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Association of preoperative depression and survival after resection of malignant brain astrocytoma

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Abstract

Background: Clinical depression has been shown to negatively influence the morbidity and mortality of multiple disease states. It remains unclear if clinical depression affects survival after surgical management of malignant brain astrocytoma. We set out to determine whether patients with a diagnosis of clinical depression before surgery experienced decreased survival independent of treatment modality or degree of disability.

Methods: One thousand fifty-two patients undergoing surgical management for malignant brain astrocytoma (WHO grade 3 or 4) performed at a single institution from 1995 to 2006 were retrospectively reviewed. The independent association of depression prior to surgery and subsequent survival was assessed via multivariate proportional hazards regression analysis.

Results: Surgical management consisted of primary resection in 605 (58%) patients, secondary resection in 410 (39%), and biopsy in 37 patients (3.5%). Pathology was WHO grade IV in 829 (79%) and grade III in 223 (21%). Forty-nine patients (5%) carried the diagnosis of depression at the time of surgery. Mean age and KPS on admission was 51 ± 16 and 80 ± 10 years, respectively. Two hundred ninety patients (28%) received Gliadel (BCNU MGI Pharma, Inc., Bloomington, MN, USA) wafer implantation and 274 (26%) received postoperative temozolomide (concomitant in 102, delayed adjuvant in 172 patients). Subsequent resection was performed at the time of recurrence in 135 (13%) patients a mean of 10 ± 6 months after surgery. Adjusting for all variables associated with survival in this model, age ($P < .001$), KPS ($P < .001$), WHO grade III vs IV ($P < .001$), primary versus secondary resection ($P < .001$), gross-total resection ($P < .001$), Gliadel wafer implantation ($P = .048$), postoperative temozolomide therapy ($P < .001$), and subsequent resection at time of recurrence ($P < .001$); preoperative depression was independently associated with decreased survival (relative risk [95% CI]: 1.41 [1.1–1.96], $P < .05$). The difference in percent survival between the depression and nondepression cohorts was most notable at 12 months (15% vs 41%) and 20 months (0% vs 21%) after surgery.

Conclusion: In our experience, patients who are actively depressed at the time of surgery were associated with decreased survival after surgical management of malignant astrocytoma, independent of degree of disability, tumor grade, or subsequent treatment modalities. In our opinion, the presence of an association between preoperative depression and survival warrants further investigation.

Keywords: Depression; Disability; Glioblastoma multiforme; Survival

Abbreviations: BCNU, Carmustine; GBM, Gliobalastoma multiforme; GTR, Gross total resection; IQR, Interquartile range; KPS, Karnofsky performance status; MRI, Magnetic resonance imaging; NTR, Near Total Resection; STR, Subtotal resection; QOL, Quality of life; WHO, World Health Organization.

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1. Introduction

Depression is one of the most common psychiatric disorders in the world today. It is estimated that, in any given year, 5% to 9% of the US population is clinically depressed [3,34]. There is a clear link between depression and health [28]. Studies have shown that depression is associated with up-regulation of proinflammatory cytokines [5,19], attenuates immunological response to disease, and may decrease physiological responses to malignancy [27,29]. Furthermore, depression may influence behavioral and self-care factors that may influence recovery from disease.

Malignant gliomas are the most commonly diagnosed of any primary brain tumor [8,14]. Psychiatric symptoms, including depression, often occur in patients with malignant brain neoplasms and have been reported to be related to location of the tumor and extent of disease [25,35]. Over the past decade, studies have suggested that there is a relationship between depression and poor outcome in patients undergoing craniotomy for brain lesions as a whole [16,20,21]. This association has also been reported after surgical therapy of nonneurological disease as well [1,12,24,29].

Currently, patient age, tumor grade, and functional status remain the known preoperative prognostic indicators of survival [7]. However, it remains unstudied if baseline depression before brain tumor diagnosis is independently associated with decreased survival after surgical management of malignant astrocytoma. In this study, we set out to determine whether malignant astrocytoma patients with a baseline diagnosis of depression prior to their terminal diagnosis had lower survival rates irrespective of treatment modality or degree of disability.

