



Distinguishing and treating depression, anxiety, adjustment, and post-traumatic stress disorders in brain tumor patients

Alec W. Gibson^{1,2^}, Jerome J. Graber^{3,4}

¹Department of Psychiatry and Behavioral Sciences, ²School of Medicine, ³Department of Neurology, ⁴Department of Neurological Surgery, University of Washington, Seattle, WA, USA

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Correspondence to: Jerome J. Graber, MD, MPH. Department of Neurology, Alvord Brain Tumor Center, University of Washington, 1959 NE Pacific Street, Seattle, WA 98105, USA. Email: jgrab@uw.edu.

Abstract: Cancer patients often suffer from psychiatric disorders as a result of their disease and its treatment. Rates of depression, anxiety, adjustment, and post-traumatic stress disorders are particularly high for individuals with cancer and differentiating between these conditions is important for providing both appropriate and high-quality care. Patients with primary and metastatic brain tumors are particularly susceptible to psychiatric morbidities as a result of direct neuropsychiatric effects from the tumor itself, as well as psychological distress stemming from their diagnosis, prognosis, or treatment. However, these morbidities are often underdiagnosed, misdiagnosed, and undertreated. Many tools exist for screening, diagnosing, and treating psychiatric disorders in brain tumor patients, and palliative care settings are well suited to both identify and treat psychiatric disorders in brain tumor patients. This review summarizes our current knowledge of psychiatric disorders in patients with brain tumors, highlights the susceptibility of brain tumor patients to psychiatric conditions, provides recommendations for differentiating and treating these conditions, and emphasizes the need for further research. The goal of this review is to inform healthcare providers of the opportunities to address psychiatric morbidities in patients with primary and metastatic brain tumors, particularly in palliative care settings, and identify areas in need of additional research.

Keywords: Adjustment; anxiety; brain tumor; depression; post-traumatic stress disorder (PTSD)

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Introduction

Psychiatric disorders can have substantial implications for the health and well-being of cancer patients yet are often underdiagnosed and undertreated. Depression, anxiety, adjustment disorder (AD), and post-traumatic stress disorder (PTSD) can all occur as a result of cancer diagnosis, prognosis, treatment, and recurrence (1,2). While some patients may have pre-existing mental health

disorders or conditions unrelated to their cancer, many individuals suffer from psychiatric morbidities directly related to their cancer experience. Differentiating and treating these disorders across the cancer care continuum is critical to improving the quality of life for affected individuals. Palliative care settings are uniquely suited to integrate cancer care and mental health care, as well as provide screening and treatments of psychiatric disorders in cancer patients and their caregivers (3). In some cases, the

[^] ORCID: 0000-0002-5709-4146.

roles of palliative and psychiatric care may be more distinct. Through effective coordination, healthcare providers from multiple areas of medicine can ensure cancer patients with mental health conditions receive appropriate treatments, including spiritual care (4-6).

Patients with primary and metastatic brain tumors are particularly susceptible to psychiatric comorbidities. However, much is still unknown about the prevalence, causes, and effective treatments of these conditions in brain tumor patients. Psychiatric impairments can stem from the cancer care experience or from direct neuropsychiatric effects of the tumor and its treatment. In addition, brain tumor patients who experience mental health problems not only have diminished quality of life but can also have worse survival outcomes (7-10). This review provides an overview of depression, anxiety, AD, and PTSD in cancer patients and how to differentiate them in clinical settings. In addition, this review aims to summarize our current knowledge of psychiatric conditions specifically in brain tumor patients and methods for identifying and treating them.

Psychiatric morbidities in cancer patients

Depression and anxiety

Cancer patients suffering from depression or anxiety often have lower qualities of life, increased suicidal ideation, low medication and treatment adherence, impaired relationships with others, longer recovery time, and in some cases shorter survival (11-14). The prevalence of depression and anxiety disorders in the general population have been estimated to be approximately 5% and 7%, respectively. However, in individuals treated for cancer the rates are much higher at 20% for depression and 10% for anxiety (13,15). In palliative care settings specifically, 25% of cancer patients have a depression disorder and 10% are noted to have anxiety, although rates for inpatient palliative care can be as high as 48% for depression and 34% for anxiety (13,16). Rates of depression and anxiety vary depending on the type of cancer, prognosis, and treatment, but it is estimated that the vast majority of cancer patients with depression do not receive treatment from a mental healthcare provider (17-19). Caregivers for cancer patients are also at risk. One study found that 29% of caregivers of cancer patients in palliative care settings had depression, while 39% had anxiety. These levels were significantly reduced several months after the patient's death, and risk factors included high distress levels at the start of palliative care, poor social support, impaired

physical function, and being a patient's spouse (20).

