120 | 1,092 | 1,053 | 1 | ,305 | 3,07 | ,361 | 26,050 |
| Intraoperative MRI | ,185 | ,956 | ,037 | 1 | ,847 | 1,20 | ,185 | 7,841 |
| Complete tumor resection | 3,463 | 1,471 | 5,545 | 1 | ,019 | 31,917 | 1,787 | 569,731 |
| Age > 60 years (1) | ,760 | 1,239 | ,377 | 1 | ,539 | 2,149 | ,189 | 24,245 |
| Preoperatively impaired ECOG (>0) | 2,412 | 1,044 | 5,337 | 1 | ,021 | 11,16 | 1,442 | 86,398 |
| Preoperative deficits (NHISS >0) | -,379 | 1,689 | ,050 | 1 | ,822 | ,68 | ,025 | 18,745 |
| Type of surgery (indicator intended gross total resection) | | | ,559 | 3 | ,906 | | | |
| Stereotactic biopsy (1) | -1,107 | 3,810 | ,084 | 1 | ,771 | ,33 | ,000 | 578,326 |
| Open biopsy (2) | -1,988 | 3,060 | ,422 | 1 | ,516 | ,14 | ,000 | 55,043 |
| Intended subtotal resection (3) | -1,909 | 2,947 | ,419 | 1 | ,517 | ,15 | ,000 | 47,800 |
| Adjuvant treatment (indicator not treatment) | | | 3,114 | 4 | ,539 | | | |
| Chemotherapy (CT) (1) | 3,811 | 2,232 | 2,916 | 1 | ,088 | 45,21 | ,569 | 3590,943 |
| Radiotherapy (RT) (2) | ,665 | 1,454 | ,209 | 1 | ,647 | 1,95 | ,112 | 33,642 |
| Consecutive RT & CT (3) | ,939 | 1,200 | ,612 | 1 | ,434 | 2,56 | ,244 | 26,860 |
| Combined RT & CT (4) | ,798 | 1,379 | ,335 | 1 | ,563 | 2,22 | ,149 | 33,166 |
| Time to surgery > 3 months from primary diagnosis | -,658 | 1,094 | ,362 | 1 | ,548 | ,528 | ,061 | 4,423 |
| Constant | -1,966 | 2,392 | ,675 | 1 | ,411 | ,14 | | |

*IDH, Isocitrat dehydrogenase; WHO, World Health Organization; MRI, Magnetic resonance imaging; NHISS, National Institute of Health Stroke Score; ECOG, Eastern Oncology Group Status Score.*

(29%). The occurrence of preoperatively impaired NIHSS was similar to the other types of surgery (1/8, 12.5% vs.10/75, 13.3%).

## DISCUSSION

Lower grade gliomas remain challenging neoplasms, since they affect typically younger patients and commonly infiltrate eloquent regions (2, 4). Tumor integration in neuronal networks may often limit extend of resection (23). There might even be a potential role of glioma's molecular subtype influencing pathway disruption or displacement (24).

We have performed a detailed evaluation of eloquently located diffuse LGGs based on Log-Glio registry and focused on clinical outcome. Interestingly, despite functional intraoperative monitoring, we found relatively high number of patients with persistent new neurological deficit 3 months after surgery. Overall, almost half of the patients show new neurological deficits right after surgery. Both severe and mild neurological deficits show an improvement in half of these patients. Yet, around one third of patients permanently deteriorate both in neurological functions and in their daily life according to ECOG performance status. Predictive for permanent deficits was an impaired preoperative ECOG and a complete tumor resection in multivariable regression. Our data show that despite improved neuromonitoring and surgical techniques, risk for a permanent neurological deficit is high and improvement within the first 3 months is limited. This holds true, especially if a progressive resection aiming for a CTR is performed. The question arises; are mild neurological impairments justified if CTR is achieved? CTR has been shown to be an independent predictor for longer overall survival and even small tumor remnants could result in inferior survival (5, 16). From our perspective this question may only be answered for each individual patient. Our data may serve as a basis for patients' informed consent before surgery to discuss potential risks and include them in decision making for surgical strategy. According to actual literature, the reported permanent deficits after glioma surgery range between 2-24% including both motor and speech deficits (5, 9, 12). Our series provides prospective multicenter data including only eloquent lesions. Most cited studies were monocentric and did not use clinical scores like NIHSS for detect deficits and hence may underestimate occurrence of postoperative deficits. This suggests that, the wide range of 2-24% of deficits might be more likely in the upper level when an unselected series is assessed. We found a prevalence of 38% at 3-month follow up. However, more than two-third of the patients improved within the first year of surgery. Especially, patients with a slight aphasia showed a good prognosis. In our series of eloquent tumors rate of intended CTR was relatively high with 48%, also intraoperative imaging was used in the majority of

cases, suggesting a rather progressive approach compared to a slightly older series from the French glioma network with a CTR of only 12% including also non-eloquent lesions (25).

Surprisingly, even though only eloquent lesions were selected in our series in 20% of cases no use of IoM was reported which may bias our results. The prevalence of IoM in our series is higher than in the above cited contemporary study by Munkvold et al. (26) (76% vs. 58%). Given that only eloquent lesions were approached, from our point of view all patients should be operated using IoM. Even though, this finding is not supported by the results of the multivariable model. We hypothesize that, similar to awake surgery, with increasing risk of surgery, more likely IoM is used. Hence, protective effects may be leveled statistically.

Timing of surgery seems to play a role also in our data. There was a correlation of permanent new deficits in NIHSS and time to surgery >3month for primary surgeries. In the descriptive data no greater differences were found between patients operated early and patients watched and scanned except, that mostly accidental findings and tumors most likely being a WHO grade II lesion were watched for a longer time. This correlates with the current German management guidelines for glioma (27). Our data shows a slightly lower but relatively similar number of watch and scan than a current large Scandinavian series with 17% of patients (26). The authors have not provided the outcome data of these patients, so far. Based on the earlier findings from Jakola et al., being still the best evidence favoring an early surgical resection, one would expect lower occurrences of watch and scan (28). In our multivariate model 'delayed' surgery independently does not show a significant influence on new permanent deficits, but impaired preoperative ECOG did. From our point of view, it is important to avoid new deficits before surgery since it may mean that plasticity and redundancy of networks is already consumed by the tumor growth. Higher preoperative ECOG is a negative predictor factor for a good functional outcome, our data underlines the importance of an early resection before tumor progress results in a functional impairment.

Awake surgery is a gold standard for resection of eloquent located tumors adjacent to or in speech-eloquent cortical areas or fiber tracts (29, 30). However, awake surgery could be interpreted as a potential risk factor for permanent deficit according to our data. This result is limited by the relatively low number of awake surgeries in our series. Further, one might assume a selection bias for these patients since larger and more eloquently located tumors might more likely be operated awake. Compared to patients who had surgery asleep the proportion of preoperative deficits is relatively similar to patients operated awake, as is the rate of tumors involving the insula. On the other hand, preoperative ECOG is impaired more often in these patients reflecting the immense burden of impaired language function for patients. We interpret the potential association of awake surgery with permanent deficits not as a risk factor and we warn to draw the conclusion that asleep surgery is more protective. In direct comparison, current literature shows a superiority in extent of resection and occurrences of neurological deficits of awake to asleep surgery as reported by a current meta-analysis (21). Our data rather demonstrate the risk of operating language eloquent tumors, even when using the awake technique, which should be discussed with patients undergoing surgery in this area. Especially, patients with preoperative deficits seem to be at higher risk for permanent impairments as also found in other series (31). Our series, provides data 3 months after surgery which represents the typical reported time point for neurological deficits also after awake surgery (21, 32). Short term language deficits usually recover during this period (33). The proportion of long-term improvement of language deficits still present at 3 months was reported relatively low. In our series we found that especially slight aphasic deficits have a high probability of improvement within the first year (13, 34). Motor deficits had a more unfavorable outcome. The data of 9-12 months follow up was only available for 2/3$^{rd}$ of patients with new deficits at first follow-up and for a better comparability to previously published data we calculated the regression models with the first follow up only. The remarkable occurrence of recovery in patients with aphasia may be biased by the detection using NIHSS. A false negative rate of 9% was reported by Grönberg et al. for stroke patients (35). Especially, a subtle anomic aphasia can remain undetected in NIHSS and may relevantly impair patients' daily routines or return to work. Our results regarding ECOG also support this theory: Functional status based on ECOG showed a relatively stable course after surgery. Patients did not recover in overall function as they do on neurological deficits. Further patient reported outcome data like health related quality of life are needed to further address this issue.

In our study we did not find an influence of tumor biology as suggested by Young et al. (24). The authors showed an association of intra-tumoral function and pathway infiltration to molecular subtype of tumor. Whether it also influences surgical outcome has not been shown so far. In our series, both WHO grade and IDH mutations were also not influencing occurrence of permanent deficits. Most likely, effects are subtle and larger series will be needed to further address this question.

Intraoperative imaging like intraoperative MRI and intraoperative ultrasound were shown to increase extent of resection, and are widely used by European neurosurgeons as also in the participating centers in our study (10). Yet, in this eloquent series proportions of CTR are lower than previously published for intraoperative imaging (36–38) since resection is obviously limited by function even in cases in which a CTR was deemed feasible preoperatively. Intraoperative imaging like iMRI was applied more often in patients with an intended CTR. Yet, while CTR highly correlated with permanent deficits and also was an independent predictor for them, intraoperative imaging did not correlate with new permanent neurological deficits in our series. One of the reasons could be that in all cases iMRI was used, it was combined with IoM, for iUS is was slightly lower with 82%. Further, an intraoperative visualization of individual anatomic structures after relevant brain shift may also increase safety. However, no evidence for this hypothesis can be found in the current data.

Interestingly, recurrent surgery showed no significantly higher risk of deficits. One explanation may be the relatively low number of cases in our series. Regarding recurrent surgery, the concept of multiply staged approaches as proposed by Duffau et al. (34) may be a relevant strategy. Cortical reorganization in relation to function by neuroplasticity may increase safety in a second surgical approach. A detailed preoperative functional imaging by functional or resting state MRI, integration of connectomics and/or non-invasive cortical mapping may foster thorough preoperative evaluation in these patients and may increase safety of resection during surgery (39–42). Further studies are needed to evaluate influence of this preoperative data on surgical outcome. Another future perspective is to study patient reported outcome measures as health-related quality of life or supportive care need to better understand how fine cognitive difficulties or motor deficits influence patients' daily life or occupational situation.

### Limitations

Our assessment is based on prospective unselected data from a multicenter registry. Hence, different surgical strategies and therapeutic strategies are entered in the assessment. This unselected overview is a strength of this assessment as it reflects routine procedures and it is more likely comparable other neurosurgical centers than single center data but, it also limits the statistical assessments and the power of our subsequent analyses.

Data of our study likely reflects the current German treatment situation in neuro-oncological centers. It may not be transferable worldwide for low grade glioma surgery.

Even if our data originate from prospectively collected dataset including NIHSS and ECOG, it does not replace detailed neuropsychological tests. Especially cognitive and language function are underrepresented in NIHSS and can only indirectly be measured in ECOG score. Functioning scores like ECOG represent an external view and may not adequately reflect everyday life of affected patients. The definition of eloquent located tumors is based on respective surgeon's assessment and does not necessarily correlate with intraoperative functional borders. Hence lesions with near eloquent location and eloquent location according to Sawaya's classification are mixed in this series (43). Exact tumor location can be defined more detailed using Broca's areas and central nuclei. In the LoG-Glio prospective registry a lobular classification is used. CTR was defined by local radiologist of certified oncological centers. Yet, no central reading was performed. Further, no volumetric assessment of residual tumor was performed. The number of parameters considered in the analysis, with respect to the population size is too large to warrant a sufficient statistical power for the negative findings of this study. Hence, potential influence of surgical techniques or other clinical markers may be missed.

Postoperative and follow up rehabilitation including speech therapy and physiotherapy may relevantly improve neurological outcome. In the LoG-Glio registry no data is included whether patients attended these programs or not. However, since all patients in the participation centers have free-access to all option for neurological rehabilitation as mentioned in material and methods, most likely it was utilized by patients with deficits.

## CONCLUSIONS

Patients harboring eloquently located LGG are highly vulnerable for permanent deficits. Almost one third of patients have a permanent reduction of their functional status based on ECOG. Risk of an extended resection has to be balanced with the respective oncological benefit. Especially, patients with impaired pre-operative status are at risk for new permanent deficits. There is a relevant improvement of neurological symptoms in the first year after surgery, especially for patients with slight aphasia.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

Ethical approval was received by the ethic committee of the University of Ulm (Ethikkommission Ulm, No. 201/15). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

Conceptualization, JC, CW, AP, GN, DR. Methodology, JC, AP. Formal analysis, JC. Investigation, JC, JO, MU, CR, KK, MN, M-TF, RG, ML. Resources, CW, VR, MC, OG, PV, MT, DR. Data curation, JC. Writing—original draft preparation, AP, JC. Writing—review and editing, all contributing authors. All authors have read and agreed to the published version of the manuscript.

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# Early Surgery Prolongs Professional Activity in IDH Mutant Low-Grade Glioma Patients: A Policy Change Analysis

*Pierre A. Robe[1]*, Matea Rados[1], Wim G. Spliet[3], Reinier G. Hoff[4], Peter Gosselaar[1], Marike L. D. Broekman[1], Martine J. van Zandvoort[1,2], Tatjana Seute[1†] and Tom J. Snijders[1†]*

*[1] University Medical Center (UMC) Utrecht Brain Center, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht, Netherlands, [2] Departement of Clinical Neuropsychology, University of Utrecht, Utrecht, Netherlands, [3] Department of Pathology, University Medical Center Utrecht, Utrecht, Netherlands, [4] Department of Anesthesiology, University Medical Center Utrecht, Utrecht, Netherlands*

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***Correspondence:**
*Pierre A. Robe*
*p.robe@umcutrecht.nl*

*†These authors have contributed equally to this work*

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**Background:** Until 2015, Dutch guidelines recommended follow-up and biopsy rather than surgery as initial care for suspected low-grade gliomas (LGG). Given evidence that surgery could extend patient survival, our center stopped following this guideline on January 1, 2010 and opted for early maximal safe resection of LGG. The effects of early surgery on the ability of patients to work remains little documented.

**Methods:** A total of 104 patients operated on at our center between January 2000 and April 2013 and diagnosed with the WHO 2016 grade 2 astrocytoma, IDH mutant or oligodendroglioma, IDH mutant and deleted 1p19q were included. The clinical characteristics, survival, and work history of patients operated on before or after January 2010 were obtained from the patients' records and compared. The minimal follow-up was 8 years.

**Results:** As per policy change, the interval between radiological diagnosis and first surgery decreased significantly after 2010. Likewise, before 2010, 25.8% of tumors were initially biopsied, 51.6% were resected under anesthesia, and 22.5% under awake conditions versus 14.3%, 23.8%, and 61.9% after this date ($p < 0.001$). The severity of permanent postoperative neurological deficits decreased after 2010. In total, 82.5% of the patients returned to work postoperatively before 2010 versus 100% after 2010. The postoperative control of epilepsy increased significantly after 2010 (74.4% vs. 47.9%). The median time from diagnosis to a definitive incapacity to work increased by more than 2 years after 2010 (88.7 vs. 62.2 months).

**Conclusion:** A policy shift towards early aggressive surgical treatment of IDH mutant LGG is safe and prolongs the patients' ability to work.

**Keywords: low-grade glioma, early resection, professional activity, awake craniotomy, return to work**

## INTRODUCTION

WHO grade 2 low-grade gliomas (LGG) often affect professionally active young adults (1). They grow slowly and seldom provoke debilitating symptoms initially. However, as these tumors progress, they induce significant disabilities and death, with a median survival of 139 months for oligodendrogliomas and 67 months for astrocytomas (2–4).

The adjuvant treatment, follow-up, and prognosis of gliomas depend on their histological type and molecular characteristics. Despite progress in metabolic imaging, radiologic techniques can neither reliably differentiate low- from high-grade gliomas nor determine their complete molecular profiles (5–7). Historically, stereotactic biopsies were reported to yield inappropriate or inconclusive histological results in up to 38% of cases, due to tumor heterogeneity, and still carry a significant risk of transient morbidity (2%–9.6%) and permanent morbidity and mortality (0.4%–0.9%) (8–11). While major genetic (IDH1/2 mutations, 1p19q codeletions) and epigenetic [e.g., MGMT promoter methylation (12)] changes seem more homogenously distributed in tumors than histologic alterations, it remains unclear whether this is the case for more specific but important changes like CDKN2A/B homozygous deletions or EGFR amplification (13) and how often sampling errors can occur with (serial) biopsies. Upfront debulking surgery does not only allow for a broader tumor sampling but also results in cytoreduction, which has been arguably associated with a survival advantage as compared with upfront biopsy (14–18). As a result, debulking is increasingly recommended rather than stereotactic biopsy in guidelines for the upfront diagnostic and decision making in these tumors (19, 20).

Despite these recommendations, the extent of the surgical management of suspected LGG remains a matter of active debate (21–23). Despite advances in intraoperative mapping techniques that have considerably reduced morbidity of resections (18, 24–26), their long-term morbidity has been little studied. Patients indeed generally show a decline in cognitive function and quality of life following surgery for gliomas (27, 28). As a result, early/larger resections could prematurely alter patients' neurologic/cognitive function and quality of life in the period prior to disease progression, as compared with biopsies.

Until April 2015, The Dutch guidelines recommended the follow-up of suspected LGGs without alarming symptoms and to simply biopsy patients with neurologic symptoms other than seizures or atypical radiologic findings (e.g., contrast enhancement). Debulking surgery was advised only in patients with radiologic progression, mass effect, or intractable seizures (16, 29–32).

Based on the abovementioned potential survival and sampling quality arguments, our center opted on January 1, 2010 to deviate from the then implemented Dutch national guidelines and to rather advocate the early maximal safe resection of suspected LGG, as recommended by the North American NCCN guideline (19). Accordingly, operable patients were proposed a maximal safe resection within 3–6 months of their first consultation at our center, even in the case of asymptomatic or seemingly stable disease. Biopsies were reserved to cases unamenable to a debulking due to a deep-seated location or patient refusal of more extensive surgery. This complete and timely defined change of policy allows to compare the short- and long-term benefits or drawbacks of primarily following-up and biopsying versus primarily being surgically more aggressive in molecularly defined low-grade gliomas.

We report here—with a minimal follow-up of 8 years for all patients—the effects of our change of policy on patient survival, return to work, and duration of professional activity following diagnosis.

## METHODS

### Study Population

This study was approved by the medical ethical committee of the University Medical Center of Utrecht (as part of protocol # 16-342). The need for informed consent was waived by the ethics committee of the UMC Utrecht for this retrospective analysis of data and material collected as part of routine clinical care. Using our institutional pathology database, we retrospectively identified all adult patients (≥18 years, $n$ = 205) operated on at our center for a supratentorial LGG between January 1, 2000 and April 30, 2013. We revised the pathological slides, charts, and preoperative imaging and attempted to classify the tumors molecularly according to the recent WHO classifications of tumors. To this end, the available slides and pathology reports (histology and molecular biology) were thoroughly reviewed, and for older tumors lacking molecular testing, we could obtain formalin-fixed, paraffin-embedded (FFPE) cores from 101 tumors from our institution's pathology department. These were processed in tissue microarrays and stained for IDH1-R132C, ATRX, H3K27M, and H3K27me3 according to Filipski et al. (33). Twelve additional FFPE samples were further processed for next-generation sequencing (NGS) and copy number variation (CNV) analysis by our pathology department laboratory, using their standard operating procedures, and yielding conclusive results in 10 cases. As this item was not a standard at the time of this study design and revision of the pathology slides, the CDK2N/B status of most tumors was not ascertained, and for this reason, tumors were classified according to the WHO 2016 and not the WHO 2021 taxonomy.

A total of 101 tumors were excluded after these steps: 14 patients who had been operated on prior to 2000, 21 patients who had actually been diagnosed prior to 2000, 25 with radiological gliomatosis cerebri as defined on MRI (i.e., extending diffusely to 3 or more lobes), one DNET, 6 glioblastoma, IDH wild type, one PMXA grade 2, one grade 1 diffuse glioma NEC, one H3K27mutant (high grade) diffuse pediatric glioma, and 21 A2 NOS, OA2 NOS, and O2 NOS tumors.

An additional 10 patients who were known at our center prior to July 2009 but were merely followed up and only operated on after 2010 were also excluded from the main analyses in order to avoid cross-over bias between our cohorts of patients.

Surgical procedures were defined as biopsy, tumor resection, and tumor resection under awake conditions. Two patients who underwent resection within 3 months after biopsy were included in the "resection" and "awake resection" groups, respectively.

## Outcomes

Surgical morbidity was defined as any adverse event that occurred within 30 days of surgery and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (24).

Tumor volumes were segmented measured from the pre- and postoperative MRI images using the Brainlab Origin planning server software. Volumetric diagnostic and preoperative MRI were available in 88/104 and 97/104 patients, respectively. Tumor volumes were considered unchanged following biopsies, and postoperative MRI volumes were assessed on imaging performed within 3 months of the surgery. Tumors were classified topographically according to Sawaya for their eloquence (34).

Survival data were obtained from the patient charts and verified on May 21, 2021 providing a follow-up of at least 8 years for the entire patient population. Overall survival (OS) was measured as the time between the first diagnostic imaging showing the tumor and death or censoring. Survival data were censored at last follow-up for patients still alive at that moment. Two patients were lost to follow-up at some time after their surgery and were censored at that time.

The work history—a standard part of the follow-up of patients at our center—was retrieved from the medical and social documents of the patients' charts. The time to loss of productivity was measured from the date of the first imaging diagnosis until the date when the patient had completely stopped to work or died. Patients who retired for nonmedical reasons while still active were censored on their date of retirement.

## Adaptation of the Surgical Policy

Our center switched acutely on January 1, 2010 from the Dutch national guidelines that then recommended the follow-up of suspected LGG until growth or progression and biopsy rather than surgery for diagnostic confirmation (13) towards the early and maximal safe resection of these lesions. As a result, patients were primarily proposed resection within 3–6 months of their first consultation even in the case of asymptomatic or stable diseases. The indication for surgical resection was set by the treating neurosurgeon in all patients with suspected LGG, unless the surgeon expected that no meaningful extent of resection could be obtained and/or patient refused resection. This change of policy allowed us to define two cohorts of patients: group 1 (operated on prior to January 1, 2010) and group 2 (after this date). Ten patients who were known at our center prior to July 2009 but were merely followed up and only operated on after 2010 were excluded from the main analyses, in order to avoid cross-over bias (**Figure 1**).

The surgical procedures are described in detail in the **Supplementary Methods**.

## Analyses and Statistics

Categorical data were analyzed using Pearson's Chi-square ($\chi^2$) test or Fisher's exact test based on sample size. Nonparametric continuous data were analyzed using Mann–Whitney *U* tests. Parametric continuous data were analyzed using an independent-sample *t*-test.

