# Efficacy of Surgery and Further Treatment of Progressive Glioblastoma

*Christoph Michael Woernle[1,*], Dominik Péus[1,*], Silvia Hofer[2], Elisabeth Jane Rushing[3], Ulrike Held[4], Oliver Bozinov[1], Niklaus Krayenbühl[1], Michael Weller[5], Luca Regli[1]*

BACKGROUND: **Treatment options for patients with glioblastoma at progression have remained controversial, and selection criteria for the appropriate type of intervention remain poorly defined. The objectives were to determine which factors favor the decision for second surgery and which factors are associated with overall survival (OS) and to evaluate the National Institutes of Health (NIH) recurrent glioblastoma scale. The scale includes tumor involvement of eloquent brain regions, functional status, and tumor volume.**

METHODS: **A retrospective single-center analysis of patients with newly diagnosed glioblastoma undergoing initial surgery between January 2007 and December 2011 was performed. Patients were separated into two groups: those with versus those without second resection surgery at disease progression. OS was compared using the multiple logistic regression model, Cox proportional hazard regression, and Kaplan-Meier survival analysis.**

RESULTS: **The data of 98 patients were statistically analyzed. Among the patients, 58 had initial surgery only (age 61.27 years; median OS [mOS] 14.81 months) and 40 underwent second surgery at disease progression (age 55 years; mOS 18.86 months). Age was the only predictor for repeated surgery ($P = 0.012$; odds ratio 0.94). At the time of tumor progression, administration of alkylating chemotherapy ($P = 0.004$; hazard ratio [HR] 0.24) or bevacizumab ($P = 0.001$; HR 0.23) was associated with longer OS. Reoperation was associated with a lower HR ($P = 0.134$; HR 0.66). The NIH recurrent glioblastoma scale showed statistically significant improvement of prognosis prediction with the addition of age.**

CONCLUSIONS: **Surgery of progressive glioblastoma and postoperative treatment at the time of progression is associated with improved OS in some patients. The addition of age may improve survival prediction of the NIH recurrent glioblastoma scale.**

## INTRODUCTION

Over the past decades the prognosis for newly diagnosed glioblastoma has improved only slightly. The median survival time is still less than 12 months (14). Standard therapy for newly diagnosed glioblastoma comprises maximal safe resection and subsequent radiation therapy with concomitant and adjuvant temozolomide (23). At time of progression the standards for clinical intervention are less well defined (25). Additional systemic therapy and repeated surgery are commonly considered options. Some retrospective studies have focused on the efficacy of second surgery at the time of recurrence. However, retrospective studies are limited by selection bias and missing data (1, 3, 6, 8, 9, 12, 18). Prognostic factors such as age, Karnofsky performance status (KPS), localization of the tumor and its volume, IDH1 mutation status, and $O^6$-methylguanine DNA methyltransferase (MGMT) promoter methylation status may be taken into consideration (4, 10, 25). On the basis of a retrospective analysis of 34 patients, Park et al.

**Key words**
- Bevacizumab
- Glioblastoma
- Neurosurgery
- Prognostic score
- Recurrence
- Temozolomide

**Abbreviations and Acronyms**
CCNU: Lomustine
GTR: Gross total resection
HR: Hazard ratio
KPS: Karnofsky performance status
MRI: Magnetic resonance imaging
NIH: National Institutes of Health
OR: Odds ratio
OS: Overall survival
RT: Radiotherapy
STR: Subtotal resection
TMZ: Temozolomide

*From the Departments of [1]Neurosurgery, [2]Oncology, [3]Neuropathology, and [5]Neurology and the [4]Horten Centre for Patient Oriented Research and Knowledge Transfer, University Hospital Zurich, Switzerland*

*To whom correspondence should be addressed: Dominik Péus, M. Med. [E-mail: dompeus@gmail.com]*

** These authors contributed equally.*

*Citation: World Neurosurg. (2015) 84, 2:301-307.*
*http://dx.doi.org/10.1016/j.wneu.2015.03.018*

*Journal homepage: www.WORLDNEUROSURGERY.org*

*Available online: www.sciencedirect.com*

proposed the NIH recurrent glioblastoma scale to preoperatively evaluate the prognostic factors of patients with progressive glioblastoma undergoing second surgery (19). Their scale includes three factors: tumor involvement of eloquent brain regions, compromised functional status (KPS $\leq$80%), and tumor volume $\geq$50 cm$^3$, thereby dividing the patients into three prognostic subgroups: patients with poor, intermediate, and good survival.