Psychological distress related to cancer diagnosis, treatment, prognosis, and even survivorship can have profound effects on mental health and subsequently manifest as depression or anxiety (1,17,21). Alternatively, depression and anxiety can be attributed to the direct neuropsychiatric effects of the cancer or its treatment. Indeed, certain tumors can induce mood dysfunction due to their location, production of hormones and cytokines, or disruption of homeostasis. Treatments such as chemotherapy, steroids, radiation, and surgery can also result in symptoms of depression and anxiety (1,22-27). Cancer patients most at risk for developing depression appear to be younger, have functional limitations, and lack social support, while risk factors for anxiety include past trauma, demoralization, and metastasis for certain cancers. A history of psychiatric disorders puts patients at high risk for both conditions following a cancer diagnosis (1,18, 28-32). Cancer patients from certain marginalized populations face a particularly large risk for psychiatric conditions. For example, lesbian, gay, bisexual, transgender, and queer (LGBTQ) cancer patients experience greater levels of isolation and depression and less targeted counseling compared to heterosexual and cisgender patients. Hispanic and low-income cancer patients also experience particularly high levels of distress, anxiety, and depression (33-37).

Treatment of depression or anxiety in cancer patients should follow standard clinical guidelines, but it is important to note that some psychiatric medications are contraindicated with certain cancers, chemotherapies, and anesthetics (1). Specific interactions between psychiatric, antiemetic, and anticancer drugs, as well as potential side effects of antidepressants in cancer patients have been extensively reviewed elsewhere (38-42). Interventions aimed at psychiatric treatment can be performed by palliative care providers, and palliative care itself can be therapeutic. For advanced cancer patients with depression, early palliative care can significantly reduce mortality risk, and psychotherapy in palliative care settings can reduce symptoms of both depression and anxiety and improve quality of life (3,43-46). Despite this evidence, a majority of palliative care physicians report difficulty managing anxiety and accessing psychological or psychiatric services. This is particularly true for marginalized and minority cancer patients. In addition, research has shown redundancy and lack of consistency in the management of psychological distress by palliative care teams (34,46-48).

AD

AD is characterized by abnormally severe distress and maladaptive behavior, often accompanied by depression and/or anxiety, that is out of proportion to the intensity of a stressful life event. While most cancer patients experience distress, people with AD have difficulty adjusting to and managing their diagnosis, and typically respond with extreme emotions that impair their personal and social functioning (49,50). Onset of AD occurs within 6 months of a stressful event and typically subsides after 6 months, and cases of AD are often more acute and situational relative to severe psychopathologies like PTSD but can manifest chronically as well. Symptoms of AD are not enough to warrant the diagnosis of a full anxiety or depression disorder, but can significantly reduce quality of life for affected individuals and can even increase cancer-specific mortality (49-52).

AD is highly prevalent in patients with cancer and is the psychiatric morbidity most often reported in this population (11,49,50). A meta-analysis of over 10,000 cancer patients in hematological and oncological settings revealed an AD prevalence of 19.4% (13), although specific studies estimate a higher prevalence ranging from 25–35% (49,53-56). In palliative care settings, the rate of AD for cancer patients is similar at 15.4% (13). Women are twice as likely to present with AD, and higher education has been found to be the most influential predictor for AD in cancer patients. Additionally, patients with metastatic disease have an 80% higher risk of developing AD compared to those with non-metastatic cancer (57). In caregivers of cancer patients, rates of AD range from 13% to 58%. Despite this, the psychiatric needs of caregivers are often overlooked and more research is needed to examine AD in this group (58,59).

Cancer patients often experience distress and anxiety as a normal part of coping with their disease, which can make it difficult to determine when these emotions become excessive and characteristic of AD. Furthermore, there is a danger of pathologizing normal distress following a cancer diagnosis, and previous studies may be guilty of this (60). Further work is needed to more clearly resolve differences between normal reactions and AD. Symptoms of AD can be precipitated by a combination of normal distress and the pathological features of the cancer or treatment, such as the anxiogenic effects of steroids and tumor secretions (1,61). Counseling on an individual and group basis can reduce symptoms of AD for cancer patients, and effective interventions include cognitive behavioral therapy (CBT),

mediation/relaxation training, and hypnotherapy. If patients do not respond to psychotherapy, psychiatric medications similar to those used for anxiety and depression can also be used to address symptoms. Overall, psychiatric intervention can improve symptoms of AD in cancer patients and more studies are needed to identify the most effective treatments for treating cancer-related AD, particularly in palliative care settings (1,49,50,61-65).

PTSD

In addition to the intense emotional stress associated with cancer in general, many patients experience significant trauma as a result of their diagnosis or treatment. The shocking discovery of their disease, the realization of their mortality, and the initial overwhelming process of medical decision making can all lead to PTSD following an individual's diagnosis (2,66,67). Subsequent treatments often cause emotional and physical pain, and even after achieving remission many patients have chronic fear of disease recurrence (2,68). As a result, the experiences following diagnosis can also contribute to PTSD symptoms. Several studies have shown that approximately half of cancer patients feel that their diagnosis and treatment were traumatic experiences (2,69-72).