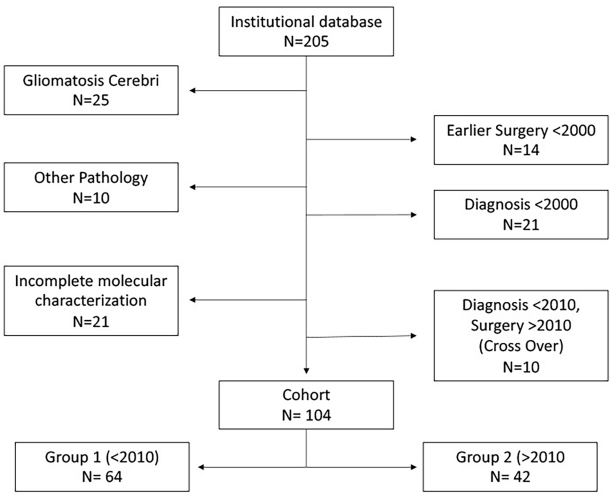


**FIGURE 1** | Flow chart of the patient selection for groups 1 (before 2010) and 2 (after 2010).

Differences in survival and the time to definitive stop of work (for the patients that were professionally active at the time of diagnosis) between groups were first quantified in a univariable analysis with the log-rank test. Multivariable analyses were performed using Cox's proportional hazards regressions.

Analyses were performed using $SPSS_{v25}$ (IBM, Chicago, IL, USA) and $Prism_{v9}$ (GraphPad, San Diego, CA, USA) with two-sided statistical significance defined at $p < 0.05$.

# RESULTS

## Study Population

The study population included 104 adult patients with a histologically confirmed supratentorial WHO grade 2 astrocytoma (IDH1/2 mutant, ATRX mutant, $n = 70$) or oligodendroglioma (IDH1/2 mutant, 1p19q codeleted, $n = 34$). Clinical and demographic characteristics are summarized in **Table 1**.

A biopsy was performed in 22 patients (21.2%), while 82 (88.8%) patients underwent primary resection. An awake resection was performed in 40 of these patients (48.8%).

Prior to imaging diagnosis, 90/104 (86.5%) of patients had been professionally active, 8 had retired at that time, 1 had stopped for unrelated medical reasons, and 2 had never been professionally active (missing data: $n = 3\%$ or 2.9%). These proportions were similar in both groups ($p = 0.23$, $\chi^2$ test). A description of the jobs performed by the patients is provided in **Supplementary Table S1**.

## Change of Policy

There was no significant difference in the age at diagnosis, symptoms at presentation, epilepsy at presentation, histology, location or eloquence [according to Sawaya (34)] and volume at

diagnosis of the tumors, or the frequency of direct adjuvant chemotherapy or radiotherapy between patients from group 1 (prior to 2010, $n = 62$) and group 2 (after 2010, $n = 42$). The KPS at time of diagnosis was also similar in both groups (range: 60–100, $p = 0.350$, $\chi^2$ test, **Tables 1**, **2**).

Eighty-eight percent of the patients were operated on within 6 months of their first diagnostic imaging after 2010 versus only 61.3% prior to this date ($p = 0.0028$, $\chi^2$ test) and the median follow-up time prior to surgery decreased from 140 to 76 days after 2010 (log rank: $p = 0.001$; **Supplementary Figure S1**). In the period between the diagnostic imaging and the first surgery, the tumor volumes increased by a mean of 32.6% (SD: 77.7%; range: 0%–395%) prior to 2010 versus only 9.8% (SD: 42.4%; range: 0%–279%) after this date ($p = 0.012$, Mann–Whitney $U$ test). The KPS of the patients at the time of their first surgery had not worsened significantly in any of the groups as compared with their KPS at time of diagnosis ($p = 0.857$ and >0.9999, respectively, Wilcoxon test).

Before January 1, 2010, 25.8% of patients primarily underwent biopsy versus only 14.3% after this date, while the proportion of awake craniotomies increased from 22.6% before 2010 to 61.9% later ($p < 0.001$, $\chi^2$ test). The extent of resection prior and after 2010 for the debulking operations did not differ significantly (79.6% vs. 74.3%, $p = 0.262$, $t$-test), and the residual postoperative tumor volumes after debulking operations likewise did not differ between both groups (14.3 ± 15.1 $cm^3$ vs 14.6 ± 16.2 $cm^3$, $p = 0.945$, $t$-test).

## Surgical Morbidity

There was no difference in the general surgical morbidity between patients from groups 1 and 2 (**Table 3**). There were one postoperative hemorrhage and one postoperative arrhythmia in group 2, and two postoperative surgical infections in group 1. No patient developed pulmonary embolism or deep venous thrombosis within 3 months from surgery, and there was no mortality in this time period.

**TABLE 1** | Clinical and demographic characteristics of the patients at the time of radiological diagnosis.

| | Total | Group 1 (January 1, 2000–December 31, 2009) | Group 2 (>January 1, 2010) | *p*-value |
|---|---|---|---|---|
| **Patients [*n* (%)]** | 104 | 62 (59.6%) | 42 (40.4%) | |
| **Gender (M/F)** | 64/40 | 35/27 | 29/13 | 0.195 ($\chi^2$) |
| **Age at diagnosis [mean (range)]** | 42 (21–72) | 43 (23–72) | 40 (21–69) | 0.282 (*t*-test) |
| **KPS at time of diagnosis (range)** | 90 (60–100) | 90 (60–100) | 90 (60–100) | 0.350 ($\chi^2$) |
| **Presentation** | | | | |
| **Epileptic seizures** | 86.5% | 88.7% | 83.3% | 0.431 ($\chi^2$) |
| **Incidental finding** | 6.7% | 6.5% | 7.1% | 0.890 ($\chi^2$) |
| **Location** | | | | |
| **Left hemisphere** | 50 (48.1%) | 26 (41.9%) | 24 (57.1%) | |
| **Both hemispheres** | 8 (7.7%) | 5 (8.1%) | 3 (7.1%) | 0.303 ($\chi^2$) |
| **Right hemisphere** | 46 (44.2%) | 31 (50%) | 15 (35.7%) | |
| **Eloquence (Sawaya)** | | | | |
| **Class I (noneloquent)** | 19 (18.3%) | 14 (22.6%) | 5 (11.9%) | |
| **Class II (near eloquent)** | 37 (35.6%) | 21 (33.9%) | 16 (38.1%) | 0.384 ($\chi^2$) |
| **Class III (eloquent)** | 48 (46.1%) | 27 (43.5%) | 21 (50%) | |
| **Volume (in $cm^3$, mean and range)** | 56.9 (3.5–244.5) | 50.8 (3.5–244.5) | 63.5 (7.4–185.6) | 0.221 (*t*-test) |
| **Pathology** | | | | |
| **Astrocytoma, IDH mutant** | 70 (67.3%) | 43 (69.4%) | 27 (64.3%) | 0.589 ($\chi^2$) |
| **Oligodendroglioma, IDH mutant and 1p19q codeleted** | 34 (32.7%) | 19 (30.6%) | 15 (35.7%) | |
| **Worked at time of diagnosis** | | | | |
| **Yes** | | 51 (82.3%) | 39 (92.8%) | |
| **No** | | 9 (14.5%) | 2 (4.8%) | 0.267 ($\chi^2$) |
| **Unknown** | | 2 (3.2%) | 1 (2.4%) | |

**TABLE 2** | Initial treatment in the entire cohort of patients and in both groups 1 and 2.

| | Total | <January 1, 2010 | >January 1, 2010 | *p*-value |
|---|---|---|---|---|
| **First surgical procedure** | | | | |
| **Awake resection** | 40 (38.5%) | 14 (22.6%) | 26 (61.9%) | |
| **Asleep resection** | 42 (40.4%) | 32 (51.6%) | 10 (23.8%) | <0.001 ($\chi^2$) |
| **Biopsy** | 22 (21.1%) | 16 (25.8%) | 6 (14.3%) | |
| **Direct adjuvant therapy** | | | | |
| **None** | 79 (76%) | 49 (79%) | 30 (71.4%) | |
| **Radiotherapy** | 20 (19.2%) | 11 (17.7%) | 9 (21.4%) | 0.496 ($\chi^2$) |
| **Chemotherapy** | 4 (3.8%) | 1 (1.7%) | 3 (7.1%) | |
| **Combined** | 1 (0.9%) | 1 (1.7%) | 0 (0%) | |

**TABLE 3 |** Postoperative morbidity of the patients operated before and after January 1, 2010.

| | Before 2010 | After 2010 | *p*-value |
|---|---|---|---|
| **No complication** | **44 (71%)** | **30 (71.4%)** | 0.959 ($\chi^2$ test) |
| **General complications** | | | |
| **Bleeding** | 0 | 1 | |
| **Cardiac arrhythmia** | 0 | 1 | 0.135 ($\chi^2$ test) |
| **Wound infection** | 2 | 0 | |
| **Temporary neurological deficits** | | | |
| **Dysphasia** | 7 | 3 | 0.515 (Fisher's test) |
| **Motor** | 1 | 2 | |
| **Permanent neurological deficits** | | | |
| **Dysphasia** | 7 | 1 | |
| **Motor** | 1 | 1 | **0.0275** ($\chi^2$ test) |
| **Visual field defect** | 0 | 3 | |

*Neurological deficits were considered permanent when still present 3 months after the surgery.*

The incidence of transient and permanent neurological deficits did likewise not differ significantly [permanent deficits: 8 (12.9%) in group 1 and 5 (11.9%) in group 2 (NS, $\chi^2$ test)]. However, the nature and severity of the permanent neurological deficits were significantly different before and after 2010. They consisted of dysphasia (11.3% vs 2.9%), paresis (1.6% vs 2.4%), and visual field defects (0% vs. 7.1%; $p = 0.0275$, $\chi^2$ test for the whole). The $CTCAE_{v3.0}$ grade of these deficits was significantly milder after 2010 ($p = 0.046$, $\chi^2$ test, **Table 4**). The visual field defects in particular were of grade 1 (asymptomatic) in two patients and 2 (symptomatic, not interfering with activities of daily living) in one.

## Survival

The median overall survival estimate from the time of diagnosis was 152.6 months (95% CI [123.8–181.5]) for the entire cohort and differed significantly between IDH mutant astrocytomas and oligodendrogliomas, IDH mutant and 1p19q deleted (respectively 115.2 and 176.1 months, $p = 0.002$, log-rank test). It was significantly different between patients who had been merely biopsied and those who underwent a craniotomy (under general anesthesia or awake), with respective survival medians of 123.9 and 159.8 months ($p = 0.047$, log-rank test). In Cox multivariable analysis, the histology, tumor volume at diagnostic, and the type of surgery (biopsy vs. debulking) significantly influenced the overall survival in our cohort, in contrast to the age and KPS at the time of diagnostic (**Supplementary Table S2**).

With respect to our change of policy, the overall survival (as measured from the time of diagnosis) of patients diagnosed before or after 2010 was similar ($p = 0.808$, log-rank test, **Figure 2**).

## Return to Work, Duration of Ability to Work, and Epilepsy Outcome

Of the 51 group 1 patients who had been professionally active prior to their diagnostic, 10 (19.6%) quit working following their diagnostic but prior to their first surgery versus only 1 out of 39 in group 2 (2.56%, $p = 0.014$, $\chi^2$ test). After their first surgery, of those patients who still worked, 33/41 (80.48%) returned to work after their operation in group 1 while 100% returned to work after their surgery in group 2. This difference in the rate of return to work was significant ($p = 0.004$, $\chi^2$ test). As mentioned, the employment status of two patients of group 1 and one patient of group 2 prior to their diagnosis was missing. We thus performed a sensitivity analysis with all missing values of group 1 being reallocated as patients who would have worked preoperatively and returned to work postoperatively and the missing values of group 2 as not having returned to work. Even in this exaggerated scenario, the difference between both groups remained significant with respect to the rate of return to work (81.4% vs. 97.4%, $p = 0.0203$, $\chi^2$ test).

Of the patients who were active at the time of diagnosis, and counting from that moment on, those of group 1 permanently lost their ability to work significantly sooner than those of group 2, with a median time to permanent work disability of 62.2 months for group 1 and 88.7 months for group 2 ($p = 0.030$, log-rank test, **Figure 3**). This difference remained significant in a multivariable Cox model taking the gender, age, KPS, history of seizures, and tumor volume at diagnosis, as well as the type of surgery, histology, and postoperative treatment into account ($p = 0.027$, HR = 0.451, 95% CI [0.223–0.911], **Table 5**).

**TABLE 4 |** Severity of the postoperative neurological deficits according to the Common Terminology Criteria of Adverse Events (CTCAE v3.0).

| CTCAE v3.0 | Before 2010 (group 1) | | | After 2010 (group 2) | | |
|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 1 | Grade 2 | Grade 3 |
| **Permanent dysphasia** | | 3 | 4 | | 1 | |
| **Permanent motor** | | 1 | | | 1 | |
| **Visual field defect** | | | | 2 | 1 | |

*The numbers represent the number of patients suffering each given type of deficit.*

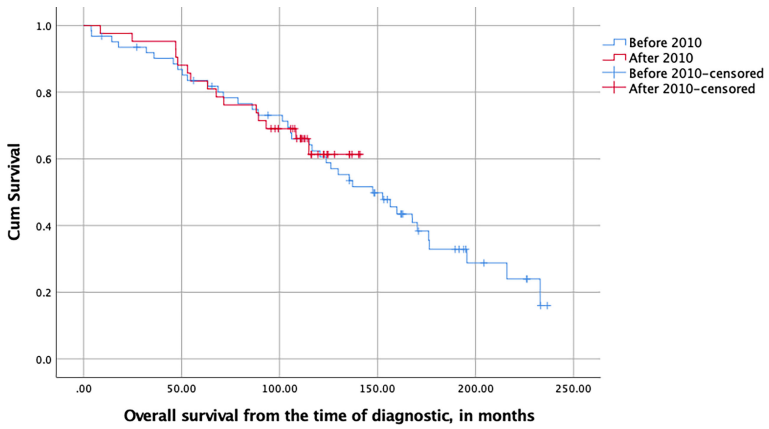


**FIGURE 2** | Kaplan–Meier plot of the overall survival of LGG patients stratified with respect to their date of surgery and measured in months from the time of first diagnostic imaging (NS, log-rank test).

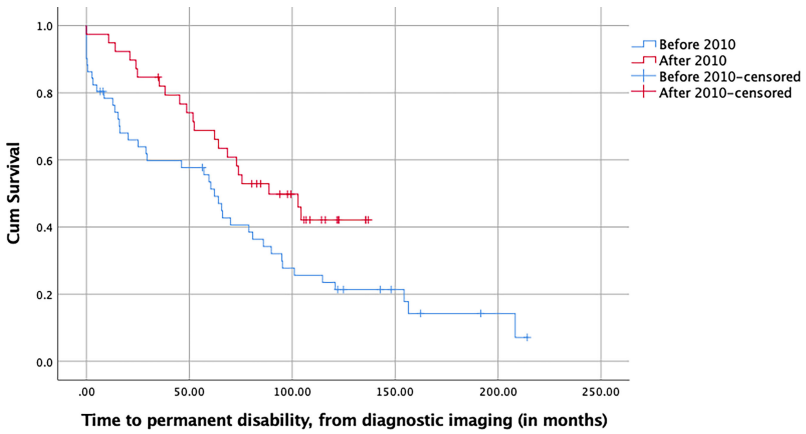


**FIGURE 3** | Kaplan–Meier plot of the time to permanent work disability of LGG patients stratified with respect to their date of surgery and measured in months from the time of first diagnostic imaging ($p = 0.030$, log-rank test).

Of note, at the time of censoring for work disability, 25/48 patients in group 1 (52.1%, unknown status for 3 patients) suffered from clinically active epilepsy (i.e., other than Engel class I) versus 10/39 in group 2 (25.6%, $p = 0.012$, $\chi^2$ test). This difference remained significant when—as a sensibility analysis—the 3 patients with unknown status in group 1 were all assumed to be free from epilepsy ($p = 0.0301$, $\chi^2$ test).

## DISCUSSION

A growing body of literature suggests a survival advantage of the early and aggressive surgical treatment of LGGs, including Evidence-Based Medicine level 2 data (14, 35). LGGs however tend to develop in young, professionally active adults. The question remains whether the aggressive surgery, while increasing survival, could result in additional morbidity and in an earlier loss of economic productivity in those young patients.

Our well-defined, thorough, and dated change of policy between a conservative treatment protocol (based on a follow-up and advocating biopsies rather than debulking) towards an early maximal safe resection of LGGs allowed us to retrospectively answer this question. Several potential biases were avoided. First, in order to avoid cross-contamination of our two cohorts (cross-over bias), we included only those patients diagnosed between specific periods of time corresponding to the two policies. Patients diagnosed during the first period ("conservative" treatment) but operated on during the second ("aggressive" treatment) period, were thus discarded from the analyses. Second, the change of policy was not associated with any shift in the demographics (at the time of diagnostic of the disease) of patients, in the allocation to adjuvant therapies, or in the nature of these adjuvant therapies.

**TABLE 5 |** Multivariable (Cox) analysis of the time to the permanent loss of ability of patients to work (measured form the time of diagnostic imaging).

| Variables in the equation | Sig. | HR | 95% CI for Exp(B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| **Pre-post-2010** | **0.027** | 0.451 | 0.223 | 0.911 |
| **Gender (male vs. female)** | 0.262 | 0.678 | 0.344 | 1.337 |
| **Age at diagnostic imaging** | 0.474 | 1.013 | 0.977 | 1.051 |
| **Epileptic seizures at diagnostic (no vs. yes)** | 0.067 | 2.322 | 0.941 | 5.727 |
| **KPS at diagnostic** | **0.038** | 0.958 | 0.921 | 0.998 |
| **Volume (in $cm^3$) at diagnostic** | **0.006** | 1.01 | 1.003 | 1.016 |
| **Pathology (astrocytoma vs. oligodendroglioma)** | 0.063 | 2.083 | 0.96 | 4.521 |
| **Early postop treatment: XRT** | 0.989 | | | |
| **Early postop treatment: none** | 0.951 | 1.031 | 0.392 | 2.71 |
| **Early postop treatment: PCV** | 0.596 | 0.536 | 0.053 | 5.375 |
| **Early postop treatment: Stupp** | 0.965 | 0.95 | 0.099 | 9.158 |
| **Early postop treatment: TMZ** | 0.833 | 0.834 | 0.154 | 4.527 |
| **Type of surgery: debulking** | 0.036 | | | |
| **Type of surgery: biopsy** | 0.244 | 1.534 | 0.747 | 3.15 |
| **Type of surgery: awake craniotomy** | **0.01** | 4.008 | 1.396 | 11.507 |

*Significant values are highlighted in bold.*

Third, our population of patients consists purely of fully characterized IDH mutant grade 2 gliomas according to the WHO 2016 classification of tumors (oligodendroglioma, IDH mutant and 1p19q codeleted or astrocytomas, IDH mutant), thus avoiding contamination bias by IDH wild-type or other types of grade 2 gliomas. This *post-hoc* selection of patients based on molecular profile differs from previous studies on surgical strategy for "presumed LGGs" (radiological diagnoses), in which beneficial results of aggressive surgery were driven—in part—by (molecularly) higher-grade tumors; this study, rather, is limited to true IDH-mutated LGGs.

Altogether, this observational study effectively constitutes a "split-wedge" design, in which the results reflect the effects of a more aggressive surgical approach on the professional functioning of LGG patients with minimal bias.

The switch of policy was effective, as demonstrated by the significantly reduced delay between diagnosis and surgery on the one hand and the 1.8-fold reduced percentage of biopsies since January 1, 2010, with a 2.75-fold increase in awake debulking. Interestingly however, only 25.8% of the patients underwent a biopsy prior to 2010. This can be inherent to the delay between diagnosis and first surgery in this group. Indeed, patients suffered significant increases in tumor volumes between the diagnosis and surgery in this group, with potentially more mass effect, a criterion for debulking in the then valid treatment guidelines.

The switch towards a policy of early maximal safe resection of LGG has thus consisted of the earlier operation of patients, more debulking in place of biopsies and more awake craniotomies. It did not result in more radical resections, as both the extent of resection and residual volumes postdebulking (excluding the biopsies) remained similar after 2010. This change of policy did not at all alter the overall survival of our patients, as measured from the time of imaging diagnosis. This can be due to the relatively low proportion of biopsies in our first cohort (14), as well as the similar residual tumor volumes postdebulking in both cohorts (35). It could also in part be due maybe to the absence of "hidden malignant tumors" in our molecularly defined cohorts of patients, as compared maybe with these previous reports on the effect of radical resection, but in agreement with other recent observations (36). Altogether, the observed survival of our patients in both cohorts was in line with the literature (37).

Survival with preserved quality of life is of utmost importance in LGG patients (21). The abundant use of awake craniotomies since January 2010 helped us reduce the severity of *de novo* permanent neurological postoperative morbidity. Altogether, the severity of permanent neurological complications decreased after 2010 and, at a maximal severity level of 2, never limited the activities of patients. These results agree with published data on the safety of tumor resections performed under neuromonitoring (24) and further support the value of maximal safe surgical strategies against LGG.

Patients treated since 2010 were also significantly more likely to return to work postoperatively than those diagnosed before, with respectively 100% and 80.48% of patients returning to their professional lives postoperatively. These results are in line with the literature. In a recent series of 25 patients with glioma operated on under awake conditions and neuromonitoring, Mandonnet et al. indeed found that 80% of patients could return to work postoperatively (38), while in a prospective, more recent prospective cohort of 74 patients, Ng and collaborators described a rate of 97.1% of return to work following surgery for low-grade gliomas (39). In addition, a significant number of group 1 patients quit working in the period between their diagnosis and their surgery versus only one in group 2 (19.6% vs. 2.6%).

In the course of their disease, patients of group 2 also remained professionally active significantly longer than patients of group 1, with a hazard ratio of 0.429, i.e., a risk to losing one's job divided by more than two, translating in an increase of more than 2 years of their median active survival. This increase in professionally active survival remained significantly different between both groups when controlling for other relevant parameters like gender, age, KPS, epilepsy at presentation, pathology, and early postoperative treatment. Another factor that could have played a role in the risk of becoming permanently disabled would be a

time-dependent change in social rules, criteria, or legislation regarding the health-related fitness to work. Major changes in this respect did however not happen in the Netherlands during the period studied, as confirmed by the statistics of the National Office of Statistics, which do not report any significant increase in disease-related leaves of absence between 2008 and 2014 (40). A potential explanation for the longer ability to work for patients of group 2 could be that more aggressive surgeries reduced the physical or cognitive burden of their brain tumors. Indeed, at the time patients definitively stopped working (or were censored if still active at the last follow-up), group 2 patients were significantly more often completely seizure-free (Engel class I) than those operated on prior to this date (74.4% vs. 47.9%). Patients with a biopsy were also significantly more likely to present symptomatic seizures at this time than those who underwent a debulking ($p$ = 0.001, $\chi$ (2) test). These finding agrees with previous literature that showed a correlation between surgical aggressiveness and epilepsy control in low-grade gliomas (41), as well as with the inverse correlation between the duration of seizure history and postoperative seizure control (42).

