



Philip C. De Witt Hamer, MD,

PhD

Martin Klein, PhD*

Shawn L. Hervey-Jumper, MD[§]

Jeffrey S. Wefel, PhD

Mitchel S. Berger, MD

*Amsterdam UMC, Vrije Universiteit, Department of Neurosurgery, Cancer Center, Amsterdam, Netherlands;

‡Amsterdam UMC, Vrije Universiteit, Department of Medical Psychology, Neuroscience Campus, Amsterdam, Netherlands; [§]University of California San Francisco, Department of Neurological Surgery, San Francisco, California;

[¶]University of Texas MD Anderson Cancer Center, Department of Radiation Oncology and Department of Radiation Oncology, Houston, Texas

Correspondence:

Philip C. De Witt Hamer, MD, PhD, Amsterdam UMC, Vrije Universiteit, Department of Neurosurgery, Cancer Center Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands. Email: p.dewitthamer@amsterdamumc.nl

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Functional Outcomes and Health-Related Quality of Life Following Glioma Surgery

Functional outcome following glioma surgery is defined as how the patient functions or feels. Functional outcome is a coprimary end point of surgery in patients with diffuse glioma, together with oncological outcome. In this review, we structure the functional outcome measurements following glioma surgery as reported in the last 5 yr. We review various perspectives on functional outcome of glioma surgery with available measures, and offer suggestions for their use. From the recent neurosurgical literature, 160 publications were retrieved fulfilling the selection criteria. In these publications, neurological outcomes were reported most often, followed by activities of daily living, seizure outcomes, neurocognitive outcomes, and health-related quality of life or well-being. In more than a quarter of these publications functional outcome was not reported. A minimum essential consensus set of functional outcome measurements would benefit comparison across neurosurgical reports. The consensus set should be based on a combination of clinician- and patient-reported outcomes, assessed at a predefined time before and after surgery. The selected measurements should have psychometric properties supporting the intended use including validity-related evidence, reliability, and sensitivity to detect meaningful change with minimal burden to ensure compliance. We circulate a short survey as a start towards reporting guidelines. Many questions remain to better understand, report, and improve functional outcome following glioma surgery.

KEY WORDS: Glioma, Neurosurgical procedures, Craniotomy, Treatment outcome, Patient outcome assessment, Patient-reported outcome measures, Quality of life

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Diffuse gliomas invade the brain, relentlessly recur, transform into higher grade gliomas, and are invariably lethal.^{1–5} Glioma surgery aims to extensively

remove tumor tissue infiltrating the brain while preserving brain functions by avoiding damage to critical brain structures, except in case the tumor is considered to be unresectable. The more extensive the resection of glioma tissue, the longer patient survival is prolonged and the greater symptoms and seizures are reduced.^{6–10} Nevertheless, when critical structures are compromised, the patient's condition worsens permanently with shortened survival as a consequence.^{11–14} This dilemma is sometimes referred to as the oncofunctional balance in glioma surgery.¹⁵ This is not necessarily a trade-off between living longer or living better, as surgery could at the same time serve both end points. If these end points of cancer treatment are presented to patients as a trade-off, patients generally prioritize a better life over a longer life, in particular when facing an incurable malignancy, in less than optimal condition and at older age,¹⁶ including patients with a glioblastoma.^{17,18}

ABBREVIATIONS: **ECOG**, Eastern Cooperative Oncology Group; **FACT-Br**, Functional Assessment of Cancer Treatment-Brain; **FACT-G**, Functional Assessment of Cancer Treatment-General; **HRQoL**, health-related quality of life; **KPS**, Karnofsky Performance Score; **MDASI-BT**, MD Anderson Symptom Inventory Brain Tumor; **MUIS-BT**, Mishel Uncertainty in Illness Scale-Brain Tumor; **NANO**, Neurologic Assessment in Neuro-Oncology; **NIHSS**, National Institutes of Health Stroke Scale; **PCI**, Patient Concerns Inventory; **PROMIS**, Patient-Reported Outcomes Measurement Information System; **QLQ-C30**, Quality of Life Questionnaire-C30; **SNAS**, Sherbrooke Neuro-Oncology Assessment Scale; **WHO**, World Health Organization

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Oncological outcome is typically measured as overall or progression free survival or time to malignant transformation. Residual tumor volume and extent of resection are surrogate markers of oncological outcome available immediately after surgery. Minimum thresholds for extent of resection and maximum residual volumes have been suggested,^{19,20} while others have argued a continuous positive relationship between extent of resection and survival.²¹⁻²³

Functional outcome of glioma surgery is defined as the alterations in how the patient functions or feels. Multiple perspectives on functional integrity exist depending on who weighs the outcome: the patient, the patient's proxy, the neurosurgeon, the neuropsychologist, or another observer. These perspectives are seldom identical and can be either subjective, which measure how patients feel about their condition, or objective, which measure how patients perform on a specific task. These clinical outcome assessments have been categorized by the rater: patient-reported indicating information directly from the patient without interpretation, such as fatigue; clinician-reported based on an interpretation by a medical professional, such as muscle strength examination; observer-reported by someone else, such as a partner questionnaire; or rater-independent performance outcomes according to standardized objective tests administered by trained professionals, such as the Trail Making Test.²⁴⁻²⁶

In this review, we structure the functional outcome measurements following glioma surgery as reported in the last 5 yr. We review meaningful measures from various perspectives on functional outcome of glioma surgery. Studies of particular interest are marked by [●], and key literature by [●●]. As part of this review, we circulate a survey to reach consensus on reporting guidelines. Consensus among neurosurgeons would facilitate comparisons and pooling of outcomes across surgical cohorts and thus development of evidence-based surgical decision algorithms to improve functional outcome.