2. Methods

The surgical management of 1052 consecutive patients with malignant astrocytomas (WHO grade 3 or 4) [18] performed at a single institution from 1995 to 2006 were reviewed. Presenting clinical, radiological, operative, and hospital course records were retrospectively reviewed. Outpatient clinic notes were available from both neurosurgical and neurooncology follow-up visits and reviewed in all cases. Demographics, presenting symptoms and signs, degree of resection, perioperative morbidity, adjuvant radiotherapy and chemotherapy regiments, and date of death were recorded. Tumor grade was histologically confirmed as WHO grade 3 or 4 in all cases by an independent neuropathologist. Tumor characteristics on pre- and postoperative MRI were assessed at the time of surgery by a neuroradiologist. Degree of resection was retrospectively classified from MRIs obtained less than 48 hours after surgical resection as GTR if no residual enhancement was noted on postoperative MRI, NTR if only rim enhancement of the resection cavity was noted on postoperative MRI, or STR if residual nodular enhancement was noted on postoperative MRI. It was recorded if patients underwent a secondary resection at a later date.

For the purpose of this study, only patients who were diagnosed with clinical depression by their primary care or psychiatric physicians prior to surgery were classified as "preoperative depression." Patients who subsequently became depressed or where later diagnosed with depression as a result of their terminal diagnosis were not classified as "preoperative depression."

Survival as a function of time after surgical management was expressed as Kaplan-Meier plots. Parametic data was expressed as mean ± SD. Nonparametric data was expressed as median (IQR). Percentages were compared via χ^2 test. Continuous variables were compared via Student t test or Mann-Whitney U test where appropriate. The independent association of clinical depression, all recorded variables, and survival was assessed via multivariate proportional-hazards regression analysis (Cox model). Variables associated with survival in univariate analysis ($P < .1$) were included in the multivariate Cox model. Variables then demonstrating $P > .05$ were then removed in a stepwise fashion.

3. Results

3.1. Patient population

One thousand fifty-two surgical procedures were reviewed for this study. Six hundred five (58%) were for primary resection, 410 (39%) were for secondary resection, and 37 (3.5%) were for biopsy. Tumor grade included WHO grade IV in 829 (79%) cases, and WHO grade III in 223 (21%) cases. Average age was 51 ± 16 years. Median (IQR) KPS at presentation was 80 (80-90). One hundred sixty-four patients (16%) presented with seizures. Two hundred forty (23%) presented with a motor deficit, 161 (15%) with a language deficit, 108 (10%) with a visual deficit, and 53 (5%) with a sensory deficit. Postoperative MRI was not available for review in 72 (7%) patients. For the 943 patients with an available postoperative MRI after craniotomy for tumor resection, gross-total, near-total, and sub-total resection were achieved in 332 (35%), 407 (43%) and 204 patients (22%), respectively. Two hundred ninety (29%) patients received Gliadel (BCNU MGI Pharma, Inc., Bloomington, MN, USA) wafer implantation at time of surgery. All patients undergoing primary resection received post-operative adjuvant Radiation Therapy (XRT). Two hundred seventy-four (26%) patients received postoperative temozolomide. Temozolomide was administered via the Stupp et al [32] protocol in 102 patients. One hundred thirty-five patients (13%) underwent a subsequent resection at time of tumor recurrence. Seven hundred twenty-six (70%) patients died during the review period. Their deaths were confirmed by referencing the US Social Security Administration Death Master File. Median (IQR) follow-up for patients lost to follow-up prior to death was 7 (2-20) months. Overall median survival after surgical resection of malignant astrocytoma (WHO grade III or IV) was 11 months.

Forty-nine patients (5%) were diagnosed with active depression prior to their tumor diagnosis and were classified as preoperative depression. The depressed and nondepressed cohorts were similar in regards to demographics, clinical presentation (including motor, language, visual and sensory deficits), radiographic tumor characteristics, surgical and adjuvant treatment regiments, and perioperative outcomes (Table 1).

3.2. Association of depression and survival

Decreasing age ($P < .001$), increasing KPS ($P < .001$), WHO grade III vs IV ($P < .001$), primary vs secondary resection ($P < .001$), gross-total resection ($P < .001$), Gliadel wafer implantation ($P = .048$), postoperative temozolomide therapy ($P < .001$), and subsequent resection at time of recurrence ($P < .001$) were independently associated with improved survival. Independent of these prognostic factors, a diagnosis of clinical depression prior to surgery was associated with decreased survival (relative risk [95% CI]: 1.41 [1.1–1.96], $P < .05$) most noted at 12 months (15% vs 41%) and 20 months (0% vs 21%) after surgery in high grade gliomas (Grades III and IV) (Fig. 1).

