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Multi-institutional validation of a preoperative scoring system which predicts survival for patients with glioblastoma

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Abstract

Glioblastoma is the most common and aggressive type of primary brain tumor in adults. Average survival is approximately 1 year, but individual survival is heterogeneous. Using a single institutional experience, we have previously identified preoperative factors associated with survival and devised a prognostic scoring system based on these factors. The aims of the present study are to validate these preoperative factors and verify the efficacy of this scoring system using a multi-institutional cohort. Of the 334 patients in this study from three different institutions, the preoperative factors found to be negatively associated with survival in a Cox analysis were age >60 years ($p < 0.0001$), Karnofsky Performance Scale score 80 ($p = 0.03$), motor deficit ($p = 0.02$), language deficit ($p = 0.04$), and periventricular tumor location ($p = 0.04$). Patients possessing 0–1, 2, 3, and 4–5 of these variables were assigned a preoperative grade of 1, 2, 3, and 4, respectively. Patients with a preoperative grade of 1, 2, 3, and 4 had a median survival of 17.9, 12.3, 10, and 7.5 months, respectively. Survival of each of these grades was statistically significant ($p < 0.05$) in log-rank analysis. This grading system, based only on preoperative variables, may provide patients and physicians with prognostic information that may guide medical and surgical therapy before any intervention is pursued.

Keywords

Glioblastoma; Prognosis; Scoring system; Surgery; Survival

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1. Introduction

Glioblastoma (GB) is the most common and aggressive type of primary brain tumor in adults, with median survival times of approximately 1 year.¹ The ability to identify which patients will have shortened or prolonged survival remains limited. More recently, from a single institutional experience, we have developed a method to prognosticate survival based only on preoperative factors (Table 1).⁴ However, this has not been validated using a multi-institutional cohort. This study aimed to (1) validate these preoperative factors as associated with survival; (2) develop a prognostic classification system using identified factors; and (3) validate the utility of this classification system using a multi-institutional cohort. The validation of this preoperative prognostic system may then be useful for guiding therapy.

2. Methods

2.1. Patient selection

Institutional Review Board approval was obtained from each participating institution prior to conducting this study. Patients with prior resections, previous adjuvant therapy (chemotherapy or radiation therapy), infratentorial gliomas, and/or who underwent needle biopsies were excluded from the analysis. Patients with incomplete medical records lacking clinical presentation, pre and postoperative MRI, and/or adjuvant therapies were also excluded. This was done to create a more uniform patient population with similar tumor types, tumor location, and treatment strategies. The pathology was determined by a neuro-pathologist for all patients, and the grading criteria were based on the World Health Organization classification system.⁵

2.2. Recorded variables

The clinical, operative, and hospital course records of the patients who met the inclusion criteria were retrospectively reviewed as previously described.⁴ The information collected from neurosurgery and neuro-oncology clinical notes included patient demographics, comorbidities, presenting symptoms, neurological imaging, neurological function, and adjuvant therapy. A reviewer blinded to patient outcomes assigned each patient a Karnofsky Performance Scale (KPS) at the clinical visit prior to surgery during a chart review. A motor deficit was defined as decreased strength, while a language deficit was defined as any combination of receptive and/or expressive aphasia. The tumor was defined as periventricular if the tumor bordered the lateral ventricles on gadolinium contrast-enhanced MRI, as previously defined.^{4,6} Extent of resection was classified from MRI obtained <48 hours after surgical resection as either gross total resection (GTR), near-total (NTR), or subtotal resection (STR) by an independent neuro-radiologist blinded to patient outcomes as previously described.^{3,7} GTR was noted if no residual enhancement was seen on postoperative MRI, NTR if only a rim enhancement of the resection cavity was seen, or STR if residual nodular enhancement was present.^{3,7} Date of death was obtained from the social security index database.⁸ Patients whose deaths were unconfirmed were classified as lost to follow-up at the time of the last clinic visit.

