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Risks and benefits of brain tumor surgery

A balancing act

Thesis for the degree of Philosophiae Doctor

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Risiko og nytte ved kirurgisk behandling av hjernesvulster – en balansekunst

Denne avhandlingen fokuserer på kirurgisk behandling av diffust infiltrerende gliomer som er den vanligste formen for primære hjernesvulster. Gliomene inndeles i lavgradige og høygradige, hvorav de høygradige er mest aggressive, hurtigvoksende og vanligst forekommende. Effekten av kirurgi er omdiskutert for både lavgradige og høygradige gliomer. Effektmålene etter svulstkirurgi i hjernen har tradisjonelt vært dødelighet og sykelighet relatert til inngrepet, pasientens funksjonsnivå, progresjonsfri overlevelse eller total overlevelse. I denne avhandlingen har man forsøkt å belyse effektene av kirurgi på en ny måte.

I den første studien brukte vi Det Norske Kreftregisteret for å se på risiko for død de første 30 dagene etter operasjon for hjernesvulster, en mye brukt kvalitetsindikator som blant annet brukes for å sammenligne kirurgiske teknikker og sykehus med hverandre. Vi fant at denne indikatoren trolig er mindre egnet enn ofte antatt på grunn av lav frekvens av hendelser, noe som vanskeliggjør meningsfulle statistiske sammenligninger. Den viktigste risikofaktoren for tidlig død etter kirurgi er sannsynligvis sykdommens prognose, noe som igjen medfører at pasientutvalget, det vil si hvem man opererer, betyr mest for risikoen for perioperativ død.

De to neste studiene omhandler pasientrapporterte endepunkt, noe som foreløpig er en ganske uvanlig som effektmål ved hjernesvulstkirurgi. Vi brukte det enkle spørreskjemaet EuroQol 5D (EQ-5D) før og etter operasjonen, og fant ut at EQ-5D korrelerer godt med funksjonsnivå rapportert av helsepersonell. En slik enkel bedømning kan gi et godt og kirurguavhengig bilde av forholdet mellom nytte og risiko vurdert av pasientene selv, og et tidlig fall i livskvalitet etter operasjon virker å være assosiert med dårligere overlevelse.

Den siste studien omhandlet kirurgisk behandling av lavgradige gliomer. Den kirurgiske tilnærmingen til slike svulster har grunnet mangel på gode studier variert mye mellom sentra, og særlig har man sett reservasjon mot kirurgi der svulstene har berørt områder i hjernen som man oppfatter som ekstra følsomme (for eksempel i språkområdene). Ved å sammenligne to populasjoner som ble håndtert svært ulikt med tanke på kirurgisk tilnærming har vi fått til den første kontrollerte studien på kirurgisk behandling av lavgradige gliom. Denne viser at en

tilnærming hvor man tidlig fjerner så mye som mulig av svulsten er å foretrekke fremfor kun å ta en vevsprøve og vente med kirurgi til fremtidig svulstvekst ses på MR.

Hovedfunnene i denne avhandlingen er:

- Hjernesvulsters langtidsprognose er en sterk prediktor for død innen 30 dager etter kirurgi. Forskjeller i pasientseleksjon, samt den lave forekomsten av perioperativ død ved hjernesvulstoperasjoner, er til hinder for pålitelige sammenlignende studier.
- Helserelatert livskvalitet målt med EQ-5D synes å være å være et bra endepunkt i forskning på pasienter med gliom i hjernen. EQ-5D har sterk korrelasjon til tradisjonelle effektmål, men bidrar med pasientsentrert tilnærming og er mer nyansert enn tradisjonelle endepunkt.
- Nevrologiske utfall etter kirurgi har en markant negativ effekt på livskvalitet hos pasienter med gliom i hjernen.
- Tidlig reduksjon i livskvalitet etter kirurgi predikerer dårligere overlevelse etter kirurgi for den mest høygradige gruppen gliomer (glioblastomer).
- Tidlig kirurgisk reseksjon gir lengre overlevelse sammenlignet med biopsi og påfølgende ekspektans hos pasienter med lavgradige gliom. Initial behandlingsstrategi ved lavgradige gliom bør oftest være tidlig kirurgisk reseksjon.

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Risks and benefits of brain tumor surgery – a balancing act

The original research presented in this thesis focuses on surgical management of diffuse gliomas which are the most common primary tumors within the brain. The gliomas are subdivided into low-grade and high-grade, and the latter are most aggressive and most prevalent. Both in low-grade and high-grade gliomas the optimal surgical management remains controversial. The usual outcome parameters in intracranial tumor surgery have been perioperative mortality and morbidity, patients' functional level, progression free survival, and overall survival. In this thesis efforts have been made to illuminate the effects of surgery in new ways.

In the first study we used the Norwegian Cancer Registry to assess the risk of death within 30 days after surgery for intracranial tumors. This indicator is often used to compare surgical techniques and hospital quality. We demonstrated that this indicator is probably of less value than often thought due to the low frequency of events which make meaningful statistical comparisons difficult. The most important factor for perioperative mortality is the inherent prognosis of the disease. This makes the patient selection the most important predictor for perioperative mortality.

In the two next studies we explored patient reported outcomes, a still rather uncommon end-point in surgical research for intracranial tumors. We used a simple generic questionnaire EuroQol 5D (EQ-5D) before and after surgery and demonstrated that EQ-5D is closely correlated to functional level as reported by healthcare personnel. Thus, this simple assessment gives a good and surgeon independent evaluation of benefit-risk ratio as evaluated by patients themselves. In addition, a decline in patient reported health shortly after surgery seems associated with impaired survival.

The last study examined the surgical management in low-grade gliomas. The surgical management in these patients has been subject to much debate and management differs considerably due to lack of clarifying studies. Lesions involving regions perceived critical for neurological function has been particular controversial. By comparing two population based cohorts of low-grade gliomas subject to radically different surgical strategy we have achieved to produce the first comparative study on surgical management in patients with low-grade

gliomas. In this study we demonstrate that initial resection is superior to biopsy and subsequent watchful waiting with respect to overall survival.

This thesis investigated risks and benefits in surgical treatment of brain tumors and the following conclusions can be drawn:

- Overall prognosis is a strong predictor of perioperative death. Differences in patient selection, and the low incidence of perioperative death in intracranial tumor surgery, greatly limit comparative analyses.
- EQ-5D seems like a good outcome measure in patients with intracranial glioma with its strong correlation to traditional variables while being patient centered and more nuanced.
- Surgically acquired deficits have a major undesirable effect on quality of life in patients with intracranial glioma.
- Early deterioration in quality of life after surgery is associated with impaired survival in patients with the most aggressive gliomas (glioblastoma).
- An initial strategy with resection improves survival as compared to biopsy and subsequent watchful waiting. Resection should be the initial treatment option in most patients with low-grade gliomas.

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Errata

In paper IV we erroneously cited the old version of the WHO classification system from 2000 when we intended to cite the newer version from 2007 which is cited in this thesis (citation #1). Also, in paper IV table 1 the percentages representing “men” should in fact be “women”, thereby giving the false impression that LGG was more common in women than in men.

Acknowledgements

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I am also indebted to my family for teaching me to appreciate the important things in life and for always accepting my restlessness. Most of all I am deeply grateful to Caroline for supporting me even though it meant late hours in my own world instead of contributing to the ever educational talks we have together. After the arrival of our wonderful daughter Ines, I realize that this period was only a small speed bump on the long journey we have started on.

Trondheim, December 2012

Asgeir Store Jakola

List of Publications

1. Incidence and causes of perioperative mortality after primary surgery for intracranial tumors: a national, population-based study. Solheim O, Jakola AS, Gulati S, Johannesen TB. *Journal of Neurosurgery.* 2012;116(4):825-834.

2. Quality of life in patients with intracranial gliomas: the impact of modern image-guided surgery. Jakola AS, Unsgard G, Solheim O. *Journal of Neurosurgery.* 2011;114(6):1622-1630.

3. Postoperative Deterioration in Health Related Quality of Life as Predictor for Survival in Patients with Glioblastoma: A Prospective Study. Jakola AS, Gulati S, Weber C, Unsgård G, Solheim O. *PLoS ONE.* 2011;6(12):e28592.

4. Comparison of a Strategy Favoring Early Surgical Resection vs a Strategy Favoring Watchful Waiting in Low-Grade Gliomas. Jakola AS, Myrmel KS, Unsgård G, Kloster R, Torp SH, Lindal S, Solheim O. *JAMA.* Oct 25 2012:1-8 (online first).

Abbreviations

5-ALA = 5-aminolevulinic acid

CT = Computer-assisted tomography

DTI = Diffusion Tensor Imaging

EORTC = European Organisation for Research and Treatment of Cancer

EQ-5D = EuroQol 5D

FLAIR = Fluid attenuated inversion recovery (an MRI sequence)

fMRI = Functional Magnetic Resonance Imaging

GBM = Glioblastoma multiforme

HGG = High-grade glioma

HR = Hazard ratio

HRQL = Health-related quality of life

LGG = Low-grade glioma

KPS = Karnofsky Performance Status

MRI = Magnetic Resonance Imaging

mRS = Modified Rankin Scale

PET = Positron emission tomography

PFS = Progression-free survival

PRO = Patient reported outcome

QOL = Quality of life

RPA = Recursive partitioning analysis

Introduction

Classification of gliomas

Gliomas arise from glial supportive tissue of the brain including astrocytes, oligodendrocytes, or ependymal cells.[1] The astrocytic tumors represent the majority of the gliomas and the World Health Organization (WHO) classifies astrocytomas on the basis of histologic features into four prognostic grades:[1] grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma), and grade IV (glioblastoma). The diffuse LGGs encompass diffuse grade II astrocytomas, oligodendrogliomas and oligoastrocytomas (mixed). Pilocytic astrocytoma is by definition a LGG, but they are most often looked upon as a separate entity due to the non-infiltrating and benign behavior. The diffuse LGGs (WHO grade II) tend to recur with time and the histological grading is often more malignant at time of progression. The grade III and grade IV tumors are collectively often named HGGs. Thus, it is common to consider the diffuse gliomas as a continuum rather than completely separate entities.

Perhaps as a consequence of being a continuum rather than distinct entities the tissue diagnosis of diffuse LGGs and anaplastic astroctytomas is associated with considerable interobserver variation.[2] Discordant results as high as 60 % was demonstrated for grade II astrocytomas, but most were of minor significance from a clinical point of view. Because of this it is important to take the necessary precautions to reduce classification bias in research on diffuse LGGs.

Epidemiology of gliomas

The incidence of gliomas is reported to be 6/100,000 persons per year.[3] High-grade gliomas are most common with approximately 5/100,000 persons per year affected with GBMs accounting for approximately 70 %.[4] Low-grade gliomas are less common than HGGs with

approximately 0.8 – 1.2/100,000 per year and LGG accounts for 15 % of primary brain tumors in adults.[5,6] Except for ionizing radiation there are no established correlations between environmental factors and the development of gliomas.[4]

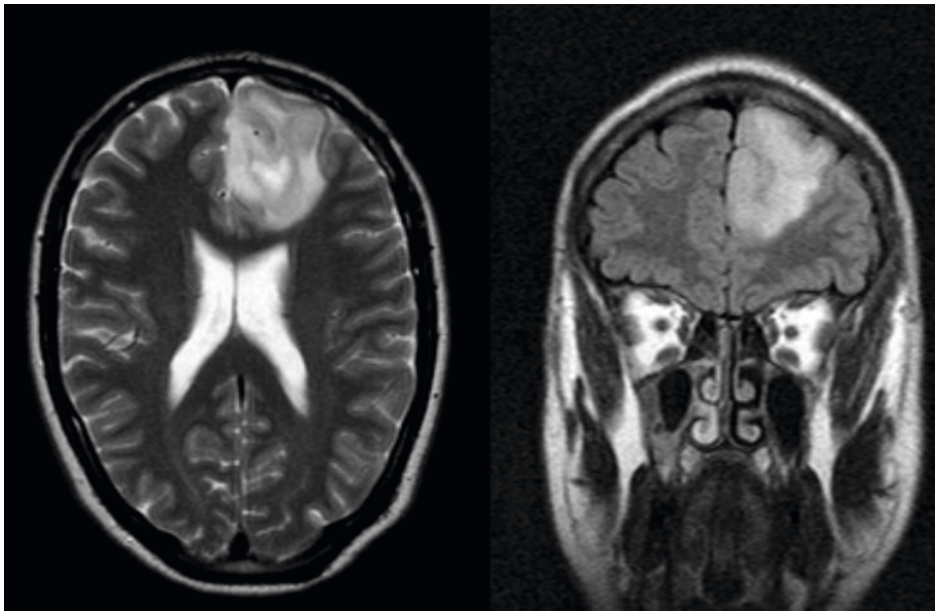
Clinical features and related imaging

Patients with gliomas most often seek medical advice due to alterations of neurological functions (i.e. speech, movement, vision and cognition), seizures or due to increased intracranial pressure (i.e. headache, vomiting, or affected consciousness). Rarely, although increasing with the widespread access to modern neuroimaging, patients receive the diagnosis after imaging due to an unrelated condition.