Table 1
Clinical, radiological, treatment, and perioperative outcome variables in patients undergoing surgical management of malignant astrocytoma

Variable	Non-depression	Depression	*P*
No. of patients	1003	49	–
Clinical presentation			
Age[a] (y)	51 ± 17	51 ± 15	.832
Men	595 (59%)	24 (48%)	.151
White	666 (66%)	37 (74%)	.186
Epilepsy	160 (16%)	4 (8%)	.162
KPS	80 (80-90)	80 (80-90)	.614
Motor deficit	225 (22%)	15 (30%)	.183
Language deficit	155 (15%)	6 (12%)	.686
WHO grade IV	790 (79%)	39 (78%)	.890
Radiological presentation			
Frontal	493 (49%)	26 (52%)	.593
Temporal	244 (24%)	7 (14%)	.107
Parietal	197 (20%)	12 (24%)	.406
Occipital	45 (4.5%)	3 (6%)	.486
Cerebellum	14 (1.4%)	1 (2%)	.513
Deep lesions[b]	10 (1%)	0 (0%)	.483
Hemorrhagic	76 (8%)	6 (12%)	.267
Treatment			
Biopsy	41 (4%)	3 (6%)	.454
Primary resection	576 (58%)	29 (58%)	.865
Sub-total resection	197 (19%)	7 (14%)	.541
Gliadel wafers	276 (28%)	14 (29%)	.875
Postoperative temodar	256 (26%)	18 (36%)	.081
Subsequent resection	130 (13%)	5 (10%)	.826
Perioperative outcome			
Deep vein thrombosis	38 (4%)	2 (4%)	.709
Pulmonary embolus	21 (2%)	2 (4%)	.344
Surgical site infection	20 (2%)	2 (4%)	.273
New motor deficit	70 (7%)	3 (6%)	.818
Hospital stay (days)[c]	5 (3-8)	4 (3-7)	.456

Other than postoperative temozolomide therapy, there were no differences between patient cohorts in demographics, preoperative disability, degree of surgical therapy, or incidence of subsequent secondary resection.

[a] Results given as mean ± SD.

[b] Thalamus or midbrain.

[c] Median (interquartile range).

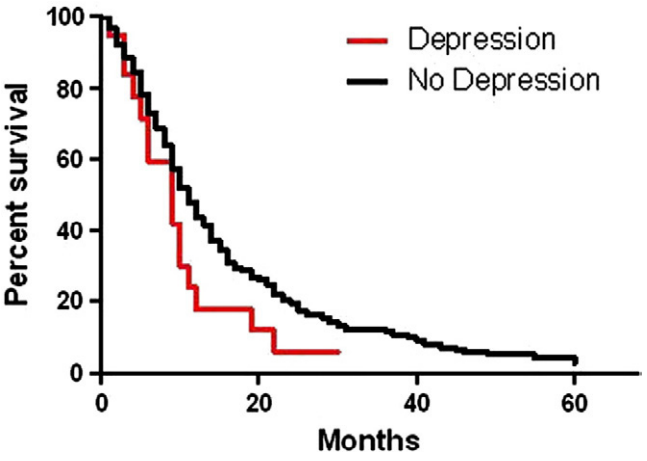

Fig. 1. Estimated Kaplan-Meier survival after primary resection of GBM (WHO grade IV) in patients with pre-operative medicated depression versus patients without pre-operative depression (median survival, 7 vs 11 months). Preoperative medicated depression was independently associated with decreased survival after resection of malignant astrocytoma ($P < .05$).

4. Discussion

In our experience, patients who were clinically depressed at baseline prior to surgery experienced decreased survival after surgical management of malignant astrocytoma independent of treatment modality. This discrepancy in survival was most noted beyond 12 months, suggesting that depression may be most detrimental for long-term survival. Of 1052 patients presenting for surgical management of malignant astrocytoma at our institution, 49 (5%) were clinically diagnosed with depression. We found that regardless of the patient's functional status prior to surgery (KPS score), WHO grade III vs. grade IV tumor, patient's age, or clinical presentation, those with depression had over a 40% increase in the relative risk of mortality versus the nondepressed cohort. This association was independent of degree of resection or postoperative treatment regimen.

The effects of depression, both preoperatively and postoperatively, are well documented in patients with glioma of all grades [16,20,21,26]. Litofsky et al [16], in their cohort of 598 patients, showed that not only is depression a predictor of poor outcome but that it was also underdiagnosed and undertreated in their study population. Their study centered around postoperative depression, which they characterized using patient report and physician report. Although their cohort included patients with glioma grade III to IV, the survival effect of depression was only significant in the GBM cohort [16]. As in our study, their survival curves depict a large difference in survival between depressed and nondepressed patients, the further out from surgery the

patients are, suggesting depression may be most detrimental for long-term survival. In addition, Litofsky et al found that patients with depression experienced more complications in the post-operative period evaluated at 0, 3 and 6 months postoperatively. Maiano et al [20] assessed level of depression by the Beck Depression Inventory in a 5-year follow-up study of 75 primary brain tumor patients. In low-grade glioma patients, they reported a median survival of 51.7 months in depressed patients vs 60 months in nondepressed patients.