2.3. Statistical analysis

An *a priori* power analysis was conducted to evaluate if the study was significantly powered. A cut-off of 0.90 was pre-assigned as being of sufficient power. Summary data were presented as mean $\pm$ standard deviation for parametric data and as median (interquartile range [IQR]) for non-parametric data. For inter-group comparison, Student's *t*-test was used for continuous data and Mann-Whitney U test for categorical data. Mean values were compared among multiple groups using two-way, non-parametric analysis of variance (Kruskal-Wallis test), with the difference between each group determined by Student-Newman-Keuls' multiple comparisons test. Multivariate proportional hazards regression analysis was used to evaluate the significance of previously identified preoperative factors with survival for patients with GB.⁴ This was done after controlling for intra and postoperative factors (extent of resection,⁹ carmustine wafer implantation,^{10,11} temozolomide chemotherapy,¹² and radiation therapy¹³) known to be associated with survival. Survival as a function of time was plotted using the Kaplan-Meier method, and the log-rank analysis was used to compare Kaplan-Meier plots (GraphPad Prism 5, La Jolla, CA, USA). In all analyses, values with $p < 0.05$ were considered statistically significant. JMP8 (SAS Institute, Carey, NC, USA) was used in all analyses, unless otherwise specified.

3. Results

3.1. Preoperative, perioperative, and postoperative patient characteristics

The pre, peri and postoperative characteristics of the patients included in this study are summarized in Table 2. A total of 334 patients underwent resection of a primary GB during the reviewed period at the three participating institutions. The average age was 60.8 ± 13.6 years at the time of surgery. The median (IQR) preoperative KPS was 80 (70–85). Ninety-five (28%) and 86 (26%) patients presented with motor and language deficits, respectively. GTR was achieved in 119 (36%) patients, NTR in 107 (31%), and STR in 108 (31%) patients. Forty-eight (14%) patients had carmustine wafers placed at the time of surgery, while 273 (82%) underwent temozolomide chemotherapy. Two hundred and eighty-six (86%) patients received postoperative radiation therapy. At last follow-up, 237 (70%) patients had died. Median (IQR) follow-up time for surviving patients was 8.3 (4.6–15.7) months. Median survival was 12.2 months, where the 6-, 12-, and 18-month survival rates were 79.4%, 52.5%, and 29.5%, respectively.

3.2. Differences in patient characteristics between institutions

The differences in pre, peri, and postoperative characteristics between patients among the different institutions are highlighted in Table 2. Patients at Johns Hopkins Hospital (JHH) more commonly presented with language deficits as compared to patients at Stanford ($p = 0.02$), but not patients at Vanderbilt ($p = 0.31$). Patients at Vanderbilt more commonly had tumors located in close juxtaposition to the ventricle compared to patients at JHH ($p = 0.0001$) and Stanford ($p = 0.0001$). In regards to extent of resection, STR occurred less commonly at JHH ($p = 0.006$). Carmustine wafers were less commonly implanted in patients at Stanford compared to patients at JHH ($p = 0.0001$) and Vanderbilt ($p = 0.0001$). There were no statistical differences between patients at the three institutions in regards to age,

KPS, presence of preoperative motor deficit, temozolomide chemotherapy, and radiation therapy.

3.3. Factors independently associated with survival

In multivariate analysis (Table 3), the factors significantly associated with survival were age ($p < 0.0001$), KPS ($p < 0.0001$), motor deficit ($p = 0.02$), language deficit ($p = 0.04$), and periventricular tumors ($p = 0.04$). The age and KPS at which statistical significance was greatest was at an age > 60 years ($p < 0.0001$) and a KPS ≥ 80 ($p = 0.03$).

3.4. Assigning prognostic classes

As previously published,⁴ one point was assigned for each factor independently associated with decreased survival (age > 60 , KPS ≥ 80 , motor deficit, language deficit, and periventricular tumor). Patients therefore could have a prognostic score from 0–5. Patients receiving a score of 0–1, 2, 3, and 4–5 were assigned prognostic classes of 1, 2, 3, and 4, respectively (Table 1). Based on these criteria, 101 (29%) patients were categorized as Class 1, 104 (30%) were Class 2, 86 (25%) were Class 3, and 42 (12%) were Class 4 (Table 4). Among the three participating institutions, Stanford had the highest percentage of patients with Class 1 patients as compared to JHH ($p = 0.02$) and Vanderbilt ($p = 0.01$). Likewise, Stanford had the lowest percentage of Class 4 patients as compared to Vanderbilt ($p = 0.04$), but not JHH ($p = 0.13$).

