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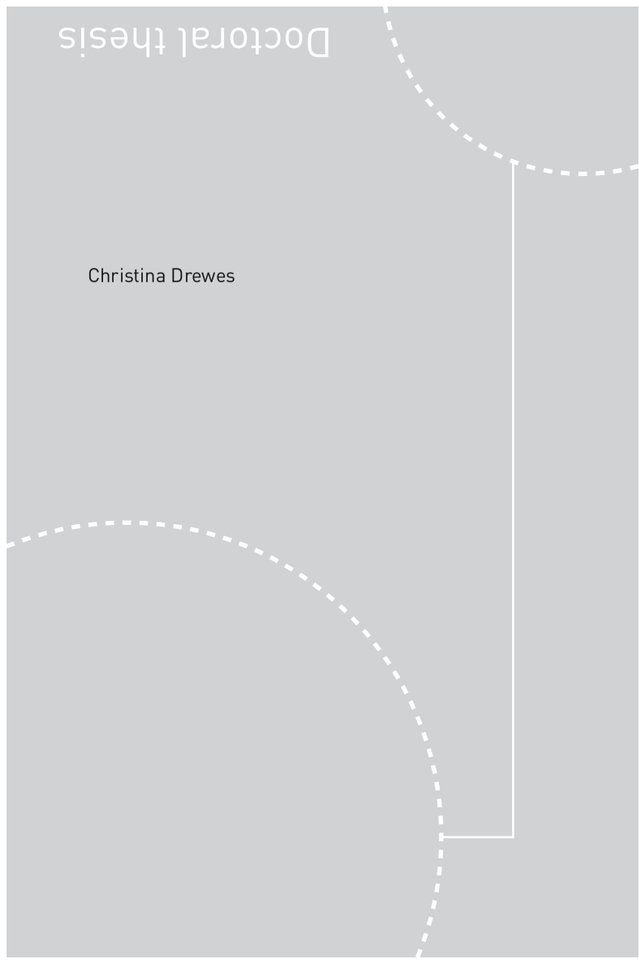
Christina Drewes

Intracranial tumor surgery - The patients' perspectives



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Trondheim, October 2018

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Sammendrag

Hjernesvulster oppstår enten fra celler i det sentrale nervesystemet (primære hjernesvulster, for eksempel meningeomer eller gliomer), eller grunnet spredning av systemiske svulster fra andre steder i kroppen (hjernemetastaser). Hjernesvulster er assosiert med betydelig morbiditet og mortalitet.

Ofte er det aktuelt med kirurgisk behandling. Når resultater etter hjernesvulst-kirurgi skal evalueres, er overlevelse viktig, men også «mykere» endepunkter, som nye nevrologiske utfall, perioperative komplikasjoner og funksjonsstatus, er vanlige kliniske endepunkter.

Pasientrapporterte endepunkter («patient-reported outcomes», PROs) er blitt tatt i bruk innen nevrokirurgisk behandling av hjernesvulster, men foreløpig i nokså liten grad. PROs har som mål å fange opp pasientens eget perspektiv på symptombelastning, effekter og bivirkninger av behandling, eller kvaliteten av den gjenværende levetiden. Livskvalitetsverktøy («quality of life», QoL) er en viktig undergruppe av måleverktøy for pasientrapporterte endepunkter og er brukt innen forskning, kvalitetssikring og helseøkonomi.

Hverken rapporteringen av tradisjonelle kliniske endepunkter eller av PROs er standardisert. Dette fører til stor heterogenitet i publiserte studier innen hjernesvulstkirurgi og vanskeliggjør sammenligning av kirurgiske teknikker, behandlingsmål, sykehus eller pasientgrupper.

I de tre originalartiklene i denne avhandlingen brukte vi PROs for å svare på forskningsspørsmål knyttet til hjernesvulstkirurgi.

I artikkel 1 sammenlignet vi kirurgenes rapportering av nye nevrologiske utfall ved utskriving fra sykehuset med pasientrapporterte nye utfall 30 dager etter operasjon for hjernesvulst. Sammenligningen resulterte i lave sensitivitetsverdier for kirurgens evaluering, 0.52 for nye motoriske utfall, 0.4 for språkproblemer og 0.07 for hukommelsesproblemer. Dermed ble en stor andel av pasientrapporterte nye utfall 30 dager etter hjernesvulstkirurgi ikke fanget opp av klinikere ved utskrivingstidspunktet.

I artikkel 2 undersøkte vi om livskvaliteten før og etter førstegangskirurgi for hjernesvulst er avhengig av hvilken side av hjernen svulsten ligger i. Den venstre hjernehalvdelen er tradisjonelt ansett som «dominant» hos de fleste, på grunn av viktige funksjoner som språk og bevegelse av dominant side, som oftest ligger i venstre hemisfære. Pasientrapportert QoL ble brukt som endepunkt. Vi fant ingen forskjell i livskvalitet hos pasienter med høyresidig sammenlignet med

venstresidig hjernesvulst, hverken før eller etter kirurgi. Patologi i høyre hjernehalvdel ser ut til å ha like stor effekt på QoL som patologi i den «dominante» venstre hemisfæren.

I artikkel 3 studerte vi utviklingen av livskvalitet etter kirurgi for høygradig eller lavgradig gliom. Pasientrapportert QoL ble målt ved tre tidspunkt: preoperativt, ved 1 måned og ved 6 måneder. På gruppenivå fant vi at pasienter med både høygradige og lavgradige gliomer rapporterte stabil livskvalitet ved 1 måned, men livskvaliteten ble signifikant dårligere hos pasienter med høygradige svulster ved 6 måneder. Individuell QoL-dynamikk varierte betydelig. Komorbiditet, histologisk høygradige svulster og radiologisk resttumor etter kirurgi ble funnet å være prediktorer for negativ utvikling av QoL mellom 1 og 6 måneder.

Sammenlagt tyder resultatene av studiene i denne avhandlingen på at PROs kan gi viktig informasjon som ikke nødvendigvis blir fanget opp ved tradisjonell klinisk evaluering i forbindelse med hjernesvulstkirurgi. PROs bør inngå som en rutinemessig del av rapporteringen knyttet til kirurgisk behandling av hjernesvulster, både i kliniske studier og i behandlingsregistre. Standardisering av måleverktøy og måletidspunkt i forbindelse med kirurgi vil kunne bidra til å heve kvaliteten av framtidig klinisk forskning. Dette gjelder både PROs og tradisjonelle endepunkter rapportert av klinikere.

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Summary

Brain tumors are a diverse group of neoplasms. Primary brain tumors, such as gliomas and meningiomas, originate from cells of the central nervous system. Brain metastases, so-called secondary brain tumors, disseminate from systemic cancers. Brain tumors are associated with considerable morbidity and mortality.

Brain tumor treatment often includes surgery. When assessing outcome after surgery, overall survival and perioperative mortality are important endpoints, but also new neurological deficits, perioperative complications and functional status are common clinician-reported outcomes. However, in the neurosurgical literature on brain tumor surgery, reporting of these "soft" outcomes is highly heterogeneous, making comparisons of surgical techniques, treatment goals, surgeons and institutions very difficult. Like in other cancer types, patient-reported outcomes (PROs) have emerged in brain tumor surgery. PROs capture the patients' own perspective on aspects of symptom burden, treatment benefits and adverse effects, or the quality of the remaining lifetime. Quality of life (QoL)-measures are an important subcategory of PROs, and are used in research, quality assurance and in health economics. As applies to clinician-reported outcomes, the reporting of PROs in brain tumor surgery is not standardized, which limits comparability.

In the three original research papers in this thesis, we used PROs as primary endpoints, aiming to supply the neurosurgical literature with topics not much investigated so far.

In paper I, we studied surgeon-reported new neurological deficits at discharge after brain tumor surgery in comparison with PROs at 30 days post-surgery in 191 patients. Sensitivity values for retrospective review of hospital records as compared to PROs were 0.52 for motor deficits, 0.4 for language deficits and 0.07 for cognitive deficits. Retrospectively collected surgeon-reported data on new deficits at the time of discharge from hospital failed to capture a considerable proportion of the new deficits reported by patients at 30 days**.**

In paper II, we investigated the impact of tumor laterality on patient-reported QoL, measured by the generic tool EQ-5D 3L, in a cohort of 248 patients scheduled for primary brain tumor surgery. Traditionally, clinicians have been regarding lesion laterality as very important, since the left "dominant" hemisphere harbors eloquent functions, such as language and motor

functions in most patients. In patients with left-sided compared to right-sided tumors, we found no difference of generic patient-reported QoL, neither pre- nor postoperatively.
In paper III, we explored the peri- and postoperative development of QoL in 136 glioma patients undergoing primary surgery. QoL was assessed with the generic tool EQ-5D preoperatively and at 1 and 6 months postoperatively. At group level, overall QoL seemed to follow the natural disease trajectories of HGG (high-grade glioma) and LGG (low-grade glioma) patients. The LGG group was stable at all three assessments, while HGG patients were similarly stable at 1 month, but deteriorated significantly at 6 months. Individual QoL-dynamics were heterogeneous. Comorbidity, high-grade histopathology and radiological residual tumor were found to be independent predictors for negative QoL-development between 1 and 6 months.

The overall results of the studies in this thesis emphasize that PROs may provide important information not necessarily captured by traditional clinician-reported measures in brain tumor surgery. PROs should be considered as a part of routine supplementary endpoints in patients undergoing surgical treatment for brain tumors, both in clinical studies and in treatment registries. To increase the quality of outcome reporting in the published literature, agreed standards for appropriate tools and assessment time points are needed, both for clinician-reported outcomes and PROs.

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Errata

In paper II, page 4, Table 1, the numbers for low-grade-glioma (15 right-sided, 15 left-sided) and high-grade glioma (44 right- sided, 44 left-sided) in the matched cohort were interchanged by mistake, giving the false impression that there were more LGG patients in the matched cohort than in the cohort including all patients.

Acknowledgements

The research in this thesis was supported by grants from the Clinic of Anesthesia and Intensive Care, St. Olavs Hospital, and from the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The first study was performed while I held a teaching position at the Institute for Circulation and Medical Imaging at NTNU, and the Institute of Neuromedicine and Movement Sciences at NTNU has been hosting my PhD study programme.

Getting into research has been an exciting, challenging and very stimulating journey for me. I would like to thank all the people without whom the research in this thesis would not have been possible, and who all have contributed to this journey in their own particular way.

Ole Solheim, my main supervisor, created the space for me to develop as a researcher in the best possible way. Although immensely hardworking and engaged in many projects both clinically and in research, he was always readily available when I needed discussions, help and feedback. His sharp mind and ability to multi-task, combined with patience and a fair share of diplomacy, never stop impressing me. My very efficient and to-the-point co-supervisor Asgeir S. Jakola moved to Sweden early in my research process, but was always available on email or during his visits to Trondheim when I needed input or advice. I greatly value his passion and seriousness when it comes to research, in addition to being a witty and down-to-earth person.

None of the articles in this thesis could have been written without the meticulous data collection done by Lisa M. Sagberg, Camilla Brattbakk and Linda M. Nordtvedt at the Department of Neurosurgery, St. Olavs Hospital. Here, special thanks go to Lisa, my research companion and co-author, who has had the main responsibility for acquisition and curation of data in the regional database on brain tumors since 2011. She keeps impressing me with her accuracy, knowledge and her strong sense of quality. I would also like to thank my colleague and co-author Sasha Gulati for his encouragement, tips and lots of valuable advice from the sideline.

Besides my research colleagues, my thanks go to the Departments of Anesthesiology and Neurosurgery at St. Olavs Hospital. My clinical work as an anesthesiologist, with my main workplace in the neurosurgical operating theatres, has counterbalanced my research work in a very healthy way. I would like to thank all the nurses, doctors and supporting personnel working in the neurosurgical operating theatres. All of you together provide a fantastic work environment!

I would like to thank Sigurd Fasting, Head of the Department of Anesthesiology at St. Olavs Hospital. He was my mentor during my specialty training and I value him tremendously as a colleague and a leader. I have never really doubted his support, although I acknowledge the fact that my periods of research leave did complicate the jigsaw puzzle of staff rosters at times.

I am deeply grateful for the support and love from my family and friends. My dear parents and brother have always encouraged me to achieve my goals. Sadly, my father passed away just a

few months ago and did not live to see me finish my degree. He would have been so proud. My dear partner Andreas deserves special thanks for good discussions about research at our kitchen table as well as for a lot of patience during the last months. He and our wonderful son Anton always keep me grounded with their love and the fun we have together.

Last but not least, my sincere thanks go to the patients who are enrolled in our studies. Despite having received a devastating diagnosis, they agreed to spend precious time and energy on participating in this research project.

List of Papers

Paper I	**Morbidity after intracranial tumor surgery – Sensitivity and specificity of retrospective review of medical records compared to patient- reported outcomes at 30 days** Drewes C, Sagberg LM, Jakola AS, Gulati S, Solheim O J Neurosurg. 2015 Oct;123(4):972-7. doi: 10.3171/2014.12.JNS142206. Epub 2015 Aug 7.
Paper II	**Quality of life in patients with intracranial tumors: Does tumor laterality matter?** Drewes C, Sagberg LM, Jakola AS, Solheim O J Neurosurg. 2016 Dec;125(6):1400-1407. Epub 2016 Mar 25.
Paper III	**Perioperative and postoperative quality of life in glioma patients – A longitudinal cohort study** Drewes C, Sagberg LM, Jakola AS, Solheim O *Submitted manuscript (revised version published in World Neurosurgery June 18th, 2018)*

Other published papers

Is duration of surgery a risk factor for extracranial complications and surgical site infections after intracranial tumor operations?
Golebiowski A, Drewes C, Gulati S, Jakola AS, Solheim O
Acta Neurochir (Wien). 2015 Feb;157(2):235-40; discussion 240. doi: 10.1007/s00701-014-2286-3. Epub 2014 Dec 2

Accuracy of operating neurosurgeons' prediction of functional levels after intracranial tumor surgery.
Sagberg LM, Drewes C, Jakola AS, Solheim O
J Neurosurg. 2017 Apr;126(4):1173-1180. doi: 10.3171/2016.3.JNS152927. Epub 2016 Jun 17.

Acronyms and Abbreviations

ADL	Activities of Daily Life
ASA	American Society of Anesthesiologists
BOLD-fMRI	Blood-oxygen-level-dependent functional MRI
CNS	Central Nervous System
COWA	Controlled Oral Word Association
CT	Computed Tomography
DTI	Diffusion Tensor Imaging
EOR	Extent of Resection
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5D
FACT-Br	Functional Assessment of Cancer Therapy- (Brain module)
FDA	(U.S.) Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GBM	Glioblastoma multiforme
GCS	Glasgow Coma Scale
GNOSIS	Guidelines for Neuro-Oncology: Standards for Investigational Studies
GTR	Gross Total Resection
HGG	High-grade Glioma
HVLT-R	Hopkins Verbal Learning Test-Revised
ICU	Intensive Care Unit
IDH	Isocitrate Dehydrogenase
iMRI	Intraoperative Magnetic Resonance Imaging
KPS	Karnofsky Performance Status
LGG	Low-grade Glioma
MAR	Missing at random
MCAR	Missing completely at random
MCID	Minimal Clinically Important Difference
MEP	Magnetic Evoked Potentials
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NANO	Neurologic Assessment in Neuro-Oncology
nTMS	Navigated Transcranial Magnetic Stimulation
OS	Overall Survival
PCV	Procarbazine, Lomustine, Vincristine

PFS	Progression-free Survival
PRO	Patient-reported Outcome
QoL	Quality of Life
RANO	Response Assessment in Neuro-Oncology
RCT	Randomized Controlled Trial
RT	Radiation Therapy
SAH	Subarachnoidal Hemorrhage
SF-36	Short-Form 36
SISAQOL	Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data
STR	Subtotal resection
TMT	Trail Making Test
UTI	Urinary Tract Infection
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WBRT	Whole Brain Radiation Treatment
WHO	World Health Organization

"The greatest enemy of knowledge is not ignorance, but the illusion of knowledge"

Daniel J. Boorstin (1914-2004), American Historian

Introduction

Despite continuous developments in surgical techniques and medical imaging, intracranial tumor surgery is still considered to be high risk (1, 2). Operating a brain tumor implies the usual risks of surgery, such as bleeding, infections or intra- and postoperative systemic complications. However, in intracranial surgery, surgical site adverse effects often have a much more devastating effect than in surgery on most other organs. Important functional structures within the brain can be harmed directly or indirectly during surgery, causing functional impairment through neurological damage. Historically, perioperative mortality has been an important outcome measure in intracranial surgery. However, today, perioperative death rates are very low owing to modern operative techniques, modern anesthesia, advanced medical imaging and antimicrobial treatment as well as peri- and postoperative surveillance, and do no longer represent a sensitive outcome measure (3). In addition to survival, progression free survival and surgical extent of resection, other clinical measures, such as functional status, acquired neurological deficits or perioperative complications have therefore gained a central role in neurosurgical outcome reporting.

Since many brain tumors are not curable, and although surgery may increase survival, treatment is often palliative. Not only survival, but the quality of the remaining life span is important. During the last decades, patient reported outcomes (PROs), especially quality of life (QoL) measures, have been increasingly used in oncology and other chronic conditions. In the neurosurgical literature on brain tumors, PROs are not used to a great extent so far. Additionally, a lack of agreement on suitable tools and time points for assessment of both clinician-reported outcomes and PROs hampers benchmarking and comparison of outcomes in brain tumor surgery.

With the studies presented in this thesis, we aimed to explore the patients' own perspective on different aspects of symptom burden and outcome after brain tumor surgery by using

PROs. In the first study, we studied surgeon-reported new neurological deficits in comparison with PROs. In the second study in this thesis, we investigated the impact of tumor laterality, a baseline feature of traditionally perceived great importance, on patient-reported QoL. In the third study, we explored the peri- and postoperative development of QoL in glioma patients.

Frequent types of intracranial tumors in adults

Brain tumors are not a frequent condition, but account for a relatively large proportion of cancer deaths. The majority of brain tumors in adults consists of meningiomas, pituitary adenoma, metastases from systemic cancer and gliomas (4). In this thesis, glioma patients represent a large proportion of the populations studied in paper I and II and represent the entire study population in paper III. Apart from the following short introductory paragraphs on meningioma and metastases, this thesis has an emphasis on glioma patients.

Meningiomas

Meningiomas represent 36.4% of all primary tumors of the CNS (4), with a prevalence of pathologically confirmed meningiomas of 97.5/100.000 in the U.S. (5). The incidence of meningioma increases with age (4), and occurrence is about twice as frequent in females than in males (6). Incidence rates of meningioma are rising with the availability of neuroimaging (7). About 2-3% of the population are estimated to have an incidental, asymptomatic meningioma (8). Risk factors are ionizing radiation and female hormone intake (6). Meningiomas arise from arachnoid cap cells and infiltrate the dura mater, most often with a slow growth pattern (6). Meningiomas are graded according to the WHO (World Health Organization)-classification, where WHO grade I is histologically benign, grade II atypical and grade III anaplastic (9). This classification has so far served as the base for deciding on treatment strategies, but a revision is expected in the near future, as molecular factors (DNA methylation) seem to have a greater ability to predict tumor recurrence and prognosis than the current WHO classification (10).
Surgery is often the preferred treatment in meningioma. In non-growing asymptomatic lesions or slow-growing lesions in the elderly, a conservative approach is often appropriate. Stereotactic radiosurgery is a treatment alternative in small, growing lesions. Location of the tumor is an

important surgical and prognostic factor. Skull base meningiomas, although more often histologically benign (grade I), often cannot be excised in total because of their involvement into important nerval and vascular structures (11). WHO-grade II and III lesions, more often located at the convexity of the brain, have a higher tendency to recur, especially when radical surgery is not possible due to venous invasion (6). Treatment plans in meningioma are usually individualized and depend on a multitude of factors (12). In cases where complete resection is not possible, incomplete resection followed by observation and possibly radiation therapy is the strategy favored by most neurosurgeons today (8). Stereotactic radiotherapy and proton beam radiation are options in meningiomas that are difficult to access surgically, as well as in recurrent meningiomas (8, 12). Chemotherapy is rarely used, but the antiangiogenic agent bevacizumab is sometimes used in patients with multiple meningioma due to neurofibromatosis type II, although with conflicting results (13, 14).