The limitations of our study stem from the retrospective nature of our data collection. As a result, 25 A2 NOS, OA2 NOS, and O2 NOS histological grade 2 tumors were excluded from our analyses. Of these, 16 worked at the time of diagnosis. A sensitivity analysis of the professionally active survival of all patients, including those 16 patients, however confirms the very significant improvement that occurred after our policy change (median 88.7 months after 2010 vs. 59.7 months before, $p$ = 0.006, log rank). In spite of the retrospective data collection, employment data were missing in only 2.9% of the patients, i.e., 2 patients in group 1 and 1 in group 2. This is unlikely to have altered our findings, as shown by our sensitivity analysis for the rate of return to work: even if those patients had all returned to work prior to 2010 and had become disabled when operated on after this date, the rate of postsurgical return to work still significantly increased after 2010. Another limitation is that allocation protocols to adjuvant treatments and tumor classifications have evolved significantly in the recent years. Our cohorts however precede the introduction of molecular data in the pathological armamentarium (our last patients were operated in April 2013), and the allocation of patients to adjuvant treatments, based on the then valid classification, has little changed between 2000 and 2013. To tackle this issue completely however, we extensively reviewed all tumors according to the WHO 2016 guidelines, selected out only fully characterized tumors for our analyses, and performed sensitivity analysis that incorporated the not otherwise specified—NOS—tumors. In addition, there was no difference between the distribution of postoperative adjuvant treatments between our two cohorts of patients.

Our study also has important strengths. First, it avoids selection bias by comparing two groups of patients defined by the thorough and dated introduction of a new surgical policy. Second, cross-over bias was also eliminated by this design and by discarding all the patients whose diagnostic and treatment did not both take place in the same defined period. Such a comparison of treatment strategies—rather than comparing groups according to treatment performed—reflects well the potential benefit of transitioning from delayed to early surgery in the clinical practice. Third, the long follow-up (minimum 8 years) of patients allows to draw matured conclusions pertinent to this slowly evolving disease.

In conclusion, a combination of early treatment and maximal use of awake craniotomies results in less serious postoperative deficits and lower epileptic burden in grade 2 astrocytomas, IDH mutant and oligodendrogliomas, IDH mutant and 1p19q codeleted as compared with a delayed, more conservative treatment strategy. As a corollary, patient remained able to work for a median of 2 years longer after their diagnosis following our change from a delayed conservative to an early "maximal safe" surgical strategy.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

This study was approved by the medical ethical committee of the University Medical center of Utrecht (as part of protocol # 16-342). The need for informed consent was waived by the Ethics Committee of the UMC Utrecht for this retrospective analysis of data and material collected as part of routine clinical care.

## AUTHOR CONTRIBUTIONS

PR: conception, data accrual, analysis, writing, and funding. MR: data accrual and analysis. WS: data accrual and pathology review. RH: data accrual. PG: data accrual and review of the manuscript. MB: data accrual and review of the manuscript. Martine van Zandvoort: data accrual and review of the manuscript. TaS: data accrual, review of the manuscript, and funding. TJS: conception, data accrual, analysis, and review of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.851803/full#supplementary-material

**Supplementary Table 1** | Methods - Surgical procedure.

**Supplementary Figure 1** | Kaplan-Meier plot of the duration of patient follow-up form the diagnosis until the first surgery.

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# Diagnostic Yield and Complication Rate of Stereotactic Biopsies in Precision Medicine of Gliomas

*Sophie Katzendobler[1], Anna Do[1], Jonathan Weller[1], Mario M. Dorostkar[2], Nathalie L. Albert[3,4], Robert Forbrig[5], Maximilian Niyazi[4,6], Rupert Egensperger[2], Niklas Thon[1], Joerg Christian Tonn[1,4] and Stefanie Quach[1]**

[1] Department of Neurosurgery, University Hospital, LMU Munich, Munich, Germany, [2] Center for Neuropathology and Prion Research, LMU Munich, Munich, Germany, [3] Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany, [4] German Cancer Consortium (DKTK), Partner Site Munich, German Cancer Research Center (DKFZ), Heidelberg, Germany, [5] Institute of Neuroradiology, University Hospital, LMU Munich, Munich, Germany, [6] Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany

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**Edited by:**
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***Correspondence:**
*Stefanie Quach*
*stefanie.quach@med.uni-muenchen.de*

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**Background:** An integrated diagnosis consisting of histology and molecular markers is the basis of the current WHO classification system of gliomas. In patients with suspected newly diagnosed or recurrent glioma, stereotactic biopsy is an alternative in cases in which microsurgical resection is deemed to not be safely feasible or indicated. In this retrospective study, we aimed to analyze both the diagnostic yield and the safety of a standardized biopsy technique.

**Material and Methods:** The institutional database was screened for frame-based biopsy procedures (January 2016 until March 2021). Only patients with a suspected diagnosis of glioma based on imaging were included. All tumors were classified according to the current WHO grading system. The clinical parameters, procedural complications, histology, and molecular signature of the tissues obtained were assessed.

**Results:** Between January 2016 and March 2021, 1,214 patients underwent a stereotactic biopsy: 617 (50.8%) for a newly diagnosed lesion and 597 (49.2%) for a suspected recurrence. The median age was 56.9 years (range 5 months−94.4 years). Magnetic resonance imaging (MRI)-guidance was used in 99.3% of cases and additional positron emission tomography (PET)-guidance in 34.3% of cases. In total, stereotactic serial biopsy provided an integrated diagnosis in 96.3% of all procedures. The most frequent diagnoses were isocitrate dehydrogenase (IDH) wildtype glioblastoma ($n$ = 596; 49.2%), oligodendroglioma grade 2 ($n$ = 109; 9%), astrocytoma grade 3 ($n$ = 108; 8.9%), oligodendroglioma grade 3 ($n$ = 76; 6.3%), and astrocytoma grade 2 ($n$ = 66; 5.4%). A detailed determination was successful for IDH 1/2 mutation in 99.4% of cases, for 1p/19q codeletion in 97.4% of cases, for TERT mutation in 98.9% of cases, and for *MGMT* promoter methylation in 99.1% of cases. Next-generation sequencing was evaluable in 64/67 (95.5%) of cases and DNA methylome analysis in 41/44 (93.2%) of cases. Thirteen (1.1%) cases showed glial tumors that could not be further specified. Seventy-three tumors were different non-glioma entities, e.g., of infectious or inflammatory nature. Seventy-five out of 597 suspected recurrences turned out to be post-therapeutic changes only. The rate of

post-procedural complications with clinical symptoms of the Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher was 1.2% in overall patients and 2.6% in the subgroup of brainstem biopsies. There was no fatal outcome in the entire series.

**Conclusion:** Image-guided stereotactic serial biopsy enables obtaining reliable histopathological and molecular diagnoses with a very low complication rate even in tumors with critical localization. Thus, in patients not undergoing microsurgical resection, this is a valuable tool for precision medicine of patients with glioma.

**Keywords: stereotactic biopsy, glioma, recurrent glioma, pseudoprogression, precision medicine, molecular diagnostics, image-guided procedures**

## INTRODUCTION

Gliomas represent a heterogeneous group of neoplasms of the central nervous system. Classification and subsequent management decisions depend on histological and molecular features. The WHO provides the framework for classification which leads to the guidelines for clinical management (1–5).

Hence, both histology and molecular diagnosis are mandatory in newly diagnosed intracerebral lesions suspicious for glioma. This can be obtained either by tumor resection or stereotactic biopsy. Whether the patient should undergo an open, microsurgical tumor resection or just a biopsy depends mainly on the clinical status of the patient, location and extent of the lesion, and the patients' preference. Gross total resection is associated with better long-term outcome but also inherits a risk of perioperative and postoperative complications despite modern neurosurgical techniques (6–8). Conversely, biopsies are not used for the reduction of tumor volume and but are administered for tissue-based diagnosis only (9). They can be minimally invasive, provide both histological and molecular diagnosis, and may be more suitable for multimorbid or frail patients with very high surgical risk factors for midline tumors or patients with gliomas in highly eloquent areas of the brain bearing a high functional risk in case of extensive tumor reduction.

Especially in *MGMT* methylated glioblastomas, and also in IDH mutated gliomas, treatment-induced changes on conventional magnetic resonance imaging (MRI) are not always easily distinguishable from true tumor progression, a phenomenon termed pseudoprogression (10, 11). Despite the added value of advanced MRI including MR perfusion and MR spectroscopy and positron emission tomography (PET) using radiolabeled amino acids (e.g., O-(2-$^{18}$Ffluorethyl)-L-tyrosine ([$^{18}$F]FET PET)) to assess the real tumor burden (12–14), tissue sampling provides the gold standard of information for further management of these uncertain cases.

Tumor relapse is not only a hallmark of IDH wild type glioblastoma but also occurs frequently in lower grade, IDH mutant gliomas (15–17). Patients, thus, are often subjected to a multitude of therapies over time given the fact that, so far, no standard treatment for recurrent gliomas exists. Individualized, targeted therapy is an emerging field in the treatment of gliomas and tissue sampling is necessary to identify the druggable targets using next-generation sequencing. Drugs directed against receptor tyrosine kinases (RTK) and downstream molecules like PI3K/AKT/mTOR as well as drugs targeting the mitogen-activated protein kinase (MAPK) signaling pathway are currently under investigation (2, 18, 19). Small-molecule inhibitors targeting IDH mutations are being tested in clinical trials (NCT02073994, NCT02481154). As mutational landscapes of gliomas may change during therapy and disease course, a safe and efficient way to obtain glioma tissue for identification of targetable molecular alterations would be of great benefit (20).

Thus, there is a growing need to obtain a tissue-based diagnosis even at multiple points in time during the clinical course of glioma. A minimally invasive approach would be desirable to accomplish the goal of having maximally informative specimens with minimal risk and burden for the patient. Whether risks and gains of stereotactic biopsies are well-balanced has been a matter of debate for a long time (21). However, the diagnostic yield in the framework of a molecular-driven brain tumor diagnosis and the associated complication rates of biopsies initially and during clinical course have not yet been investigated comprehensively. In this retrospective study, we aimed at analyzing both the diagnostic yield and the safety of a standardized biopsy technique between 2016 and 2021 in a single high-volume center with a high number of tertiary referrals.

## MATERIALS AND METHODS

### Patient Evaluation

The local database of the Department of Neurosurgery of the University Hospital Munich (Ludwig-Maximilians University) was screened for all biopsy procedures in a 5-year period between January 2016 and March 2021. Only patients with a suspected diagnosis of glioma were included. After histological confirmation of a glioma through biopsy, molecular analyses were performed. Clinical parameters such as age at diagnosis, Karnofsky Performance Status (KPS), initial symptoms, date of stereotactic biopsy, postoperative clinical course, and last follow-up were assessed retrospectively. All patients or caregivers gave written informed consent. The local ethics committee of the University Hospital Munich approved the study (project number 325-2011).

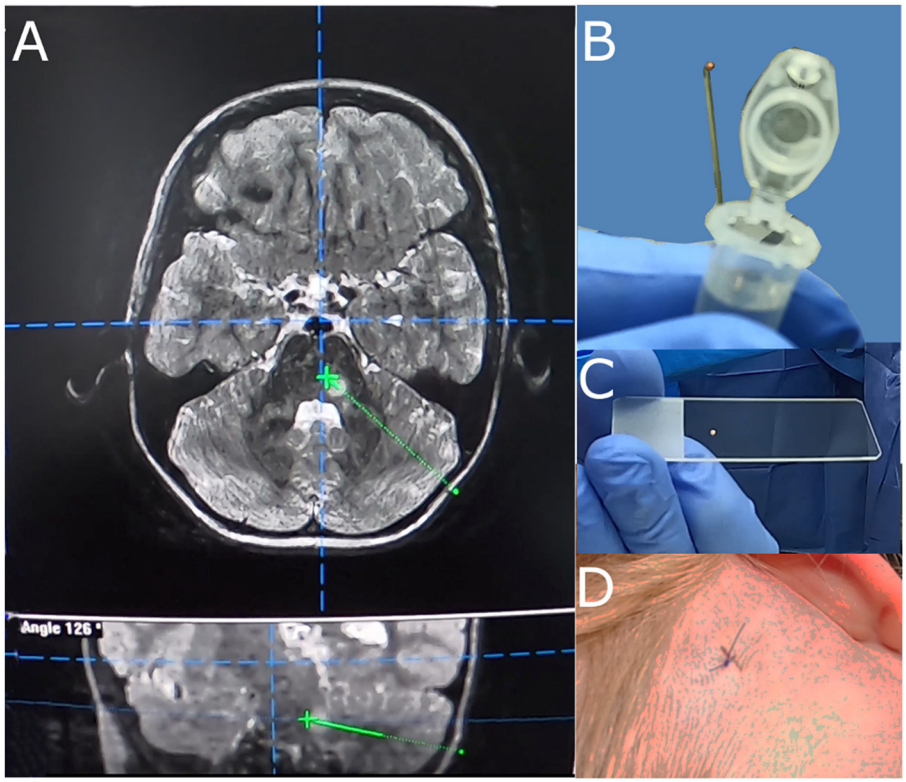


**FIGURE 1 |** Biopsy trajectory planning **(A)**, sample size of acquired specimen [arrows, **(B,C)**], and skin incision **(D)**.

## Biopsy Technique

A standardized frame-based imaging-guided stereotactic biopsy technique was used in all patients. The preoperative workup comprised a 1.5 or 3T MRI scan (with T2 and T1 sequences before and after application of a Gadolinium-based contrast agent and MR-angiography sequences) that was acquired 1 day prior to surgery and fused with an intraoperative, contrast-enhanced CT angiography scan (**Figure 1**). If available, the PET imaging data based on [$^{18}$F]FET PET was included in the triplanar trajectory planning (**Figure 2**). Each trajectory was meticulously planned to avoid any risk of vascular damage, contact to sulci, or drainage of the cerebrospinal fluid (CSF), which may lead to an intraoperative brain shift with a subsequent mismatch between planning MRI and real anatomy. A phantom frame was used to confirm the correct 3-dimensional angulation prior to the surgery in all patients. If present, the T1 contrast-enhancing lesions and/or suspicious [$^{18}$F]FET PET foci were targeted. After attaching the frame under sterile conditions, a skin incision of 4–6 mm is made and followed by a frame-guided burr hole trepanation with a diameter of 3 mm. After perforation of the dura through advancing a sharp trocar, a blunt trocar inside a guiding tube (1.4 mm guide tube and trocar, Medical High Tech GmbH, Bad-Krozingen-Biengen, Germany) is used to reach the lesion. Subsequently, with the guide tube in place, multiple small tissue samples of 1 mm$^3$ each are taken by utilizing the designated biopsy forceps (Medical High Tech GmbH, Bad-Krozingen-Biengen, Germany) inserted into the guide tube. Usually, 5–30 individual specimens per trajectory were taken depending on tumor size and the relation between solid tumor and necrosis. Thereafter, the skin is closed with a single stitch. The average length of the procedure, including the intraoperative CT scan, is 50.4 min.

An experienced neuropathologist is on site in the OR during the procedure to check *via* smear preparation whether the material obtained is sufficient in terms of quantity and quality for diagnosis.

## Complications and Follow-Up

Complications were classified according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0; **Supplementary Table 1**) (22). Complications receding within 3 months were classified as transient, else they were classified as permanent. The routine follow-up after biopsy consisted of a postoperative CT scan on the first day after the procedure and an MRI follow-up in 3–6 months intervals for high-grade gliomas and low-grade gliomas, respectively.

## Histology and Molecular Markers

All glioma specimens were classified according to the WHO 2016 at the Center for Neuropathology and Prion Research of the University Hospital Munich and retrospectively re-classified according to the WHO 2021 (3). Routine molecular analysis at

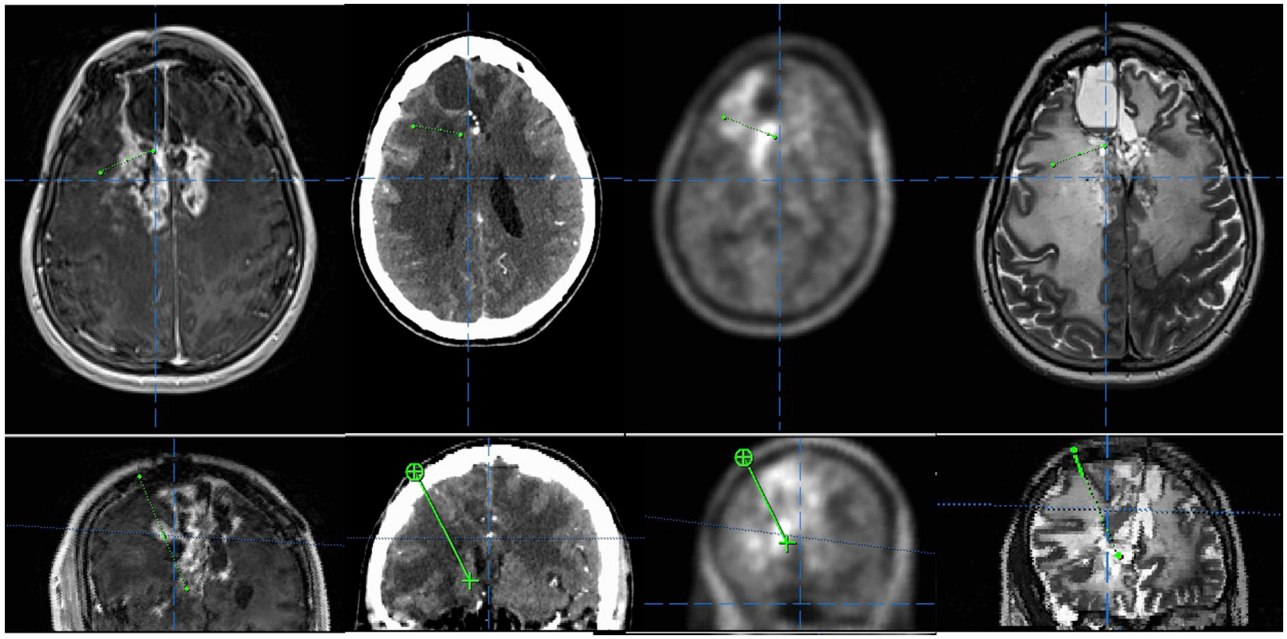

**FIGURE 2 |** Example of a multimodal trajectory planning targeting both contrast- and (fluorethyl)-L-tyrosine (FET)-enhancing areas in a case of a suspected recurrence of a multimodally treated oligodendroglioma, IDH mutated and 1p/19q co-deleted, the central nervous system (CNS) WHO grade 3. **(Upper panel)** Axial view of contrast enhanced T1, CT, FET positron emission tomography (PET), and T2. **(Lower panel)** Inline view depicting the trajectory plane.

first diagnosis comprised immunohistochemical staining against R132H-mutated IDH1 and ATRX and PCR-based analysis of the IDH1 and 2 mutational hotspots, R312 and R172, respectively (PyroMark Q24 System, Pyro Gold reagents kit, Qiagen, Hilden, Germany); a microsatellite marker analysis was used for the detection of 1p and 19q deletions (23, 24). The mutations within the TERT promoter sequence were detected by the Sanger sequencing utilizing the QIAquick PCR Purification Kit (Qiagen, Hilden, Germany), the BigDye Terminator V3.1 Cycle Sequencing kit (Life Technologies, Carlsbad, USA), the DyeEX 2.0 Spin Kit (Qiagen, Hilden, Germany), and 3130 Genetic Analyzer (Life Technologies, Carlsbad, USA) (25). The DNA methylation status of the *MGMT* promoter was determined by bisulfite modification and subsequent nested methylation-specific PCR and sequencing analysis. Tumors were classified binarily as methylated or unmethylated (26). Further molecular analyses were initiated when the results were inconclusive or when aiming at identifying targetable mutations in patients with conventional treatment failure. In these cases, next-generation sequencing was performed using a combined DNA and RNA panel (Trusight Oncology 500, Illumina, San Diego, CA, USA). The DNA methylation profiling was performed for tumor not classifiable by other means or to detect clinically or diagnostically relevant copy number alterations such as homozygous CDNK2A/B deletions. The methylation profiling was done using an Illumina Infinium MethylationEPIC BeadChip array (Illumina, San Diego, CA, USA) with subsequent data analysis using the DNA methylation-based brain tumor classifier provided by the Deutsche Krebsforschungszentrum (v11b4) (27).

## Statistics

The final database contained patient-related, clinical, and tumor-specific information such as patient age at diagnosis, gender, clinical status utilizing the KPS, localization of the tumor, histological and molecular glioma features, and postinterventional complication rates. Based on this data, descriptive statistical analyses were performed utilizing the SPSS Statistics 25 software (IBM, Armonk, New York, USA).

# RESULTS

## Patients and Procedural and Tumor Characteristics

In total, 1,214 consecutive biopsy procedures were analyzed. The median age of patients was 56.9 years (range 5 months−94.4 years). Of the total patients, 58.6% were men and 41.4% were women. A KPS of 80 or higher was reported in 82.1% of all patients. In 50.8% of cases, a biopsy was performed to obtain tissue in a newly diagnosed tumor and in 49.2% of cases for suspected recurrence. Image guidance was based on MRI in 99.3% cases and on CT in 0.7% cases due to contraindications for MRI imaging. Additionally, [$^{18}$F]FET PET was used in 34.3% cases.

A total of 596 tumors (49.1%) were located on the left and 535 (44.1%) on the right side, and 83 patients (6.8%) had a bilateral midline tumor. The tumor site was lobar in 1,011 (83.3%), deep seated (insula, thalamus, corpus callosum, pineal region) in 123 (10.1%), cerebellar in 40 (3.3%), and

**TABLE 1 |** Biopsy location in primary and recurrent diseases.

| Location | | First diagnosis *n* (%) | Recurrence *n* (%) | Total *n* (%) |
|---|---|---|---|---|
| Lobar | Frontal | 155 (12.8) | 232 (18.4) | 378 (31.1) |
| | Temporal | 158 (13.0) | 161 (13.3) | 319 (26.3) |
| | Parietal | 79 (6.5) | 78 (6.4) | 157 (12.9) |
| | Occipital | 15 (1.2) | 12 (1.0) | 27 (2.2) |
| | Pre-/postcentral gyrus | 67 (5.5) | 63 (5.2) | 130 (10.7) |
| Deep-seated | Callosal | 12 (1.0) | 3 (0.2) | 15 (1.2) |
| | Insular | 27 (2.2) | 26 (2.1) | 53 (4.4) |
| | Thalamic | 31 (2.6) | 6 (0.5) | 37 (3.0) |
| | Pineal | 15 (1.2) | 3 (0.2) | 18 (1.5) |
| | Cerebellar | 25 (2.1) | 15 (1.2) | 40 (3.3) |
| Brainstem | Mesencephalon | 8 (0.7) | 3 (0.2) | 11 (0.9) |
| | Pons | 14 (1.2) | 4 (0.3) | 18 (1.5) |
| | Medulla oblongata | 11 (0.9) | 0 (0.0) | 11 (0.9) |
| Total | | 617 (50.8) | 597 (49.2) | 1,214 (100.0) |

brainstem in 40 (3.3%) patients (for detailed location see **Table 1**).