3.5. Prognostic classes and differential survival

An *a priori* power analysis was conducted and showed that there was sufficient power (> 0.90) to detect significant differences in treatment regimens between these four classes. Patients with a prognostic class of 1 had a median survival of 17.9 months, with a 6- and 12-month survival rate of 89% and 68%, respectively. Patients with a prognostic class of 2 had a median survival of 12.3 months, with a 6- and 12-month survival rate of 83% and 52%, respectively. Patients with a prognostic class of 3 had a median survival of 10 months, with a 6- and 12-month survival rate of 76% and 42%, respectively. Patients with a prognostic class of 4 had a median survival of 7.5 months, with a 6- and 12-month survival rate of 55% and 32%, respectively. Importantly, there were no differences between the classes in regards to GTR, carmustine wafers, temozolomide, or radiation.

In log-rank analysis, the survival times for patients with different prognostic classes were statistically significant ($p < 0.05$; Supp. Fig. 1). Patients with a prognostic class of 1 had a statistically longer survival than patients with a class of 2 ($p = 0.002$), 3 ($p < 0.0001$), and 4 ($p < 0.0001$). Likewise, patients with a prognostic class of 2 had a statistically longer survival than patients with a class of 3 ($p = 0.02$) and 4 ($p < 0.0001$). Finally patients with a prognostic class of 3 had a statistically longer survival than patients with a class of 4 ($p = 0.04$). Interestingly, no (0%) patients in Class 4 survived beyond 18 months. Importantly, survival among the institutions was not significantly different ($p > 0.05$; Supp. Fig. 2).

4. Discussion

4.1. Preoperative factors independently associated with survival

Recent studies have shown that survival for patients with GB has not significantly increased in the past several decades despite advances in surgical, medical, and radiation therapy.¹⁴ Mean survival is approximately 1 year, but individual survival is heterogeneous.¹ Several studies have focused on identifying factors associated with survival for patients with GB. The majority of these studies, however, have focused on peri and postoperative factors including extent of resection, temozolomide chemotherapy, carmustine wafer implantation, and radiation therapy.^{3,7,15,16} While the focus has been on peri and postoperative factors, the identification of preoperative factors remains understudied. The ability to prognosticate survival based on preoperative factors would be paramount to guiding the timing, mode, and aggressiveness of treatment strategies.⁴

The only preoperative factors shown to be associated with survival for patients with GB are older age and poor preoperative functional status.^{2,4,17} The present study validates both of these factors. Tumors in older patients may have different molecular profiles and resistance genes that create a more aggressive-behaving tumor.¹⁸ Older patients may also be less able to withstand neurological insults incurred during surgery, chemotherapy, or radiation.^{2,17} As with older age, patients with poorer functional status may be less able to tolerate neurological insults incurred during therapies.^{2,15–17}

The novel factors associated with survival that were validated by this study include presence of preoperative motor deficits, language deficits, and/or periventricular tumor location. A tumor causing neurological deficits might indicate a more infiltrate tumor since the location of the tumor on neurological imaging was not significantly associated with survival.

Periventricular tumors may reside in the so-called subventricular zone, which has been found to be a source of stem-like cells with self-renewal and multi-potential capabilities.¹⁹ There is also a growing belief that this site may be a source of tumors with higher self-renewal, proliferative, and/or invasive capacities leading to poorer patient outcomes.²⁰

4.2. Preoperative classification scale

Prior glioma classification schemes have been limited to patients with low grade gliomas²¹ or high grade gliomas (anaplastic gliomas and GB).¹ Chang et al. devised a preoperative classification system for adult patients with hemispheric low grade gliomas.²¹ This system used age, KPS, presumed eloquent brain location, and tumor size to categorize patients.²¹ Curran et al. used recursive partitioning analysis (RPA) to design a regression tree for patients with anaplastic gliomas and GB.¹ This RPA used age, histology (anaplastic *versus* GB), and presence of altered mental status to define study subgroups.¹ These prior studies, however, are not necessarily applicable to patients with GB.