Although meningiomas in surgically well accessible sites have a good prognosis, recurrence is not a rare event, with reported 10-year-recurrence rates even of so-called completely resected tumors of 20-39 % (15). With the increasing incidence rates due to the availability of modern neuroimaging, more asymptomatic lesions will be diagnosed. This may lead to overtreatment with an inherent danger of treatment side effects being worse for the patient than the disease.

Brain metastases

Brain metastases are more common than primary brain tumors (16), but their exact incidence is unknown. Estimates from population-based studies suggest that 8-10% of adults with cancer will experience development of brain metastases in their lifetime (17, 18). The frequency of brain metastases is increasing, due to the aging population, earlier detection, increased use and quality of medical imaging and more advanced, survival-extending systemic therapy that does not cross the blood-brain-barrier (19). The most common primary cancers in patients with brain metastases are lung, breast and melanoma (19). If left untreated, survival after developing symptoms from brain metastases is only about 1-2 months (20, 21), extending to 2-3 months with corticosteroids (22). Before, patients with brain metastases had universally low survival rates, and treatment recommendations were influenced by a correspondingly fatalistic attitude (23). This has been subject to gradual change during the past decades, and prognostic assessment schemes have been suggested to facilitate tailoring of treatment regimens based on expected survival in individual

patients (24, 25). Although there is no standard oncological treatment for brain metastases today, there are a number of treatment options. In addition to symptomatic measures such as corticosteroids and anticonvulsants, surgery can be an option in selected patients. Surgery has a role in tissue diagnosis as well as in symptom relief of space-occupying lesions. The effect of surgery alone on survival is not well documented, since clinical studies usually are small, involve combination with radiation therapy and include selected patients (26-28). Surgery in combination with radiation may improve functionally independent survival (26) and decrease recurrence and deaths from neurological causes (28). Of different radiotherapy options, whole brain radiation therapy (WBRT) is the historical standard approach to the treatment of brain metastases, but there are considerable side effects in terms of fatigue, loss of quality of life, and cognitive impairment (29-31). Today, different types of stereotactic radiosurgery are increasingly used (29, 32). Very occasionally, chemotherapy is used, and there are several ongoing clinical trials studying systemic treatments for some subtypes of brain metastases (33). The prognosis of metastatic disease of the brain depends on age, functional status, the number of brain metastases, the type of primary tumor and control of extracranial tumor activity (19). The Karnofsky performance score (KPS) has shown to be a major determinant of survival (19, 24). With surgery or radiotherapy for brain metastases, few patients die from the intracranial disease, but prognosis is strongly linked to the prognosis of the extracranial disease (27, 33).

Gliomas

Glioma is the most common malignant primary brain tumor. This tumor group consists of astrocytomas, oligodendrogliomas and ependymomas, as well as a variety of rare histological types (9). According to the WHO-classification, gliomas are classified into grade I to IV, where grade I and II are low-grade gliomas (LGG) and grade III and IV high-grade gliomas (HGG). The incidence of gliomas is about 6/100.000 persons per year (34), and HGG account for the majority with an incidence of 5/100.000. Glioblastoma (WHO grade IV) is the most frequent glioma histology, accounting for around 75% of HGG tumors (35). LGG histopathology is much less common, with reported incidence rates between 0.8 and 1.2/100.000 (36), and is more often found in younger age groups, with a peak incidence rate in age group 0-19 years for grade I glioma (0.87) and age group 35-44 for grade II (0.33-0.45). HGG have higher incidence rates in older age groups, glioblastoma peaking at 75-84 years (15.24) (4). There are no established risk

factors for the development of gliomas, apart from a correlation with ionizing radiation (37, 38) and, as a recent study from our institution found, intracranial volume (39).

Gliomas originate from the glial tissue of the brain parenchyma (ependymal cells, astrocytes, oligodendrocytes), most likely the glial stem cells. The WHO-classification is based on histopathological properties of the tumor: Grade I (pilocytic astrocytoma, subependymoma), Grade II (diffuse astrocytic and oligodendrocytic tumors and ependymoma), grade III (anaplastic astrocytoma, oligodendroglioma or ependymoma) and grade IV (glioblastoma) (9). Gliomas arising from astrocytic cells are the most common. In the latest update of the WHO classification from 2016, molecular characteristics are included in addition to histopathological features, as different molecularly defined mutant types have shown to be associated with prognosis (9). Grade II and III astrocytomas and oligodendrogliomas and grade IV gliomas (glioblastomas) are often called “diffuse gliomas”. Diffuse Gliomas exhibit an invasive growth pattern, and spread by migrating tumor cells far from the tumor mass visualized with modern neuroimaging (40-42). Ependymomas (WHO grade II) and subependymomas (WHO grade I) are classified as low-grade gliomas, but often presented as entities separate from the diffuse gliomas found in brain parenchyma. The histologic features of ependymomas resemble ependymal cells in the ventricular lineage. In adults, they occur mostly in the spinal canal, but also in the ventricles of the brain or, sporadically, in the brain parenchyma. Subependymomas are infrequent tumors usually found in the ventricular system, often in the 4^{th} ventricle, with benign behavior. Also pilocytic astrocytomas are non-invasive and benign and are therefore often considered an entity of their own. Diffuse grade II gliomas have a slower growth pattern than HGG, but usually recur and often show increased malignancy with transition to grade III or IV histopathology over time. This is the reason why diffuse gliomas often are considered a continuum rather than isolated histopathological entities.

Tumor size, location, speed of growth and the presence of edema influence symptomatology. A range of symptoms may develop over the course of days, weeks or months, and may include headache, seizures, neurological focal symptoms such as limb weakness, aphasia, visual spatial disorders, as well as sensory loss and cognitive dysfunction (43). A recent case series of patients with diffuse glioma found seizures and cognitive disorder to be the most frequent presenting symptoms (44). In patients with slower growing lesions, brain plasticity may conceal symptoms, while patients with fast growing tumors may present with symptoms earlier. For slower growing

lesions, epileptic seizures are a common presenting symptom, while faster growing lesions with surrounding edema may more often present with acute or subacute neurologic deficits or symptoms of raised intracranial pressure.

The diagnosis is suspected after MRI-imaging, and the histopathological diagnosis is secured by tissue diagnostics, either after a diagnostic biopsy alone or following resection of the tumor. Surgery is usually not curative in diffuse gliomas, due to the invasive growth pattern. Nevertheless, surgery is a very important part of the treatment for tissue diagnosis and, if resection is possible due to tumor location and patient clinical condition, improvement of survival.

If tumor location and the patient's general health allow, HGG are usually surgically resected upon diagnosis. Oncological treatment of HGG includes postoperative radiotherapy as well as concomitant and adjuvant chemotherapy, with alkylating agent temozolomide. Nowadays, also LGG are often resected after initial diagnosis, if surgically possible. There is a large survival advantage in surgically resected LGG patients (45, 46).

The strongest prognostic factors for survival in grade II diffuse glioma are pre- and postoperative tumor volume and molecular markers (47). In high-risk patients, long-term results from a recent RCT showed increased overall survival in LGG patients treated with PCV (Procarbazine, Lomustine, Vincristine) in addition to radiotherapy (RT) as opposed to patients treated with RT alone (48). However, the long-term toxicity of radiotherapy is a concern.

In all diffuse gliomas (Grade II to IV), also after macroscopic and radiological complete resection, there inevitably are remaining tumor cells, making relapse at some time point inevitable. Most patients eventually succumb to the disease, but for subgroups, such as patients with small IDH mutant, 1p19q co-deleted tumors undergoing complete resection, the prognosis is often good with decades of survival (47). In contrast, unselected patients with glioblastoma have a median overall survival of 10 months (49, 50), increasing to 16.2 months after surgery followed by a radiotherapy and chemotherapy regimen (50). Also after this treatment, the 2-year-survival rate in glioblastoma is only 25.6% (51).

An important concept in intracranial tumor surgery: The role of lesion location

Location in a rigid anatomical space

Located inside the skull, the brain contains vital and executive functions for the whole body. Due to the rigidity of the surrounding structures, there is little space for the brain to expand when pathology occurs. With increasing size, space-occupying lesions within the brain will lead to non-specific symptoms, such as headache, nausea, impaired consciousness, seizures, or focal neurological deficits related more specifically to lesion location. Invasive lesions also infiltrate functional brain tissue and thereby destroy functions directly.

Eloquence of lesions

The semantic meaning of "eloquence" refers to functions of language, i.e. fluent or persuasive speaking or writing. The neurosurgical use of the term "eloquent location" is not uniformly defined, but usually includes motor functions and visual functions in addition to language functions. Preoperative and intraoperative identification of eloquent brain areas is important to facilitate maximal safe tumor resection. Sawaya et al suggested a classification of eloquent regions of the brain depending on neuroanatomical location (non-eloquent, intermediate, eloquent) (52). This classification has been used by clinicians, but the reliability of eloquence linked to neuroanatomy has been questioned (53). An alternative grading system for eloquence has recently been suggested (54). Even in the normal brain, there is variability in the functional role of anatomical structures (55). Eloquent areas within the healthy brain can be identified by structural landmarks, but pathology such as tumors can distort anatomy. This can make it impossible to identify eloquent areas based on anatomy alone. The interpatient anatomical variability already present in the healthy brain is increased further in these cases (53, 56). Brain plasticity, i.e. relocation of functional regions as a response to pathology has been described, modifying the functional-anatomical relationship (57). Therefore, a pure anatomical definition of eloquence is not reliable enough in individual patients, and extensive use of preoperative fMRI, DTI (diffusion tensor imaging) tractography, and MEP (magnetic evoked potentials) has been suggested instead (53). When it comes to consideration of eloquent lesions in the planning stage of the individual brain tumor surgery, three main methods are practiced these days: One is intraoperative mapping in awake, cooperating patients by means of cortical and subcortical

stimulation and/or somatosensory evoked potentials mapping (58). The second option is tractography with DTI and/or matching and fusing of blood-oxygen-level-dependent (BOLD) functional MRI (fMRI) and high-resolution MR images, which are then integrated into a neuronavigation system used intraoperatively ("functional neuronavigation"). The evidence on the use of functional neuronavigation for detection of functional cortical motor and, to a larger degree, language areas, is conflicting (59-61). A third option is navigated transcranial magnetic stimulation (nTMS) (62). Its use for mapping of motor functions has gained increasing acceptance in motor functions, while its reliability in language mapping is less clear (63).

Laterality and hemisphere dominance

Ever since Broca and Wernicke published their works on cerebral lesions in the second half of the 19th century, the functional and structural asymmetry of the brain and the preeminent role of the left hemisphere have been an established factuality in medicine (64-66). A number of important brain functions are lateralized to one side of the brain, for example executive language functions, typically located in the left hemisphere. Left- and right-handedness are preferences for one side of the body resulting from the lateralization of such brain functions (65). Ninety percent of individuals are right-handed. In 90%–96% of right-handed as well as in 70%–86% of left-handed individuals, the left hemisphere is the dominant one for processing language (67, 68). "Hemisphere dominance" is a concept often linked with handedness, but there is increasing doubt if the dominance of one hemisphere actually does exist- the brain hemispheres are linked through the corpus callosum and usually operate together (65). Earlier, popular reports have suggested a categorization into whole-brain phenotypes ("left-brain-types" and "right-brain types"). Today, such a subject-specific global brain lateralization difference is regarded as highly doubtful, as the authors of a recent study on resting state functional connectivity-MRI conclude (69). Nevertheless, in most right-handed individuals, the brain area processing language functions is located in the left hemisphere, while visuospatial functions are located in the right hemisphere (70, 71). The basis of this functional specialization of the hemispheres is not well understood (72). Atypical lateralization of these functions has been described (73), and may in some cases be associated with neuropsychiatric disorders, such as schizophrenia or autism spectrum disorders (65, 74). Still, also in normally developing individuals, there is a considerable

variation in the sidedness of specific functions such as language, especially in left-handers and ambidextrous individuals (75).

Operability of brain tumors

The special anatomy within the skull can cause difficulties to access brain tumors surgically. A lesion can be histologically benign, but still not be surgically well treatable due to an inaccessible location, for example meningioma in the cavernous sinus. A lesion can also be histologically benign, but may show a tendency to frequent recurrence and thus have a malignant disease course (as for example craniopharyngeoma or anaplastic pituitary adenoma). Brain metastases may be possible to remove, but with very few exceptions, this will not cure the disease, as these tumors are linked to a disseminating primary cancer. Complete resection of some skull base- and brain stem tumors may not be possible (or at least not be advisable), due to their location close to vital or at least functionally important nerval or vascular structures (6), and diffuse gliomas show an invasive growth pattern into the white matter, making complete removal of all tumor cells impossible. The clinical assessment of operability of a brain tumor can be demanding. It may also result in different conclusions, dependent on the surgeon asked, since there is no standard definition of resectability (76).

A superordinate concept in modern brain tumor surgery is the aim of so-called "maximal safe resection". This term means maximal tumor resection while preserving neurological function or at least minimize damage to an acceptable level (77). Techniques such as image-guided surgery, electrophysiological monitoring or awake craniotomy with intraoperative cortical and subcortical stimulation mapping are used to avoid major neurological deficits while at the same time resecting as much of the tumor as possible. "Gross total resection" and "maximal safe resection" are terms that are mainly used in glioma surgery, due to the invasive growth pattern of these tumors and impact of extent of resection on survival. Of note, "maximal safe resection" is not possible to state during surgery. Unless intraoperative MRI (iMRI) is available, the conclusion on completeness of a resection cannot be drawn before postoperative MRI-screening is done, and neither can neurological integrity be stated before performing a postoperative examination, unless surgery is done awake. As such, maximal safe resection is usually not a real-time measure with the potential to guide surgery. It rather represents a measure of intention, evaluated in

hindsight. Also, the term “maximal” may duly be met with skepticism in a postoperative situation without new neurological deficits, but with presence of residual tumor on MRI-scans.

Clinician-reported outcomes in brain tumor surgery

Reporting surgical outcomes in terms of survival and complications is not a recently developed concept in neurosurgery, as documented by Harvey Cushing’s reports about one century ago (78). Modern neurosurgery is characterized by considerably decreased perioperative mortality on the one hand and limited resources and an ever-increasing number of costly treatment options on the other hand. Hence, the reporting of “soft” outcomes such as progression-free survival, newly acquired neurological deficits and perioperative complication rates has gained great importance for assessment of therapies, and, increasingly so, for evaluation and comparison of health systems and single providers (79).

Overall survival

Overall survival is of obvious interest in neuro-oncology. However, little is known about the natural course of many brain tumors if left untreated. The actual clinical range probably stretches from about 1 month in untreated brain metastases (20, 21) to a much longer, probably normal life expectancy in life-long asymptomatic, slow-growing meningiomas. Still, in unselected meningioma patients, large studies from Finland and Sweden have shown a decreased long-term survival, compared to matched cohorts (80, 81). Surgery has been found to be associated with better survival rates in patients with meningioma, compared to not undergoing surgery (80, 82). Also in brain metastases, surgery has an increasingly acknowledged role in extending survival (16), although usually in combination with radiotherapy (26, 27, 83). In malignant glioma, complete surgical resection has shown to increase survival (84). The role of subtotal resections for survival is not clear. In diffuse low-grade glioma, resective surgery has been found to increase survival time when compared to a strategy of watchful waiting (45, 46) and biopsy (85). However, the effect of surgery is much higher for the most extensive resections (86). In a recent volumetric study, no effect on survival was found in LGG patients with a residual tumor volume > 25 ml (47).

To evaluate the impact of surgery on survival, it is important to remember that overall survival as an endpoint may not reflect the effect of surgery on its own, since the most aggressive brain tumors usually are treated with a combination of radiation, surgical tumor resection and often chemotherapy. On the other hand, there are brain tumors, such as most meningiomas with their generally low mortality, and LGG with slow growth rates, which require extremely long follow-up periods to assess and report overall survival. Not surprisingly, there are very few comparative studies on survival in LGG (45, 46, 85), and few randomized trials study survival with or without surgical resection in patients with intracranial tumors (26, 27, 87, 88), and knowledge about survival benefit from surgery is mainly based on observational studies. An important issue in observational studies is that selection to different surgical strategies (e.g. complete resection, subtotal resection or biopsy) is not random, but depends on clinical features. Therefore, bias may result, as "operability" is a factor not easy to adjust for.

Although survival is very important for most patients, patients with aggressive cancers may not necessarily be prepared to sacrifice important brain functions or quality of life to gain a few extra weeks of life. Patients with very slow growing lesions, on the other hand, may not always be willing to sacrifice functions to gain a theoretical survival benefit in the distant future.

Progression-free survival

In addition to overall survival (OS), progression-free survival (PFS) is the most established outcome in clinical oncological trials. This endpoint is linked to the radiographic evaluation of treatment response and tumor progression. During the last decade, efforts by the RANO (Response Assessment in Neuro-Oncology)-group (89, 90) have led to an increasing implementation of a response classification that includes imaging-related criteria as well as clinical ones (physical status, corticosteroid use). Still, advanced volumetric measurements, especially in HGG, can mislead the treating physicians: Pseudoprogression, mainly seen after addition of temozolomide to radiotherapy (35), is the finding of contrast-enhancing new lesions on MRI that are difficult to discriminate from real tumor progression. In LGG, response and PFS are more difficult to assess because these tumors respond more slowly to adjuvant therapy than HGG, are usually not contrast enhancing, and have irregular and diffuse tumor margins which make measurement difficult. Additionally, treatment may improve neurological function (which is part of the RANO-criteria) and alleviate symptoms without significantly reducing tumor size

(35). Recently, modification of the RANO criteria has been agreed on for LGG and for brain metastases (90). For meningiomas, with usually more sharply defined borders, volumetric approaches to measure treatment response and progression have been suggested by the RANO group (91). Regardless of the radio-oncologic criteria applied, the use of standardized MRI-protocols is necessary to result in comparable and reliable outcome measures for the use in clinical studies (90). Volumetric assessment based on various image segmentation methods increase the sensitivity in assessment of growth and response, but is time consuming and therefore seldom done in clinical practice. So far, the RANO group has landed on assessing growth based on measures of perpendicular diameters, but segmentation methods will likely be incorporated in the future. When assessing tumor progression from MRI-images, inter-rater variability is a problem, which in the future hopefully will be less prevalent, due to increasing use of software programs with automated segmentation algorithms (92). At the biological level, assessing progression as a dichotomous variable (yes/no) is not unproblematic, as most brain tumors exhibit continuous growth (93-95). Thus, "no growth" as classified based on image criteria merely reflects the sensitivity of measurements and diagnostic imaging and not necessarily tumor biology. Also, for many patients, progression or relapse is not always an important endpoint. For example, a local asymptomatic recurrence of a brain metastasis may not be important if the extracranial disease is causing a lot of symptoms and the prognosis is very limited. Likewise a small recurrence of a meningioma that is often rather easily and effectively managed with stereotactic radiosurgery might be much preferable to advocating extensive, mutilating resections upfront to reduce the chance of recurrence.

Perioperative mortality

In the early days of brain tumor surgery, around the year 1900, perioperative mortality was often as high as 50%. Harvey Cushing reported a mortality of 13% from a series of his own cases (78). In 1925, Norwegian pioneer neurosurgeon Vilhelm Magnus reported 10.5% surgical mortality in a series of 189 brain tumor patients he had operated during a 20-year period (96). Today, perioperative mortality is considerably lower. A recent large U.S. registry study on 7376 patients reported a 30-day mortality rate of 2.6% following craniotomy for primary malignant brain tumors (97). Another study from an administrative registry in the U.S., studying the correlation between hospital caseload and complications during a 12-year period in over 500.000 patients

even report a risk-adjusted in-hospital mortality rate of 8.8% in patients undergoing surgery for intracranial neoplasms (98). Conversely, a recent single-center study on adult patients undergoing 4423 procedures in a 5-year period in a high-volume academic referral center reports a 30-day perioperative mortality of only 0.3% (99). This is an example for a tendency of single-center studies to report lower rates of adverse events than registry-based reports.

Perioperative morality is a rather infrequently occurring endpoint that additionally is linked to case selection. Therefore, comparisons across studies are difficult. Also, some studies (most studies from the U.S.) assess in-house mortality rates while others assess 30-day mortality rates. The former may be considerably affected by local routines for transfers and discharge of patients.