On MRI the HGGs usually present with heterogeneous contrast enhancement in a ring-like pattern in T1 images.[4] Glioblastomas usually have a central core which is non-enhancing representing necrosis as the tumor has outgrown its blood supply and due to microthrombosis in tumor vessels. Also, glioblastomas usually present with more peritumoral edema than the anaplastic gliomas, a feature best appreciated on MRI in T2-weighted or FLAIR sequences.[4]

Diffuse LGGs appear hyperintense on T2-weighted or FLAIR MRI sequences, and in contrast to HGGs little or no edema is present. Evidence of hemorrhage and calcifications are more common in oligodendrogliomas.[7] Lesions usually extend along white matter tracts and it is not uncommon with growth in corpus callosum and even into the contralateral hemisphere.[8,9] Rarely diffuse LGG involves three or more lobes and is then termed gliomatosis cerebri, and although histopathologically a grade II tumor the widespread disease is associated with a worse prognosis. Contrast enhancement when present is usually patchy and occurs in 15-39 % of cases with diffuse LGG.[7] Areas of particular interest that could go unnoticed with the use of conventional methods only can be detected by metabolic imaging where focal hot spots may represent areas of malignant degeneration. Such imaging may be particular important for representative sampling within a heterogeneous tumor, that again could lead to a lower number of contrast enhancing tumors in the “true” diffuse LGG population.[10]

Figure 1



MRI of typical low-grade glioma. To the left is a T2-weighted axial image demonstrating hyperintense signal in the left frontal lobe. To the right is the corresponding coronal FLAIR image. Contrast enhanced T1-images did not demonstrate any contrast enhancement. The patient underwent complete resection of the tumor and the histopathology concluded with oligoastrocytoma, WHO grade II.

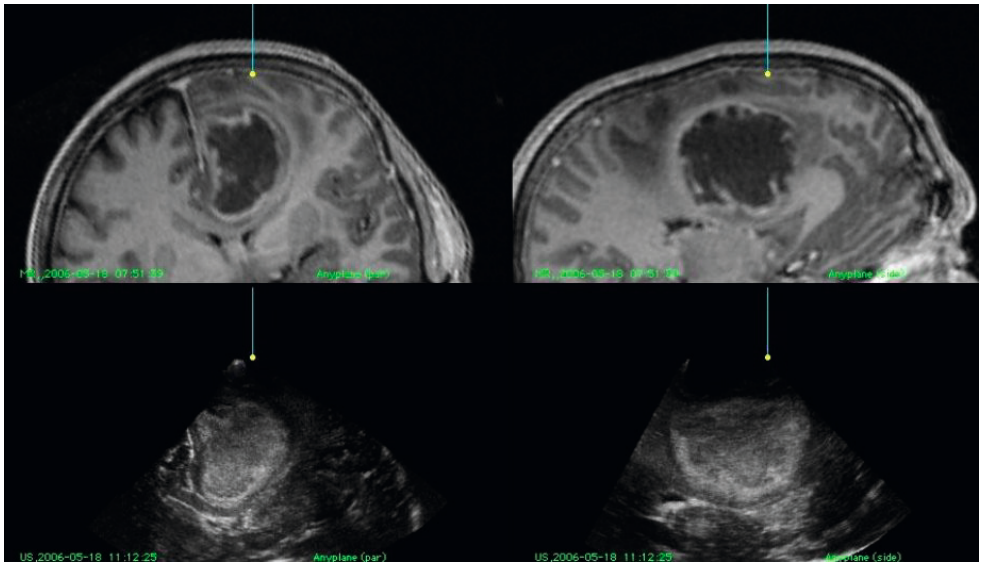
The tumors' anatomical relationship to so-called eloquent brain regions can be suggested from preoperative MRI. The term eloquent is somewhat ill-defined, but a common interpretation is that sensorimotor regions, language cortices, visual cortex, basal ganglia and/or larger white matter tracts represent eloquent regions.[11] Since these regions have critical role for basic neurological function, the involvement of tumor in these regions often influence treatment strategies. To grade the lesions proximity to these regions a classification system was proposed by Sawaya *et al*, and this is perhaps the most common way to grade eloquence from an anatomical point-of-view (table 1).[12] As seen, grading eloquence even with the use of a classification system is subject to interpretation, especially for the intermediate group.

Table 1: Grading of eloquence in according the system suggested by Sawaya

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 parietooccipital	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

Modern neuroimaging with fMRI for identification of cortical functions and DTI to identify the course of white matter tracts is increasingly used in planning of brain tumor surgery. Using these techniques areas important for movement, vision and language functions can be visualized and incorporated into the neuronavigation system for guidance during surgery.[4,13] This is a useful technique since it reveals the relationship between the tumor and these critical structures. At neurosurgical department, St. Olavs University Hospital we have used a strategy combining import of fMRI and DTI data into a navigation system with intraoperative 3D ultrasound.[13] In our experience, the eloquent areas visualized with fMRI and DTI usually lie outside the tumor margins visualized by ultrasound in patients without neurological deficits. Resections were performed according to these tumor margins in the 3D ultrasound images, with particular care in areas neighboring eloquent areas. To correct for the brain shift caused by the resection, the 3D ultrasound acquisition was repeated several times during the operation. Other commonly used methods for achieving extensive resections while preserving neurological functions postoperatively are intraoperative MRI,[14] fluorescence (5-ALA),[15] and the use of various mapping techniques.[16,17]

Figure 2



Images from a typical glioblastoma. The images are from the neuronavigation system. The preoperative MR images are presented above with corresponding intraoperative ultrasound images below (acquisition taken before resection).

For surgical planning and treatment monitoring modern MRI techniques are increasingly utilized.[3] Perfusion MRI adds information on angiogenesis that again correlates with WHO grade, diffusion weighted sequences adds information on cellularity, and tumor metabolism is visualized by MR spectroscopy and MR PET using radiolabelled tracers.[3,10,18,19]

The most common presentation of diffuse LGG is seizures occurring in about 60-80 % of patients.[8,20] Occasionally patients with LGG are diagnosed when seeking medical advice for unrelated conditions and this occurs in about 2-10 % of cases.[21,22] However, with the increased use of modern neuroimaging this number is expected to increase slightly in the time to come. Incidental diffuse LGGs are reported to be smaller and with a better prognosis than the symptomatic LGGs,[21,22] a finding that may be linked to an earlier diagnosis per se (lead time bias).

In HGG the clinical presentation may be a true medical emergency with increased intracranial pressure leading to impaired consciousness. The mass effect caused by the tumor and its surrounding edema can in most cases effectively be relieved with surgery and corticosteroids.

Prognostic factors

Prognostic factors at time of diagnosis include patient characteristics and findings on diagnostic imaging. There have been numerous efforts to divide the patient population into different prognostic groups.[8,9,23] In the neurosurgical literature the controlled clinical studies, both prospective and retrospective, are clearly in minority.[24] Therefore, efforts in defining prognostic factors are meaningful to researchers in an attempt to adjust for case-mix between studies to compare results in a reliable manner. However, clinicians and patients cannot solely rely on such indexes when deciding among the therapeutic options since the prognostic factors are usually too imprecise for use in individual patients.

The median survival in patients with diffuse LGG is often reported between 5 to 10 years.[7-9] It needs to be acknowledged that the survival time clearly depends upon prognostic groups. For prediction of survival in diffuse LGGs the Pignatti score is much used.[8] Age ≥ 40 years, diameter ≥ 6 cm, tumor crossing midline, neurological deficit, and astrocytoma histology constitute the score, and one point is given for each factor present where a higher score indicates a worse prognosis.

The median survival in HGG with modern treatment is reported to be 14 to 15 months in randomized trials,[25,26] with 2-year survival of 27 % and 5-year survival of 10 %.[27] Since randomized trials consist of highly selected patients the results from real-life conditions in unselected cases differ considerably as median survival is 9.5 months with 2-year survival of 17 % in population based data.[28] For HGGs the established clinical risk-factors are age and preoperative clinical condition, often measured with KPS.[29,30] A prognostic system, the RPA classes, in HGG has been much used which includes tumor grade and treatment related factors in addition to the prognostic pretreatment clinical characteristics.[27,31-33] The RPA system has been shown to be more important for prognosis than the subsequent oncological treatment[31,34] and is significantly associated with survival also in the modern era.[27,33] To adjust for co-

morbidity the most used score is the Charlson co-morbidity index.[23] Although not much utilized in neurosurgical research, the scale seems feasible and valid.[35-37] The index has demonstrated predictive capabilities for overall survival in a wide range of patient populations including intracerebral hemorrhage[38] and ischemic stroke.[39] It is also suggested that modern metabolic imaging offers prognostic information in patients with gliomas.[40]

Recently it has been acknowledged that molecular markers add important prognostic information. Most important in HGG is the presence of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation which predicts response to the chemotherapeutic agent temozolomide.[27,41,42] In oligodendroglial tumors the combined loss of chromosomes 1p/19q represents a favorable subgroup of patients.[43,44]

Surgical strategy

The growth pattern in gliomas has generally been considered incompatible with the idea of achieving total surgical removal of all tumor cells. Several different surgical approaches have evolved, perhaps as a consequence of not being able to offer a cure for these patients. In example, the range of treatment options in a typical diffuse LGG case is from serial imaging ("watchful waiting") to attempting for early total resection of the tumor. The most common factors when deciding the surgical strategy include age, co-morbidity and the perceived resectability of the tumor. Therefore, patient selection is presumably the key to achieve excellent results, and when reading the literature it has to be remembered that uncontrolled series have an inherent selection bias, since higher resection grades are often obtained in patients with a better prognosis to begin with.

In HGG there is now strong evidence in favor of reaching for radical surgical resection in selected patients.[26,45] However, the optimal treatment strategy for HGG patients where the complete removal of the tumor bulk is not achievable remains controversial. Whether subtotal resection offer a clinical meaningful survival benefit remains unclear. The survival benefit of an aggressive strategy is likely smaller and risks may perhaps outweigh the potential benefits from subtotal debulkings. New deficits and deterioration of HRQL postoperatively seems associated with impaired survival,[46,47] possibly by enhancing the invasiveness of the

remaining tumor cells due to regional hypoxia,[48] or due to withholding adjuvant oncological treatments in functionally dependent patients.[49] Thus, aiming for gross total resection in all HGG patients is probably an overly aggressive approach.