The most common diagnosis was glioblastoma IDH wild type with 596 cases (49.2%), followed by oligodendroglioma grade 2 ($n = 109$; 9.2%), astrocytoma grade 3 ($n = 108$; 8.9%), oligodendroglioma grade 3 ($n = 76$; 6.4%), astrocytoma grade 2 ($n = 66$; 5.4%), IDH 1/2 mutated astrocytoma WHO grade 4 ($n = 45$; 3.7%), and diffuse midline glioma, H3K27M- or FGFR1-mutated ($n = 15+1$; 1.3%) (**Table 2**).

## Diagnostic Yield and Molecular Analyses

Among all newly diagnosed lesions, histopathology and molecular analyses provided a definite diagnosis in 595/617 cases (96.4%). Among the 22 unclear results, 14 patients were followed up by MRI imaging, as a low-grade tumor in an eloquent location was histologically and clinically the most likely diagnosis. None of these patients experienced tumor progression during a mean follow-up of 21 months. In six cases, the treatment was initiated based on recommendations by our interdisciplinary tumor board according to the most likely diagnosis (3 glial tumors without further subclassification; 3 diagnoses other than glioma). In only two cases, a second invasive procedure was required for obtaining the diagnosis: one patient underwent re-biopsy after 2 weeks, confirming IDH wild type glioblastoma, and another patient underwent open tumor resection revealing ganglioglioma.

Among all suspected recurrences, vital tumor was detected in 522 out of 597 cases (87.1%), while predominantly post-therapeutic changes were found in 75 cases (12.6%). In 3 cases (4% of all tissues showing post-therapeutic changes), recurrence within 3 months suggested a false negative sampling. In three cases with histologically diagnosed tumor recurrence (0.6%), further clinical course suggested mainly post-therapeutic changes, i.e., false-positive sampling. This amounts to a positive predictive value of 99.4% and a negative predictive value of 96%.

The standard molecular analyses, required by the WHO 2021 grading system, were successfully obtained in the vast majority of tumors being identified as gliomas by histology. The molecular status was informative for IDH 1/2 mutation in 99.4%, for 1p/19q codeletion in 97.4%, for TERT mutation in 98.9%, and for *MGMT* promoter methylation in 99.1%. Next-generation sequencing was attempted in 67 cases and evaluable in 64. The DNA methylation analysis was attempted in 44 cases and evaluable in 42. Twelve, thereof, showed no match with known methylation classes. Altogether, a successful molecular characterization for integrated diagnosis was obtained in 93% of all newly diagnosed and in 88.3% of all recurrent lesions.

## Complications

The routine postoperative CT showed no visible conspicuity in 816 (67.2%) cases, a minimal (<5 mm) hemorrhage in 305 (25.1%) cases, a local (>5 mm) hemorrhage in 51 (4.2%) cases, and a space-occupying hemorrhage in 10 (0.8%) cases. In 30 cases, no postoperative CT scan was performed in young patients without relevant deficit. **Table 3** lists clinical complications in relation to imaging features. No clinical sequelae of the stereotactic biopsy were observed in 1,164 (95.9%) of procedures. Mild complications (CTCAE grade 1) were documented in 14 (1.2%) and moderate (CTCAE° 2) in 21 (1.7%) cases. Complications of CTCAE grade 3 occurred in 11 procedures (5 hemiparesis, 4 seizure series, 3 cases of delirium, 1 reduced level of consciousness, total 0.9%). Four patients (0.3%) required urgent intervention (CTCAE grade 4): three patients with postoperative bleeding required craniotomy and hematoma evacuation. One of these patients re-bled a second time after an initially successful hematoma evacuation and needed a second revision craniotomy, possibly due to a decreased level of fibrin stabilizing factor (factor XIII) diagnosed after the second revision surgery. All three patients with hematoma evacuation improved to CTCAE grade 1 or 0 within 3 months. One superficial wound infection required local debridement. Regarding the subgroup of brainstem lesions, two patients (5.3%) experienced mild complications and one (2.6%) a moderate complication (local hemorrhage with transient aggravation of a preexisting

**TABLE 2 |** Histological diagnoses.

| Entity | | Newly diagnosed lesion n (%) | Recurrence *n* (%) | Total *n* (%) |
|---|---|---|---|---|
| Glioma | Glioblastoma, IDH wild type | 354 (29.2) | 243 (20.1) | 596 (49.2) |
| | Midline glioma, H3K27M-mutated | 12 (1.0) | 3 (0.2) | 15 (1.2) |
| | Astrocytoma WHO grade 4, IDH-mutant | 4 (0.3) | 41 (3.4) | 45 (3.7) |
| | Astrocytoma WHO grade 3, IDH-mutant | 19 (1.6) | 89 (7.3) | 108 (8.9) |
| | Astrocytoma WHO grade 2, IDH-mutant | 34 (2.8) | 32 (2.6) | 66 (5.4) |
| | High-grade astrocytoma with piloid features | 3 (0.2) | 1 (0.1) | 4 (0.3) |
| | Oligodendroglioma WHO grade 3, IDH-mutant and 1p/19q-codeleted | 8 (0.7) | 68 (5.6) | 76 (6.3) |
| | Oligodendroglioma WHO grade 2, IDH-mutant and 1p/19q-codeleted | 37 (3.0) | 72 (5.9) | 109 (9.0) |
| | Ganglioglioma | 7 (0.6) | 4 (0.3) | 11 (0.9) |
| | Pilocytic astrocytoma | 11 (0.9) | 13 (1.1) | 24 (2.0) |
| | Pleiomorphic xanthoastrocytoma | 0 (0.0) | 1 (0.1) | 1 (0.1) |
| | Pleiomorphic astroglial tumor | 2 (0.2) | 0 (0.0) | 2 (0.2) |
| | Ependymoma | 1 (0.1) | 1 (0.1) | 2 (0.2) |
| | Anaplastic ependymoma | 2 (0.2) | 3 (0.2) | 5 (0.4) |
| Other gliomas, not elsewhere classified (NEC) | *Glioma (NEC)* | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| | Glial tumor | 11 (0.9) | 1 (0.1) | 12 (1.0) |
| | Glioneural tumor | 7 (0.6) | 0 (0.0) | 7 (0.6) |
| | Neuroepithelial tumor | 7 (0.6) | 1 (0.1) | 8 (0.7) |
| Other | Initially suspected glioma, diagnosis other than glioma | 41 (3.4) | 4 (0.3) | 45 (3.7) |
| | Metastasis | 31 (2.6) | 2 (0.2) | 33 (2.7) |
| | Medulloblastoma | 3 (0.2) | 4 (0.3) | 7 (0.6) |
| | Meningioma | 6 (0.5) | 4 (0.3) | 10 (0.8) |
| | Neurocytoma | 3 (0.2) | 2 (0.2) | 5 (0.4) |
| | Germinoma | 6 (0.5) | 1 (0.1) | 7 (0.6) |
| | Other entities (pineocytoma, neurinoma, diffuse leptomeningeal glioneuronal tumor, papillary tumor of the pineal region, pineoblastoma, solitary fibrous tumor, craniopharyngioma, yolk sac tumor) | 7 (0.7) | 7 (0.7) | 14 (1.3) |
| Total | | 617 (50.8) | 597 (49.2) | 1,214 (100.0) |

hemiparesis). In total, 74% of all clinical complications were resolved within 3 months (**Table 4**). There were no procedure-related deaths in the overall cohort.

## Brainstem Biopsies

A subgroup of 40 patients underwent a stereotactic biopsy of a brainstem lesion, whereof 13 were pediatric patients. The most frequent diagnosis was diffuse midline glioma, H3K27M mutated ($n = 8$), glioblastoma IDH wild type ($n = 5$), IDH 1/2 mutated astrocytoma ($n = 7$), and pilocytic astrocytoma ($n = 5$). All diagnoses of brainstem tumors are detailed in **Table 5**. In six cases, another diagnosis other than tumor was made, which was confirmed also by a further clinical course. NGS and DNA methylation analysis was attempted and successfully performed in three cases each. Two patients (5.3%) experienced mild complication and one (2.6%) patient had a moderate complication (local hemorrhage which transient aggravation of a preexisting hemiparesis).

# DISCUSSION

With the help of image-guided stereotactic biopsy, we could establish a histopathological and molecular diagnosis and distinguish true progression from pseudoprogression in a consecutive series of 1,214 patients with suspected glioma with a very high diagnostic accuracy of 96.4% in terms of histology, over 97% for molecular markers, and over 95% in 850 k/NGS arrays. The rate of non-gliomas among all suspected gliomas was low, possibly reflecting that an interdisciplinary tumor board with dedicated experienced neuroradiologists and nuclear medicine physicians had put forward the biopsy indications. Most previously published studies comprised sample sizes of a few dozen to a couple hundred patients (28–36). The largest retrospective monocentric study comprised 622 patients biopsied over the course of 20 years as compared to a sample size of 1,214 patients over 5 years reported in our study (28, 30). The rate of biopsies investigating

**TABLE 3 |** Complications according to postoperative imaging and severity.

| Blood on postoperative CT scan (*n*, % of total) | Clinical complications (CTCAE grade) | Newly diagnosed lesions; *n* (%) | Recurrent lesions; *n* (%) | Total; *n* (%) |
|---|---|---|---|---|
| No visible blood | 0 (none) | 395 (98.0) | 406 (98.3) | 801 (98.2) |
| (*n* = 816; 67.2%) | 1 (mild) | 2 (0.5) | 3 (0.7) | 5 (0.6) |
| | 2 (moderate) | 6 (1.5) | 2 (0.5) | 8 (1.0) |
| | 3 (severe) | 0 | 2 (0.5) | 2 (0.2) |
| Minimal (<5 mm) | 0 (none) | 149 (96.1) | 142 (94.7) | 291 (95.4) |
| hemorrhage | 1 (mild) | 0 | 4 (2.7) | 4 (1.3) |
| (*n* = 305; 25.1%) | 2 (moderate) | 5 (3.2) | 4 (2.7) | 9 (3.0) |
| | 3 (severe) | 1 (0.6) | 0 | 1 (0.3) |
| Local (>5 mm) | 0 (none) | 26 (81.3) | 16 (84.2) | 42 (82.4) |
| Hemorrhage | 1 (mild) | 2 (6.3) | 1 | 3 (5.9) |
| (*n* = 51; 4.2%) | 2 (moderate) | 1 (3.1) | 1 (5.3) | 2 (3.9) |
| | 3 (severe) | 2 (6.3) | 1 (5.3) | 3 (5.9) |
| | 4 (life-threatening) | 1 (3.1) | 0 | 1 (2.0) |
| Space occupying | 2 (moderate) | 1 (16.7) | 1 (25.0) | 2 (20.0) |
| hemorrhage | 3 (severe) | 2 (33.3) | 3 (75.0) | 5 (50.0) |
| (*n* =10;0.8%) | 4 (life-threatening) | 3 (50.0) | 0 | 3 (30.0) |
| Ischemia | 0 (none) | 0 | 1 (50.0) | 1 (50.0) |
| (*n* = 2;0.8%) | 1 (mild) | 0 | 1 (50.0) | 1 (50.0) |
| No imaging available | 0 (none) | 20 (95.2) | 9 (100) | 29 (96.7) |
| (*n* = 30; 2.5%) | 1 (mild) | 1 (4.8) | 0 | 1 (3.3) |
| Total | 0 (none) | 590 (95.6) | 574 (96.1) | 1,164 (95.9) |
| (*n* = 1,214; 100%) | 1 (mild) | 5 (0.8) | 9 (1.5) | 14 (1.2) |
| | 2 (moderate) | 13 (2.1) | 8 (1.3) | 21 (1.7) |
| | 3 (severe) | 5 (0.8) | 6 (1.0) | 11 (0.9) |
| | 4 (life-threatening) | 4 (0.6) | 0 | 4 (0.3) |

**TABLE 4 |** Fraction of transient or permanent complications among all complications.

| Clinical complications (CTCAE grade) | Transient *n* (% of total) | Permanent *n* (% of total) | Total *n* (% total) |
|---|---|---|---|
| 1 | 12 (0.9) | 2 (0.2) | 14 (1.2)[a] |
| 2 | 17 (1.4) | 4 (0.3) | 21 (1.7) |
| 3 | 4 (0.3) | 7 (0.6) | 11 (0.9) |
| 4 | 4 (0.3) | 0 (0.0) | 4 (0.3) |
| Total | 37 (3.0) | 13 (1.1) | 50 (4.1) |

[a]*Percentages do not add up due to rounding.*

**TABLE 5 |** Diagnoses of brainstem biopsies in adult and pediatric patients.

| | Adult *n* (%) | Pediatric *n* (%) | Total *n* (%) |
|---|---|---|---|
| Midline glioma | 3 (11.1) | 5 (38.5) | 8 (20.0) |
| Glioblastoma, IDH wildtype | 3 (11.1) | 2 (15.4) | 5 (12.5) |
| Astrocytoma, IDH mutated | 6 (22.2) | 1 (7.7) | 7 (17.5) |
| Astrocytoma with piloid features | 1 (3.7) | 0 (0.0) | 1 (2.5) |
| Oligodendroglioma, IDH mutated, 1p/19q codeleted | 1 (3.7) | 0 (0.0) | 1 (2.5) |
| Pilocytic astrocytoma | 3 (11.1) | 2 (15.4) | 5 (12.5) |
| Glial tumor, NEC | 3 (11.1) | 0 (0.0) | 3 (7.5) |
| Glioneuronal tumor | 1 (3.7) | 0 (0.0) | 1 (2.5) |
| Papillary tumor of the pineal region | 0 (0.0) | 1 (7.7) | 1 (2.5) |
| Metastasis | 2 (7.4) | 0 (0.0) | 2 (5.0) |
| Other diagnoses than tumor | 4 (14.8) | 2 (15.4) | 6 (15.0) |
| Total | 27 (100) | 13 (100) | 40 (100) |

suspected tumor recurrence is relatively high, as we provide an effective, low-risk stereotactic biopsy technique and have many patients with suspected recurrences coming to our tertiary referral center for second opinions and to get a tissue-based diagnosis, which is decisive to maintain a successful therapy or enable an informed change of therapy. Unspecific therapy-related changes and pseudoprogression phenomena mimicking tumor relapse gain more importance in light of emerging immunotherapies (37). In our series, more than one in ten (12.5%) of suspected tumor recurrences showed only therapy-induced changes histologically, obviating the need for more invasive procedures in this patient collective. In addition, in analogy to solid cancers and brain metastases, the search for druggable targets in newly diagnosed and recurrent gliomas just embarks and will increase in the future. As new therapies being recommended by a molecular tumor board become available, tissue diagnosis of possible druggable targets should not be withheld from "biopsy-only" patients. Consequently, in all cases where open microsurgical resection is not deemed feasible or medically justified and in all "diagnostic-only" situations, the need for a minimal invasive and maximal effective technique to obtain an informative diagnostic material is beyond doubt. This has also been adopted now for diffuse brainstem gliomas (38, 39).

Earlier, small biopsies did not yield enough viable tissue for obtaining a valid and, presently, mandatory molecular diagnosis; however, the contemporary refined technologies of molecular biology enable the analysis of a panel of different molecular markers even from very small specimens (40, 41). Only with access to elaborate the neuropathological technique and expertise, stereotactic biopsies are adequate to gain all diagnostic information in case open resection is not deemed feasible or justified. In our series, over 96% of biopsies were informative concerning histology and the molecular signature of the tumor. Prerequisite for a proper molecular diagnosis is to obtain the material out of the solid parts of the tumor since any "contamination" of the specimen with either normal adjacent brain or else tumor necrosis might hamper diagnostic yield and accuracy. Moreover, the neuropathologist has to be experienced in working up these small samples. In our practice, the pathologist is on site in the OR during the procedure to check *via* smear preparation whether the material obtained is sufficient in terms of quantity and quality for diagnosis.

Serial sampling with multiple specimens along the trajectory allows to "map" the tumor, including its infiltration zone. This is extremely useful in heterogeneously composed tumors where one single biopsy might lead to a sampling error like misdiagnosing or undiagnosed. MR features such as contrast enhancement on T1-weighted imaging or cell density on T2-weighted sequences can highlight the suspicious areas that should be targeted preferentially. PET with amino acid tracers such as [$^{18}$F]FET, [$^{11}$C]Methionine, or [$^{18}$F]FDOPA are particularly useful to detect the relevant areas for diagnostic biopsies in either diffuse, non-contrast enhancing gliomas or in multimodally pretreated lesions with differential diagnosis of recurrent tumor vs. treatment-related phenomena (12, 13, 42, 43). While [$^{18}$F]FET PET and perfusion MRI can give important hints about the likelihood of true progression vs. pseudoprogression (12), our data support the continued use of histology as the gold standard for identifying both with high reliability and low risk. Furthermore, image-guided biopsies allow to precisely target and sample different areas within heterogeneously composed tumors to address the mutational and clonal analyses with a high spatial resolution.

As long as molecular alterations within the tumor are homogeneously distributed, sampling errors are not an issue. Referring to this, the homogeneous distribution of the alteration has to be shown in a systemical order to elucidate whether a risk of sampling error might be relevant for a given particular marker. This has been demonstrated for most of the relevant basic molecular signatures in gliomas (26, 43, 44). The earlier a molecular alteration appears in the timeline of tumor evolution, the more likely it can appear homogeneously within the tissue (45). Conversely, especially for late events, more heterogeneous patterns evolve, which have to be taken into account for biopsy (46).

The patterns of either diagnostic or therapeutic targets may change during the course of disease, so recurrent tumors may have a completely different pattern compared to the original newly diagnosed tumor. Again, early events in the tumorigenesis may not change, whereas new subclones during tumor progression may carry new mutations (45). Especially, therapy-driven alterations and an increase in mutational burden may necessitate re-biopsy (47–50). Whereas, *MGMT* promoter methylation does not change over time (51), other therapy relevant markers do (52, 53). Hence, it may not justified to include patients with recurrent tumors into clinical trials for targeted therapy just on the basis of the initial specimen. Instead, dependent on the target, the molecular status has to be newly defined by either resection or biopsy (54, 55).

The complication rate was low with only 0.6% permanent and 0.6% transient severe complications overall. In the subgroup of brainstem lesions, moderate or severe complications occurred at a slightly higher rate of 2.6%. Thus, even in patients with gliomas located in delicate areas such as the brainstem or the midbrain, tissue can be acquired with a low risk of permanent deficit and a high diagnostic yield. The low complication rate reported in this study justifies the application of stereotactic biopsies less reluctantly whenever diagnostic uncertainties occur during the course of disease and treatment. The low number of symptomatic hemorrhages suggests waiving the routine CT scan. Previous series of frame-based biopsies report mortality rates of 0.7–4% (28, 30–36). Post-procedural morbidity (i.e., transient or permanent neurological deficits, epileptic seizures, coma) ranged from 3 to 13%. Asymptomatic bleedings on postoperative CT scans have been reported in up to 60% of patients and symptomatic bleedings occurred in up to 8.6% of cases. In our series with no mortality, the rate of severe transient and permanent complications was much lower. In previous studies, brain biopsies typically yielded diagnoses at rates of 89–92% and even higher when intraoperative histological smears were carried out (21, 28, 31, 56–59). By comparing frame-based with frameless biopsies, no clear advantage of either technique regarding complication rates or diagnostic yield could be shown so far (29, 32, 57–60). In our experience, a high personal and interdisciplinary expertise is required to obtain

constant procedural safety and efficiency. A high caseload being taken care of by a group of few dedicated neurosurgeons is, in our opinion, important. In addition, high-resolution vascular imaging, including MR and CT angiography, meticulous planning of the trajectories by avoiding vessels, ventricular puncture, and arachnoidal contact, as the subarachnoid space is especially prone to hemorrhage, is required. Furthermore, the presence of a dedicated neuropathologist on site not only ensures specimen quality but also prevents an unnecessary high number of specimens, which is especially important in delicate locations. Also, as always in neurosurgery, proper selection of indications and patients is key. Despite low complication rates, the indication for brain biopsy must be strict as it still is an invasive procedure.

In the future, determination of changes in the molecular signature of gliomas and very early detection of therapy response or failure will gain further importance. Whether several techniques and concepts of "liquid biopsy" using CSF, plasma, or even urine may complement or even replace stereotactic biopsies for at least some indications remains yet uncertain (61–66). Also, molecular imaging using novel specific tracers might help to non-invasively better characterize gliomas in the future (67, 68).

With a mean duration of 50 min, frame-based biopsy in a streamlined setting is a time- and cost-efficient procedure. At our institution, we can perform up to five biopsies in the same OR within the regular working hours. We could obtain a high diagnostic yield with a very low rate of either inconclusive biopsies or complications. This leads to a low rate of re-biopsies, which is an important factor for both the safety and the effectiveness in the process of decision making and patient management. Hence, we consider the balance between the complexity and the costs on one side and the benefit for the patient/patient management on the other side to be in due proportion.

## CONCLUSION

In conclusion, a streamlined stereotactic biopsy procedure proved to be time-effective and low-risk in primary and recurrent glioma. A high diagnostic yield enables the diagnostics of molecular markers, as required by the current WHO classification, as well as in the increasingly important context of molecular tumor boards. A postoperative CT scan should only be performed when clinically indicated. A good technical setup with easily accessible CT and a specialized team for trajectory planning and neuropathological analysis are recommended.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of national and institutional laws to protect patient confidentiality. Requests to access the datasets should be directed to the Center for Neuropathology and Prion Research of the University Hospital of Munich.

## AUTHOR CONTRIBUTIONS

JT and SQ contributed to the conception and design of the study. AD, SK, and SQ organized the database, evaluated the clinical courses, and performed the image analyses. SQ carried out the statistical analysis. SK, SQ, JW, and JT wrote the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.822362/full#supplementary-material

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# Neurocognitive Outcome and Seizure Freedom After Awake Surgery of Gliomas

*Sarah Christina Reitz[1,2]*, Marion Behrens[2], Irina Lortz[1], Nadine Conradi[3], Maximilian Rauch[4], Katharina Filipski[5,6,7,8], Martin Voss[2,6,9], Christian Kell[2,3], Marcus Czabanka[1] and Marie-Therese Forster[1,6]*

[1] Department of Neurosurgery, University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany, [2] Department of Neurology, University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany, [3] Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany, [4] Institute of Neuroradiology, University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany, [5] Edinger Institute, Institute of Neurology, University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany, [6] University Cancer Center Frankfurt (UCT), University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany, [7] German Cancer Consortium (Deutsches Konsortium für Translationale Krebsforschung), Partner Site Frankfurt/Mainz, Heidelberg, Germany, [8] German Cancer Research Center (Deutsches Krebsforschungszentrum), Heidelberg, Germany, [9] Dr. Senckenberg Institute of Neurooncology, University Hospital Frankfurt, Goethe University, Frankfurt/Main, Germany

**Objectives:** Gliomas are often diagnosed due to epileptic seizures as well as neurocognitive deficits. First treatment choice for patients with gliomas in speech-related areas is awake surgery, which aims at maximizing tumor resection while preserving or improving patient's neurological status. The present study aimed at evaluating neurocognitive functioning and occurrence of epileptic seizures in patients suffering from gliomas located in language-related areas before and after awake surgery as well as during their follow up course of disease.

