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Woernle, C M ; Péus, D ; Hofer, S ; Rushing, E J ; Held, U ; Bozinov, O ; Krayenbühl, N ; Weller, M ; Regli, L

Abstract: **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 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 vs. 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 was statistically analyzed. 58 patients had initial surgery only (age 61.27y; mOS 14.81 months), 40 patients underwent second surgery at disease progression (age 55y; 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; HR 0.24) or bevacizumab (P 0.001; HR 0.23) was associated with longer OS. Reoperation was associated with a lower hazard ratio (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.

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Efficacy of Surgery and Further Treatment of Progressive Glioblastoma

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Abbreviations:

CCNU = lomustine; GTR = gross-total resection; HR = hazard ratio; KPS = Karnofsky performance status; MRI = magnet resonance imaging; NIH = national institute of health; OR = odds ratio; OS = overall survival; RT = radiotherapy; STR = subtotal resection; TMZ = temozolomide.

Abstract

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 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 vs. 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 was statistically analyzed. 58 patients had initial surgery only (age 61.27y; mOS 14.81 months), 40 patients underwent second surgery at disease progression (age 55y; 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; HR 0.24) or bevacizumab (P 0.001; HR 0.23) was associated with longer OS. Reoperation was associated with a lower hazard ratio (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 O⁶-methylguanine DNA methyltransferase (MGMT) promoter methylation status may be taken into consideration ^{4, 10, 25}. Based on a retrospective analysis of 34 patients, Park et al. 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 cm³, 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 criteria¹⁶. Medical records were reviewed to identify patients ≥ 18 years, diagnosed with glioblastoma, who had undergone 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 therapy²³ 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 magnetic resonance imaging (MRI). At this point the findings were discussed at an interdisciplinary tumor board including four different surgeons. Patients with initially lower grade gliomas, infratentorial tumor location, younger than 18 years or without MRI confirmed progression were excluded.

In total, 98 patients met our inclusion criteria (**Fig. 1**). Of these, 40 underwent a second, maximal safe surgical resection and further neurooncological 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 regards to age, gender, tumor volume (ellipsoid: $\frac{4}{3} \cdot \pi \cdot x \cdot y \cdot z / 2$), tumor localization, 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), ≤ 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 (i) factors at disease progression associated with the subsequent decision for reoperation, (ii) prognostic factors for OS and (iii) 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 (1st surgery), tumor volume (1st surgery) and tumor location (1st surgery), and time from diagnosis to progression as predictor variables. The results are presented as odds ratios (OR). In a second step, a Cox proportional hazards model was fit to OS time, with independent variables regarding time to progression: age at time of diagnosis, post-second surgery temozolomide, lomustine or bevacizumab, recurrent resection and tumor localization. When we evaluated the NIH recurrent glioblastoma scale (**Table 1**), the

dependent time variable was calculated as time from second surgery to death. To calculate the NIH recurrent glioblastoma scale, data from the second surgery was used. The estimated effects from the Cox models are presented as hazard ratios (HR). All analyses were performed with R programming (Team RDC, Vienna, Austria).

Results

Patients

In total 98 patients were included in this analysis. The study group A consisted of 40 patients (mean age 55, SD 8.33), 29 males and 11 females. At initial surgery 30 patients underwent GTR and 10 patients STR. At second surgery 27 patients had GTR and 13 STR. After the second surgery 8 patients received temozolomide postoperatively, two patients were treated with lomustine, 28 patients with bevacizumab and 2 patients received no postoperative therapy (**Table 2**).

The control group (B) consisted of 58 patients (mean age 61, SD 11.20), 35 males and 23 females. Of these, 39 patients had GTR and 14 STR. 5 patients underwent a biopsy at initial surgery. At progression, 8 patients received temozolomide, 1 patient lomustine, 38 patients bevacizumab and 11 received no systemic therapy. By definition, no patient of group B had second surgery at disease progression. The initial median KPS score was 80 % for both groups (**Table 2**).

