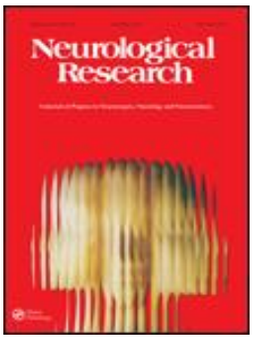

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Neurological Research

A Journal of Progress in Neurosurgery, Neurology and Neuro Sciences

ISSN: 0161-6412 (Print) 1743-1328 (Online) Journal homepage: www.tandfonline.com/journals/yner20

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To cite this article: Kaisorn L. Chaichana, Matthew J. McGirt, Graeme F. Woodworth, Ghazala Datoo, Rafael J. Tamargo, John Weingart, Alessandro Olivi, Henry Brem & Alfredo Quinones-Hinojosa (2010) Persistent outpatient hyperglycemia is independently associated with survival, recurrence and malignant degeneration following surgery for hemispheric low grade gliomas, Neurological Research, 32:4, 442-448, DOI: 10.1179/174313209X431101

To link to this article: https://doi.org/10.1179/174313209X431101

Persistent outpatient hyperglycemia is independently associated with survival, recurrence and malignant degeneration following surgery for hemispheric low grade gliomas

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Objective: Hyperglycemia has been shown to augment tumor growth *in vitro*. However, the effects of persistent hyperglycemia on survival, recurrence and malignant degeneration in patients undergoing surgery for low grade gliomas remain unknown.

Methods: All patients who underwent a craniotomy for hemispheric low grade glioma (WHO grade II) from 1996 to 2006 at a single institution were retrospectively reviewed. Persistent hyperglycemia was defined as serum glucose >180 μg/dl occurring three or more times between 1 and 3 months post-operatively. The independent association of outpatient glucose levels and recorded clinical and treatment variables with overall survival, tumor recurrence and malignant degeneration was assessed via separate multivariate proportional-hazards regression analyses.

Results: In this study, 182 patients (89 fibrillary astrocytomas, 82 oligodendrogliomas and 11 mixed gliomas) were available for analysis. Eighteen (10%) patients experienced persistent hyperglycemia. Patients experiencing persistent hyperglycemia were older (44 ± 16 versus 34 ± 15) and more frequently diabetic [3 (17%) versus 4 (2%)]. All other clinical and treatment variables were not significantly different between the two cohorts. After adjusting for inter-group differences including age and diabetes and variables associated with survival and recurrence, persistent hyperglycemia was independently associated with decreased survival (p=0·001), increased recurrence (p=0·0001) and increased malignant degeneration (p<0·0001). This remained true after excluding all patients with diabetes and those on continued steroid administration. Five-year overall survival, progression-free survival and malignancy-free survival for persistent hyperglycemia versus relatively euglycemic cohorts were 43% versus 84%, 16% versus 46% and 46% versus 77%, respectively.

Discussion: These findings may provide useful insight for increasing survival, decreasing tumor recurrence and decreasing malignant degeneration in patients undergoing surgery for low grade gliomas.

Keywords: Hyperglycemia, low grade gliomas, malignancy, recurrence, survival

Introduction

Patients with low grade gliomas often have a better prognosis than patients harboring higher grade tumors. However, approximately 50–75% of patients with low grade gliomas will eventually die from their disease[1]. The median survival time for these patients ranges from 5 to 10 years, with the 5 year median survival rate ranging from 30 to 70% in most series[2–8]. As such, there has been an emphasis on ascertaining factors associated with prolonged survival. The factors consistently known to be associated with improved survival include younger age[4,9,10], higher Karnofsky performance scores (KPS)[7,11], oligodendroglioma pathology[6], post-operative radiation therapy[8,11] and gross total resection[12–14]. The majority of these factors are non-modifiable.

