The Risk of Getting Worse: Surgically Acquired Deficits, Perioperative Complications, and Functional Outcomes After Primary Resection of Glioblastoma

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Key words
- Brain neoplasms
- Neurosurgery
- Quality control

Abbreviations and Acronyms
GTR: Gross total resection
KPS: Karnofsky performance score
MRI: Magnetic resonance imaging
NTR: Near total resection
STR: Subtotal resection

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OBJECTIVE: **Gross total resection (GTR) prolongs survival but is unfortunately not achievable in the majority of patients with glioblastoma multiforme (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.**

METHODS: **We retrospectively included 144 consecutive adult patients operated on for primary GBM at a single institution between 2004 and 2009. Reporting of adverse events was done in compliance with Good Clinical Practice Guidelines.**

RESULTS: **A total of 141 (98%) operations were resections and 3 (2%) were biopsies. A decrease in Karnofsky performance status (KPS) scores was observed in 39% of patients after 6 weeks. There was a significant decrease between pre- and postoperative KPS scores ($P < 0.001$). Twenty-two (15.3%) patients had surgically acquired neurological deficits. Among patients who underwent surgical resection, those with surgically acquired neurological deficits were less likely to receive radiotherapy ($P < 0.001$), normofractioned radiotherapy ($P = 0.010$), and chemotherapy ($P = 0.003$). Twenty-eight (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 ($P = 0.019$), surgically acquired neurological 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.**

CONCLUSION: **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.**

INTRODUCTION

Malignant gliomas are the most common primary brain tumors and the second most common cause of cancer-related death in the young adult age group (9, 46). The overall prognosis for patients with glioblastoma is poor, with median survival less than 1 year (44). Age at diagnosis and Karnofsky Performance Status (KPS) score are important and established prognostic factors in high-grade glioma patients (16, 22). According to current guidelines, surgery is warranted to establish a histopathologic diagnosis and to achieve safe, maximal, and feasible resection (10, 11, 28, 31). There is now level 2b data (Oxford Centre for Evidence-based Medicine) showing that gross total resection prolongs survival (36). The effect of mere cytoreductive debulkings on survival, functional outcome, and quality of life is not clarified. Regardless of operative technique, gross total resection is not achievable in the majority of unselected glioblastoma patients. The percentage of patients receiving gross total resection varies between studies, probably reflecting the considerable variations in inclusion criteria (34). The frequently cited retrospective study by Lacroix (22) and data from the 5-ALA (5-aminolevunilic study)–Glioma study (36) indicate that if other prognostic factors and treatment factors are adjusted for, surgical resections need to be extensive (>98% or complete) to affect survival. Thus, although the majority of glioblastoma patients are offered surgical treatment that does not even affect survival, it has been reported that surgically acquired motor and language deficits may have a negative impact on survival (26) and quality of life (19). Even though mere debulkings may relieve symptoms of mass effect, it is not known how long such effects sustain and to what degree the potential benefits exceed risks. In the present study, we explore the impact

of surgical morbidity and functional outcome on survival in unselected glioblastoma patients.

MATERIALS AND METHODS

We retrospectively included all adult (≥18 years) cases operated for primary glioblastoma at the Department of Neurosurgery, St. Olavs University Hospital, in the 6-year period between January 1, 2004, and December 31, 2009. All included tumors were classified and graded by one neuropathologist. Neuropathologic classification was done according to the WHO classification for brain tumors (25). Patients were followed until death or through December 2010. No patients were lost to follow-up.

