Sasha Gulati

Surgical Resection of High-Grade Gliomas

Thesis for the degree of Philosophiae Doctor

Trondheim, April 2012

Norwegian University of Science and Technology
Faculty of Medicine
Department of Laboratory Medicine,
Children's and Women's Health

NTNU – Trondheim
Norwegian University of
Science and Technology

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ISBN 978-82-471-3488-7 (printed ver.)
ISBN 978-82-471-3489-4 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2012:105

Printed by NTNU-trykk

Reseksjon av høygradige gliomer

Høygradige gliomer er den vanligste formen for primær hjernesvulst. Glioblastomer (Verdens Helseorganisasjon grad IV) og anaplastiske astrocytomer (Verdens Helseorganisasjon grad III) utgjør mellom 70 og 85 % av høygradige gliomer. Høygradige gliomer er assosiert med både høy morbiditet og mortalitet. Nærmest alle pasienter med høygradige gliomer opplever tilbakefall og dør som følge av sykdommen. Til tross for kirurgi, strålebehandling og cellegift, er median overlevelse for pasienter med glioblastom fremdeles under 12 måneder. For pasienter med anaplastisk astrocytom er median overlevelse 2 til 3 år.

Høygradige gliomer infiltrerer omkringliggende hjernevev, og hensikten med kirurgi er, foruten å histopatologisk verifisere diagnosen, å fjerne så mye av svulsten som mulig uten å påføre pasienten nye eller økte nevrologiske utfall. I vår avdeling benytter vi et navigasjonssystem under operasjonene som nyttiggjør tredimensjonale preoperative MR-bilder og tredimensjonal ultralydavbildning under operasjonen. Dette navigasjonssystemet gjør at kirurgen til en hver tid kan se posisjonen til sine instrumenter i forhold til hjernen og svulsten. Ved hjelp av funksjonell MR (eller mer presist *blood-oxygenation-level-dependent functional magnetic resonance imaging*) og diffusjon tensor traktografi (DTT) kan en henholdsvis kartlegge viktige områder i hjernens grå og hvite substans før operasjonen. Disse undersøkelsene utføres som regel når svulster ligger i nær relasjon til ekstra følsomme områder av hjernen (for eksempel språkområder og viktige områder for bevegelse). Informasjon fra disse undersøkelsene kan også importeres i navigasjonssystemet som benyttes under operasjonen.

I de to første studiene i denne avhandlingen ønsket vi å undersøke hvordan funksjonell MR og DTT ble brukt i preoperative vurderinger. Vi evaluerte om funksjonell MR og DTT i kombinasjon med tredimensjonal ultralydavbildning under operasjonen la forholdene til rette for skånsom fjerning av høygradige gliomer beliggende i ekstra følsomme områder av hjernen. I den tredje studien undersøkte vi konsekvensene av kirurgiske komplikasjoner og nevrologiske utfall som følge av kirurgi på

glioblastompasienters funksjonsnivå og overlevelse. Videre gjorde vi volumetriske analyser for å beregne hvor mye svulstvev vi klarte å fjerne hos pasienter med primære glioblastomer behandlet i vår avdeling. I den fjerde studien undersøkte vi om det var noen sammenheng mellom overlevelse og fall i selvrapportert livskvalitet kort tid etter kirurgi hos pasienter med glioblastomer. Den femte studien var basert på data fra Kreftregisteret og undersøkte overlevelse og behandling blant eldre pasienter (≥66 år) med glioblastomer over en tyve års periode.

Hovedfunnene i denne avhandlingen er:

- Kombinasjonen av funksjonell MR, DTT og tredimensjonal ultralydavbildning kan være nyttig når en utfører kirurgisk reseksjon av høygradige gliomer beliggende i ekstra følsomme områder av hjernen.
- Pasienter som opplevde komplikasjoner og nevrologiske utfall som følge av kirurgi hadde lavere sannsynlighet for å motta strålebehandling og kjemoterapi.
- Tidlig fall i helserelatert livskvalitet etter kirurgi synes å være en sterk og uavhengig negativ prognostisk faktor for pasienter med glioblastom.
- Økende alder er en sterk og uavhengig negativ prognostisk faktor for pasienter med glioblastom. Selv om det har vært en intensivering av behandling over tid, har gevinsten i den eldste aldersgruppen vært begrenset. Prognosen for de eldste er fremdeles svært dårlig til tross for multimodal behandling.

Candidatus medicinae Sasha Gulati
Nevrokirurgisk avdeling, St. Olavs Hospital
Institutt for laboratoriemedisin, barne- og kvinnesykdommer, NTNU

Hovedveileder: Professor dr.med Sverre H. Torp, NTNU
Biveilder: Overlege Ph.D. Ole Solheim, NTNU

Surgical Resection of High-Grade Gliomas

High-grade gliomas are the most common primary brain tumour. Glioblastomas (World Health Organization Grade IV) and anaplastic astrocytomas (World Health Organization Grade III) account for 70-85% of high-grade gliomas. High-grade gliomas are associated with high morbidity and mortality. Virtually all patients with high-grade glioma will experience recurrence and will eventually die from progressing disease. Despite surgery, radiotherapy, and chemotherapy, median survival in patients with glioblastoma still does not exceed 12 months. The median survival for patients with anaplastic astrocytoma (AA) has been reported to be between 2 and 3 years. According to current guidelines, surgery is warranted to establish a histopathologic diagnosis and to achieve safe, maximal, and feasible resection. However, these aggressive tumours cannot be cured and overly aggressive resection is not recommended due to the risk of new neurological deficits. High-grade glioma surgery is a delicate balance between achieving maximal tumour resection and inducing new deficits.

In our department a neuronavigation system based on preoperative 3D magnetic resonance imaging (MRI) and intraoperative 3D ultrasound is utilised when resecting high-grade gliomas. Blood-oxygenation-level-dependent functional magnetic resonance imaging (BOLD fMRI) and diffusion tensor tractography (DTT) are specialized MRI techniques for imaging eloquent cortices and neural tracts in grey and white matter, respectively. The neuronavigation system allows the integration of BOLD fMRI and DTT data if the tumours are located in eloquent regions.

In the two first studies of this thesis we sought to investigate the use of BOLD fMRI and DTT for preoperative assessments and determine whether using these data together with 3D intraoperative ultrasound enabled safe resection of high-grade gliomas situated in eloquent regions. In the third study we wanted to explore the impact of surgical morbidity on functional outcome and survival in GBM patients. Further, we sought to determine extent of tumour resection achieved in a consecutive sample of primary GBM from our own department. In the fourth study we wanted to determine if changes in

health related quality of life early after surgery could be a predictor for survival in patients with glioblastoma. The aims of the fifth study were to explore survival and the treatment provided to elderly patients (≥66 years) diagnosed with glioblastoma during a 20-year time period in a population-based cohort using the Norwegian Cancer Registry.

This thesis investigated the role of surgical resection in the treatment of high-grade gliomas and the following conclusions can be drawn:

- The combination of BOLD fMRI, DTT, and 3D intraoperative ultrasound may facilitate resection of high-grade gliomas harboured in eloquent areas while preserving motor and language function.
- Functional neuronavigation combined with intraoperative 3D ultrasound can, in most patients, enable resection of brain lesions with general anaesthesia without jeopardizing neurological function.
- Patients with perioperative complications and surgically acquired deficits were less likely to receive adjuvant therapy.
- Early deterioration in HRQL after surgery was independently and markedly associated with impaired survival in patients with glioblastoma.
- Advancing age remains a very strong and independent negative prognostic factor in glioblastoma. Although there has been an increase in the aggressiveness of treatment provided to elderly with glioblastoma, the gain for the oldest age group seems at best very modest. The prognosis of the oldest age group remains very poor, despite multimodal treatment.

Sasha Gulati M.D.
Department of Neurosurgery, St. Olavs Hospital
Department of Laboratory Medicine, Children's and Women's Health, NTNU

Main supervisor: Professor Sverre H. Torp, NTNU
Second supervisor: Ole Solheim M.D. Ph.D., NTNU

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Acknowledgements

The research presented in this thesis was performed while I was working full time as a resident at the Department of Neurosurgery, St. Olavs Hospital in the period 2007-2011. Financial support was provided by Sparebanken Møre, The Blix Family Fund for Medical Research, and the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology. I am indebted to my supervisor, Professor Sverre H. Torp, for his continuous support and advice that made this work possible. I am very thankful to my second supervisor, Dr. Ole Solheim, for his expertise in the field of neurosurgery and ability to propose original hypotheses in combination with feasible methodological approaches.

Many other colleagues have contributed to this thesis in different ways, particularly: Professor Geirmund Unsgård, for always encouraging and facilitating scientific work, Dr. Johan Cappelen, for giving and keeping me in my job, Dr. Asgeir S. Jakola, for his enthusiasm and constructive feedback, and Dr. Erik M. Berntsen, for his knowledge and experience of functional neuroimaging. I am thankful to my co-authors Ulf S. Nerland, Clemens Weber, Asta Håberg, Tom B. Johannesen, Tormod Selbekk, and Kjell A. Kvistad. I would like to express my gratitude to everyone at the Department of Neurosurgery for providing such a positive working environment.

I would like to thank my parents, Anjali and Gurcharan, and my brother, Michel, for their unconditional support. Above all, I am deeply grateful to my wife Agnete for her patience. She has pushed and encouraged my research and talked me through my uncertainties and confusions about it. And she made writing this thesis possible alongside everything else in our life. Our son, Mateo, is the sunshine of my life.

Trondheim, January 2012

Sasha Gulati

List of Publications

1. Surgical resection of high-grade gliomas in eloquent regions guided by blood oxygenation level dependent functional magnetic resonance imaging, diffusion tensor tractography, and intraoperative navigated 3D ultrasound **Gulati S, Berntsen EM, Solheim O, Kvistad KA, Håberg A, Selbekk T, Torp SH, Unsgård G;** ***Minimally Invasive Neurosurgery 2009***

2. Functional magnetic resonance imaging and diffusion tensor tractography incorporated into an intraoperative 3-dimensional ultrasound-based neuronavigation system: impact on therapeutic strategies, extent of resection, and clinical outcome **Berntsen EM, Gulati S, Solheim O, Kvistad KA, Torp SH, Selbekk T, Unsgård G, Håberg AK;** ***Neurosurgery 2010***

3. The risk of getting worse: Surgically acquired deficits, perioperative complications and functional outcomes after primary resection of glioblastoma **Gulati S, Jakola AS, Nerland US, Weber C, Solheim O;** ***World Neurosurgery 2011***

4. 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***

5. Survival and treatment patterns in elderly patients with glioblastoma – A population based study **Gulati S, Jakola AS, Johannesen TB, Solheim O;** ***World Neurosurgery 2012***

Abbreviations

AA = Anaplastic astrocytoma
5-ALA = 5-aminolevulinic acid
BOLD = Blood Oxygenation Level Dependent
CNS = Central nervous system
CT = Computer-assisted tomography
CUSA = Cavitron ultrasonic aspirator
DTI = Diffusion Tensor Imaging
DTT = Diffusion Tensor Tractography
fMRI = Functional Magnetic Resonance Imaging
GBM = Glioblastoma
HRQL = Health related quality of life
KPS = Karnofsky Performance Status
LEAD = Lesion-to-Eloquent-Area Distance
MRI = Magnetic Resonance Imaging
mRS = Modified Rankin Scale
PFS = Progression-free survival
PRO = Patient reported outcome
RCT = Randomized controlled trial

Introduction

The Task at Hand

High-grade gliomas are the most common primary brain tumours (139). Glioblastomas and anaplastic astrocytomas account for 70-85% of high-grade gliomas (134). The work presented in this thesis focuses on anaplastic astrocytomas and glioblastomas, collectively often referred to as high-grade astrocytomas. They are associated with tremendous morbidity and virtually all patients with will experience recurrence and die of progressive disease despite maximal therapeutic efforts.

The median survival for patients with anaplastic astrocytoma (AA) has been reported to be between 2 and 3 years (69, 74). The majority of glioblastoma (GBM) patients, particularly the elderly, succumb to the disease within a year (69, 74). Even with maximal surgical resections using modern technical aids, and despite advances in radiotherapy and chemotherapy, the prognosis remains dismal.

Classification of High-Grade Astrocytomas

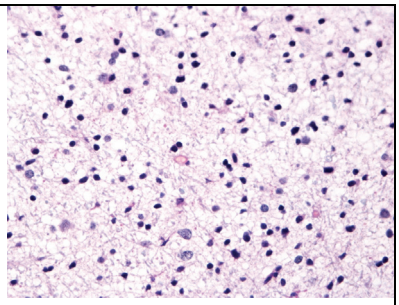
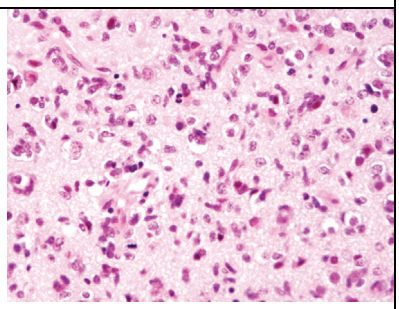
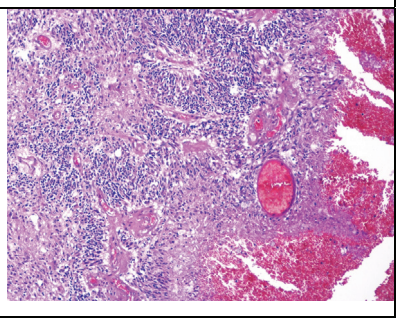
Gliomas arise from glial supportive tissue of the brain including astrocytes, oligodendrocytes, or ependymal cells (74). The astrocytic tumours represent the majority of the gliomas and show a wide range of differentiation and histopathological features. The World Health Organization (WHO) classifies astrocytomas on the basis of histologic features into four prognostic grades (74): grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma), and grade IV (glioblastoma). Anaplastic astrocytoma and glioblastoma are commonly referred to as high-grade or malignant astrocytomas. Pilocytic astrocytomas are regarded as non-infiltrating and are distinguished from the other forms by their particular pathological appearance and benign behaviour. They occur in children and young adults and are

usually located in the midline in structures such as the cerebellum, brain stem, hypothalamus, and optic nerves. WHO grade II, III, and IV astrocytomas, collectively also termed diffuse infiltrating astrocytomas, have a high recurrence rate due to the high propensity of infiltrating adjacent brain tissue. In addition, they have an intrinsic tendency to become more malignant over time, so a recurrent tumour is frequently of a higher malignancy grade. Actually, these tumours can be viewed as a continuum along an axis of increasing malignancy.