The percentage of cancer patients with PTSD ranges between 7.3% and 13.8% based on self-reported symptoms, while data from structured clinical interviews estimate a lifetime prevalence of 12.6% and a current prevalence of 6.4% (73). An additional subset of cancer patients may experience subsyndromal PTSD, which can also result in a lower quality of life and social impairments (74). Patients at greatest risk for developing PTSD are younger, have recently undergone treatment, have advanced disease, have a history of prior trauma, or have a family or personal history of psychiatric disease (2,73,75). Many risk factors mirror those for non-cancer-related PTSD such as poor social support and peritraumatic dissociation (2,75). Biological factors may also play a role in cancer-related PTSD. Numerous studies have linked glucocorticoid dysregulation and cortisol levels with PTSD (2,76-79); however, there is little work specifically focused on the biology of cancer-related PTSD and more research is needed in order to draw definitive conclusions.

Rates of post-traumatic stress symptoms (PTSS) and PTSD are even higher for caregivers of cancer patients and vary depending on type of cancer and relationship with the patient. Spouses and parents of patients are most

severely affected (80-83). One study found that 18.7% of caregivers of advanced cancer patients screened positive for PTSD (82), and rates of PTSS ranging from 25.7% to 36.8% have been reported for caregivers of leukemia and head and neck cancer patients (81,83,84). Caregivers who perceive numerous symptoms and little treatment benefit for patients, use avoidant coping strategies, or have a prior history of patient-related trauma are at greatest risk for PTSS or PTSD (85,86).

Although psychiatric medications including antidepressants, anxiolytics, and benzodiazepines can be used for symptom management, research focused on the use of these medications to treat cancer-related PTSD is lacking (1,2). CBT is an effective treatment for cancer-related PTSD, more so than supportive therapy, and can reduce symptoms of PTSD in patients with different types of cancer (87-89). Other behavioral and psychological therapies that can be effective for treating PTSD in cancer patients include supportive expressive group therapy, cognitive behavioral stress management, and eye movement desensitization and reprocessing (2,90-92). Regular palliative care interventions that address both physical and psychological distress can directly improve symptoms of PTSD (77,93-95), although care must be taken to avoid exacerbating symptoms through mandatory informational and emotional support meetings (96).

Differentiating psychiatric disorders in cancer patients

There is a growing body of evidence that demonstrates a high prevalence of psychiatric morbidities associated with cancer. Most of this data comes from either self-reported questionnaires or structured clinical interviews. Questionnaires are useful for initial screening and estimating the prevalence of psychiatric conditions for various cancers; however, they can overestimate actual rates and rely solely on patient interpretations of questions (51,73,97). Numerous studies have validated the clinical use of questionnaires, such as the PTSD Checklist Civilian Version (PCL-C), the Patient Health Questionnaire (PHQ), and the General Anxiety Disorder-7 (GAD-7) questionnaire for screening cancer patients (69,97-101). However, structured clinical interviews are the gold-standard for diagnosing cancer patients with depression, anxiety, AD, or PTSD (2,51). Unlike questionnaires, clinical interviews can determine etiology and assess the exact nature and functional impact of symptoms. This is important for evaluating whether the disorder is directly related to a

patient's cancer diagnosis or is a comorbid condition that developed separately before or during cancer care.

There is little data reporting the differentiation of anxiety, depression, AD, and PTSD in cancer patients, and there are few studies that screen for both AD and PTSD (2,51). The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes both AD and PTSD as "Trauma and Stress-Related Disorders", and both disorders can have similar presentations (102). It is critical to differentiate these conditions in cancer patients due to their different etiologies, outcomes, and treatments (*Table 1*). Individuals with AD typically have more time-limited and less severe symptoms than individuals with PTSD. Indeed, a diagnosis of AD can be appropriate and should be considered for people with subsyndromal symptoms of PTSD or for people whose cancer diagnosis was not traumatic but who still experience excessive symptoms of anxiety or depression (2,102). Most studies that describe specific psychiatric disorders in cancer patients do not address whether symptoms may be better explained by a different disorder. As such, careful diagnostic evaluations should be done to differentiate between psychiatric conditions (51). Further, substance abuse disorders are also common in cancer patients and should also be a consideration during psychiatric evaluation (103). The majority of palliative care settings do not routinely screen patients for substance abuse despite a high prevalence in palliative care populations (104).