Outpatient hyperglycemia, which is potentially modifiable, may serve as an additional prognostic marker for patients with low grade gliomas. In fact, patients with hyperglycemia often incur higher

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DOI 10.1179/174313209X431101

incidences of morbidity and mortality in several disease states[15–18]. This includes processes involving the central nervous system, such as surgery for aneurysms[19], intracranial biopsies[20] and intramedullary tumors[21]. Interestingly, tumor cells, which rely on anaerobic glycolysis, preferentially grow in high-glucose solutions[22–25]. Therefore, it remains plausible that hyperglycemic conditions may augment tumor growth, making low grade tumors more prone to recurrence and malignant degeneration. We set out to determine if persistent hyperglycemia following surgical resection of a hemispheric low grade glioma was associated with survival, recurrence and malignant degeneration.

Methods

Patient selection

The 248 patients who underwent surgery for a low grade glioma at an academic tertiary-care institution between 1996 and 2006 were retrospectively reviewed after obtaining approval from the Institutional Review Board. Patients at least 18 years old with a tissue-proven diagnosis of hemispheric WHO grade II glioma (fibrillary astrocytoma, oligodendroglioma or mixed glioma)[26] were included in the study. The majority (88%) of pathological specimens were reviewed by a senior neuro-pathologist (P. C. Burger, MD). Patients with infratentorial gliomas and/or who underwent needle biopsy were excluded from the analysis. This was carried out to create a more uniform patient population with similar tumor locations, as well as to minimize the chance of sampling error from needle biopsies.

Information collected included patient demographics, co-morbidities, medications, presenting symptoms, pre-operative magnetic resonance imaging (MRI), intra-operative pathological findings, post-operative neurological function, additional resections and adjuvant therapy. Pre-operative KPS[27] and post-operative neurological status were recorded for all patients. Peri-operative mortality was defined as death within 30 days of surgery. Extent of resection was determined by comparing pre-operative FLAIR signal abnormality with post-operative MRI obtained within 48 hours of surgical resection from neuro-radiology reports. Subtotal and gross total resection were defined as having residual and no residual FLAIR signal abnormality, respectively by an independent neuro-radiologist blinded to patient outcomes.

Before the initiation of the study, persistent hyperglycemia was defined as a random serum glucose value >180 mg/dl occurring three or more times between 1 and 3 months post-operatively[19,21,28,29]. This cutoff was used because it has been identified as significant in previous studies[19,21,28,29]. Outpatient laboratory tests (complete blood counts, basic metabolic profiles) were routinely obtained between 1 and 3 months post-operatively to detect possible hematological complications of adjuvant therapy. Timing of laboratory evaluations was not standardized, were taken under non-fasting conditions and typically occurred weekly during the 3 month follow-up period. Patients without serum glucose values were excluded from the analysis. For purposes of this study, only serum glucose was retrospectively recorded. To ascertain whether outpatient hyperglycemia was a result of steroid dependence due to higher tumor burden, patients' ability to be weaned off of steroids by 3 months post-operatively was recorded.

Date of death was recorded for all patients. Patients whose deaths were unconfirmed were classified as lost to follow-up at the time of the last clinic visit. Additionally, patients whose tumor recurrence or malignant degeneration was unconfirmed were classified as lost to follow-up at the time of the last MRI. Tumor recurrence was defined as definitive evidence of tumor recurrence or progressive growth on MRI. Malignant degeneration was defined as pathology-proven malignant degeneration (WHO grade III or IV)[26] from tissue acquired during repeat biopsy or resection.

Statistical analysis

Summary data were presented as mean $\pm$ standard deviation for parametric data and as median [inter-quartile range (IQR)] for non-parametric data. Percentages were compared via Fisher's exact test, and p-values $<0{\cdot}05$ were considered significant. For inter-group comparison, Student's t-test was used for parametric data and Mann-Whitney U test for non-parametric data. The independent association of outpatient glucose levels with factors known to be associated with survival was assessed via multivariate proportional-hazards regression analysis (Cox model)[30] (JMP 7, SAS Institute, Carey, NC, USA). Variables with $p<0{\cdot}05$ were considered significant (JMP 7). The same model was also used to identify independent associations for both tumor recurrence and malignant degeneration. Survival, recurrence and malignant degeneration as a function of time after surgical resection were expressed as estimated Kaplan–Meier plots.