The histological malignancy grading is based on the following features: cellularity, atypia, mitotic activity, necrosis, and microvascular proliferation. In Table 1 typical images and descriptions of diffuse astrocytomas grade II-IV are presented. Increasing malignancy is characterized by increasing cellularity, increasing number of mitoses, and cellular and nuclear atypia. Presence of microvascular proliferation and/or necrosis justifies the diagnosis of glioblastoma. Secondary glioblastomas develop from grade II or III astrocytomas, whereas primary or de novo glioblastomas occur without any previous history of a less malignant lesion. Amplification and overexpression of the epidermal growth factor receptor gene is the major genetic pathway in development of the secondary glioblastomas, whereas tumour protein 53 gene mutations are important in the development of primary glioblastomas (56). Typical routes of high-grade astrocytoma infiltration are the corpus callosum, internal capsule, fornix, anterior commissure, and optic radiation. On the other hand, glioblastomas tend not to grow into the leptomeninges and thus rarely metastasize via cerebrospinal fluid. Invasion of the dura, venous sinuses, and bone is also exceptional, and distant metastases are extremely rare (4, 8, 74).

The histopathological diagnostics of diffuse astrocytomas can be challenging, and despite histopathological criteria given by the WHO, considerable interobserver variability exists. While there is usually a good concordance in diagnosis for glioblastomas between pathologists, disagreement in more than 30% of samples is common for anaplastic astrocytomas (120).

Table 1. WHO classification system for diffuse astrocytomas WHO grade II-IV (Photos provided by Prof. S. H. Torp)

Grade II	Moderate cell density Minor nuclear atypies Minor mitotic figures No necrotic areas	
Grade III	High cell density Moderate nuclear atypies High rate of mitotic figures No necrotic areas	
Grade IV	High cell density High rate of nuclear atypies High rate of mitotic figures High rate of necrotic areas Microvascular proliferations	

Epidemiologic Features

The incidence of WHO grade III and IV gliomas is approximately 5-7 cases per 100,000 people per year (134, 136). Annually, approximately 25 adult patients are operated for primary GBM in our department (paper 3). Improved and more readily available neuroimaging may have slightly increased the incidence of malignant glioma, especially in the elderly (35). The incidence of GBM increases with advancing age, peaking between the ages of 65 to 84 (139). In the age group 65-74 the incidence is 13 per 100,000 person-years and in the age group 75-84 it is 15 per 100,000 person-years (80). The mean age of primary GBM patients operated in our department between 2004 and 2009 was 62 years (paper 3). For secondary GBM, the mean age is about 45 years (1).The median age of patients at the time of diagnosis is 45 years in the case of anaplastic gliomas (134). Malignant gliomas are rare in childhood, comprising between 6-9% of all intracranial neoplastic disorders in the pediatric population (18, 32).

In most patients with malignant astrocytomas no underlying cause can be identified. Inherited syndromes such as neurofibromatosis types 1 and 2, tuberous sclerosis, Cowden's disease, Turcot's syndrome, and Li-Fraumeni syndrome, predispose to developing astrocytomas (120, 134, 138). Age at diagnosis and Karnofsky performance score (KPS) are important and established prognostic factors in high grade glioma patients (36, 63). The only proven environmental risk factor for gliomas is exposure to ionizing radiation (35). Evidence for an association with occupational risk factors, use of cellular phones, certain foods, and exposure to electromagnetic fields is inconclusive (35, 41, 64, 134). Interestingly, an inverse association between atopy and the risk of glioma has been observed (71).

Clinical features

High-grade gliomas produce symptoms by a combination of focal neurologic deficits from compression and infiltration of the surrounding brain and raised intracranial pressure. Most patients with high-grade gliomas present with headaches, progressive

sensorimotor neurologic deficits, cognitive changes, or seizures (13). Corticosteroids are often administered before surgery to relieve tumour symptoms and improve neurological symptoms.

Neuroimaging

Imaging with CT or MRI will show a localized expansive process with associated oedema (120). On CT, GBM frequently present as irregularly shaped lesions with a peripheral ring-like area of contrast enhancement around a hypodense central area of necrosis. On enhanced MR images, the contrast-enhancing ring structure in GBM represents the cellular and highly vascularized peripheral area of the neoplasm and the dark centre corresponds to necrosis. Anaplastic astrocytomas often present as ill-defined masses with partial contrast enhancement, although both intense enhancement and non-enhancement can be seen. Differential diagnoses for malignant gliomas include abscesses, metastases, primary central nervous system lymphomas, and other primary brain tumours (120). Proton MR spectroscopy is based on the measured intensity of several metabolites. This modality can be a useful supplement for differentiating gliosis or radiation necrosis from recurrent tumour in patients where repeated resection is considered (34).

High-grade astrocytomas are larger than seen by any modern imaging technology, and the actual extension of a tumour is typically beyond what is indicated by CT and MR imaging. The greatest numbers of tumour cells can be found within the MRI-defined abnormality. However, stereotactic serial biopsies have shown that isolated tumour cells coexist with intact parenchyma in the peritumoural oedema surrounding the contrast-enhancing area and as far as 7 cm from any MRI-defined abnormality (54). This means that tumour cells coexist with functional brain parenchyma, and that there usually is no defined border between infiltrated parenchyma and normal brain.

Treatment

The first reported instance of surgery for cerebral glioma appears to have been performed by Godlee and Bennett in 1884 in London, England (9). Initially the patient did well, following what was considered to be a complete removal of a subcortical tumour, but succumbed to infectious complications on the 28th postoperative day. At this time there were no radiographic tests available. The preoperative localization of the tumour and the technical details of the procedure were graphically described by the authors since they felt that the localization of the tumour and its removal 'without any immediate injurious effects on the intelligence and general condition of the patient' were the main features of interest. In the following years, pioneers of neurosurgery such as Horsley, Cushing, Mackenzie, and Dandy presented a diversity of technical approaches and operative recommendations for gliomas (102). In the early twentieth century, meticulous hemostasis was introduced by Cushing with his development of the vascular clip and the electrocautery. This lead to a progressive decline in operative mortality (68). The next major advance was the advent of radiographic imaging, first with ventriculography introduced by Dandy and then with the discovery of cerebral angiography by Moniz and Lima (102). Over the past 40-50 years we have seen the introduction of technological appliances such as the operating microscope, image-guided surgery, ultrasonic imaging, volumetric stereotaxy, intraoperative CT and MR imaging, and fluorescence guided surgery (53). These discoveries have further contributed to reduce perioperative morbidity and mortality rates (86).

Current treatments for patients with malignant glioma include surgery, radiation therapy, and chemotherapy. Surgery has become the cornerstone in the initial treatment of high-grade gliomas, and is the most efficient method for the reduction of tumour burden available. There is now level 2b data (Oxford Centre for Evidence-based Medicine) showing that gross total resection (resection of contrast enhancing tissue on T1 MRI) prolongs survival (116). According to current guidelines surgery is warranted to establish a histopathologic diagnosis and to achieve safe, maximal, and feasible resection (20, 27, 29, 36, 78, 106). However, these aggressive tumours are only rarely cured (24) and overly aggressive resection is not recommended due to the risk of new

neurological deficits. High-grade glioma surgery is a delicate balance between achieving maximal tumour resection and inducing new deficits.

Radiotherapy has been shown to add several months to survival (61, 133), and has become part of the standard of care. Postoperative fractionated external-beam radiotherapy is routine. It is usually administered as 60 Gy in 30 fractions over a period of about six weeks. Evidence supporting the use of radiotherapy in the elderly was provided by a randomized controlled trial (RCT) where patients who underwent surgery were allocated to radiotherapy or supportive care only (51). This study from 2007 showed that patients above 70 years with Karnofsky performance status score ≥70 undergoing radiotherapy may experience a modest survival benefit compared to supportive care (median 29.1 vs. 16.9 weeks). Less aggressive radiotherapy protocols have been advocated in older patients. An RCT in patients 60 years or older compared standard normofractioned radiotherapy (60 Gy in 30 fractions over 6 weeks) to a hypofractioned regimen (40 Gy in 15 fractions over 3 weeks) and found similar survival in the two groups (97). In a younger, fairly unselected population (<70 years), lower radiotherapy doses (45 Gy over 4 weeks vs. 60 Gy over 6 weeks) were associated with both inferior progression-free and overall survival (14).

In 2005 Stupp et al published an RCT comparing radiotherapy alone with radiotherapy plus the alkylating agent temozolomide (119). The addition of temozolomide to radiotherapy showed a survival benefit with little additional toxicity. Median survival was 14.6 months with radiotherapy and temozolomide, and 12.1 months with radiotherapy alone. This in turn resulted in a shift from the intravenously administered PCV treatment to the orally administered temozolomide.

Recurrent tumour is more difficult to treat. These patients may be considered for surgery again if they have a good performance status (43). Re-do radiotherapy may be an option in selected patients, although increased toxicity may be a problem. Many neuro-oncologists recommend re-do adjuvant temozolomide in patients who did not progress while on their first course of chemotherapy (1).

Surgical Procedures

All craniotomies are performed in general anaesthesia without intraoperative electrocortical mapping. The patient's head rests in a Mayfield frame system (OMI, Inc., Cincinnati, OH, USA) attached to a reference frame for neuronavigation. In our department the Sonowand® neuronavigation system, based on preoperative 3D MRI data and intraoperative 3D ultrasound is utilised when resecting malignant gliomas (38, 126). The 3D ultrasound volume is reconstructed from 100-200 2D images, created by making a recording over the area of interest with a tracked ultrasound probe. The preoperative MRI data are imported into the navigation system and used for surgical planning and resection guidance. Intraoperative 3D ultrasound can be used alone for navigation, but we usually register preoperative 3D MR volumes to the patient's head before commencing surgery. The neuronavigation system also allows the integration of high-quality blood oxygenation-level-dependent functional magnetic resonance imaging (BOLD fMRI) and diffusion tensor tractography (DTT) data if the tumours are located in eloquent regions (95).

There is always some inaccuracy when the preoperative images are registered to the patient (registration inaccuracy). In addition, there may be inaccuracy in the navigation system itself (technical inaccuracy). Moreover, craniotomies lead to a displacement or shift of intracranial structures. The main reasons for brain shift are removal of cerebrospinal fluid and tumour tissue. The brain shift is usually most pronounced at the cortical surface, whereas it is smaller in deeper structures of the brain. For 3D ultrasound, the registration inaccuracy is eliminated as both ultrasound acquisition and navigation based on 3D ultrasound volumes are performed in the same system. Updated intraoperative ultrasound volumes can be acquired several times during surgery in order to minimise and detect possible errors of brain shift.

The first ultrasound volume is usually acquired after the craniotomy has been performed and before opening of the dura. The multimodal 3D data sets from intraoperative ultrasound and preoperative MRI, BOLD fMRI, and DTT are used for resection control and guidance. The Cavitron ultrasonic aspirator (CUSA) is applied to fragment and

aspirate the tumours. If desired, an attached tracking frame can be used for tracking of the CUSA in the image volumes. The position of the tip and the trajectory of the CUSA can be monitored in the MRI and updated ultrasound volumes for close to real-time resection guidance. The navigation system also allows visualization of vessels based on recordings of power Doppler signals from the blood stream, which also may be of use in tumour operations (100).

Biopsies are useful for histopathological classification, although there is a risk of sampling error. Gliomas are often heterogeneous, and it is a concern that small tissue samples through a biopsy may not be representative of the tumour as a whole. A prospective study of patients undergoing biopsy first and then resection a few weeks later, found that biopsy correctly guided therapy in 91% of the patients (137). Biopsies are also performed when there is considerable doubt concerning the etiology of a brain lesion (e.g. glioma vs. lymphoma). If necessary, patients can undergo subsequent tumour resection after a biopsy procedure. Biopsy is considered a low risk procedure, with a morbidity rate from retrospective series of around 3.5% and a mortality rate of less than 1% (40). Biopsy may be preferred over resection in patients with poor functional performance status, of older age, or when the tumour is in an anatomically prohibitive location for resection (e.g. in deep regions), although the biopsy rates can vary much from centre to centre.

Functional Imaging and Mapping of Eloquent Brain Areas

Eloquence can be defined as fluent, forcible, elegant or persuasive speaking. However in neurosurgery, the term has been adopted to describe regions of the brain that control speech, motor functions, and senses. Surgical resection of lesions surrounding the eloquent brain areas is often a challenge. In cases of high-grade astrocytomas located within or adjacent to the central sulcus, basal ganglia, and subcortical motor pathways, it is often hard to intraoperatively perceive the relationship between lesions and functional structures of the sensorimotor cortex and pyramidal tracts. Even in the normal brain there is variability between function and anatomy. In case of undistorted

anatomy, eloquent areas may be recognized using specific sulcal landmarks. As an example, hand-function can be located at the omega-shaped structure of the "hand region" in the precentral gyrus (143). Mass effect associated with high-grade gliomas can distort these common relations, making anatomy-based localization of functional areas more challenging. Functional regions may also be relocated to other brain areas, thereby changing the normal relationships between function and anatomy (130).

Intraoperative electrical motor cortex mapping and recording phase reversal of somatosensory evoked potentials have traditionally been considered as gold standard when performing surgery close to eloquent cortex. The classic procedure for language localization is intraoperative electrocortical mapping in awake and cooperative patients (90, 104). Motor mapping can be performed while the patient receives a general anaesthetic. These techniques do not assist in preoperative planning, and intraoperative mapping often requires a craniotomy larger than necessary with respect to the tumour to be resected (104, 130). In recent years the technique of preoperative mapping of functionally important brain areas has made advances. Positron emission tomography, functional magnetic resonance imaging (fMRI), and magnetoencephalography have been used as tools for the localization of sensorimotor cortex.