Scales used to predict survival for patients with GB are limited. Stupp et al. devised a nomogram to attempt to prognosticate survival for patients with newly diagnosed GB.²² The factors used to risk stratify patients include O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, age, performance status, extent of resection, and

mental status.²² Park et al. evaluated 34 patients with recurrent GB, and found that the predictors of poor postoperative survival were eloquent tumor involvement, preoperative status, and tumor volume.²³ These scoring systems rely on intraoperative data,²² previous history of GB and resections,^{22,23} and did not control for disparate adjuvant therapies.^{22,23}

An effective preoperative classification system would allow clinicians to prognosticate survival as well as guide surgical and medical strategies for patients with GB before any treatment is pursued. Patients with poorer prognoses may benefit from more conservative therapy, while patients with better prognoses may be better candidates for more aggressive therapy. This may also have quality of life ramifications, as well as stratify patients based on risk for future clinical trials. We have previously attempted to devise this system based on a single institutional experience.⁴ However, a single institution is often subjected to institutional biases including patient selection, timing and aggressiveness of surgery, and choice of adjuvant therapies. This current study has used a multi-institutional, geographically dispersed cohort to address this limitation. This study validates not only these factors as independent predictors of survival, but identifies four distinct populations with statistically different survival rates. This system may be useful for guiding surgical and medical management as there is with arteriovenous malformations, intracranial hemorrhage, or spinal injury.

4.3. Strengths and limitations

We believe this study provides several useful insights. First, studies ascertaining preoperative factors associated with survival are few and limited. The present study not only confirms the associations of older age and impaired functional status with decreased survival, but also adds motor and language deficits as well as periventricular tumor location. Second, validated studies predicting survival based on preoperative factors have yet to be established. Third, this study validates the potential effectiveness of a four-class system for prognosticating survival independent of perioperative factors before any treatment is pursued. Lastly, this study may provide useful information that may help guide treatment strategies for physicians, patients, and their family. While the median survival between the classes is statistically significant, the actual difference in survival may not seem large. However, this should be taken in the context that survival for patients with GB is relatively short so each month difference in survival is actually quite dramatic. Future studies stratified by class may make these differences in survival times even more significant.

This study, however, has some limitations. One limitation is the need for a prospectively followed cohort. This process is currently ongoing. This study also does not analyze the prognostic implication of molecular markers and genotypes. These factors may also play a role in predicting survival, but cannot typically be ascertained preoperatively. Furthermore, the majority of patients in this study did not undergo GTR and/or receive triple combinatorial adjuvant therapy (carmustine wafer, temozolomide, and radiation). As a result, the relevance of this prognostic model may be altered in the context of those patients receiving the most aggressive of treatment regimens. Additionally, this study is inherently limited by its retrospective design, and, as a result, it is not appropriate to infer direct causal relationships. However, we tried to create a uniform patient population by utilizing strict

inclusion and exclusion criteria, thus providing more relevant information for patients with primary intracranial GB. We used a multi-institutional cohort and included only adult patients with primary GB since children and patients with secondary GB may have tumors with different molecular and cytogenic profiles.¹⁸ In addition, we excluded patients with incomplete medical records and patients who received prior resections, previous adjuvant therapies, needle biopsies, and infratentorial tumors. We also performed multivariate analyses and controlled for potential perioperative confounding variables (extent of resection and adjuvant therapy) to minimize the effects of disparate treatment. Given these statistical controls and a relatively precise outcome measure, we believe our findings offer useful insights into the management of patients with primary GB. However, prospective studies are needed to provide better data to guide clinical decision-making.

5. Conclusions

Individual survival for patients with intracranial GB is heterogeneous, with some patients surviving for a few months while others survive for several years. The ability to predict which patients will have better outcomes is limited. We previously used a single institutional experience to ascertain preoperative factors associated with survival, and used these factors to devise a prognostic scoring system. In the present study we found that preoperatively, older age, poor performance status, motor deficit, language deficit, and periventricular tumor location independently predicted poorer survival. We validated these factors and the prognostic scoring system using a multi-institutional cohort with presumably different treatment strategies. The factors and classification system validated by this study may provide patients and physicians with prognostic information that may guide medical and surgical therapy. These can be employed before any treatments are pursued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Primary glioblastoma prognostic scoring system

Variables	Yes	No
Age > 60	1	0
KPS 80	1	0
Motor deficit	1	0
Language deficit	1	0
Periventricular tumor location	1	0

KPS = Karnofsky Performance Scale.