SYSTEMATIC REVIEW OF FUNCTIONAL OUTCOME MEASUREMENTS

To determine the practice of reporting in the last 5 yr, we extracted the functional outcome measurements in glioma surgery cohorts according to the PRISMA statement.²⁷ We retrieved citations from PubMed by using these search terms: “Glioma”[MeSH] AND (“Surgical Procedures, Operative”[MeSH] OR “resection”[tiab]) AND (“Patient Outcome Assessment”[MeSH] OR “outcome”[tiab]). The search was conducted on April 2, 2019. The set was restricted to publications from January 1, 2014 in any language. We included cohorts of 20 or more adults, reporting on surgery for supratentorial diffuse glioma (WHO grade II-IV). A meta-analysis of the functional outcomes and risk of bias assessment was not performed, because the diverse outcome measurements and patient eligibility criteria precluded quantitative data synthesis. The main reasons for exclusion were opinionated reviews, case reports, pediatrics, and epidemiological studies from registries.

TABLE. Distribution of Functional Outcome Measurements After Glioma Surgery in Publications From 5 Years (2014-2018)

Publications on functional outcome in glioma surgery	n = 160
Neurological examination	92 (58%)
Muscle strength	40 (25%)
Language	31 (19%)
Vision	9 (6%)
Unspecified	48 (30%)
NIH Stroke Scale	3 (2%)
Neurological Assessment Neuro-Oncology scale	1 (1%)
Activities of daily living	40 (25%)
Karnofsky Performance Scale	34 (21%)
Eastern Cooperative Oncology Group/WHO scale	4 (3%)
Barthel index	1 (1%)
Modified Rankin Scale	2 (1%)
Seizure outcome	21 (13%)
Engel	8 (5%)
Neurocognitive performance	12 (8%)
Well-being/health-related quality of life	9 (6%)
QLQ-C30/BN20	6 (4%)
EuroQol-5D	4 (3%)
No functional outcome	43 (27%)

The titles and abstracts of identified studies were reviewed, and any study reporting on surgical outcome was included for full-text review. The search strategy retrieved 2779 unique publications. After screening of titles and abstracts, 294 eligible publications were reviewed in full text.

The inclusion criteria were met in 160 publications from which we extracted the reported measurements and the timing of assessment in relation to surgery, as summarized in [Table](#) and detailed in the [Datatable, Supplemental Digital Content 1](#). Of these studies, neurological outcome was reported most often (58%), followed by activities of daily living (25%), seizure outcome (13%), neurocognitive outcome (8%), and health-related quality of life (HRQoL, 6%). No functional outcome was addressed in 27% of these studies. This indicates an opportunity to standardize reporting of functional outcomes after glioma surgery.

Functional outcome of glioma surgery can therefore be categorized in at least 5 contexts ([Figure](#)). Neurological, neurocognitive performance, and seizure activity are direct indicators of brain function. Activities in daily life and HRQoL are higher order aggregates of objective consequences and subjective perceptions of brain function.

In the following sections, for each functional outcome category we consecutively describe the applicable measures, review the recent literature, and offer suggestions for the use of measurements.

Neurological Outcome

Neurological examination before and after glioma surgery is standard care. Variation in reported outcomes can be explained by differences in patient selection, in criteria for the severity of