Extent of surgical resection (EOR)

To measure resection grade in meningioma surgery, the macroscopic, intraoperatively assessed grading I to V as suggested by Simpson in 1957 (100) is still in use, with Simpson grade I being removal of tumor bulk including attached dura and bone, and grade V being mere decompression. Ascending recurrence rates were found related to ascending Simpson grade I to III (grade IV and V imply the presence of macroscopic residual tumor) (8). Still, good results of stereotactic radiotherapy treatment of small residual tumors may decrease the prognostic importance of lower Simpson grades in this setting. For a more modern, image-based assessment of resection grade in meningiomas, the RANO-group (90) suggests the RANO-criteria to be used if three-dimensional volumetric measuring is available.

In modern glioma surgery, the aim is maximal resection of tumor tissue, commonly called “gross total resection” (GTR). The term “gross total resection” has its origin from the time before CT and MRI-imaging, from the way the surgeons assessed tumor resection through visual and tactile impression in the operating field when tumor resection was completed (89). According to the RANO criteria, GTR is equivalent to the complete removal of contrast enhancing tumor in HGG and the removal of all T2/FLAIR hyperintense tissue visible on MRI scans in LGG (89). Neurosurgeons often report the degree of any subtotal resection, i.e. resection grades other than GTR, by a percentage of the original tumor volume. Unfortunately, different percentages as cut-off values to discriminate between GTR and STR are used in the literature. Importantly, a

reported resection grade does not contain information on the actual size of the remaining tumor burden. There are several newer studies indicating that residual tumor volume is at least equally well suited as a prognostic factor as EOR (47, 101, 102). The importance of EOR as an outcome measure has been established in both HGG and LGG patients. In HGG, EOR has been shown to be positively related to survival (84, 103-109), but there is disagreement on risks and benefits of aggressive resection (110, 111). A recent systematic review on the role of EOR in glioblastoma concluded that GTR substantially improves overall and progression free survival, but the evidence was judged to be of low quality (112) . In studies on patients with LGG, larger resection grades have been reported to be associated with increased overall survival (47, 58, 86, 113, 114). A few other studies comparing cohorts of non-treated and surgically treated LGG patients found a survival benefit in patients undergoing surgical resection (45, 46, 85). A newer study by Wijnenga et al. (47) re-investigated a cohort of LGG patients to evaluate the impact of surgery in the molecular subtypes described by the revised 2016 WHO-classification (9). Their findings were that preoperative and postoperative tumor volume in addition to molecular subgroup were the only independent predictors of survival in LGG. As other authors have stated, less extensive resection in order to avoid surgically acquired deficits (115) may be the reason for impaired survival in LGGs in eloquent regions (115, 116).

New neurological deficits

Neurological deficits are common in glioma patients, and often represent the first symptom leading to diagnosis. The Glioma outcome project found that in 565 patients with HGG, the most frequent symptoms at presentation were headache, memory problems, neurocognitive impairment, seizures, as well as motor and language disturbances (117, 118). A more recent paper found seizures and cognitive disturbances to be the most frequent symptoms in glioma patients at diagnosis, but more than 25% of patients had aphasia and 21.8% had motor deficits at presentation (44).

New deficits or worsening of existing neurological deficits following tumor surgery are of utmost concern for neurosurgeons. New deficits have been associated with decreased survival in high-grade glioma (111, 119), and may also affect QoL negatively (120). Modern technologies such as fMRI, DTI, transcranial MEP, intraoperative imaging and intraoperative functional mapping have led to more aggressive surgery without necessarily increasing the risk of new or

worsened deficits (1). It has to be remembered that new deficits cannot be avoided entirely by identifying eloquent areas by pre-or intraoperative imaging or through intraoperative mapping or awake surgery. Deficits do not necessarily result from resection of functional tissue, but may also be due to vascular damage (often as peritumoral infarctions). Complications such as postoperative hemorrhage, empyema, encephalitis, ventriculitis may cause neurological sequelae as well. In addition, a fair share of patients who undergo craniotomies report long lasting fatigue, depression, epileptic seizures or pain, negatively affecting postoperative brain function. Even so, the frequency of new deficits following intracranial tumor surgery varies from 0% to 33% in newer reports (1, 99, 121, 122). Importantly, detection methods vary from crude clinical assessment to advanced neuropsychological testing. Also, there is heterogeneity in definition of new deficits- sometimes, only motor and language deficits are accounted for and reported (58, 111, 123), while others include more subtle symptoms such as cognitive problems and examine a much broader range of neurological and neuropsychological domains (122, 123).

Cognitive changes can be found in the majority of brain tumor patients (124). Tucha et al found that 91% of patients with frontotemporal tumors had neurocognitive impairment when undergoing neuropsychological testing at admission, prior to treatment (125). Habets et al found 79% of HGG patients to present presurgical cognitive impairment in at least 1 domain (126). These cognitive problems can be caused by the tumor itself, edema, hydrocephalus or epilepsy. Oncological and irradiation treatment have their own negative impact on cognitive performance, the latter becoming especially apparent in long-term survivors (127, 128), but these treatments may also alleviate neurocognitive problems due to disease control (128). This implies that neurocognitive testing in brain tumor patients usually does not lead to firm conclusions about the causal relationship of symptoms and treatment, and makes cognitive deficits an especially intricate outcome variable in this patient population. The importance of cognitive evaluation in brain tumor surgery has been addressed in the oncological literature (123, 124, 129, 130), but there is no standardized reporting. Of specific measures addressing cognitive function, The Mini Mental State Evaluation (MMSE) has been used, but is regarded to be an insensitive measure in other than severe cognitive dysfunction (123, 131). Other tests used are the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Hopkins Verbal Learning Test-Revised (HVLT-R), the Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) (132, 133). A test battery including the latter three of the mentioned tests has been suggested for use in brain

tumor clinical trials. Its completion is supposed to last about 20 minutes (132), and has been suggested to require involvement of a neuropsychologist at the data collection and supervision level (132).

In assessments that implement change, for example preoperative versus postoperative, it is worth to look at the baseline. In a preoperative situation, the patient may be anxious or even in a crisis following diagnosis, or may suffer from side effects of antiepileptic medication and steroids, and may not be able to perform optimally in a neurocognitive test. In those situations, postoperative cognitive impairment may be obfuscated by a compromised preoperative test. Some authors have reported postoperative improvement of neurocognitive function in small series of LGG patients (134, 135), but these results may tell as much about a suboptimal situation when tested at baseline, or about a learning effect in repeated neuropsychological testing.

Surgical complications

Surgical complications after brain tumor surgery are not uncommon, but reports vary immensely in definition, timing and methods of detection. All grades of severity of complications can be seen following craniotomy, from urinary retention or UTI (urinary tract infection) to fatal postoperative hematomas. Post-craniotomy-complications may be detected when the patient develops symptoms, such as a decrease in GCS (Glasgow Coma Scale) when developing a cavity hematoma or cerebral edema, or shortness of breath when suffering from a pulmonary embolism. Alternatively, complications may be detected by routine surveillance, e.g. postoperative MRI, urine dipsticks, bladder scanning and pulse oximetry (99, 136). Complication rates, especially those reported from single institutions, depend on case mix and complexity of surgery performed at the respective institution (97), as well as local routines for surveillance, documentation and follow-up (136). Complex tumor operations in multimorbid patients harbor an inherently higher risk of complications than easily removable tumors in otherwise healthy patients. Some authors have therefore used risk adjustment when reporting complications (98). The experience and expertise of the operating surgeons most likely also plays an important role. Two studies have reported a greater morbidity (137) and perioperative mortality (98, 137) in patients undergoing brain tumor surgery in low-volume hospitals compared to high-volume hospitals. How the individual researcher defines a complication influences reported results. Taking into account intraoperative complications in addition to postoperative morbidity, counting neurological

complications as a perioperative complication or not, as well deciding to account for perioperative deaths through complications rates or report fatalities separately, will all influence reported complication rates. This illustrates that complication rates are complex composite endpoints, but, importantly, without agreed standards on their composition. Based on earlier attempts by the general surgical community to classify complications (138, 139), Landriel Ibañez and colleagues published a neurosurgical classification system for complications, where complications are graded dependent on the intervention necessary. Additionally, the authors suggest distinction between surgical and medical complications (140). In paper III in this thesis, we used this grading to report complications.

Physical functional levels

Clinician-reported physical functional scales are frequently used measures both in baseline preoperative assessment and as an outcome measure in brain tumor surgery. There is a large variety of functional scales, and the Karnofsky performance score (KPS) is probably the one most frequently used in brain tumor surgery. The KPS was originally suggested to predict cancer patients' suitability to receive chemotherapy, and contains 11 levels in intervals of 10, where 0 equals death and 100 refers to completely normal level of function. Frequently, KPS scores are dichotomized in scientific reports, usually with a cut-off at 70, where the ability to self-care is preserved. As "normal function" is different from patient to patient, this may affect assessment. For example achieving the full KPS score of 100 is more difficult in a busy professional with a stressful job and a demanding social life, than in a retired, relatively inactive elderly individual. KPS focuses primarily on physical functions and daily activities and does not necessarily cover all aspects of neurological dysfunction or cognitive impairment in a satisfactory way. Symptom scales have therefore been claimed to be of importance in brain tumor patients (141, 142). Other functional outcome measures include the WHO performance status, the modified Rankin Scale (mRS) for neurologic disability and the Barthel Activities of Daily Living (ADL) scale, mainly used in stroke rehabilitation. One limitation of these functional measures is that motor function is central in the assessment. Even small motor impairments have the ability to impact the scoring in these scales considerably and to a larger degree than for example cognitive and language problems. Nevertheless, the KPS, despite being a rather crude measure, remains a strong prognostic factor both in HGG, LGG, metastases and meningioma patients (6, 24, 143-145).

Patient-reported outcomes (PROs)

Paradigm shifts in medicine

Since the 1970s, medical practice has gradually gone through a value shift from the traditional paternalistic view on medical treatment and care to patient-centered medicine. Patient-centered healthcare is defined as "care provision that is consistent with the values, needs and desires of patients and is achieved when clinicians involve patients in healthcare discussions and decisions" (146). This has led to an increasing integration of patients' opinions, needs and perspectives into decision-making in clinical practice, healthcare organization and planning and conduction of research projects.

The other, at least equally fundamental paradigm shift in medicine, mainly from the 1990s and onwards, is the shift from experience-based to evidence-based medicine. Of note, evidence-based medicine is not at all diametrical to patient-centered medicine. Even in the early days of publications on basic concepts and frameworks of evidence-based medicine, "integration of both evidence and patients' choices and preferences" was claimed to be an important part of well-conducted evidence-based treatment (147). Integration of patient values is one of the five steps suggested for the good practice of evidence-based medicine (148).

Patient-centered healthcare and evidence-based medicine are central frameworks in modern clinical practice. Both concepts are under continuous discussion, revision and development by the medical community.

Concept and current usage of PROs

The change towards patient-centered medicine has led to development of new outcome measures to evaluate treatments. Patient-reported outcomes (PROs) including health-related quality of life (QoL) measures, have emerged during the last two decades and have become increasingly incorporated into research on clinical outcomes. According to the definition by the FDA, PROs are "measurements of any aspect of a patient's health status that come directly from the patient" (149). PRO measures can consist of single questions, for example on the occurrence of complications or on the extent of change in health following a treatment intervention, or can

consist of many questions, so-called multi-item PRO measures (150). Instruments for patient-reported health-related QoL are a subgroup of PRO measures. Generic PRO measures address general aspects of health, such as ability for self-care or pain, for example the QoL-instrument EQ-5D 3L (151). These generic measures, by concept, do not cover disease-specific dimensions such as specific symptoms, but rather address overall health and wellbeing. Thereby, generic PROs can facilitate comparison with other patient groups or cost-effectiveness analyses. There are also numerous disease-specific or symptom specific PROs which address symptoms and their impact on function (or QoL) of a specific condition, for example the Oswestry disability index for low back pain (152) or QoL-tools specifically designed for the use in cancer such as the EORTC C30 (153) and the FACT-Br (154).

PROs have been proposed to have a number of advantages as clinical outcomes: They cover aspects that only patients can assess, such as symptom burden and quality of life. To address these universally important aspects is the aim of most healthcare (150). Observer bias is not an issue when using PROs, and additionally, they can be used to increase public accountability of healthcare providers. It has also been postulated that involvement is appreciated by patients, and that this "may have health benefits in itself" (150). It is important to distinguish between PROs and patient satisfaction measures. The latter have gained popularity as quality measures for the comparison of providers in some countries (155) as well of steering of reimbursement (156). Conversely, the reliability of patient satisfaction as a quality marker of medical treatment or as an outcome marker is questionable from the results of some studies in cardiology, surgical and surgical oncology patients (157-160). Of special note in the context of this thesis, patient satisfaction has not shown to be a marker of quality of care in patients undergoing elective craniotomy (161).

Analogous to the concerns in outcome reporting by clinicians, systematic reviews on PROs found that methodological concerns and heterogeneity of studies limit the strength of inference and hamper firm conclusions (149, 162). General obstacles in studies using PROs are limited power when comparing subjective measures obtained from few patients with wide confidence intervals, the response shift that may occur over time (163), and the inability of some patients to comply to detailed and complex questionnaires (164). Finally, missing data is problematic, causing selection bias.

A complex PRO: measuring health-related Quality of life (QoL)

QoL-instruments are an important subgroup of PRO-measures and have gained substantial weight as outcome measures in chronic illnesses and cancer during the past decades. The concept of QoL involves a multidimensional approach, including different dimensions of subjective wellbeing: physical (i.e. symptoms and treatment side effects, functional (usual activities and role performance), social (quality of communication and relationship with others) and emotional (psychological impacts of disease and treatment) (165). To be comprehensive, a feasible QoL-instrument has been suggested to comprise of at least three dimensions(165), but most instruments contain more. QoL-instruments are presented to patients in the form of questionnaires, and are usually answered by the patients themselves or, in debilitated patients, by their next of kin as proxies. Longitudinal QoL-assessments before and after an intervention can assess the impact of treatments on QoL. Importantly, although QoL measures can contain questions about symptoms, symptoms alone do not determine QoL. QoL-instruments are not intended to be mere measures of symptoms (162).

Use of PROs in brain tumor surgery

In low back surgery, for example, a PRO (the Oswestry Disability Index) has become a universally embraced part of scientific reports and treatment registries (166). Conversely, in brain tumor surgery, the use of PROs can be claimed to be still in its infancy. A frequently used PRO in brain tumor patients nowadays is QoL, although predominantly reported in oncological observational studies (167-169) and as accompanying protocols in clinical oncological trials (170-172). Disease-specific extensions of QoL-instruments, containing items relevant for brain tumor patients such as the EORTC BN20 (153) and the FACT-Br (154), are often used in these studies. These are designed to capture the effects of oncological treatment and contain questions covering aspects of oncological treatment of brain cancer, such as nausea and hair loss. There is no validated disease-specific QoL-instrument specifically addressing implications of surgery in brain tumor patients. In publications from our group, including paper II and III in this thesis, the generic tool EQ-5D 3L has been used to measure QoL (116, 119, 120, 173-179).
Studies addressing the impact of surgical treatment on QoL by providing both pre-and postoperative QoL-assessments are scarce in brain tumor surgery.

In meningioma patients, some studies with cross-sectional QoL-data exist, measuring either preoperative (180, 181) or postoperative QoL (182-186). In a recent systematic review, these studies were found to be highly heterogeneous and reporting of PROs was assessed to be of low quality (187). Only two cases series compared pre-and postoperative QoL longitudinally in meningioma patients. Miao et al found QoL in meningioma patients to be lower than in healthy controls, and report postoperative QoL to be better, compared to preoperative measurements. EOR, WHO-grade and tumor size were found to be predictors of QoL (188). Another case series from our institution found a modest average improvement of QoL following surgery, but postoperative worsening of QoL in 1 out of 5 patients (176). In a recent large population-based case-control study that explored cross-sectional QoL in 1722 patients within one year after meningioma surgery, Benz and colleagues found that the patient group experienced statistically significant lower QoL measured by the generic tool SF-36, compared to healthy controls (189).
In glioma surgery, there are a few studies addressing the impact of surgery on QoL longitudinally, by both pre- and postoperative assessments, most of them by our group (119, 120, 174, 177), in addition to a small pilot study by a German group (190). Jakola et al found early postoperative deterioration of QoL to be strongly associated with impaired survival in patients with glioblastoma (119). In another study, new deficits after surgery were found to be associated with impairment of QoL in glioma patients, and that only about half of functionally dependent patients with glioblastoma reported improved or unchanged QoL postoperatively (177). Two published studies explored longitudinal follow-up at more than one time point after surgery, as does paper III in this thesis. Wolf and colleagues recently published a complete-case analysis on a small series of heterogeneous glioma patients with QoL-assessments preoperatively, at discharge from hospital and at 3 months, and found no correlation between QoL and the patients' neurological or neuropsychological status (190). A series from our institution with frequent follow-ups during the first year after glioblastoma surgery found both positive and negative changes of QoL to occur more often after surgery than after radio- or chemotherapy, and found that patients in whom GTR was achieved reported better QoL than patients who underwent subtotal resections (174).
Also, a recent study on patients with various brain tumor types assessed both pre- and postoperative QoL, and the authors report improved or unchanged PRO-outcomes following

surgery in most patients with only 6% patients reporting worsening of QoL at 3 months after surgery (191).

Studies from a Finnish group on the use of PROs in neurosurgical patients undergoing elective craniotomies were recently added to the literature on PROs in cranial neurosurgery. Reponen et al. used postoperative PROs to predict in-hospital morbidity and concluded that PROs are promising patient-centered tools for outcome reporting (155). Another study by the same group found that preoperative PROs assessing general health and cognitive function were better predictors of major in-hospital morbidity than the ASA score (192).

In all papers in this thesis, PROs are used. In paper I, we used patient-reported new neurological deficits and complications, while in paper II and III, patient-reported QoL was the main outcome measure.

Aims and Methodological Considerations

Overall aim

The overall aim of this thesis was to study different scopes of patient reported outcome assessment in patients with brain tumors undergoing surgery, with emphasis on patients with glioma

Paper I

Morbidity after intracranial tumor surgery: sensitivity and specificity of retrospective review of medical records compared with patient-reported outcomes at 30 days

In 191 patients who underwent planned resection of intracranial tumors, we assessed postoperative morbidity based on retrospective review of medical records compared with morbidity reported by the patients themselves at 30 days after surgery.

Paper II

Quality of life in patients with intracranial tumors: does tumor laterality matter?

In this prospective cohort study in 248 patients with intracranial tumors, we aimed to explore whether patient-reported QoL before and after surgery is dependent on tumor laterality.

Paper III

Perioperative and postoperative quality of life in glioma patients- A longitudinal cohort study

Our aim in this study was to explore the peri- and postoperative development of patient-reported QoL in 136 newly diagnosed glioma patients

Study populations

All three studies in this thesis are based on prospective, consecutive inclusion of consenting patients (≥ 18 years) who underwent surgery for intracranial tumors at the Department of

Neurosurgery, St. Olavs Hospital, Trondheim, Norway, in the period from January 2007 through November 2015 (Research project ”Quality of life in patients with intracranial neoplasms” REC no. 2011/974). In paper I, the patient population included patients undergoing first-time or repeat craniotomy for different histological types of brain neoplasms. The study population in paper II included patients undergoing first-time surgery for meningioma or glioma, while paper III included patients undergoing first-time surgery for glioma.

Histopathology

In all three studies, intracranial tumors were histopathologically confirmed by a neuropathologist and classified according to the 2007 WHO classification. Data collection for all papers was finished before the new 2016 WHO classification was published.

Assessment of images

In the studies in paper II and III, patients underwent 1.5 T or 3.0 T MRI scans preoperatively and within 72 hours after surgery, as is usual routine in our department. The interpretation of image data was performed by a neurosurgeon. The volumes of spherically shaped lesions were calculated by using the ellipsoid volume formula ($4/3 \cdot \pi \cdot r1 \cdot r2 \cdot r3$) based on the maximum tumor diameters in the available image dimensions. In cup-shaped residual tumors, volume was calculated by subtracting the ellipsoid-shaped resection cavity from the volume of the tumor/cavity complex, as previously done by others (109). In very complex configurations, several volumes within the residual lesion were defined and measured using the above-mentioned methods as appropriate, and summed up. Compared to manual segmentation or use of semi-automated software systems (92), this method is less refined, but represents a pragmatic approach in our research context.
In paper III, eloquence of tumor location was graded in a validated and thus reproducible system according to Sawaya et al. (52) (Table 1).