The aim of this single-center study was to retrospectively analyze the impact of second resection surgery at the time of glioblastoma progression in patients exclusively treated in the area of modern standard therapy. For this the factors favoring the decision for reoperation and the prognostic factors for overall survival (OS) were examined. A secondary goal of the present study was to evaluate the NIH recurrent glioblastoma scale with regard to this patient group.

## PATIENTS AND METHODS

### Patients

From January 2007 to December 2011, 341 patients underwent surgery for primary and secondary glioblastoma at the University Hospital Zurich. The diagnosis was confirmed histopathologically according to the World Health Organization criteria (16). Medical records were reviewed to identify patients $\geq$18 years, diagnosed with glioblastoma, who had undergone magnetic resonance imaging (MRI) resection control within 72 hours, as well as postoperative standard therapy (radiotherapy with concomitant temozolomide and at least one cycle of 5/28 temozolomide therapy (23) or, if patients were older than 65 years, postoperative radiotherapy with 40 gy (13, 20)). The time of progression or recurrence (in the text labeled progression for simplification) was assessed in all patients and validated by contrast-enhancing mass on T1-weighted MRI. Patients with initially lower-grade gliomas, infratentorial tumor location, <18 years, or without MRI confirmed progression were excluded.

In total, 98 patients met our inclusion criteria (Figure 1). Of these, 40 underwent a second, maximal safe surgical resection and further neuro-oncological treatment at time of progression, defined as "study group A." The control group consisted of 58 patients without additional surgery, but further treatment at progression, defined as "group B."

### Variables and Goals

Medical records were reviewed with regard to age, gender, tumor volume (ellipsoid: $4/3 \star \pi \star x \star y \star z/2$), tumor localization, and number of eloquent brain regions involved: presumed motor area; presumed speech area; areas directly adjacent to the M1 and/or M2 segments of the middle cerebral artery (equivalent to the motor-speech-middle cerebral artery [MSM] score, introduced by Park et al. (19)); four categories of symptoms (motor, speech, vision, neuropsychological deficits); NIH recurrent glioblastoma scale (Table 1); KPS; and preoperative need of steroids. In addition, the Ki-67 labeling index and MGMT promoter methylation status detected by methylation-specific PCR were documented. Contrast T1-weighted MRI images from before and immediately after resection were used to quantify the extent of resection: >95% gross total resection (GTR), $\leq$95% subtotal resection (STR), and biopsy (4, 21). A detailed history of the therapeutic modalities was recorded. IDH1 status was identified by immunohistochemical staining for the study group A (Table 2). The primary objective of this retrospective analysis was to define 1) factors at disease progression associated with the subsequent decision for reoperation, 2) prognostic factors for OS, and 3) to validate the NIH recurrent glioblastoma scale. The study was approved by the local ethic committee (KEK-ZH-Nr. 2012-0257).

### Statistics

Baseline characteristics are shown as median and interquartile range for continuous variables and as numbers and percentages of the total for categorical variables. The statistical analysis was a two-step procedure. In the first step, a multiple logistic regression model was fit to the dependent variable recurrent resection (1 = yes, 0 = no), with age at diagnosis, preoperative KPS (first

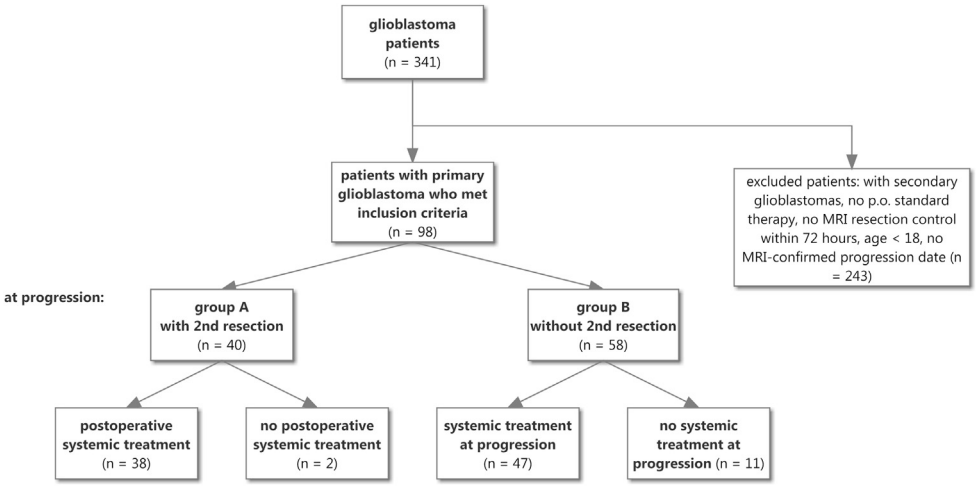


**Figure 1.** Graphical description of patient stratification into two groups (A and B), based on treatment decision at time of progression.