Current diagnostic criteria for anxiety, depression, AD, and PTSD can present challenges for screening and diagnosis. According to the DSM-5 criterion A for PTSD, the traumatic event that results in the disorder involves "exposure to actual or threatened death, serious injury, or sexual violence" but notes that "a life-threatening illness or debilitating medical condition is not necessarily considered a traumatic event. Medical incidents that qualify as traumatic events involve sudden, catastrophic events" (102). This statement can cause debate about whether the diagnosis of cancer meets the criterion, and there are no studies that examine whether failure to meet this criterion affects the proportion of cancer patients with PTSD since the majority of research to date has used DSM-IV criteria. Criterion A also excludes caregivers who learn of a patient's cancer. Even if an individual does not meet criterion A they can still be diagnosed with PTSD if they meet multiple other criteria: at minimum one intrusion symptom (criterion B), one avoidance symptom (criterion C), two negative cognitive and/or dissociation symptoms (criterion D), and two arousal and reactivity symptoms

Table 1 Distinguishing features and prevalence of psychiatric disorders in cancer patients

Psychiatric disorder	Distinguishing features	Prevalence in cancer patients
Depression	Depressive symptoms (cognitive, affective, volitional, somatic) not explained by cancer-associated somatic symptoms (e.g., fatigue, somnolence, lethargy, functional impairment)	20% of general cancer patients
	Not intermittent, time-limited, or situational	25% of cancer patients in palliative care settings
	Can stem from neuropsychiatric effects of the tumor or treatments	22% of brain tumor patients
	Should be considered in patients with severe symptoms who do not meet the criteria for AD or PTSD	
Anxiety	Anxiety-related symptoms not explained by cancer-associated somatic symptoms (e.g., sleep disturbances, anorexia, functional impairment)	10% of general cancer patients
	Not intermittent, time-limited, or situational	10% of cancer patients in palliative care settings
	Can stem from neuropsychiatric effects of the tumor or treatments	
	Should be considered in patients with severe symptoms who do not meet the criteria for AD or PTSD	
Adjustment disorder	Symptoms not explained by neuropsychiatric effects of the tumor or treatments	19% of general cancer patients
	Characterized by difficulty adjusting to or managing one's diagnosis, treatment, or prognosis	15% of cancer patients in palliative care settings
	Symptoms are often time-limited, situational, and linked to distress regarding future health	
	Symptoms are often less severe and numerous than other psychiatric disorders	
Post-traumatic stress disorder	Symptoms not explained by neuropsychiatric effects of the tumor or treatments	6.4% of general cancer patients (13% lifetime prevalence)
	Results from traumatic cancer-related experiences in the past	
	Associated with involuntary and intrusive distressing memories	
	Symptoms occur over relatively longer periods of time compared to AD	

AD, adjustment disorder; PTSD, post-traumatic stress disorder.

(criterion E). Symptoms must all be present for at least one month (criterion F) and cause substantial distress and impairment (criterion G). These criteria are stricter than DSM-IV criteria and will likely result in a lower reported prevalence of PTSD in relation to other psychiatric disorders over time. Further, the DSM-5 states that AD is common with medical illness and can be the predominant response to an illness (102). If a patient does not have “*involuntary and intrusive distressing memories*” (criterion B) but rather experiences anxiety or fear regarding their future well-being, which seems to be the case for many cancer patients (105), they should be considered for cancer-related AD or anxiety rather than PTSD.

Symptoms that meet the criteria for AD are vague and somewhat non-specific. Consequently, it can be difficult

to differentiate between normal and excessive distress for cancer patients. Symptoms of anxiety and depression can be components of AD, which obfuscates the distinction between AD and generalized anxiety or depression disorders for patients who experience distress about their future health (106,107). Thus, careful clinical evaluation is needed to achieve an accurate diagnosis of AD. Stressful life events such as cancer diagnoses and treatments can result in all of the aforementioned disorders, but direct neuropsychiatric effects of cancer or treatments themselves exclude diagnoses like AD and PTSD (2). The DSM-5 criteria for depression disorders also excludes symptoms directly related to medical conditions, which poses a problem for diagnosing cancer patients and has led some to call for a change in these criteria to better address cancer-

related depression (2,11,102). In palliative care settings, somatic symptoms such as fatigue, functional impairment, and sleep disturbances associated with cancer can further hamper the identification of depression in advanced stages of cancer. Several screening tools exist for identifying and distinguishing depression, such as packages and guidelines from the European Palliative Care Research Collaborative and the PHQ-2, 4, and 9 (2,11,99,100,108). The National Comprehensive Cancer Network (NCCN) also provides a distress thermometer and guidelines for identifying and managing distress-related conditions prior to formal psychiatric evaluations (109-111). Integration of cancer and psychiatric care is key to ensuring appropriate diagnoses and treatments, particularly since most cancer patients are unable or unwilling to seek additional and separate mental healthcare (2,112). Palliative care settings provide an opportunity to facilitate this integration. Ultimately, healthcare providers may use the presence or absence of symptoms to exclude psychiatric disorders in order to distinguish between these conditions.