In diffuse LGG a review article stated that the only management option supported with strong evidence is tissue diagnosis.[50] In the years after this review several papers have reported on the benefit of extensive resection.[6,51,52] However, in diffuse LGG there have been no controlled studies providing a higher level of evidence even in recent years – although the accumulating surgical series indicate a survival benefit with resection. The consequence of the lack of high-quality evidence was exemplified in a recent study on management in LGG demonstrating large differences in preferred treatment strategies.[53]

Adjuvant treatment in diffuse gliomas

Adjuvant therapy, in the form of chemotherapy and radiotherapy, has been extensively studied. In the primary management of diffuse LGG the role for either is questioned.[6,7] Radiotherapy has been proven to delay progression, but it is not associated with prolonged survival.[54-56] Thus, deferring radiotherapy until progression to reduce its long term side-effects[57] is common practice. The exact role of chemotherapy in LGG patients is still to be defined,[6,7] but a recent study has suggested that a regimen consisting of procarbazine, lomustine and vincristine (commonly referred to as PCV regime) may have a role in patients undergoing subtotal resection.[58] Also, specific genetic markers (MGMT promoter methylation and the combined loss of 1p/19q) may help to better identify a favorable subgroup of patients. At our institution it is uncommon to offer chemotherapy as part of the first-line treatment unless a very large remnant is left behind or the histology reveals the more aggressive gemistocytic astrocytoma.[7]

In HGG the standard regime consists of temozolomide concomitant to radiotherapy.[4,25] At our institution a neuro-oncologist assess all patients postoperatively to evaluate if they are candidates for radio- and/or chemotherapy. Patients are in practice evaluated for such therapy regardless of age, and there is now strong support in favor of offering radiotherapy also to elderly with a high functional level.[59] Some claim that there is a true multimodal effect

between adjuvant treatment and surgical therapy, meaning that the effect of adjuvant therapy is particularly good if an extensive resection has been performed.[60,61]

Evidence is lacking in favor of specific treatments for recurrent tumor,[62] but there are now several papers on the use of bevacizumab in recurrent tumors claiming modest effects.[4,63,64]

Addressing the invasion

The diffuse gliomas are characterized by the widespread local invasion by migrating tumor cells distant from the gross tumor visible on MRI, by intraoperative 3D ultrasound or in the microscope during surgery.[48,65-67] It is known that HGG spread along myelinated axons, along basement membranes and subependemyma.[48] This invasiveness was demonstrated already in the early era of brain tumor surgery. In 1928 Walter E. Dandy published a report after hemisperectomies in patients presenting with severe neurological deficits, a clinical presentation suggesting widespread disease.[68] Of the patients surviving surgery, all died of recurrent glioma. A biopsy study from 1987 demonstrated infiltrating tumor cells well beyond the tumor bulk, and at least as far as the edematous zone on seen on 1.5 T MRI T2 weighted images.[69] However, despite discouraging results after extensive resections there might be some patients with less extensive disease at diagnosis that perhaps could benefit from an aggressive surgical approach aiming for super-radical resections.[48] In diffuse LGG migrating tumor cells have also been identified well beyond the tumor margins as defined by MRI.[66] However, in an attempt to halt malignant progression a more refined concept of super-radical resection was recently described in a highly selected subgroup, an approach made possible by modern imaging. In diffuse LGG located away from eloquent areas super-radical resections, as defined by MRI, were guided with functional mapping. Although this was a highly selected case-series their seemingly good results are noteworthy.[70] Thus, with a targeted patient selection and with the guidance of modern surgical tools, there might be a small role for this approach in diffuse gliomas also in the future.

Adjuvant therapies targeting the remaining tumor cells have so far been somewhat disappointing despite of progress with the use of temozolomide in HGG.[25,27] One possible explanation for this relative radio- and chemoresistance is perhaps that the migratory cells left

behind after surgery are different from cells in the tumor core in that they are not highly proliferating.[48,71] Thus, some advocate the need for addressing the invasion.[48] Recently there was a promising report in rats when the migrating glioma cells was targeted with a substance called imipramine blue.[65] If similar results can be obtained in humans this could represent a shift of paradigm and an emerging hope for glioma patients.

Outcome measures in glioma surgery

The traditional studies in patients with primary brain tumors are often focused on disease related outcomes (i.e. overall survival, progression-free survival)[26,52] and surgically related outcomes (i.e. resection grades, new neurologic deficits, complications, and perioperative mortality).[15,72,73] These measures are invaluable for understanding the impact of surgery, improving surgical technique and for understanding the progress in neuro-oncology over time. For instance, the surgical mortality may provide information of the surgical technique and the pre- and postoperative care, all which are cornerstones in brain tumor surgery. In the era of Harvey Cushing the perioperative mortality was often as high as 50 percent, but some pioneers were able to demonstrate better results. In Cushing's personal series of brain tumor operations mortality was 13 percent.[74] The father of Norwegian neurosurgery and pioneer in the field, Vilhelm Magnus, reported in 1925 a surgical mortality of 10.5 % in the 189 patients with brain tumors he had operated in a period of 20-years.[75]

To measure outcomes from the patients' point of view, so-called patient reported outcomes (PROs), HRQL is much utilized in clinical research. However, in brain tumor surgery the idea of measuring PROs is rather new, and much work is still left to be done on this topic.[76,77] This is perhaps surprising given that surgery is not a curative solution for these patients and quality of life should be in focus. Until recently it was common to use one-dimensional scales such as KPS (which is not a PRO) to report HRQL, but it is generally accepted that HRQL constitutes of several dimensions including physical status, emotional and social well-being.[77] There are numerous instruments available for measuring HRQL and each have strengths and weaknesses, but none developed specifically for assessing the results of brain surgery. Generic instruments are usually less sensitive for the specific patient group, but allows for

comparison between other groups. Generic instruments are usually simpler which may be of benefit in patients having trouble with cognition. Being shorter and simpler the questionnaire burden is reduced, thus possibly improving inclusion rates and patient compliance. Even though PROs are subjective by nature, HRQL is presumably not unaffected by the traditional outcome measures in brain tumor patients, i.e. disease progression or surgical morbidity.[46,78]

Aims and Methodological Considerations

The overall aim of this thesis was to study the implications of surgery in patients with primary brain tumors.

Paper I

Incidence and causes of perioperative mortality after primary surgery for intracranial tumors: a national, population-based study

In this study we used the national cancer registry to study the frequency and possible causes of surgical mortality following primary intracranial tumor operations. We also sought to explore a possible predictive value of perioperative mortality rates from a neurosurgical centre in relation to long-term survival.

Paper II

Quality of life in patients with intracranial gliomas - the impact of modern image guided surgery

In this prospective study we aimed to assess changes in HRQL after glioma surgery, to explore the relationship between HRQL and traditional outcome parameters, and to examine possible predictors of change in HRQL.

Paper III

Postoperative deterioration in health related quality of life as predictor for survival in patients with glioblastoma: a prospective study

In this prospective study the aim was to determine if changes in HRQL was a predictor for survival in patients with glioblastoma.

Paper IV

Comparison of a Strategy Favoring Early Surgical Resection vs a Strategy Favoring Watchful Waiting in Low-Grade Gliomas

In this retrospective cohort study with parallel group design we studied the impact of surgery in a population based quasi-experiment involving two centers with different surgical treatment strategies.

Study populations

The Norwegian Cancer Registry

Study data in Paper I was provided by the Norwegian Cancer Registry. Reports to the Norwegian Cancer Registry have been compulsory by law since 1952. Information to the registry comes from several independent sources, thus securing a high grade of completeness and quality of data. A study from 2001-2005 demonstrated a 93.8% completeness of data in all central nervous system tumors, including cases without histological verification.[79]

Prospective studies

In papers II and III the included patients were operated for gliomas at the department of neurosurgery, Trondheim, Norway in the period from 2007 through 2010. Patients willing to participate gave their written informed consent.

Population based

In paper IV we have population based inclusion from two of the four geographical health regions in Norway, North and Mid-Norway. Population based in this context means inclusion of all patients receiving a tissue diagnosis of LGG at two university hospitals serving exclusively in the health regions with regional referral practice. The inclusion of the cohort was retrospective and based on histopathology alone.

Interobserver variability

In paper IV patients were recruited from two Norwegian university hospitals. In both studies inclusion was based on histopathology alone without any exclusion criteria (so-called pragmatic design).[80] This was a deliberate strategy to maximize external validity by reducing assessment bias. However, when dealing with diffuse LGGs a high level of caution is necessary since the histopathological diagnosis of diffuse LGGs is associated with considerably interobserver variability.[2] To confirm diagnoses and rule out classification bias in comparative analyses it was mandatory to conduct a review of histopathology. Patients

with grade I and II gliomas were identified in the histopathological databases and these patients were re-investigated by a neuropathologist from the other hospital for inclusion in the study, blinded for the initial diagnosis and clinical characteristics'. Discordant results were settled during a meeting between the neuropathologists where consensus was obtained by evaluation of the slides in a multi-headed microscope. In total, 47 % of the supratentorial tumors screened for inclusion had to be evaluated at the consensus meeting.

Quasi-experiment

Experimental studies in brain tumor surgery are very rare for several reasons, such as the low incidence of tumors, the strong local treatment traditions, patients and surgeons unwillingness to randomize between invasive treatments.[81] In Paper IV we have had the opportunity to use a somewhat unconventional study method. Patients with diffuse LGGs have for several years been subject to very different treatment traditions at two adjacent Norwegian university hospitals. In retrospect we compared results of the diverging treatment strategies. The centers have population based referral eliminating referral bias associated with other referral patterns. Norway has a socialized health care system with equal distribution of resources and uniform training and licensing of health care personnel. The design with central histopathological review ensured uniform inclusion criteria in an unbiased fashion. Thus, our study was a result of a natural occurring and practically random experiment where patients were "allocated" to treatment based on the residential address. Data collection was done in retrospect making it prone to bias, and as a consequence of this we attempted to focus on the hard clinical data less subject to interpretation by the investigators. The study, being the first controlled surgical study in diffuse LGG provides the most convincing evidence to date on surgical decision making in diffuse LGG.

Assessment of HRQL

EQ-5D is a generic (not developed for any specific patient group) and preference-weighted measure of HRQL.[82] There are many different instruments available for measuring HRQL. We chose to use EQ-5D in Paper II and III due to the simplicity of the instrument, to enhance patient perception and perhaps also compliance. Generic instruments such as EQ-5D lack

disease specific questions that may be relevant to the patient group (e.g. cognitive functions). Generic instruments may therefore lack sensitivity to measure small benefits or negative consequences of surgery. We decided to measure HRQL preoperatively (in most cases after the effect of preoperatively administered corticosteroids, if relevant) and 4-6 weeks postoperative in an attempt to measure the impact of surgery, and hopefully minimize the effect of disease progression or subsequent therapy.

Assessment of images

Patients in Paper II – III routinely underwent 1.5 T or 3.0 T MRI scans a few days before and within 72 hours of surgery. The assessment of tumor volume and resection grades were based on these pre- and postoperative MRI investigations using an ellipsoid volume formula ($4/3 \cdot \pi r^1 r^2 r^3$) based on the maximum tumor diameters in the perpendicular dimensions.[26] This is a crude measure and obviously a simplification compared to the manual segmentation or use of semi-automated software systems,[83] but we have considered it a reasonable approach in this context. In paper 2, an "eloquent location" was defined as cases in which fMRI or DTI was used for mapping functional areas. In paper III – IV a validated and more reproducible grading system for anatomical eloquence was used.[12]

Limitations of studies

The main limitations in Paper I is the completeness of reporting and uncertainty of data quality in register-based studies. However, analyzing survival is not affected by this data quality and the large number of patients reduces impact of possible uncertainty associated with single patients.

Paper II and III were prospective studies with the main focus being exploration of HRQL in glioma patients. Since Paper II was the first paper on this topic with the use of EQ-5D we explored many potential variables with a high-risk of false-positive findings (type I error). The results from this study should therefore be considered hypothesis generating. In addition, the high non-compliance may limit the external validity of the findings. In Paper III a less explorative approach was used. However, the use of postoperative predictors together with

preoperative predictors may treat the preoperative factors with unjust since more information is clearly available in the follow-up period.