Variables that determine repeated surgery at time of progression

After combining the study group (group A) with the reference group (group B), a logistic regression model with the dependent variable of recurrent surgery was used. As shown in table 3, only age was significantly associated with recurrent surgery (odds ratio=0.944; 95% CI 0.902-0.987; p=0.012); preoperative KPS, tumor volume and the time period between diagnosis and recurrence were not significant (**Table 3**).

Prognostic variables for post-progression survival

At the time of progression, the Cox proportional hazards model resulted in a statistically significant association of systemic treatment with temozolomide or lomustine (HR=0.240, 95% CI 0.091-0.637, p=0.004) and bevacizumab (HR=0.235, 95% CI 0.099-0.557, p=0.001) and OS. For these two variables a protective effect was recognized in terms of a HR considerably smaller than 1. The significance is limited because only two patient had no alkylating therapy at progression. The HR rises with increasing age (10 % significance level). The estimated HR for repeated resection (HR=0.664; 95% CI 0.389-1.134; p=0.134) and age at diagnosis (HR=1.025, 95% CI 0.997-1.055, p=0.085) were not statistically significant.

Evaluation of the NIH recurrent glioblastoma scale

Applying the NIH recurrent glioblastoma scale to our patient series scored 20 patients with 0 points, 16 patients with one point and four patients with two points. These correspond to the following NIH prognostic groups: good (score value = 0) 20 patients, intermediate (score values = 1 or 2) 20 patients, and poor (score value =3) none. The median postoperative survival was 8.33 months (SD 1.01; 95% CI 5.93 to 13.1) in the intermediate category and 13.93 months (SD 1.23; lower 95% CI 11.48) in the good category, respectively (**Fig. 2**). The distinction was statistically significant (HR 2.526, 95% CI 1.207 to 5.287).

Improvement proposal for the NIH recurrent glioblastoma scale

Three models for amending the NIH recurrent glioblastoma scale were examined: (1) NIH + residual tumor at initial surgery, (2) NIH + postoperative complications after initial surgery, and (3) NIH + age at initial diagnosis. The examined models were based on variables, that were of known prognostic relevance and available at time of progression. Cox proportional hazards models for OS after recurrent surgery were used to explore the three additional variables. As a result, only the addition of the age at initial diagnosis (dichotomized with cut off $\geq / < 50$ years) resulted in an independent and significant refinement of the existing score. The Cox model with age and NIH recurrent glioblastoma scale resulted in a HR=3.972 (95% CI 1.681-9.382, p=0.002).

Having established the independent effect of age, we propose to update the NIH recurrent glioblastoma scale accordingly. In order to evaluate the single effects of the four predictors of the scale, namely KPS, tumor volume, motor-speech-middle cerebral artery score and age, we applied a Cox model to the four predictors. The resulting estimated HRs were 2.372 (KPS ≤ 80), 17.049 (tumor volume ≥ 50), 4.110 (MSM ≥ 2) and 4.142 (age ≥ 50). Therefore, we recommend assigning one point for KPS ≤ 80 %, MSM ≥ 2 and age ≥ 50 , and two points for tumor volume ≥ 50 (**Table 1**). Accordingly, the new scale ranges from 0-5. Applying the new scale to the present data, results in eight patients with zero points, 17 patients with one point, 12 patients with two points, zero patients with three points and three patients with four points. Again, it is desirable to distinguish between patients with a good, an intermediate or a poor prognosis. For this reason, the Kaplan-Meier curves of the separate score values were considered (**Fig. 2**). Based on this analysis we suggest that patients with score = 0 are considered to have a good prognosis, with score = 1 or 2 an intermediate and with a score ≥ 3 a poor prognosis (**Table 1**).