For caregivers of cancer patients, it is important to differentiate psychiatric conditions from other processes such as anticipatory grief, bereavement, and demoralization. Anticipatory grief is the process of dealing with an impending loss, including mourning and planning, while bereavement occurs when an individual loses a significant other (113). Both anticipatory grief and bereavement can be accompanied by emotional distress, depressive symptoms, separation anxiety, and functional impairment. As such, care should be taken to differentiate these processes from more severe psychiatric disorders. Several screening tools exist that help identify grief-related issues, including the Caregiver Grief Scale (CGS) and Prolonged Grief Disorder Questionnaire (PG-D), and treatments include psychoeducation and psychotherapy (e.g., CBT), which should be tailored to caregivers' specific situations (113). Demoralization occurs in 13–18% of patients diagnosed with a progressive disease or cancer (114). It is a condition characterized by feelings of hopelessness/helplessness, loss of meaning/purpose in life, reduced coping, and social isolation; consequently, patients who experience demoralization often have a desire for hastened death (115,116). While demoralization and other psychiatric disorders such as depression share similar symptoms, demoralization can be distinguished based on a lack of anhedonia, improvement of mood with positive emotional experiences, and a lack of response to medications (114-116). Thus, psychotherapeutic interventions are the most

effective treatment for demoralization, and screening tools exist to specifically identify this condition in cancer patients (114,115).

Susceptibility of brain tumor patients to psychiatric morbidities

Patients with both primary and metastatic brain tumors exhibit high rates of psychosocial distress. The estimated prevalence of brain tumor patients suffering from cancer-related distress or psychiatric disorders ranges from 38–48%, with common diagnoses of AD, anxiety, and depression. Patients frequently report the initial tumor detection as their most distressing experience, and these psychiatric conditions dramatically reduce quality of life (100,117-120). A meta-analysis of over 4,500 brain tumor patients estimated that the prevalence of depression alone is 22%, although rates of self-reported symptoms of depression are much higher, and depressive symptoms are associated with shorter survival in patients with glioblastoma (7-10). Suicidal ideation occurs in 6% of patients undergoing surgery for brain tumors and is another concern for healthcare providers (121). Partners of brain tumor patients have high rates of psychiatric morbidities as well (47%), the majority of whom report that their distress stems from fear of surgical outcomes (117). Experience with brain tumors can also be a traumatic experience. Thirty-five percent of pediatric brain tumor survivors and 29% of their parents have severe levels of PTSS (122), but there is a scarcity of research focused on brain tumor-related PTSS or PTSD in adults. Due to the nature of their disease, brain tumor patients are particularly susceptible to neuropsychiatric symptoms that result directly from the cancer and its treatment (*Table 2*). Interestingly, the rate of mental health disorders for central nervous system (CNS) cancer patients begins to increase as early as 10 months before their diagnosis, increases rapidly and peaks the week after diagnosis, and remains elevated 8–10 years after diagnosis. Compared to cancer-free individuals, the use of psychiatric medications begins to increase approximately one month before diagnosis, rapidly increases around the time of diagnosis, peaks approximately 3 months after diagnosis, and remains elevated 2 years after diagnosis. Peak use of psychiatric medications is particularly high for patients with cancers of the CNS compared to other cancers (123).

Brain tumors can alter the structure and function of regions critical for regulating emotional state, personality,

Table 2 Neuropsychiatric effects of brain tumors, symptoms, and their treatments

Cause	Neuropsychiatric effect	Recommendations
Frontal lobe tumors	Depression	Treat/debulk tumor, antidepressants
Temporal lobe tumors	Epilepsy, panic	Treat/debulk tumor, antiseizure medications
Pituitary tumors	HPA axis dysfunction, depression, anxiety	Check HPA axis, treat hormonal dysregulation, treat/debulk tumor
Tumor-related cognitive impairment/sleep dysfunction	Emotional dysfunction, depression, anxiety	Evaluate cognitive function, antidepressants/anxiolytics
Tumor-related seizures	Depression, anxiety	Antiseizure medications, antidepressants/anxiolytics
Glucocorticoids	Depression, anxiety, dysphoria, mania, delirium, insomnia, increased appetite, cognitive impairment	Rotate steroids, alter steroid dose or type, antipsychotics
Anticancer drugs (e.g., methotrexate, pemetrexed, vincristine, etoposide, procarbazine)	Mood alterations, depression, anxiety, mania	Consider alternative anticancer drugs, antidepressants/anxiolytics (avoid drug interactions)
Brain radiotherapy	HPA axis dysfunction, mood alterations, depression, anxiety	Check HPA axis, treat hormonal dysregulation, antidepressants/anxiolytics

HPA, hypothalamic-pituitary-adrenal.