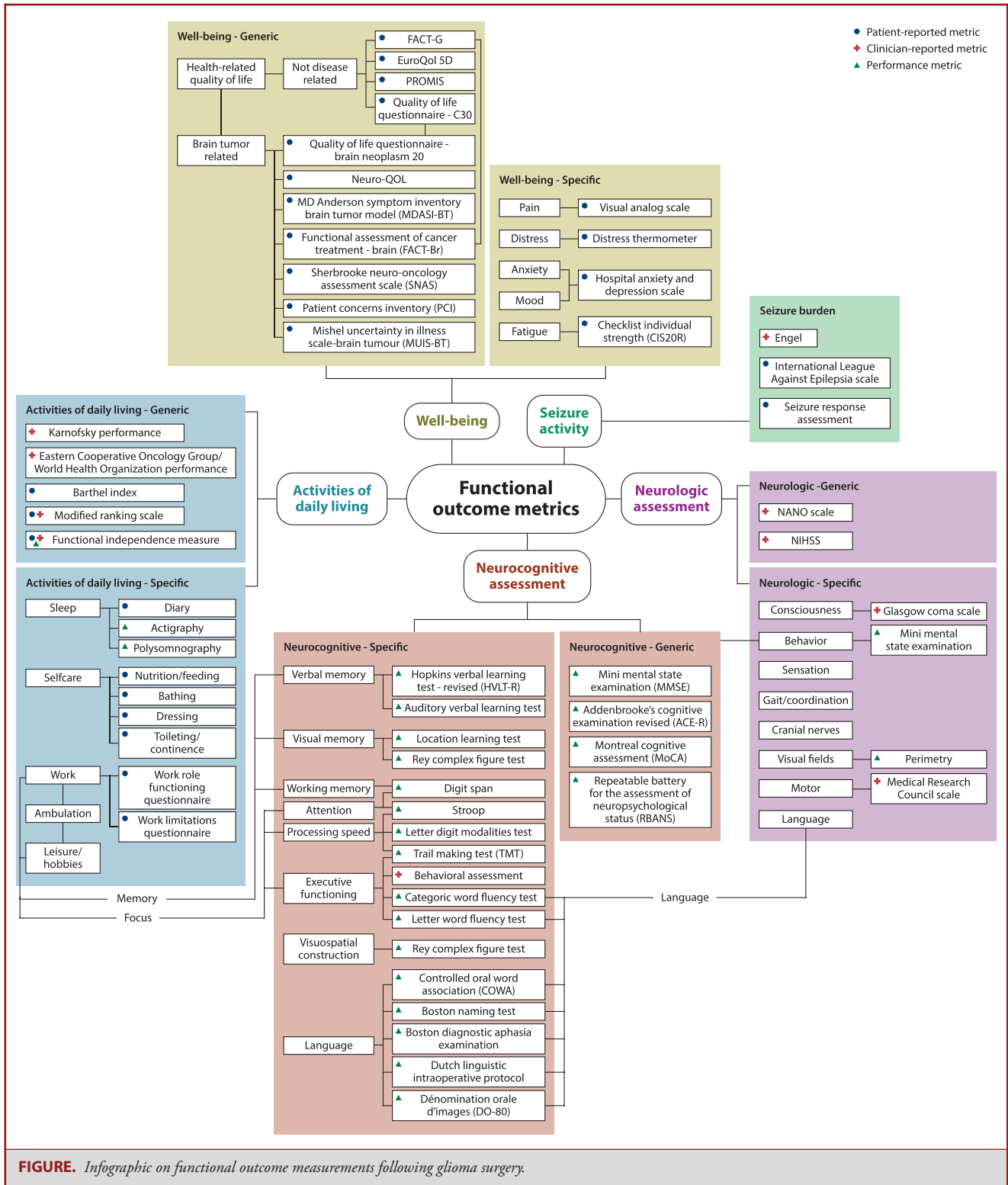


FIGURE. Infographic on functional outcome measurements following glioma surgery.

deficits, in timing of assessment and in applied surgical techniques to minimize neurological deficits. Furthermore, the neurological examination findings are also known to vary between neurologists.^{28,29} This is not surprising, because many elements of neurological examination are indiscrete or descriptive observations. An exception is muscle strength that is usually measured in 6 Medical Research Council grades,³⁰ although its reliability has been criticized.³¹ Language examination in standard care is typically based on self-report or history taking. Structured language assessments are discussed in the section on neurocognitive outcome. Visual field examination is measured with technician-reported perimetry based on patient responses to stimuli. Two examples of generic scales for neurological assessment are the Neurologic Assessment in Neuro-Oncology (NANO) scale and the National Institutes of Health Stroke Scale (NIHSS). The NANO scale has been developed for response assessment as a clinician-reported measurement covering 9 neurological domains: gait, muscle strength, ataxia, sensation, visual fields, facial muscle strength, language, consciousness, and behavior.³² The NANO scale has discrete levels of functioning, high interobserver agreement, and can be assessed in 4 min by neurologists and non-neurologists. The NIHSS is designed to quantify impairment from stroke in subdomains: level of consciousness, gaze, visual fields, facial palsy, motor arm and leg, ataxia, sensory, language, articulation, extinction, and inattention.³³ It is reasonably reliable and can be administered in 10 min.^{34,35}