Discussion

Treatment modalities of patients with glioblastoma at time of progression are variable and remain controversial^{1, 3, 7, 9, 12, 25}. Studies often show bias because of insufficient data regarding the efficacy of treatment modalities after resection of recurrent glioblastoma. Direct comparison between data published before 2005 and after is limited due to the change in paradigm for firstline therapy^{14, 15, 24}. Furthermore, additional data has accumulated with the advent of bevacizumab in 2009 and its partial implementation into treatment protocols^{15, 25}.

To evaluate which factor determines a second surgery, a logistic regression analysis was performed. The results revealed that younger age was the only significant predictor for repeated surgery. No other factors, e.g. preoperative KPS, tumor volume and tumor location were predictive for the decision for reoperation. This is in line with the results described earlier by Helseth et al. 2010, who reported that primarily younger patients undergo repeated surgery¹². It is interesting to note that a consistent clinical selection bias in series of 2nd surgery is age.

In addition, this study tries to analyze the influence of repeated surgery followed by postoperative systemic therapy in glioblastoma patients. The Cox proportional hazards model revealed an association of postoperative systemic treatment after 2nd surgery and OS. Whether systemic treatment after second surgery definitively leads to a better outcome in patients with progressive glioblastoma, warrants further investigations. Second surgery as such was not statistically significant in this model, but the hazard ratio implied a trend towards improved OS, which may become significant in a larger dataset. Some studies showed a longer OS for patients with second surgery^{6, 12, 22}, whereas Clark et al. 2011 described no significant effect with regards to the 6 months progression-free survival in the re-operated versus not operated group⁷. These results suggest that a careful

patient selection at the time of progression is compulsory in order to improve their OS on the basis of the as aforementioned measures.

Validation and refinement of the NIH recurrent glioblastoma scale

To our knowledge, the present analysis is the first trial to validate the NIH recurrent glioblastoma scale published by Park et al. in 2010. The distinction between the prognostic groups was statistical significant in our dataset. Several studies have described the significant influence of age as a prognostic factor for primary glioblastoma ^{5, 11, 19, 26}. However, age was not considered in the NIH recurrent glioblastoma scale. In the present analyses we identified age with a cut off ≥ 50 years as an additional significant prognostic factor (**Fig. 2**). This study does not demonstrate that the prognostic groups depend on resurgery. However, the modified NIH scale seems to improve the predictive strength of the prognostic groups for OS. This may prove to be a useful clinical decision tool before considering 2nd surgery.

Limitations and need of a prospective randomized trial

The appraisal of repeated surgery and postoperative treatment after 2nd surgery on OS survival is difficult for various reasons. First, just as in the present study, data in the literature is derived mostly from retrospective analyses. Second, bias regarding inclusion criteria, patient selection and treatment protocols exist. To limit these factors, we included only patients from 2007 to 2011 in order to provide data consistency with a homogenous cohort of patients. Group B constitutes therefore a solid comparison group. The statistical analyses with the multiple logistic regression model and Cox proportional hazards model also reduces some bias. This retrospective analysis does not give evidence of the benefit of a second surgery, because it cannot prove, whether a patient lived longer

due to surgery or to systemic treatment or both, or whether it was natural course. Prospective randomized trials to validate repeated surgery and postoperative treatment modality in patients with glioblastoma at time of progression are still lacking^{2,17}.

Conclusion

To our knowledge this is the first study on the influence of surgery combined with postoperative systemic therapy at time of progression in patients with recurrent glioblastoma. Furthermore, it represents the first attempt of validation and refinement of the existing NIH recurrent glioblastoma scale. The retrospective evaluation of the impact on OS of repeated surgery is difficult. Nevertheless, in patients that are eligible for a second resection surgery this study defines prognostic criteria of OS, which may be useful when counseling patients. To date, the benefit of reoperation has not been proven prospectively and no widely recognized criteria for treatment recommendations at progression exist. Although ethical concerns are often mentioned, a prospective, randomized, controlled trial with this issue may be inevitable.