Blood oxygenation-level-dependent (BOLD) fMRI may be applied for mapping of eloquent cortices using colour-coded statistical parametric maps overlaid on the anatomical images of the brain. Diffusion tensor imaging (DTI) can be used for mapping of neural tracts in the white matter, which through an analysis called diffusion tensor tractography (DTT) can visualize the neural tracts as 3D fibre bundles. The information obtained through fMRI and DTT is matched and fused with high-resolution MR images. The integration of fMRI and DTI activation maps into neuronavigation is often referred to as "functional neuronavigation".

The physical basis for the BOLD signal is provided by the properties of deoxyhemoglobin, which is paramagnetic and has the ability to influence the MRI signal (87). Changes in the level of deoxyhemoglobin compared to oxyhemoglobin will give rise to a variation in the measured MRI signal, known as the BOLD signal (88).

The physiological basis for the BOLD signal lies in changes of blood flow, volume, and level of oxygenation following neuronal activity, also referred to as the neurovascular coupling (16).

A BOLD fMRI investigation consists of several steps, starting with a patient inside an MRI-scanner performing particular tasks at given times while magnetic resonance images are acquired. These images then need to be pre-processed before statistical analyses are performed, in order to produce colour-coded statistical parametric activation maps. The activation maps are then co-registered to anatomical images. The process from image acquisition to interpreted functional maps consists of several steps each vulnerable to different sources of error (11, 17, 89, 130). Many stimulation paradigms have been used for preoperative mapping, the most commonly mapped functions being sensorimotor functions, language generation (often referred to as Broca's area), language perception (often referred to as Wernicke's area), and vision. It is important that the patient is able to lie still when solving the task, as movement of the head during scanning produces signal distortions. Motion is the most important reason for unsuccessful BOLD fMRI investigations (44, 59). The ability to correctly carry out the tasks may vary with patients' cognitive function and intracranial pathology. There are no standardized tasks, scanning procedures, administration of tasks, pre-processing or interpretation of activations for clinical applications of BOLD fMRI, which makes comparisons between publications difficult (121, 130).

The validity of fMRI in detecting sensorimotor activation has been evaluated in a number of studies (7, 98, 141, 144). One of the largest studies compared the results of fMRI motor areas co-registered into neuronavigation with electric cortical stimulation in 32 patients who underwent surgery for a brain tumour or for chronic pain (98). There was a good correlation between the two methods in 87% of the patients, and the authors found the fMRI data helpful in surgical planning and guiding intraoperative brain mapping. A similar study with 18 patients undergoing surgery for a brain tumour, found that the fMRI sensitivity for localizing the primary hand motor cortex detected by electrostimulation was 71% (7). The authors urge caution when using the results of fMRI in intraoperative navigation, and recommend that it is combined with electric

cortical stimulation. There are few studies focusing on validation of functional MR imaging in detecting language cortices, and results are conflicting (12, 98, 99). When it comes to resecting tumours in close proximity to language areas, the role of BOLD fMRI in detecting language cortices has not yet reached the status of full clinical acceptance. Although some believe that BOLD fMRI still cannot replace intraoperative electrocortical stimulation mapping, it has also been suggested that it can be used to speed up intraoperative electrocortical mapping procedures and to guide the extent of the craniotomy.

Some studies have shown that the BOLD response in the vicinity of tumours does not reflect the neuronal signal as precisely as in healthy brain tissue. Schreiber et al report that fMRI activation is reduced near glial tumours, whereas it is not affected by non-glial tumours (107). It is suggested that this might be due to the infiltrative growth of gliomas. In paretic brain tumour patients, studies have also shown a smaller BOLD response in the primary motor area (60, 94). The reasons for this may be altered cortical function or altered hemodynamic response, or both.

Diffusion tensor imaging (DTI) is developed from diffusion weighted MRI. DTI enables the measurement of the anisotropic diffusion of water in neural fibre bundles. It can give delineations of white matter tracts that do not show up on other forms of MRI scanning. The fractional anisotropy (FA) map is the principal form of DTI post-processing images. Another way of presenting the DTI images is through fibre tracking or diffusion tensor tractography (DTT). Fibre tracking algorithms can be used to track a fibre along its whole length (for example within the pyramidal tract) (11). Suggested tracts need to be manually and individually processed with a region-of-interest tool to virtually dissect plausible tracts of interest by choosing anatomical localization tracts are known to run within. For the pyramidal tract, potential region-of-interests are the cerebral peduncles, posterior limb of the internal capsule, and the superior part of the precentral gyrus. In this way the fibres can be tracked from the motor cortex to the spinal cord. Two studies have provided intraoperative electrophysiological verification of DTI-based functional neuronavigation (10, 31). Wu et al conducted an RCT to assess the contribution of functional neuronavigation with DTI in glioma surgery (140). They

used DTI to delineate the pyramidal tract in fractional anisotropy maps and registered these data with the navigation datasets for intraoperative guidance. Compared with the control group, in which the patients underwent operation with navigation guidance without visualization of the pyramidal tract, they achieved a significant reduction of postoperative neurological deficits, a higher number of gross total resections, improved Karnofsky Performance Scale score, and improved survival in high-grade gliomas.

Unlike BOLD fMRI, a DTI investigation does not require the patient to perform a task. The patient only needs to lie still while the images are acquired. The main reasons for reduced quality of DTI are related to pathological processes such as tumour oedema and compression of the white matter tracts. White matter regions where there are several fibre bundles with different orientations or where they "kiss", cross, merge or diverge, are particularly troublesome for the tracking algorithms (28, 79).

It is important to remember that knowledge of the exact position of functional cortices and white matter tracts can not entirely prevent neurological deficits. Intraoperative or postoperative events such as damage to passing or adjacent vessels or postoperative hematomas may result in circulatory changes in functional areas, leading to neurological deficits.

Adverse Events

Risk of adverse events related to treatment is considerably high in neurosurgery compared with many other medical specialties (49). Focus on adverse events has the potential to improve quality of care. At present there is no accepted, uniform way of reporting adverse events in neurosurgical series. Thus, comparisons between various publications are often not feasible. The list of adverse events that can occur during or after resection of malignant astrocytomas is exhaustive. Adequate planning may presumably decrease the risk of complications. This includes detailed study of the preoperative magnetic resonance imaging, neuronavigation, and surgical and interdisciplinary team discussion. Specific thought should be placed on the indication

for surgery and the surgical aim (i.e. gross total resection, subtotal resection, or biopsy). The patient's general physical status should be optimized including the management of increased intracranial pressure. Complete work-up and preparation by the anaesthesiologist and eventually other specialists is often performed in hope of limiting systemic complications.

Aims and Methodological Considerations

The overall aim of this thesis was to study the role of surgical resection in the treatment of high-grade astrocytomas.

Paper 1

Surgical resection of high-grade gliomas in eloquent regions guided by blood oxygenation level dependent functional magnetic resonance imaging, diffusion tensor tractography, and intraoperative navigated 3D ultrasound

We sought to determine clinical outcome, extent of tumour resection, and the practical usefulness of BOLD fMRI and DTT in patients with high-grade gliomas in eloquent regions.

Paper 2

Functional magnetic resonance imaging and diffusion tensor tractography incorporated into an intraoperative 3-dimensional ultrasound-based neuronavigation system: impact on therapeutic strategies, extent of resection, and clinical outcome

We sought to assess the use of fMRI and DTT for preoperative assessments and determine whether using these data together with 3D ultrasound during surgery enabled safe lesion resection in eloquent locations.

Paper 3

The risk of getting worse: Surgically acquired deficits, perioperative complications and functional outcomes after primary resection of glioblastoma

We sought to explore the impact of surgical morbidity on functional outcome and survival in GBM patients.

Paper 4

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

The aim was to determine if changes in health related quality of life could be a predictor for survival in patients with glioblastoma.

Paper 5

Survival and treatment patterns in elderly patients with glioblastoma – A population based study

The aims of this study were to explore survival and the treatment provided to elderly patients (≥66 years) diagnosed with glioblastoma in a population-based cohort using data from the Norwegian Cancer Registry.

Patient Population

All patients included in papers 1, 2, 3, and 4 were treated at the Department of Neurosurgery, St. Olavs University Hospital. The retrospective inclusion of patients in studies 1, 2 and 3 was done through systematic searches in hospital records. Prospective inclusion of patient data based on informed consent was used in study 4. Patients were otherwise selected according to the inclusion and exclusion criteria of each study.

Study data in paper 5 were provided by the Norwegian Cancer Registry. Reports to the Norwegian Cancer Registry have been compulsory by law since 1952. All neoplasms and certain precancerous lesions are to be registered. Cancer information comes from several independent sources, thus securing a high grade of completeness and quality of data. Since 1993 the Norwegian Cancer Registry has also included primary intracranial neoplasms that are solely based on a clinical diagnosis (i.e. neuroimaging) without histological verification. The completeness of patient registration has improved over the years, especially for non-operated cases. There is presumably no other systematic bias in missing data. A study from 2001-2005 demonstrated a 93.8% completeness of data in all central nervous system tumours, including cases without histological verification (67).

Ethical Approval

All studies were approved by the Regional Committee for Medical Research Ethics in Health Region Mid-Norway. Storage of data was approved by the Norwegian Social Science Data Services. Study protocols adhered to guidelines of the Helsinki Declaration. Studies 1, 2, and 3 were also approved by the Norwegian Ministry of Health, which allowed for review of patient data without informed consent. Study 4 was prospective and based on informed consent.

Surgery

Patients presented in studies 1, 2, 3, and 4 were operated at the Department of Neurosurgery, St. Olavs Hospital. The commercially available ultrasound-based neuronavigation system Sonowand was used in the operations. Patients underwent anatomical and functional MRI investigations within 72 hours prior to surgery. Preoperative functional MRI used in most eloquent lesions and aimed at identifying motor and/or language cortices and diffusion tensor tractography sought to identify the corticospinal tract, the optic radiation or the arcuate fasciculus. The preoperative data were imported into the Sonowand system and used for surgical planning and guidance. Intraoperative 2D and 3D ultrasound volumes were acquired when desired during surgery and the multimodal data were used for guidance and resection control. Brain shift and changes in structural anatomy during surgery were detected with intraoperative ultrasound.

Assessment of Tumour Resection and Eloquence

Patients in our department routinely undergo 1.5 T or 3.0 T contrast-enhanced MRI scans a few days before and within 72 hours of surgery. The assessment of tumour resection grades in all papers were based on these pre- and postoperative MRI investigations. To determine resection grades in paper 1 and paper 2, tumour borders were segmented manually in each slice of pre- and postoperative T1-weighted or T1-weighted contrast enhanced MRI images. Tumour volumes were calculated based on the voxel resolution and the total number of voxels segmented. In paper 3 and paper 4 tumour volumes were determined using an ellipsoid volume formula ($4/3 \cdot лг_1г_2г_3$) based on the maximum tumour diameters in the perpendicular dimensions (113, 115). In paper 2, lesion to eloquent area distance (LEAD) was used as a measurement of tumour location relative to functional areas. A more feasible grading system for intraparenchymal brain tumours according to functional location has been presented by Sawaya (106) and this was used in paper 4.

Summary of Papers

Paper 1

Surgical resection of high-grade gliomas in eloquent regions guided by blood oxygenation level dependent functional magnetic resonance imaging, diffusion tensor tractography, and intraoperative navigated 3D ultrasound

Gulati S, Berntsen EM, Solheim O, Kvistad KA, Håberg A, Selbekk T, Torp SH, Unsgård G

Minimally Invasive Neurosurgery 2009

The aims of this study of patients with high-grade gliomas in eloquent brain areas were 1) to assess the postoperative functional outcome, 2) to determine the extent of tumour resection in these difficult locations, 3) to evaluate the practical usefulness of navigated blood oxygenation level-dependent functional magnetic resonance imaging and diffusion tensor tractography.

In this study 25 consecutive patients were included. The patients' gross functional neurological status was determined using the 7-step mRS. The extent of tumour resection was determined using pre- and postoperative T(1)-weighted or T(1)-weighted, contrast-enhanced MRI images.

The average preoperative modified Rankin scale was 1.56+/-0.77, whereas the average postoperative modified Rankin scale was 1.08+/-1.29. There was a significant improvement in mean modified Rankin scale score after surgery. The mean percentage of residual tumour was calculated to 16+/-22% of the original tumour volume (median 8%). Blood oxygenation level-dependent functional magnetic resonance imaging and diffusion tensor tractography were performed in 23 and 18 patients, respectively. Blood oxygenation level-dependent functional magnetic resonance imaging and diffusion tensor tractography facilitated identification of probable functional regions in 91% and 94% of the respective investigations.

We believe that the combination of blood oxygenation level-dependent functional magnetic resonance imaging, diffusion tensor tractography, and 3D ultrasound facilitated maximal tumour resection with minimal deficits. The method permits an image-based functional monitoring of the brain during surgery that may aid the preservation of motor and language function.

Paper 2

Functional magnetic resonance imaging and diffusion tensor tractography incorporated into an intraoperative 3-dimensional ultrasound-based neuronavigation system: impact on therapeutic strategies, extent of resection, and clinical outcome

Berntsen EM, Gulati S, Solheim O, Kvistad KA, Torp SH, Selbekk T, Unsgård G, Håberg AK

Neurosurgery 2010

In this study, functional magnetic resonance imaging (fMRI) and diffusion tensor tractography (DTT) were used to map eloquent areas. We assessed the use of fMRI and DTT for preoperative assessments and determined whether using these data together with 3D ultrasound during surgery enabled safer lesion resection.

We reviewed 51 consecutive patients with intracranial lesions in whom fMRI with or without DTT was used to map eloquent areas. To assess a possible impact of fMRI/DTT, we reviewed and analyzed the quality of the fMRI/DTT data, any change in therapeutic strategies, lesion to eloquent area distance (LEAD), extent of resection, and clinical outcome.

As a result of the fMRI/DTT mapping, the therapeutic strategies were changed in 4 patients. The median tumour residue for glioma patients was 11% (n = 33). For gliomas, there was a significant correlation between decreasing LEAD and increasing tumour residue. Of the glioma patients, 42% underwent gross total resection (≥95%) and 12% suffered neurological worsening after surgery. Of glioma patients with an LEAD of ≤5 mm, 24% underwent gross total resection and 10% experienced neurological deterioration.

This study demonstrates that preoperative fMRI and DTT had direct consequences for therapeutic strategies and indicates their impact on intraoperative strategies to spare eloquent cortex and tracts. Functional neuronavigation combined with intraoperative 3D

ultrasound may, in most patients, enable resection of brain lesions with general anaesthesia without jeopardizing neurological function.