Results

Patient population

The patient information is summarized in *Table 1*. A total of 182 patients met the inclusion criteria. Average age was 36 $\pm$ 15 years. One hundred and thirty-eight (76%) underwent primary resection and 44 (24%) underwent secondary resection. Tumor pathology included fibrillary astrocytoma in 89 (49%), oligodendroglioma in 82 (45%) and mixed glioma in 11 (6%). Median KPS at presentation was 80 (70–90). One hundred and twenty-one (66%) patients presented with seizures, 59 (32%) with signs of increased intracranial pressure (headache, nausea, vomiting), 18 (10%) with speech or language difficulty, 18 (10%) with mental status changes, 16 (9%) with visual deficits, 15 (8%) with motor deficits and 14 (8%) with sensory deficits. Seven (4%) patients had a pre-operative diagnosis of diabetes mellitus. Gross total resection was achieved in 67 (37%) patients. There were no cases of peri-operative mortality. Fifty-nine (32%) and 34 (19%) patients received

radiation therapy and Temodar chemotherapy at last follow-up, respectively. Thirty-five (19%) patients died during the review period. Seventy-two (40%) of the tumors recurred and 41 (23%) underwent malignant degeneration, respectively. For the 147 (81%) surviving patients, the median follow-up time was 61 (28–91) months. Overall, the median survival was 57 (28–86) months.

Outpatient hyperglycemia

Eighteen (10%) patients experienced persistent outpatient hyperglycemia between 1 and 3 months after surgery. Persistent hyperglycemia was secondary to diabetes mellitus in three (17%) cases and secondary to continued steroid use in one (6%) patient. Patients experiencing persistent hyperglycemia were older [44 $\pm$ 14 versus 34 $\pm$ 13 ($p<0{\cdot}05$)] and more frequently diabetic [3 (17%) versus 4 (2%) ($p<0{\cdot}05$)]. All other clinical, radiographic and treatment variables were similar between patients who had persistent hyperglycemia and patients who had relative euglycemia (*Table 1*). Of note, only three (17%) of the hyperglycemic patients were receiving glucose-modulating therapy.

Hyperglycemia and survival

In a multivariate analysis, after controlling for all factors consistently shown to be associated with survival, persistent hyperglycemia remained independently associated with survival [RR (95% CI): 5·111 (2·000–11·782), $p=0{\cdot}001$] (*Table 2A*). Additionally, after controlling for inter-group differences (age and diabetes) and continued outpatient steroid administration, persistent outpatient hyperglycemia remained statistically significant [RR (95% CI): 4·7200 (2·105–9·562), $p=0{\cdot}0005$]. Furthermore, in sub-group multivariate analysis, persistent outpatient hyperglycemia remained independently associated with survival after excluding all patients with a formal diagnosis of diabetes and those who were on steroids in the outpatient period (1–3 months post-operative) [RR (95%CI): 4·252 (2·350–8·763), $p<0{\cdot}001$]. Persistent hyperglycemia in the absence of diabetes and steroid administration made it four-fold less likely that a patient would survive following surgical resection of a low grade glioma. The 5 year overall survival rates for patients with hyperglycemia versus euglycemia were 43% versus 84%; the 8 year overall survival rates were 35% versus 72% ($p=0{\cdot}0001$) (*Figure 1*).

Hyperglycemia and recurrence

As with survival, persistent outpatient hyperglycemia was independently associated with tumor recurrence after controlling for all factors consistently shown to be associated with recurrence in a multivariate analysis [RR (95% CI): 5·349 (2·470–10·967), $p=0{\cdot}0001$] (*Table 2B*). Additionally, after controlling for inter-group differences (age and diabetes) and continued outpatient steroid administration, persistent outpatient hyperglycemia remained statistically significant [RR (95% CI): 6·004 (2·815–11·646), $p<0{\cdot}0001$]. Furthermore, in sub-group multivariate analysis, persistent outpatient hyperglycemia remained independently associated with recurrence after excluding all patients with a formal diagnosis of diabetes and those who were on steroids in the outpatient period [RR (95%CI): 2·572 (1·430–4·306), $p=0{\cdot}003$]. Persistent hyperglycemia in the absence of diabetes and steroid administration made it

Table 1 Summary of pre- and post-operative characteristics in 182 total patients with hemispheric low grade gliomas, consisting 164 and 18 patients, respectively, who had and did not have persistent outpatient hyperglycemia (18 patients with hyperglycemia versus 164 with euglycemia)