Many neurosurgical reports have included clinician-reported measures, typically muscle strength and language. New long-term motor deficits after glioma surgery were observed in 3% of 591 patients [●],³⁶ 4% of 207,³⁷ 4% of 648,³⁸ 5% of 294 [●],³⁹ 6% of 306,¹² 7% of 309 [●],⁴⁰ 8% of 222 [●],⁴¹ 9% of 1229 [●],⁴² and 11% of 734.⁴³ New long-term language deficits were observed in 2% of 250 patients [●●],⁴⁴ 2% of 306,¹² 2% of 207,³⁷ 4% of 648,³⁸ 5% of 222 [●],⁴¹ 6% of 1229 [●],⁴² and 14% of 309 [●].⁴⁰ None of these reports used the NIHSS or NANO scale. The NIHSS group average was unchanged in 22 patients 3 mo following glioma surgery, while 26% of patients had a neurological deterioration.⁴⁵ Others used the NIHSS to define severity as more than one point change compared to preoperative, in 2% of 288 patients 3 mo after low-grade glioma surgery,⁴⁶ and in 26% of 110 patients 1 mo after recurrent glioblastoma resection [●].⁴⁷ The NANO score group average was unchanged after surgery in 342 patients with glioblastoma.⁴⁸ In a prospective database from 52 hospitals in North America, worse neurological status was observed in 10% of 499 patients.⁴⁹ In a meta-analysis on neurological outcome after glioma surgery severe deficits were observed at 3 mo postoperative in 4.6% (95% CI, 3.3%-6.1%) and deficits of any severity were observed in 7.1% (95% CI, 5.3%-9.0%) of 6095 patients from 75 publications [●●].⁵⁰ These consisted of 254 hemipareses, 28 severe monopareses, 38 aphasias, 107 dysphasias, and 40 combined motor and language deficits. Other less often reported deficits included hemianopia, facial palsy, somatosensory syndrome, parietal syndrome, dysnomia, and cranial nerve deficits. It is unclear whether less often

reported neurological events have a lower incidence after glioma surgery or whether these events are missed because not systematically examined. The use of intraoperative stimulation mapping reduced the late severe deficit rate from 8.3% without mapping to 3.4% with mapping (odds ratio: 0.39; 95% CI 0.23-0.64).

For outcomes research, neurological outcome should be standardized. Criteria for severity could be guided by the NANO or NIHSS scale. Standardized baseline assessment should be shortly before surgery, ideally on the day of hospital admission. Standardized follow-up assessment after surgery should not be too early, because many patients will recover from transient neurological deficits in the first weeks to months. Timing should also not be too late, because the neurological condition could have declined from other treatments or glioma progression. Three months postoperative is probably optimal for recovery of most transient neurological deficits, in absence of clinical and radiological progression. Furthermore, observer bias could be diminished by a baseline and follow-up examination by an (oncological) neurologist or another team member other than the neurosurgeon who performed the surgery.

Activities of Daily Living

Activities of daily living reflect the ability in everyday tasks for the patient due to a change in general condition, neurological, or neurocognitive deficits. Daily activities include bathing, feeding, dressing, functional transfers, ambulation, and continence. More complex instrumental activities are included as well, such as transportation, meal preparation, household and financial management, medication management, companionship, and social interaction. Generic measurements include the Karnofsky Performance Score (KPS) and the Eastern Cooperative Oncology Group or World Health Organization (ECOG/WHO) score. The KPS was designed to evaluate the effect of chemotherapeutics in 11 grades.⁵¹ The ECOG/WHO consists of 6 grades.⁵² Both scales have overall good inter-rater agreement in the existing literature,⁵³⁻⁵⁸ although some have found poor agreement.⁵⁹ Alternative measurements include the Barthel index, the modified Rankin Scale, and the Functional Independence Measure. The Barthel index is based on 10 items (feeding, bathing, grooming, dressing, bowel and bladder control, toilet use, transfers, mobility on level surface, and on stairs) with a sum score ranging from 100 to 0,⁶⁰ which has been shown to be reliable in stroke patients.⁶¹⁻⁶³ The modified Rankin Scale has 7 grades, was designed for stroke, and has good reliability.⁶⁴⁻⁶⁷ The Functional Independence Measure has 18 items measured on a 7-point scale with a sum score ranging from 18 to 126, was designed for inpatient rehabilitation, and has good reliability.^{68,69} The Lawton Instrumental Activities of Daily Living Scale for older adults indexes the ability to perform tasks in 8 domains: telephone use, shopping, food preparation, housekeeping, laundry, transportation, responsibility of own medications, and handling finances. Administration takes 15 min.⁷⁰ Detailed activities of daily living can be measured as specific items from the generic metrics. In addition,

for employment status, the Work Role Functioning Questionnaire is available consisting of 27 self-reporting items with 5-point scales,⁷¹ and the Work Limitations Questionnaire consisting of 25 self-reporting items in 4 subscales: time management, physical demands, mental demands, and output demands.⁷² To measure sleep, a number of approaches are available including diaries,⁷³ questionnaires,⁷⁴ actigraphy,⁷⁵ or polysomnography. Many questionnaires for patients with brain tumors include items on activities of daily living covering a wide range of content.⁷⁶

Activities of daily living have been reported before and after glioma surgery mainly as KPS, and less often as ECOG/WHO score. The median KPS after surgery has been reported to be similar to the median KPS before surgery.^{48,77-79} Alternatively, the percentage of KPS decline was reported to be 5% of 292 patients [●],¹⁹ 24% of 330,⁸⁰ and 13% of 250 at 3 mo.⁸¹ The KPS improved in 53% of 330 patients,⁸⁰ and in 13% of 250.⁸¹ The Barthel index,⁸² the modified Rankin score,⁸³ and the Functional Independence Measure⁸⁴ were each reported in single publications. Employment status after lower grade glioma surgery has recently been described as functional outcome measure in several reports demonstrating return to work in 74% of 78 patients [●],⁸⁵ 80% of 20,⁸⁶ 82% of 34,⁸⁷ 85% of 39,⁸⁸ and 91% of 68 [●].⁸⁹