Paper 3

The risk of getting worse: Surgically acquired deficits, perioperative complications and functional outcomes after primary resection of glioblastoma

Gulati S, Jakola AS, Nerland US, Weber C, Solheim O

World Neurosurgery 2011

Gross total resection (GTR) prolongs survival, but is unfortunately not achievable in the majority of patients with GBM. Cytoreductive debulkings may relieve symptoms of mass effect, but it is unknown how long such effects sustain and to what degree the potential benefits exceed risks. We explore the impact of surgical morbidity on functional outcome and survival in unselected GBM patients.

We retrospectively reviewed 144 consecutive adult patients operated for primary GBM at a single institution between 2004 and 2009. 141 (98%) operations were resections whilst 3 (2%) were biopsies. A decrease in Karnofsky performance status (KPS) scores was observed in 39% of patients after 6 weeks. On average, there was a significant decrease between pre- and postoperative KPS scores ($p<0.001$). 22 (15.3%) patients had new neurological deficits. Among patients who underwent surgical resection, those with new neurological deficits were less likely to receive radiotherapy ($p<0.001$), normofractioned radiotherapy ($p=0.010$), and chemotherapy ($p=0.003$). 28 (19.4%) patients had perioperative complications. Among patients who underwent surgical resection, those with perioperative complications were less likely to receive normofractioned radiotherapy ($p=0.010$) and chemotherapy ($p=0.009$). Age ($p=0.019$), new deficits ($p<0.001$), and surgical complications ($p=0.006$) were significant predictors for worsened functional outcome after 6 weeks. GTR ($p=0.035$), perioperative complications ($p=0.008$), radiotherapy ($p<0.001$), and chemotherapy ($p=0.045$) were independent factors associated with 12 month postoperative survival.

Patients with perioperative complications and surgically acquired deficits were less likely to receive adjuvant therapy. While cytoreductive debulking may not improve

survival in GBM, it may decrease the likelihood of patients receiving adjuvant therapy that does.

Paper 4

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

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

Sixty-one patients with complete HRQL data were included. 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 (49.2 %) patients reporting deterioration 6 weeks after surgery, forming the basis for the analysis concerning association between change in HRQL data and survival. In a Cox multivariate survival analysis we evaluated deterioration in HRQL after surgery together with established risk factors (age, preoperative condition, radiotherapy, temozolomide and extent of resection).

We found 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 and actually strengthened the association between deterioration in HRQL after surgery with overall survival (HR 2.4, p=0.022).

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

Paper 5

Survival and treatment patterns in elderly patients with glioblastoma – A population based study

Gulati S, Jakola AS, Johannesen TB, Solheim O

World Neurosurgery 2012

The aims of this study were to explore survival and the treatment provided to elderly patients (≥66 years) diagnosed with GBM between September 1988 and September 2008 in a population-based cohort using the Norwegian Cancer Registry. From the Norwegian Cancer Registry, we included 2882 patients who were diagnosed with glioblastoma between September 1988 and September 2008.

The proportion of patients ≥66 years was 42.5 % (n =1224), and 15.9% of patients (n = 459) were ≥75 years at diagnosis. We found that treatment patterns varied significantly between age groups. Elderly patients were more likely to receive supportive care only and resection only and less likely to receive multimodal treatment with resection combined with radiation and/or chemotherapy. In addition, elderly patients were more likely to receive a diagnosis of GBM without histopathological verification. Among patients receiving multimodal treatment with resection, radiation, and chemotherapy, there was statistically significant shorter survival in the age groups 66-74 years and ≥75 years. Belonging to the age group ≥75 years was identified as the strongest predictor of decreased survival. Increasing age, no tumour resection, no radiation, and no chemotherapy were identified as independent predictors of reduced survival. There was a statistically significant survival advantage for patients diagnosed in the last five years of the study.

There is still a need for clinical studies to clarify the role of treatment modalities in all patients with GBM. The evaluation of surgical resection, radiotherapy and chemotherapy must involve patients with demographic characteristics that are representative of the majority of patients with glioblastoma, and elderly patients can therefore no longer be excluded. Providing guidelines on GBM resection to the elderly

on the basis of trial information obtained mainly from younger patients is not recommended as age remains a very strong and independent prognostic factor.

Discussion

The vast amount of medical technical publications indicates that there are very sincere efforts going on to improve safety and quality in high-grade glioma surgery. However, defining, measuring, and reporting outcomes in this field of research are difficult challenges. In the research presented in this thesis, we have used several different outcome parameters including overall survival, resection grades, functional outcomes, adverse events, and patient reported health related quality of life. We have experienced that defining quality in high-grade glioma surgery remains an elusive task.

Extent of resection and its impact on survival

In papers 1 and 2, one of the aims was to determine the extent of tumour resection in patients with malignant astrocytomas located in eloquent regions. Pre- and postoperative tumour volumes were also provided for the patients in paper 3. A central question in neuro-oncology is whether more extensive resections of malignant gliomas are beneficial to patients. In the last decade numerous studies investigating the impact of resection on survival have been published. There are both studies which advocate more extensive resections (22, 23, 63, 65, 84, 105, 114, 117, 127) and those in which the statistical analyses did not favour any resection group (52, 70, 92, 93, 125). Most are retrospective series where direct comparisons are compounded by differences in patient characteristics, surgical technique, and outcome assessment and reporting.

As for patient characteristics, factors such as age, time of enrolment, preoperative functional status, eligibility for GTR, tumour location, and tumour size may be associated with outcome. Biopsy or limited resections may more often be preferred in patients with poor performance status, of older age, or when the tumour is in an anatomically prohibitive location for gross total resection. Survival comparisons in retrospective studies are often made between patients who have merely been biopsied

and those who have undergone resection (103). This selection bias makes it difficult to assess the impact of resection on postoperative survival.

The manner in which the extent of resection is calculated is also of importance. Many studies rely on the surgeons' reports or two-dimensional analysis based on postoperative MRI scans. Surgeons' estimates of resection grades are often inaccurate and they have a tendency to estimate a more radical resection than calculated from postoperative MRI imaging (113). Most studies divide resections qualitatively into gross total, subtotal, and partial or biopsy categories. However, the definition of gross total resection may vary between studies. Volumetric MRI analysis is now regarded as the accepted standard (103), but is only provided in a few studies (52, 63, 92, 105, 117).

Some studies recruit patients from previously conducted prospective trials (103). As a histological verification of the diagnosis is mandatory, nearly all these trials enrol patients after recovery from surgery. However, there are often predefined lower bounds of functional performance status at the time of inclusion. This means that patients who suffered significant morbidity or died perioperatively were excluded due to the study design. This can result in a selective loss of patients injured by the treatment which is assessed.

Even though maximal safe surgical resection is advocated (20, 134), the role of incomplete tumour resection in prolonging survival is controversial (58, 77, 131). If resection is performed it seems like it needs to be extensive to affect survival. In a frequently cited retrospective study, 416 consecutive patients with GBM who underwent tumour resection were analysed. A statistically significant survival advantage was associated with resection of 98% or more of the tumour volume (63). Some limitations have been pointed out in the methodology of this paper (82, 105). Most importantly the study included both newly diagnosed and recurrent GBM, and the timing of postoperative imaging acquisition was inconsistent. The statistical methods used in an article can greatly influence results. In a recently published retrospective study with 500 patients by Sanai et al (105), it is claimed that subtotal resections as low as 78% correspond to a survival benefit. However, the 78% cut-off seems to be found in

univariate analyses only, apparently through an explorative approach with serial dichotomizations in Kaplan Meier curves. In search of the resection threshold, serial Kaplan-Meier survival curves were generated at 2% extent of resection intervals. This method did not account for confounding or effect modification by other covariates. Achieved resection grades and overall survival are affected by several patient and tumour characteristics, making this an important flaw of the study (111). Moreover, multiple pair-wise comparisons are known to produce cumulative type I errors increasing the risk of false positive findings.

A post-hoc analysis of 243 patients involved in a trial of 5-ALA showed that extent of resection has a positive correlation with survival (117), but only so-called complete resection (i.e. GTR) had an impact on survival. All patients in the ALA-study were eligible for complete resection. Patients in this study were randomised to resection of a primary high-grade glioma by either white light or fluorescence guided resection (with orally administered 5-ALA). However, external validity is low in this study since patients were very highly selected, not reflecting those in routine clinical practice.

For the majority of patients with GBM, GTR cannot be achieved. GTR is usually achieved in less than 20% in more or less unselected patient series with postoperative imaging (2, 6, 57, 109, 129). In a pooled analysis of 893 patients from several phase II GBM studies, resection of >90% of the tumour volume (NTR or better) was only seen in 17% (25). In paper 3 we achieved GTR in one third of the patients, which is good compared to other unselected series in the literature.

In paper 3, only GTR (defined as ≥98% tumour removal) was associated with prolonged survival in a multivariate analysis ($p=0.035$). The statistical method used in this paper can be criticized as we used a minimum probability value method (3). Unfortunately, this strategy is associated with an increase in the false-positive rate. This strategy attempts to define a statistical cut-off by categorizing the data set into two groups on the basis of a single variable, in our case extent of resection. Further, inclusion of a cut-off determined in such a manner as a binary variable in the Cox multiple regression analysis can lead to an inflated effect at the expense of other variables.

There are clear limitations in the data examining the effect of subtotal resection on postoperative survival. Due to the lack of evidence it is difficult to establish convincing guidelines for extent of resection of malignant gliomas. Each institution has to determine if the quality of evidence is sufficient to influence their practice standards. There is still a need for clinical studies to clarify the role of resection in patients with malignant gliomas, but careful thought needs to be placed regarding study designs. Possible trial designs include true randomized trials of surgery (such as biopsy versus maximal safe resection in patients ineligible for gross total resection), randomized trials of surgical techniques designed to improve resection grades (117), or prospective community-based registration of all patients who undergo surgery (142). The latter provides high external validity, but difficulties establishing certain causality.

Reporting of functional outcomes

Functional and neurologic outcomes related to GBM surgery have been presented in numerous studies. However, it is difficult to compare functional outcomes as there is a considerable variation in inclusion criteria, classification of outcomes, and time of follow-up between different studies. Many published surgical series exclude biopsies or include only patients in whom gross tumour resection was attempted, complicating comparisons of results between studies and lowering external validity of the findings. Data from the Glioma Outcomes Project report of a potential selection bias as image guided resections tend to be carried out in patients with a more favourable prognosis (72). The better functional outcomes reported in papers 1 and 2 compared to paper 3, can probably be explained by a stricter patient selection. Even though specific scales exist for a number of neurologic conditions, there is no uniform method to define significant neurologic change for malignant glioma trials. Malignant glioma trials have yet to identify the functional outcome scale of choice for consistent use across studies.

In papers 1 and 2 patients' functional status was determined using the 7-step mRS. The mRS is primarily intended for measuring the degree of disability or dependence in the

daily activities of patients who have suffered a stroke, and it has become the most widely used clinical outcome measure for stroke clinical trials. It has been shown that the mRS has good interobserver agreement for the assessment of handicap in stroke patients (128). Patients' functional status was not provided in paper 5 as this information is unfortunately unavailable in the Norwegian Cancer Registry. In papers 3 and 4 patients' functional status was described using the Karnofsky Performance Status (KPS). This is a widely evaluated metric across many oncology trials, and is an established prognostic factor for overall survival in high-grade gliomas. The KPS score was registered in a prospective fashion in paper 4. As the clinical presentation is highly dependent on the location of the tumour, the KPS and mRS scores might not adequately reflect the extent of disease or disease burden in all patients. As an example, a patient with a very small tumour in the motor cortex may have much lower scores on these metrics of functional status than a patient with a large tumour in one of the frontal lobes.

One concern regarding our use of the mRS and KPS is that they were utilized in a retrospective manner in papers 1, 2 and 3. It is also difficult to distinguish reductions in mRS and KPS scores due to adverse effects of surgery from tumour progression, comorbid events, and concurrent adjuvant therapy. In papers 1, 2 and 3 we therefore also included information about specific neurologic deficits before and after surgery.

Evaluating adverse events

We attempted to report adverse events in concurrence with Good Clinical Practice Guidelines in paper 3 (http://www.ema.europa.eu: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), a system most often used in clinical drug trials. Adverse events are defined as any unexpected medical occurrence in a patient undergoing surgical treatment, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporarily associated with surgical treatment. Serious adverse events are defined as any unexpected medical occurrence in the operative period, which resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity. The subjectiveness of reporting is reduced since all events are reported, even though there may not always be a causal relationship between the treatment and the event. The potential advantage of this classification is the ability to compare surgical results among different centres and time periods, as well as providing an opportunity to perform future meta-analyses. The Good Clinical Practice Guidelines provided a simple, practical, and reproducible way to report adverse events, comparable to interventional drug trials. Information from such a classification system of adverse events could provide valuable insight for neurosurgeons regarding how to manage and avoid surgical complications. It could also provide patients with more complete information about the risks of surgical complications.

There are a few publications that attempt to classify complications associated with general neurosurgical and spinal interventions (15, 45). A recent study by Ibanez et al, which has received enthusiastic appraisal, introduces a new classification system for complications in neurosurgery (46). Their classification is based on a system from general surgery but modified to fit neurosurgical procedures (30). The authors suggest using a four-grade scale based on the therapy used to treat the complication. Adverse events are further divided into surgical or medical complications. This proposed classification system of complications has many of the same advantages and challenges as the Good Clinical Practice guidelines. Whereas the Good Clinical Practice guidelines

are applicable to almost any medical specialty, the classification system suggested by Ibanez has been tailored to better fit neurosurgical procedures. However, none of the two classification systems take preoperative morbidity into account and both rely on surgeon self-reporting.

The main strength of paper 3 is the unselected, practically population-based inclusion, ensuring high external validity of results. However, due to the retrospective study design it is fair to assume that some adverse effects of surgery may have gone unnoticed. In paper 3 a comparison with other relevant studies with regards to adverse events is provided. For now, a systematic or unsystematic review of the incidence of adverse events in malignant glioma surgery remains difficult because such events are not always well defined, and assessments are often subjective, arbitrary, and probably under-reported. The numbers of adverse events vary considerably between studies, and this can probably be explained by differences in reporting and patient selection.