**Materials and Methods:** In this prospective study we included patients who underwent awake surgery for glioma in the inferior frontal gyrus, superior temporal gyrus, or anterior temporal lobe. Preoperatively, as well as in the short-term (median 4.1 months, IQR 2.1-6.0) and long-term (median 18.3 months, IQR 12.3-36.6) postoperative course, neurocognitive functioning, neurologic status, the occurrence of epileptic seizures and number of antiepileptic drugs were recorded.

**Results:** Between 09/2012 and 09/2019, a total of 27 glioma patients, aged 36.1 ± 11.8 years, were included. Tumor resection was complete in 15, subtotal in 6 and partial in 6 patients, respectively. While preoperatively impairment in at least one neurocognitive domain was found in 37.0% of patients, postoperatively, in the short-term, 36.4% of patients presented a significant deterioration in word fluency (p=0.009) and 34.8% of

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***Correspondence:**
*Sarah Christina Reitz*
*sarah.reitz@kgu.de*

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patients in executive functions (p=0.049). Over the long-term, scores improved to preoperative baseline levels. The number of patients with mood disturbances significantly declined from 66.7% to 34.8% after surgery (p=0.03). Regarding seizures, these were present in 18 (66.7%) patients prior to surgery. Postoperatively, 22 (81.5%) patients were treated with antiepileptic drugs with all patients presenting seizure-freedom.

**Conclusions:** In patients suffering from gliomas in eloquent areas, the combination of awake surgery, regular neurocognitive assessment - considering individual patients´ functional outcome and rehabilitation needs – and the individual adjustment of antiepileptic therapy results in excellent patient outcome in the long-term course.

**Keywords: glioma, neurocognitive outcome, quality of life, epilepsy, neurocognition, awake surgery**

## INTRODUCTION

Gliomas are the most frequent malignant primary brain tumors, with an incidence of 7.1 per 100 000 persons/year (1). Most common clinical manifestation of low grade gliomas are epileptic seizures, whereas patients with high grade gliomas additionally often suffer from neurologic deficits at the time of diagnosis of the tumor (2–4).

One of the major determinants of quality of life in glioma patients is neurocognitive functioning (5). Seizures as well as cognitive symptoms affecting higher cerebral functions (e.g. attention, memory, communication, executive functions) may have great impact on patients' daily life, including their neuropsychological wellbeing (6).

Current standard of therapy is maximal tumor resection followed by adjuvant therapy (7, 8). Especially tumors located in "eloquent" areas need to be resected with utmost care. In order to optimize the neurologic and simultaneously oncological outcome of these patients, awake surgery is the method of choice to balance maximal extent of tumor resection (EOR) with preservation of neurologic function (9–11).

Several studies focusing on patients´ neurologic and neurocognitive outcome after awake surgery have been published during recent years (10, 12, 13). However, reports on patients suffering from glioma in language-related localizations as well as longitudinal long-term follow-up evaluations on patient's neurocognitive performances beyond 6 months after surgery are scarce.

We therefore aimed at evaluating neurocognitive functioning in patients suffering from gliomas located in language-related areas before and after awake surgery as well as during their follow up course of disease. We assessed changes in patients´ neurocognitive functioning across different time points of the disease as well as epileptic seizure occurrence. Such information could be of clinical relevance to refine patients neurocognitive monitoring on an individual basis.

**Abbreviations:** AED, antiepileptic drugs; EOR, extent of resection; CI, confidence interval; GBM, Glioblastoma; GTR, gross total resection; HADS, Hospital Anxiety and Depression Scale; HGG, High grade glioma; IDH-1, isocitrate dehydrogenase 1; IQR, interquartile ranges; KPS, Karnofsky performance score; LGG, low grade glioma; MMSE, mini-mental state examination; PD, progressive disease; PR, partial resection; SD, stable disease; STR, subtotal resection.

## METHODS

### Study Design

We performed a prospective single-center study in patients who underwent awake surgery of glioma located in language-related areas of the dominant hemisphere between 09/2012 and 09/2019 in our department. Patients underwent neuropsychological evaluation as part of their pre-surgical work-up, as well as during the follow up of their disease. Patients´ clinical characteristics as well as data on seizure outcome were recorded at each follow-up visit.

Study approval was granted by the local Ethics Committee (SNO 08/2016). All procedures performed were in accordance with the ethical standards of the institutional research committee and with the standards laid down in the Declaration of Helsinki (14). All patients gave written informed consent prior to data collection.

### Patients

During the above-mentioned period, all patients meeting the criteria for study inclusion were identified. Inclusion criteria comprised (1) adult patients aged ≥ 18 years (2), tumor localization in language-related areas, i.e. the inferior frontal gyrus (IFG), the anterior temporal lobe (ATL), the dorsal superior and middle temporal gyrus and the supramarginal gyrus (dMTG/STG), in the language-dominant hemisphere (language-dominance was determined by fMRI) (4), left hemispheric dominance (5), fluent knowledge of German and, thus (6), indication for awake tumor surgery. Regarding exclusion criteria these were (1) age ≤ 18 years (2), right hemispheric dominance (3), other tumor locations as indicated above as well as general exclusion criteria for awake craniotomy such as (4) severe language deficits to the extent of clinically relevant aphasia at tumor diagnosis as well as (5) only sparse knowledge of German, English or French. Indication for surgical treatment as well as postoperative treatment was recommended by a multidisciplinary tumor-board for each patient.

Awake tumor resection was performed employing awake mapping and monitoring techniques to allow for intraoperative testing and preservation of speech function, in addition to motor or sensory evoked potential monitoring. In detail, an asleep-awake-asleep technique was employed. Brain mapping was

performed using bipolar stimulation applying a frequency of 50Hz and a stimulation intensity of 3 to 6 mA once the patient was awake before tumor resection. After cortical mapping tumor resection was begun with regard to functional boundaries, repeating electrical stimulation at intervals during subcortical preparation. Language tasks comprised counting and naming in all patients, while reading, word and sentence comprehension, calculation and repetition tasks were used according to the location of the tumor (15).

Early postoperative MRI to assess EOR was performed within 72 hours after surgery in all patients. EOR and tumor progression were evaluated by a board-certified neuroradiologist, with EOR being defined as complete (gross-total tumor resection; GTR), subtotal (STR; with less than 10% of the original volume as residual tumor) or partial (PR; with residual tumor coming up to more than 10% of the original volume), and disease progression being determined according to the RANO criteria (16). Brain tumor diagnoses were assigned according to the 2016 *WHO Classification of Tumors of the Central Nervous System* (17) ($4^{th}$ and $4^{th}$ revised version, respectively, according to the year of inclusion into the study). Formalin-fixed paraffin-embedded tumor tissue sections were mounted on slides, H&E-stained following established protocols and evaluated by an experienced neuropathologist (KF). For IDH mutation analysis tissue sections were stained with a mutation specific antibody against IDH1_R132H (clone H09, Dianova, Hamburg, Germany). Representative tumor regions with highest cancer cell ratios were selected for punch biopsy or 4-10x10 µm whole slide tumor tissue collection and further molecular pathological analysis. Tumors from patients included since 2017 were subjected to large-scale DNA methylation analysis by use of the Illumina EPIC Human Methylation array (Illumina, California, USA) after DNA isolation. Patients´ clinical characteristics, including the Karnofsky-Performance score (KPS), data on seizure outcome, and results of magnetic resonance imaging were recorded at regular, usually three-months, follow-up visit.

Occurrence of epileptic seizures (seizures yes/no) and number of antiepileptic drugs (AED) were retrospectively assessed on basis of the electronic patient file timed to the neurocognitive assessments (median time difference between the evaluation of postoperative epileptic seizures and patients´ neurocognitive performances: t2, 0.4 (IQR 0-1.6) months; t3, 0.7 months, IQR 0-1.9).

## Neurocognitive Assessment

Neurocognitive assessment was performed at three different time points; as part of the preoperative work-up (t1), at follow up <9 months (median 4.1 months, IQR 2.1-6.0) after surgery (t2) and at follow up >9 months (median 18.3 months, IQR 12.3-36.6) after surgery (t3). While neurocognitive performance was evaluated in all patients before surgery, data on postoperative assessments had to remain incomplete, either due to patients' non-compliance or due to refusal to undergo further evaluation. Thus, follow-up evaluations at time points t2 and t3 were conducted in a subset of 23 patients and 20 patients, respectively. As a result, complete longitudinal neurocognitive assessment with evaluations at all three time-points was possible in 16 patients.

Each assessment was performed by a trained neuropsychologist and took patients approximately 1.5 h to complete. The applied test-battery included tests for attention, verbal fluency, verbal memory, figural memory, working memory, executive functioning, visuospatial functioning, as well as the assessment of emotion such as anxiety and depression. A z-score <-1.5 was defined as the cut-off for the definition of an impairment, a change in z-score > ± 1 was defined as the cut-off for a significant change in cognitive performance. A detailed list of all tests is provided in **Table 1**.

## Statistical Analysis

Regarding baseline characteristics, values are presented as numbers with percentages and medians with inter quartile range (IQR) or means (depending on the presence of normal-distribution, tested by quantile-quantile plots), unless otherwise indicated.

**TABLE 1** | Neurocognitive assessment, tasks per neurocognitive domain.

| Cognitive domain | Test | Cognitive function |
|---|---|---|
| **Attention** | TAP Alertness (18) | Response time |
| | TAP Geteilte Aufmerksamkeit II (18) | Divided attention |
| **Verbal fluency** | Wortschatztest (WST) (19) | Vocabulary (passive) |
| | Regensburger Wortflüssigkeitstest (RWT) (20) | Verbal fluency (active) |
| **Verbal memory** | Wechsler Memory Scale – Revised (WMS-R) (21) | Verbal memory span |
| | Verbaler Lern- und Gedächtnistest (VLMT) (22) | Verbal short- and long-term memory |
| **Figural memory** | Benton Test (23) | Figural short-term memory |
| | Rey–Osterrieth complex figure test (ROCFT) (24) | Figural long-term memory |
| **Working memory** | Wechsler Memory Scale – Revised (WMS-R) (21) | Verbal working memory |
| | TAP Arbeitsgedächtnis (18) | Verbal working memory |
| **Executive functioning** | Verbaler Lern- und Gedächtnistest (VLMT) (22) | Interference |
| | TAP Inkompatibilität (18) | Inhibitory control |
| | Leistungsprüfsystem (LPS) (25) | Reasoning |
| | Tower of London (ToL) (26) | Problem solving/planning |
| **Visuospatial functioning** | Rey–Osterrieth complex figure test (ROCFT) (24) | Visual-spatial ability |
| **Mood** | Beck Depressionsinventar 2 (BDI-II) (27) | Depression |
| | Beck Angstinventar (BAI) (28) | Anxiety |

Comparing dependent binary variables (impairment yes/no) at different timepoints Cochrans Q Test was used, for *post-hoc* tests McNemar Test was performed. Comparing continuous interval scaled variables (z-values) dependent samples student-t-Test was used. The significance level was set to $p<.05$.

Statistical analysis was performed with SPSS 26.0 for Windows (2019, IBM Corp.; Armonk, NY) and GraphPad Prism 9.0 for MacOS (2021, GraphPad Software, La Jolla CA). Measurement of tumor resection volume was performed using the SmartBrush tool of the Brainlab Elements software (Brainlab AG, Munich, Germany).

# RESULTS

The study cohort comprised 27 patients meeting the inclusion criteria. Patient baseline characteristics are listed in **Table 2**.

All patients had a left hemispheric dominance according to the Edinburgh Handedness Inventory (29). Gliomas were all located in the left hemisphere involving the inferior frontal gyrus, the anterior temporal lobe or the dorsal superior and/or medial temporal gyrus in 16, 4 and 7 patients, respectively. Tumor histology revealed astrocytoma in 15 patients, oligodendroglioma in 8 patients and glioblastoma in 4 patients. IDH mutation was present in 19 patients. Early postoperative MRI revealed that complete (gross total resection, GTR) or subtotal tumor resection (STR) could be achieved in 15 and 6 (55.6% and 22.2%) patients, respectively, while partial resection (PR) could only be achieved in 6 (22.2%) patients. Of note, tumor resection had been stopped as soon as a patient experienced speech function worsening beyond slight semantic or phonological paraphrasia or if a patient had got too tired to perform the respective tasks allowing safe tumor resection without harming speech function. During the first days after surgery 13 patients suffered from transient slight aphasia.

As a consequence, as well as with regard to patients´ postoperative neurocognitive performance, 17 (63%) patients underwent postoperative rehabilitation therapy in highly-specialized neurological rehabilitation hospitals. All other patients were recommended to undergo individual physical, neurocognitive, linguistic and/or occupational therapy in an outpatient setting.

Following tumor board recommendation and patients' personal preference, 21 (77.8%) patients received adjuvant therapy - either after in-patient or during out-patient rehabilitation therapy - with concomitant radio-chemotherapy, and 6 (22.2%) patients were treated only surgically, without adjuvant treatment.

**TABLE 2** | Demographic data.

| Characteristics | [1]number (percentage), [2]median (IQR), [3]mean (standard deviation) |
|---|---|
| **Gender, female** | 10 (37%)[1] |
| **Age, years** | 36.1 (11.8)[3] |
| **Education, years** | 13 (10-13)[2] |
| **Left hemispheric dominance** | 27 (100%)[1] |
| **Histology** | |
| Astrocytoma | 15 (55.6%)[1] |
| Oligodendroglioma | 8 (29.6%)[1] |
| Glioblastoma | 4 (14.8%)[1] |
| **WHO grade** | |
| I | 2 (7.4%)[1] |
| II | 6 (22.2%)[1] |
| III | 15 (55.6%)[1] |
| IV | 4 (14.8%)[1] |
| **IDH mutation** | 19 (70.4%)[1] |
| **Tumor location** | |
| IFG | 16 (59.3%)[1] |
| ATL | 4 (14.8%)[1] |
| dMTG/STG | 7 (25.9%)[1] |
| **Preoperative tumor volume, $cm^3$** | 15.3 (7.5-37)[2] |
| **EoR** | |
| 100% (GTR) | 15 (55.6%)[1] |
| 90-99% (STR) | 6 (22.2%)[1] |
| <90% (PR) | 6 (22.2%)[1] |
| **Adjuvant treatment** | |
| Combined radiochemotherapy | 21 (77.8%)[1] |
| No adjuvant treatment | 6 (22.2%)[1] |

*Data is presented as [1]number (percentage), [2]median (IQR) or [3]mean (standard deviation). WHO (world health organization), EoR (extent of resection), IFG (inferior frontal gyrus), ATL (anterior tempral lobe), dMTG/STG (dorsal medial and superior temporal gyrus/ supramarginal gyrus), GTR (gross total resection), STR (subtotal resection), PR (partial resection).*

## Outcome and Epileptic Seizures

After the first follow-up period of 18.3 months (t2), 21 (91.3%) patients showed stable disease, presenting a median KPS of 100% (IQR 90-100). Most importantly, in the long-term follow-up (t3), stable disease was still diagnosed in 19 (70.4%) patients, and their median KPS came up to 100% (IQR 90-100).

Regarding epileptic seizures, prior to surgery, 18 (66.7%) patients suffered from epilepsy, of which 8 patients had generalized tonic-clonic epileptic seizures, 10 patients had focal seizures. 20 patients reported a regular intake of at least one AED. At the last visit (t3) no patient suffered from ongoing epileptic seizures, thus 100% of the patients corresponded to an Engel Class 1 according to the ILAE classification (30). Thus, significant decrease in the occurrence of epileptic seizures was observed after glioma treatment, comparing seizure activity at baseline (t1) and at patients´ last visit (n=27, time between visit and surgery median 15.9 months, IQR 7.5-34.2; $\chi^2=27.0$, $p<0.001$). However, at this time point, 22 (81.5%) patients still reported on the intake of at least one AED (1 AED 66.7%, 2 AED 14.8%; z=-.894, p=.371). **Table 3** gives an overview about the outcome.

## Neurocognitive Performance – Number of Impairments

Prior to surgery, impairment in at least one neurocognitive domain was found in 37% of patients. With deterioration of 22% of patients working memory was the most frequently impaired domain. Mood disturbances were observed affecting 66.7% of patients.

With regard to significant changes in the number of cognitively impaired patients over time these were found for the domains verbal fluency (Cochran's Q (14)=9.33, p=.009), executive functioning (Cochran's Q (15)=6.0, p=.049) and mood (Cochran's Q (15)=7.0, p=.030).

**TABLE 3** | Outcome data.

| | t1 n=27 | t2 n=22 | t3 n=20 | last visit n=27 |
|---|---|---|---|---|
| **KPS (median, IQR)** | 100 (100-100) | 100 (90-100) | 100 (90-100) | 100 (90-100) |
| **MRI, SD, n (%)** | | 21 (91.3%) | 19 (95.0%) | 25 (92.6%) |
| **Seizures, yes, n (%)** | 18 (66.7%) | 2 (8.7%) | 0 (100%) | 0 (100%) |
| **Number of AEDs, n (%)** | | | | |
| 0 | 7 (25.9%) | 3 (13.0%) | 4 (20.0%) | 5 (18.5%) |
| 1 | 18 (66.7%) | 14 (60.9%) | 13 (65.0%) | 18 (66.7%) |
| ≥2 | 2 (7.4%) | 6 (26.1%) | 3 (15.0%) | 4 (14.8%) |

*Data is presented as number (%) or if marked as median (IQR).*

*Timepoints: t1 (preoperatively), t2 (after a median follow-up period of 4.1 months) and t3 (after a median follow-up period of 18.3 months). The fourth column ("last visit") considers the last available visit for each patient (n=27, time between visit and surgery median 15.9 months). KPS (Karnofsky performance score), MRI (magnetic resonance imaging), SD (stable disease), AED (antiepileptic drugs).*

In detail, for the domain verbal fluency, *post-hoc* tests showed that the number of impaired patients increased significantly from t1 to t2 (p=.031). At t3, this number had decreased nearly to baseline, however, this change did not reach the level of significance (t3 vs. t2, p=.125; t3 vs t1, p=.5; t1 7.7% impairment vs. t3 10.5% impairment).

Although for executive functioning similar tendencies were observed, *post-hoc* analysis found no significant changes between t2 and t1 (p=.219) and between t3 and t1 (p=1.0), and only a trend for improvement between t3 and t2 (p=.063). Nevertheless, at t3, impairment in executive functioning was observed in only 5% of patients compared to 14.8% of patients preoperatively.

As mentioned, patients´ mood was especially affected prior to surgery (t1 66.7%). However, *post-hoc* tests showed a trend for improvement comparing t1 and t2 (p=.07), with at t3 only 35% of patients presenting mood disturbances.

For each neurocognitive domain, the percentage of patients impaired is presented in **Figure 1**. Moreover, a detailed table with Cochran Q's and *post-hoc* tests for all domains is available as supplementary material (**Supplementary Table 1**).

## Neurocognitive Performance – Individual Changes

Comparing the mean z-scores, for none of the domains the cut-off of -1.5, defining neurocognitive impairment, was reached (**Figure 2**). Considering observed differences over time and applying a change in z-score > ± 1 as cut-off for a significant change in cognitive performance, a trend of improved neurocognitive functioning was found for attention between t3 and t2 (t (14)=2.03, p=.062).

For verbal fluency patients showed a significant worsening for t2 vs. t1 (t (21)=2.82, p=.010 as well as a significant improvement for t3 vs. t2 (t (14)=5.20, p=<.001). For verbal memory patients showed significant improvement for t3 vs. t2 (t (14)=3.41, p=.004). For figural memory patients showed a significant improvement after surgery for t2 vs. t1 (t (21)=2.59, p=.017), t2 vs. t3 (t (12)=3.33, p=.006) and overall comparing t3 vs. t1 (t (18)=3.37, p=.003). For working memory there was a significant worsening for t2 vs. t1 (t (21)=2.67, p=.014) and a trend for improvement comparing t3 vs. t2 (t (14)=2.03, p=0.061).

A detailed table with student t-tests for all domains is available in the supplementary material (**Supplementary Table 2**).

# DISCUSSION

Diagnosis as well as treatment of gliomas represent a significant strain in patients' lives. The confrontation with a life-threatening disease entails a serious psychological burden for both the patients and their relatives (31). Moreover, tumor- and therapy-related impairments of neurologic and neurocognitive functions often not only decrease patients´ quality of life, but also immediately influence their working ability, subsequently, their financial situation and, most importantly, their social life. Therefore, maintenance or even improvement of patients´ neurologic and neurocognitive functions has to be the utmost aim of glioma patients´ treatment.

We could demonstrate that an individual therapy of glioma patients allows them to return to or even improve their preoperative conditions compared with baseline in the long-term, despite a deterioration of most cognitive functions in the short-term (compare 4). First and foremost, no significant changes were observed in patients´ verbal memory, although proportionally many tumors were located in the temporal lobe (41%), with surgery in the temporal lobe being known to negatively affect verbal memory (32, 33). Nevertheless, to our clinical experience these patients frequently report on short-term memory difficulties. That this experience is not mirrored in the results of the present study might be due to the fact that the respective z-values all ranged between 0 and -0.9, not exceeding the cut off value of -1.5. Thus, at first sight, patients might not have had a relevant deficit in the corresponding domains, neither pre- nor postoperatively. However, despite not crossing the cut off values, z-scores differed significantly over time for the domain verbal fluency, verbal memory, and working memory, demonstrating that patients´ neurocognitive functions change individually in the context of their performance. Therefore, in practice, we recommend both approaches: On the one hand, a development of deficits should be monitored in order to define disturbances relevant to everyday life. On the other hand, patients´ individual changing clinical conditions should be considered in order to recognize changes in their individual framework. Each individual patient´s functions change differently over time, so that a patient-centered, individual assessment and refraining from rigid cut-off values is recommended.

Several measures may have positively influenced the present patients´ neurocognitive outcome and their quality of life, all

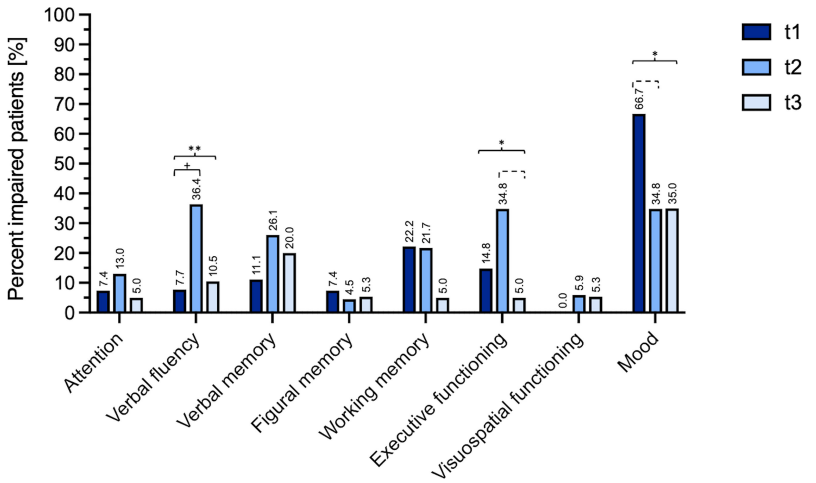


**FIGURE 1** | Percent of impaired patients at T1 (preoperatively), T2 (after a median follow-up period of 4.1 months) and T3 (after a median follow-up period of 18.3 months). Long brackets mark results of the Cochran's analysis (*=p < 0.05, **=p < 0.01), small brackets mark the *post-hoc* tests performed for serial follow up data (+=p < 0.05, dashed bracket p < 0.1). Complete data with Cochran Q's and *post-hoc* tests for all domains is available as supplementary material (**Supplementary Table 1**).

above the applied neurosurgical technique of awake surgery. A plethora of previous studies has provided evidence that awake surgery is the method of choice for achieving maximal EOR while preserving patients´ neurologic and neurocognitive functions (9–11). Accordingly, GTR and STR could be achieved in 55% and 22% of patients, respectively, with only a small percentage of all patients presenting neurocognitive impairments after a median follow-up period of 18.3 months (t3).