Table 2
Pre, peri, and postoperative characteristics of patients undergoing primary resection of an intracranial glioblastoma from Johns Hopkins Hospital, Stanford, and Vanderbilt.
The bolded values are statically different than one or more of the other institutions ($p < 0.05$)

Study population ($n = 334$)				
Characteristics	JHH $n = 146$	Stanford $n = 92$	Vanderbilt $n = 95$	Total number
<i>Preoperative characteristics</i>				
Age *	61.3 $\pm$ 13.4	59.5 $\pm$ 11.9	61.3 $\pm$ 14.3	60.8 $\pm$ 13.6
KPS **	80 (75–80)	80 (70–90)	70 (60–85)	80 (70–85)
Motor deficit	47 (32%)	24 (26%)	24 (25%)	95 (28%)
Language deficit	46 (32%)	16 (17%)	24 (25%)	86 (26%)
Periventricular location	31 (21%)	18 (20%)	56 (59%)	105 (31%)
<i>Perioperative characteristics</i>				
Extent of resection				
Gross total resection	56 (38%)	40 (43%)	23 (24%)	119 (36%)
Near-total resection	55 (38%)	13 (14%)	39 (41%)	107 (31%)
Subtotal resection	36 (25%)	39 (42%)	33 (35%)	108 (31%)
Adjuvant therapy				
Carmustine wafer	33 (23%)	0 (0%)	15 (16%)	48 (14%)
Temozolomide	120 (82%)	80 (87%)	73 (77%)	273 (82%)
Radiation therapy	123 (84%)	84 (91%)	79 (84%)	286 (86%)
<i>GBM Classes</i>				
Class 1	39 (27%)	39 (42%)	23 (24%)	101 (29%)
Class 2	49 (34%)	29 (32%)	26 (27%)	104 (30%)
Class 3	39 (27%)	18 (20%)	29 (31%)	86 (25%)
Class 4	19 (13%)	6 (7%)	17 (18%)	42 (12%)
<i>Survival</i>				
Died at last follow-up	91 (62%)	69 (75%)	77 (81%)	237 (70%)
Median survival (months)	12.2	13.5	12.8	12.2
6-month survival rate	80%	91%	65%	79%
12-month survival rate	54%	54%	44%	52%
18-month survival rate	25%	40%	23%	29%
24-month survival rate	13%	22%	8%	15%

GBM = glioblastoma, JHH = Johns Hopkins Hospital, KPS = Karnofsky Performance Scale.

* Mean $\pm$ standard deviation.

** Median (interquartile range).

Table 3
Associations of preoperative variables with survival for adult patients undergoing surgical resection of primary intracranial glioblastoma at three different institutions after controlling for extent of resection, carmustine wafer implantation, temodar chemotherapy, and radiation therapy

Multivariate associations with survival		
Variables	Hazard ratio (95% confidence interval)	<i>p</i> value
Older age		
Age > 60 years	1.035 (1.024–1.046)	<0.0001
Improved KPS	2.268 (2.201–2.335)	<0.0001
KPS 80	0.989 (0.981–0.998)	0.01
Motor deficit	1.384 (1.307–1.461)	0.03
Language deficit	1.334 (1.262–1.406)	0.02
Periventricular tumor location	1.085 (1.008–1.142)	0.04
	1.241 (1.136–1.456)	0.04

KPS = Karnofsky Performance Scale.

Table 4
Survival outcomes for the different prognostic classes. All classes had statistically different survival rates ($p < 0.05$)

	Survival outcomes by different prognostic classes			
	Class 1 ($n = 101$)	Class 2 ($n = 104$)	Class 3 ($n = 86$)	Class 4 ($n = 42$)
Median survival (months)	17.9	12.3	10	7.5
6-month survival rate	89%	83%	76%	55%
12-month survival rate	68%	52%	42%	32%
18-month survival rate	48%	29%	18%	0%
24-month survival rate	26%	13%	8%	0%