Survival as an outcome parameter

Overall survival

In papers 2, 4, and 5 we presented data on overall survival for patients with high-grade glioma, whereas one-year and two-year survival were presented in paper 3 as follow-up time was limited for the patients operated in the last part of the study period. As overall survival reflects a clinically meaningful benefit that can be objectively and unambiguously assessed, it is generally considered the definitive primary end point for patients with malignant glioma. However, the use of overall survival as a primary end point has its drawbacks. A major challenge using overall survival as an end point is that many patients undergo multiple therapies, making it difficult to determine the attributable effect of a single treatment modality. In studies based on overall survival a longer follow-up time might be desired as compared to the other outcome parameters. As exemplified in the famous 5-ALA study (115), the impact of the intervention on overall survival may be less pronounced than its impact on resection grades and progression-free survival, resulting in the need for larger sample sizes. These factors

may increase required study duration, sample size, and cost. Factors such as age and preoperative performance status also affect survival time and may introduce greater variability in outcome. It is also important to keep in mind that start times may vary across studies and this can impact the presented overall survival.

Progression-free survival

Progression-free survival (PFS) measures time from treatment initiation to progression. There is evidence that PFS correlates with overall survival (5, 66). One of the main advantages using PFS as an end point is that studies can be completed in a shorter time frame. In addition, PFS-based studies require smaller sample sizes because a treatment effect is often greater on PFS than overall survival. Finally, PFS end points may be less affected by subsequent therapies or 2^{nd} line treatments (e.g. re-do surgeries, 2^{nd} line chemotherapy, repeated radiotherapy) compared to overall survival. The main reason for not using PFS as an end point in our studies is evaluation time bias due to non-uniform patient assessment and follow-up. Studies on growth dynamics or progression free survival require standardized MRI protocols at predefined intervals. Another disadvantage of PFS end points are the non-uniform definitions of tumour progression used. Determination of PFS is dependent on a standardized method to define tumour progression. Current radiographic methods to define progression are problematic due to confounding factors such as pseudoprogression and pseudoresponse (96). Recently the Response Assessment in Neuro-Oncology (RANO) Working Group established new criteria to determine tumour progression in a more reliable and objective manner (135).

Perioperative mortality

Perioperative mortality or surgical mortality is usually defined as death occurring during the 30 first days after an operation. However, definitions such as death within 2 or 4 weeks are also used. In publications based on administrative databases, in-house-mortality is often used as this measure is more readily available. Surgery related mortality has historically been a highly relevant outcome measure in neurosurgery, allowing a comparison of outcome between surgeons and different surgical techniques. By 1910 Harvey Cushing had performed 250 brain tumour operations with a surgical mortality of 13%. In comparison, operative mortalities of contemporary surgeons were

approximately 50% (73). Still today, surgical mortality is a frequently studied and published outcome parameter. Surgical mortality has been endorsed as an Inpatient Quality Indicator by the US Agency for Healthcare Research and Quality for eight surgical procedures in adults, including craniotomies. Surgical mortality rates are also increasingly publicly reported as an indicator of hospital quality, despite often considerable limitations in data concerning differences in referral and case mix (37).

While the pioneers in brain tumour surgery dealt with perioperative deaths quite frequently, early postoperative deaths now occur very seldom. The overall risk of perioperative death after first time surgery for primary intracranial tumours is currently around 2.2% (110). This low incidence greatly limits the power in comparative analyses, such as between patient series or between centers, and certainly between surgeons. Although, by consensus considered surgically related if occurring within the 30 first days of surgery, most early postoperative deaths after brain tumour surgery may occur independent of the handwork of the operating surgeon. The overall prognosis of the tumour disease seems to be a strong predictor (110), perhaps to no surprise since the 30-day mortality rate is merely the intonation of the Kaplan Meier curve. Both referral and treatment policies at a neurosurgical centre will therefore affect such early outcomes markedly. Further, the correlation between a hospital's perioperative mortality rates and long term survival rates seems weak (110). The value of perioperative mortality rates as a quality indicator in modern neurosurgical tumour operations may therefore be questionable.

Health related quality of life

Whereas functional outcomes (e.g., KPS and mRS) and resection grades are measured by health care workers, health related quality of life (HRQL) is a patient reported outcome (PRO). Differences probably exist between the doctor and cancer patients' assessment of their health. With a range of therapeutic options for patients with malignant glioma and with various risks of adverse effects, PROs can be used to evaluate different treatments (76). For patients with brain tumours, there are several

HRQL questionnaires available that can be used to assess the physical, psychological, and social impact of the disease and its treatment (96). HRQL is established as an outcome parameter for treatment comparisons in many malignant diseases, particularly in palliative settings (19). The most common cancer-specific HRQL tool is the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) which also has an extensively validated supplement for patients with brain tumours (QLQ-BN-20) (122).

In paper 4 we used the EuroQol 5D (EQ-5D) questionnaire to assess HRQL. This is a generic questionnaire (not developed for any specific patient group) that has been applied to a wide range of health conditions and treatments. The EQ-5D has also been validated in a Norwegian population (85). A recent study showed that EQ-5D correlated well with KPS in patients with glioma and was responsive to surgically induced neurological deficits (48).

The usefulness of baseline HRQL data for patients with brain tumours remains a debated topic (76). There are conflicting data regarding the prognostic significance of baseline HRQL for patients with malignant gliomas and whether it may have additional value over other well known prognostic factors (21, 75). One study has shown that baseline HRQL was predictive of quality of life over time, and that gross total resection was associated with longer survival and improved quality over time for patients with high-grade gliomas (22). In previous studies baseline HRQL data were generally obtained after surgery. In paper 4, where baseline HRQL data were collected preoperatively, we found a negative effect on survival if HRQL deteriorated early after surgery in patients with GBM. Evaluation early after surgery most likely represents treatment related factors compared to later assessments that would be more likely to represent disease related factors. Thus, in 6 weeks we believe it is less likely that the majority of patients with deterioration in HRQL have experienced significant progression or adverse effects of adjuvant therapies.

Susceptibility to response shift over time is one of the drawbacks of using HRQL to assess clinical benefit or deterioration in clinical trials. Another concern is selection bias

as patients in poor clinical condition are less likely to respond. Missing data are also a concern for the interpretation of patients' HRQL, potentially introducing bias to the statistical analyses. Administrative failure is a common cause of missing data (132). The perception that the severity of the disease will affect the patient's ability to fill out the questionnaire may also hinder the use of HRQL assessments. Patients who rapidly deteriorate are less likely to fill out the questionnaires than the fitter ones, and this may lead to an overestimation of patients' HRQL (132).

For many patients with high-grade gliomas, surgical resection is thought to relieve symptoms. Increased extent of tumour resection should be weighed against clinical performance and quality of life. It has even been suggested that in the palliative care setting, which is relevant for many patients with malignant glioma, clinical trials should be designed also with softer endpoints, such as HRQL, perhaps even with extended survival reported as a secondary end-point (55). The benefits of extended survival or progression delay have to be balanced alongside adverse effects of surgery. We therefore believe that HRQL assessments provide a meaningful end point in surgical trials of high-grade gliomas.

Neurosurgical tools in high-grade glioma resection

The main rationale for the use of intraoperative imaging is to correct for brain shift during tumour resection. In addition to intraoperative ultrasound, intraoperative visualization tools that can be applied when resecting of high-grade gliomas include fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) and intraoperative MRI. When performing surgery close to eloquent regions, intraoperative electrical motor cortex mapping and recording phase reversal of somatosensory evoked potentials are considered the gold standard. The classic procedure for language localization is intraoperative electrocortical mapping in awake patients, although seldom reported as routine procedure in suspected high-grade gliomas.

Papers 1, 2, and 3 are limited by their retrospective nature and the absence of control groups. Papers 1 and 2 are feasibility studies of technical applications presenting clinical data related to the use of this technology. We believe the external validity is fairly high in paper 3. Based on the research presented in this thesis, it is difficult to assess how surgery guided by 3D intraoperative ultrasound and preoperative BOLD fMRI and DTT compares to other surgical techniques with regards to resection grades, functional outcome, HRQL, and survival. To answer these questions a randomized trial or at least a pseudo-randomised population based registration with validated end points seem necessary. Using 3D intraoperative ultrasound also has some challenges and limitations. Whereas most neurosurgeons are used to interpreting CT and MR images, 3D intraoperative ultrasound images may be unfamiliar to many and require some time to fully understand. Another disadvantage is that the acquired volume only covers the region of interest. This can be compensated by either displaying corresponding preoperative MR and ultrasound images, or superimposing the ultrasound volumes on the preoperative MR images. Further, there may be a decline in ultrasound image quality during the operation (101). The quality of ultrasound acquisitions in patients undergoing repeated glioma surgery with previously administered radiotherapy can be variable. The image quality also depends on a clean resection cavity without blood clots and cottonoids. Some thought also needs to be placed on patient positioning as the head should be positioned such that a vertical access to the lesion can be obtained. This allows air bubbles to rise to the surface when the operation cavity is filled with saline for ultrasound recordings.

Recently, 5-aminolevulinic acid (5-ALA) has emerged as a drug with usefulness as a metabolic marker of malignant glioma cells that can be used intraoperatively to detect tumour tissue (118). This technique is based on the synthesis and accumulation of fluorescent and photosensitizing endogenous porphyrins after excess administration of 5-ALA, a naturally occurring metabolite in the heme biosynthesis pathway. Patients receive orally administered 5-ALA three hours before surgery. Intraoperatively, fluorescence is observed through an operating microscope equipped with a fluorescent ultraviolet light and filters. An RCT by Stummer et al showed how 5-ALA guided surgery enabled more complete resections of contrast-enhancing tumour, leading to

improved PFS in patients with malignant glioma (115). The study demonstrated early postoperative MRI to be devoid of contrast-enhancing tumour in 65% of patients with GBM in the 5-ALA group compared with 36% in a conventional microsurgical control group. Fluorescence-guided surgery can be combined with neuronavigation, intraoperative ultrasound, and awake surgery. There are some challenges associated with fluorescence-guided surgery (124). Timing of the oral administration of 5-ALA is important. Blood in the resection cavity reduces the fluorescence signal. There is also an exponential decline of excitation light intensity with growing distance; thus distance between the microscope and resection cavity should be kept small. Further, small corticotomies shade illumination light and also result in low fluorescence intensities. Ambient light within the operating room will interfere with the fluorescence signal, and care must be taken to reduce this. Due to the transient sensitization of the skin associated with the administration of 5-ALA, one should try to prevent excessive illumination of the patient's skin.

There are numerous publications on the added value of both low-field-strength (≤0.5 Tesla) and high-field-strength (≥1.5 Tesla) intraoperative MRI-guided resection of brain tumours compared with conventional neuronavigation. Fibre tracking using diffusion tensor imaging has been reported on high-field strength MRI systems (83). In a thorough review by Kubben et al, several limitations and sources of bias which may lead to an overestimation of the attributable value of intraoperative MRI-guided surgery for resection of GBM are pointed out (62). One source of bias is attribution bias as intraoperative imaging may lead to a more conservative resection before the first intraoperative control scan is performed. This might lead to the conclusion that extent of resection is increased after intraoperative scanning. Attribution bias is also relevant for intraoperative 3D ultrasound recordings. Other concerns regarding research on intraoperative MRI-guided surgery are the various definitions of tumour volume and GTR. In addition, control groups may not be equivalent to study groups, mainly with regard to tumour location. Few studies provide explicit data on patients' clinical performance and data on quality of life seems to be lacking. The review points out the need for randomized trials to show the added value of intraoperative MRI-guided surgery. In a recent study by Senft et al, 58 patients with suspected gliomas were

randomly assigned to undergo intraoperative low-field-strength (0.15 Tesla) MRI-guided surgery or conventional microsurgery (without intraoperative ultrasound or 5-ALA) (108). Higher resection grades and improved PFS were found in patients who underwent intraoperative MRI-guided surgery. There are some practical challenges with intraoperative MRI systems. For example, intraoperative MRI is an expensive technique. In addition, a longer preparation time before incision and longer preparation times before and immediately after image acquisition need to be taken into account (62, 108).

Several studies have reported the feasibility of intraoperative brain mapping and its possibly positive influence on clinical outcomes (33, 81, 91, 123). Patients with a high-grade glioma close to an eloquent area such as the motor strip or sites possibly related to language function are potential candidates for brain mapping. Brain mapping is achieved by direct cortical stimulation with bipolar stimulation forceps, bipolar stimulation electrode or electrodes in form of stripes or grids. When applying stimulation, a function can be either elicited (such as motor response) or suppressed (such as execution of language). Positive cortical stimulation identifies cortical sites associated with and sites not associated with motor, somatosensory, or language function, whereas negative cortical stimulation typically identifies only sites not associated with such function. Thus, functionally relevant areas can be identified. The same can be achieved by stimulating white matter tracts. In a study published in 2008, Sanai et al advocate negative mapping through intraoperative cortical stimulation (negative cortical stimulation) instead of traditional positive cortical stimulation to preserve language function during glioma resection in or near language areas (104). Monitoring of language function requires the patient to be awake, oriented, and cooperative during the procedure of testing. This means that not all patients are eligible for brain mapping of language areas. Other challenges associated with awake surgery include epileptic convulsions due to cortical mapping and patient positioning on the OR-table. Patients who undergo brain mapping for identification of cortical motor function do not necessarily need to be awake during surgery. Motor evoked potentials can be recorded from muscles following direct stimulation of exposed motor cortex, and

somatosensory evoked potentials phase reversal can help identify the central sulcus. Interestingly, an RCT comparing resection under general versus local anesthesia awake surgery for tumours in eloquent areas showed that operative time and blood loss were less in the general anesthesia group. Better neurological outcome and a higher degree of resection were also achieved in the general anesthesia group (39).