Another prognostic favorable aspect was patients´ excellent preoperative KPS. All patients reported on normal daily activity and were presumably asymptomatic at the moment of presentation in our department and prior to surgery – despite a recent first epileptic seizure having led to tumor diagnosis in 18 (66.7%) patients. The fact that only detailed neurocognitive evaluation revealed cognitive impairments in patients presenting with a KPS of 100% suggests the importance of preoperative assessment, particularly with regard to longitudinal evaluation. Likewise, patients presented a median KPS of 100% also at long-term follow-up, confirming the effectiveness of individual glioma therapy.

Finally, cognitive rehabilitation might have positively influenced patients´ outcome. As demonstrated by a randomized controlled

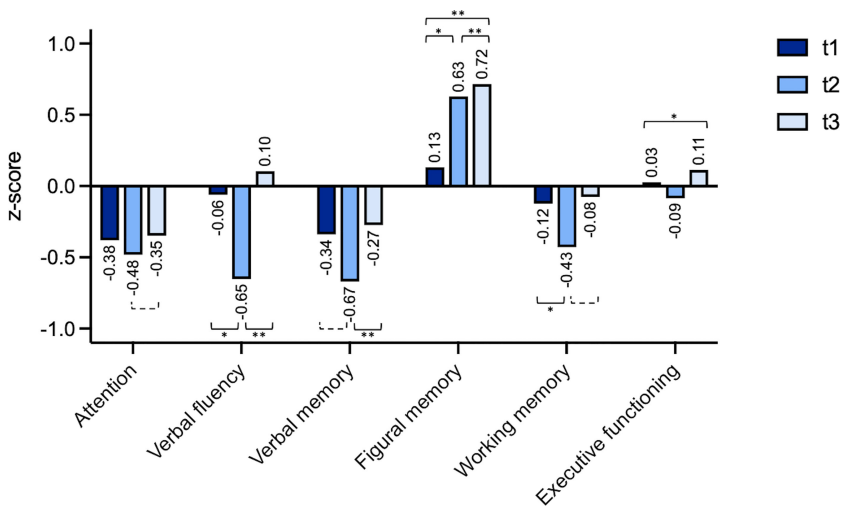


**FIGURE 2** | Individual changes (z-scores) t1 (preoperatively), t2 (after a median follow-up period of 4.1 months) and t3 (after a median follow-up period of 18.3 months). The domain "visuospatial functioning" was excluded because the underlying test has no variance of the standardized value in the performance range rated as unimpaired. *=p < 0.05, **=p < 0.01, dashed bracket p < 0.1.

trial, rehabilitation with therapist-guided cognitive training significantly improves patients´ cognitive functions (34). Adequate rehabilitation, especially with regard to speech therapy and cognitive rehabilitation, had been initiated in all our patients immediately after surgery, however, whether and to which extent they pursued rehabilitation therapy in the outpatient setting over time could not be derived from patients´ records. Nevertheless, the premise of cognitive rehabilitation achieving optimal outcomes is meticulous assessment of changes in patients´ neurocognitive performance over time. We therefore strongly recommend glioma patients´ neurocognitive evaluation by a clinical neuropsychologist pre-, peri- and postoperatively. Through appropriate cognitive rehabilitation patients´ return to work, their family life as well as social life will be positively influenced, which in turn will be reflected in higher quality-adjusted life-years and lowered economic burden (35).

The results of the present study are only partially in line with the previously published literature, most obviously due to their heterogeneity of inclusion criteria and the difference of time-intervals between neurocognitive assessments. In the most recent review on supratotal resection of high-grade glioma Tabor et al. reported on a decline in all neurocognitive domains immediately after surgery with return to baseline after a follow-up period of 1 to 4 months, with the exception of memory (36). Another meta-analysis on neuro-cognition after glioma surgery, including both low- and high-grade glioma patients, reported on improved language, attention and memory already in the immediate postoperative period, whereas executive function showed sustained decline also at long-term follow-up 3 to 6 months after surgery (37). A third review by Satoer et al. equally observed a decline in most cognitive domains in the immediate postoperative phase, but found no general significant neurocognitive changes after further 3 to 12 months, with the exception of three reports on improvements in language, memory, attention and/or executive function (38).

However, the present study identified improvements in all neurocognitive domains at long-term follow-up, both compared to preoperative baseline as well as the short-term postoperative phase. Of particular note, we conducted long-term follow-up examinations after a median period of 18.3 months, whereas previous studies evaluating neurocognitive changes over the postoperative period reported on long-term neurocognitive assessments 3 to 6 months after surgery (32, 39–42). By contrast, we defined neurocognitive assessments within the first 9 postoperative months to fall into short-term evaluations (with the median coming up to 4.1 months), since we observed a significant change in patients´ neurocognitive performances at this time point during their course of disease. Considering this relatively "late" first postoperative follow-up evaluation the percentage of cognitively impaired patients was quite high at this time point, however, the respective z-scores all ranged far above -1.5, confirming the mild character of patients´ neurocognitive deterioration.

The results in the present study might, however, have been confounded by the presence of epileptic seizures preoperatively, by ongoing anti-epileptic therapy thereafter and adjuvant oncologic treatment. While all patients were seizure-free after tumor surgery, 22 (81%) patients continued using anti-epileptic drugs, most probably to maintain or return to an independent and fulfilled social and working life (43). However, in contrast to previous studies (44) anti-epileptic therapy did not result in a relevant deterioration of cognition in our patients. We therefore advocate to achieve seizure freedom by the use of "newer" anti-epileptic drugs such as Lacosamide or Levetiracetam, which were applied to our patients, and which have been shown to improve neurocognition and behavior through its effect on seizure control (45, 46).

Regarding adjuvant oncologic treatment, 21 (77.8%) patients of the present cohort underwent combined chemo-radiotherapy. Although several studies have reported on cognitive decline affecting all domains already 6 months following adjuvant treatment (47, 48), especially after radiotherapy (49), we did not observe a correlation of the present patients´ neurocognitive performance and adjuvant treatment.

## LIMITATIONS

This study had some limitations. First, follow-up neurocognitive data sets were not available for all patients. Due to patients' refusal to undergo further postoperative cognitive evaluation, longitudinal follow-up evaluations were only possible in 16 patients. Unfortunately, the number of patients did not allow for a multivariant analysis which would have been necessary to confirm that neurocognitive outcome is influenced by tumor characteristics, surgical and seizure outcome as well as adjuvant treatment.

Thus, the heterogeneity of patient cohorts may have biased presented results. A valid objection is, that low grade and high grade gliomas were mixed. Since the present study aimed at analyzing the longitudinal neurocognitive outcome after awake surgery depending on glioma localizations (IFG, ATL, dMTG/STG) the analysis of both, low and high grade glioma patients was accepted. Moreover, it is likely that only patients with relatively good clinical performance biased our results. On the one hand, only patients with tumors being amenable to a great extent of tumor resection were included into our study; on the other hand, only patients who were willing and able to undergo long-term follow-up cognitive evaluations were included and might have possibly caused an overestimation of clinical and neurocognitive results.

Moreover, data on patients´ individual physical, neurocognitive, linguistic and occupational therapies were not evaluated in detail, since detailed records on these therapies were incomplete. Nevertheless, since 17 of 27 patients underwent postoperative rehabilitation therapy in highly-specialized neurological rehabilitation hospitals, and since those other patients who displayed minor deficits either regarding neurocognition and/or language function and/or fine motor function deficits were recommended to undergo neurocognitive, linguistic and occupational therapies in the outpatient setting, we presume that nearly all patients received one or more types of postoperative therapies.

For the analysis of the neurocognitive data the calculation of reliable change indices (RCIs) is also possible. The rationale for not using this method came from the fact that they are rarely calculated in clinical practice and data would have not been

comparable. Another lack in neurocognitive testing is not using basal language tests [e.g. Aachen Aphasia Test (50) or Boston Naming Test (51)] which should be considered for future studies. Regarding patients´ consistently good KPS, it should be discussed that neurocognitive deficits, which were assessed with detailed psychometric tests, did not seem to be functionally relevant in simple everyday situations (such as clinical rounds). Further evaluation in a bigger cohort of patients is therefore mandatory, in order to allow for further meaningful correlations of clinical, surgical, and cognitive data.

## CONCLUSION

Awake surgery in patients with eloquently located gliomas allows for an excellent functional outcome and seizure-freedom in the long-term course. With regard to neurocognitive assessment, individual patients´ functional courses of disease need to be considered in addition to cut-offs values. In light of these favorable outcomes the results of the present study may help neurosurgeons and neuro-oncologists in deciding on personalized therapeutic strategies and in counselling of glioma patients.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee University Hospital Frankfurt. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

M-TF, MB, and SR conceived the presented idea and developed the experimental design. Neurocognitive assessments were conducted by IL, MB, and NC. KF was involved in the neuropathological workup. MV participated regarding neurooncological issues. Intra-operative testing during awake surgery was performed by IL and CK. MR provided advice on neuroradiological issues. M-TF, MB, and SR prepared the submitted manuscript. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.815733/full#supplementary-material

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# GNG12 as A Novel Molecular Marker for the Diagnosis and Treatment of Glioma

*Runze Liu[1†], Zhendong Liu[2†], Yaoye Zhao[3†], Xingbo Cheng[2†], Binfeng Liu[3], Yanbiao Wang[2], Jialin Wang[2], Xiaoyu Lian[3], Yongjie Zhu[1] and Yanzheng Gao[2*]*

*[1] Henan University People's Hospital, Henan Provincial People's Hospital, Zhengzhou, China, [2] Department of Surgery of Spine and Spinal Cord, Henan Provincial People's Hospital, Henan International Joint Laboratory of Intelligentized Orthopedics Innovation and Transformation, Henan Key Laboratory for Intelligent Precision Orthopedics, People's Hospital of Zhengzhou University, People's Hospital of Henan University, Zhengzhou, China, [3] Zhengzhou University People's Hospital, Henan Provincial People's Hospital, Zhengzhou, China*

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****Correspondence:***
*Yanzheng Gao*
*yanzhenggaohn@163.com*

*[†]These authors have contributed equally to this work*

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**Purpose:** GNG12 influences a variety of tumors; however, its relationship with glioma remains unclear. The aim of this study was to comprehensively investigate the relationship between GNG12 and the clinical characteristics and prognosis of glioma patients and reveal the mechanisms causing the malignant process of GNG12.

**Materials and Methods:** We obtained information on clinical samples from multiple databases. The expression level of GNG12 was validated using a RT-qPCR and IHC. KM curves were used to assess the correlation between the GNG12 expression and OS of glioma patients. An ROC curve was drawn to assess the predictive performance of GNG12. Univariate and multivariate Cox analyses were performed to analyze the factors affecting the prognosis of patients with glioma. GSEA and TIMER databases were used to estimate the relationship between GNG12 expression, possible molecular mechanisms, and immune cell infiltration. CMap analysis was used to screen candidate drugs for glioma. Subsequent *in vitro* experiments were used to validate the proliferation and migration of glioma cells and to explore the potential mechanisms by which GNG12 causes poor prognosis in gliomas.

**Results:** GNG12 was overexpressed in glioma patients and GNG12 expression level correlated closely with clinical features, including age and histological type, etc. Subsequently, the K-M survival analysis indicated that the expression level of GNG12 was relevant to the prognosis of glioma, and the ROC curve implied that GNG12 can predict glioma stability. Univariate and multivariate analyses showed that GNG12 represents a risk factor for glioma occurrence. GNG12 expression is closely associated with some immune cells. Additionally, several *in vitro* experiments demonstrated that down-regulation of GNG12 expression can inhibits the proliferation and migration capacity of glioma cells. Ultimately, the results for the GSEA and WB experiments revealed that GNG12 may promote the malignant progression of gliomas by regulating the cell adhesion molecule cell signaling pathway.

**Conclusion:** In this study, we identified GNG12 as a novel oncogene elevated in gliomas. Reducing GNG12 expression inhibits the proliferation and migration of glioma cells. In summary, GNG12 can be used as a novel biomarker for the early diagnosis of human gliomas and as a potential therapeutic target.

**Keywords: Guanine nucleotide-binding protein subunit gamma-12, prognosis, biomarker, oncogene, glioma**

## INTRODUCTION

Gliomas represent the most common primary intracranial malignant tumors found in adults, accounting for 81% of intracranial brain malignancies (1). An increasing number of scholars have studied this disease because it is difficult to detect at its early onset and has a poor prognosis. According to the fifth revised edition of the Guidelines for Central Nervous System Tumors published by the World Health Organization (WHO) in 2016, gliomas are mainly divided into two categories: diffuse and non-diffuse under restricted growth patterns. With progress in research on the molecular mechanisms of glioma, glioma subtypes have gradually shifted from histological classifications, such as diffuse astrocytomas and oligodendroglial cell tumors, to molecular classifications, such as isocitrate dehydrogenase 1 and 2 (IDH1/IDH2) point mutations and 1p/19q co-deletions (2). Temozolomide is often used to administer chemotherapy within 6 months of surgery for high-grade gliomas (3, 4), and combining this treatment with radiation therapy is becoming widely accepted by clinicians and patients (5). Although patients with low-grade gliomas tend to have a better prognosis after surgical resection, some studies have shown that a better prognosis would be obtained in combination with radiotherapy or chemotherapy (4, 6). In addition, patients with IDH mutations or 1p/19q co-deletions have had mutated genes that were highly sensitive to alkylating agents, so their survival time after temozolomide chemotherapy tended to be longer than that of patients with wild-type IDH or without 1p/19q co-deletions (7). Thus, an increasing number of molecular targets are being used in clinical diagnosis and treatment, and they play a crucial role in managing various types of gliomas. Despite several treatment options being available, the 5-year survival rate of patients with diffuse glioma remains poor. Therefore, the search for increasingly effective and highly specific biomarkers is urgently needed to improve this discouraging situation.

Guanine nucleotide-binding proteins (G proteins) are a family of signaling proteins composed of α, β, and γ subunits that can bind to guanosine diphosphate and demonstrate GTP hydrolase activity, which functions as a molecular switch during signal transduction (8). GNG12 belongs to the G protein family and influences cellular functions such as cell division, differentiation, and metastasis (9, 10). Previous studies have shown that BV-2 protects neurons as an immune cell within the nervous system, and after knocking down GNG12 in BV-2 cells, the expression of the inflammation-related factor TNF-α increases (11). Therefore, GNG12 acts as a regulatory factor that inhibits inflammation. GNG12 is not only involved in the inflammatory response; in recent years, the relationship between G proteins and tumors has received considerable attention. Many studies have confirmed that some members of the G protein family strongly influence the pathology of cancer. Notably, GNG12 overexpression regulates PD-L1 expressions by activating the NF-κB signaling pathway and promoting the proliferation of pancreatic cancer cells, thus leading to a poor prognosis (12). GNG12 is involved in the malignant process of osteosarcoma (13). Therefore, GNG12 may influence the development and progression of malignant tumors, and may be used as a potential biomarker for prognostic evaluation and treatment. However, there is no evidence of the function of GNG12 in brain malignancies, especially in gliomas. Thus, it is important to further explore the role of GNG12 in gliomas.

In summary, our study analyzes a large sample of data from multiple databases. This is the first study to explore the relationship between GNG12 expression levels and the clinical features and prognosis of gliomas. Concurrently, we used basic experimental validation to reveal the role of GNG12 in the disease progression of gliomas and some of the mechanisms leading to poor prognoses. Therefore, we believe that this study will provide a new biomarker for prognostic assessments of gliomas and a new target for gene therapy to benefit patients with glioma.

## MATERIALS AND METHODS

### Data Collection

The Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn) is an interactive online analysis platform developed by Peking University. The platform contains a large amount of RNA sequencing data from human tumor tissues and mutually matched normal tissues (14). Based on this platform, we analyzed the expression levels of GNG12 in some common tumors and then used box plots to compare the differences in GNG12 expressions between tumor tissues (n=163) and normal brain tissues (n=207). The Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) contains high-throughput gene expression data submitted by research institutions worldwide and provides a range of web-based interfaces and applications (15). To explore GNG12 expression levels in gliomas, we examined microarray data from two datasets: GSE4290 (glioma=77, normal=23) and GSE50161 (glioma=34, normal=13). RNA sequencing data from 1,018 gliomas and their corresponding clinical information were obtained from the Chinese Glioma Genome Atlas (CGGA, http://www.cgga.org.cn) database. From the 1,018 glioma samples, patients with complete relevant clinical information were selected for this study (**Supplementary Table 1**) (16). Based on the Human Protein Atlas (HPA; https://www.

proteinatlas.org/), an immunohistochemical database, the differential expression of GNG12 between glioma and control groups was explored at the protein level (17). The IVY-GAP database (http://glioblastoma.alleninstitute.org/), an immunofluorescence database, was used to explore the differential expression of GNG12 between the glioma and control groups at the nucleic acid level.

## Patients and Tissue Preparation

From June 2019 to September 2019, tissue samples were collected from 24 patients with glioma and seven patients with epilepsy at Henan Provincial People's Hospital (Zhengzhou, China). All the samples contained complete clinical information about the patients. Samples were obtained surgically by dividing the tissue into 1 cubic centimeter sizes, and then placing them in liquid nitrogen for freezing and storage at -80°C until total RNA was isolated. Real-time quantitative polymerase chain reaction (RT-qPCR) was used to verify the expression levels of GNG12 in glioma and non-tumor brain tissues. The study protocol was approved by the Ethics Committee of Henan Provincial People's Hospital (Zhengzhou, China). All experiments were performed according to the guidelines approved by Henan Provincial People's Hospital.

## Cell Culture and Transfection

Human glioma cell (LN229) were purchased from Wuhan Procell Biotechnology (Wuhan, China). Cells were incubated at 37°C in an incubator with a gas environment of 95% O2 and 5% CO2, and the medium used was Dulbecco's modified eagle medium (DMEM) (Procell, Wuhan, China) containing 10% fetal bovine serum (Gibco, USA) and a 1% penicillin-streptomycin mixture (Procell Wuhan, China); next, the cells were passaged and reserved. Transient transfection was used in this study, and the transfection reagent was Lipo3000 (Thermo Fisher, USA). Cells were evenly inoculated into 6-well plates, and then a mixture of siRNA-Mate (GenePharma, Shanghai, China) and lipo3000 was added to each well separately. Transfection was performed using serum-free medium, and the complete medium was replaced after 6 h of action. The knockdown efficiency was determined *via* RT-qPCR after the siRNA was functional (approximately 36 h). The dishes with siRNA-NC were added as a blank control (NC), and those with siRNA-1, siRNA-2, and siRNA-3 were added as the experimental group (KD). Sequences with the highest siRNA knockdown efficiency were selected for subsequent experiments (primers and siRNA sequences are listed in **Table S2**).

## RNA Extraction and RT-qPCR

After transfection with Si-RNA, total RNA was isolated from sample tissues and corresponding cell lines using TRIzol® (Invitrogen, Thermo Fisher Scientific, USA). Then, the RNA's concentration was determined using a NanoDrop One spectrophotometer (Thermo Fisher Scientific, USA), and reverse transcription was performed to obtain cDNA (Novoprotein). Finally, the expression level of GNG12 was determined *via* RT-qPCR using the NovoStart SYBR qPCR SuperMix Plus (Novoprotein). Primers for GAPDH and GNG12 were purchased from Henan Shangya Biotechnology Co. Ltd., with the following sequences: GAPDH-F:5'-CAAGGTCATCCATGACAACTTTG-3', GAPDH-R:5'-GTCCACCACCCTGTTGCTGTAG-3', GNG12-F:5'-GAGCCCTTAGAGACCGAG -3', GNG12-R:5'-AGACTTTGTGTGGTCCAATGT-3'. The thermal cycling conditions were as follows: initial denaturation at 95°C for 10 min, denaturation at 95°C for 10 s, and annealing and extension at 60°C for 30 s for a total of 40 cycles.

## Cell Counting Kit-8 (CCK-8) Assay

Untreated LN229 cells were inoculated in 96-well plates (1000 cells/well), and after waiting for wall attachment and interference with siRNA, the absorbances at 0, 24, 48, 72, and 96 h after transfection were measured. The absorbance at 450 nm was measured using an enzyme marker after incubation in a 37°C incubator for 4 h prior to each measurement.

## Immunochemical Staining

For immunohistochemical staining (IHC), paraffin sections with a thickness of 4 μm were first dewaxed by placing them in an oven at 55°C for 1 h and then in xylene and concentration gradient ethanol for dewaxing and hydration. Antigen repair was performed in an ethylenediaminetetraacetic acid (EDTA) buffer (pH 8.0) with microwave heating for 18 min. Blocking was then performed using 10% goat serum to reduce nonspecific staining. GNG12 (1:100, Bioss, Beijing, China) primary antibody working solution was added dropwise to the slides and placed in a wet box overnight at 4°C. The following day, the secondary antibody was washed with PBST and incubated for 1 h. The exposed GNG12 protein was then labeled with 0.01% DAB chromogenic solution and the nuclei were stained with hematoxylin. Finally, the staining results were observed under a light microscope at 400x magnification, and five fields of view were selected for photography. The IHC results were processed using ImageProPlus (version 6.0). To verify the effect of GNG12 on cell proliferation, we performed cellular immunofluorescence analysis using Ki67. An equal number of LN229 glioma cells were first inoculated uniformly in 3 cm culture dishes, and the culture medium was discarded after 36 h of transfection, fixed with 4% paraformaldehyde for 10 min at room temperature, and then permeabilized with 0.5% Triton X-100 for 30 min. After washing thrice with PBS, the Ki-67 primary antibody (1:200, Abcam, China) was incubated at 4°C for 24 h. Following this incubation, the cells were washed thrice with PBS for 5 min each, and then incubated with the DyLight 594Ig G (1:200, Invitrogen, USA) secondary antibody at room temperature and protected from light for 1 h. Subsequently, the nuclei were stained with DAPI for 10 min. Finally, the Ki67 expression levels in the experimental and control groups were observed by fluorescence microscopy and photographed.

## Scratch Wound Healing Assay

Experiments were performed to verify whether GNG had any effect on glioma cell migration. Equal amounts of cells were uniformly inoculated into 6-well plates. The experimental and control groups were set, and three wells were used for parallel experiments. After the cells reached 70% confluency, the

experimental group was transfected with siRNA-GNG12, and the control group was transfected with siRNA-NC. Once the cells in the culture dish were fully grown, three parallel vertical lines were drawn in each of the six wells with a 200 μL sterile spiking gun tip, and the detached cells were washed with PBS. A 2 mL sample of serum-free medium was added to each well; next, a 0 h sample was taken with an inverted microscope at 200x magnification as the first experimental data, and then placed in a 37°C incubator for 48 h. Scratches were then taken at the same position as the previous one.