and behaviors (124,125). These tumors, as well as associated edema, can also induce neuroinflammatory reactions that are associated with various psychiatric conditions including depression and anxiety (126-128). Tumor location can influence the types of psychiatric symptoms patients experience. Frontal lobe tumors have been linked to depression and apathy, and temporo-limbic tumors can cause panic attacks. Tumor-associated temporal lobe epilepsy can be misdiagnosed as a panic disorder, and it is important to recognize the potential psychiatric presentations of both frontal and temporal lobe brain tumors (10,129). Some studies failed to show an effect of tumor location on the incidence of depression; however, the size of tumors does seem to influence mood dysfunction. Tumors with diameters larger than 4 cm are associated with higher rates of depression (10). Affective symptoms are also related to the integrity of white matter tracts in brain tumor patients, which can be visualized with diffusion tensor imaging (130). Finally, the type of tumor can play a role in the development of psychiatric morbidities. Pituitary tumors can cause depression and anxiety via hormonal dysregulation and alterations to the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis dysfunction is often associated with increased secretion of corticotropin releasing hormone (CRH) and/or adrenocorticotrophic hormone (ACTH), which results in abnormally high levels of glucocorticoids

and catecholamines that can be detrimental to mental and physical health. Both neurosurgical and radiation treatments of tumors can also induce HPA axis dysfunction in 22–65% of patients (131). Laboratory tests can identify HPA axis dysfunction, and patients can also present with physical and mental changes (e.g., Cushing's syndrome) that can further aid diagnosis (132). Excessive ACTH and growth hormone secretion from pituitary tumors can result in depression rates of 63% and 75%, respectively, while excess prolactin secretion causes more anxiety-related symptoms (10,133). Patients with meningiomas seem to have a higher prevalence of depression (30%) compared to other tumors like gliomas and vestibular schwannomas, although these tumors also have higher depression rates compared to the general population (10). It is important to note that certain tumors, such as those located in the thalamus, basal ganglia, or reticular formation, can present with symptoms of fatigue, lethargy, somnolence, or apathy that can mimic symptoms of depression (10,134).

Cognitive impairment is one of the most common presenting symptoms of brain tumor patients. Primary and metastatic tumors can invade and compress brain regions critical for executive function, attention, memory, and emotional regulation. Edema associated with brain tumors can also result in cognitive deficits and other somatic symptoms such as fatigue and headaches (124,125). The

prevalence and type of cognitive impairment varies widely depending on tumor location, size, type, and the cognitive domain tested (e.g., memory versus attention). Rates of cognitive impairment as high as 83% have been reported for glioma patients, and 92% of brain tumor patients in general have been shown to have episodic memory deficits (125,135-138). Treatment of brain tumors can also have a profound effect on cognitive function. In some cases, treatment can be a greater risk factor for impairment than tumor location, and adverse cognitive effects following chemotherapy and radiotherapy for brain tumors have been particularly well-described (137,139-141). Mental deficits can lead to emotional dysfunction, and cognitive impairment is associated with both anxiety and depression in patients with brain tumors (142-145). In addition, many patients with brain tumors experience sleep dysfunction, which can also contribute to the development of depression (10). At the same time, associated symptoms of cognitive impairment such as fatigue, somnolence, and lack of interest in activities can be confused with or mask symptoms of depression. Patients with cognitive impairment and dementia also experience high fall rates which can result in serious injuries (146).

A majority of individuals with brain tumors experience seizures as a result of their disease. In fact, cognitive impairment and seizures are the most common symptoms in patients with primary brain tumors and more commonly present in patients with brain tumors compared to other cancers (137,147,148). Low grade and primary tumors are more likely to cause seizures than high grade or metastatic tumors, with epilepsy rates as high as 85% for low-grade glioma (149-151). Although complete overview of epilepsy and psychiatric disorders is outside the scope of this review, there have been numerous studies demonstrating a relationship between seizures and conditions such as depression, anxiety, and PTSD (152). Patients with seizures show higher rates of comorbid psychiatric disorders, and levels of depression and anxiety strongly correlate with frequency of seizures (148,153-157). First-line treatment of seizures in brain tumor patients involves monotherapy with an antiseizure medication, and many patients are placed on medication as a prophylactic therapy. While some antiseizure medications like valproate, lamotrigine, and benzodiazepines are anxiolytic and can have positive effects on mood, others like levetiracetam, topiramate, and barbiturates can worsen mood and lead to depression, anxiety, or aggression (158-160). Additionally, 30-40% of brain tumor patients experience side-effects from

antiseizure medications, a higher incidence than in non-cancer patients, so careful consideration of potential neuropsychiatric consequences is necessary when treating seizures in this population (151,161). Antiseizure medications are not an appropriate substitute for formal psychiatric treatment, and psychiatric drugs are typically safe to use in conjunction with antiseizure medications at therapeutic doses. However, interactions can occur depending on the medication. Antiseizure drugs can alter the concentration of psychiatric medications in the plasma and vice versa, which can hinder the efficacy of these drugs or result in toxicity. At higher levels, psychiatric medications including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) can potentially lower the seizure threshold and display proconvulsive properties (162-164). As such, careful clinical monitoring is required when treating patients with seizures and psychiatric comorbidities.