The limitation in Paper IV is mainly the retrospective data collection. Also, occasional patients, such as elderly with considerable co-morbidity, may have been followed with "wait-and-scan" without histopathological confirmation, although rarely in both institutions. Unfortunately we had no information on resection grades. As we compared different treatment strategies another potential bias is the possibility of sampling error in brain tumor histopathology. Studies comparing the diagnostic accuracy of biopsy with resection have reached conflicting results.[84,85] Altogether with histopathological inclusion criteria this is an unavoidable drawback and potential criticism to any study comparing resection and biopsy. To overcome this challenge a prospective study in suspected low-grade gliomas based on radiographic findings would need to be conducted. It may also be argued that the threshold for biopsy could differ between institutions and thereby recruiting more patients with worse prognosis at one centre. However, in Norway the LGG diagnosed with imaging only is low and stable around 0.1/100,000 per year.[86] With balanced baseline data and similar incidence rates in both geographical regions it seems unlikely that the study findings only reflect skewed patient recruitment or the diagnostic accuracies of the two procedures. With respect to morbidity that was the secondary end-point, the strategy with regional comparison is not the most sensitive for detecting differences.

Ethical considerations

All studies were approved by the Regional Committee for Medical Research Ethics in Health Region Mid-Norway.

Paper II and III were prospective and based on informed consent. The need for informed consent was waived by the Regional Committee for Medical Research Ethics in Paper I and IV.

Summary of Papers

Paper I

Incidence and causes of perioperative mortality after primary surgery for intracranial tumors: a national, population-based study

Solheim O, Jakola AS, Gulati S, Johannesen TB

Journal of Neurosurgery. 2012;116(4):825-834.

Surgical mortality is a frequent outcome measure in studies of volume-outcome relationships, and the Agency for Healthcare Research and Quality has endorsed surgical mortality after craniotomies as an Inpatient Quality Indicator. Still, the frequency and causes of 30-day mortality after neurosurgical procedures have not been much explored. We sought to study the frequency and possible causes of death following primary intracranial tumor operations. We also sought to explore a possible predictive value of perioperative mortality rates from neurosurgical centers in relation to long-term survival.

Using population-based data from the Norwegian cancer registry we identified 15,918 primary operations for primary CNS tumors treated in Norway in the period from August 1955 through December 2008. Patients were followed up until death, emigration, or September 2009. Causes of mortality as indicated on death certificates were studied. Factors associated with an increased risk of perioperative death were identified.

The overall risk of perioperative death after first-time surgery for primary intracranial tumors is currently 2.2% and has decreased over the last decades. An age ≥ 70 years and histopathological entities with poor long-term prognoses are risk factors. Overlapping lesions are also associated with excess risk, indicating that lesion size or multifocality may matter. The overall risk of perioperative death is also higher in biopsy cases than in resection cases. Perioperative mortality rates of the 4 Norwegian neurosurgical centers were not predictive of their respective long-term survival rates.

Although considered surgically related if they occur within the first 30 days of surgery, most early postoperative deaths can happen independent of the handiwork of the operating surgeon or anesthesiologist. Overall prognosis of the disease seems to be a strong predictor of perioperative death—perhaps not surprisingly since the 30-day mortality rate is merely the intonation of the Kaplan-Meier curve. Both referral and treatment policies at a neurosurgical center will therefore markedly affect such early outcomes, but early deaths may not necessarily reflect overall quality of care or long-term results. The low incidence of perioperative death in intracranial tumor surgery also greatly limits the statistical power in comparative analyses, such as between published patient series or between centers and certainly between surgeons. Therefore we question the value of perioperative mortality rates as a quality indicator in modern neurosurgery for tumors.

Paper II

Quality of life in patients with intracranial gliomas - the impact of modern image guided surgery

Jakola AS, Unsgård G, Solheim O

Journal of Neurosurgery. 2011;114(6):1622-1630.

Outcome following brain tumor operations is often assessed by health professionals using various gross function scales. However, surprisingly little is known about how modern glioma surgery affects quality of life (QOL) as reported by the patients themselves. In the present study the authors aimed to assess changes in QOL after glioma surgery, to explore the relationship between QOL and traditional outcome parameters, and to examine possible predictors of change in QOL.

Eighty-eight patients with glioma were recruited from among those 16 years or older who had been admitted to the authors' department for brain tumor surgery in the period between January 2007 and December 2009. A 3D ultrasonography–based navigation system was utilized in nearly all operations and functional MR imaging data on eloquent lesions were incorporated into the neuronavigation system. Preoperative scores for QOL (EuroQol 5D [EQ-5D]) and functional status (Karnofsky Performance Scale [KPS]) were obtained. The EQ-5D and KPS scores were subsequently recorded 6 weeks postoperatively, as were responses to a structured interview about new deficits and possible complications.

There was no change in the median EQ-5D indexes following surgery, 0.76 versus 0.75 ($p = 0.419$). The EQ-5D index value was significantly correlated with the KPS score ($p < 0.001$; rho = 0.769). The EQ-5D index values and KPS scores improved in 35.2% and 24.1% of cases, were equal in 20.5% and 47.2% of cases, and deteriorated in 44.3% and 28.7%, respectively. Thus, both improvement and deterioration were underestimated by the KPS score as compared with the patient-reported QOL assessment. New motor deficits ($p = 0.003$), new language deficits ($p =0.035$), new unsteadiness and/or ataxia ($p = 0.001$), occipital lesions ($p = 0.019$), and no use of ultrasonography for resection control ($p = 0.021$) were independent predictors of worsening QOL in a multivariate model.

The surgical procedures per se may not significantly alter QOL in the average patient with glioma; however, new deficits have a major undesirable effect on QOL. It seems that the active use of intraoperative ultrasonography may be associated with a preservation of QOL. The EQ-5D seems like a good outcome measure with a strong correlation to traditional variables while offering a more detailed description of outcome.

Paper III

Postoperative deterioration in health related quality of life as predictor for survival in patients with glioblastoma: a prospective study

Jakola AS, Gulati S, Weber C, Unsgård G, Solheim O

PLoS ONE. 2011;6(12):e28592.

Studies indicate that acquired deficits negatively affect patients' self-reported health related quality of life (HRQL) and survival, but the impact of HRQL deterioration after surgery on survival has not been explored. We aimed to assess if change in HRQL after surgery is a predictor for survival in patients with glioblastoma.

Sixty-one patients with glioblastoma were included. The majority of patients (n=56, 91.8 %) were operated using a neuronavigation system which utilizes 3D preoperative MRI and updated intraoperative 3D ultrasound volumes to guide resection. HRQL was assessed using EuroQol 5D (EQ-5D), a generic instrument. HRQL data were collected 1-3 days preoperatively and after 6 weeks. The mean change in EQ-5D index was -0.05 (95 % CI -0.15 – 0.05) 6 weeks after surgery (p=0.285). There were 30 patients (49.2 %) reporting deterioration 6 weeks after surgery. In a Cox multivariate survival analysis we evaluated deterioration in HRQOL after surgery together with established risk factors (age, preoperative condition, radiotherapy, temozolomide and extent of resection).

There were significant independent associations between survival and use of temozolomide (HR 0.30, p=0.019), radiotherapy (HR 0.26, p=0.030), and deterioration in HRQL after surgery (HR 2.02, p=0.045). Inclusion of surgically acquired deficits in the model did not alter the conclusion.

Early deterioration in HRQL after surgery is independently and markedly associated with impaired survival in patients with glioblastoma. Deterioration in patient reported HRQL after surgery is a meaningful outcome in surgical neuro-oncology, as the measure reflects both the burden of symptoms and treatment hazards and is linked to overall survival.

Paper IV

Comparison of a Strategy Favoring Early Surgical Resection vs a Strategy Favoring Watchful Waiting in Low-Grade Gliomas.

Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgård G, Solheim O.

JAMA. 2012:Nov 14;308(18):1881-8

There are no controlled studies on surgical treatment of diffuse low-grade gliomas (LGGs), and management is controversial.

Objective was to examine survival in population-based parallel cohorts of LGGs from 2 Norwegian university hospitals with different surgical treatment strategies.

Both neurosurgical departments are exclusive providers in adjacent geographical regions with regional referral practices. In hospital A diagnostic biopsies followed by a “wait and scan” approach has been favored (biopsy and watchful waiting), while early resections have been advocated in hospital B (early resection). Thus, the treatment strategy in individual patients has been highly dependent on the patient's residential address. Histopathology specimens from all adult patients diagnosed with LGG from 1998 through 2009 underwent a blinded histopathological review to ensure uniform classification and inclusion. Follow-up ended April 11, 2011. There were 153 patients (66 from the center favoring biopsy and watchful waiting and 87 from the center favoring early resection) with diffuse LGGs included.

The prespecified primary end point was overall survival based on regional comparisons without adjusting for administered treatment.

Initial biopsy alone was carried out in 47 (71%) patients served by the center favoring biopsy and watchful waiting and in 12 (14%) patients served by the center favoring early resection ($P < .001$). Median follow-up was 7.0 years (interquartile range, 4.5-10.9) at the center favoring biopsy and watchful waiting and 7.1 years (interquartile range, 4.2-9.9) at the center favoring early resection ($P = .95$). The 2 groups were comparable with respect to baseline parameters. Overall survival was significantly better with early surgical resection ($P = .01$). Median survival was 5.9 years (95% CI, 4.5-7.3) with the approach favoring biopsy only while median survival was not reached with the approach favoring early resection. Estimated

5-year survival was 60% (95% CI, 48%-72%) and 74% (95% CI, 64%-84%) for biopsy and watchful waiting and early resection, respectively. In an adjusted multivariable analysis the relative hazard ratio was 1.8 (95% CI, 1.1-2.9, $P = .03$) when treated at the center favoring biopsy and watchful waiting.

In conclusion, for patients in Norway with LGG, treatment at a center that favored early surgical resection was associated with better overall survival than treatment at a center that favored biopsy and watchful waiting. This survival benefit remained after adjusting for validated prognostic factors.

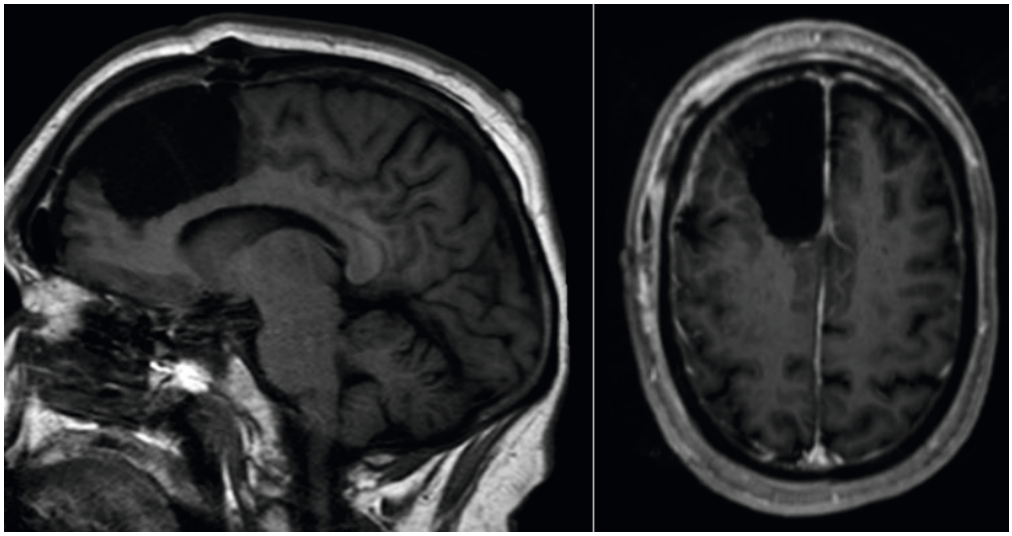
Discussion

Innovations and achievements in surgical treatment of diffuse gliomas

The first reported brain tumor surgery was performed in 1884 by Godlee and Bennett.[87] Since then, many new concepts have been introduced to benefit the patients with neurosurgical conditions in general.[74] Cushing performed his first brain tumor operation using monopolar electrocautery in 1926, an achievement in close collaboration with its inventor, William Bovie.[88] Bipolar electrocautery made commercially available by Leonard Malis in 1955,[88,89] the appearance of the ultrasonic aspirator in neurosurgery in the late 1970's[90] and the emergence of neuronavigation systems have moved the field of glioma surgery forward. Further, the introduction of the microscope in a neurosurgical operating theater first described in 1957,[74] was the fundament for the modern field of microneurosurgery and its many advances. With these surgical tools in hand the surgical procedures may be performed more targeted, perhaps more radical, but also gentler and safer than before. However, the field has continued to be influenced by technical improvements also in the last decades(s). Several visualization techniques and functional techniques have moved into the operating room with special emphasis on detecting the border between tumor and normal tissue. There are promising reports with intraoperative use of 3D ultrasound,[67,91,92] intraoperative MRI[14,93,94] or the use of 5-ALA which makes high grade gliomas visible under fluorescent light.[15,26,45,95] The functional border may also be assessed intraoperatively using various sorts of mapping.[16,17,96,97] It is not a problem to find ambassadors for the use of a certain tool, but in what way has this improved care for patients? First of all, brain tumor surgery is much safer than it was in the beginning.[73,74] Paper I demonstrates that the risk of perioperative death has gradually declined the last four decades.[73] In glioma surgery important answers concerning benefits have been provided in later years. There seems to be a survival advantage when GTR is achieved in surgical treatment of glioblastomas.[45] Results provided in this thesis also significantly strengthen the evidence in support of early and extensive surgery for diffuse LGGs.[20] Still, the level of evidence in neurosurgery as a field remains poor, and it is necessary

to both improve quality of future research and to continue the tradition with technical innovation.[98]

Figure 3



Early postoperative MRI images following resection of an anaplastic glioma (WHO grade 3) in the right frontal lobe. The primary operation was performed in 2007 and adjuvant radiotherapy and chemotherapy was administered. The patient is doing well (2012) except for persistent fatigue and some cognitive impairment.