Figures

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

Fig. 2. Kaplan-Meier plots (abscissa = time period starts at second surgery) of patients with second surgery divided according to the NIH recurrent glioblastoma scale (A1 and A2) and to the adapted NIH recurrent glioblastoma scale (B1 and B2). The proposed updated scale includes age as an additional variable, nearby tumor involvement of eloquent brain regions, compromised functional status and tumor volume.

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Tables

Table 1. NIH recurrent glioblastoma scale and adapted scale: Preoperative risk assessment in progressive glioblastoma patients

NIH Score	Prognostic Group	Modified NIH Score	Prognostic Group
0	Good	0	Good
1-2	Intermediate	1-2	Intermediate
3	Poor	≥ 3*	Poor
Additive scale, 1 point for: Number of critical brain regions ≥ 2; KPS ≤ 80; Tumor volume ≥ 50 cm ³ ;		Additive scale, 1 point for: Age ≥ 50 years; number of critical brain regions ≥ 2; KPS ≤ 80; 2 points for: Tumor volume ≥ 50 cm ³ ;	

* If ≥ 3 correlates with poor prognosis need of further validation because in our dataset patients with a score of ≥ 3 are lacking.

Abbreviation: KPS, Karnofsky performance status.

Table 2. Baseline demographic and clinical characteristics of glioblastoma patients at at first surgery

[brackets () = %]

		Group A	Group B	p-value
Number		40	58	
Gender male / female		29 / 11	35 / 23	
Overall survival	median	18.86	14.82	0.001
Age	median	55.04	62.63	0.004
KPS (preoperative)	median	80	80	
Corticosteroid use at admission		14 (35)	21 (36)	0.441
Seizures		27 (68)	29 (50)	
Side of tumor location	right	22 (55)	26 (44.8)	
	left	18 (45)	28 (48.3)	
	bilateral	0 (0)	4 (6.9)	
Predominant lobe of tumor location	frontal	11 (27.5)	22 (37.9)	
	temporal	13 (32.5)	22 (37.9)	
	parietal	6 (15)	10 (17.2)	
	occipital	2 (5)	1 (1.7)	
Eloquent regions involved	0	31 (77.5)	44 (75.9)	
	1	9 (22.5)	12 (20.7)	
	2	0 (0)	2 (3.4)	
	3	0 (0)	0 (0)	
MGMT promoter methylation	hypermethyl.	7 (17.5)	10 (17.2)	
	negative	15 (37.5)	20 (34.5)	
	NA	18 (45)	28 (48.3)	
Tumor volume, cm³	median	17.44	21.5	0.377
IDH 1 status	positive	2 (5)	0 (0)	
	negative	38 (95)	18 (31)	
	NA	0 (0)	40 (69)	
Type of primary surgery	GTR	30 (75)	39 (67.2)	
	STR	10 (25)	14 (24.2)	
	biopsy	0 (0)	5 (8.6)	
Complications of 1st surgery		6 (15)	5 (8.6)	
Radiotherapy	part RT 60 gy with concomitant TMZ	38 (95)	45 (77.6)	
	part RT 40 gy * without TMZ	2 (5)	13 (12.4)	
Treatment at progression	TMZ / CCNU	10 (25)	9 (22.5)	
	bevacizumab	28 (70)	38 (65.5)	
	no	2 (5)	11 (19.0)	
Number of TMZ cycles	median	5	3	0.00

* Only patients older than 65 years.

Abbreviation: CCNU, lomustine; IDH1, isocitrate dehydrogenase 1; KPS, Karnofsky performance status; MGMT: O6-methylguanine-DNA-methyltransferase promoter; RT: radiotherapy; TMZ: temozolomide.

Table 3. Logistic regression model (dependent variable recurrent resection)

Variables	Odds ratio	95% confidence interval	p-value
Age at diagnosis	0.944	0.902-0.987	0.012
Tumor volume (1st surgery)	0.997	0.983-1.011	0.661
Preoperative KPS (1st surgery)	1.006	0.977-1.036	0.688
Time between diagnosis and progression	1.014	0.949-1.084	0.691

Abbreviation: KPS, Karnofsky performance status.