Activities of daily living provide a perspective on everyday tasks as a consequence of neurological and/or neurocognitive dysfunction, mediated by compensatory strategies and environmental factors. Efforts strive towards objective standardized measures that test patients in the absence of mediating factors in a controlled environment. The measure should be standardized in timing of assessment before and after surgery and in observer, in parallel with neurological examination. Of note, the ADL measurements are ordinal categories and not linear continuous measurements, which are inadvertently summarized as average of study populations in many reports. It would be more informative to report the incidence per grade before and after surgery and as individual difference scores. For instance, a threshold for improved or declined KPS was proposed with difference scores of over 20 or under 20.^{19,90} Furthermore, distinction should be made between ability to return to work and ability to return to work full time in the same capacity as prior to surgery.

Seizure Outcome

Seizure outcome according to the Engel classification is customarily used in the literature on epilepsy surgery outcomes.⁹¹ Four classes are distinguished of which class I is considered seizure freedom without auras. An alternative measure is the classification from the International League Against Epilepsia consisting of 6 classes,⁹² which aims to avoid some of the ambiguities in the Engel classes. The inter-rater reliability and correlation of both scales were demonstrated to be very good.⁹³ Seizure status is also queried in questionnaires on well-being.

The benefit of glioma resections on seizures has been well documented. Seizure freedom was reported after surgery in 68% of 40 patients,⁹⁴ 79% of 57,⁹⁵ 80% of 15,⁹⁶ 84% of 74,⁹⁷ 84% of 105,⁹⁸ 89% of 335,⁹⁹ 90% of 107 [●],⁸⁵ 97% of 73,¹⁰⁰ and 100% of 25.⁸⁶ The timing of postoperative assessment was not always mentioned, but usually occurred at 6 mo.^{85,86} Seizure outcome has sometimes been reported as Engel I classification consisting of seizure freedom at 1 yr postoperative in 36% of 147 patients,¹⁰¹ 65% of 65,¹⁰² 66% of 53,¹⁰³ 67% of 52,¹⁰⁴ 77% of 47,¹⁰⁵ 78% of 40,¹⁰⁶ 81% of 150,¹⁰⁷ and 86% of 51.⁸⁸ Clearly, seizure outcome depends on the preoperative seizure types, frequencies and durations, and the antiepileptic drug dosing changes, which partly explains this variation. Some authors describe new postoperative seizures as complication.^{97,108} The median seizure freedom rate after low-grade glioma resections was 71% in recent meta-analyses, with gross total resection as the main predictor [●●].^{9,10}

Comparison between surgical cohorts would be possible with reporting of seizure freedom at 1 yr postoperative for patients with preoperative seizures despite medication.

Neurocognitive Outcome

Generic measures are in use to screen for overall neurocognitive outcome, typically designed to detect dementia. The Mini Mental State Examination consists of 11 questions resulting in a maximum score of 30, which can be administered in 5 to 10 min.¹⁰⁹ A score below 22 is considered clinically significant neurocognitive impairment. The Mini Mental State Examination has however very poor sensitivity to detect less than severe neurocognitive impairment, limiting its utility in glioma patients.¹¹⁰ The test-retest reliability is high in several patient populations.¹¹¹ Alternative generic measures with potentially better sensitivity are the Addenbrooke's Cognitive Examination-Revised,¹¹² the Montreal Cognitive Assessment,¹¹³ and the Repeatable Battery for the Assessment of Neuropsychological Status.¹¹⁴ These alternatives have so far not been validated in glioma patients. Neurocognitive tests can be summarized in cognitive domains, including attention/concentration, receptive and expressive language, memory/learning, visual-perceptual/spatial skills, and executive functions. Mood and personality variables as confounders of neurocognitive functioning are often also indexed. Usually the tests selected by the neuropsychologist depend on the referral question, for instance to direct a rehabilitation program. For language, several structured assessments are available. The Boston Diagnostic Aphasia Examination includes subtests of conversation, auditory comprehension, oral expression, reading, and writing; has excellent reliability; and is available in many languages.¹¹⁵ The extended version lasts 2 h, the shortened version 45 min. The Boston Naming Test has 60 items for picture naming and administration takes 20 min.¹¹⁶ The Dutch Linguistic Intraoperative Protocol comprises phonological, semantic, syntactic, naming, and articulatory tasks in

90 min and has been translated in other languages.¹¹⁷ The Dénomination Orale d'Images (DO-80) consists of picture naming with an 80-item set based on word frequency in French.¹¹⁸