Improving quality in neurosurgical research

As seen, neurosurgery is a highly technical field where innovations and developments of new techniques have been embraced and quickly integrated. There is no doubt that improved diagnostics and refinement of surgical tools and techniques have increased safety in brain tumor surgery.[74] Even though neurosurgery can clearly be performed more safely than before, the evidence for performing the operations in the first place can be paradoxically low. This is problematic and has contributed to large local variations in practice based on personal experience and tradition more than scientific evidence.

When evaluating innovative strategies and tools, the neurosurgical researchers have focused on case-series rather than randomized controlled trials.[24,98] This makes the evaluations prone to selection bias and assessment bias and in the end it may be difficult to tell the treatment effect from prognostic factors or confounding variables. On the other hand, the surgical specialties constantly change with minor adjustments of tools and techniques. Such small adjustments are not in isolation expected to contribute to significant differences in outcome.[81] The clinical benefit of each new tool to a steadily increasing arsenal of possibilities is no longer obvious as perhaps was the situations by some earlier innovations (e.g. the operating microscope).[99] Since most current improvements are of lesser magnitude a development should be reflected in the neurosurgical research by improved scientific methodology, and in fact a few methodological high-quality studies were published recently.[14,26] It needs to be acknowledged that surgical research is different and more complex compared to pharmaceutical research, and the conventional randomized trial is not always feasible. There may also be situations where only minor modifications are performed to techniques and tools may not be proper for testing in time-consuming and costly trials since detection of important clinical difference is unlikely. Randomized controlled trials, although desired, is not necessarily the solution if clinical equipoise is no longer the case. As experienced in a randomized controlled trial assessing neuronaviagtion in glioma surgery, clinical equipoise was present in very few patients (16 % of total), seriously threatening external validity.[100] Due to the inclusion criteria the patient recruitment was consequently very slow and if continuing in the same pace would need 11 years to reach the prespecified sample size, a discouraging finding presumably leading to the early discontinuation of the trial.[100] Despite the best intentions the trial is not capable of guiding treatment decisions and in practice neurosurgeons discard the results. However, proper randomized trials should be conducted in situations where important difference in surgical strategies exist.[81] Initiatives to improve methodology of surgical research and innovation should be acknowledged and supported.[99,101-103] In example, evaluation of surgical innovation described stepwise as IDEAL[101] (Innovation, Development, Exploration, Assessment, Long-term) is helpful for recognizing the stages of innovation and it provides a useful framework when deciding on the most appropriate study design and outcome for the current stage. Another important way to improve quality of surgical research would be increased use of prospective designs, reduce bias in outcome assessment, and reporting outcome measures in a standardized fashion.

Evidence based versus technology driven research

It is often claimed that when several presumably equally good options exist, none of the options are actually good and neither is superior to the other. However, to reach such conclusions the hypothesis should be subject to rigorous investigation. In diffuse LGG patients the surgical options were steadily increasing for decades, each having their advocates. And as pointed out by others, a randomized trial seemed unlikely in the future as well, much due to the infrequent nature of the disease, the need for long follow-ups in combination with strong and diverse local treatment traditions.[50,52,104,105] The various tools and techniques developed and marketed for the use in diffuse LGG operations includes neurophysiological monitoring and various forms of neuronavigation and intraoperative imaging. Paradoxically, there was limited evidence supporting that diffuse LGG patients benefit from surgery in the first place since the common research strategy had been to investigate the results using the tool available without comparing strategies or different tools. Within this myriad of strategies and tools some of the differences were perhaps of a magnitude that could be clinical important? And is there a way to perform a reliable comparative study? This was the situation we were dealing with in Paper IV.[20] Researchers occupied with diffuse LGG had failed to assess efficacy of a certain strategy or procedure against other strategies, making almost every strategy being locally considered as established good practice. However, in recent years an increasing *amount* of papers supporting surgical resection were published,[6] but the strength of evidence remained equally low since only case-series with different tools were conducted. Even though case-series and registries provide information on treatment results and safety, the treatment efficacy cannot always be properly assessed in this manner. As a consequence of this complete lack of consensus we identified a marked regional difference in treatment strategy between two centers in Norway – a difference so large that we considered it a natural occurring experiment. With a pragmatic design with histopatholoical inclusion criteria we were able to analyze the difference in treatment policy, a conservative statistical approach when searching for a difference. With this study we were able to provide the first properly controlled surgical study on diffuse LGG, and it now seems clear that the preferred surgical strategy should be resection in most cases. However, while the improvement in survival was a result of innovations and technical developments, introduction was based on scarce evidence.

While only 8% of patients with histologically diagnosed LGGs in Norway underwent resections in the 1980s, the percentage has increased to 80% on a National level today (source: Norwegian Cancer registry). Modern neuroimaging, neuronavigation and intraoperative imaging have facilitated the aggressive surgery seen in many centers today. Based on the observation that tumors recurred locally work was done at our institution to improve quality of resections. This ultimately led to the development of a 3D ultrasound based neuronavigation system that facilitated the aggressive strategy at our institution from the late 1990's.[91,106] Fortunately, our data now show that the radical change in surgical aggressiveness made possible by this technology has contributed to improved patient survival.[20,107] This was not obvious when the pioneers in the field promoted the idea and this demonstrates how a surgical field may evolve as a consequence of technical innovation.

It should be acknowledged that some conditions are not optimal for a conventional randomized trial, and patients may even be unwilling to undergo randomization for radically different interventions in brain tumor surgery.[81] However, with good collaboration between institutions better studies with higher level is of evidence is achievable, and this should be the goal also in a technology driven field like neurosurgery.

Modernized outcome measures

In this thesis both old and new outcome measures are explored. Perioperative death rate is considered a quality indicator and the publications of death rate have traditionally been important in neurosurgery.[74] In Paper I we examined a national cohort from 1955 through 2008 with 15,918 primary operations with respect to frequencies and differences in perioperative death rate and it relation to long-term outcome. Due to the very infrequent occurrence of death within 30 days of intracranial tumor surgery the comparison of perioperative death does not seem very meaningful in a modern context.[73] However, such numbers are still important to acknowledge the risk of an intervention, and it should perhaps still be a part of regular work in quality assurance. The main focus in Paper II and III was HRQL, a relatively new measure in neurosurgery.[46,77,78] PROs were the natural next step in neurosurgical research, mainly for two reasons: 1) it's a trend in medicine to move away from paternalistic care to patient-centered care and 2) the clinical benefit of a new intervention and

tool is no longer obvious in terms of hard clinical end-points such as perioperative death rate or overall survival. To evaluate changes of an intervention a more sensitive tool was needed, and with PROs we are able to do patient-centered research as well. Even though we reported average values using EQ-5D index, the impact for individual patients may naturally differ. Also, significant changes, was not established for EQ-5D in this cohort of patients. However, it is common to consider 0.07-0.10 to represent a minimal important difference,[108-110] and determination of the minimal important difference in EQ-5D for brain tumor patients is part of our group's further research strategy. With the use of minimal important difference the results of the less intuitive HRQL-scores become more meaningful for clinicians and patients.

Another positive aspect of PROs is its prospective nature, which is a necessary step in the right direction for neurosurgical research. To best assess the effect of a procedure a preoperative, early postoperative (weeks) and late postoperative (months to years) assessments should be done. Patients treated with intracranial tumors at St. Olavs University Hospital are now invited to be part of such prospective research on HRQL. To us this is a major improvement and clearly a reduction of bias compared to surgeons' evaluations of own results in retrospect which is still a fairly common practice.

In this thesis we utilized a generic instrument (EQ-5D). Although less sensitive for the specific patient group, it still offers the patient perspective in a less biased manner. EQ-5D is simple, a feature that may be of benefit in patients with cognitive disturbances. Also, the short and simple format reduce questionnaire burden and may improve inclusion rates and patient compliance. In addition, being generic it is also possible to compare across diseases. There are also disease specific HRQL measures available for patients with brain tumor. The EORTC QLQ-C30 consist of cancer specific questions in addition to assessment of overall health and HRQL.[111] A brain tumor specific module called EORTC QLQ-BN20 is also available and intended for use together with the QLQ-C30. [112] These questionnaires are more sensitive since they consist of 50 questions compared to the 5 questions in EQ-5D. They are still not developed for the evaluation of neurosurgical interventions, but are developed by oncologists. As a consequence the questionnaires focus less on effects of brain surgery, but more on known adverse reactions to chemotherapy and radiotherapy. Not to be underestimated in this context is the psychological distress of answering 50 questions pre-operatively related to cancer and brain tumor in patients without a histopathological diagnosis. Also, the questionnaire burden is high if several follow-up assessments are scheduled. The different

properties of the generic and disease specific PRO measures should be carefully considered when planning a study. In general, the disease specific measures should perhaps be chosen in comparative studies since the higher sensitivity makes them better equipped to identify between groups differences.

Comparing outcome

To fairly compare results between centers, regions or countries or study groups, several factors need to be considered. The factor probably being most important for achieving good results in surgery, and perhaps in every medical discipline, is the selection of patients. This was exemplified in a recent study.[113] However, outside clinical trials patient selection is difficult to control, but clear reporting of eligibility criteria, predictors, follow-up and data collection, as stated in the STROBE statement,[114] ensures transparency and this again could allow for more just comparisons. In addition, to compare more honestly, at least co-morbidity[23,115] and the clinical condition[29] should be adjusted for to prevent the results from just reflecting the institutions' case-mix.

Unfortunately comparing across studies, to reach self-evident conclusions on the basis of case-mix, is not uncommon. Recently a meta-analysis receiving much attention on intraoperative stimulation was published. In the pooled analysis of mainly retrospective case studies, increased early morbidity rates and lower late morbidity rates were seen when intraoperative stimulation was in use, and the authors concluded that intraoperative stimulation should be standard of care in glioma surgery.[116]. However, attempts at scientific alchemy by constructing hard evidence from pooling weak evidence are often dubious, as the weaknesses are also pooled. Also, there are reasons to argue that the generalization to everyday glioma surgery, recommending universal use of intraoperative stimulation mapping, is problematic and scientifically unjustified. Low-grade gliomas and HGGs were analyzed together in the meta-study. Although biologically related, the disease courses, age groups, presenting symptoms, aims of treatment, treatments, surgical results in terms of functional outcomes and resection grades, and the use of surgical tools are clearly very different. In unselected patients with glioblastoma survival is still only 10 months[117] and the impact of surgery on survival remains modest even in highly selected patients.[26] Any new deficits in

patients with HGGs (also early deficits) are clearly negative and should not be compromised against extents of resection since early deficits have a direct negative impact on HRQL.[78] The younger and often highly functional LGG patient may also tolerate a deficit better, equivalent to better outcomes in younger patients with traumatic brain injury.[118,119] Thus, comparing results after intraoperative stimulations in LGGs with results from operations without intraoperative stimulations in patients with HGGs, is really like comparing apples and oranges. The HGG publications, which were overrepresented in the non-stimulation group, probably contribute with higher morbidity due to the disease itself and morbidity was indeed higher in HGG surgery (6.4% vs 3.4% late deficits). Since the aims of surgery are so different in LGG and HGG, outcome should also have been analyzed or reported differently. The conclusion of the meta-study may just as well have been: avoid intraoperative stimulation in HGGs as it increases the chance of early deficits.