Stommel et al [31] studied the survival effect of depression and/or depressive symptoms on newly diagnosed lung, breast, colon and prostate cancer patients. They showed that the existence of depressive symptoms in a patient before diagnosis of a cancer was associated with lower survival rates. Adjusting for all prognostic variables, depressed patients survived a mean of 468 days vs 538 days for nondepressed patients. In addition, they found that patients with no history of emotional disturbances who developed postoperative depression did just as well as their nondepressed counterparts [31]. This may suggest that the preoperative depression, rather than a depressed emotional response to diagnosis and treatment, may carry prognostic significance.

The effects of depression on QOL have also been studied [11]. With the lifespan of patients with a newly diagnosed malignant astrocytoma often less than 15 months, QOL is an important factor to consider in patient care. Mainio et al [21] showed that depression is a strong predictor of poor QOL. This study showed that low QOL in these patients was associated with decreased postsurgical survival, although this effect was only seen in patients with low-grade (grade I-II) gliomas despite analysis of both high-grade [4] (grade III-IV) astrocytoma and benign lesions including meningiomas, acoustic neuromas, and pituitary adenomas) [21]. Brown et al [4], in their cohort of 194 patients, found that increased fatigue, a measure of QOL and major symptom of depression, was an independent predictor of overall survival as well.

Despite multiple series demonstrating greater rates of depression in cancer populations [30], and increased mortality among patients with depression [36], there has been no consensus hypothesis explaining these associations. The cancer-depression association could be either uni- or bidirectional. Depression has been studied both as a predisposition to cancer incidence and as a consequence of tumor biology and disease progression [10,13,22]. Depression could possibly represent of a prodromal stage of malignant brain astrocytomas, as is seen in patients with pancreatic malignancy [6,9]. However, this may be specific to pancreatic cancer, as depression more commonly preceded pancreatic versus all other intra-abdominal malignancies [6]. Conversely, it may be possible that astrocytomas may alter neural networks and therefore alter mood.

Multiple hypotheses have also been proposed regarding a mechanism for association between depression and tumor outcome. Immunomodulation is the most commonly cited of these hypotheses [13]. Both depression and stress have been shown to down-regulate the immune system [27,33]. Specifically, gliomas are associated with an immunosuppressive effect at both the systemic [23] and local intratumoral level [2]. Conversely, the proinflammatory state caused by release of cytokines [15] has been shown to trigger depression in otherwise undepressed patients in some malignant disease states [15,17].

While our study is a large series that utilized a multivariate model to demonstrate an independent association of preoperative depression and survival, it is subject to the weakness inherent to all retrospective studies. Our study reports association only and causation cannot be inferred. Although patients classified as depressed in this study were diagnosed before neurosurgical evaluation and terminal diagnosis, a proportion of patients with baseline depression may have gone undiagnosed. While we used strict criteria for preoperative depression (medicated and diagnosed by a physician independent of their neurosurgical care) in order to improve specificity of our diagnosis, many patients with clinical depression may have been undiagnosed and off medication, lowering the sensitivity of our classification scheme and resulting in their inclusion of clinically depressed patients in the nondepressed cohort. Unfortunately, we were also unable to assess whether patients received adequate pharmacologic treatment for depression, as patient response to treatment was not available due to outside psychiatric/primary care follow-up in many cases. Lastly, it remains unstudied whether the sequelae of depression, for example, a decreased ability to self-care, underlies the decreased survival observed in our medicated depression cohort. Further research investigating the survival of patients with non-medicated versus medicated depression is warranted to address this issue.

Patients with baseline clinical depression prior to surgery for high grade gliomas (grades III and IV) demonstrated worse survival independent of all clinical, radiological, and treatment variables.

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Commentary

This is a retrospective study of a large cohort of patients with malignant brain astrocytoma that is the first to address the relationship between preoperative depression and postoperative survival. At present, there are 3 known preoperative prognostic factors of survival: patient age, tumor grade, and functional status. Clearly, all these indicators are fixed. However, a preoperative diagnosis of depression is not a fixed state and is amenable to improvement throughout treatment, using psychopharmacological and/or psychotherapeutic interventions. This underscores the importance of the findings of this study that baseline depression significantly decreased the chances of survival at 12 months (15% vs 41%) and 20 months (0% vs 21%). This finding suggests that optimal care for these patients must include a careful search for depression —which is often underdiagnosed in routine care— followed by aggressive treatment. A follow-up prospective study demonstrating this longevity secondary to the treatment of depression would be welcome.

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