The interplay among psychological distress, the immune system, and brain tumor patient outcomes

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A malignant brain tumor diagnosis is often accompanied by intense feelings and can be associated with psychosocial conditions including depression, anxiety, and increased distress levels. Previous work has highlighted the impact of uncontrolled psychological distress among brain tumor patients. Given the negative impact of maladaptive psychosocial and biobehavioral factors on normal immune system functions, the question remains as to how psychological conditions potentially affect the brain tumor patient anti-tumor immune response. Since immunotherapy has yet to show efficacy at increasing malignant glioma patient survival in all randomized, phase III clinical trials to-date, this review provides new insights into the potential negative effects of chronic distress on brain tumor patient immune functions and outcomes.

Challenges of immunotherapy for malignant glioma

Brain tumors are a relatively rare but potentially life-threatening diagnosis, accounting for approximately 1–2% of cancers in the United States [1]. Nearly 80% of primary malignant brain tumors are a form of glioma, with glioblastoma (GBM, WHO grade IV) representing the most common, deadly subtype and accounting for over half of all malignant glioma cases [2]. Despite the current standard of care, GBM remains incurable with a median overall survival (OS) ranging from 9 to 21 months, and a five-year survival of only 5%–14% [3–5]. Standard of care for GBM patients consists of surgical resection, radiation, chemotherapy, and tumor treating fields, which prolongs survival and may transiently reduce symptom burden. However, these treatments may impair quality of life in addition to a diagnosis that already induces significant psychological distress [6].

Recent research efforts aimed at enhancing treatment efficacy for GBM have focused on immunotherapy, an effective treatment strategy for some cancer patients diagnosed with melanoma [7], non-small cell lung [8], and renal cell [9] malignancies, as well as many others that originate outside of the central nervous system (CNS) [10–14]. In contrast, high-grade glioma patients treated with immunotherapy have not demonstrated an OS benefit in all phase III clinical trials to-date [15,16]. Several immunotherapeutic strategies have been investigated, including: (i) vaccines (i.e. rindopepimut, HSPPC96, or dendritic cells); (ii) checkpoint inhibitors — drugs that enhance immune system efficacy in destroying cancer cells [i.e. nivolumab (anti-PD-1 mAb)]; and (iii) chimeric antigen receptor (CAR) T cells. However, despite the excitement from early phase trials, immunotherapy has yet to translate into an effective clinical solution for patients, as demonstrated in late phase, randomized, multi-site clinical evaluation [15,17–19].

Additional challenges likely contributing to the effective application of immunotherapy for treating GBM include the: (i) highly infiltrating nature of the disease, which prevents surgical resection from completely removing all associated tumor burden; (ii) potentially immunosuppressive microenvironment, characterized by a relatively low...
level of tumor-infiltrating effector T cells, combined with an accumulation of immunosuppressive regulatory T cells (Tregs; CD4+CD25+FoxP3+) and myeloid suppressor cells; (iii) older age of the patient; and (iv) anatomical location that impedes a routine use of tumor biopsies for monitoring the response to therapy. A critical factor that may be overlooked during immunotherapeutic treatment considerations is the impact of high psychosocial and biobehavioral levels of distress. The subject of distress, specifically its prevalence and influence on the immune system and outcomes in patients with a malignant brain tumor, forms the basis of our review. Research in the past two years will be emphasized, with attention to the associations among increased distress levels, the negative impact of systemic immune/neuroendocrine functions, and preclinical and clinical outcomes in the setting of primary brain cancer.

**Psychological distress in patients with a brain tumor**

Depression and anxiety are common in patients with a terminal illness [20]. Meta-analyses have found that cancer patients in the palliative care setting have a rate of mood disorders, including depression, anxiety, and adjustment disorder, of 29% [20]. Notably, this rate of psychological conditions is likely underappreciated and/or underreported, as cancer patients experience chronic distress and demoralization without the presence of a psychiatric diagnosis [21–23].

Psychological distress, depression, and anxiety may be particularly enhanced in patients with primary brain tumors. A recent analysis found that 24% of a 4000 mixed-cancer patient cohort possessed clinical signs of depression, significantly higher than the general population [24]. Strikingly, the rate among patients with primary brain cancer was markedly higher, with 36% showing signs of depression. In contrast, patients diagnosed with malignant melanoma and prostate cancer had reduced rates of depression, at 16% and 10% respectively. Additional meta-analyses and prospective studies have discovered an increased rate of psychological conditions and distress among brain tumor patients as compared to the general population [25,26] and as compared to patients diagnosed with non-CNS tumors [27].

Furthermore, psychological distress in brain tumor patients is not always appropriately acknowledged or well-managed. Although attention to the mental health care of malignant brain tumor patients has increased [28–30], a recent review by the European Association of Neuro-Oncology emphasized the lack of evidence for appropriately treating depression and anxiety in glioma patients and, as such, was unable to provide strong recommendations on the subject [31]. The direct neurological involvement of primary brain tumors further complicates management guidance from a psychosocial standpoint compared to non-CNS cancers.