Descriptions in reports on glioma surgery outcome have so far included qualitative summaries,⁸⁶ quantitative summaries limited to one domain, such as detailed language assessment,^{85,119,120} memory,¹⁰² executive functions,¹²¹ or a combination of separate subtests^{45,122} and domain summaries [●]¹²³⁻¹²⁵ during the perioperative period.¹²⁶ Some reports have described group means only.^{125,126} The timing of neurocognitive assessment varies from the point of hospital discharge¹¹⁹ to longer postoperative follow-up at 3 wk,¹²⁴ 3 mo,^{45,86,120-122} 1 yr,^{102,123,125} and 40 mo.¹²⁶ One study compared neurocognitive follow-up at 3 and 12 mo postoperative and observed further improvement in language, although the effects were small [●].¹²⁵ In a recent meta-analysis on neurocognitive outcome, only 11 (10%) of 115 identified publications met the PRISMA criteria [●●].¹²⁷ Attention, language, and executive function were the most frequently reported cognitive domains. A positive impact of surgery was observed at 1 wk postoperative and at 6 mo follow-up for most cognitive domains, except for executive functions. This meta-analysis may have been positively skewed, because several studies were excluded that used z-score standardization and demonstrated less favorable outcome.¹²⁸ In another meta-analysis, the level of neurocognitive outcome reporting of randomized controlled trials in brain tumor patients was of "high quality" in 20 (31%) of 65 studies [●●].¹²⁹ Key common shortcomings were unclear processing of missing data and not discussing the limitations and the generalizability of the tests.

Comprehensive testing of neurocognitive performance in all domains in standard care is likely unnecessary and unrealistic. Shorter assessment may improve compliance of patients and avoid selection bias. Reviews on neurocognitive outcome after glioma surgery have been descriptive and concluded that the test battery and the timing of baseline and follow-up assessment should be standardized for comparison between study cohorts [●].¹³⁰⁻¹³² Specific testing focused on the domains of greatest importance remains the best clinical option. The neurocognitive domains deemed essential to be evaluated include attention, executive functions, verbal memory, and psychomotor speed. Such a standard test battery would ideally meet the following criteria: measuring the neurocognitive domains that are most vulnerable for tumor effects and treatment; standardization of test materials and procedures for administration; availability of normative data; sufficient test-retest reliability; limitation of practice effects by alternate versions of test material; availability in several languages; and an administration time within 40 min. A test battery meeting these criteria has also been recommended for brain tumor cohorts, the general cancer population, and multicenter clinical studies [●●].¹³³⁻¹³⁷ This clinical trial core test battery covers learning and memory by the Hopkins Verbal Learning Test-Revised, verbal fluency by the Controlled Oral Word Association test, visual-motor scanning speed by the Trail Making Test part A, and

executive function using the Trail Making Test part B.¹³⁸ This test set can be administered by trained team members.

Health-Related Quality of Life

HRQoL is defined as a multidimensional concept consisting of at least physical, psychological, and social capacity as reported by the patient, which is distinct from objective patient performance.¹³⁹ The generic EORTC Quality of Life Questionnaire-C30 (QLQ-C30) provides 15 scores from 6 single-item questions, consisting of dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact, and 9 scales with multiple items, covering global health/quality of life, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea/vomiting, and pain.¹⁴⁰ The brain neoplasm specific module EORTC QLQ-BN20 provides 11 scores consisting of 7 single items, consisting of general condition, headache, seizures, fatigue, hair loss, pruritus, and bladder control, and 4 multi-item scales, covering future uncertainty, visual disorder, motor dysfunction, and communication deficit.^{141,142} The EuroQol-5D is a measure of health status that consists of 6 items and has been used in many conditions and treatments. Based on 5 single-item scales, covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, a single score is produced with 0 representing dead, 1 perfect health, and negative values for states worse than death.¹⁴³ A 3-level and a 5-level answer version are available on paper, electronic, or by telephone. Administration takes 5 min. The EuroQol-5D has been extensively studied in many healthy and diseased populations in various countries, and was shown to be reliable and sensitive.¹⁴⁴ The MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) provides a composite score for symptom severity and for symptom interference. The 21 symptom items and 7 interference items take less than 5 min to complete on paper, electronic or by telephone, and has been shown to be reliable and sensitive.¹⁴⁵ The Functional Assessment of Cancer Treatment-Brain (FACT-Br) includes 27 items measuring general (FACT-G) cancer-related physical, social, emotional, and functional well-being, and a 23-item scale for symptoms and problems specific to brain tumors.¹⁴⁶ Administration takes 15 min, and it has been shown to be reliable and sensitive. Alternative brain tumor specific scales that measure well-being are the Sherbrooke Neuro-Oncology Assessment Scale (SNAS),¹⁴⁷ the Patient Concerns Inventory (PCI),¹⁴⁸ as a holistic needs assessment tool, and the Mishel Uncertainty in Illness Scale-Brain Tumor (MUIS-BT),¹⁴⁹ which indexes disease-related uncertainties. The Patient-Reported Outcomes Measurement Information System (PROMIS) was established by the National Institutes of Health and measures key patient-reported health indicators and symptoms covering several domains: pain, fatigue, emotional distress, physical functioning, and social role participation.¹⁵⁰ NeuroQOL is a PROMIS-based measurement system for patients with neurological disease covering 13 domains, each consisting of 8 to 9 questions.¹⁵¹