High-grade gliomas in the elderly

The lack of sufficient evidence makes it difficult to establish recommendations for surgical treatment of GBM in the elderly. Each department has to determine if the quality of evidence is sufficient to influence their practice standards. There is still a need for clinical studies to clarify the role of resection in all patients with GBM, but careful thought needs to be placed regarding study designs. Possible trial designs include true randomized trials of surgery (such as biopsy versus maximal safe resection in patients ineligible for gross total resection), randomized trials of surgical techniques designed to improve resection grades (117), or more extensive prospective population based registrations (including performance status, quality of life registrations, volumetric tumour data, functional outcomes, and adverse events related to surgery) of all patients who undergo surgery. The evaluation of surgical resection must involve patients with demographic characteristics that are representative of the majority of patients with GBM, and elderly patients should not routinely be excluded. Providing guidelines on GBM resection to the elderly on the basis of trial information obtained mainly from younger patients does not necessarily constitute good clinical practice. One study tried to estimate how surgical resection affected postoperative survival compared to biopsy in patients over 65 years old with a suspected diagnosis of malignant glioma (131). In total, 30 patients were included in this study. The authors reported their findings as being in favour of resection. Due to methodological limitations, described in detail in a Cochrane review, the findings in this study are tainted by a high chance of being affected by bias (42). The findings of this trial are of insufficient reliability to be used to influence treatment decisions. However, the study should be viewed as evidence that randomised controlled trials in elderly patients with GBM are possible.

Recommendations for future research

Based on the discussion in this thesis and the results presented in papers 1-5, a few recommendations for future studies on high-grade glioma resection can be made. First, if extent of tumour resection is to be used as an end point, a clear definition of postoperative tumour volume and a valid method to measure volume is of paramount importance. Second, more population-based prospective studies with high external validity and also randomized studies, such as the ones by Stummer (115) and Senft (108), are needed when comparing different types of surgical techniques. Third, outcome data should be more detailed and not only present functional outcome as judged by the surgeon, but also include PROs (i.e. HRQL). HRQL should be evaluated together with resection grades and survival to find a balance that can be used to benchmark treatment results in patients with high-grade gliomas. Fourth, adverse events should be recorded and presented in a uniform way. This will help evaluating different surgical techniques and provide valuable insight for neurosurgeons regarding how to manage and avoid complications. Studies should not solely focus on survival as there are several ways to improve patient care in patients with high grade glioma. In addition, standardized reporting of surgically based neuro-oncology trials should be encouraged (26).

The Norwegian Cancer Registry is a valuable source of information, and has formed the basis of several neuro-oncology publications (50, 112). However, the quality of future research might be improved if more details regarding patient and tumour characteristics along with additional outcome parameters are sampled in the registry. Information about HRQL, pre- and postoperative functional levels, adverse events, tumour size and localization, surgical complexity (e.g., eloquence), operative technique, and resection grades could help further clarify the role of surgical resection of high-grade gliomas. Prognostic models have been constructed for patients with cerebral metastases (47), and the concept of constructing and investigating similar scales for high-grade gliomas based on population based registry data is intriguing.

Conclusions

This thesis has investigated the role of surgical resection in the treatment of malignant astrocytomas and the following conclusions can be drawn:

- The combination of blood oxygenation level-dependent functional magnetic resonance imaging, diffusion tensor tractography, and 3D ultrasound may facilitate resection of malignant astrocytomas harboured in eloquent areas while preserving motor and language function.
- Functional neuronavigation combined with intraoperative 3D ultrasound can, in selected patients, enable resection of brain lesions with general anaesthesia without jeopardizing neurological function.
- Patients with perioperative complications and surgically acquired deficits were less likely to receive adjuvant therapy.
- Early deterioration in HRQL after surgery was independently and markedly associated with impaired survival in patients with glioblastoma.
- Advancing age remains a very strong and independent negative prognostic factor in glioblastoma. Although there has been an increase in the aggressiveness of treatment provided to elderly with glioblastoma, the gain for the oldest age group seems at best very modest. The prognosis of the oldest age group remains very poor, despite multimodal treatment.

References

[1] Adamson C, Kanu OO, Mehta AI, Di C, Lin N, Mattox AK, Bigner DD: Glioblastoma multiforme: a review of where we have been and where we are going. Expert Opin Investig Drugs 18:1061-1083, 2009.

[2] Albert FK, Forsting M, Sartor K, Adams HP, Kunze S: Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. Neurosurgery 34:45-60; discussion 60-41, 1994.

[3] Altman DG, Lausen B, Sauerbrei W, Schumacher M: Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst 86:829-835, 1994.

[4] Armstrong TS, Prabhu S, Aldape K, Hossan B, Kang S, Childress A, Tolentino L, Gilbert MR: A case of soft tissue metastasis from glioblastoma and review of the literature. J Neurooncol.

[5] Ballman KV, Buckner JC, Brown PD, Giannini C, Flynn PJ, LaPlant BR, Jaeckle KA: The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro Oncol 9:29-38, 2007.

[6] Barker FG, 2nd, Prados MD, Chang SM, Gutin PH, Lamborn KR, Larson DA, Malec MK, McDermott MW, Sneed PK, Wara WM, Wilson CB: Radiation response and survival time in patients with glioblastoma multiforme. J Neurosurg 84:442-448, 1996.

[7] Bartos R, Jech R, Vymazal J, Petrovicky P, Vachata P, Hejcl A, Zolal A, Sames M: Validity of primary motor area localization with fMRI versus electric cortical stimulation: a comparative study. Acta Neurochir (Wien) 151:1071-1080, 2009.

[8] Bekar A, Kahveci R, Tolunay S, Kahraman A, Kuytu T: Metastatic gliosarcoma mass extension to a donor fascia lata graft harvest site by tumor cell contamination. World Neurosurg 73:719-721.

[9] Bennett AH, Godlee RJ: A case of cerebral tumor--the surgical treatment. CA Cancer J Clin 24:171-181, 1974.

[10] Berman JI, Berger MS, Mukherjee P, Henry RG: Diffusion-tensor imaging-guided tracking of fibers of the pyramidal tract combined with intraoperative cortical stimulation mapping in patients with gliomas. J Neurosurg 101:66-72, 2004.

[11] Berntsen EM: Preoperative Planning and Functional Neuronavigation - with functional MRI and Diffusion Tensor Tractography in Patients with Brain Lesions. PhD thesis, NTNU, 2009.

[12] Bizzi A, Blasi V, Falini A, Ferroli P, Cadioli M, Danesi U, Aquino D, Marras C, Caldiroli D, Broggi G: Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology 248:579-589, 2008.

[13] Black PM: Brain tumor. Part 2. N Engl J Med 324:1555-1564, 1991.

[14] Bleehen NM, Stenning SP: A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. The Medical Research Council Brain Tumour Working Party. Br J Cancer 64:769-774, 1991.
[15] Bonsanto MM, Hamer J, Tronnier V, Kunze S: A complication conference for internal quality control at the Neurosurgical Department of the University of Heidelberg. Acta Neurochir Suppl 78:139-145, 2001.
[16] Bonvento G, Sibson N, Pellerin L: Does glutamate image your thoughts? Trends Neurosci 25:359-364, 2002.
[17] Bookheimer S: Pre-surgical language mapping with functional magnetic resonance imaging. Neuropsychol Rev 17:145-155, 2007.
[18] Borgo MC, Pereira JL, Lima FB, Brandao RA, Carvalho GT, Costa BS: Glioblastoma multiforme in childhood: a case report. Clinics (Sao Paulo) 65:923-925.
[19] Bottomley A, Flechtner H, Efficace F, Vanvoorden V, Coens C, Therasse P, Velikova G, Blazeby J, Greimel E, European Organisation for R, Treatment of Cancer Data C, Quality of Life G: Health related quality of life outcomes in cancer clinical trials. Eur J Cancer 41:1697-1709, 2005.
[20] Brem SS, Bierman PJ, Brem H, Butowski N, Chamberlain MC, Chiocca EA, Deangelis LM, Fenstermaker RA, Friedman A, Gilbert MR, Hesser D, Junck L, Linette GP, Loeffler JS, Maor MH, Michael M, Moots PL, Morrison T, Mrugala M, Nabors LB, Newton HB, Portnow J, Raizer JJ, Recht L, Shrieve DC, Sills AK, Jr., Vrionis FD, Wen PY: Central nervous system cancers. J Natl Compr Canc Netw 9:352-400, 2011.
[21] Brown PD, Ballman KV, Rummans TA, Maurer MJ, Sloan JA, Boeve BF, Gupta L, Tang-Wai DF, Arusell RM, Clark MM, Buckner JC: Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. J Neurooncol 76:283-291, 2006.
[22] Brown PD, Maurer MJ, Rummans TA, Pollock BE, Ballman KV, Sloan JA, Boeve BF, Arusell RM, Clark MM, Buckner JC: A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. Neurosurgery 57:495-504; discussion 495-504, 2005.
[23] Buckner JC, Schomberg PJ, McGinnis WL, Cascino TL, Scheithauer BW, O'Fallon JR, Morton RF, Kuross SA, Mailliard JA, Hatfield AK, Cole JT, Steen PD, Bernath AM: A phase III study of radiation therapy plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioma. Cancer 92:420-433, 2001.
[24] Bucy PC, Oberhill HR, Siqueira EB, Zimmerman HM, Jelsma RK: Cerebral glioblastomas can be cured! Neurosurgery 16:714-717, 1985.
[25] Butowski N, Lamborn KR, Berger MS, Prados MD, Chang SM: Historical controls for phase II surgically based trials requiring gross total resection of glioblastoma multiforme. J Neurooncol 85:87-94, 2007.
[26] Chang S, Vogelbaum M, Lang FF, Haines S, Kunwar S, Chiocca EA, Olivi A, Quinones-Hinojosa A, Parsa A, Warnick R, American Association of Neurological S, Congress of Neurological S: GNOSIS: guidelines for neuro-oncology: standards for investigational studies--reporting of surgically based therapeutic clinical trials. J Neurooncol 82:211-220, 2007.

[27] Chang SM, Parney IF, McDermott M, Barker FG, 2nd, Schmidt MH, Huang W, Laws ER, Jr., Lillehei KO, Bernstein M, Brem H, Sloan AE, Berger M, Glioma Outcomes I: Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg 98:1175-1181, 2003.
[28] Ciccarelli O, Catani M, Johansen-Berg H, Clark C, Thompson A: Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. Lancet Neurol 7:715-727, 2008.
[29] Ciric I, Ammirati M, Vick N, Mikhael M: Supratentorial gliomas: surgical considerations and immediate postoperative results. Gross total resection versus partial resection. Neurosurgery 21:21-26, 1987.
[30] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250:187-196, 2009.
[31] Coenen VA, Krings T, Axer H, Weidemann J, Kranzlein H, Hans FJ, Thron A, Gilsbach JM, Rohde V: Intraoperative three-dimensional visualization of the pyramidal tract in a neuronavigation system (PTV) reliably predicts true position of principal motor pathways. Surg Neurol 60:381-390; discussion 390, 2003.
[32] Dohrmann GJ, Farwell JR, Flannery JT: Glioblastoma multiforme in children. J Neurosurg 44:442-448, 1976.
[33] Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, Van Effenterre R, Capelle L: Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. J Neurol Neurosurg Psychiatry 76:845-851, 2005.
[34] Fink JR, Carr RB, Matsusue E, Iyer RG, Rockhill JK, Haynor DR, Maravilla KR: Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects. J Magn Reson Imaging, 2011.
[35] Fisher JL, Schwartzbaum JA, Wrensch M, Wiemels JL: Epidemiology of brain tumors. Neurol Clin 25:867-890, vii, 2007.
[36] Frappaz D, Chinot O, Bataillard A, Ben Hassel M, Capelle L, Chanalet S, Chatel M, Figarella-Branger D, Guegan Y, Guyotat J, Hoang-Xuan K, Jouanneau E, Keime-Guibert F, Laforet C, Linassier C, Loiseau H, Maire JP, Menei P, Rousmans S, Sanson M, Sunyach MP, Fnclcc, Neuro-oncology Group of the Federation Nationale des Centres de Lutte Contre le C, Association of French-speaking N-o: Summary version of the Standards, Options and Recommendations for the management of adult patients with intracranial glioma (2002). Br J Cancer 89 Suppl 1:S73-83, 2003.
[37] Glance LG, Osler TM, Mukamel DB, Dick AW: Impact of the present-on-admission indicator on hospital quality measurement: experience with the Agency for Healthcare Research and Quality (AHRQ) Inpatient Quality Indicators. Med Care 46:112-119, 2008.
[38] Gronningsaeter A, Kleven A, Ommedal S, Aarseth TE, Lie T, Lindseth F, Lango T, Unsgard G: SonoWand, an ultrasound-based neuronavigation system. Neurosurgery 47:1373-1379; discussion 1379-1380, 2000.

[39] Gupta DK, Chandra PS, Ojha BK, Sharma BS, Mahapatra AK, Mehta VS: Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex--a prospective randomised study. Clin Neurol Neurosurg 109:335-343, 2007.
[40] Hall WA: The safety and efficacy of stereotactic biopsy for intracranial lesions. Cancer 82:1749-1755, 1998.
[41] Hardell L, Carlberg M, Soderqvist F, Mild KH, Morgan LL: Long-term use of cellular phones and brain tumours: increased risk associated with use for > or =10 years. Occup Environ Med 64:626-632, 2007.
[42] Hart M, Grant R, Metcalfe SE: Biopsy versus resection for high grade glioma. The Cochrane Collaboration., 2011.
[43] Helseth R, Helseth E, Johannesen TB, Langberg CW, Lote K, Ronning P, Scheie D, Vik A, Meling TR: Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. Acta Neurol Scand 122:159-167, 2010.
[44] Hoeller M, Krings T, Reinges MH, Hans FJ, Gilsbach JM, Thron A: Movement artefacts and MR BOLD signal increase during different paradigms for mapping the sensorimotor cortex. Acta Neurochir (Wien) 144:279-284; discussion 284, 2002.
[45] Houkin K, Baba T, Minamida Y, Nonaka T, Koyanagi I, Iiboshi S: Quantitative analysis of adverse events in neurosurgery. Neurosurgery 65:587-594; discussion 594, 2009.
[46] Ibanez FA, Hem S, Ajler P, Vecchi E, Ciraolo C, Baccanelli M, Tramontano R, Knezevich F, Carrizo A: A new classification of complications in neurosurgery. World Neurosurg 75:709-715; discussion 604-711, 2011.
[47] Jakola AS, Gulati S, Nerland US, Solheim O: Surgical resection of brain metastases: the prognostic value of the graded prognostic assessment score. J Neurooncol 105:573-581, 2011.
[48] Jakola AS, Unsgard G, Solheim O: Quality of life in patients with intracranial gliomas: the impact of modern image-guided surgery. J Neurosurg, 2011.
[49] Jena AB, Seabury S, Lakdawalla D, Chandra A: Malpractice risk according to physician specialty. N Engl J Med 365:629-636, 2011.
[50] Johannesen TB, Langmark F, Lote K: Progress in long-term survival in adult patients with supratentorial low-grade gliomas: a population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993. J Neurosurg 99:854-862, 2003.
[51] Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, Guillamo JS, Jadaud E, Colin P, Bondiau PY, Menei P, Loiseau H, Bernier V, Honnorat J, Barrie M, Mokhtari K, Mazeron JJ, Bissery A, Delattre JY, Association of French-Speaking N-O: Radiotherapy for glioblastoma in the elderly. N Engl J Med 356:1527-1535, 2007.
[52] Keles GE, Chang EF, Lamborn KR, Tihan T, Chang CJ, Chang SM, Berger MS: Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg 105:34-40, 2006.
[53] Kelly PJ: Technology in the resection of gliomas and the definition of madness. J Neurosurg 101:284-286; discussion 286, 2004.