Recent studies have found that psychological needs are highly unmet among brain tumor patients [32,33]. A longitudinal investigation of mostly high-grade glioma patients found that despite increased distress in approximately half of the patients during various time points, only 14% of the distressed patients received psychological care as an in-patient, and less than half of the distressed patients received psychological care in an outpatient setting [34]. Collectively, the above studies indicate psychological distress and depression as common concerns for patients with primary brain cancer.

The etiology of distress among primary brain cancer patients may be related to the inherently high load of stressors accompanying their diagnosis. However, neurological insult, regardless of tumor burden, has been shown to be correlated with increased depression and distress. Patients who present with a stroke have an increased rate of depression as compared to those with a myocardial infarction [35], and the prevalence of depression is also higher for individuals diagnosed with the CNS autoimmune disease multiple sclerosis (MS), as well as for traumatic brain injury (TBI) patients [36,37]. Although potentially resulting from the reduced quality of life suffered by patients with neurological insult(s), increased depression may be the direct result of enhanced inflammation. There is a well-established link between the development of depression and stressors that trigger inflammatory phenotypes and increased immune activity through the sympathetic nervous system (SNS) [38,39]. Indeed, inflammation resulting from stroke, MS, and TBI is associated with depression, further supporting a role for generalized inflammation in the pathogenesis of depression [40–43]. The connection between inflammation and depression is not well-characterized for patients with primary brain cancer. However, levels of inflammatory cytokines are significantly increased in GBM patients and may play a role in outcomes dependent on levels of depression, anxiety, and distress [44–46] (Figure 1). Additional work is necessary to comprehensively profile the incidence of psychosocial conditions in brain tumor patients and their effects on OS outcomes and responses to therapy.

**Interactions among distress, immunosuppression, and cancer**

Untreated distress may affect brain tumor patient outcomes through the interactions between psychosocial distress and the immune system. The relationship between excess adrenergic signaling and immune dysregulation, inflammation, and tumor growth is well-established [47–49]. Increased distress promotes the release of stress hormones, primarily in the form of catecholamines including epinephrine and norepinephrine via the sympathetic nervous system (SNS), as well as glucocorticoids via the hypothalamic–pituitary–adrenal axis. Chronic release of these molecules, in turn, increases
Proposed interactions among inflammation, depression, and immune cell dysfunction in subjects with brain cancer. Brain tumors and psychosocial stress independently contribute to brain inflammation, which provide favorable conditions for the development of depression. High distress levels lead to a cycle of increased sympathetic signaling and dysfunctional HPA signaling. Together, signaling due to the sympathetic and HPA axes decrease immune effector control of tumor cell proliferation, resulting in worse outcomes for patients. Breaking these cycles and addressing increased distress/depression in brain cancer patients may improve survival outcomes.

Immunosuppression that facilitates uncontrolled tumor growth by inhibiting the anti-tumor immune response, as demonstrated in preclinical models of lymphoma and fibrosarcoma [50,51]. Interestingly, beta blockers, which inhibit catecholamine-induced beta-adrenergic receptor signaling, inhibit proliferation and tumor growth in models of liver cancer, early stage breast cancer, and melanoma [52–54], although this effect is not universal [55]. Additionally, recent studies found that the inhibition of beta-adrenergic signaling with the pan-beta blocker propranolol enhances PD-1 checkpoint inhibitor efficacy in preclinical, syngeneic, mice melanoma models [54,56]. Notably, beta-adrenergic blockade increased the frequency of CD8+ tumor-infiltrating lymphocytes, as well as the ratio of CD8+ effector T cells to Tregs in B16-OVA tumors [56]. Altogether, these studies suggest a potential role for targeting beta-adrenergic signaling to decrease tumor cell proliferation and synergize with immunotherapy.

Although once thought to be an immuno-privileged site, it is now well-established that leukocytes infiltrate the brain upon receiving appropriate activation signals [57–59]. However, potent immunosuppressive factors are normally present in the brain, including TGF-β, IL-10, and VEGF, which dampen cytotoxic T lymphocyte migration while enhancing Treg accumulation [60]. Parenchymal cells of the CNS also express Fas ligand (FasL), which can facilitate brain-infiltrating Fas+ T cell apoptosis through cell-to-cell signaling. Collectively, these characteristics contribute to the profoundly immunosuppressive environment under normal circumstances that likely enhances the poor immune response against malignant glioma. Increased beta-adrenergic signaling in response to psychosocial distress would exacerbate the profoundly immunosuppressive microenvironment and facilitate the immune escape of GBM cells.