## Gene Set Enrichment Analysis (GSEA)

Gene Set Enrichment Analysis(GSEA) is an ideal bioinformatics analysis tool developed by the research team of MIT and Harvard University's Broad Institute and is used to analyze cell signaling pathways. The RNA-sequencing data obtained from the CGGA database were batch corrected and normalized using SVA and LIMMA, and then divided into the "H" (high expression) or "L" (low expression) groups according to GNG12 expression levels. The GSEA (v.4.0.3) software was used for enrichment analysis; the number of permutations was set to 1000, and the "KEGG cell signaling pathway" was selected as the gene set database.

## Western Blotting

The transfected cells were added to RIPA lysate and protease inhibitor to extract total protein (EpiZyme, Shanghai, China). After lysis on ice for 30 min, the proteins were centrifuged at 12000 rpm for 15 min at 4°C. The loading volume of each sample was measured using a BCA kit (GenStar, Beijing, China). Identical masses of proteins were separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Subsequently, the proteins were transferred to PVDF membranes (Bio-Rad, UK) and sealed with skim milk powder. PVDF membranes were incubated overnight at 4°C with primary antibodies against VCAM-1 (1:500, Proteintech, USA), ICAM-1 (1:2500, Proteintech, USA), CDH2 (1:1500, Proteintech, USA), and GAPDH (1:10000, Proteintech, USA). Finally, the HRP-labeled goat anti-mouse secondary antibody (1:5000, Proteintech, USA) was incubated with the filter membrane for 1 h. GNG12 protein expression levels were detected using an imager and a chemiluminescent substrate (ECL) kit (Thermo Fisher Scientific, USA).

## Co-Expression and Drug Analysis

Gene co-expression is an analytical method that uses a large amount of gene expression data to construct correlations between genes and gene functions. The co-expression analysis of GNG12 was performed using Pearson's method. According to the correlation coefficients, the P-value obtained ten genes were positively and negatively correlated with GNG12. Based on the positive and negative related top 10 genes, the complex algorithm of CMap (Connectivity Map, https://portals.broadinstitute.org/cmap) was used to obtain related genes that may downregulate the expression level of GNG12 and screen GNG12 gene therapy drugs in the PubChem database (https://pubchem.ncbi.nlm.nih.gov); this information included the name and chemical formula of the drug and 2D and 3D structures.

## TIMER Database Analysis

The Tumor Immune Estimation Resource (TIMER, https://cistrome.shinyapps.io/timer) is a rich database of tumor immunology and genetics, including gene expression, mutation, and copy number variation (18). In this study, we evaluated the association of GNG12 expression with the infiltration of six different immune cell types (B cells, CD4 + T cells, CD8 + T cells, macrophages, neutrophils, and dendritic cells).

## Statistical Analysis

R software (v.3.6.1) was used to perform the statistical data analysis. Survival and clinical characteristic data were obtained from the CGGA database. The overall survival of GNG12 was determined *via* COX regression and the Kaplan-Meier(KM) method. In addition, Wilcox or Kruskal tests were used to test the relationship between the expression level of GNG12 and clinical characteristics. A time-dependent receiver operating characteristic (ROC) curve shows the evaluation value of the clinical prognosis of GNG12 for glioma. Univariate and multivariate analyses were used to analyze the factors affecting the prognosis of glioma patients. The expression differences between the experimental and control groups of GNG12 were tested using GraphPad Prism software (9.1.0) with a Mann-Whitney test, Chi-square test, or Fisher's exact test ($P<0.05$, considered statistically significant).

# RESULTS

## GNG12: Highly Expressed in Glioma

GEPIA was used to analyze the expression of GNG12 in different tumors. GNG12 was highly expressed in various tumors, including glioblastoma multiforme (GBM), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), pancreatic adenocarcinoma (PAAD), and thymoma (THYM) (**Figure 1A, B**). The GSE4290 and GSE50161 datasets from the GEO database revealed that the expression level of GNG12 was higher in gliomas than in normal brain tissue (**Figures 1C, D**). Moreover, GNG12 protein expression levels were similarly elevated in HPA immunohistochemistry and IVY-GAP *in situ* hybridization data (**Figures S1** and **S2**, respectively). More importantly, we obtained the same results as those predicted by the database through further RT-qPCR and IHC experimental validations (**Figures 1E, F**). Combined with the above database analysis and experimental results, GNG12 was overexpressed in glioma.

## Clinical Characteristics of Studied Patients and Their Relationship With GNG12 Expression

Subsequently, the relationship between GNG12 expression levels and patients clinical characteristics with glioma was analyzed. Wilcoxon and Kruskal-Wallis tests were used to analyze the relationship between clinically relevant patient information and the expression levels of GNG12. We observed that the expression level of GNG12 significantly correlated with age, WHO classification, histological type, primary recurrence classification,

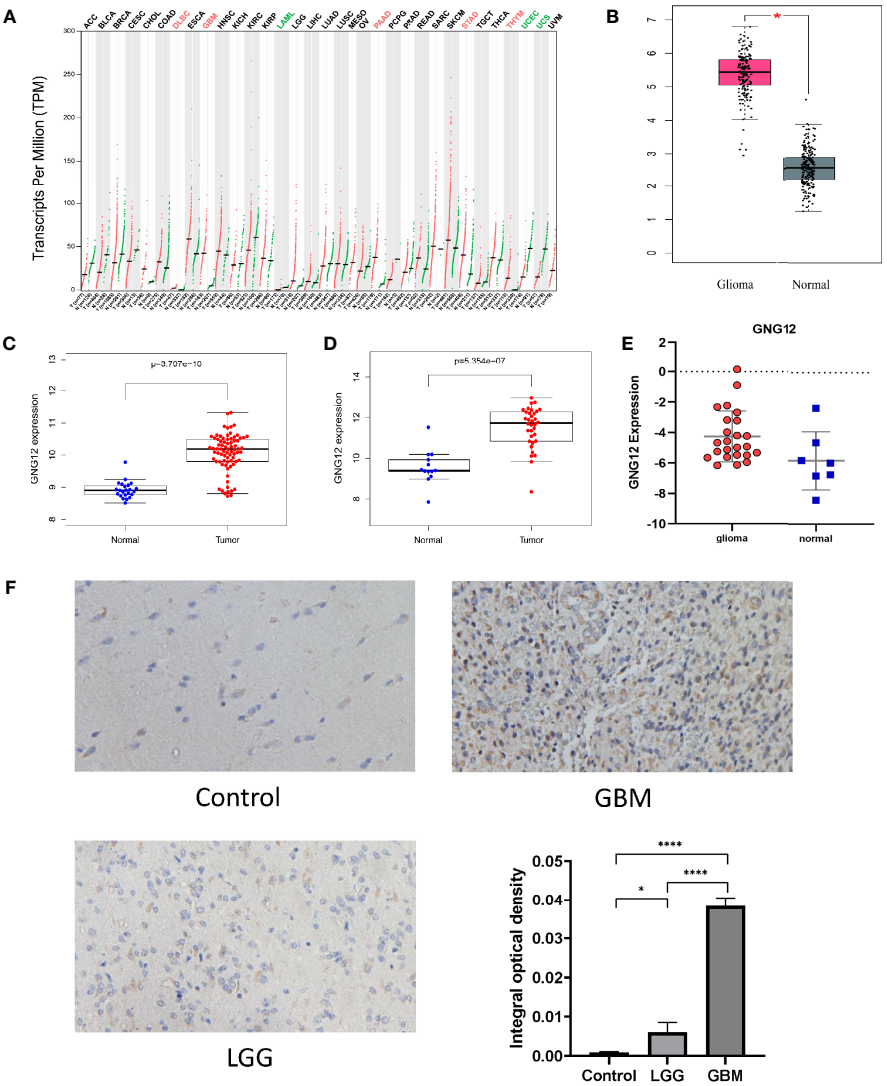



**FIGURE 1** | The expression of GNG12 at different levels (mRNA, protein, gene microarray and gene sequencing) in gliomas. **(A)** The expression of GNG12 in different types of tumor tissues in the GEPIA, the expression of GNG12 in glioma (n=163) and normal brain tissue (n=207), red and green respectively represent the difference in expression level. Green means that the gene is under-expressed in tumor tissues, and the red means the gene is highly expressed in tumor tissues. **(B)** In the GEPIA database, the expression of GNG12 is different in glioma and normal brain tissue. **(C)** Box plot based on the expression level of GNG12 in the GSE4290 (Glioma=77, Normal=23). **(D)** Box plot based on the expression level of GNG12 in the GSE50161(Glioma=34, Normal=13). **(E)** RT-qPCR experimental results show that the expression of GNG12 in gliomas is higher than that in normal tissues. **(F)** Results of immunohistochemical experiments in normal brain tissue, low-grade glioma and glioblastoma and statistical analysis (Magnification: *400). (****P<0.0001, *P<0.05) .

1p19q coding data, and IDH mutation status. As shown in **Figure 2**, the expression of GNG12 in glioma tissues from patients aged >41 years was significantly higher than that in patients aged ≤ 41 years (p =0.009). The expression level of GNG12 was positively correlated with the WHO grade of glioma (P < 0.001). Regarding the 1p19q co-deletion status, there were lower gene expression levels in patients with a codeletion of 1p19q than in patients with non-codeletion of 1p19q (p < 0.001). Moreover, for the IDH mutation status, there was a higher level of gene expression in the wild type than in the mutant (p < 0.001). In addition, recurrent gliomas had higher GNG12 expression levels than primary gliomas, which explains why patients with recurrent gliomas had a worse prognosis (p<0.05). The strong association between GNG12 expression levels and the clinical characteristics of glioma patients suggests that GNG12 may be related to the survival prognosis of glioma.

## GNG12 Associated With Poor Prognoses in Patients With Glioma

We further explored the relationship between GNG12 expression levels and the survival prognoses of patients with glioma. First, the survival analysis results showed a significant correlation

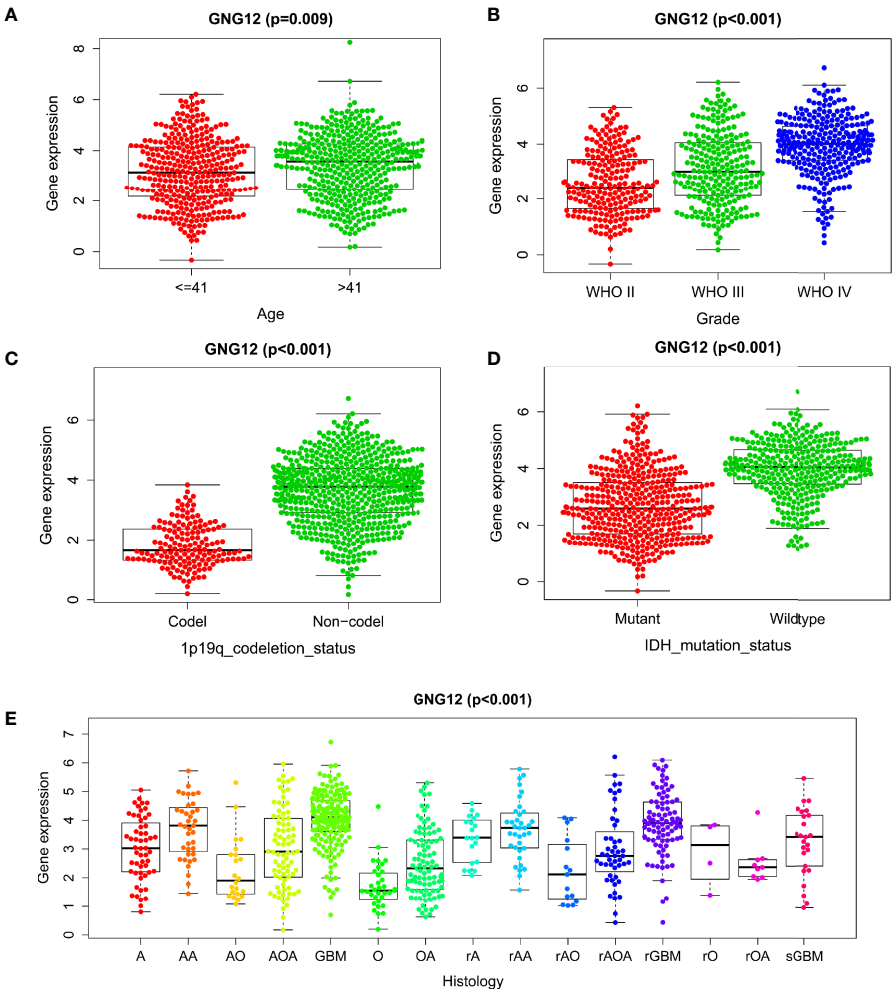



**FIGURE 2** | Correlation between GNG12 and different clinical characteristics based on CGGA database. **(A)** age. **(B)** WHO grade. **(C)** 1p19q co-deletion. **(D)** IDH mutation. **(E)** Histology.

between high GNG12 expression and reduced survival rates of patients with glioma. Subsequently, the survival rates of the different molecular subtypes in each grade were analyzed separately. In grade II and III gliomas and in all samples, the results showed that the survival rate of the GNG12 high expression group was lower than that of the low expression group, regardless of the presence of IDH mutations or 1p/19q co-deletions (**Figures 3A–C**). In grade IV gliomas, the results were not statistically significant, which probably resulted from the poor prognoses of high-grade gliomas and the associated lower survival rate of the patients (**Figure 3D**). However, we nonetheless observed an overall trend that was consistent with the results of the analysis of grade II and III gliomas. Moreover, ROC analysis showed that the area under the ROC curve (AUC) was 0.701, 0.766, and 0.803 for the one, three, and five-year Overall Survival (OS), respectively (**Figure 3E**). The AUC data were meaningful for different WHO classifications (**Figures 3F–H**). Therefore, our results indicate that GNG12 may serve as a biomarker for glioma, especially in the five-year OS group. Univariate and multivariate analyses showed that high levels of GNG12 expression, PRS grading ($p < 0.001$; HR = 2.032; 95% CI, 1.724-2.393), WHO grading ($p < 0.001$; HR = 2. 623; 95% CI, 1.918-3.586) and age ($p < 0.003$; HR = 1.351. 95% CI, 1.105-1.652) may represent an independent risk factor for poor prognoses in patients with glioma. IDH mutation status ($p < 0.019$; HR = 0.750; 95% CI, 0.590-0.953) and 1p/19q co-deletion ($p < 0.005$; HR = 0.596; 95% CI, 0.415-0.856) may represent protective factors (**Figures 3I, J**, respectively). These data indicate that GNG12 may serve as a predictive biomarker for poor prognosis.

## Correlations of GNG12 With Immune Cell Infiltration

The correlation between GNG12 expression levels and tumor immune cell infiltration was analyzed using the TIMER database. After adjusting for purity, the expression levels of GNG12 in

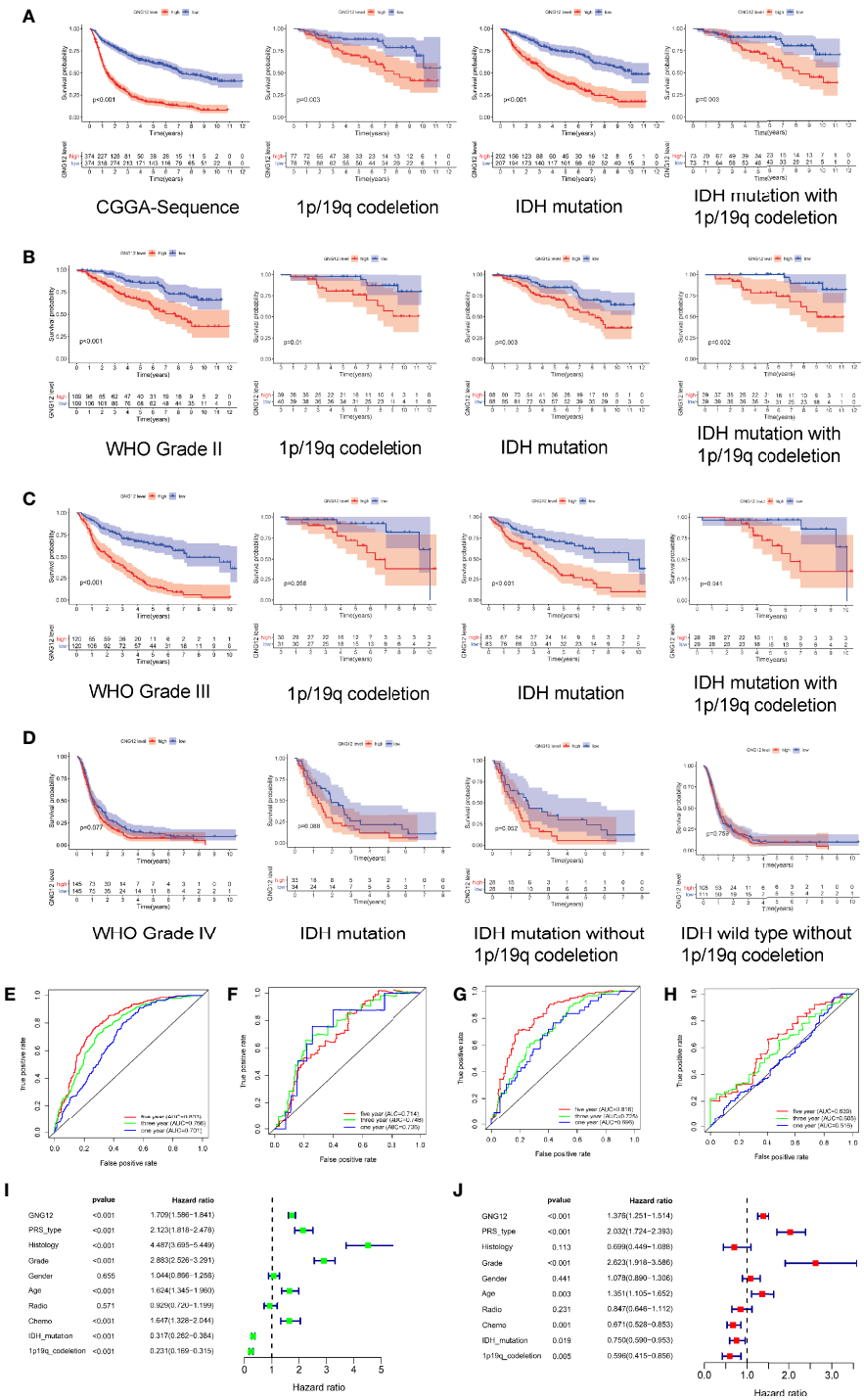



**FIGURE 3** | Relationship between different expression status of GNG12 and prognosis of glioma patients based on CGGA RNA-seq data. **(A)** In order, overall survival based on CGGA database, survival with 1p/19q co-deletion, survival with IDH mutation and survival with IDH mutation with 1p/19q co-deletion. **(B)** Survival rates for WHO grade 2, survival with 1p/19q co-deletion in grade 2, survival with IDH mutation and survival with IDH mutation with 1p/19q co-deletion, in that order. **(C)** In order, the survival rate of WHO grade 3, the survival rate of 1p/19q co-deletion in grade 3, the survival rate of IDH mutation and the survival rate of IDH mutation with 1p/19q co-deletion. **(D)** In order, the survival rate of WHO grade 4, the survival rate of IDH mutation in grade 4, the survival rate of IDH mutation without 1p/19q co-deletion and the survival rate of IDH wild type without 1p/19q co-deletion. **(E–H)** ROC curve shows that GNG12 has good diagnostic value in glioma, ROC curves of overall glioma based on CGGA and different WHO classifications. **(I, J)** Analysis of univariate and multivariate factors affecting the prognosis of patients with glioma. **(I)** Univariate regression analysis; **(J)** Multivariate analysis.

GBM and LGG correlated positively with the degree of infiltration of $CD4^+$ T cells (P = 2.71e-02, GBM; P = 1.42e-28, LGG), dendritic cells (P = 2.57e-12, GBM; P = 3.99e-49, LGG), and neutrophils (P = 5.96e-03, GBM; P = 6.70 e-46, LGG) (**Figure 4**). In addition, GNG12 expression was associated with the degree of infiltration of B cells (P = 3.43e-40, LGG), $CD8^+$ T cells (P = 1.09e-16, LGG), and macrophages (P = 1.99e-37, LGG), but no significant differences were found in GBM. In glioma patients, a loss of the GNG12 copy number resulted in decreased infiltration of $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells (**Figure S5**). In addition, the infiltration of B cells and $CD8^+$ T cells also decreased in the LGG. Therefore, we further used Kaplan-Meier curves to verify our hypothesis (**Figure S4**), and the results indicated that high GNG12 expression level in enriched B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells were associated with worse prognoses in patients with LGG, whereas high GNG12 expression level in enriched dendritic cells were associated with poor overall survival outcomes. In addition, owing to the broad prospects of immunotherapy, we further determined the relationship between the GNG12 expression and PD-1, PD-L1, and PD-L2 expressions. Encouragingly, GNG12 was positively correlated with PD-L1 (r = 0.293, P = 5.23e-04) and PD-L2 (r = 0.22, P = 9.73e-03) in GBM. We also found that GNG12 was positively correlated with PD-1 (r = 0.347, P = 5.76e-15), PD-L1 (r = 0.474, P = 4.39e-28), and PD-L2 (r = 0.684, P = 4.01e-67) in LGG (**Figure S4**). In conclusion, it is possible that a high GNG12 expression leads to reduced immune cell infiltration and may be an important factor contributing to poor prognoses in patients with glioma.