Table 1 Grading of eloquence of brain regions according to Sawaya et al.

Grade 1 (non-eloquent brain)	Grade 2 (intermediate)	Grade 3 (eloquent brain)
Frontal or temporal polar	Near motor or sensory area	Motor/sensory area
Right parieto-occipital	Near visual area	Visual area
Cerebellar hemispheric	Near speech center	Speech center
	Near dentate nucleus	internal capsule
	Near brain stem	Basal ganglia
		Hypothalamus/thalamus
		Dentate nucleus
		Brain stem

Assessment of new neurological deficits

In paper I, surgeon-reported new or worsened neurologic deficits were obtained from medical records at discharge. For comparison, patient-reported new or worsened deficits were collected by telephone interviews at 1 month. In the study on peri-and postoperative development of QoL presented in paper III, we aimed to capture deficits present at 1 month post-surgery, as these were thought to have a possible impact on the longitudinal QoL-assessments. "Permanent new or worsened deficits" were therefore defined by categorizing surgeon-reported new or worsened deficits which were confirmed by the patients at 1 month as "permanent".

Assessment of perioperative complications

In paper I, perioperative medical and surgical complications were assessed by reviewing hospital records of the first 30 days after discharge. Additionally, patient-reported complication data were collected at the 30-day telephone interview.

In paper III, perioperative complications during the first 30 postoperative days were classified as suggested by Landriel Ibanez et al. (140) and thereafter transformed into a dichotomous variable (Landriel Ibanez class I, "mild complications" versus Landriel Ibanez class II, III and IV "moderate, severe or fatal complications").

QoL assessment

The EQ-5D 3L instrument

Health-related quality of life (QoL) in paper II and III was assessed by the generic (i.e., not developed for a specific patient group) tool EQ-5D 3L (151). This instrument is widely used in a range of different health conditions, including cancer (193). The EQ-5D 3L questionnaire covers the 5 subdomains mobility, self-care, usual activities, pain and anxiety/depression. For each domain, the respondent can apply 1 of 3 grades: "no problems", "some problems", or "extreme problems". A single summary index value is calculated from the responses to these subdomains, ranging from "1" ("perfect health") to "0" ("equal to death"). Negative index values are possible, indicating a QoL worse than death (Table 2). We used the U.K. trade-off tariff for calculation of index values (194). The EQ-5D 3L has been validated for the Norwegian population (195).

Table 2 EQ-5D 3L scores and their interpretation

Outcome measure	**What is assessed?**	**Score range**	**Improved score**	**Interpretation**
EQ-5D 3L index	Global QoL	-0.48* to 1.00	Higher values	<0 = worse than death 0 = death 1.0 = perfect health
EQ-5D 3L subdomains**	Mobility Selfcare Usual activities Pain/discomfort Anxiety/depression	1-3	Lower values	1 = No problems 2 = Some problems 3 = Extreme problems

**in the study populations in this thesis **scores for subdomains are aggregated and converted into EQ-5D 3L index values(194)*

To measure HRQoL, many different validated instruments are available. We chose the simple, generic instrument EQ-5D 3L with only 3 possible rating levels to enhance patient compliance and to facilitate ratings by telephone interviews, as well as proxy ratings.

The EQ-5D questionnaire was completed 1 to 3 days prior to surgery, by the patients themselves or, if necessary, with help from a research nurse or next of kin. At 1 month (paper II and III) and 6 months (paper III), the questionnaire was completed in a structured telephone interview, performed by a research nurse.

Proxy ratings of the EQ-5D instrument by lay caregivers (next of kin) were used in paper II and III in patients who were not able to answer the questionnaires themselves.

Minimal clinically important difference

The minimal clinically important difference (MCID) represents "the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and which would lead the clinician to consider a change in the patient's management." (196). The MCID in patients undergoing glioma surgery has been found to range from 0.13 to 0.15 in an earlier study performed by our group (173), and was set to +-0.14 in paper II and +- 0.15 in paper III.

Statistics and study design

In the three studies in this thesis, SPSS versions 21.0 to 24.0 were used for data analysis. P-values were considered significant at the 0.05-level. Student's t-test was used for comparison of normally distributed data. Mann-Whitney U was used for ranked comparison in skewed data. Friedman test was used for comparison of skewed data resulting from repeated measurements. Spearman's rho was used to test correlation in skewed data. In logistic regression analyses, p-values < 0.1 in univariate analyses were included in the multivariate analyses.

Paper I

In paper I, we used retrospectively obtained information on surgeon-reported new deficits at discharge from hospital as a clinical test, while prospectively collected new deficits reported by patients (PROs) served as the "gold standard" for assessing the test properties sensitivity and specificity in contingency tables (Table 3). We included all types of brain tumors, but only those where craniotomy was performed.

Table 3 Contingency table for calculation of sensitivity =a/(a+c) and specificity=d/(b+d)

		Patient-reported new deficits ("gold standard")	
Surgeon-reported new deficits ("clinical test")		**yes**	**no**
	yes	a	b
	no	c	d

Paper II

In paper II the study population consisted of supratentorial meningiomas and gliomas with unilateral location. Patient-reported QoL, measured with EQ-5D 3L was obtained prospectively, and EQ-5D index values in patients with right-versus left-sided lesions were compared. To adjust for possible confounding by larger tumor volumes in patients with right-sided tumors, a result-driven matched analysis on a subgroup was performed (please see next paragraph). For the comparison of longitudinal EQ-5D values, we calculated the change from preoperative to postoperative EQ-5D-3L index scores with a MCID of 0.14 as the cut-off value.

Matching procedure

For the matching procedure, tumor volumes in right- and left-sided tumors were grouped into quartiles. We then performed a pairwise matching (right-left) of tumor volumes of similar size (same volume quartile) and same histopathology (LGG, HGG, meningioma), resulting in comparable average tumor volumes within quartiles. Cases with no match in histopathology and volume (within the same quartile) were excluded from the 1:1 matched analyses. The matching procedure was performed blinded for QOL scores and all clinical variables other than the matching variables (laterality, tumor volume, and histopathology).

Paper III

In paper III, patients with low-grade gliomas (WHO class I and II) and high-grade gliomas (WHO-class III and IV) were included. Patient-reported QoL, assessed by the generic tool EQ-5D 3L, was prospectively obtained prior to surgery, and at 1 and 6 months postoperatively. EQ-5D index values in LGG versus HGG at group level were compared by Mann Whitney U-test, while longitudinal change in index values over the course of the three QoL-assessments were analyzed by Friedman test. Individual development was explored by assessing and categorizing

change greater than MCID (+-0.15). Univariate and multivariate logistic regression analyses were performed to identify predictors for negative development of QoL over time.

Missing data

In studies on QoL in brain tumor patients, missing data due to loss to follow-up or death are a common problem. Fayers and Machin suggest a proportion of <5% of missing QoL-data to be "very small" (197). Only including patients with a complete data set (*complete case analysis*) or including all available information on QoL collected at specific time points (*available case analysis*) may lead to bias, because the actually collected data may not be representative of all data for the study population. Data may be missing of different reasons. When missing QoL-data is independent of both earlier observed and expected values for the patient, it can be assumed as *missing completely at random* (MCAR). This would be the case when the research nurse responsible for data collection is on sick leave at the time of assessment, and the patient therefore has not been handed out a QoL-questionnaire at that time point. If missing data have a correlation to observed data on known baseline factors, but not to the non-observed data, they are termed *missing at random* (MAR). For example, older people may have a higher rate of missing single items on a QoL- questionnaire, and may also have impaired physical functioning scores. In this case, the true levels of QoL-items on physical functioning in patients with missing data are likely to differ from complete cases. The third category of missing data is missing not at random (MNAR). Here, the missing data is dependent on the unobserved scores, such as missing QoL-forms at follow-up because of clinical deterioration of a patient. Here, the missing data is likely to contain important information that would distinguish missing cases from patients with a complete set of QoL-data. To avoid complete case-analyses, different imputation methods have been suggested, as for example *last value carried forward, simple mean* (derived from collected values of the same patient) and *sample mean* (using the whole dataset or a subset of patients) imputation (197). Statistical methods such as multiple imputation do exist, but require large sample sizes, as in population surveys. No ideal solution for imputation of QoL-data exists (198). The main problem with imputation of data is that it may lead to the assumption that one has collected more data than is actually the case. On the other hand, the missing data in individual patients may contain important information on these patients, and complete case analyses may not be representative for the whole study population and lead to biased conclusions.

In paper II and III, we used patient-reported QoL data and had to deal with both missing single subdomain-data and missing forms at the times of follow-up. In both papers, we chose a pragmatic approach to imputation of missing values. Our main aim was to estimate missing values for individual patients as best as possible by using the available information on the patients. In the preoperative analysis of EQ-5D forms in paper II, 10 single subdomains in 8 patients were missing. These were assumed to be MAR and were imputed by sample mean for the whole study population. In the longitudinal analysis in paper II, 33 patients had missing forms at the 1-month-assessment and were excluded from further analyses, while 2 single subdomains in 2 patients were imputed by sample mean. 4 cases had missing data on postoperative tumor volume and 4 cases lacked data on time to follow-up. These data were missing mainly due to administrative reasons and thus assessed as MCAR. These values were handled as "missing" by pairwise exclusion in SPSS.

In paper III, we focused on including as many patients as possible, also those who died during follow-up, to avoid presentation of a complete-case analysis. Therefore, we imputed a number of completely missing EQ-5D questionnaires in this study, as well as some single lacking subdomains. We included 25 patients who had died during follow-up and therefore were not able to complete postoperative EQ-5D forms at one or two postoperative assessment time points, and set the EQ-5D index value to zero, i.e. "equal to death" at these time points (Table 2). Four patients were dead at 6 months and lacked the 1-month-assessment as well. In those patients, EQ-5D index values at 1 month were imputed by sample mean of those patients' subgroup, i.e. the other patients who were dead at 6 months, a method described by Fayers and Machin (197). Additionally, twelve single lacking EQ-5D subdomains were imputed by sample mean derived from the whole study population, since we assumed these values to be MAR. Patients who were still alive after 6 months, but had missing forms at follow-up, were excluded from the analyses.

Population-based referral system in Norway

All three studies in this thesis were performed at the Department of Neurosurgery, St.Olavs University Hospital, a tertiary institution in Trondheim in Central Norway. Since the referral system in Norway is based on the patients' residential address, the Department of Neurosurgery

serves a geographically defined catchment area, resulting in population-based, unselected referral of patients. This is thought to enhance the external validity of our results.

Limitations

One common possible limitation of all the three papers in this thesis is non-inclusion because patients declined participation in the research project. Some non-inclusion during the early years of data collection (2007 to September 2011) was due to administrative reasons/staffing. Still, as a general problem in this type of studies, there is a real possibility for the non-included patients to differ from the ones who consented to participation. The same applies to loss to follow up, which was only moderate in all the three studies, but may have introduced a degree of selection bias.

We used pragmatic imputation methods for missing QoL-data in paper II and III, as described above. In patients lost to follow up, we did not impute data, since we felt that a "best guess" on the lacking data could not be made. This resulted in exclusion of patients who may have different characteristics than the patients who were not lost to follow-up.

In paper II and III, we used the generic QoL-tool EQ-5D 3L. The advantages of this tool (explained in the discussion chapter in this thesis), especially its simplicity, may influence the instrument's sensitivity and responsiveness. Thereby, information on the patients' QoL may be lost. Also, a ceiling effect at baseline (i.e. when the highest possible EQ-5D index score is the baseline value), will influence variables containing "change compared to baseline". There also is evidence for the instrument's responsiveness to functional improvement being poorer than to deterioration (173), which may result in a failure to detect improvement following surgery.

For the exploration of perioperative QoL-development in paper III, we dichotomized the study population into LGG (WHO grade I and II) and HGG (WHO grade III and IV). Data collection for this paper was finished in October 2015, and the revised 4th edition of the WHO-classification was published in 2016, containing molecular markers as part of the classification. The use of data on molecular markers (IDH receptor status, methylation status and 1p-19q co-deletion) may have been of additional use for our analyses if these data had been collected routinely already before the 2016 revision of the WHO-classification.

Ethical considerations

The studies in this thesis were approved by the Regional Ethics Committee of Central Norway as parts of a larger research project (”Quality of life in patients with intracranial neoplasms” REC no. 2011/974), and adhered to the Declaration of Helsinki.

Summary of papers

Paper I

Morbidity after intracranial tumor surgery – Sensitivity and specificity of retrospective review of medical records compared to patient- reported outcomes at 30 days

Drewes C, Sagberg LM, Jakola AS, Gulati S, Solheim O

Journal of Neurosurgery 2015

Background/Aim: In the neurosurgical literature, outcome reporting is commonly based on retrospective review of hospital records at discharge from hospital. New neurological deficits following brain tumor surgery are an outcome of great importance, but sensitivity and specificity of retrospective assessment of surgical morbidity are not known. Our aim with this study was to compare surgeon-reported new deficits at discharge with patient-reported outcomes at 30 days postoperatively.

Methods: In 191 patients operated for intracranial tumors, structured telephone interviews were conducted at median 30 days post-surgery. The patients were asked about newly acquired neurologic deficits within three domains: motor, language and cognitive problems. Furthermore, patients were interviewed about postoperative complications. Traditional retrospective surgeon-reported data on new deficits were collected by review of clinical information from the patient records at discharge from hospital. Data on perioperative medical and surgical complications were obtained from both patient interviews and hospital records at 30 days. We compared clinician-and patient-reported data by using the surgeons' report of new deficits as a clinical test, while patient-reported data on new deficits served as the "gold standard" (i.e. the clinical "truth"). The test properties "sensitivity" (i.e. the proportion of patient-reported new deficits correctly identified by the surgeons at discharge) and "specificity" (i.e. the proportion of patients without new deficits at 30 days who had no surgeon-reported new deficits in the hospital records at discharge) were calculated from contingency tables.

Results: Sensitivity values for retrospective review of hospital records as compared to patient reported outcomes were 0.52 for motor deficits, 0.4 for language deficits and 0.07 for cognitive deficits. According to medical records, 158 patients left hospital without new or worsened deficits, but only 117 of these patients (74%) confirmed this when interviewed at 30 days. Specificity values were high (0.97-0.99), indicating that new deficits were unlikely to be found by retrospective review of hospital records at discharge when the patients did not report any at 30 days. Major perioperative complications were all identified through retrospective review of hospital records within 30 days after surgery.

Conclusion: Retrospective assessment of medical records at discharge from hospital may underestimate the incidence of new neurologic deficits after brain tumor surgery when compared to patient-reported outcomes after 30 days. Assessment of new deficits during a routine clinical consultation at discharge may neither be an ideal setting nor a good time point when aiming to capture non-obvious new deficits. Although routines for when and how to assess surgical morbidity vary between institutions and publications, the reporting of new deficits by the surgeon at discharge is very common. Thus, our findings may be relevant for a disconcertingly large proportion of the neurosurgical outcome literature.

Paper II

Quality of life in patients with intracranial tumors: Does tumor laterality matter?

Drewes C, Sagberg LM, Jakola AS, Solheim O

Journal of Neurosurgery 2016

Background/Aim: Traditionally, the dominant (usually left) cerebral hemisphere is regarded as more important by clinicians. Everyday clinical decisions, for instance concerning tumor resection, surgical approaches, or for example use of tools like intraoperative stimulation mapping are influenced by this view. However, in the literature on quality of life in brain tumor patients, reports on the impact of lesion laterality are scarce, and results are inconsistent. We aimed to study which cerebral hemisphere is the most important to patients with intracranial tumors, with respect to health-related quality of life (QoL).
Methods: We prospectively included a cohort of 248 patients with unilateral, unifocal gliomas or meningiomas, scheduled for primary surgery. Generic QoL was measured by the generic tool EQ-5D 3L, both preoperatively and after 4-6 weeks. Cross-sectional and longitudinal analyses of data were performed.
Results: Tumor volumes were significantly larger in right-sided tumors at diagnosis and language or speech problems were more common in left sided lesions. Otherwise, there were no statistical differences in baseline characteristics between patients with left-sided versus right-sided tumor. Median EQ-5D 3L index was 0.73 (range -0.24 to 1.00) in patients with right-sided tumors and 0.76 (range -0.48 to 1.00) in patients with left-sided tumors (p=0.709). Due to the difference in tumor volumes at baseline, a result-driven matching of histopathology and tumor volumes in 198 patients was done. The matching procedure was performed blinded for QoL-data and all clinical data apart from tumor volume and histopathology. EQ-5D 3L index scores in this 1:1 matched analysis was 0.74 (range -0.7 to 1.00) for patients with right-sided and 0.76 (range -0.48 to 1.00) for left-sided lesions, p=0.342. In the analysis of longitudinal data, we found no association between tumor laterality and postoperative EQ-5D 3L index scores (p=0.957) or clinically significant change in QoL following surgery (p= 0.793).

Conclusion: Tumor laterality does not seem to be of significant importance for generic QoL in patients with intracranial tumors. Our findings may imply that the importance of functions of the right cerebral hemisphere may be underestimated by clinicians.

Paper III

Perioperative and postoperative quality of life in glioma patients – A longitudinal cohort study

Drewes C, Sagberg LM, Jakola AS, Solheim O

Submitted manuscript (revised version published in World Neurosurgery in June 2018)

Background/Aim: There is a paucity of longitudinal studies on patient-reported quality of life (QoL) in glioma surgery. Hence, knowledge about the impact of surgery on QoL and postoperative QoL-changes over time in glioma patients is lacking. We sought to explore peri- and postoperative development of generic QoL during the first six months after primary surgery for high-grade (HGG) and low-grade (LGG) glioma.

Methods: 136 unselected adult patients undergoing first-time surgery for HGG or LGG were prospectively included in this explorative, longitudinal cohort study. Patient-reported QoL was measured with the generic tool EQ-5D 3L at baseline prior to surgery, and at 1 and 6 months after surgery. To avoid a complete-case analysis and to include also unfavorable disease courses in our study, we used proxy-ratings as well as imputation of EQ-5D index values in patients who were dead at the time of assessment.

Results: At group level, EQ-5D index values were not clinically or statistically different in patients with HGG and LGG at baseline and QoL remained stable at 1 month. At 6 months, group-level EQ-5D index values in HGG patients had deteriorated significantly ($p<0.001$), while LGG patients were stable.

At the individual level, QoL-development was very heterogeneous and covered a wide range of EQ-5D index values in both HGG and LGG. Still, the most enhanced tendencies seem to reflect our findings at group level. In LGG patients, the most common pattern of dynamics of EQ-5D index value and subdomain changes at 1 and 6 months, was “unchanged” compared to baseline. In HGG patients, postoperative QoL patterns were dominated by “unchanged” at 1 month followed by “worse” compared to baseline at 6 months, alternatively “worse” at both time points. American Society of Anesthesiology (ASA) class ≥3, resection grades other than gross total

resection and HGG-histopathology were identified as independent predictors for negative QoL-development between 1 and 6 months after surgery.

Conclusion:

Postoperative dynamics of generic QoL in HGG and LGG after primary surgery seem to reflect the natural disease course to a great degree. Relative stability in QoL from baseline to 1 month was reported in both LGG and HGG patients. QoL in LGG patients remains stable at 6 months, while a deterioration can be seen in HGG patients at that stage, both clinically and statistically. Individual dynamics were found to be heterogeneous. Independent predictors of negative QoL-development between 1 and 6 months were comorbidity, resection grades other than GTR as well as HGG histopathology.

Discussion

Defining and reporting outcomes following brain tumor surgery by other than overall survival, the traditional "hard" endpoint, is a challenging task. Clinician-reported outcomes on neurological deficits, surgical complications and functional status are most common in the neurosurgical literature and in in daily clinical practice, while patient-reported outcomes (PROs) are not much employed in brain tumor surgery to date. In the papers in this thesis, PROs from brain tumor patients were employed to measure aspects of symptom burden and impact of surgery that may not always be acknowledged when clinician-reported outcomes are used.

Clinician- reported versus patient- reported new deficits after primary brain tumor surgery

In Paper I, we found that the neurosurgeons at discharge from hospital underestimated the occurrence of new neurological deficits, compared to PROs at 30 days. If surgeons systematically underestimate risks of surgery, overtreatment and overly aggressive management strategies may be the consequence. This is of special concern in a palliative setting, such as HGG or metastasis surgery, where a main goal is to maintain functions and quality of life.