The most frequently used generic HRQoL measures for well-being after glioma surgery are the EORTC QLQ-C30 and the QLQ-BN20.^{45,152} Improvement and deterioration of these measurements after glioma resection occurred in 29% and 35% of patients [●].⁴⁵ Some publications only report the group average before and after surgery.¹⁵²⁻¹⁵⁵ Others have used the EuroQol-5D measurement. Improvement and deterioration were respectively observed in 27% and 14% of patients,¹⁵⁶ 17% and 13%,¹⁵⁷ and 20% and 25% [●].¹⁵⁸

DISCUSSION

For functional outcome assessment following glioma surgery, the aim is to measure the functional integrity compared to the situation before surgery on a scale that captures how the patient functions or feels. The measure of assessment should be valid in content, be reliable, and be able to detect change over time.²⁴

A valid metric measures what it is supposed to measure. For glioma surgery, the measurement would be meaningful to the patient and reflect how the patient functions or feels, such as return to work.

A reliable metric provides consistent results. For glioma surgery, consistent measurements would be robust against timing, environment, and rater. Timing of assessment is critical because brain functions can fluctuate after surgery due to other treatments and medication. Measurements should be robust against measurement variation by the environment, such as a walking test providing similar results on the hospital ward, at home, or in a rehabilitation facility. Furthermore, some measurements have better agreement between raters than others.

The metric should detect meaningful changes. In essence, the research question determines what is meaningful and should guide a selection of generic and specific measures. Generic measurements, such as the NIHSS, may deviate only little on the dynamic range, if one item has deteriorated. For instance, a global aphasia would be measured as 3 on the NIHSS with a maximum sum of 32, which might not adequately reflect the meaning of this change to a patient.

Reporting Guidelines With a Selection of Functional Outcome Measurements

As research questions are diverse, so are selections of functional outcome measurements. For outcomes research on functional assessments in glioma surgery cohorts, however, a minimum essential standard set of functional measurements should be available from reports. This set would follow clinical practice closely, have minimal burden from measurement, and encompass the most important components for comparison across surgical cohorts. As a first step towards consensus on a standard set in the neurosurgical community, we provide a short survey in the **Survey, Supplemental Digital Content 2**. Supporting materials with details on the functional outcome measurements and scales are available from the author by request.

For studies with more specific purposes, new metrics, subscales, or individual items within measures can be added to the minimum essential standard set. For instance, in a study evaluating a Stroop test for intraoperative stimulation mapping, it naturally follows to compare baseline and longitudinal Stroop test assessments in addition to the standard outcome set. This would be a highly sensitive measure for the study purpose and at the same time serve to correlate changes in the new measure with the standard outcomes.

Practical Implication

A practical implication from systematic preoperative neurocognitive screening is to identify patients unable to contribute to shared decision making due to reduced mental capacity from tumor effects.¹⁵⁹ This is important to recognize for informed consent for surgery or for study participation. Preoperative mental incapacity is common (25%) in glioma patients and often underestimated by clinicians.¹⁶⁰

Future Directions

Several open questions may direct future efforts to better understand functional outcome after glioma surgery and to improve reporting.

Inter-Rater Agreement in Functional Outcomes

In recent publications of glioma surgery, clinician-reported outcomes of neurological examination are most frequently reported. Usually, the raters and their expertise have not been described. Likely, the attending neurosurgeons, residents, or nurse practitioners accounted for the examinations. What is the agreement among raters and between disciplines, eg, neurosurgeons versus neurologists, in commonly used measurements, such as neurological examination or activities of daily living?

Correlation Between Functional Outcomes

Furthermore, the correlation between functional outcomes has seldom been studied, in particular perioperatively. If 2 measures would be confirmed to correlate well, then one score could be converted into another to enable comparison among cohorts, such as the KPS and the ECOG/WHO performance.¹⁶¹ If an absence of association between measures would be established, this may indicate distinct sources of information with mutually contributing perspectives on functional outcome.

Response Shift and Noncompliance

Response shift is the longitudinal change in the patient's perception of their self-reported outcomes related to an internally shifting reference. By nature, people can lower their reference when facing terminal disease or meeting others with a lower perceived performance. As a consequence, patients can self-report their health status as good, not because it was unaffected by surgery, but because of their adaptation to new life circumstances with limitations, which may have been worse. Response shift can be measured by a so-called then test to correct self-reported

outcomes.^{162,163} In one study, a relevant response shift for the EuroQol-5D was documented for patients with a decline or improvement in their reported quality of life at 6 mo after surgery, but absent on average [●].¹⁶⁴ In patients with cancer other than glioma, response shift for self-reported outcomes was frequently detected, but the effect sizes were generally small.^{162,163}

Noncompliance is also important for interpretation of functional outcomes. If patient competence becomes compromised for completion of questionnaires, then data would not be missing at random and missing outcomes of the sickest patients could lead to too favorable interpretation of results. Additionally, completion of burdensome questionnaires is oftentimes restricted for ethical reasons in patients near the end of life.¹⁶⁵ The EuroQol-5D 6 mo after glioma surgery was completed by 62% of patients, with dropout mainly due to patient death, reporting by proxies, patient withdrawal, and nonresponsiveness [●].¹⁶⁴ The EORTC QLQ-C30/BN20 was completed by 82% at hospital discharge after glioma surgery, and by 74% patients at 3 mo postoperative,⁴⁵ and by only 28% of patients at 1 yr after second-line therapy.¹⁵² A potential direction for a solution is to replace reported outcomes of patients by proxies, such as a relative. However, the level of agreement between patient and patient-by-proxy ratings of HRQOL tends to be lower in patients with more severe neurocognitive deficits, limiting its validity.¹⁶⁶ Another solution is to keep the measurement as short and simple as possible for a responsive and valid measurement.