Data collection was based on review of patient hospital files and image data. The patients' gross functional neurologic status was determined using the KPS scale. The preoperative KPS score was retrospectively determined from a routine neurologic examination at patient admittance, usually 1–3 days before surgery. The postoperative KPS score (approximately after 6 weeks) was also retrospectively determined from reviews of medical records. Adverse events related to surgery were divided into perioperative complications and surgically acquired neurologic deficits. We included all adverse events and serious adverse events in relation to the surgical procedure, without attempts to define causality. This is in coherence with Good Clinical Practice Guidelines (http://www.ema.europa.eu: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). 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 unfavorable and unintended sign, symptom, or disease temporally associated with surgical treatment. Serious adverse events are defined as any unexpected medical occurrence (at any dose) 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. Patients who experienced new or worsened neurologic deficits at hospital discharge were classified as having a surgically acquired deficit. Seizures arising after surgery in patients with no preexisting seizure disorder were classified as perioperative complications. Demographics, presenting symptoms and signs, perioperative morbidity, adjuvant radiotherapy and chemotherapy regimens, number of repeated resections for tumor recurrence, and postoperative survival were recorded from the hospital files. Decisions regarding adjuvant radiotherapy and chemotherapy for all included patients were made by the neuro-oncologists and radiation oncologists in our hospital.

Pre- and postoperative images were reviewed to determine resection grades. Tumor volumes were determined using an ellipsoid volume formula ($4/3 \cdot \pi r_1 r_2 r_3$) based on the maximum tumor diameters in the perpendicular dimensions (34, 35). Early postoperative MRI (<48 hours) was used to determine resection grades. Gross total resection (GTR) was defined as ≥98% tumor removal. Near total resection (NTR) was defined as no gross total resection but resection of at least 90% of the lesion. Subtotal resection (STR) was defined as resection of less than 90% of the tumor volume, excluding biopsies.

All operations were performed under general anesthesia. An ultrasound-based neuronavigation system (SonoWand, Trondheim, Norway) was available if preferred during surgery. This system allows conventional neuronavigation based on preoperative magnetic resonance images as well as intraoperative 2D and 3D ultrasound imaging (29, 34). Functional neuronavigation based on preoperative functional MRI or diffusion tensor imaging was used in most eloquent lesions. We did not perform any intraoperative electrophysiological monitoring when resecting tumors in eloquent regions, but relied entirely on anatomic landmarks visible on intraoperative ultrasound along with preoperative MRI, functional MRI, and diffusion tensor tractography. We have previously suggested that using this approach of combining preoperative functional data with navigation and repeated ultrasound imaging produces a sufficient balance between feasibility and quality without a need of intraoperative stimulation, brain mapping, or intraoperative MRI (4, 17).

Statistical analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA). Two-sided P values less than 0.05 were regarded as statistically significant. Normal distribution was tested using Q-Q plots. In univariate analysis, the chi-square test was used for categorical variables and the Student's t test for continuous variables. To compare outcomes before and after surgery, we used paired-samples t test. Logistic regression was used for the multivariate analyses. Multiple Cox regression was used for survival analyses.

The study was approved by the Regional Committee for Medical Research Ethics in Health Region Mid-Norway and the Norwegian Ministry of Health. Study protocols adhered to guidelines of the Helsinki Declaration.

RESULTS

Of the 144 consecutive glioblastoma operations, 141 (98%) were resections whereas 3 (2%) were biopsies. The average patient age was 62 ± 12 years, and the mean KPS score at presentation was 73 ± 15. The median stay in the neurosurgical department was 5 days. In our study, gross total removal was achieved in 34% of the cases in which resection was performed (n = 141). The 1-year survival rate was 47.5%. Among patients operated through December 2008, the 2-year survival rate was 16.0%. Preoperative functional MRI and diffusion tensor imaging were performed and imported into the neuronavigation system in 20% and 23% of the cases, respectively.

Based on volumetric data, patients undergoing surgical resection were divided into three groups (GTR, NTR, and STR). There were no statistically significant differences between the groups in terms of gender (P = 0.455), age >70 years (P = 0.261), preoperative tumor volume (P = 0.467), preoperative KPS score >70 (P = 0.495), 1-year survival (P = 0.176), worsened functional status (P = 0.219), perioperative complications (P = 0.547), surgically acquired neurologic deficits (P = 0.972), use of functional MRI (P = 0.269), use of DTT (P = 0.316), and use of intraoperative ultrasound (P = 0.389).

Risk of Getting Worse (Karnofsky Performance Status Before Surgery vs. 6 Weeks)

A worsening of functional status 6 weeks after surgery was observed in 39% of all