Treatments for primary and metastatic brain tumors often come with increased risks of psychiatric complications. Glucocorticoids are routinely used to treat cerebral edema and increased intracranial pressure associated with brain tumors (165,166). These steroids are effective but can induce numerous neuropsychiatric symptoms including depression, anxiety, dysphoria, mania, delirium, insomnia, increased appetite, and cognitive deficits (167-169). Many of these symptoms are addressed by standardized screening tools such as the PHQ. Depression has been particularly noted for brain tumor patients on steroids 6 months post-surgery (9). Patients with a personal or family history of depression or alcoholism have a higher risk of steroid-induced affective disorders, and higher doses of steroids cause more severe symptoms (170,171). Chemotherapeutic agents used to treat a variety of brain cancers also have potential neuropsychiatric effects. For example, methotrexate and pemetrexed can cause mood alterations, vincristine and etoposide can produce depressive symptoms, and procarbazine can induce mania (1,24,172). Procarbazine in particular has monoamine oxidase inhibitor (MAOI) activity which can cause interactions with antidepressants and other psychiatric medications. This MAOI activity can also result in severe interactions with tyramine-containing foods, which should be avoided in patients taking procarbazine (38,173). Partial and whole brain radiotherapy can result in depression, anxiety, and mood alterations which can be secondary consequences of post-radiation hormonal deficiencies (1,172,174). Neurosurgical interventions can result in emotional and behavioral

changes depending on the site of resection. Decompression of brain regions that regulate emotional responses (e.g., limbic regions) can potentially alleviate affective symptoms. Additionally, some studies indicate that gross total resection can improve symptoms of depression (10). However, the act of undergoing surgery can itself cause distress and anxiety, and patients who adopt coping strategies that aid with emotional adjustment have better emotional responses than those who display excessive rumination (1,172,175-177).

Finally, headaches are a common symptom in patients with brain tumors and are often treated with opioid analgesics (178,179). Opioids have the potential to cause serotonin toxicity or serotonin syndrome which can result in altered mental status and numerous other symptoms, particularly when combined with psychiatric medications such as SSRIs/SNRIs. Consequently, other medications such as triptans have been recommended for headache treatment, which are safer to use for patients taking SSRIs/SNRIs (180). The risk of serotonin syndrome with opioid medications should also be considered in cases of general pain management, particularly in palliative care settings.

Diagnosing and treating psychiatric disorders in patients with brain tumors

Depression and anxiety are the most well-studied psychiatric disorders in brain tumor patients and can occur across the cancer care continuum. Screening for depression and anxiety should be a routine and integrated component of cancer care. The NCCN's distress thermometer and other surveys such as the PHQ-2, PHQ-4, and GAD-7 are effective means for identifying symptoms of depression and anxiety in brain tumor patients (99-101,181). Although screening is essential for identifying potential mental health conditions, structured clinical interviews and formal psychiatric evaluations should follow in order to make an appropriate diagnosis based on DSM-5 criteria and current guidelines. This is particularly important because somatic symptoms associated with brain tumors can mimic or mask symptoms of anxiety and depression. Many brain tumor patients experience fatigue, somnolence, functional limitations, or normal distress that are not associated or occur simultaneously with an affective disorder. It is also important to differentiate between neuropsychiatric symptoms that directly result from the tumor or cancer therapies themselves versus psychosocial causes of depression or anxiety, since diagnoses and treatments can differ based on symptom etiology (1,9,10,124,125).

The symptoms for anxiety and depression are divergent enough to differentiate between these conditions during routine screening, but formal evaluation should be used to distinguish depression or anxiety disorders from other conditions such as AD or PTSD (1,51).

The presence of certain risk factors can indicate the need for additional screening and evaluation. Large tumors (greater than 4 cm in diameter), pituitary tumors, and meningiomas all carry high risks of depression and anxiety symptoms. Cognitive impairment and seizures that result from brain tumors, along with treatments such as glucocorticoids, also put patients at risk (9,10,133,142-145,148,154,159). From a psychosocial standpoint, cancer patients who are younger, have functional limitations, and lack social support are at increased risk for depression, while past trauma, demoralization, and metastasis can increase risk for anxiety. Cancer patients from certain marginalized and minority populations and patients with a history of mental health issues are also more likely to have cancer-related depression or anxiety (1,18,28-34). Research focused on brain tumor patients specifically indicates that female gender, lower tumor grade, lower education level, and a history of psychiatric illness all predict anxiety and depression (182). Healthcare providers should be aware of these risk factors when screening brain tumor patients for depression and anxiety disorders.