Characteristics	Outpatient hyperglycemia no. (%)	Outpatient euglycemia no. (%)	*p*-value
Age (years)	44 $\pm$ 14*	34 $\pm$ 13*	**0·007**
Male	10 (56%)	97 (59%)	0·77
Diabetic	3 (17%)	4 (2%)	**0·003**
KPS	80 (80–90)†	80 (80–90)†	0·79
Symptom duration (months)	3 (1–10)†	3 (1–12)†	0·81
Seizures	12 (67%)	109 (66%)	0·98
Headache/nausea/vomiting	4 (22%)	55 (34%)	0·33
Speech deficits	2 (11%)	16 (10%)	0·86
Motor deficits	1 (6%)	14 (9%)	0·66
Sensory deficits	1 (6%)	13 (8%)	0·72
Visual deficits	1 (6%)	15 (9%)	0·61
Mental status changes	1 (6%)	17 (10%)	0·52
Primary resection	14 (78%)	125 (76%)	0·88
Largest tumor dimension (cm)	4·5 $\pm$ 1·8*	4·0 $\pm$ 2·0*	0·68
Pathology			
Fibrillary astrocytomas	9 (50%)	80 (49%)	0·96
Oligodendrogliomas	7 (39%)	75 (46%)	0·61
Mixed gliomas	2 (11%)	9 (5%)	0·34
Gross total resection	7 (39%)	60 (37%)	0·85
New post-operative deficit	3 (17%)	23 (14%)	0·76
Outpatient continued steroid administration	1 (6%)	5 (3%)	0·57
Up-front post-operative radiation	1 (6%)	13 (8%)	0·72
Any radiotherapy	6 (33%)	53 (32%)	0·93
Up-front Temodar chemotherapy	0 (0%)	0 (0%)	0·99
Any Temodar chemotherapy	5 (28%)	29 (18%)	0·30

*Mean $\pm$ standard deviation.
†Median (interquartile range).

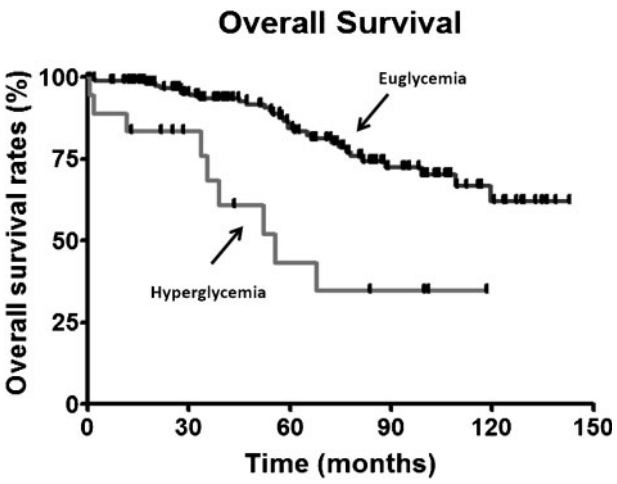

Figure 1 Kaplan–Meier plots of overall survival rates for patients with low grade gliomas that experience persistent post-operative hyperglycemia versus euglycemia. Five and 8 year overall survival rates for patients with hyperglycemia versus euglycemia were 43% versus 84% and 35% versus 72%, respectively (p=0·0001)

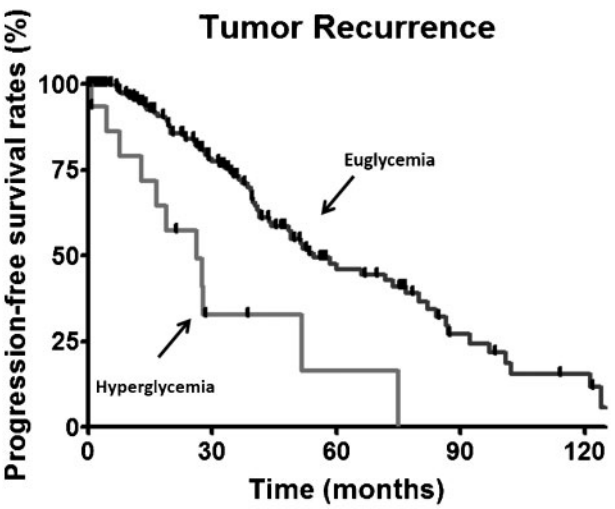

Figure 2 Kaplan–Meier plots of progression free survival rates for patients with low grade gliomas that experience persistent post-operative hyperglycemia versus euglycemia. Five and 8 year progression free survival rates for patients with hyperglycemia versus euglycemia were 16% versus 46% and 0% versus 24%, respectively (p<0·0001)