To counteract immunosuppressive beta-adrenergic signaling, propranolol has been considered for adjuvant therapy in patients diagnosed with malignant glioma. However, this consideration is primarily based on the results observed in other cancers, or as direct evidence in GBM cells [61]. Interestingly, isoproterenol, a beta-adrenergic receptor agonist, enhances GBM U251 cell proliferation and metalloproteinase expression — an effect inhibited by propranolol treatment [62]. Treatment with the adrenergic antagonist prazosin also inhibits glioblastoma tumor growth in an orthotopic, immunocompetent, syngeneic mouse model, although this effect was thought to be independent of adrenergic signaling mechanisms [63]. Beyond adult brain tumors, beta-adrenergic receptors are expressed by malignant pediatric brain tumor cells [64], raising the possible generalizability of targeting the beta-adrenergic signaling axis in both the pediatric and adult brain tumor settings.

Cortisol, a glucocorticoid released during periods of distress, may also play a dominant role in promoting potent immunosuppression [65]. The chronic release of glucocorticoids, as mediated by mechanisms associated with chronically high levels of distress, may promote tumor
progression by suppressing the anti-GBM immune response [66,67]. While the impact of endogenous glucocorticoid signaling and their associated outcomes have not been characterized among brain tumor patients, a large body of evidence suggests that the exogenously administered dexamethasone (trade name, Decadron), is potently immunosuppressive [68]. Dexamethasone is a corticosteroid commonly used to relieve symptomatic effects and intracranial edema during therapy for high-grade glioma. Treatment with dexamethasone is associated with a worse prognosis of patients with GBM [69,70]. In contrast, the fast tapering of dexamethasone is associated with significantly better outcomes [71]. Furthermore, phase I trial evaluation of GBM patients treated with the immune checkpoint inhibitor, atezolizumab, had a decreased level of circulating lymphocytes and a trend toward decreased OS when concurrently treated with corticosteroids [72]. Strikingly, long-term survivors in the trial were not treated with corticosteroids. While it is inappropriate to assume that the effects of synthetic steroids are directly comparable to endogenous glucocorticoid signaling, it is possible that the chronic release of cortisol due to high distress levels suppresses leukocyte functions and results in a worse patient prognosis, similar to those effects associated with dexamethasone treatment.

**Impact of distress on outcomes in brain cancer patients**

Psychological distress has been linked to a reduced quality of life among individuals diagnosed with glioma and in other brain tumor patients [24,73]. A recent meta-analysis found a decrease in glioma patient OS when the patient was also diagnosed with depression [74]. Similarly, a retrospective analysis of 1003 patients undergoing surgical management of high-grade glioma found that a clinical diagnosis of depression before surgical intervention was associated with a decreased landmark rate of survival [75]. Although there was significant heterogeneity within the studies, these collective results suggest a potential for depression to negatively impact the physical health of glioma patients. In contrast, demographic factors associated with the potential strengthening of a glioma patient’s support system, including marriage, are predictors for improved GBM patient OS [76]. Exercise also improves glioma outcomes [77,78] potentially by decreasing the effects of inflammation and/or inflammatory mediator-induced depression [79,80]. Therefore, interventions that decrease the level of psychological distress may improve future prognoses among patients with malignant glioma (Figure 2).

Standardized surveys have been proposed as mechanisms to better assess psychological distress levels in patients with brain cancer [81–83]. Reducing stigma to increase participation in psychosocial assistance programs is also necessary to properly care for patients with elevated distress levels [84,85]. After identification and connection with psychosocial services, proper treatment can be initiated. Currently, home-based psychosocial interventions and other therapies have been shown to address distress in brain cancer patients [86,87].

Few studies have previously evaluated the role of medications in addressing psychosocial distress in malignant brain tumor patients. Although beta blockers may help improve survival in distressed glioma patients based on evidence from the treatment of patients diagnosed with non-CNS cancers, the use of selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) may be another beneficial option. Exposure of tumor cells to SSRIs causes anti-proliferative effects in vitro and in mouse models of GBM. Theoretically, SSRIs would also decrease distress levels in glioma patients [88–90]. A study of 160 individuals diagnosed with glioma showed an OS benefit for 35 patients treated with an SSRI, while several reports have advocated for their use as potential adjunct therapy during standard of care [91,92]. Ultimately, more investigation is needed to objectively evaluate the efficacy of psychosocial modifiers in patients with malignant brain cancer.

**Conclusions**

Malignant brain tumors are a profoundly devastating disease associated with significant increases in depression, anxiety, and distress among patients. We propose a
direct biological link between psychosocial stressors and poor outcomes in malignant glioma patients. High adrenergic signaling and endogenous steroid activity may impair immune system functions, resulting in the uncontrolled proliferation of tumor cells, as observed in non-CNS cancer patients. Notably, high levels of distress are not always appropriately identified or managed among brain tumor patients. Therefore, additional work is required for understanding the role of distress on prognosis, immune suppression, tumor growth, and clinical care. Ultimately, this future work may substantially improve the quality, and potentially quantity, of life.

**Funding**

This work was supported by NIH grants R00 NS082381 (D.A.W.), R01 NS097851-01 (D.A.W.), P50 CA221747 Project 2 (D.A.W. and R.V.L.), and T32 CA070085 (E. L.).

**Conflict of interest statement**

Nothing declared.

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