New language and motor deficits have earlier been found to affect median survival in GBM (111), as well as being associated with impaired QoL (120). Thus, detection of deficits is important. Studies by others on the detection of depression and symptoms have found a discrepancy in surgeon-versus patient-reported outcomes in brain tumor surgery. In 2004, Litofsky and colleagues found that neurosurgeons underreported depression in patients after surgery for HGG (199). Diagnosing depression is not a swift task, and, accordingly, Arnold and colleagues stated that depression in neurooncological patients "may not be revealed in the clinical setting through usual surgeon-patient-interaction" (200). This statement could be interpreted as partly absolving the surgeons of responsibility. Yet, given that Pelletier and colleagues found depression to be the most important independent predictor of QoL in brain tumor patients (201), it is of concern that such an important symptom evades the surgeons' attention in a common clinical setting. This may point towards the need for other detection methods for subtle or complex symptoms. Ediebah and colleagues reported that LGG patients reported more problems at symptom level than their family proxies were aware of (202). The

latter supports the impression that many patients may be able to give a more complete account of their symptoms than both professional and lay caregivers.

When interpreting both our own and others' findings, it seems tempting to- at least partly- relate these to surgeons' presumed "stereotypical" clinical behavior, possibly shaped by a confident attitude towards their operative results on the one hand, and a high workload and thus substantial time-pressure on the other hand. In a recent study by our group, we found that surgeons right after leaving the operating theatre after surgery were overoptimistic when trying to guess the patient's expected functional status (203). Also in other surgical disciplines, overly positive estimates by the surgeons have been described (204, 205). It could be claimed that such an overoptimistic attitude may influence the surgeons when assessing their own work, in terms of finding- or not finding- new deficits postoperatively. At the time of discharge from hospital after brain tumor surgery, one could hypothesize that neurosurgeons might be preoccupied with looking at the "big" picture, mainly assessing MR-images and crude patient functions such as the ability to walk or talk. If this global assessment seems satisfactory and the patient does not express any specific complaints, performing tests and grading of subtle dysfunctions may simply not be a priority in the everyday clinical setting at discharge after surgery. In a study on SAH-survivors, Buchanan and colleagues found a discrepancy in reporting between surgeons and patients, where patients reported disabling psychosocial and neurobehavioral problems although the neurosurgeon had stated "good recovery" or "moderate disability" (206). Another study compared surgeon- versus patient-reported postoperative complications in a general surgical population, where the surgeons overlooked or under-documented post-discharge complications during the first month postoperatively (207). Conversely, in the study in paper I, we found that the neurosurgeons captured and documented close to all patient-reported surgical and medical complications during the first month after surgery. This suggests that, at least in our material, the timing of assessment may have played a role, and not only the neurosurgeons' presumptive swiftness of assessing the patients' neurological status or, even more severe, a degree of negligence.

In the common clinical context, the time of discharge from hospital is a rather usual time point for documentation of postoperative physical status and may be also be the time point where the operating neurosurgeon ceases scheduled contact with the patient. After postoperative discharge,

the immediate clinical follow-up during convalescence may either be handled by local primary hospitals, rehabilitation institutions, general practitioners or oncologists, dependent on factors such as local medical culture, referral systems, the patient's physical condition and place of patient residency. The larger time frame (30 days) for the PRO "new or worsened deficits" may have led to higher rates of patient reported new deficits. One month post-surgery is a time point when most patients have little by little reengaged in their usual daily activities and social lives, and may recognize subtler impairments in motor, language and cognitive functions in an equally gradual manner. Also, during the first month, the cumulative detection of neurological problems likely plays a greater role, as opposed to a short hospital stay. It could be argued that the comparison between PROs and surgeon-reported outcomes should have taken place at the same time point in this study. On the other hand, initial assessment of outcomes both in usual clinical practice and in published case series often takes place at discharge from the operating department, and in this way, our time point for reporting of new deficits by clinicians seemed to reflect common clinical practice. As it is stated in paper I, this may make our findings relevant for a disconcertingly large part of the literature on outcomes after brain tumor surgery (208).

Our findings in paper I point towards the need of feasible and agreed assessment time points and tools for reporting of new deficits after brain tumor surgery.

Tumor laterality and QoL

In Paper II, we found that tumor laterality in patients with unilateral meningioma and glioma did not significantly affect health-related quality of life (QoL).

Laterality in terms of hemisphere dominance is an increasingly questioned concept, most likely due to the use of modern imaging techniques such as functional MRI (fMRI) and reports from the use of intraoperative stimulation mapping and awake surgery (66, 209, 210). Still, also nowadays, when fMRI often is performed as part of the preoperative evaluation and planning prior to brain tumor surgery in eloquent locations, hemisphere dominance is a persisting concept among neurosurgeons (211). This influences clinical decisions about preoperative functional assessments, on the choice of tools or techniques (e.g. awake craniotomy), on the indication for tumor resection, surgical approaches, site of placement of ventricular catheters, as well as

decisions on evacuating intracerebral bleedings or performing decompressive hemicraniectomy after stroke or brain trauma.

Assessing the impact of lesion laterality on specific functions will obviously yield results dependent on the individual functional map of a patient's brain. A right-handed patient with a left hemisphere tumor in an area linked to language function will most likely show impaired scores when going through functional testing for language. Testing the same in a right-handed patient with a left-sided lesion without involvement of language areas may not show language impairment, but the patient may still suffer from other symptoms and limitations that do not become apparent if not specifically tested. In paper II, we used QoL, measured by the generic tool EQ-5D 3L as an outcome to assess the impact of tumor laterality. For our task, generic QoL as an outcome measure seemed to be of advantage when comparing the global, non-specific effect of lesions in the two hemispheres of the brain. A more specific, symptom-targeted testing would have resulted in differences dependent on individual distribution of functional areas, with a statistically clearly greater probability of the left hemisphere being "dominant" for language and fine motor skills in right-handers. Yet, this type of testing favors "testable" features and symptoms and neglects symptoms which are difficult to test or simply not asked for, or too subtle to impact test results. Also, function-specific tests are not informative regarding the importance of a symptom or deficit for the patients and the impact on the patients' life. The sparse literature on the impact of tumor laterality on QoL (212, 213) has not been supplied since we published paper II. When studying long-term QoL following decompressive hemicraniectomy after ischemic stroke, two research groups found that hemisphere dominance as assessed by handedness (214) or the presence of aphasia and handedness (215) did not influence QoL. Albeit studying a different condition, these findings seem to support our findings in paper II.

In most individuals, the left hemisphere executes motor tasks of the preferred side of the body (i.e. the right side of the body in right-handed individuals) as well as grammar, vocabulary and arithmetic skills (65). The right hemisphere harbors more subtle functions such as so-called prosodic language functions, i.e. intonation and accentuation (216) and expressing or interpreting the emotional tone of speech (217), as well as face recognition (218), interpretation of facial expressions (219), and visuospatial orientation (71). A recent report on experiences with DES

intraoperative mapping claims a "pivotal role" of the right hemisphere in movement control, some aspects of language, vision, spatial cognition, executive functions (e.g., attention and working memory), and social cognition (e.g. empathy) (66). Additionally, there is a growing body of evidence describing interconnectivity (220), i.e. the co-work of the right and left brain hemispheres, as well as brain plasticity following lesions (221, 222). Taken this into account, our findings in paper II are not surprising. If a tumor in the left hemisphere can influence QoL negatively because of aphasia, it is equally imaginable that a tumor located on the right side has an impact on QoL due to neglect, a lack of ability to recognize faces or to interpret other people's emotional state, attention and orientation deficits or even the development of neuropsychiatric symptoms. The latter has been described in only one case report in brain tumor patients (223), but in the neurological and psychiatric literature, affection of the right hemisphere has been linked to delusional misidentification syndromes, which for example may lead affected patients to mistaking close persons for identically looking imposters (64, 224). Left-sided neglect, although not as common as in patients with ischemic stroke, can be observed in patients with right-sided brain tumors, leading the patient to act as if the left half of the world did not exist (71). It does not take a lot of imagination to appreciate that these types of right-hemisphere-related symptoms have the potential to affect a patient's QoL rather severely.

The concept of the left, dominant hemisphere was established after lesion reports published 150 years ago (66), and, concordantly, led to the implicit assumption of the "right, non-dominant" hemisphere. Also today, awake brain tumor surgery with intraoperative stimulation mapping is more often performed if lesions are on the left side, while patients with right-sided tumors are operated under general anesthesia (66). Nevertheless, the dogma of left hemisphere dominance, although still used by clinicians, should most likely be considered as obsolete (225-228). The increasing use of advanced modern imaging, individualized preoperative planning and operative cortical stimulation methods may help to replace this simplistic view of brain functional anatomy with refined and individualized mapping of functionally important brain areas.

Due to the different functional roles of the left and right hemisphere, as described above, conclusions from advanced neurophysiological or neuropsychological testing will invariably yield different assessment results for the hemispheres, but without information on the actual importance of these outcomes for patients. The same applies when PROs are exclusively used for

assessing specific symptoms. Generic QoL, as used in paper II, may have a potential to serve as a global, non-function-specific outcome measure in future studies on lesion location as well as in comparative studies on imaging- and mapping tools in neurosurgery.

Quality of life in glioma surgery

In Paper III, we explored the perioperative development of QoL in patients undergoing first-time surgery for glioma. We found that QoL-dynamics at group level seem to largely resemble the natural disease trajectories of LGG and HGG, while individual dynamics were very heterogeneous, indicating that surgery is not without an impact on QoL in individual patients.

In neuro-oncology, QoL has become an established outcome parameter, also in clinical trials (141), acknowledging the fact that not only gain of lifetime, but also maintaining the quality of this time is an important treatment goal. QoL outcomes from patients can help balancing potentially burdensome side effects of treatment with the benefit of longer survival due to active treatment in this setting (229). In the surgical treatment of brain tumors, the potential for the use of QoL outcomes has very similar features: Also in this field, adverse treatment effects have to be counter-balanced by quality of the survival time that is hoped to be gained. Yet, QoL as an outcome measure has not been embraced equally by neurosurgeons as by oncologists.

Glioma surgery is a field where QoL as an outcome may have great relevance as a marker of quality of care. Notwithstanding advanced surgical and oncological treatment, the prognosis remains dismal for the majority of cases. Surgical treatment of gliomas, especially in eloquent areas, can come at a price: the invasive growth pattern of these tumors can cause neurological deficits when attempting to remove as much tumor as possible to extend survival time. New deficits are associated with decreased survival in HGG (111, 119) and impaired QoL (120). Therefore, the aim of prolonging survival comes with the inherent question about the quality of this survival time. Yet, somewhat strikingly, only a few studies on perioperative QoL in glioma with surgical endpoints are published. A recent multicenter-study presented cross-sectional QoL data obtained during the first year after tumor resection in HGG patients and concluded that biopsy was associated with poorer QoL compared to STR, while intraoperative imaging was correlated to better QoL, but awake surgery was not (230). One study by Wolf and Campos provides longitudinal pre-and postoperative data on QoL. The authors aimed to investigate the

impact of neurological deficits on QoL, but any conclusions seem to be hampered by a small (n=22) study population at baseline that is additionally reduced by high dropout percentages (190). During recent years, several papers from our own research group have used longitudinal QoL as an outcome (116, 119, 120, 174). One of these studies analyzed perioperative QoL of 61 patients with glioblastoma, and an association between early deterioration of QoL and reduced survival was found (119). Another longitudinal study in 88 glioma patients (complete cases) found that surgery did not necessarily impact QoL negatively, but that newly acquired deficits did (120). A cross-sectional study on longterm survivors with LGG found no difference in QoL in patients with eloquent vs non-eloquent lesions (116). A longitudinal study with frequent follow-ups during the first year after surgery for glioblastoma found progression-free survival to be a surrogate marker for quality of survival (174). All of the above cited studies from our group use the generic tool EQ-5D as an outcome measure. Glioma patients are highly heterogenous in both symptoms and deficits. Therefore, it is difficult to find a "one-size-fits-all"-instrument for measuring QoL. In more than a decade with observational research on QoL in brain tumor patients, our group has experienced that detailed instruments (i.e. the EORTC C30 and BN20) have a major disadvantage: Mainly clinically stable patients with few deficits are able to answer them. This leads to missing data and a skew in patient selection- towards the younger, fitter ones with less symptoms and deficits. A simple instrument like the EQ-5D 3L can be answered within a few minutes, proxy-ratings and telephone interviews are possible, and the instrument thereby helps to avoid missing data and the resulting selection bias. When collecting preoperative QoL data, a generic instrument like the EQ-5D seems to have an additional advantage. Since this tool is not disease-specific, it is avoided to expose patients without a histologically confirmed cancer diagnosis to the psychological stress of answering a QoL-questionnaire with numerous cancer-related questions. Being a generic QoL instrument, the EQ-5D is not capable of detecting all dimensions or symptoms relating to the disease or its treatment. Nevertheless, the instrument is valid for the more general aspects of health that it has been designed to measure: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D 3L has been validated for many different health states, including cancer (193). The instrument is validated for the Norwegian population (195). It has been found to be responsive (i.e. sensitive to changes over time) in patients undergoing glioma surgery, and the minimal clinically important difference (MCID) in glioma patients has earlier been documented by our group (173). Of note, the

sensitivity of the EQ-5D 3L for detecting deterioration is often higher than for detecting improvement, due to a ceiling effect in patients reporting unimpaired QoL at baseline.

In paper III, we found the baseline (preoperative) median EQ-5D index value in both LGG and HGG to be only slightly lower than previously studied in a Scandinavian general population of healthy individuals in the respective age groups (231). This is in concordance with findings on an earlier cohort studied by our group (120), and suggests that glioma patients do not experience a dramatically reduced generic Qol at this early stage after diagnosis. Of note, surgical cohort studies like this likely reflect some degree of selection bias. Some patients may not be scheduled for surgery in the first place, due to severe preoperative morbidity and dismal prognosis. Due to our group's earlier work (119, 120, 173, 174), it seems safe to conclude that the stable EQ-5D index values at group level in LGG over the course of all three time points of assessment and in HGG at baseline and 1 month after surgery represent true stability, and are not due to a lack of sensitivity of the instrument.

The findings in paper III may be able to support the discussion on suitable time points for QoL-assessment in glioma patients after surgery. Since both LGG and HGG patients at group level reported stable and comparable QoL-scores from baseline to 1 month postoperatively, this could be a practical common assessment time for both glioma groups. QoL in LGG patients at group level does not change clinically or statistically from 1 to 6 months, while follow up at 6 months in HGG patients is clearly too late unless substantial loss to follow up is accepted. The recommendation of 1 month as a good assessment time for LGG may be controversial. During recent years, the trend to maximal resection has led some surgeons to suggesting and practicing "supratotal" resection, which is resection beyond the tumor margins visible on medical images, with the help of intraoperative stimulation mapping in awake patients (232). This has also led to introduction of the term "planned deficits" and "onco-functional balance" (232). Evaluation of the postoperative status after 3-4 months has been practiced by some in this context, to allow time for regression of transient postoperative deficits (124, 233). Still, if seeking markers for assessing quality of care and the impact of surgery in a general glioma patient population, a common instrument and assessment time for LGG and HGG may be advantageous of practical reasons. Assessment as late as 3-4 months after LGG surgery may increase the risk of measuring effects of non-surgical therapy rather than surgery, such as radiation therapy, chemotherapy, rehabilitation, and may also be more prone to response shift than assessment at 1 month.

Individual QoL dynamics in our study population in paper III were found to be heterogeneous. For clinicians with experience with glioma patients, this is not unexpected at all. In a qualitative study, Salander and colleagues performed in-depth-interviews with 19 HGG patients with high functional level (WHO 0-2) and without any personality changes or cognitive impairment at discharge from hospital after surgery and 2 months later (after radiotherapy). The attitudes of these patients towards their diagnosis and life with the disease appeared to be mixed. One group gave a "steady and positive impression", and "seemed to be full of basic confidence". Another group was "also positive, but less steady" and had "bouts of anxiety and despair". The third group consisted of only 2 patients who "mainly felt hopeless and in despair" (234). Together with the heterogeneity in tumor related symptoms, such differences in coping might contribute to the heterogeneity in individual courses of patient-reported QoL found in paper III. Of note, the patient population studied in paper III in this thesis was in itself much more heterogeneous than in the Salander study when it comes to tumor histology and grades of functional status. This may potentially enhance the heterogeneity of QoL- development observed in our study population.

In the study in paper III, HGG patients undergoing STR showed a trend to deterioration of QoL at the end of the 6-month-follow-up period. QoL in HGG patients undergoing only biopsy plummeted at this time point. We also identified resection grades other than GTR as predictors for negative development of postoperative QoL, alongside with HGG histopathology and ASA grade>2. Also other authors have reported a positive association of extent of resection with QoL (135, 230, 235). Nevertheless, it is important to remember that such findings may be influenced by selection bias and thus have to be interpreted with caution. Patients eligible for GTR most likely have other baseline characteristics than patients undergoing biopsy. Still, since more extensive resection grades seem to affect survival and progression-free survival in both LGG and HGG (236), our findings may indicate that GTR has a benefit in terms of extending survival and, by achieving QoL-stability, quality of survival as well.

Looking for evidence in the neurosurgical literature

Issues in outcome reporting in neurosurgery

Unfortunately, the scientific reporting and publishing of outcomes in brain tumor surgery face a number of challenges and inadequacies. Observational studies and case series by single surgeons or institutions dominate the neurosurgical literature in general. Yarascavitch and colleagues (237) found that 89.8% of the articles published in the three highest-impact neurosurgical journals consisted of level III, IV and V evidence, resulting in a mean level of evidence around IV, which corresponds to case series and poor quality cohort- and case control studies (237). When compared to findings by Rothoerl and colleagues one decade earlier (238), it turned out that the average level of evidence had not improved, despite the increased awareness of evidence-based medicine and levels of evidence in recent years. Surprisingly, Yarascavitch et al even found that grouping of the higher levels of evidence (level I and II), resulted in a decrease of published papers from 22.8 % of in 1999 to 10.3% in 2010 (237). Assuming the studied three top neurosurgical journals to be representative for the rest of the neurosurgical literature, the largest part of the literature on brain tumor outcomes in neurosurgery can likely be assumed to be purely observational, mainly consisting of case series from single institutions or surgeons. An inherent problem of case series is observer bias, which, quite obviously, may occur when surgeons themselves evaluate the results of their own work. Neither is it possible to exclude that personal interest bias colors such studies in some cases. In countries with private health care or considerable competition between providers of health care, publication of surgical results is not trivial. Assessment bias is presumably a major issue and sometimes, published results are simply too good to be true (239, 240). Furthermore, reported mortality rates in observational studies depend largely on referral routines and case mix, and assessment of progression-free survival has numerous pitfalls (35), which may influence reported results. As mentioned earlier, selection bias is an issue, for example when reporting of EOR as a possible predictor for survival, since patients with a predicted better outcome may be selected for more aggressive surgery (241). Choice of outcome measures and timing of assessment for brain tumor patients has by no means been standardized, causing discrepancies in reporting and, ultimately, hampering comparison of outcomes across surgeons, hospitals or studies. DeWitt Hamer and colleagues published a much-noticed systematic review on the impact of intraoperative stimulation brain mapping on

outcomes in glioma surgery and found almost 100% heterogeneity in included studies. Yet, the authors did not abstain from performing a meta-analysis where HGG and LGG were pooled, which in itself is problematic due to the large differences in patient population and prognosis in the two groups. Thus, to a certain degree, late outcomes after HGG surgery in general anesthesia were compared to late outcomes after LGG surgery with functional mapping. Regardless of these issues, the systematic review and metaanalysis by DeWitt Hamer have been heavily relied on when claiming intraoperative stimulation mapping as the standard technique in glioma surgery (242-244).

The issues discussed above point towards the need for agreed outcome measures and time points for outcome assessment in brain tumor surgery. Such efforts could lead to more feasible and valid pooling of data in future meta-analyses, and thus increase the quality of evidence.