approximately three-fold more likely that the tumor would recur following surgical resection of a low grade glioma. The 5 year progression-free survival rates for patients with hyperglycemia versus euglycemia were 16% versus 46%; the 8 year progression-free survival rates were 0% versus 24% (p<0·0001) (*Figure 2*).

Hyperglycemia and malignant degeneration

As with survival and recurrence, persistent outpatient hyperglycemia was independently associated with malignant degeneration after controlling for all factors consistently shown to be associated with malignant degeneration in a multivariate analysis [RR (95%CI): 10·130 (3·595–25·918), p<0·0001] (*Table 2C*). Additionally, after controlling for intergroup differences (age and diabetes) and continued outpatient steroid administration, persistent outpatient hyperglycemia remained statistically significant [RR (95%CI): 6·875 (2·809–15·159), p=0·0001]. Furthermore, in sub-group multivariate analysis, persistent outpatient hyperglycemia remained

Table 2 Multivariate proportional hazards analyses of survival, recurrence and malignant degeneration. A: multivariate proportional hazards analysis of survival for known associations with survival for patients with low grade gliomas; B: multivariate proportional hazards analysis of recurrence for known associations with recurrence for patients with low grade gliomas; C: multivariate proportional hazards analysis of malignant degeneration for known associations with malignant degeneration for patients with low grade gliomas

A. Survival	Covariate	Relative risk (95% CI)	*p*-value
	Age	7·178 (2·378–18·816)	0·001
	KPS>80	1·774 (0·633–6·085)	0·29
	Outpatient hyperglycemia	5·111 (2·000–11·782)	**0·001**
	Oligodendroglioma	0·496 (0·237–0·990)	0·05
	Post-operative XRT	1·857 (0·624–4·487)	0·24
	Gross total resection	0·511 (0·246–0·998)	0·05
B. Recurrence	Covariate	Relative risk (95% CI)	*p*-value
	Age	1·036 (1·016–1·058)	0·004
	KPS>80	0·988 (0·501–2·151)	0·97
	Outpatient hyperglycemia	5·349 (2·470–10·967)	**0·0001**
	Oligodendroglioma	0·844 (0·522–1·358)	0·49
	Post-operative XRT	0·809 (0·350–1·639)	0·58
	Gross total resection	0·627 (0·381–1·009)	0·04
C. Malignant degeneration	Covariate	Relative risk (95% CI)	*p*-value
	Age	1·050 (1·020–1·083)	0·0008
	KPS>80	2·421 (0·769–9·743)	0·14
	Outpatient hyperglycemia	10·130 (3·595–25·918)	**<0·0001**
	Oligodendroglioma	0·390 (0·192–0·767)	0·006
	Post-operative XRT	1·257 (0·465–2·883)	0·63
	Gross total resection	0·501 (0·243–0·975)	0·04

