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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.