Also other quality issues in scientific reporting are not uncommon in the neurosurgical literature. A recent review article, published in one of the largest neurosurgical journals, on patient-reported outcomes in neurosurgical literature (245) did not identify any of the studies that describe the use of EQ-5D in brain tumor patients (116, 119, 120, 174-177, 179), most likely due to an extremely narrow search strategy. Accordingly, Faggion and colleagues criticize the quality of search strategies in systematic reviews on stereotactic radiosurgery (246). Nesvick and colleagues reported that the majority of studies in the neurosurgical literature identifying themselves as "case-control-studies" were labeled incorrectly (247).

The scientific publishing system of peer-reviewed literature has been criticized for introducing bias above the level of the single study. Publication bias, when papers are not submitted in the first place or rejected on the basis of (negative) research results introduces a substantial danger of over-representation of studies biased by type 1-error. This, in turn, results in false positive results biasing the literature as a whole. Other common issues causing bias during the submission- and peer-review process are authors' suggestion of reviewers; biases on both the editors' and the reviewers' sides; "pleasing" reviewers in responses and revisions of articles or by selection of references, as well as focus on the impact factor. Janssen and colleagues found potential conflicts of interest declared by 29% of editorial board members of five leading spine journals, 42% of these reported financial ties of more than $10,000 the previous year (248). It seems only reasonable to assume that such biases also may influence outcome reporting in brain tumor surgery.

In an interesting recent report, Hirshman and colleagues introduced the concept of "journal bias" (249). They screened the HGG surgical literature on the impact of resection grade on survival and identified two different medical-academic "genealogies", where a large proportion of the key authors of the assessed papers belonged to one of two family-tree-like "lines" (one founded by a neurosurgeon, the other by a radiation oncologist). Belonging to one of those two genealogies by sharing clinical training or part of their academic career with other genealogy members was associated with preferred publication in selected journals and with findings either favoring or disfavoring maximal resection for survival benefit (249). It seems unlikely that this "journal bias" is restricted to the literature on resection of HGG, and illustrates that the current scientific publishing system meets tremendous challenges when it comes to balanced reporting of the available evidence.

Ongoing initiatives to improve and standardize outcome reporting in brain tumor surgery

In neuro-oncology, a few international expert groups have started initiatives to improve and standardize outcome reportings. The already mentioned RANO initiative assesses the radiological response to treatment (89), and specifies that clinical status needs to be incorporated in the overall assessment. As a complementary initiative addressing this request, the NANO group (Neurologic Assessment in Neuro-Oncology) has suggested and studied a scale for neurological assessment, containing 9 important domains (gait, strength, ataxia, sensation, visual fields, facial strength, language, level of consciousness, behavior) (133). They found high inter-observer agreement and state that the application of the scale takes approximately 4 minutes, making it applicable in an average clinical office setting (133).

The European Organisation for Research and Treatment of Cancer (EORTC) directs the SISAQOL-initiative (Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data) (250). The goal of this consortium is to make recommendations to standardize outcome reporting and thereby increase comparability of results of QoL measures and other PROs in cancer randomized trials.

In neurosurgery, there is a paucity of comparable initiatives. A specification of the GNOSIS guidelines (Guidelines for Neuro-Oncology: Standards for Investigational Studies) addressing reporting in surgically based therapeutic clinical trials has been published (251), but has obviously not found broad appliance due to the virtual absence of surgical RCTs on brain tumor

patients. In an attempt to standardize reporting of complications in neurosurgery, Landriel Ibanez and colleagues published a classification system (140), but its use in brain tumor patients is limited to very few groups so far (79, 136, 203, 252), and has been subject to criticism (253).

Challenges in systematic assessment and reporting of outcomes in brain tumor surgery

A highly complex condition

The etiology of neurological changes in brain tumor patients following surgery is multifactorial. These changes can be treatment-related, be due to comorbidity or changes in medication, due to tumor activity, due to somatoform or psychological reactions to being ill, or a combination of all these factors. Variety in tumor location and size and the resulting neurological symptoms, the time point of diagnosis as well as the heterogeneity of the patient population when it comes to age and comorbidity make evaluation of outcomes in brain tumor surgery a challenging task. Longitudinal analyses, measuring changes in symptom burden or QoL over time to capture the impact of surgery, are facing severe assessment difficulties due to loss to follow up (164). Discriminating possible adverse effects of surgery from symptoms of tumor growth or side effects of adjuvant treatment can seem close to impossible. Also, the preoperative baseline assessment may be influenced by corticosteroid medication, which blunts tumor-related symptoms and may thus contribute to a ceiling effect (i.e. maximum score at baseline) that may make it difficult to detect a possible positive impact of surgical treatment. On the other hand, preoperative anxiety, seizures, early side effects from antiepileptic drugs, post-ictal function loss, and psychosomatic stress/shock reactions may increase symptom load and reduce quality of life as well as neurological and neuropsychological test scores at baseline.

Detecting and reporting complications

In the field of general surgery, there have been several attempts to define the term “surgical complication” (138, 254). Sokol and Wilson suggested that a surgical complication is “any undesirable, unintended, and direct result of an operation affecting the patient, which would not have occurred had the operation gone as well as could reasonably be hoped” (254). Importantly,

the authors acknowledge that this definition implies that a surgical complication is “not a fixed reality”. The surgical context (country, surgical skills, equipment as well as the historical period when the surgery takes place) may influence the notion of what may be seen as a complication and what, on the other hand, is regarded an inevitable adverse outcome. Advances of surgical skills and equipment in modern surgery lead to increased expectations and thus, paradoxically, increase the number of events potentially rated as complications (254). An adverse effect of surgery does not necessarily represent a complication. Some adverse effects of surgery are absolutely unavoidable, such as the presence of a scar following surgical skin incision. Others are practically unavoidable, such as loss of hearing after surgery for large acoustic schwannomas or loss of smell after surgery for large olfactory groove meningiomas. This illustrates the challenges of classifying adverse effects and complications of brain tumor surgery and likely represents one of the reasons for the large variations in reporting in brain tumor surgery. Some authors include new neurological deficits in their considerations of overall complications (1, 99), while others decide to concentrate on complications other than neurological (i.e. wound related or medical) (136) and report acquired deficits separately. Two recently published case series from single institutions reported risk of complications of 13.2% (including new neurological deficits) (99) and 36% (not including new neurological deficits) (136). Recently published data from a U.S. multicenter-database with 30-day prospectively reported complications found a 16.4% overall complication rate and 12.9% major complications, excluding neurological deficits (97). All these data are on modern neurosurgery, but impossible to compare due to non-standardized reporting. Additionally, complications in case series are usually accounted for in a retrospective manner.

Combining postoperative complications in a single variable is not without pitfalls either. A so-called composite endpoint is created when accounting for an uncomplicated postoperative UTI and life-threatening postoperative hematoma, multi-organ failure or even death within the same variable (“complications”). Quite obviously, this endpoint is characterized by a considerable imbalance regarding the impact and consequences for the patient. In clinical trials, it is advocated to combine components in a composite endpoint only if they are of similar clinical importance, as well as reporting outcomes within the composite separately, to enhance transparency (255). The Landriel Ibanez classification of complications in neurosurgery, used in paper III in this thesis, addresses this problem by classifying complications into grades of severity (140). Based

on the general surgical classification suggested by Dindo et al (139), the Landriel classification represents a respectable attempt to standardize reporting in neurosurgery. Nevertheless, this classification is based on the need for invasive treatment, and will thus possibly classify a complication of great importance for the patient (e.g. postoperative hemiplegia) as grade 1, "mild", because no drug- or operative treatment is performed, while minor complications requiring invasive treatment automatically are ranged as grade 2, "moderate". This has led to criticism of the Landriel classification (253), and may be one reason why it has not been embraced extensively. On the other hand, it could be discussed if a non-optimal, but widely used and agreed scale would be a better measure to secure comparability and accountability than home-made classification systems used only by single authors or institutions.

Complications may be subject to detection bias. Local routines of ICU-surveillance following surgery and the length of such an ICU-stay, routines and time points for postoperative MRI-control as well as the number and timing of diagnostic tests performed (urine dipsticks, pulse oximetry, bladder scanning, routine blood tests) are factors probably influencing whether and when postoperative complications are detected (136). For a reliable reporting of postoperative complications during the whole 30 day period commonly referred to as the postoperative period, it will also often be necessary to access medical documentation from health care providers other than the operating neurosurgical department. Still, also a 30-day-complication rate is only part of the clinical picture: Already before 30 days, there may be adverse events not related to surgery, for example of adjuvant treatment in cancer patients. Conversely, some clearly surgery-related complications, such as osteomyelitis after craniotomy, often are detected after the 30-day "perioperative" period.

A pragmatic agreement on how and when to measure complications after brain tumor surgery is clearly needed, although an ideal time point does probably not exist.

Importance of newly acquired neurological deficits

The literature on neurological deficits following brain tumor surgery is highly heterogeneous, with numbers from newer reports varying between 0 and 20% (1, 99, 121). The risk of new deficits clearly is dependent on the case mix studied. Patients with skull base menigiomas with involvement of cranial nerves or gliomas in eloquent locations are per se at greater risk of neurological injury, compared to, for example, patients with small convexity meningiomas,

transsphenoidally removed pituitary tumors or patients undergoing resections of small, non-eloquent lesions. Detection of neurological deficits necessarily depends on the method used- a quick, generic assessment of motor functions and language, or advanced neuropsychological testing by a specialist (122). Also, timing of assessment necessarily plays a role when transient deficits are involved (233).

There is evidence that new deficits lead to impaired survival (111, 119), and reduction in QoL(120). In glioma surgery, the trade-off between maximal resection of tumor tissue to extend survival, and avoidance of new deficits, is not always clear-cut. Individual patients may have own priorities and their own view on this issue. In a qualitative study on the ethical aspects of maximal safe resection, Brennum and colleagues collected views from patients with LGG. They found a large variance of the patients' perspectives on quality of life and acceptance for new deficits or, reduced survival time, dependent on life situation and individual priorities (77). If possible, the risk-benefit trade-offs of treatment should be discussed with the patients.

Defining adequate outcome measures for subtle problems

In paper II, we used generic QoL, a global, non-specific measure, as an endpoint when studying the impact of tumor laterality. In brain tumor patients undergoing surgery, QoL instruments may be able to play an important role in assessing the overall burden of disease and treatment, rather than selective specific brain functions and symptoms, as the latter are highly dependent on lesion location. Still, it is challenging to define and study outcome measures (both neuropsychological and PROs) which are able to capture functions that are less obvious, but may be of great importance for patients.

When using QoL assessed by the EQ-5D instrument, a ceiling effect can represent a problem. People with a high functional status and little symptoms may report maximum EQ-5D scores at baseline and thus, it will not be possible to detect a possible improvement of subtle symptoms following surgery. On the other hand, in a surgical context in brain tumor patients, deterioration is probably the outcome of greater concern, and the EQ-5D has been found to be responsive to change in glioma patients (173). In general, the more specific the addressed facets of QoL, the greater sensitivity is required of the instrument. This, on the other hand, results in longer and more complex questionnaires that may be more difficult to respond to for patients, and result in more missing data (164). Thus, there usually is a pragmatic trade-off between sensitivity and

feasibility when choosing a QoL-instrument. Missing data may be a bigger threat to the generalizability of results than the lack of sensitivity for subtle problems.
Also limited economic and personnel resources in clinical daily life may hamper the detection and reporting of refined measures of symptoms and QoL. Both neuropsychological testing and administration of QoL-questionnaires require specialized staff with dedicated time to collect good quality data.

Assessing outcomes in cognitively impaired patients

A large proportion of brain tumor patients will face cognitive problems at an early or late stage of their disease (124, 125). These cognitive problems can be caused by the disease itself, or by surgical or oncological treatment, or by a combination of all factors. In brain tumor patients, not only do the cancer diagnosis and symptom burden influence the patients' subjective assessment of QoL. Additionally, patients with brain tumor face a progressive neurodegenerative condition with an own impact on cognition. Decreased ability to medical decision-making in patients with brain metastases (256) and brain tumor patients before (257) and after surgery (258) are well described. It seems obvious that cognitive impairment also may cause problems when these patients are asked to complete QoL-questionnaires, and if they do, the accuracy of their self-assessment may be questionable (129, 259). On the other hand, excluding cognitively impaired patients may introduce bias when using patient-reported QoL for evaluating the impact of treatment (259). Despite of possible limitations, QoL- assessments by cognitively impaired patients may be far from invalid. Kim et al (260) found a cognitive symptom cluster in meningioma patients to be predictive of QoL, and Li and colleagues found cognitive function and QoL in patients with brain metastases to be correlated, with cognitive deterioration preceding deterioration in QoL (261). This suggests both association and covariation of QoL and cognitive function.
As seen, QoL assessment in cognitively impaired brain tumor patients is intricate. The combination of QoL- assessments and objective neuropsychological evaluation has therefore been suggested (123, 124), as these methods may have the potential to complement each other.

Loss to follow-up and use of proxies in QoL-assessment

Patients in a poor clinical condition or those with cognitive impairment or fatigue may face severe difficulties when presented for questionnaires concerning symptoms or quality of life, possibly more so when multi-item questionnaires are used (164). Especially in longitudinal analyses, loss to follow up due to impairment of the patient's condition or possibly questionnaire fatigue can be a considerable problem. In an oncological study on malignant glioma, Walker and colleagues found that patients compliant with a 6-month follow up were younger, fitter, and with a greater probability of survival than non-compliant patients (164). Conversely, in a study on LGG patients with stable disease, Ediebah and colleagues report that 18% of the included patients declined participation in the part of the study that involved neuropsychological testing, "the main reasons being that participation was too burdensome, or that they were reluctant to be confronted with what they believed to be a cured illness" (202). The latter exemplifies that not only poor clinical condition or disease progression may cause attrition and questionnaire fatigue. Also clinically fit patients may be lost to follow up, which makes the interpretation of drop-out rates and their possible reasons even more complex. Conclusions based on complete case analyses of QoL-data should therefore be interpreted with caution. The characteristics of patients lost to follow up may be different from patients completing all questionnaires (164).
When patients are not able to complete QoL-questionnaires on their own, proxy ratings by lay caregivers, usually family members, are an option. It has been argued that the QoL assessment per definition is not a PRO any more when proxies are used (141), but it has also been acknowledged that the alternative to proxy ratings in functionally or mentally impaired patients can mean "no assessment", with the resulting selection bias (262). In dementia patients, next-of-kin proxies have been found to report a greater impairment in QoL than the patients themselves (263). There are only a few published studies on proxy ratings in brain tumor patients, with conflicting results. Sneeuw and colleagues reported moderate to good agreement of patient and proxy ratings of QoL (measured by the EORTC questionnaire) in cognitively intact patients with brain tumors, but a more pronounced response bias when using proxy ratings in cognitively impaired patients (264). Moinpour and colleagues examined a small sample of patients with brain metastases and concluded that proxies are a generally poor substitute for capturing a patient's QoL (265). Giesinger et al found proxy ratings feasible when studying a sample of brain tumor patients and proxy ratings provided by family caregivers (266). More recently,

Ediebah and colleagues found a lower agreement of QoL-assessments in LGG-patient-proxy pairs where the patient was cognitively impaired, than in cognitively intact patients (202). It is important to remember that patients with a very severe cognitive impairment, i.e. patients who are not able to provide self-reported QoL at all, cannot be studied in comparison to proxy assessments. This means that there are virtually no data on the feasibility of proxy ratings in the most cognitively hampered patients, although the need for proxy ratings is probably greatest in this patient population. From the scarce and conflicting literature as well as from our own experience, it seems reasonable to conclude that, in observational studies in poorly functioning patients, proxy ratings most likely make an important contribution ("better than nothing"), to avoid complete case analyses with subsequent selection bias. Still, if used, the percentage of proxy ratings should be subject to reporting, and possible limitations of the QoL data have to be taken into account (164). When criticizing the use of proxy ratings or imputation of missing data in QoL-studies, one thing has to be kept in mind: Sub-optimal assessment due to missing data is common also for conventional clinician-reported outcomes, it is just less spoken about. For example, in reports of 30-day complication rates after surgery, losses to follow-up (for the entire 30 day period) are rarely accounted for. Also, in retrospective reviews of medical records, missing data are not unusual. "Educated guesses" to replace lacking data on KPS, ASA-class, new deficits or complications from information in the patient records in these situation are probably common, but their validity is highly dependent on the quality of documentation in the individual hospital's medical record system.

Capturing the patients' perspective on symptom burden and treatment effects in brain tumor surgery

Patient-centered approach

In the contemporary clinical climate, patient-centeredness has evolved into a central aim, resulting from a gradual modification of doctors' attitudes and behavior towards patients over the last decades. From the doctors' traditional, slightly paternalistic question to patients: "What is the matter with you?" the focus in clinical practice and health systems has transformed to a more open, patient-centered attitude characterized by asking "What matters to you?" instead (267). This change may be of special importance to vulnerable patient groups such as ageing people

and those who cannot expect cure from their disease. Palliative care and end-of-life issues have not only shown to be of great interest for the medical community, but also for the general public. For example, in the widely acclaimed bestselling publication "Being mortal", U.S. surgeon Atul Gawande questions the values and viewpoints on incurable disease and death purported by a technology- and possibility-driven medical culture (268). Gawande describes everyday clinical situations, mainly in geriatric care and oncology, and discusses possibilities for enhanced patient-centeredness in clinical practice and palliative care (267, 268).

Potential of PROs as an outcome in brain tumor surgery

Increased focus on what is important to patients has led to the widespread use of PROs in medical research, quality assurance, comparisons of providers and cost-benefit analyses (150). In brain tumor surgery, PROs have not been widely used so far (245). A series of studies from Finland utilize PROs in prognostic studies (155, 192). Other, there are the already mentioned neurosurgical studies on QoL in brain tumor patients (116, 119, 120, 173-179, 190, 191, 230). As our findings in paper I and II in this thesis indicate, PROs in general (both patient-reported symptoms and QoL) may be able to provide information prone to non-detection and hence underreporting by neurosurgeons. Traditional neurosurgeon- reported outcomes suffer from a wide range of challenges and inadequacies, as discussed above. Thus, PROs may harbor a considerable potential of supplying clinician-reported information on outcomes after surgery. This is thought to apply to both QoL and symptom-level PROs, and may be especially relevant for symptoms and aspects of disease burden which may not be obvious for clinicians, but still may have a preeminent impact on patients. Additionally, as discussed further above, assessment bias is circumvented by the use of PROs.

QoL- assessment in patients undergoing brain tumor surgery

Patient-reported QoL has developed into an established secondary outcome in neuro-oncological clinical trials (141). Remarkably, and notwithstanding the fact that the same condition is studied, there still is a paucity of studies on QoL in brain tumor surgery. QoL as an outcome measure in neurosurgery has the advantage of being intrinsically patient-centered, measuring the quality of survival in patients with a limited expected life span following surgery, as well as providing prognostic information (119, 174).

Nevertheless, despite their considerable unused potential in neurosurgery, QoL measures are not without drawbacks. First, QoL measures do not replace assessment of symptoms or clinical findings important for neurosurgeons, such as surgically acquired deficits or complications, and neither are there QoL-measures available that specifically address the impact of neurosurgical treatment. Secondly, condition-related limitations for self-assessment such as cognitive impairment and fatigue are problematic. Their impact on results and conclusions of QoL-studies is very likely, but is challenging to quantify and control for. Thirdly, non-inclusion due to poor clinical or cognitive status as well as attrition due to reasons such as questionnaire fatigue, clinical impairment and death are serious issues causing selection bias and hampering generalizability of results in studies with QoL as an outcome.

As we found in the glioma population in paper III, there is a variety of individual courses following brain tumor surgery. A recent qualitative study resulted in very complex, individual pictures of quality of life described by patients in interviews. These concepts were not found to be covered by commonly used tools measuring health-related QoL (the disease-specific EORTC C30 and BN20) (269). Although QoL assessment through validated tools is a large step forward towards a patient-centered holistic approach, it has to be acknowledged that QoL- tools are no more than structured questionnaires covering a limited specter of the real experience by patients. Still, the comprehensiveness of QoL as a concept and the inherent importance of QoL-measures for patients may have an important advantage: Brain tumor treatment presents a tremendously complex situation. It can seem impossible to disentangle causalities and associations of the disease itself and the different treatment modalities, and disease-and surgery-related endpoints reported by clinicians do not cover the impact of disease as experienced by the patients. Patient-reported QoL may be able to provide important information on the joint impact of symptom burden, treatment effects and natural disease course in patients undergoing brain tumor surgery.