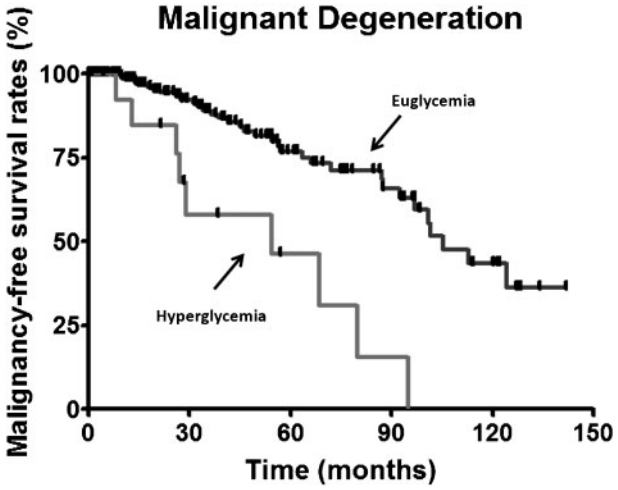

Figure 3 Kaplan–Meier plots of malignant free survival rates for patients with low grade gliomas that experience persistent post-operative hyperglycemia versus euglycemia. Five and 8 year malignant free survival rates for patients with hyperglycemia versus euglycemia were 46% versus 77% and 0% versus 63%, respectively ($p<0{\cdot}0001$)

independently associated with malignancy after excluding all patients with a formal diagnosis of diabetes and those who were on steroids in the outpatient period [RR (95%CI): 3·712 (1·510–8·283), $p=0{\cdot}006$]. Persistent hyperglycemia in the absence of diabetes and steroid administration made it approximately four-fold more likely that the tumor would undergo malignant degeneration following surgical resection of a low grade glioma. The 5 year malignancy-free survival rates for patients with hyperglycemia versus euglycemia were 46% versus 77%; the 8 year malignancyfree survival rates were 0% versus 63% ($p<0{\cdot}0001$) (*Figure 3*).

Discussion

In this study of 182 adult patients with hemispheric low grade gliomas (fibrillary astrocytomas, oligodendrogliomas and mixed gliomas), 164 (90%) and 18 (10%) patients experienced relative euglycemia and hyperglycemia within 1–3 months following surgical resection, respectively. Patients experiencing persistent hyperglycemia were older and more frequently diabetic. Adjusting for inter-group differences and variables associated with survival in this model, persistent outpatient hyperglycemia was independently associated with decreased survival, increased recurrences and increased malignant degeneration. Five-year overall survival, progression-free survival and malignancy-free survival rates for persistent hyperglycemic versus euglycemic cohorts were 43% versus 84%, 16% versus 46% and 46% versus 77%, respectively.

Low grade gliomas are relatively rare tumors with an annual incidence of ~4700 cases, which is ~7% of all brain tumors[31]. They are one-third as common as glioblastomas[31]. Unlike their higher grade counterparts, the optimal management of these tumors remains less well-defined[32]. Management greatly varies according to anatomic location and clinical presentation, as well as among different institutions. This may include some combination of vigilant observation, radical surgery, radiation and/or chemotherapy[32]. Despite maximal treatment, the majority of these tumors undergo malignant transformation over time and most patients eventually succumb to their disease. The risk of malignant degeneration varies between 21 and 90%, and the 5 year survival rate ranges between 30 and 70% in several works[2–8].

Individual outcomes for low grade glioma patients remain heterogeneous, with some patients having tumors that remain indolent for several years, while others have tumors that progress rapidly causing neurological decompensation and subsequent death. As a result of the inherent variability in the natural history, there has been an increased effort to find predictors of survival and recurrence for patients with low grade gliomas. In several studies, age[8,10,11,13,33,34] and pre-operative neurological function[7,11,13,34,35] are prognostic indicators, where younger patients and those with intact pre-operative neurological function have improved outcomes. Other factors also associated with improved outcomes include oligodendroglioma pathology[6,34,36] and post-operative radiation therapy[8,11,33,34]. A more controversial variable is the extent of resection. Some works have shown that more extensive resection is associated with improved outcomes[7,11–14,33,35,37], while other works have failed to find any statistical association[7,8,10,38,39]. With the exception of extensive resection, the majority of these risk factors are non-modifiable.

In the present study, hyperglycemia is independently associated with decreased survival, increased recurrence and increased malignant degeneration, and may therefore serve as a potentially modifiable risk factor. The mechanism by which hyperglycemia contributes to these outcomes is beyond the scope of the present study, but several basic science works may provide possible explanations. As early as the 1920s, Warburg noted that tumor cells preferentially rely on anaerobic glycolysis for cellular metabolism[22,25]. This preference for anaerobic glycolysis means that tumor cells rely on high glucose states for both cellular maintenance and proliferation[40–42]. In fact, glioma cell lines exhibit a three-fold increase in glycolysis compared with non-tumor astrocytes[24], and the withdrawal of glucose leads to selective apoptosis in tumor as opposed to non-tumor cell lines[23].