Another necessary factor for a meaningful comparison of risks and benefits between studies or patient groups is the use of standardized outcome measures. The heterogeneity in assessment with respect to definitions, timing and length of follow-up precludes reproduction and meaningful comparisons of techniques, studies and institutions. Today's practice assessment of brain tumor surgery includes crude measures in a myriad of different ways. In example, even the assessment of perioperative morbidity has until recently not been reported in a standardized manner.[49,103] From another surgical discipline a review of 107 studies identified 56 different definitions of anastomotic leak after gastrointestinal surgery,[99,120] and there is no reason to believe that the neurosurgical literature is more consistent. There is also much potential for both bias and conflicts of interests in the common neurosurgical series where the operating surgeon is to rule on whether surgery was a success or not. The recently published Ibañez classification[103] attempt to introduce a standard way of reporting complications in neurosurgery, but researchers in clinical neurosurgery are still lacking a feasible tool for assessment of severity and frequency of neurological sequelas. As demonstrated in this thesis, PROs is a valuable adjunct that may have potential as an outcome parameter in brain tumor surgery.[46,78] Cognitive assessment,[57,121,122] albeit not offering the patients' perspective, offers a more standardized, detailed and perhaps more relevant assessment in modern neurosurgery than the traditional outcome measures.

Further innovation and refinement

Diffuse gliomas located within regions perceived to contain critical neurological functions (eloquent regions) is associated with impaired survival compared to patients with gliomas in other regions of the brain.[123] This difference is most likely explained by less extensive resection in an attempt to avoid surgically acquired deficits.[11] In modern neurosurgery various tools are available to improve resection and safety. But despite the use of intraoperative MRI,[14,93] 3D ultrasound[13,124,125] and intraoperative mapping[11,17,116,126] these patients remain a challenge. In example, it is not uncommon that patients with gliomas deteriorate in language and memory functions postoperatively (i.e. cognitive functions).[121,122] These functions may be at particular risk if the tumor is involving language areas.[121] Thus, further innovation and refinement of preoperative assessment together with surgical tools and techniques should be encouraged. Also, the combination of techniques may also be beneficial.[127,128]

Despite the fact that surgery is no cure for diffuse gliomas it is still a very important treatment modality both for obtaining tissue diagnosis and for improving survival if safe and radical resection are performed. In the short term HRQL is not improved after surgery in the average patient with diffuse glioma.[78,100] This is perhaps no surprise since little may be gained in patients with diffuse LGG having subtle symptoms and in HGG patients the short term gain may be modest after the effect of corticosteroids. However, tapering of corticosteroids may be possible after surgery – and this may presumably allow patients to maintain their perioperative HRQL for a longer period before signs of progression again occur. Even though patients as a group did not seem to get short-term benefit from the surgical treatment with respect to HRQL it is necessary to emphasize that differences in terms of significant subjective changes were not analyzed. It is suggested from our study that about half of the patients with glioma remain stable or improve early after surgery.[78] In assessment of cognitive functions pre- and postoperatively the numbers are quite similar.[121,122] This may indicate that cognitive problems are strongly correlated with HRQL, perhaps even more so than physical symptoms (e.g. a limb paresis).[123,129] This may be especially true in LGG patients with time for rehabilitation and response shift.[77] Despite major technical improvements to date in brain tumor surgery patients still experience a high symptom burden and further improvements to maximize HRQL is needed.

It has to be remembered that safety should remain the primary goal and it should not be jeopardized as acquired deficits clearly reduces HRQL[78] and an association with impaired survival has been reported, at least in HGG.[46,47] One theory linking survival with acquired deficits is that surgery may lead to vascular damage causing regional hypoxia. This hypoxia in relation to the tumor site may induce the remaining tumor cells to migrate leading to increased local invasion.[48] Our research group is currently investigating the amount of circulatory alterations, as defined by diffusion weighted MRI,[130,131] occurring after glioma resections and the possible association with acquired deficits. Follow-up studies from this work may be able to detect possible differences in recurrence patterns or time to recurrence in patients with or without MRI detected circulatory alterations. However, it is not only the neurological complications that influence outcome. A recent study demonstrated an association between complications (not associated with new deficits) and decreased survival, a finding possibly related to deferral of postoperative adjuvant treatment.[49] This suggests the obvious that a high quality of care is needed in all aspects of patient management.

In the further process of innovation and refinement it is important not only to rely on case-series without controls. During the late exploration phase of surgical innovation the procedure or tool is starting to lose its experimental nature and becoming familiar to many surgeons. For conducting an assessment study on efficacy, this has been suggested to be the critical time point.[99,101,102] Afterwards it will often be widely adopted, and deserved or not, regarded as established good practice. However, if missing a step in the innovative hierarchy it is important to continue to monitor the effects, either through prospective cohort studies or clinical registries. Even though the efficacy of the procedure is better evaluated in controlled and preferably randomized studies, the benefit-to-harm ratio of the procedure may be monitored in this manner. Also to be emphasized is that slight adjustments of existing techniques or tools are probably poor candidates for randomized trials as important clinical difference is unlikely.

Primum non nocere

Despite improved safety in brain tumor surgery there is still room for improvement, and it is still considered a high-risk field of surgery.[132] A recent publication summarizes the main

focus areas for prevention of adverse events in intracranial tumor surgery, and they mention several strategies including systematic work to reduce deep-vein thrombosis, seizures, and infection.[132] To reduce surgical related morbidity it is crucial to identify the risks associated with surgery in individual patients, but this is not always an easy task. Neurosurgeons have perhaps been less focused on the systemic complications of treatment, but rather on neurological risks and particularly interest for the tumor's relationship to certain critical regions, a factor being of major importance in clinical decision making. However, anatomical eloquence which neurosurgeons have heavily relied on in the past is not reliable enough in individual patients.[133] With the increased possibilities in modern technologies in preoperative planning with fMRI and DTI,[13,124,134] intraoperative imaging[14,125] and functional mapping[17,126] the boundaries have been pushed towards more aggressive surgery without a clear increase in neurological risks. Even though surgical cure of diffusely infiltrating gliomas is yet to be demonstrated, we are now able to remove larger part of the tumor in a safer way, and as stated by Kelly in a famous editorial: "we just do not hurt patients as badly as we did 40 years ago".[135] However, we would discourage nihilism when caring for these patients since radical resection of HGG[45] and an aggressive strategy in LGG (Paper IV)[20] improves survival, and radical resection may act synergistically with adjuvant therapy in HGG.[42,60,61]

Recommendations for future research

Based on this thesis a few future research recommendations can be made. First, as a field is moving forward there is a need for adjusting the outcome measures similarly. As an example, comparing institutions on the basis of perioperative mortality after craniotomy seems outdated. It may also be advisable to supplement the crude physicians rated outcome measures, like KPS, with more detailed and patient centered outcome measures. This would provide prospective and less biased research findings. Second, where genuine uncertainty exists (clinical equipoise) between strategies or tools believed to be clinically important a randomized trial should be the default setting for researchers also in neurosurgery. There is now an active debate on resection grades "threshold" for achieving survival benefit in patients with glioblastoma.[45,136-138] Whether or not to perform non-radical debulkings in lesions where radical resection is not expected should be subject to a rigid and adequately powered randomized controlled trial. Third, a practical tool for assessing neurological function (a clinimetric equivalent to the NIH stroke scale for patients with stroke)[139] should be accessible

for evaluating brain tumor patients. With a reliable and efficient tool that preferably could be integrated into clinical practice, researchers would be better equipped to assess perioperative neurological function in a standard way and thereby enhance possibilities for comparisons. In fact, clinical trials are dependent on a sensitive and reliable outcome measure to detect both deterioration and improvement. Together with the Ibãnez classification for complications such a tool would also better illuminate the periopeartive risks and benefits associated with brain tumor surgery.

Conclusions

This thesis investigated the risks and benefits associated with surgical treatment of brain tumors and the following conclusions can be drawn:

- Overall tumor prognosis is a strong predictor of perioperative death. The low incidence of perioperative death in intracranial tumor surgery limits the statistical power in comparative analyses, such as between published patient series or between centers and certainly between surgeons. Therefore the value of perioperative mortality rates as a quality indicator in modern neurosurgery for intracranial tumors may be questioned.
- Surgically acquired deficits have a major undesirable effect on HRQL measured with a generic instrument. EQ-5D seems like a good outcome measure with a strong correlation to traditional variables while offering a more detailed and less biased description of outcome.
- Early deterioration in HRQL after surgery is independently and markedly associated with impaired survival in patients with glioblastoma. Deterioration in patient reported HRQL after surgery is a meaningful outcome in surgical neuro-oncology, as the measure reflects both the burden of symptoms and treatment hazards and is linked to overall survival.
- Early surgical resection improves survival as compared to biopsy and subsequent watchful waiting. Resection should be the initial treatment option in most patients with LGG.

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Postoperative Deterioration in Health Related Quality of Life as Predictor for Survival in Patients with Glioblastoma: A Prospective Study

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Abstract

Background: Studies indicate that acquired deficits negatively affect patients' self-reported health related quality of life (HRQOL) and survival, but the impact of HRQOL deterioration after surgery on survival has not been explored.

Objective: Assess if change in HRQOL after surgery is a predictor for survival in patients with glioblastoma.

Methods: Sixty-one patients with glioblastoma were included. The majority of patients (n = 56, 91.8%) were operated using a neuronavigation system which utilizes 3D preoperative MRI and updated intraoperative 3D ultrasound volumes to guide resection. HRQOL was assessed using EuroQol 5D (EQ-5D), a generic instrument. HRQOL data were collected 1–3 days preoperatively and after 6 weeks. The mean change in EQ-5D index was −0.05 (95% CI −0.15–0.05) 6 weeks after surgery (p = 0.285). There were 30 patients (49.2%) reporting deterioration 6 weeks after surgery. In a Cox multivariate survival analysis we evaluated deterioration in HRQOL after surgery together with established risk factors (age, preoperative condition, radiotherapy, temozolomide and extent of resection).

Results: There were significant independent associations between survival and use of temozolomide (HR 0.30, p = 0.019), radiotherapy (HR 0.26, p = 0.030), and deterioration in HRQOL after surgery (HR 2.02, p = 0.045). Inclusion of surgically acquired deficits in the model did not alter the conclusion.

Conclusion: Early deterioration in HRQOL after surgery is independently and markedly associated with impaired survival in patients with glioblastoma. Deterioration in patient reported HRQOL after surgery is a meaningful outcome in surgical neuro-oncology, as the measure reflects both the burden of symptoms and treatment hazards and is linked to overall survival.

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Competing Interests: Prof. Unsgård has approximatly 0.1% of the stocks in SonoWand, the company making the neuronavigation system. All operations were performed under general anesthesia. The SonoWand® neuronavigation system was available if requested by the surgeon and was used in 56 (91.8%) of the operations. There are no patents, products in development, or marketed products to declare. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials, as detailed online in the guide for authors.