Implications for future research

Perioperative mortality is a rare event in modern brain tumor surgery, and is therefore not suited as the only outcome when comparing institutions or studies any more. To strengthen outcome assessment and increase comparability of “soft” outcomes in brain tumor surgery, universally agreed outcome measures are needed. To assess the impact of surgery in this challenging patient

population, agreement on and standardization of clinician-reported outcomes such as complications and new deficits are necessary. Development and implementation of symptom-based PROs to measure the same endpoints could harbor a potential to supply surgeon-reported outcomes from the patients' viewpoint and thereby increase detection of subtle symptoms. To date, there is no QoL-instrument tailored to specifically address the impact of brain tumor surgery. An ideal instrument would contain items detailed enough to be able to detect between group-differences in a comparative study, but would still not be too long and burdensome that its application is resulting in missing data in this vulnerable patient population. The development and validation of such an instrument may be a challenge for future research initiatives.

As discussed related to paper I and III, defining good and pragmatic time points for outcome assessment is also necessary to ensure that the measured outcomes contain a maximum of relevant information, balanced with minimal attrition.

To make new treatment options and surgical tools in brain tumor surgery subject to evidence-based rather than mere experience-based evaluation, increasing the level of evidence and quality of reporting in the neurosurgical literature is of paramount importance. In future scientific work on outcomes following brain tumor surgery, conscientious collection of prospective data and, where possible, performance of rigorously designed comparative studies are recommended.

Also, to increase external validity in observational studies, the literature is in need of population-based studies covering a broad range of patients. Population-based inclusion applied in comparative studies could provide information on effectiveness of a treatment (i.e. what works in the general population) method rather than efficacy (i.e. what works in an ideal setting with an optimal case selection).

To conclude, it is worth mentioning that refinement and implementation of the above suggested measures require conjoint efforts from the entire neurosurgical community.

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Papers

Paper I

Drewes, Christina; Sagberg, Lisa Millgård; Jakola, Asgeir Store; Gulati, Sasha; Solheim, Ole. Morbidity after intracranial tumor surgery: sensitivity and specificity of retrospective review of medical records compared with patient-reported outcomes at 30 days. Journal of Neurosurgery 2015 ;Volum 123.(4) s. 972-977.

Paper II

Drewes, Christina; Sagberg, Lisa Millgård; Jakola, Asgeir Store; Solheim, Ole. Quality of life in patients with intracranial tumors: does tumor laterality matter?. Journal of Neurosurgery 2016 ;Volum 125.(6) s. 1400-1407.

Paper III

Title

Perioperative and postoperative quality of life in glioma patients – A longitudinal cohort study

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Abstract

Objective: Few studies provide longitudinal data on patient-reported quality of life (QoL) in glioma patients undergoing surgery. .Accordingly, there is little knowledge about changes of QoL over time in glioma patients. We sought to explore peri- and postoperative development of generic QoL during the first six months after primary glioma surgery.

Methods:136 unselected adult patients undergoing primary surgery for glioma were prospectively included in this explorative, longitudinal study. Patient-reported QoL was measured with the generic tool EQ-5D 3L preoperatively and at 1 and 6 months after surgery.

Results: At group level, there was no difference in EQ-5D index values in patients with HGG (high-grade glioma) compared to patients with LGG (low-grade glioma) at baseline or at 1 month. At 6 months, EQ-5D index values in HGG patients had deteriorated significantly ($p<0.001$) in HGG patients, but remained stable in LGG patients. Individual level QoL development were more diverse.. American Society of Anesthesiology class ≥3, resection grades other than gross total resection and HGG were identified as independent predictors for "negative dynamics of QoL" between 1 and 6 months after surgery.

Conclusions: In glioma patients, development of generic QoL between baseline and 1 and 6 months postoperatively seems to reflect the natural disease trajectories of LGG and HGG. Individual dynamics are heterogeneous. . Resection grades other than GTR and comorbidity are predictors of postoperative QoL-impairment.

Keywords: Brain neoplasms, glioma, oncology, patient-reported outcome measures, quality of life

Abbreviations:

ASA=American Society of Anesthesiologists

GTR= gross total resection

HGG= high grade glioma

KPS= Karnofsky Performance Scale

LGG= low grade glioma

MCID= minimal clinically important difference

MRI= magnetic resonance tomography

QoL= quality of life

STR= subtotal resection

Introduction

The credo of glioma surgery is maximal safe resection, attempting to extend survival without jeopardizing functions or health-related quality of life (QoL). Frequently, safety is assessed by measures of functional levels, neurological deficits, or complications. So far, there is no agreement how to measure such "soft" outcomes after glioma surgery. In a much-cited systematic review and meta-analysis, De Witt Hamer and colleagues found close to 100% heterogeneity in outcomes across surgical glioma studies, suggestive of large variations in assessment.[1] Observer bias is a potential issue when neurosurgeons evaluate their own surgical results, and traditional physician rated outcomes of function and deficits do not necessarily reflect the impact of disease and operative treatment as experienced by patients. By using patient-reported QoL as an outcome, this type of bias is avoided,[2] and QoL-measures are, by concept, relevant to patients. In neuro-oncology, QoL as an outcome measure has become increasingly embraced.[3] However, in the neurosurgical context, QoL has not been studied very much to date. Especially longitudinal studies with a preoperative baseline assessment are scarce. Knowledge about perioperative development of QoL in glioma patients undergoing primary surgery may support clinical decisions, such as selection of patients who are expected to profit from surgery and, equally important, those who are not.

Furthermore, this knowledge may be useful when informing patients about what to expect during the weeks and months after their operation.

In the present study, we sought to explore longitudinal peri- and postoperative development of patient-reported QoL in single-surgery glioma patients, measured by the generic tool EQ-5D[4] preoperatively and at 1 and 6 months.

Materials and methods

We consecutively included 136 of in total 209 patients ≥ 18 years undergoing first-time surgery for glioma at the Department of Neurosurgery at St. Olavs University Hospital (Trondheim, Norway) in the period from September 2011 through November 2015. All tumors were histopathologically confirmed. Our neurosurgical department serves a defined geographical catchment area, ensuring population-based, unselected referral. Patients who underwent reoperations in the follow-up period were excluded. The inclusion process is presented in Figure 1.

Data collection

The EQ-5D 3L is a generic QoL instrument which has been used and validated in a large variety of conditions including cancer.[5,6] It covers the five dimensions “mobility”, “self-care”, “usual activities”, “pain/discomfort”, and “anxiety/depression”. For each domain, the respondent can apply one of three grades: “no problems,” “some problems,” or “extreme problems.” A single summary index value is calculated from the responses to the subdomains, ranging from “1” (“perfect health”) to “0” (“equal to death”). Negative index values are possible, indicating a QoL “worse than death”. We used the United Kingdom EQ-5D 3L index tariff to calculate index scores.[7] The EQ-5D 3L has been validated for the

Norwegian population,[8] and the instrument's responsiveness to postoperative deterioration as well as its minimal clinically important difference have been established earlier by our group.[9]

The EQ-5D 3L questionnaire was completed 1–3 days before surgery by the patients themselves or with assistance from a nurse or next of kin. Follow-up assessments took place at 1 month postoperatively (median 31 days, range 24 to 66 days) and at 6 months postoperatively (median 184 days, range 162 to 217 days). Patient-reported follow-up data were collected through structured telephone interviews, performed by a research nurse. New or worsened motor- and language deficits were part of the structured interviews at one month. Proxy ratings by spouses/close relatives were used if the patient was not able to answer the questions due to speech impairment, severe cognitive problems or poor clinical condition (13.3% of all follow-up interviews). The Karnofsky Performance Scale (KPS) was rated by the operating surgeon just prior to surgery. Complications during the first 30 postoperative days were categorized as suggested by Landriel Ibanez and colleagues.[10] New or worsened neurologic deficits after surgery were recorded from hospital records. Only persistent language and motor deficits confirmed by the patients themselves at 30 days were taken into account in the analyses. Other clinical variables, imaging findings, and histopathological variables were obtained retrospectively from electronic hospital records.

The interpretation of image data was performed by a neurosurgeon from preoperative and postoperative 1.5 T or 3.0 T MRI scans, routinely taken ≤ 48 hours after surgery. The volumes of spherically shaped lesions were calculated by using the ellipsoid volume formula ($4/3 \cdot \pi \cdot r_1 \cdot r_2 \cdot r_3$) based on the maximum tumor diameters in the available image dimensions. In cup-shaped residual tumors, volume was calculated by subtracting the ellipsoid-shaped resection cavity from the volume of the tumor/cavity complex, as previously done by others.[11] In very complex configurations, we defined several volumes within the residual

lesion and measured using the above-mentioned methods as appropriate, and summed up these volumes. Eloquence of tumor location was graded according to Sawaya et al.[12]

Ethics

Data collection was approved by the Committee for Medical and Health Research Ethics for Health Region Central Norway (reference no. 2011/974) and adhered to the guidelines of the Helsinki Declaration and its later amendments. All included patients provided their explicit written, informed consent at admission.

Statistical analyses

All statistical analyses were performed using SPSS 23.0. Q-Q tests were used to test distribution of data. Student's *t*-test was used for comparison of means in normally distributed continuous data, while Mann-Whitney U-test was used for ranked comparison of medians in skewed data. Friedman test was performed in analysis of skewed longitudinal data. Contingency tables and Chi-square tests were used in dichotomous variables (continuity correction in 2x2 tables). Fisher's exact test was used when the expected number per cell was ≤ 5. To group change in EQ-5D index scores, the previously published minimal clinically important difference (MCID) of ± 0.15 for glioma patients was applied.[9] MCID represents "the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and which would lead the clinician to consider a change in the patient's management".[13] Variables possibly associated with positive and negative dynamics of EQ-5D index values were tested by logistic regression (p=0.10 in univariate and p=0.05 in multivariate analyses).

Patients who were still alive after 6 months, but had missing forms at 1 month, at 6 months or both, were treated as dropouts and were excluded from the analyses (n=21, 13%), see Figure

1 for details. We included 25 patients with missing postoperative EQ-5D forms who died during the follow-up period and set the EQ-5D index value to zero, i.e. “equal to death”, in those forms where the patient actually was dead at the time of the planned assessment. Four patients were dead at 6 months and lacked the 1-month-assessment as well. In those patients, following the method described by Fayers and Machin,[14] EQ-5D index values at 1 month were imputed by sample mean of their subgroup (i.e. the other patients who were dead at 6 months). This imputation accounts for 1% of all index values. Additionally, twelve single lacking EQ-5D subdomains (0.9% of subdomains in collected forms) were imputed by sample mean derived from the whole study population, since these values were assumed to be missing at random.

Results

As seen in Table 1, patients with high-grade glioma (HGG) were older and scored higher in the American Society of Anesthesiologists (ASA) classification compared to patients with low-grade glioma (LGG). They also had lower functional levels before surgery, a greater occurrence of preoperative motor, language and cognitive deficits, as well as larger tumor volumes. 77.1 % received preoperative corticosteroids for symptom control, compared to 10% of LGG patients. Gross total resection (GTR) was more often achieved in LGG, and fewer patients with LGG received postoperative radiotherapy and/or chemotherapy. There was no difference in the occurrence of postoperative complications or new language- or motor deficits between patients with HGG and LGG.

Table 2 shows QoL scores at group level. When comparing patients with HGG and LGG, there was no difference in EQ-5D index values at baseline or at 1 month. However, at 6

months, HGG patients reported clinically (MCID) and statistically significantly worse QoL than LGG patients. Analysis of longitudinal data showed a statistically significant change in EQ-5D index values over the 6-month follow-up period in patients with HGG, while LGG patients remained clinically and statistically stable.

Figure 2 illustrates EQ-5D index values in LGG and HGG patients with different resection grades at 1 month and at 6 months. As seen, the range of values is considerably larger in HGG patients. Compared to all other subgroups, HGG patients undergoing biopsy show a noticeably lower median EQ-5D index value of 0.59 at 1 month. At 6 months, their median index value plunges to 0.

Figure 3 illustrates clinically significant change from baseline to 1 and to 6 months at an individual level, here with "death" as a separate category. As seen, the distribution of individual perioperative changes is rather similar in patients with LGG and HGG at 1 month. However, from baseline to 6 months, greater dynamics are seen in patients with HGG. A larger proportion of patients with HGG are dead by the end of that period. Also, fewer HGG patients report "unchanged" QoL from baseline to 6 months (28.1%). In patients with LGG, "unchanged" from baseline to 1 month is reported in 60%, improvement in 15% and worsening in 25%. The latter percentage remains stable in LGG patients at 6 months and the proportion with "unchanged" pattern is lower (53%) at this stage, while the proportion reporting improvement is slightly higher, 20%.

Figures 4 and 5 visualize changes in the five EQ-5D subdomains from baseline to 1 and 6 months. At 1 month, the dominating tendency in both HGG and LGG is "unchanged compared to baseline" in all subdomains. "Usual activities" is the subdomain with the greatest negative change in both glioma groups. Both worsening of pain and improvement of pain is reported more often in HGG patients. At 6 months, the main difference between HGG

and LGG (apart from the different proportion of patients who are dead at that point) is seen in the subdomains “usual activities”, “self-care” and “mobility”, where a larger proportion of HGG patients report worsening. None of the LGG patients report impairment in the “self-care” domain at this point. Also at 6 months, the dominating pattern of development of EQ-5D subdomains in LGG patients is “unchanged”.

To identify possible predictors for negative QoL-dynamics between 1 and 6 months (i.e. worsening), we performed a logistic regression analysis where the variables age, ASA-class, eloquent Sawaya grade, resection grade, histopathology, postoperative complications and persistent new or worsened deficits were tested first in univariate analyses, thereafter in a multivariate analysis. As seen in Table 3, HGG histopathology, non-GTR and ASA-class ≥3 were factors statistically significantly associated with negative QoL development from 1 to 6 months postoperatively. The full model, containing the five predictors which were found significant at 0.1-level in univariate analyses, was statistically significant, chi-square (5 df, N=136) = 34.55, $p<0.001$. The model as a whole explained between 22.4 (Cox and Snell R square) and 30.2% (Nagelkerke R square) of the variance in negative development, and correctly classified 72.1% of cases. Only three of the independent variables made a unique statistically significant contribution to the model (ASA-class, HGG and GTR). Thus, non-GTR, ASA-grade 3 and HGG are identified as the strongest predictors for negative development of QoL between 1 and 6 months, all increasing the odds by a factor of around three. An attempt to build a regression model for possible predictors of “positive dynamics” failed, probably due the low number of patients experiencing positive development, and large heterogeneity within this patient group. Sensitivity of the model was zero, and no ability to predict the dependent variable correctly could be found.

Discussion

No cure for glioma is available to date, making all treatment efforts essentially palliative. Therefore, the quality of the remaining life span in glioma patients is of utmost importance. In our present longitudinal study, we explored the peri-and postoperative QoL-development in glioma patients undergoing primary surgery. We found generic QoL at group level to be similar in LGG and HGG patients at baseline as well as at 1 month after surgery, despite considerable differences in age, comorbidity, function and symptoms. This may seem surprising, but exemplifies that functional level or deficits as assessed by health care professionals are not necessarily proxies for patient-reported QoL. QoL development in the 6 month observation period was associated with extent of resection for HGG at group level, but not for LGG. On the one hand, selection bias may explain a rapid loss of QoL in many HGG patients after biopsy or subtotal resection. On the other hand, our findings may reflect that gross total resection has a potential to stabilize QoL over time in these patients. At the individual level, we found heterogeneous development in both HGG and LGG, demonstrating that surgery is not without impact on individual patients. Still, also at the individual level, the main pattern in LGG patients was “unchanged compared to baseline” at both follow-up points, while more than half of the HGG patients reported worsening or death at 6 months.

QoL-development at group level

EQ-5D index values at group level obtained at 1 month were stable compared to baseline and did not differ significantly between LGG and HGG, indicating that the completely different natural course of disease does not have a major impact on QoL at this early stage after surgery. More importantly, if there has been a dip in QoL in the immediate postoperative period, this is no longer the case when looking at the median EQ-5D values at 1 month,

suggesting that a possible negative impact of surgery on QoL at group level has resolved by that stage. Considering the short life expectancy of HGG patients, this is reassuring. However, at 6 months, EQ-5D index values had deteriorated markedly in HGG, whereas LGG patients still reported stable median scores. This is well in accordance with the different disease courses and treatment characteristics in the two glioma categories. We did not collect data on timing of radio- and chemotherapy during the 6 month follow-up period. In published oncological studies, there are conflicting results on the impact of adjuvant therapy on QoL[15,16]. Therefore, it is not clear whether negative effects of adjuvant treatment contributed to the observed deterioration of QoL in HGG at 6 months.

In the present study, the EQ-5D index values for the HGG group at 6 months are influenced by our choice to include patients who died during follow-up and rate their (missing) EQ-5D index value as "zero". Exclusion of these patients would have resulted in higher median index values for the HGG group at 6 months. A post hoc analysis of complete cases (i.e. the 111 survivors at 6 months) resulted in a median EQ-5D index value of 0.7 for HGG, which is statistically lower than in HGG at 1 month (p=0.003) and in LGG at 6 months (p=0.034), but does not gain clinical significance measured by MCID for glioma patients (+-0.15).[9] However, a complete case analysis was not our aim, as selective omission of the sickest patients would reduce the relevance of our results in this explorative study setting.

Individual dynamics

When exploring individual dynamics during the entire 6-month follow-up period, findings were heterogeneous, but the most enhanced tendencies in both LGG and HGG seem to reflect the findings at group level. In LGG patients, the most common pattern of dynamics of EQ-5D index value and subdomain changes at 1 and 6 months, was "unchanged" compared to baseline. The subdomain analysis in LGG patients (Fig 4 and 5) revealed a tendency to

postoperative improvement in several domains: at 6 months, a slightly larger percentage reported improved mobility, none of the patients complained about worsening of selfcare ability any more, and fewer reported impaired activity level, compared to the changes from baseline that were reported at 1 month. Conversely, the percentage of LGG patients reporting increased levels of anxiety/depression rose from 10 percent at 1 month to 17.5 percent at 6 months. One could speculate that increased awareness of the severity of the diagnosis may be affecting a few more patients at that later time point. In HGG patients, postoperative QoL patterns were dominated by "unchanged" at 1 month followed by "worse" compared to baseline at 6 months, alternatively "worse" at both time points. Deterioration over time was seen more often in the subdomains "usual activities", "self-care" and "mobility" in HGG patients. This may reflect the lower functional level at baseline, resulting in a smaller functional reserve in this group. Interestingly, positive and negative development of the subdomain "anxiety/depression" in HGG patients seemed balanced at both 1 and 6 months, but was most often unchanged compared to baseline. This seems counter-intuitive when looking at the considerably shorter remaining life span HGG patients are facing on average. Possible explanations might cover several facets of this patient population: higher age, but perhaps also cognitive impairment and steroid medication, which might influence QoL scores. Ultimately, when hope is gradually fading during disease progression, coping and acceptance or maybe a degree of indifference may gain dominance over anxiety.

The multivariable regression analysis demonstrated that high ASA-class, HGG and resection grades other than GTR were independent predictors in the model on "negative dynamics between 1 and 6 months". A part of these findings is in accordance with findings by Brown and colleagues,[17] who found that patients where GTR was achieved were less likely to report impaired QoL. This is also supported by our previous findings demonstrating poor survival[18] and poor QoL in patients with subtotal resections.[19] This may seem intuitive, since patients

eligible for GTR are per se different from patients undergoing subtotal resection or biopsy. Still, there is strong evidence that complete resections extend progression-free survival,[11,20] most likely due to disease control by cytoreduction. Our findings indicate that GTR does not seem to come at the price of significantly reduced QoL in most cases.