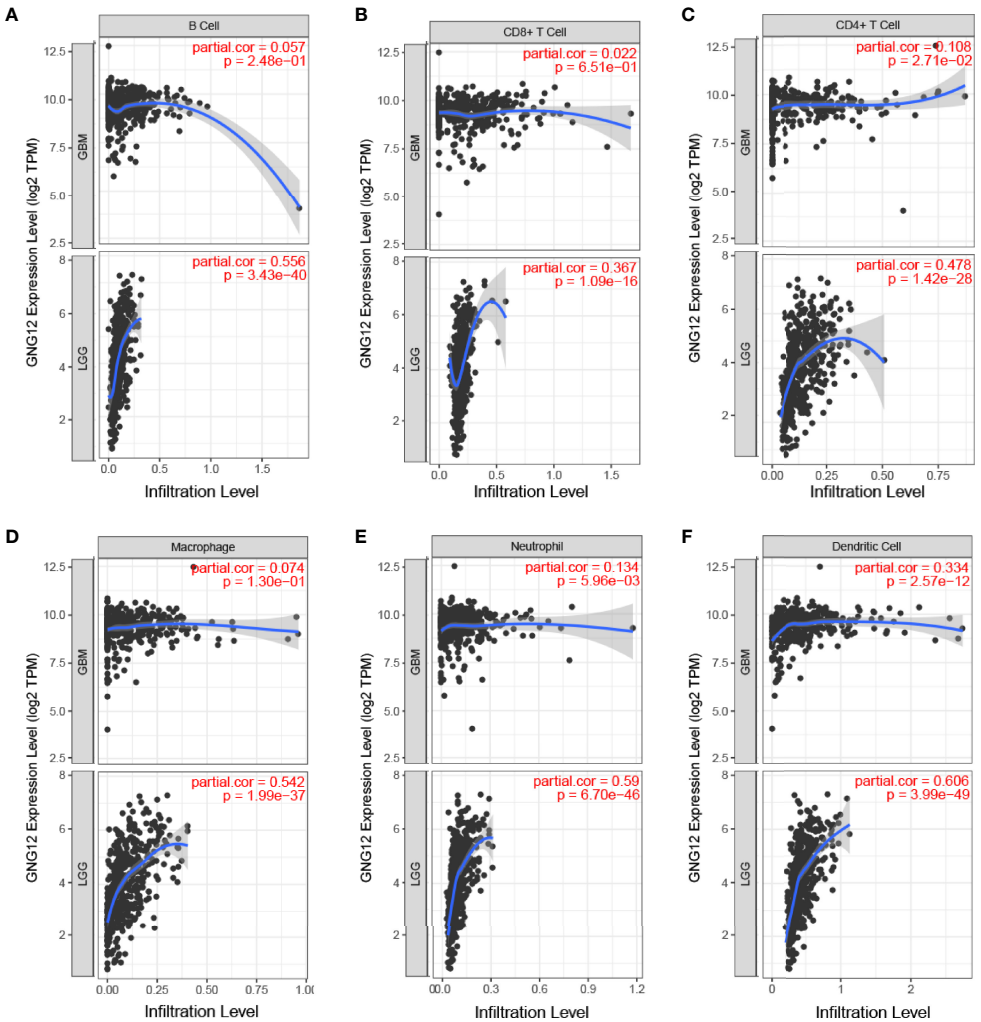
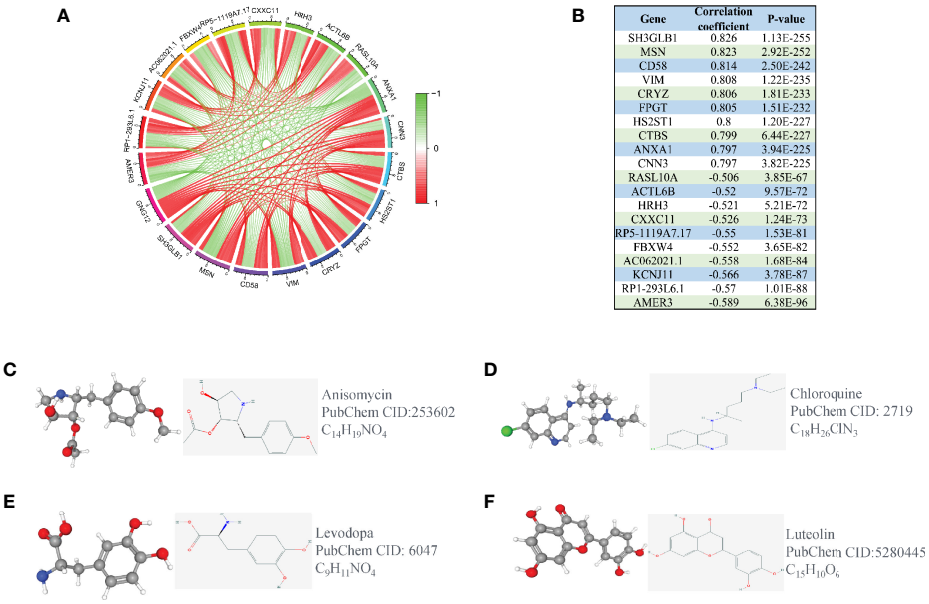



**FIGURE 4** | Relationship between expression of the GNG12 gene and proportion of immune infiltrates. **(A)** B Cell **(B)** CD8+T Cell **(C)** CD4+T Cell **(D)** Macrophage **(E)** Neutrophil **(F)** Dendritic Cell.




| Gene | Correlation coefficient | P-value |
|---|---|---|
| SH3GLB1 | 0.826 | 1.13E-255 |
| MSN | 0.823 | 2.92E-252 |
| CD58 | 0.814 | 2.50E-242 |
| VIM | 0.808 | 1.22E-235 |
| CRYZ | 0.806 | 1.81E-233 |
| FPGT | 0.805 | 1.51E-232 |
| HS2ST1 | 0.8 | 1.20E-227 |
| CTBS | 0.799 | 6.44E-227 |
| ANXA1 | 0.797 | 3.94E-225 |
| CNN3 | 0.797 | 3.82E-225 |
| RASL10A | -0.506 | 3.85E-67 |
| ACTL6B | -0.52 | 9.57E-72 |
| HRH3 | -0.521 | 5.21E-72 |
| CXXC11 | -0.526 | 1.24E-73 |
| RP5-1119A7.17 | -0.55 | 1.53E-81 |
| FBXW4 | -0.552 | 3.65E-82 |
| AC062021.1 | -0.558 | 1.68E-84 |
| KCNJ11 | -0.566 | 3.78E-87 |
| RP1-293L6.1 | -0.57 | 1.01E-88 |
| AMER3 | -0.589 | 6.38E-96 |

**FIGURE 5** | Co-expression analysis of GNG12. **(A)** The ten most significant genes of positive and negative correlating with GNG12; **(B)** The correlation coefficients and P values of the ten most important positive and negative genes related to GNG12. Screening of gene therapy drugs for GNG12 in the CMap and PubChem database (Drug name, chemical structure, 2D structure, 3D structures). **(C)** Anisomycin **(D)** Chloroquine **(E)** Levodopa **(F)** Luteolin.

## Co-Expression Analysis and Medical Therapy Related to GNG12

To explore the related genes that could have positive or negative regulatory effects on GNG12, we performed a co-expression analysis. The genes that positively regulated GNG12 were SH3GLB1, MSN, CD58, VIM, CRYZ, FPGT, HS2ST1, CTBS, ANXA1, and CNN3. The negatively regulated genes were RASL10A, ACTL6B, HRH3, CXXC11, RP5-1119A7.17, FBXW4, AC062021.1, KCNJ11, RP1-293L6.1, and AMER3 (**Figures 5A, B**). We also screened for gene therapy drugs for GNG12 in the CMap and PubChem databases. Four possible gene therapy drugs were identified for GNG12: anisomycin, chloroquine, levodopa, luteolin (**Figures 5C–F**).

## Knockdown of GNG12 Expression Level Inhibits the Proliferation and Migration of Glioma Cells

To further validate the effect of GNG12 on glioma, we performed a series of *in vitro* experiments. First, we designed three small molecule-interfering RNAs to inhibit the expression of GNG12 in glioma cells. The results showed that siRNA-1 was screened with the highest knockdown efficiency using RT-qPCR; therefore, we selected siRNA-1 for the subsequent target downregulation of GNG12 (**Figure 6A**). Knocking down the expression level of GNG12 clearly affected the proliferation and migration abilities of glioma cells. The results of the CCK-8 assay showed that the proliferation efficiency of glioma cells in the KD group was significantly lower than that in the NC group (**Figure 6B**). In parallel, the Ki-67 immunofluorescence assay suggested that the Ki-67 expression level was higher in the NC group than in the KD group, and the differences between the groups were statistically significant (**Figures 6C, D**, respectively). The diminished migratory capacity of glioma cells within 48 h of GNG12 downregulation was ultimately verified using a cell scratch healing assay (**Figures 6E, F**). In summary, our targeted downregulation of GNG12 expression levels in glioma cell lines resulted in a certain degree of diminished proliferation and migration; therefore, we speculate that a high GNG12 expression may be an important factor in the poor prognoses of glioma patients.

## Regulation of Cell Adhesion Molecules Cell Signaling Pathway Proteins by GNG12

We performed a GSEA to further explore the potential mechanisms through which GNG12 affects the malignant biological behavior of glioma cells. The results showed that GNG12 was enriched in tumor-related pathways, including the cell adhesion molecule signaling pathway, JAK-STAT signaling pathway (**Figure 7A**), TOLL-LIKE receptor signaling pathway, focal adhesion, VEGF signaling pathway, and MAPK signaling pathway (**Figure S6**). These cellular signaling pathways showed significant different enrichment rates in samples from patients showing the GNG12 high-expression phenotype based on NES, NOM P-values, and FDR values (**Table 1**), thus indicating a potential role for GNG12 in developing glioma. To probe the specific mechanism by which GNG12 leads to poor prognosis of glioma, we verified the predicted results of GSEA in WB experiments. After the GNG12 expression level was knocked down and the NC group was used for comparison, the assay revealed that the protein expression levels of VCAM-1 and

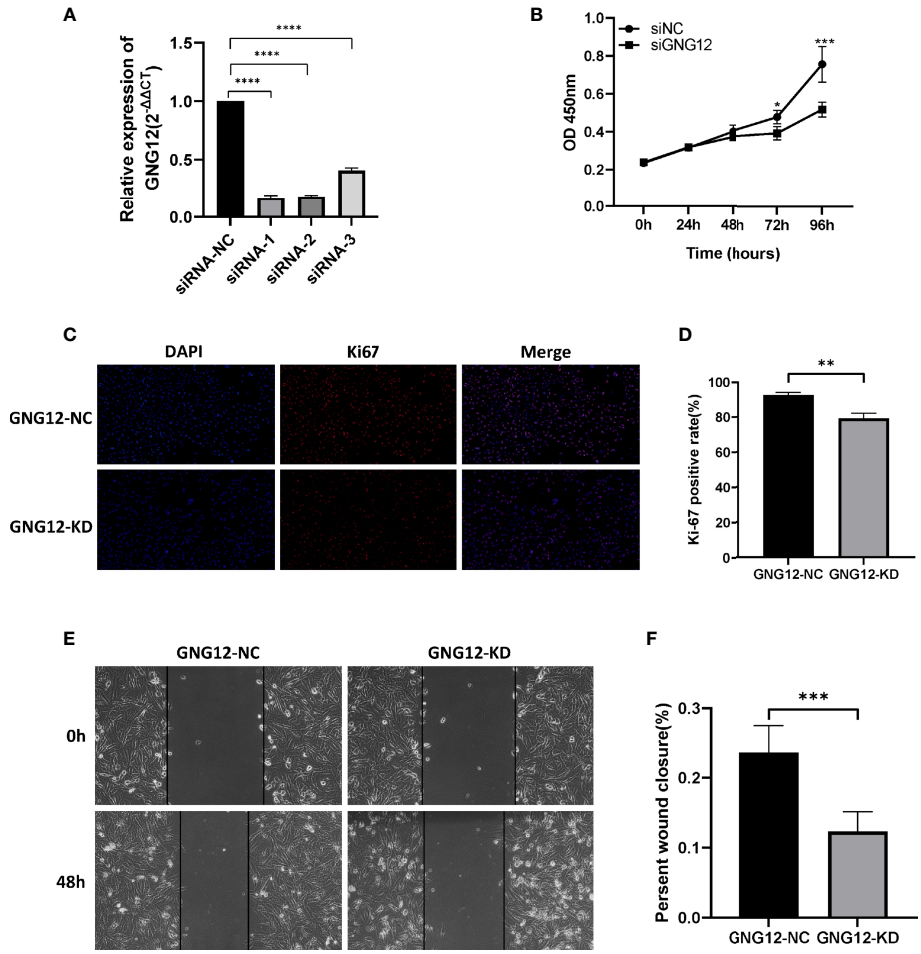



**FIGURE 6** | Effects on proliferation and migration of glioma cells by down-regulating GNG12 expression levels. **(A)** Detection of knockdown efficiency of different siRNA sequences in the glioma cell line LN229. **(B)** CCK-8 assay to compare the effect on cell proliferation after down-regulation of GNG12. **(C)** Immunofluorescence assay comparing the positive rate of Ki-67 after transfection with siRNA-NC and siRNA-KD (Magnification: *400). **(D)** Immunofluorescence assay to analyze the results. **(E)** Cell scratch healing assay using LN229 cell line to compare the migration distance between GNG12-NC group and GNG12-KD group (Magnification: *200). **(F)** Results of statistical analysis of cell scratching experiments. (****P<0.0001, ***P<0.001, **P<0.01, *P<0.05).

CDH2 in the cell adhesion molecule pathway were significantly decreased in the KD group, and the ICAM-1 protein expression level was also decreased to an extent (**Figure 7B**). This suggests that GNG12 may help regulate the cell adhesion molecule pathway involved in the malignant process of gliomas.

## DISCUSSION

Diffuse glioma cells are characterized by extreme invasiveness, which leads to poor prognoses in patients with glioma (19). Therefore, there is a need to identify biomarkers with a high

**TABLE 1** | The gene set enriches the high GNG12 expression phenotype.

| Gene set name | NES | NOM p-val | FDR q-val |
|---|---|---|---|
| KEGG JAK STAT SIGNALING PATHWAY | 1.86 | 0.006 | 0.050 |
| KEGG TOLL LIKE RECEPTOR SIGNALING PATHWAY | 1.89 | 0.006 | 0.042 |
| KEGG FOCAL ADHESION | 1.95 | 0.004 | 0.051 |
| KEGG VEGF SIGNALING PATHWAY | 1.76 | 0.004 | 0.070 |
| KEGG MAPK SIGNALING PATHWAY | 1.67 | 0.012 | 0.078 |
| KEGG CELL ADHESION MOLECULES CAMS | 1.83 | 0.0041 | 0.058 |

*Gene sets with NOM P-value <0.05 and FDR q-value <0.25 were considered as significantly enriched.*
*NES, normalized enrichment score; NOM, nominal; FDR, false discovery rate; GNG12, Guanine nucleotide-binding protein subunit gamma-12.*

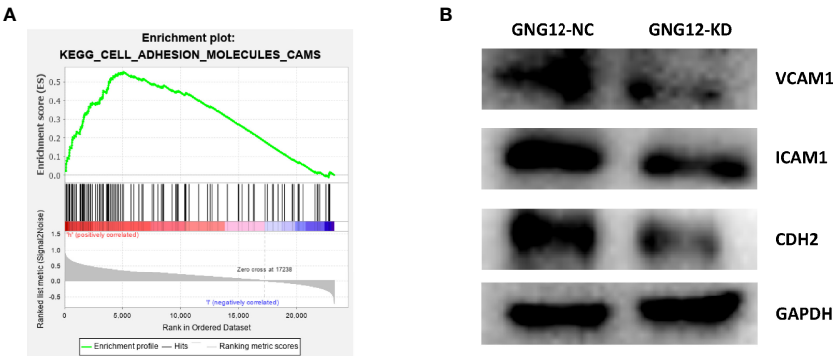



**FIGURE 7** | The involvement of GNG12 in the regulation of cell adhesion molecule signaling pathway. **(A)** Analysis of the significant enrichment of GNG12 in cell adhesion molecule signaling pathway based on GSEA. **(B)** Western blotting assay to detect the effect of knockdown of GNG12 on the expression of VCAM-1, ICAM-1, CDH2.

sensitivity and. Most recent studies have shown that GNG12, as a novel biomarker, plays a key regulatory role in the malignant behavior of tumors. For example, GNG12 can promote pancreatic cancer cell growth *in vitro* and *in vivo* by activating the NF-βB/PD-L1 signaling axis (12). However, the relationship between GNG12 and glioma prognoses as well as related clinical features has not received much attention. Therefore, this study utilized a multi-omics approach and comprehensive bioinformatics analysis to explore the relationship between GNG12 and the malignant biological behavior of gliomas.

To explore this relationship, we performed various bioinformatics analyses. First, using the GEPIA, GEO, and HPA databases, we found that the expression level of GNG12 was significantly increased in gliomas. Our RT-qPCR and IHC results further verified that GNG12 was consistently overexpressed in gliomas. Second, this study showed that high expression r level of GNG12 were significantly correlated with related clinical features, such as age, WHO classification, and molecular typing (20). Interestingly, the results of some studies are similar to ours. For example, Juan Li confirmed that GNG12, as an oncogene in pancreatic cancer and lung cancer, was closely associated with clinical features, and predicted poor prognoses in patients (12, 21). Survival analysis showed that overexpressing GNG12 reduced overall survival rates in patients with grade II and III gliomas, and the same conclusion was obtained for more detailed typing, such as IDH mutation status and 1p/19q co-deletion status; this is a finding that has diagnostic value for prognoses using an ROC curve. However, there was no significant difference in GNG12 expression level among the grade IV gliomas. A possible explanation for this phenomenon is that GBM, one of the most malignant tumors in the human body, is influenced by several genetic and environmental factors (2). Finally, we excluded the influence of random factors *via* univariate and multivariate analyses, from which we reached the scientific conclusion that a high GNG12 expression level may serve as an important predictor of poor prognoses in patients with glioma. Thus, based on the above studies, GNG12 may represent a risk factor for poor glioma prognoses; however, its pathological mechanism needs to be explored in depth.

Previous studies have shown that tumor-infiltrating immune cells are important entities in the tumor microenvironment and are closely associated with the malignant biological behavior of gliomas and patient survival rates (22–25). To explore the relationship between GNG12 and immune cell infiltration, we analyzed the correlation between the expression level of GNG12 and the infiltration level of glioma immune cells using TIMER. The results showed that GNG12 is associated with the infiltration of various immune cells in gliomas, especially B cells, $CD4^+$ T cells, macrophages, and dendritic cells in low-grade gliomas. Although there have been no studies evaluating the correlation between GNG12 and immune cells, the correlation between single genes and cancer immunity has been extensively studied. For example, there is a positive correlation between JAK1 and the infiltration of immune cells, such as $CD8^+$ T cells and dendritic cells in breast cancer (26). CD70 promotes macrophage infiltration into glioma (27). Interestingly, our study's GNG12 expression was positively correlated with immune checkpoints, including PD-1, PDL-1, and PD-L2 in gliomas; therefore, we can combine this gene with immune checkpoint inhibitors to provide a novel glioma immunotherapy. These combined results suggest that GNG12 may interfere with the tumor microenvironment of gliomas by affecting the infiltration of various immune cells, which in turn leads to the development and poor prognosis of gliomas.

To explore small-molecule drugs that could potentially inhibit GNG12, this study screened four small-molecule compounds with potential therapeutic effects on glioma using a CMap analysis. Each drug was obtained through the PubChem database and showed varying degrees of antitumor properties. For example, anisomycin, a monohydroxypyrrolidine and organonitrogen heterocyclic antibiotic, interferes with protein and DNA synthesis by inhibiting the peptidyl transferase or 80S ribosomal system. Previous studies have confirmed that anisomycin promotes cell apoptosis through regulating PP2A/C secretion and plays an important role in the treatment of glioma (28). Some researchers have also found that anisomycin may enhance tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in kidney cancer cells by downregulating the

expressions of Bcl-2, c-FLIP(L), and Mcl-1 (29). This directly or indirectly demonstrates the active anticancer properties of anisomycin in different types of tumors and suggests its promise for eventual clinical applications. In addition, lignocaine has demonstrated antioxidant, antitumor, and immunomodulatory effects in treatments of tumors and may act as an angiogenesis inhibitor through exerting anti-tumor effects. However, lignocaine is poorly hydrophilic; therefore, researchers have combined it with folic acid-modified polyethylene glycol PCL nanoparticles for application. Surprisingly, a significant inhibition of glioma angiogenesis and tumor cell proliferation was observed (30). The reliability of the CMap tool for drug predictions has therefore been demonstrated by previous studies (31). This approach expands the indications for drugs that have not yet been investigated in tumors, and may provide a new direction for subsequent glioma drug therapy.

We conducted a series of experiments to explore the effect of GNG12 on gliomas. The *in vitro* results showed that downregulating GNG12 expression level inhibited the proliferation and migration ability of gliomas, which may represent a potential link between poor glioma prognoses and GNG12. To further understand the pathological mechanism by which GNG12 causes poor glioma prognoses, we applied the GSEA enrichment method. As shown in **Figure S6**, GNG12 was related to some signaling pathways that participate in the occurrence and development of cancer. Although GSEA only indirectly revealed the mechanism of GNG12 in promoting glioma, these results were based on a comparison of GNG12 with thousands of genes. Several researchers have used this method to identify promising biomarkers of gliomas; one such example was Xu and Liu (32, 33). Therefore, the results obtained from the present study were scientific and can be confirmed. Importantly, we conducted WB to further verify this result, which showed that targeted downregulation of GNG12 may impact key targets of the cell adhesion molecule pathway, including ICAM-1, VCAM-1, and CDH2 (34). Other studies have shown that cell adhesion molecules play an essential role in the malignant progression of tumors, and that downregulating key molecular targets can inhibit tumor proliferation and migration (35). Among them, ICAM-1, a cell surface glycoprotein and adhesion receptor, can easily influence inflammatory responses and strongly impacts tumor cell survival and propagation (36). Furthermore, VCAM1 derived from cancer-associated fibroblasts (CAFs) interacts with integrin αvβ1/5 in gastric cancer and promotes tumor invasion in the organism (37). This could prove that our study's results represent a step in the right direction. In conclusion, this study has objectively verified that GNG12 contributes to glioma development and poor prognoses by regulating cell adhesion molecular pathways.

During this study, we conducted a scientific in-depth analysis using a large sample of data from multiple databases, and some unavoidable limitations occurred. First, because some of the samples in this study were obtained from multiple databases, multicenter studies inevitably have some drawbacks, such as a possible bias in sample collection and detection methods. Second, the small size of the health samples obtained from public databases compared with the sample size of the tumor tissues may lead to statistical errors. Finally, specific and personalized treatment information, such as the extent of surgical resection and tumor morphological characteristics, was unfortunately not available in the database based analysis. Therefore, we used *in vitro* cellular assays to verify that the knockdown of GNG12 significantly inhibited the proliferation and migration abilities of glioma cell lines and explored some of the molecular mechanisms of GNG12 in cell signaling pathways. We accordingly reduce the errors caused by incomplete information in the database and other uncontrollable factors.

## CONCLUSION

First, our study showed that GNG12 is overexpressed in gliomas, and that there are some common clinical characteristics and molecular staging that are closely related to GNG12 expression. A high expression level of GNG12 often predicts a poor prognosis in patients with gliomas. Reducing GNG12 expression levels may inhibit tumor cell proliferation and invasion. Furthermore, GNG12 may regulate glioma development and progression by participating in the cell adhesion molecule pathway. Finally, this study provides a new molecular biological target for improving the prognosis and prolonging the survival of glioma patients, and provides important basic support for attacking the pathogenesis of glioma.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request. Requests to access the datasets should be directed to lrz13633858566@163.com.

## AUTHOR CONTRIBUTIONS

ZL and YG developed the original idea and the protocol, abstracted and analyzed data, RL and XC wrote the manuscript, and is the guarantor. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.726556/full#supplementary-material

**Supplementary Table 1** | Characteristics of patients with glioma based on CGGA. CGGA, Chinese Glioma Genome Atlas; WHO, World Health Organization; IDH, Isocitrate dehydrogenase.

**Supplementary Table 2** | Primer sequence of GNG12. siRNA sequences with the highest knockdown efficiency of GNG12.

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