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Introduction

Surgical studies in patients with glioblastoma have focused much on resection grades and maximal safe resection is usually advocated. However, measurements of both extents of resection and safety vary between studies and there are few controlled trials. Due to non-uniform inclusion criteria and assessments of outcomes, direct comparison of results and techniques are difficult, if not impossible [1]. Nevertheless, it seems like resections need to be extensive to improve survival, but the resection grade threshold for a probable clinical benefit remains debated [2–4]. Safety is less often assessed and there is no uniform and accepted method for reporting of adverse events in surgical trials [5]. Often clinicians or operating surgeons report clinical outcomes in gross functional scales with a potential of assessment and interest bias.

The combination of this ultimately fatal disease with the delicate balance between potential effect and hazards of surgery makes patients' perioperative HRQOL of particular interest. However, the impact of glioblastoma surgery on patient reported outcomes has not been explored much [6]. We have earlier described possible predictors of HRQOL in patients undergoing glioma surgery. The study clearly demonstrated the devastating effect of acquired deficits on patient reported HRQOL [7]. A recent paper found that surgical acquired deficits may be associated with decreased survival as well [8], but the possible impact of postoperative loss of HRQOL on survival has not been explored.

In the present prospective study we aimed to assess if changes in HRQOL after surgery added any prognostic information to the already established risk factors.

Materials and Methods

Ethics statement

All patients included have given their written and informed consent. The Data Inspectorate in Norway approved registration and management of data. The study was approved by the Regional Ethical Committee for Health Region Mid-Norway.

Methods

Study subjects were recruited from patients aged ≥18 years admitted to our department for scheduled brain tumor surgery, in the period from January 2007 through December 2010. Patients were followed until death or until May 15th, 2011. Survival was calculated from the date of surgery. Only patients with histopathological confirmed glioblastoma according to the WHO classification were included in this study. Patients provided written informed consent and filled out the EuroQol 5D (EQ-5D) questionnaire 1–3 days before surgery. A study nurse scored preoperative Karnofsky Performance Status (KPS) on admission. Patient follow-up by a study nurse was scheduled at 6 weeks (median time to follow up: 47 days) after surgery. We decided to use 6 weeks to allow for some recovery from transient surgically induced deficits. In addition, few patients experience significant tumor progression in this time frame. At this time point some patients may have started adjuvant therapy and this could influence the HRQOL, however this is expected to be the same between the groups and therefore unlikely to influence the results. Adverse effects are also quite rare during the initiating phase of adjuvant radiotherapy and/or concomitant temozolomide treatment. Structured interviews were used to assess HRQOL (EQ-5D) using the same questionnaire as preoperatively. The patients were also interviewed about possible complications, acquired and/or worsened deficits (motor, language, vision, unsteadiness and other) and altered mental functions (memory, personality and other) experienced after the procedure. Only patients with complete HRQOL data were included in the analyses. Tumor volumes and resection grades were determined from preoperative and early postoperative MRI volumes using an ellipsoid model ($4\Pi \times r^3/3$), as described by others [9]. Gross total resection (GTR) was defined as no visible contrast enhancing tumor tissue on the early (<72 hours) postoperative 1.5 T or 3.0 T MRI scans.

Study population

Sixty-seven patients with glioblastoma were included from baseline, but 6 (9.0%) patients did not complete the EQ-5D questionnaire after surgery. All patients who did not respond were dead at last follow-up. Three were lost to follow-up as they were already dead or in a terminal condition at 6 weeks, whereas the other three patients who were lost to follow- up lived for a median 30 weeks. The only in-hospital registered complication among these six patients was seizures in one patient who had no seizures preoperatively. Median preoperative HRQOL for these six patients was 0.59 (range 0.27–0.74).

Sixty-one patients had complete EQ-5D forms before and after surgery and were included in the analyses. Clinical characteristics are presented in Table 1. The mean age of included patients was 58 years (range 26–81) and 29 (47.5%) were female. The median preoperative KPS was 80 and 84.7% were functionally independent (KPS 70–100). Thirty eight (62.3%) of the operations were primary and 23 (37.7%) were reoperations.

Surgical procedure

All operations were performed under general anesthesia. The SonoWand® neuronavigation system was available if requested by the surgeon and was used in 56 (91.8%) of the operations. The system utilizes 3D preoperative MRI and updated intraoperative 3D ultrasound volumes to guide resection [10]. In eloquent lesions functional neuronavigation was incorporated utilizing a method described in detail earlier [11,12]. Functional MRI and diffusion tensor imaging data was incorporated into the system in 19 (31.1%) and 23 (37.7%) of the operations respectively. Sixty (98.4%) of the 61 included patients underwent craniotomy and tumor resection. One patient underwent biopsy only. The median preoperative tumor volume was 18.4 cm^3 and the median resection grade was 96.3% with GTR achieved in 24 (39.3%) of the patients.

Table 1. Clinical characteristics of the patient population.

Clinical characteristics	No. (%)
Age (mean, range)	58 years (28–81)
Female	29 (47.5)
Preoperative KPS[a] (median, range)	80 (50–100)
Assumed eloquent[b]	33 (54.1)
Primary operation	38 (62.3)
Tumor volume (median, range)	18.4 cm^3 (1.1–233.5)
Gross total resection	24 (39.3)
Radiotherapy (now or prior)	56 (91.8)
Temozolomide (now or prior)	46 (75.4)
Acquired neurological deficits	23 (37.7)
Complications	15 (24.6)
Complications leading to reoperation	2 (3.3)

[a]KPS, Karnofsky Performance Status.
[b]Eloquence is here defined as grade II and grade III according to the definition by Sawaya et al. [37].
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The EuroQol 5D

EQ-5D is a generic (not developed for any specific patient group) and preference-weighted measure of HRQOL [13]. The questionnaire has been applied to a wide range of health conditions and treatments as well as population based health surveys [14,15]. There are many different instruments available for researchers interested in assessing HRQOL. We chose to use EQ-5D due to the simplicity of the instrument, to enhance patient perception and perhaps also compliance. Generic instruments such as EQ-5D lack disease specific questions that may be relevant to the patient group (e.g. cognitive functions). Generic instruments may therefore lack sensitivity to measure small benefits or negative consequences of surgery. However, we have earlier demonstrated that EQ-5D shows good correlation to KPS in patients with gliomas and is responsive to new neurological deficit which is highly relevant in this patient group. Also, compared to KPS it offers a more nuanced picture with respect to change after surgery. Since KPS only measures one physical dimension of HRQOL it is insensitive to changes in other dimensions [7]. Another important difference between EQ-5D and KPS is that the latter most often is reported by the physician whereas the former is a patient reported outcome. The EQ-5D has been validated in a Norwegian normal population [16], but so far not in glioma patients. In EQ-5D, five dimensions of HRQOL are scored; mobility, self-care, usual activities, pain/discomfort and anxiety/depression with 3 possible answers to each dimension, i.e 'no problem', slight problem' or 'major problem'. This results in the 243 different possible health

states which are transformed into a single index value based on a large survey in the UK population [17]. EQ-5D index value is from −0.594 to 1, where 1 corresponds to perfect health, and 0 to death. Negative values are considered to be worse than death. To provide examples a patient scoring 2, 1, 1, 1, and 2 receives a score of 0.78, while a patient scoring 2, 3, 3, 2 and 2 receives a score of 0.08. A visual analogue scale where patients rate their current health state on a line ranging from 0–100 (worst to best imaginable health) forms the second part of the EuroQol questionnaire. In this study only the index value was assessed.

Statistics

All analyses were done with the PASW statistics, version 18.0. Statistical significance level was set to $P<0.05$. Q-Q plots were used to test for normal distribution of data. Central tendencies are presented as means if data is normally distributed and as medians when skewed. When analyzing changes in EQ-5D (e.g. before and after surgery) paired sample t-test was used. For comparison of groups with skewed distribution we utilized Mann-Whitney U test. For binominal data we used Pearson's chi square test.

In the Cox multivariate survival analysis the variables were chosen on the basis of current evidence. The most consistent factors affecting survival in patients with glioblastoma are age [18] and preoperative functional status, usually evaluated with Karnofsky Performance Status (KPS) [19,20]. High quality evidence for the efficacy for adjuvant treatment with radiotherapy and temozolomide in selected patients is now available [21,22]. There is also growing evidence suggesting that achieving gross total resection improves survival [2,23]. We performed univariate analyses for each risk factor and included all in the multivariate model. The Cox multivariate model included the following variables: Age (linear), extent of resection (linear), radiation (yes, no), temozolomide (yes, no), preoperative Karnofsky (linear) and deterioration in patient reported HRQOL (yes/no). We are aware that use of linear data is preferable for statistical reasons (no loss of information), but dichotomizing variables makes clinical interpretation easier, especially when scores consist of several summarized variables, making the immediate interpretation of a number less intuitive. For radiation and temozolomide "yes" indicates that the treatment has been provided at any time during the course of the disease.

Results

HRQOL evaluated with EQ-5D

The mean preoperative EQ-5D index was 0.67 compared to 0.62 postoperatively. The mean decline of −0.05 (95% CI −0.15–0.05) is a non-significant change ($p = 0.285$). There was a wide range in the difference (−0.96 to 0.87) after surgery. There were 30 patients (49.2%) who reported a deterioration 6 weeks after surgery while 9 (14.8%) were unchanged and 22 (36.1%) reported improved HRQOL. Treatment and outcome characteristics comparing the patients with deterioration in HRQOL with the others are presented in Table 2. Patients who reported deterioration in HRQOL had EQ-5D index 0.41 postoperatively as compared to 0.81 in their counterparts ($p<0.001$). The group of patients who experienced a deterioration in HRQOL after surgery ($n = 30$) more often had acquired deficits ($p = 0.017$). There was also a trend for better HRQOL preoperatively ($p = 0.051$), although not statistically significant.

Survival

At the end of follow up 22 patients (36%) were still alive. Median survival was 64 weeks (95% CI 44–84) and a survival curve is presented in Figure 1.

In a Cox multivariate survival analysis we evaluated the impact of the established risk factors together with deterioration in HRQOL. The results are presented in Table 3 and Figure 2A, 2B and 2C. There were independent associations between survival and use of temozolomide (HR 0.30, $p = 0.019$, Figure 2A), radiation therapy (HR 0.26, $p = 0.030$, Figure 2B), and deterioration in HRQOL after surgery (HR 2.02, $p = 0.045$, Figure 2C). Patients with deterioration in HRQOL more often died during the first six months following surgery (TYable 2, $p = 0.017$). Preoperative KPS or surgical extent of resection did not reach statistical significance. Using KPS as a dichotomous variable (KPS≥70) or categorical values for extent of resection (gross total, subtotal and biopsy) did not change the conclusion. Inclusion of surgically acquired deficits in the model did not alter the conclusion either, and actually strengthened the association between deterioration in HRQOL after surgery with overall survival (HR 2.4, $p = 0.022$). Since requested in the review process, primary and redo operations were analyzed separately. Ad-hoc testing verified that temozolomide and radiation therapy were statistically significant predictors ($p<0.05$) when the 38 primary operations were analyzed separately. Deterioration in HRQOL did not reach statistical significance (HR 2.9, $p = 0.05$). No statistically significant predictor was found when analyzing the 23 reoperations separately.

Discussion

In this prospective follow-up study of 61 glioblastoma patients we found that deterioration in HRQOL early after surgery seems to be an independent negative prognostic factor for survival. Deterioration in HRQOL occurs in about half of the patients despite the use of modern image guided surgery. The effect of deteriorating HRQOL was independent of the established risk factors, such as age, extent of resection, preoperative functional status (KPS), and adjuvant treatment. The difference in survival appears to be due to a difference in early mortality. A decline in HRQOL in the early postoperative phase may be suggestive a rapidly growing lesion or perhaps negative effects from surgery. It has been reported that acquired deficits can be associated with both suboptimal adjuvant therapy [5] and reduced survival [8]. Still, we found that the negative impact of lost HRQOL remained significant after adjustment for reported acquired neurologic deficits. Our findings indicate that evaluation of the patients' perception of own health may be of high prognostic value. If so, this may allow for new and interesting outcome measures in glioblastoma surgery that reflect the biology of the disease, the tolls and the benefits from surgery, while maintaining the relevance for overall survival. HRQOL measures allow for comparisons across studies and techniques while avoiding the potential bias associated with surgeons' evaluation of own results.