Timing of assessment

Unfortunately, as is the case for acquired neurological deficits, there is no agreement on when to assess QoL after surgery. Our results show that outcome assessment at 6 months is too late to be able to reflect the impact of surgery on QoL in HGG patients. When aiming to measure the impact of surgery in glioma patients, assessment of QoL at 1 month, compared to preoperative baseline, may be a feasible time point. One month after surgery as a reasonable time of assessment has previously been suggested for other important outcome measures after neurosurgery, such as perioperative mortality,[21] new neurological deficits[22] and surgical complications.[10] Although some patients, especially those with LGG, may still experience clinically significant improvement after 1 month, a comparable proportion deteriorates within the same time period. Moreover, response shift may affect changes over time in late QoL scores.[23]

QoL-instruments in glioma surgery

To date, there are no QoL instruments that are developed to specifically assess the effects or side effects of brain tumor surgery. The available disease-specific tools, e.g. the brain neoplasia module of the EORTC-questionnaire[24] and the FACT-Br[25] are designed to capture side effects of oncologic treatment (such as nausea, itching and hair loss) rather than consequences of surgical treatment. In the present study, we used the generic instrument EQ-5D 3L for assessment of QoL. The EQ-5D 3L has been validated for many conditions, also for cancer patients.[5] Earlier, our group reported that perioperative change in EQ-5D scores is

associated with survival in glioblastoma,[26] and that new or worsened deficits have a negative effect on QoL.[27] The responsiveness to deterioration and the minimal clinically important difference of the instrument in glioma patients are earlier described by our group.[9] More recently, we assessed QoL in 30 patients undergoing primary surgery for glioblastoma, with several follow-ups during the first year after primary surgery. Quality of survival (i.e. QoL over time) was found to be a surrogate for progression-free survival, and patients with GTR reported better and more stable QoL.[19] Also in the present study, results of a multiple regression analysis indicated that subtotal resection or biopsy in HGG is associated with negative dynamics of EQ-5D scores from baseline to 1 and 6 months. This supports a potential for EQ-5D as a marker of quality of care in glioma surgery.

We cannot exclude that our findings could have been different with the use of disease-specific QoL- instruments. The EQ-5D-tool does not respond as well to functional improvement as to deterioration.[9] Probably, we could have detected subtle improvements at symptom level after surgery with a more detailed instrument. Nevertheless, especially in the HGG group, we have experienced that missing data are a considerable problem when using more detailed patient-reported outcome tools like the EORTC QLQ C-30 and BN20. Others have also met this problem, as seen in a randomized clinical trial by Reijneveld et al, with around 35% dropouts at the 24-month- QoL-assessment.[28] There is an obvious risk of systematic bias if the sickest patients are noncompliant or even excluded by protocol, as is the case in published in glioma clinical trials with QoL as an outcome.[15,16] Aim of the present explorative study was to capture as many clinical courses as possible, including patients in a clinically poor condition. Therefore, we chose the EQ-5D 3L for measurement of perioperative patient-reported QoL. In our experience, this rather simple instrument can be used even in severely ill patients with a limited attention span or fatigue and with possibly limited motivation to complete extensive questionnaires. Additionally, assessment by

telephone interview as well as proxy ratings are considerably more practicable with the EQ-5D 3L than with disease-specific instruments like the EORTC QLQ C-30 and BN20. Thereby, missing data can be minimalized, which is important considering the explorative nature of our study. Only 21 of 157 eligible patients (13%) were lost to follow-up or excluded due to missing QoL forms.

Implications of study findings

Although our results from the longitudinal analyses may not surprise experienced clinicians, knowledge about the perioperative course of QoL in glioma may be useful when informing patients prior to surgery. In a recent study on prognostic awareness,[29] it was demonstrated that patients with glioma desire more prognostic information and communication. A systematic review identified several studies where glioma patients complained about a lack of information and communication.[30] There is no reason to believe that these unmet needs do not include the patients' desire for information about what to expect in the weeks and months after surgery. Our results may also contribute to clinical decision-making. Subtotal resections in HGG patients ASA group 3 or higher require careful consideration, bearing in mind the high risk of negative development of QoL over the following 6 months.

In addition to its potential for application in clinical settings, knowledge about the course of QoL in glioma may prove helpful in the process of identifying and agreeing on good tools and time points for QoL assessments in a perioperative setting. Unfortunately, the lack of consensus on definitions and assessment times for "soft" outcomes hampers comparisons across studies. Too early assessment after surgery may not allow enough time for rehabilitation and recovery from transient deficits. Too late assessment may reflect the disease course and effects/side effects of adjuvant therapy more than surgery.

As a consequence of the focus on patient-centered care in the modern clinical climate, patient-reported QoL and changes in QoL are increasingly recognized as important outcome measures. Who would know better than the patients themselves how they experience their functional level, symptom burden and quality of life? Physician rated scores of deficits and function may underestimate symptoms and deficits greatly when directly compared to patient-reported outcomes.[22,31] Also, the highly problematic observer bias, when surgeons themselves or close co-workers assess the results of their own work, is omitted by utilizing patient-reported outcomes.[2] However, to further increase the validity of patient-reported QoL as markers of quality of care, we need to agree on tools and feasible time points for assessment of such outcomes.

Strengths and limitations

To our knowledge, our study with 136 cases is the largest longitudinal study on perioperative dynamics of QoL in unselected patients undergoing primary glioma surgery so far. Due to the population-based referral system in Norway, we think that our findings hold high external validity. We attempted to keep imputation to a minimum and included deaths during follow-up in our analyses. Thereby, we avoid at least a part of the considerable selection bias associated with the common complete-case analysis in this patient population. We consider our study to describe real-life data, covering a wide range of the various perioperative clinical courses in glioma patients. Nevertheless, we cannot exclude an extent of selection bias due to moderate non-inclusion and loss to follow-up after the baseline QoL-assessment. Furthermore, a ceiling effect of EQ-5D index values at baseline did most likely influence our results to some degree.

Conclusions

In the longitudinal analyses performed in this study, we found that postoperative dynamics of generic QoL in HGG and LGG after primary surgery seem to reflect the natural disease course to a great degree. Relative stability in QoL from baseline to 1 month was reported in both LGG and HGG patients. QoL in LGG patients remains stable at 6 months, while a deterioration can be seen in HGG patients at that stage, both clinically and statistically. Individual dynamics were found to be heterogeneous. Independent predictors of negative QoL-development between 1 and 6 months were comorbidity, resection grades other than GTR as well as HGG histopathology. .

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Conflicts of interest

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

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Table 1 Baseline and treatment characteristics **N= 136**

	Variable	HGG[#], n (%) n= 96	LGG[**], n (%) n= 40	p Value
Patient characteristics	Female	29 (30.2)	13 (32.5)	0.952
	Age (mean, SD)	63.9 (10.4)	46.7 (16.2)	*<0.001*
	ASA[*]-class			
	1-2	65 (67.7)	37 (92.5)	*0.005*
	3	31 (32.3)	3 (7.5)	
	KPS[†]			
	≥70	75 (78.1)	38 (95)	*0.032*
	<70	21 (21.9)	2 (5)	
Preoperative symptoms	Headache	34 (35.4)	14 (35)	1.00
	Seizures	32 (33.3)	15 (37.5)	0.789
	Cognitive changes	45 (46.9)	4 (10)	*<0.001*
	Nausea	9 (9.4)	2 (5)	0.507
	Impaired vision	7 (7.3)	2 (5)	1.00
	Language problems	30 (31.3)	1 (2.5)	*<0.001*
	Motor deficits	16 (16.7)	1 (1.5)	*0.029*
Tumor characteristics	Laterality			
	Right	36 (37.5)	18 (45)	
	Left	42 (43.8)	16 (40)	0.704
	Bilateral/midline	18 (18.8)	6 (15)	
	Eloquent location	42 (43.8)	18 (45)	
	Preoperative tumor volume (cm^3), median (range)	25.2 (1.3 - 321.5)	8.8 (0.513-160.4)	*<0.001*
Treatment characteristics	Preoperative corticosteroids	74 (77.1)	4 (10)	*<0.001*
	GTR[‡]	20 (20.8)	18 (45)	
	STR[§]	46 (47.9)	17 (42.5)	*0.007*
	Biopsy only	30 (31.3)	5 (12.5)	
	Moderate, severe or fatal complications[‖]	9 (9.4)	5 (12.5)	0.552
	Postoperative new or worsened deficits[¶]	18 (18.9)	11 (27.5)	0.381
	Postoperative radiotherapy and/or chemotherapy	91 (94.8)	5 (12.5)	*<0.001*

[*] American Society of Anesthesiologists
[†] Karnofsky Performance Scale
[‡] Gross Total resection = 100%
[§] Subtotal resection = 1-99%
[‖] Landriel Ibanez grade II to IV
[¶] Persistent deficits (motor or language) confirmed by patient at 30 days
[#] High-grade glioma
[**] Low-grade glioma

Table 2 EQ-5D index values at group level in high-grade versus low-grade glioma

EQ-5D index value, median (range)	HGG*	LGG†	p Value‡
Baseline	0.76 (-0.48 to 1.0)	0.76 (0.03 to 1.0)	0.373
1 month	0.76 (-0.2 to 1.0)	0.73 (0.1 to 1.0)	0.518
6 months	0.38 (-0.43 to 1.0)	0.78 (-0.1 to 1.0)	*<0.001*
p Value§	*<0.001*	0.293	

*‡ Mann-Whitney U test § Friedman test * High-grade glioma † Low-grade glioma*

Table 3 Logistic regression analyses: Predictors of negative QoL- development from 1 to 6 months postoperatively

	Univariate Analyses		Multivariate analyses	
	OR (95% CI)	p Value	OR (95% CI)	p Value
HGG*	5.12 (2.07 - 12.71)	*≤0.001*	3.09 (1.06 - 9.03)	*0.039*
GTR†	0.22 (0.09 - 0.54)	*0.001*	0.35 (0.13 - 0.93)	*0.035*
Moderate to severe postoperative complications‡	0.2 (0.04 - 0.95)	*0.042*	0.21 (0.04 - 0.12)	0.067
Age	1.04 (1.01 - 1.07)	*0.003*	1.01 (0.98 - 1.05)	0.562
ASA§-class ≥3	5.02 (2.15 - 11.69)	*≤0.001*	2.95 (1.16 - 7.47)	*0.023*
Eloquent location‖	1.6 (0.81 - 3.19)	0.179		
New or worsened postoperative deficits	0.39 (0.1 - 1.49)	0.169		

* High-grade glioma † Gross total resection ‡ Landriel Ibanez grade II-IV § American Society of Anesthesiologists ‖ Sawaya grade III

Fig. 1 Inclusion Process

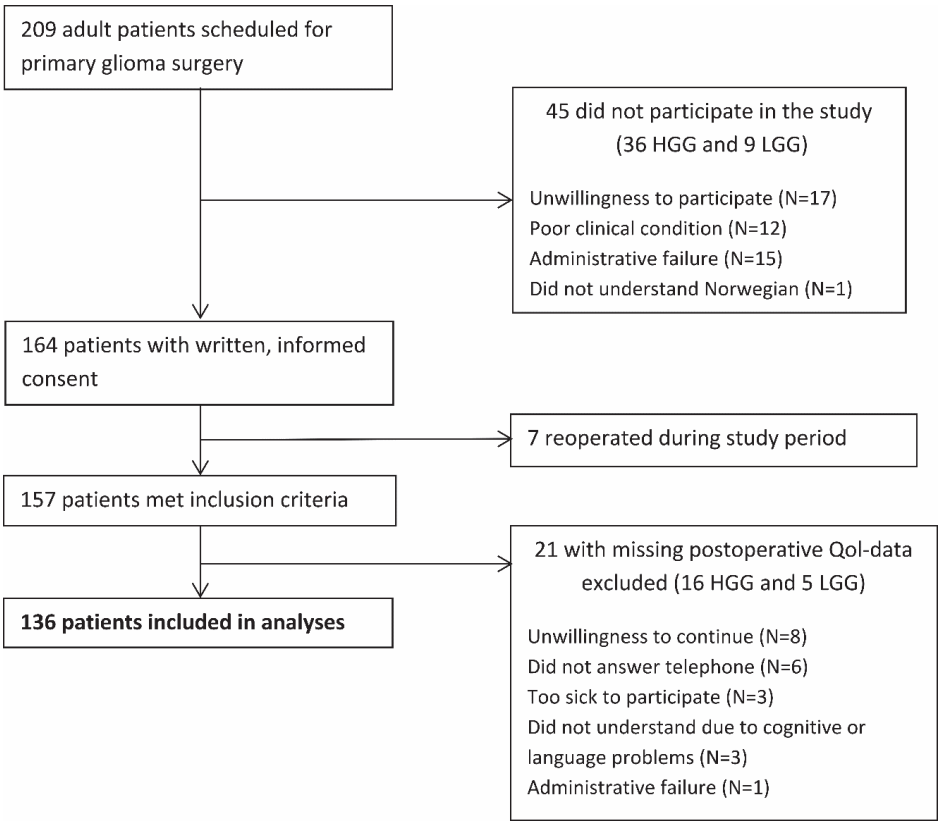

Fig. 2 EQ-5D index values at group level in high-grade versus low-grade glioma following biopsy, subtotal resection and gross total resection at 1 and 6 months postoperatively

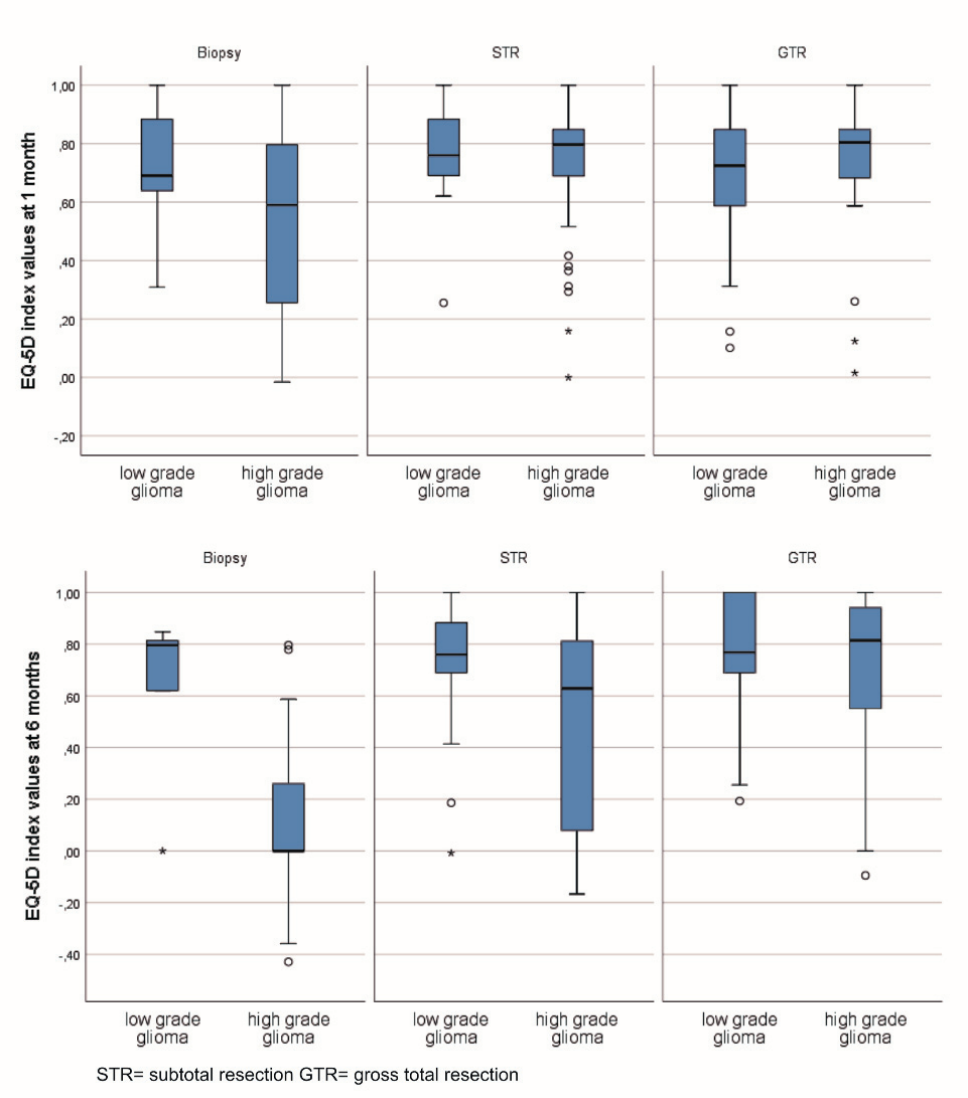

Fig. 3 Clinically important change in EQ-5D index values at the individual level from baseline to 1 month and to 6 months in high-grade versus low-grade glioma

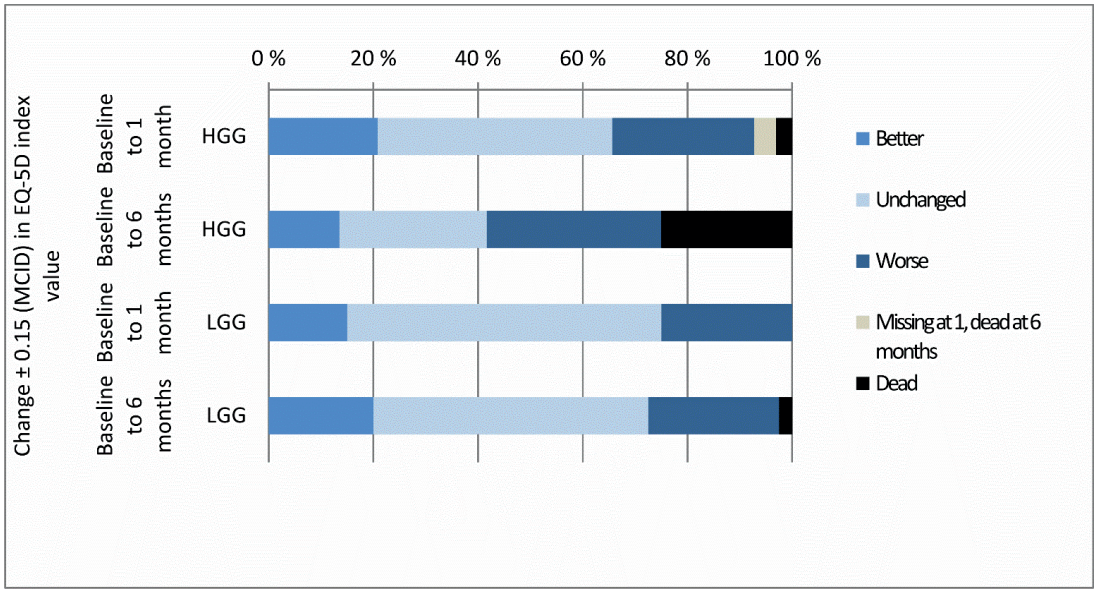

Fig. 4 EQ-5D subdomains: Change from baseline to 1 month in high-grade versus low-grade glioma

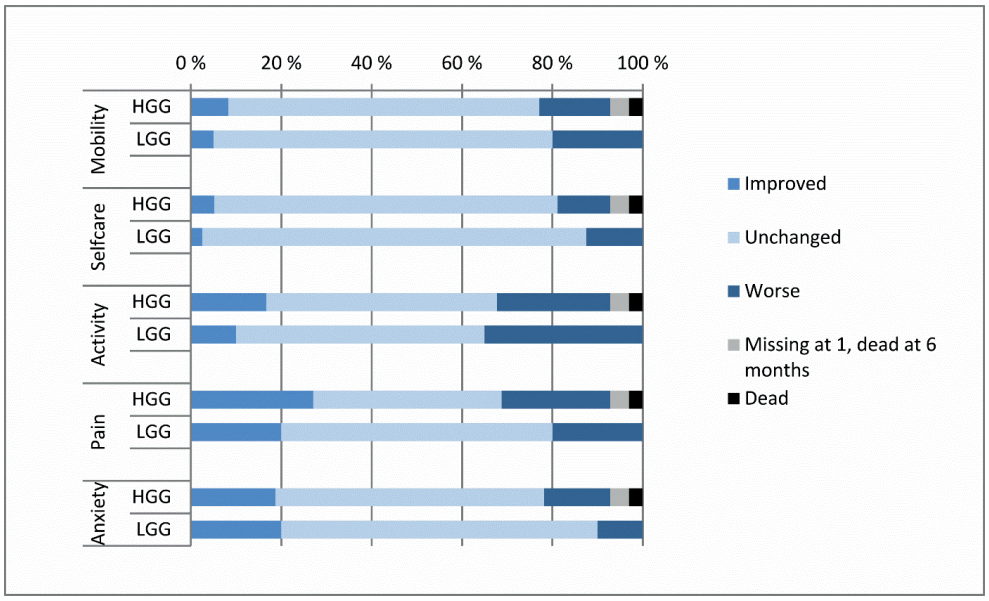

Fig. 5 EQ-5D subdomains: Change from baseline to 6 months in high-grade versus low-grade glioma