Objective Versus Subjective Outcome

Should functional outcomes be objective measures of performance, or subjective perceptions of condition and capacity, or a combination? Objective deficits or lower performance following glioma surgery can be acceptable for some patients, but others without deficit and unchanged capacity can be unsatisfied with poor quality as they refer their new situation to their premorbid status. To some patients any change in the type of work or in professional efficiency may be unacceptable, but to others not returning to their same job or to work at a different capacity could be acceptable. Some patients may prefer more on the quantity of life versus the quality and to function reasonably well for many years, while others prefer to live a shorter life at full capacity. Consequently, the patient's personal goals are the main determinants of what is an acceptable dysfunction following glioma surgery. And personal goals are diverse: between cultures, between continents, between countries, between teams, between patients, and importantly within patients due to response shift. Subjective patient-reported outcome is undoubtedly most important for individualized patient care. But comparison across cohorts would become meaningless, if subjective measurements would be the only source of information. Perhaps subjective measurements should be corrected for their most important, yet unknown, drivers? Perhaps we should develop 'interventions' to enforce patients to shift from one perspective to another to improve how they feel about their situation?

As far as we are aware, only 2 interventions have shown to improve some aspects of functional outcome in glioma patients.¹⁶⁷ Neurocognitive performance and fatigue improved in patients with stable gliomas after a cognitive rehabilitation program for 6 wk [●●].¹⁶⁸ Memory and information speed improved moderately in patients with brain tumors using Donepezil.¹⁶⁹ Apart from efforts towards new interventions to improve functional outcome after surgery, a greater impact can be expected from neurosurgeons preoperatively identifying the patients prone to decline, and better understanding how to avoid deterioration, as neurosurgical complications seem to be closely related to functional outcomes.^{124,156,170}

Predictors and Confounders of Functional Outcome

We would like to better understand why some patients improve and others deteriorate from glioma surgery. Reporting of changes in group averages may mask important individual changes [●].¹⁷¹ Patients can improve in outcome due to effects other than surgery, such as practice effects from serial testing, seizure reduction due to medication, initiation or discontinuation of corticosteroids, mood altering medication, analgesics, or other treatments. Patients can on the other hand also decline due to effects other than surgery, such as early tumor progression, increased seizure burden, or toxicity from other treatments and medication. And patient-related factors modulate how they function and feel, such as age, education, employment, social interactions, anxiety, distress, fatigue, depression, impaired judgment, coping strategies, and prior medical experiences. In addition, noise inherent to the measure will result in measurement error. How can measurement changes due to surgery be distinguished from other effects? Theoretically by randomizing surgery, but ethical concerns, patient preference, and perceived absence of equipoise by clinicians have precluded success. When does a measure detect a meaningful change? A potential solution for this is the Reliable Change Index, for which the difference between measurements before and after surgery is corrected for practice effects and measurement error, as measured in test-retest variation.¹⁷² It is common practice to refer neurocognitive tests results to a healthy population.¹⁷³ Instead, for the purpose of isolating glioma surgery as causative factor for functional outcome, the reference population should probably be glioma patients whose measurements are subject to all mentioned effects, except for the surgery.

In a simplified causative model with surgery causing a change in functional outcome, all mentioned factors could be considered response modifiers or confounders of functional outcome, not unlike prognostic factors in survival analysis. Another approach, however, may be able to capture the complexity of the interdependent components to perioperative changes in functional measurements as symptom cluster or to use network analysis on the multiple dimensions of functional outcome.¹⁷⁴⁻¹⁷⁶

Ultimately, accurate predictions on functional outcome would be modeled based on a standardized data collection of outcome measurements and confounders in a large representative

population with pooled data from many neurosurgical teams. After validation of these predictive models, neurosurgeons and their patients will be able to make surgical decisions guided by patient-specific risk estimates on the multiple dimensions of functional outcome according to individualized patient goals.

CONCLUSION

Functional outcome is a coprimary end point of glioma surgery, together with oncological outcome. In the most recent neurosurgical literature, neurological outcome was reported most often, followed by activities of daily living, seizure outcome, neurocognitive outcome, and HRQoL. A minimum essential consensus set of functional outcome measurements would benefit comparison between neurosurgical reports, based on a combination of clinician- and patient-reported outcomes and performances, subjective and objective, measured with measurements that are valid, reliable, and able to detect meaningful change. Many questions remain to better understand, report, and improve functional outcome following glioma surgery.

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