Overall survival is considered the gold standard when evaluating treatment of glioblastoma and its role is indisputable. However as survival benefits from surgery can be modest, survival as study end-point may require multicentre inclusion and years of recruitment to avoid a statistical power shortage, as experienced in the 5-ALA study [9]. Further, this measure can be quite unspecific in a surgical setting as it reflects the results from non-surgical interventions as well. Progression free survival (PFS) may be used instead as in the 5-ALA-study [9], but the definitions vary and interpretation is problematic [24]. Pseudoprogression occurs in approximately 20% and this makes a pure imaging based outcome unreliable [25]. There may be contrast enhancement due to the treatment itself which can be impossible to distinguish from recurrent disease [24]. Another problem is pseudoresponses, seen

Table 2. Comparisons of treatment related factors and outcome among patients experiencing deterioration in HRQOL after surgery with patients with equal or better HRQOL after surgery.[a]

	Deterioration in HRQOL (n = 30)	Equal or improved HRQOL (n = 31)	P-value
Primary operation[b]	17 (56.6%)	21 (67.7%)	0.375
KPS (median) preop[c]	80	90	0.586
Tumor volume (median)[c]	24.1 cm^3	15.9 cm^3	0.322
Extent of resection (median)[c]	95.1%	96.5%	0.715
Gross total resection[b]	11 (36.7%)	13 (41.2%)	0.532
Complication[b]	8 (26.7%)	7 (22.6%)	0.401
New/worse deficit[b]	16 (53.3%)	7 (22.6%)	0.017
EQ-5D index (mean) preop[d]	0.75	0.59	0.051
EQ-5D index (mean) postop[d]	0.41	0.81	<0.001
Deaths in month 0–6[b]	11 (36.7%)	3 (9.7%)	0.012
Deaths in month 7–12[b]	6 (20.0%)	5 (16.1%)	0.694
Deaths >12 months[b]	6 (20.0%)	8 (25.8%)	0.590
Total deaths in follow up[b]	23 (76.7%)	16 (51.6%)	0.042

[a]HRQOL, health related quality of life; KPS, Karnofsky Performance Status; $p<0.05$ is considered significant.
[b]Pearson chi-square.
[c]Mann-Whitney U test.
[d]Independent sample t-test.
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with antiangiogenic agents where the disappearance of contrast enhancement is not necessarily related a clinical response [24,26]. However, the dynamics of tumor progression, the speed of growth, and patterns of growth may be of prognostic importance if a reliable measure becomes available.

Extensive resections are advocated by numerous studies due to the association with improved survival. The association seems logical, but it is difficult to differentiate the efficacy of treatments from treatment selection as most studies are neither randomized, controlled nor prospective [4,23,27]. As mentioned earlier, differences in patient selection are obstacles for meaningful comparisons between institutions and techniques. Lastly, with the exception of the 5-ALA study [9] most studies are not even designed to evaluate the efficacy of surgical treatment. The present study does not indicate that extensive resection negatively affects HRQOL in itself, but it indicates that there is serious potential for harm in surgical treatment of glioblastomas. We believe careful therapeutic considerations should be made in cases where safe gross total resection seems unlikely as the risk might outweigh the benefit.

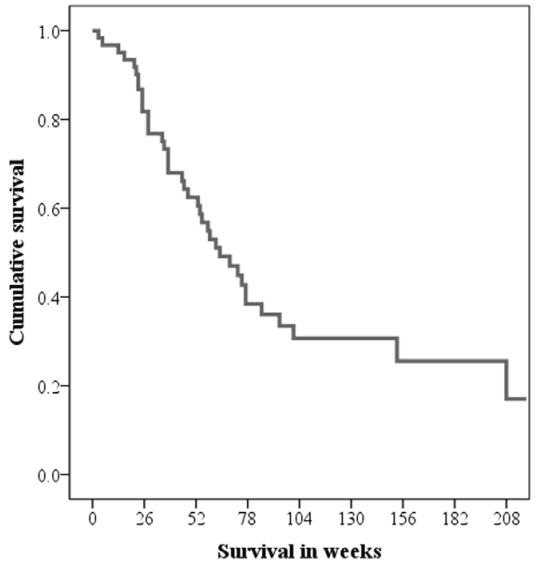

Figure 1. Overall survival in the cohort (n = 61) presented in a survival plot.
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These common end-points all have drawbacks which can be problematic for meaningful clinical interpretation. Since the prognosis with respect to survival remains unfavorable despite maximal therapeutic efforts, measuring patients' quality of survival is an important supplement [6]. We believe HRQOL adds useful information both for clinical use and research. Met with the individual patients, neurosurgeons should take into account the potential hazards of surgery on patients' HRQOL and carefully weigh this up against the likelihood of a survival benefit. Perhaps the patients' subjective HRQOL reflects the dynamics of their disease of prognostic importance, although difficult to quantify even in serial MRI scans. HRQOL reflects both the burden of treatment and the severity of the disease and together with the association to overall we believe that deterioration in HRQOL, or deterioration free survival after surgery, can be a meaningful endpoint in surgical trials in neuro-oncology.

In demonstrating prognostic potential of self reported HRQOL we are in line with earlier studies [28–31]. However, we are not aware of any other study assessing the prognostic effect of HRQOL where baseline scores are collected preoperatively. Other neuro-oncological studies evaluating HRQOL and survival are usually in the setting of medical clinical trials using initiation of chemotherapy or radiotherapy as baseline [29–32]. This neglects

Table 3. Cox multivariate regression.[a]

	HR univariate	P-value	HR Multivariate	P-value	95% CI for multivariate HR	
					Lower	Upper
Age	1.04	0.023	1.00	0.990	0.97	1.03
EOR	0.99	0.176	0.99	0.403	0.97	1.00
Radiotherapy	0.12	<0.001	0.26	0.030	0.08	0.88
Temozolomide	0.20	<0.001	0.30	0.019	0.11	0.82
KPS preoperative	0.98	0.083	0.99	0.325	0.96	1.01
HRQOL deterioration	2.11	0.022	2.02	0.045	1.02	4.00

All variables included in the model are presented both for univariate and multivariate analyses. Radiotherapy, use of temozolomide and deterioration in quality of life 6 weeks after surgery were independently associated with overall survival.

[a]EOR, extent of resection; KPS, Karnofsky Performance Status; HRQOL, health related quality of life; HR, hazard ratio; CI, confidence interval; $p<0.05$ is considered significant.

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the potential effect and hazards of surgery which undoubtedly is the most invasive form of treatment in patients with glioblastoma.

Patients may perceive their health and HRQOL differently with regards to sex, tumor location and histopathology [6,7]. Therefore it is difficult to find an optimal cut-off-value with clinical significance, and searching for a so called "best cut-off" may be somewhat dubious and increase the risk for false positive findings [33]. Utilizing changes instead of absolute values seems clinically more useful in individual patients. This approach takes individual differences into consideration as patients are their own controls. This approach may reduce the problems mentioned above. However, interpreting changes in HRQOL is not necessarily straightforward. Changes should be evaluated as clinically meaningful rather than simply statistically significant. This can be achieved by anchoring HRQOL to therapy, changes with disease progression or life events [34].

EQ-5D, a generic HRQOL measure, shows good correlation with traditional outcome measures [7], and in this study it also demonstrates an association with hard clinical end-points. Thus it is seemingly a valuable tool in assessing HRQOL in patients with glioblastoma. Despite potential shortcomings of generic instruments, we are convinced that patient related outcomes with a validated questionnaire are interesting, valuable, and perhaps less biased adjuncts to traditional physician rated outcome measures. The use of EQ-5D for the entire glioblastoma patient population should be subject of further studies i.e. defining minimal important change or measuring HRQOL at multiple time points to better understand the HRQOL throughout the course of the disease. However, we would insist on using a preoperative evaluation as baseline to avoid loss of important information.

The relative high number of complications and acquired deficits in our patients are most likely explained by the assessment method used. All adverse events were patient reported, including uncommon outcome parameters used in the neurosurgical literature, namely memory difficulties, unsteadiness and personality changes. When using a more common method of assessment we have reported complications in 21% and deteriorated functional outcome in 13% in a consecutive, unselected series in patients with high grade gliomas [1]. Comparing adverse events between studies is difficult due to different inclusion criteria and the lack of a standardized way of reporting [5]. With this in mind we believe these findings are comparable to a large study where 34% of patients experienced perioperative complications and 9.9% displayed worsened neurological status within 3 weeks after primary craniotomy for malignant glioma [35]. For the future we would encourage researches to use one standard way of reporting since this would facilitate meaningful comparisons, i.e. using the system for neurosurgical patients recently described [36].

Our study has several limitations. The patients included represent an unsystematic selection that may not be representative for the entire population of patients with glioblastoma. We believe the lost-to follow-up rate of 9% is low. How these lost-to-follow-

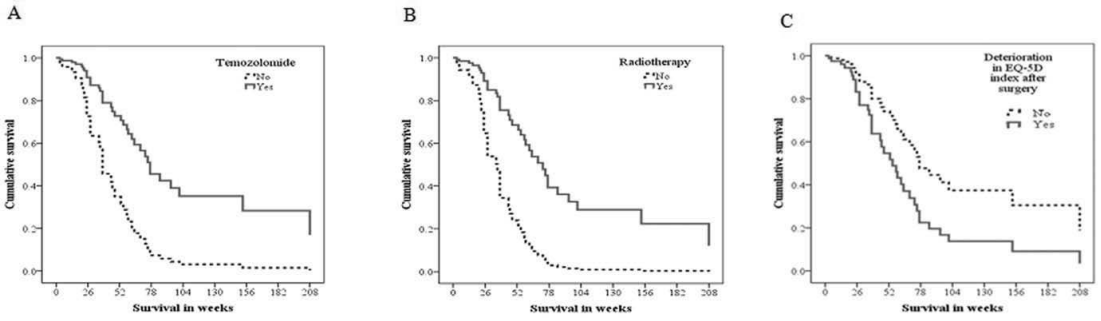

Figure 2. Survival curves for the independent predictors presented in Table 3.
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ups would have affected the results remains speculative, but as three were dead or in a terminal condition, it is reasonable to believe their HRQOL had deteriorated as well and further strengthened the association. Adjuvant treatment (yes/no) was included in the Cox regression model in spite of the risk of survivorship effect overestimating the actual effect of the intervention. A case-mix with 37.7% reoperated patients where most had already received adjuvant treatment could possibly lead to underestimation of the effect of adjuvant treatment. Although the effect of lost HRQOL seems independent of given adjuvant treatment, details of treatment protocols were not studied. We therefore advise to interpret the effects of adjuvant therapy in this study with some caution. Results from the ad-hoc analyses for primary operations and reoperations separately, as requested in the review process, may likely be due to type II errors and should not alter the interpretation of the study. They suggest that the findings in this study may be more representative for primary operations than for reoperations, but this finding needs to be verified in a larger study. Finally, the statistical method used in creating a dichotomous variable (worse HRQOL: yes/no) from a single variable is associated with an increase in false positive findings [33]. However the cut-off chosen is not created on the basis of finding the ''optimal'' cut-off, but out of logic and what we thought would be of clinical relevance. Another important statistical culprit is the floor-ceiling effect since patients in a good preoperative condition can only become worse and vice versa.

Conclusion

Balancing risks with potential survival benefit and clinical improvement is the key in surgical treatment of patients with glioblastoma. Resection grades, overall survival, and PFS are much used outcome parameters in surgical research, but they offer no information on quality of survival. In this study we have demonstrated that early deterioration in HRQOL after surgery is independently and markedly associated with impaired survival. Deterioration in patient reported HRQOL after surgery is a meaningful outcome in surgical neuro-oncology as HRQOL reflects the burden of symptoms, the treatment hazards and is linked to survival.

Author Contributions

Conceived and designed the experiments: ASJ SG GU OS. Analyzed the data: ASJ SG CW OS. Contributed reagents/materials/analysis tools: ASJ SG CW GU OS. Wrote the paper: ASJ SG CW GU OS.

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Paper IV

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