[54] Kelly PJ, Daumas-Duport C, Scheithauer BW, Kall BA, Kispert DB: Stereotactic histologic correlations of computed tomography- and magnetic resonance imaging-defined abnormalities in patients with glial neoplasms. Mayo Clin Proc 62:450-459, 1987.
[55] Kirkbride P, Tannock IF: Trials in palliative treatment--have the goal posts been moved? Lancet Oncol 9:186-187, 2008.
[56] Kleihues P, Ohgaki H: Primary and secondary glioblastomas: from concept to clinical diagnosis. Neuro Oncol 1:44-51, 1999.
[57] Kowalczuk A, Macdonald RL, Amidei C, Dohrmann G, 3rd, Erickson RK, Hekmatpanah J, Krauss S, Krishnasamy S, Masters G, Mullan SF, Mundt AJ, Sweeney P, Vokes EE, Weir BK, Wollman RL: Quantitative imaging study of extent of surgical resection and prognosis of malignant astrocytomas. Neurosurgery 41:1028-1036; discussion 1036-1028, 1997.
[58] Kreth FW, Warnke PC, Scheremet R, Ostertag CB: Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme. J Neurosurg 78:762-766, 1993.
[59] Krings T, Reinges MH, Erberich S, Kemeny S, Rohde V, Spetzger U, Korinth M, Willmes K, Gilsbach JM, Thron A: Functional MRI for presurgical planning: problems, artefacts, and solution strategies. J Neurol Neurosurg Psychiatry 70:749-760, 2001.
[60] Krings T, Topper R, Willmes K, Reinges MH, Gilsbach JM, Thron A: Activation in primary and secondary motor areas in patients with CNS neoplasms and weakness. Neurology 58:381-390, 2002.
[61] Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R, Hatlevoll R, Lindgren M, Brun A, Lindgren S, Notter G, Andersen AP, Elgen K: Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. Cancer 47:649-652, 1981.
[62] Kubben PL, Ter Meulen KJ, Schijns OE, Ter Laak-Poort MP, van Overbeeke JJ, Santbrink HV: Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. Lancet Oncol, 2011.
[63] Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95:190-198, 2001.
[64] Lahkola A, Auvinen A, Raitanen J, Schoemaker MJ, Christensen HC, Feychting M, Johansen C, Klaeboe L, Lonn S, Swerdlow AJ, Tynes T, Salminen T: Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 120:1769-1775, 2007.
[65] Lamborn KR, Chang SM, Prados MD: Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro Oncol 6:227-235, 2004.
[66] Lamborn KR, Yung WK, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, Robins HI, Lieberman FS, Fine HA, Fink KL, Junck L, Abrey L, Gilbert MR, Mehta M, Kuhn JG, Aldape KD, Hibberts J, Peterson PM, Prados MD, North

American Brain Tumor C: Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 10:162-170, 2008.
[67] Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, Moller B: Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 45:1218-1231, 2009.
[68] Laws ER, Jr.: Neurosurgery's man of the century: Harvey Cushing--the man and his legacy. Neurosurgery 45:977-982, 1999.
[69] Laws ER, Parney IF, Huang W, Anderson F, Morris AM, Asher A, Lillehei KO, Bernstein M, Brem H, Sloan A, Berger MS, Chang S, Glioma Outcomes I: Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg 99:467-473, 2003.
[70] Levin VA, Yung WK, Bruner J, Kyritsis A, Leeds N, Gleason MJ, Hess KR, Meyers CA, Ictech SA, Chang E, Maor MH: Phase II study of accelerated fractionation radiation therapy with carboplatin followed by PCV chemotherapy for the treatment of anaplastic gliomas. Int J Radiat Oncol Biol Phys 53:58-66, 2002.
[71] Linos E, Raine T, Alonso A, Michaud D: Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst 99:1544-1550, 2007.
[72] Litofsky NS, Bauer AM, Kasper RS, Sullivan CM, Dabbous OH, Glioma Outcomes Project I: Image-guided resection of high-grade glioma: patient selection factors and outcome. Neurosurg Focus 20:E16, 2006.
[73] Liu CY, Apuzzo ML: The genesis of neurosurgery and the evolution of the neurosurgical operative environment: part I-prehistory to 2003. Neurosurgery 52:3-19; discussion 19, 2003.
[74] Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P: The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97-109, 2007.
[75] Mauer M, Stupp R, Taphoorn MJ, Coens C, Osoba D, Marosi C, Wong R, de Witte O, Cairncross JG, Efficace F, Mirimanoff RO, Forsyth P, van den Bent MJ, Weller M, Bottomley A: The prognostic value of health-related quality-of-life data in predicting survival in glioblastoma cancer patients: results from an international randomised phase III EORTC Brain Tumour and Radiation Oncology Groups, and NCIC Clinical Trials Group study. Br J Cancer 97:302-307, 2007.
[76] Mauer ME, Bottomley A, Taphoorn MJ: Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in experimental trials and clinical practice. Curr Opin Neurol 21:745-753, 2008.
[77] Metcalfe SE, Grant R: Biopsy versus resection for malignant glioma. Cochrane Database Syst Rev:CD002034, 2001.
[78] Meyer FB, Bates LM, Goerss SJ, Friedman JA, Windschitl WL, Duffy JR, Perkins WJ, O'Neill BP: Awake craniotomy for aggressive resection of primary gliomas located in eloquent brain. Mayo Clin Proc 76:677-687, 2001.
[79] Mori S, van Zijl PC: Fiber tracking: principles and strategies - a technical review. NMR Biomed 15:468-480, 2002.

[80] Nayak L, Iwamoto FM: Primary brain tumors in the elderly. Curr Neurol Neurosci Rep 10:252-258.
[81] Neuloh G, Pechstein U, Cedzich C, Schramm J: Motor evoked potential monitoring with supratentorial surgery. Neurosurgery 61:337-346; discussion 346-338, 2007.
[82] Ngwenya LB, Chiocca EA: Extent of resection. J Neurosurg 115:1-2; discussion 2, 2011.
[83] Nimsky C, Ganslandt O, Fahlbusch R: Implementation of fiber tract navigation. Neurosurgery 58:ONS-292-303; discussion ONS-303-294, 2006.
[84] Nomiya T, Nemoto K, Kumabe T, Takai Y, Yamada S: Prognostic significance of surgery and radiation therapy in cases of anaplastic astrocytoma: retrospective analysis of 170 cases. J Neurosurg 106:575-581, 2007.
[85] Nord E: EuroQol©: health-related quality of life measurement. Valuations of health states by the general public in Norway. Health Policy 18:25-36, 1991.
[86] Oertel J, von Buttlar E, Schroeder HW, Gaab MR: Prognosis of gliomas in the 1970s and today. Neurosurg Focus 18:e12, 2005.
[87] Ogawa S, Lee TM, Kay AR, Tank DW: Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87:9868-9872, 1990.
[88] Ogawa S, Lee TM, Nayak AS, Glynn P: Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med 14:68-78, 1990.
[89] Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE: Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. Neuroimage 6:156-167, 1997.
[90] Ojemann JG, Ojemann GA, Lettich E: Cortical stimulation mapping of language cortex by using a verb generation task: effects of learning and comparison to mapping based on object naming. J Neurosurg 97:33-38, 2002.
[91] Peraud A, Ilmberger J, Reulen HJ: Surgical resection of gliomas WHO grade II and III located in the opercular region. Acta Neurochir (Wien) 146:9-17; discussion 17-18, 2004.
[92] Pope WB, Sayre J, Perlina A, Villablanca JP, Mischel PS, Cloughesy TF: MR imaging correlates of survival in patients with high-grade gliomas. AJNR Am J Neuroradiol 26:2466-2474, 2005.
[93] Puduvalli VK, Hashmi M, McAllister LD, Levin VA, Hess KR, Prados M, Jaeckle KA, Yung WK, Buys SS, Bruner JM, Townsend JJ, Davis R, Sawaya R, Kyritsis AP: Anaplastic oligodendrogliomas: prognostic factors for tumor recurrence and survival. Oncology 65:259-266, 2003.
[94] Pujol J, Conesa G, Deus J, Lopez-Obarrio L, Isamat F, Capdevila A: Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. J Neurosurg 88:863-869, 1998.
[95] Rasmussen IA, Jr., Lindseth F, Rygh OM, Berntsen EM, Selbekk T, Xu J, Nagelhus Hernes TA, Harg E, Haberg A, Unsgaard G: Functional neuronavigation combined with intra-operative 3D ultrasound: initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. Acta Neurochir (Wien) 149:365-378, 2007.

[96] Reardon DA, Galanis E, DeGroot JF, Cloughesy TF, Wefel JS, Lamborn KR, Lassman AB, Gilbert MR, Sampson JH, Wick W, Chamberlain MC, Macdonald DR, Mehta MP, Vogelbaum MA, Chang SM, Van den Bent MJ, Wen PY: Clinical trial end points for high-grade glioma: the evolving landscape. Neuro Oncol 13:353-361, 2011.
[97] Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, Fisher B, Fulton D, Gulavita S, Hao C, Husain S, Murtha A, Petruk K, Stewart D, Tai P, Urtasun R, Cairncross JG, Forsyth P: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 22:1583-1588, 2004.
[98] Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I: Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. Neurosurgery 52:1335-1345; discussion 1345-1337, 2003.
[99] Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW: Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. Ann Neurol 51:350-360, 2002.
[100] Rygh OM, Nagelhus Hernes TA, Lindseth F, Selbekk T, Brostrup Muller T, Unsgaard G: Intraoperative navigated 3-dimensional ultrasound angiography in tumor surgery. Surg Neurol 66:581-592; discussion 592, 2006.
[101] Rygh OM, Selbekk T, Torp SH, Lydersen S, Hernes TA, Unsgaard G: Comparison of navigated 3D ultrasound findings with histopathology in subsequent phases of glioblastoma resection. Acta Neurochir (Wien) 150:1033-1041; discussion 1042, 2008.
[102] Salcman M: Historical development of surgery for glial tumors. J Neurooncol 42:195-204, 1999.
[103] Sanai N, Berger MS: Glioma extent of resection and its impact on patient outcome. Neurosurgery 62:753-764; discussion 264-756, 2008.
[104] Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. N Engl J Med 358:18-27, 2008.
[105] Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 115:3-8, 2011.
[106] Sawaya R, Hammoud M, Schoppa D, Hess KR, Wu SZ, Shi WM, Wildrick DM: Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 42:1044-1055, 1998.
[107] Schreiber A, Hubbe U, Ziyeh S, Hennig J: The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. AJNR Am J Neuroradiol 21:1055-1063, 2000.
[108] Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V: Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol, 2011.
[109] Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, Isaacson S, Rotman M, Asbell SO, Nelson JS, et al.: Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results

of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys 26:239-244, 1993.
[110] Solheim O, Jakola AS, Gulati S, Johannesen TB: Perioperative death rate - a proxy for quality of care? Incidence and causes of perioperative mortality after primary surgery for intracranial tumours - a national, population based study. J Neurosurg (In press), 2011.
[111] Solheim O, Jakola AS, Gulati S, Salvesen Ø: Is 78% the new extent of resection threshold? J Neurosurg, 2011.
[112] Solheim O, Salvesen O, Cappelen J, Johannesen TB: The impact of provider surgical volumes on survival in children with primary tumors of the central nervous system--a population-based study. Acta Neurochir (Wien) 153:1219-1229; discussion 1229, 2011.
[113] Solheim O, Selbekk T, Jakola AS, Unsgard G: Ultrasound-guided operations in unselected high-grade gliomas-overall results, impact of image quality and patient selection. Acta Neurochir (Wien) 152:1873-1886, 2010.
[114] Stark AM, Nabavi A, Mehdorn HM, Blomer U: Glioblastoma multiforme-report of 267 cases treated at a single institution. Surg Neurol 63:162-169; discussion 169, 2005.
[115] Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, Group AL-GS: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7:392-401, 2006.
[116] Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, Group AL-GS: Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 62:564-576; discussion 564-576, 2008.
[117] Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, Group AL-GS: Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 62:564-576, 2008.
[118] Stummer W, Stocker S, Wagner S, Stepp H, Fritsch C, Goetz C, Goetz AE, Kiefmann R, Reulen HJ: Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery 42:518-525; discussion 525-516, 1998.
[119] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, European Organisation for R, Treatment of Cancer Brain T, Radiotherapy G, National Cancer Institute of Canada Clinical Trials G: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-996, 2005.
[120] Stupp R, Reni M, Gatta G, Mazza E, Vecht C: Anaplastic astrocytoma in adults. Crit Rev Oncol Hematol 63:72-80, 2007.
[121] Sunaert S: Presurgical planning for tumor resectioning. J Magn Reson Imaging 23:887-905, 2006.