The effects of hyperglycemia on survival and tumor recurrence for patients with primary brain tumors remain unstudied. However, its effects on tumor development and progression have been observed for various cancers including breast, pancreas, prostate and colon, among others[43–46]. Furthermore, hyperglycemia may also play a role in decreasing the central nervous system's tolerance to pathology by increasing the number of advanced glycosylation end-products. This in turn reduces circulating levels of important vasodilators such as adenosine and nitric oxide, and predisposes nervous tissue to ischemic injury[47–50]. In fact, several clinical works have shown

that hyperglycemia increases morbidity and mortality, length of hospital stay and long-term functional deficits in critically ill patients[15,17,21,51]. Hyperglycemia is also associated with peri-operative morbidity and mortality for several processes involving the central nervous system, including surgery for aneurysms[19], intracranial biopsies[20] and intramedullary tumors[21]. In fact, we have found that persistent hyperglycemia is associated with decreased survival for patients with malignant astrocytomas, and is independent of extent of resection, tumor grade, diabetes, steroid use and adjuvant therapy[52]. It therefore makes intuitive sense that hyperglycemia may play a role in promoting glioma cell proliferation and decreasing the brain's tolerance to pathology, thus contributing to decreased survival and increased recurrence.

Despite these plausible mechanisms, some would argue that hyperglycemia could be just a surrogate marker for sicker, more critically ill patients[15,17,21,51]. Patients who are critically ill including those who have surgical site infections, sepsis and organ failure are at risk of developing hyperglycemia[15,17,21,51]. However, while hyperglycemia may be associated with sicker patients, there have been no clinical works documenting an association between hyperglycemia and tumor recurrence or malignant degeneration. Moreover, glucose levels were obtained from 1 to 3 months post-operatively, and none of the patients were critically ill (requiring inpatient hospitalization) during this period.

Strengths and limitations

This observational study has identified a potentially modifiable risk factor for patients with low grade gliomas. This study, however, is inherently limited by its retrospective design, and as a result, it is not appropriate to infer direct causal relationships. We also acknowledge that the findings presented in this observational study may be confounded by the fact that patients in general ill health may be more likely to be detected as hyperglycemic. Furthermore, the relatively low number of patients with hyperglycemia in this study makes a true comparison between patients with normal and abnormal glucose difficult. Additionally, since survival, recurrence and malignant degeneration is time-dependent, works with longer follow-up times may provide clearer insight. Nonetheless, we feel that this study may identify a novel risk factor for patients with low grade gliomas. It may also provide a new avenue for prolonging survival and delaying recurrence for patients with low grade gliomas, and warrants evaluating the effects of controlling post-operative glucose for patients with low grade gliomas.

The strengths of this study are that we tried to create a uniform patient population utilizing strict inclusion criteria, thus providing more relevant information for adult patients with hemispheric low grade gliomas. We included only patients who underwent surgical resection of their tumor, and excluded variants known to effect survival including pediatric patients[10,11], pilocytic astrocytomas (WHO grade I)[7,10] and biopsies[7,10]. In addition, we used multivariate analyses to control for inter-group differences (age and diabetes), as well as each variable previously shown to have a strong clinical relationship with survival and recurrence for patients with low grade gliomas. Moreover, we performed subgroup analyses to further control for the effects associated with diabetes and continued steroid administration. Given these statistical controls and a relatively precise outcome measure, we believe that our findings offer useful insights into the management of patients with low grade gliomas. However, before hyperglycemia can be deemed a modifiable prognostic factor for patients with low grade gliomas, prospective works are needed to provide better data for guiding clinical decision-making.

Conclusion

Patients harboring low grade gliomas, despite having a better prognosis than patients with high grade gliomas, will eventually undergo tumor recurrence and death following surgical resection and/or adjuvant treatment of their tumor. Persistent outpatient hyperglycemia may be a potential modifiable risk factor that affects survival, recurrence and malignant degeneration. This may provide useful insight into prolonging survival and delaying recurrence for patients with low grade gliomas.

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