[122] Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, Stupp R, Mirimanoff RO, van den Bent MJ, Bottomley A, Group EQoL, Brain Cancer N, Radiotherapy G: An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer 46:1033-1040, 2010.
[123] Taylor MD, Bernstein M: Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: a prospective trial of 200 cases. J Neurosurg 90:35-41, 1999.
[124] Tonn JC, Stummer W: Fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid: practical use, risks, and pitfalls. Clin Neurosurg 55:20-26, 2008.
[125] Tortosa A, Vinolas N, Villa S, Verger E, Gil JM, Brell M, Caral L, Pujol T, Acebes JJ, Ribalta T, Ferrer I, Graus F: Prognostic implication of clinical, radiologic, and pathologic features in patients with anaplastic gliomas. Cancer 97:1063-1071, 2003.
[126] Unsgaard G, Ommedal S, Muller T, Gronningsaeter A, Nagelhus Hernes TA: Neuronavigation by intraoperative three-dimensional ultrasound: initial experience during brain tumor resection. Neurosurgery 50:804-812; discussion 812, 2002.
[127] Ushio Y, Kochi M, Hamada J, Kai Y, Nakamura H: Effect of surgical removal on survival and quality of life in patients with supratentorial glioblastoma. Neurol Med Chir (Tokyo) 45:454-460, 2005.
[128] van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19:604-607, 1988.
[129] Vecht CJ, Avezaat CJ, van Putten WL, Eijkenboom WM, Stefanko SZ: The influence of the extent of surgery on the neurological function and survival in malignant glioma. A retrospective analysis in 243 patients. J Neurol Neurosurg Psychiatry 53:466-471, 1990.
[130] Vlieger EJ, Majoie CB, Leenstra S, Den Heeten GJ: Functional magnetic resonance imaging for neurosurgical planning in neurooncology. Eur Radiol 14:1143-1153, 2004.
[131] Vuorinen V, Hinkka S, Farkkila M, Jaaskelainen J: Debulking or biopsy of malignant glioma in elderly people - a randomised study. Acta Neurochir (Wien) 145:5-10, 2003.
[132] Walker M, Brown J, Brown K, Gregor A, Whittle IR, Grant R: Practical problems with the collection and interpretation of serial quality of life assessments in patients with malignant glioma. J Neurooncol 63:179-186, 2003.
[133] Walker MD, Alexander E, Jr., Hunt WE, MacCarty CS, Mahaley MS, Jr., Mealey J, Jr., Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA, Strike TA: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg 49:333-343, 1978.
[134] Wen PY, Kesari S: Malignant gliomas in adults. N Engl J Med 359:492-507, 2008.
[135] Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent

MJ, Chang SM: Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28:1963-1972, 2010.
[136] Westphal M: Classification of brain tumors and corresponding treatments. Practical Handbook of Neurosurgery Volume 2 Intracranial tumors, Intraoperative Explorations, Pediatrics:3-28, 2009.
[137] Woodworth G, McGirt MJ, Samdani A, Garonzik I, Olivi A, Weingart JD: Accuracy of frameless and frame-based image-guided stereotactic brain biopsy in the diagnosis of glioma: comparison of biopsy and open resection specimen. Neurol Res 27:358-362, 2005.
[138] Wrensch M, Lee M, Miike R, Newman B, Barger G, Davis R, Wiencke J, Neuhaus J: Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am J Epidemiol 145:581-593, 1997.
[139] Wrensch M, Minn Y, Chew T, Bondy M, Berger MS: Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol 4:278-299, 2002.
[140] Wu JS, Zhou LF, Tang WJ, Mao Y, Hu J, Song YY, Hong XN, Du GH: Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts. Neurosurgery 61:935-948; discussion 948-939, 2007.
[141] Yetkin FZ, Mueller WM, Morris GL, McAuliffe TL, Ulmer JL, Cox RW, Daniels DL, Haughton VM: Functional MR activation correlated with intraoperative cortical mapping. AJNR Am J Neuroradiol 18:1311-1315, 1997.
[142] Yoshimoto Y: Publication bias in neurosurgery: lessons from series of unruptured aneurysms. Acta Neurochir (Wien) 145:45-48, 2003.
[143] Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P: Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 120 (Pt 1):141-157, 1997.
[144] Yousry TA, Schmid UD, Jassoy AG, Schmidt D, Eisner WE, Reulen HJ, Reiser MF, Lissner J: Topography of the cortical motor hand area: prospective study with functional MR imaging and direct motor mapping at surgery. Radiology 195:23-29, 1995.

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

Asgeir S. Jakola[1,2,3]*, Sasha Gulati[1,4], Clemens Weber[1], Geirmund Unsgård[1,3], Ole Solheim[1,2,3]

1 Department of Neurosurgery, St.Olavs University Hospital, Trondheim, Norway, **2** Medical Imaging Lab and Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway, **3** Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway, **4** Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

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.

Citation: Jakola AS, Gulati S, Weber C, Unsgård G, Solheim O (2011) Postoperative Deterioration in Health Related Quality of Life as Predictor for Survival in Patients with Glioblastoma: A Prospective Study. PLoS ONE 6(12): e28592. doi:10.1371/journal.pone.0028592

Editor: Zheng Su, Genentech Inc., United States of America

Received July 16, 2011; **Accepted** November 11, 2011; **Published** December 9, 2011

Funding: These authors have no support or funding to report.

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.

* E-mail: asgeir.s.jakola@ntnu.no

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].
doi:10.1371/journal.pone.0028592.t001

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.
doi:10.1371/journal.pone.0028592.t002

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.

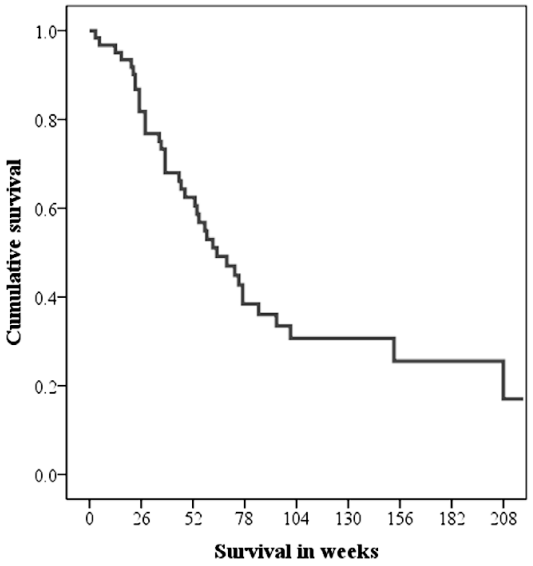

Figure 1. Overall survival in the cohort (n = 61) presented in a survival plot.
doi:10.1371/journal.pone.0028592.g001

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.

doi:10.1371/journal.pone.0028592.t003

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-

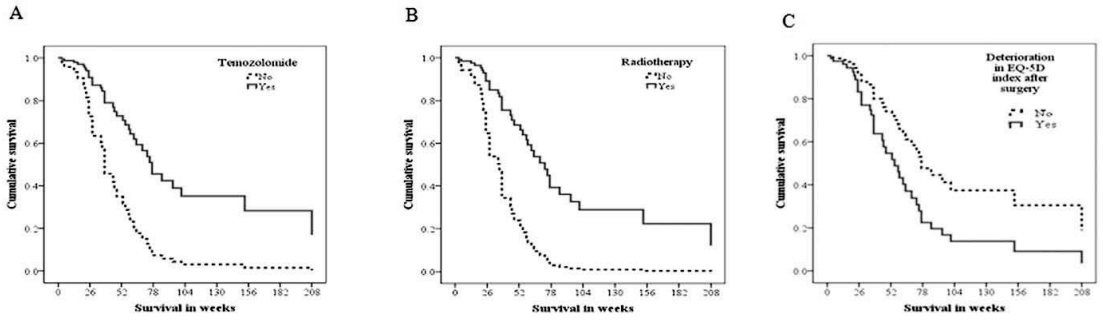

Figure 2. Survival curves for the independent predictors presented in Table 3.

doi:10.1371/journal.pone.0028592.g002

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.

References

1. Solheim O, Selbekk T, Jakola AS, Unsgård G (2010) Ultrasound-guided operations in unselected high-grade gliomas—overall results, impact of image quality and patient selection. Acta Neurochirurgica. pp 1–14.
2. Stummer W, Reulen H-J, Meinel T, Pichlmeier U, Schumacher W, et al. (2008) Extent of Resection and Survival in Glioblastoma Multiforme: Identification of and Adjustment for Bias. Neurosurgery 62: 564–576.
3. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, et al. (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. Journal of Neurosurgery 95: 190–198.
4. Sanai N, Polley M-Y, McDermott MW, Parsa AT, Berger MS (2011) An extent of resection threshold for newly diagnosed glioblastomas. Journal of Neurosurgery 0: 1–6.
5. Gulati S, Jakola AS, Nerland US, Weber C, Solheim O (2011) The risk of getting worse: Surgically acquired deficits, perioperative complications and functional outcomes after primary resection of glioblastoma. World Neurosurgery In press.
6. Cheng J-x, Zhang X, Liu B-L (2009) Health-related quality of life in patients with high-grade glioma. Neuro Oncol 11: 41–50.
7. Jakola AS, Unsgård G, Solheim O (2011) Quality of life in patients with intracranial gliomas: the impact of modern image-guided surgery. Journal of Neurosurgery 0: 1–9.
8. McGirt MJ, Mukherjee DM, Chaichana KL, Than KD, Weingart JD, et al. (2009) Association of Surgically Acquired Motor And Language Deficits on Overall Survival After Resection of Glioblastoma Multiforme. Neurosurgery 65: 463–470.
9. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, et al. (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. The Lancet Oncology 7: 392–401.
10. Unsgaard G, Rygh OM, Selbekk T, Müller TB, Kolstad F, et al. (2006) Intra-operative 3D ultrasound in neurosurgery. Acta Neurochirurgica 148: 235–253.
11. Gulati S, Berntsen EM, Solheim O, Kvistad KA, Håberg A, et al. (2009) Surgical Resection of High-grade Gliomas in Eloquent Regions Guided by Blood Oxygenation Level Dependent Functional Magnetic Resonance Imaging, Diffusion Tensor Tractography, and Intraoperative Navigated 3D Ultrasound. Minim Invasive Neurosurg 52: 17–24.
12. Rasmussen IA, Lindseth F, Rygh OM, Berntsen EM, Selbekk T, et al. (2007) Functional neuronavigation combined with intra-operative 3D ultrasound: Initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. Acta Neurochirurgica 149: 365–378.
13. The EuroQol Group (1990) EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 16: 199–208.
14. Rabin R, Charro Fd (2001) EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine 33: 337–343.
15. Burström K, Johannesson M, Diderichsen F (2001) Swedish population health-related quality of life results using the EQ-5D. Quality of Life Research 10: 621–635.
16. Nord E (1991) EuroQol©: health-related quality of life measurement. Valuations of health states by the general public in Norway. Health Policy 18: 25–36.
17. Dolan PD (1997) Modeling Valuations for EuroQol Health States. Medical Care 35: 1095–1108.
18. Lutterbach J, Bartelt S, Momm F, Becker G, Frommhold H, et al. (2005) Is older age associated with a worse prognosis due to different patterns of care? Cancer 103: 1234–1244.
19. Chaichana KL, Chaichana KK, Olivi A, Weingart JD, Bennett R, et al. (2011) Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival. Journal of Neurosurgery 114: 587–594.
20. Marina O, Suh JH, Reddy CA, Barnett GH, Vogelbaum MA, et al. (2011) Treatment outcomes for patients with glioblastoma multiforme and a low Karnofsky Performance Scale score on presentation to a tertiary care institution. Journal of Neurosurgery 0: 1–10.
21. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, et al. (2005) Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med 352: 987–996.
22. Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, et al. (2007) Radiotherapy for Glioblastoma in the Elderly. N Engl J Med 356: 1527–1535.
23. Sanai N, Berger MS (2008) Glioma Extent of Resection and its Impact on Patient Outcome. Neurosurgery 62: 753–766.
24. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, et al. (2010) Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. Journal of Clinical Oncology 28: 1963–1972.
25. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. The Lancet Oncology 9: 453–461.
26. de Groot JF, Lamborn KR, Chang SM, Gilbert MR, Cloughesy TF, et al. (2011) Phase II Study of Aflibercept in Recurrent Malignant Glioma: A North American Brain Tumor Consortium Study. Journal of Clinical Oncology.
27. McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, et al. (2009) Independent association of extent of resection with survival in patients with malignant brain astrocytoma. Journal of Neurosurgery 110: 156–162.
28. Gotay CC, Kawamoto CT, Bottomley A, Efficace F (2008) The Prognostic Significance of Patient-Reported Outcomes in Cancer Clinical Trials. Journal of Clinical Oncology 26: 1355–1363.
29. Brown P, Ballman K, Rummans T, Maurer M, Sloan J, et al. (2006) Prospective Study of Quality of Life in Adults with Newly Diagnosed High-grade Gliomas. Journal of Neuro-Oncology 76: 283–291.
30. Brown PDMD, Maurer MJMS, Rummans TAMD, Pollock BEMD, Ballman KVPD, et al. (2005) A Prospective Study of Quality of Life in Adults with Newly Diagnosed High-grade Gliomas: The Impact of the Extent of Resection on Quality of Life and Survival. Neurosurgery 57: 495–504.
31. Quinten C, Coens C, Mauer M, Comte S, Sprangers MAG, et al. (2009) Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. The Lancet Oncology 10: 865–871.
32. Mauer M, Stupp R, Taphoorn MJB, Coens C, Osoba D, et al. (2007) The prognostic value of health-related quality-of-life data in predicting survival in

glioblastoma cancer patients: results from an international randomised phase III EORTC Brain Tumour and Radiation Oncology Groups, and NCIC Clinical Trials Group study. Br J Cancer 97: 302–307.
33. Altman DG, Lausen B, Sauerbrei W, Schumacher M (1994) Dangers of Using "Optimal" Cutpoints in the Evaluation of Prognostic Factors. Journal of the National Cancer Institute 86: 829–835.
34. Lydick E, Epstein RS (1993) Interpretation of quality of life changes. Quality of Life Research 2: 221–226.
35. Chang SM, Parney IF, McDermott M, Barker FG, 2nd, Schmidt MH, et al. (2003) Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg 98: 1175–1181.
36. Ibañez FAL, Hem S, Ajler P, Vecchi E, Ciraolo C, et al. (2011) A New Classification of Complications in Neurosurgery. World Neurosurgery 75: 709–715.
37. Sawaya R, Hammoud M, Schoppa D, Hess KR, Wu SZ, et al. (1998) Neurosurgical Outcomes in a Modern Series of 400 Craniotomies for Treatment of Parenchymal Tumors. Neurosurgery 42: 1044–1055.

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35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
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