Patients with symptoms of depression or anxiety that stem from their tumor or cancer therapy can sometimes benefit from treating the tumor itself or altering the causative therapy. Neurosurgical resection of brain tumors can alleviate neuropsychiatric symptoms by decompressing affected brain regions or removing hormone-secreting tumors. Alterations to the dose or type of medications that induce depression or anxiety symptoms can also provide relief. Patients who experience steroid-associated psychiatric morbidities may benefit from rotating the type of steroid used or treatment with antipsychotic medications such as risperidone (183). Healthcare providers should also check the HPA axis to monitor for potential hormonal causes of psychiatric symptoms, particularly in patients with pituitary tumors or individuals who receive radiotherapy. Restoring HPA axis balance could improve psychiatric symptoms. However, it may be beneficial or necessary to utilize psychiatric and psychological interventions in conjunction with cancer-targeted therapies (1,9,10,164). Pharmacological treatment of depression and anxiety should follow normal standards of care for non-cancer patients, while avoiding interactions with chemotherapeutic and

other cancer-related agents as described in previous reviews (1,38-40,42). Although it is important to be cautious when treating brain tumor patients with psychiatric medications, they are relatively safe to use in cancer patients and the therapeutic benefit of medical intervention can be substantial (41). Thus, healthcare providers should consider the use of these drugs when warranted by a psychiatric diagnosis. Some studies have also demonstrated the success of psychedelics and ketamine for treating cancer-related psychiatric distress, particularly in hospice settings (184-186). Evaluation of ketamine for treating depression in brain tumor patients is currently ongoing, but psychedelic or ketamine therapy may be additional options for brain cancer patients (187).

Psychosocial interventions also improve symptoms of depression and quality of life for brain tumor patients, and continued psychological care can reduce depression and anxiety levels while lowering seizure frequency (188,189). Brain tumor patients who exhibit emotional stability and openness about their disease have less general depression and anxiety, while patients who integrate the disease into their identity and blame themselves experience more depression (190,191). Neurosurgical patients who employ optimism and trust as coping strategies have less surgery-related anxiety and better emotional well-being. Conversely, excessive rumination results in greater surgery-related anxiety and psychiatric morbidity (177). Thus, interventions focused on helping brain tumor patients with their coping strategies and emotional responses can improve cancer-related mood disorders. Early interventions in palliative care settings can reduce depression and anxiety and enhance quality of life for brain tumor patients, and these settings are uniquely suited to integrate psychiatric screening and treatment with cancer care (3,43-46,192).

Brain tumor patients with symptoms of depression or anxiety may suffer from cancer-related AD. AD is the most common psychiatric disorder in general cancer patients and is often associated with anxious or depressive behaviors (13,49,50). Therefore, psychiatric evaluations should be used to carefully differentiate between general depression or anxiety disorders and AD in patients with brain tumors. DSM-5 criteria for AD are somewhat ambiguous and present challenges for clearly distinguishing AD from other psychiatric disorders in cancer patients (102,106,107). In general, AD stems from problematic adjustment to or management of stressful life events such as the diagnosis or treatment of brain tumors,

rather than direct neuropsychiatric consequences of the disease (although these consequences can contribute to the development of AD). Symptoms of AD are generally not severe enough to meet the criteria for general depression or anxiety disorders and are typically more acute and situational (1,2,50-52,61,102). There is a lack of research focused on the differentiation of AD from other psychiatric disorders in brain tumor patients, as well as the risk factors for AD in this population. Data on more general cancer patient populations can provide insight for providers during screening for AD until further data become available. The majority of brain tumor patients suffering from psychiatric disorders, including AD, report that the initial tumor detection is their most distressing experience (117). Therefore, screening for AD should take place early and continue throughout patients' cancer care. There are no studies to date that examine AD treatments for brain tumor patients, but research with general cancer patient populations indicate that CBT, relaxation interventions, and psychiatric medications for symptom management are effective therapies for cancer-related AD (1,49,50,62-65).

The DSM-5 outlines specific criteria that enable the differentiation of PTSD from AD and general depression or anxiety disorders. In particular, cancer patients with PTSD are often burdened with uncontrolled and distressing cancer-related memories, rather than distress about their future which is more indicative of adjustment or anxiety disorders. Receiving cancer diagnoses, prognoses, and treatments can be traumatic and lead to distressing memories and other PTSD symptoms (2,51,102). It is important to consider whether a brain tumor-related experience meets the formal classification of a traumatic event according to the DSM-5; however, brain tumor patients can still meet the criteria for PTSD even if their diagnosis or treatment is not considered "sudden" and "catastrophic". Brain tumor patients with PTSS but not formal PTSD should also be considered for an AD diagnosis (51,102). Like AD, PTSD in brain tumor patients is greatly understudied, and more work is needed to evaluate the traumatic nature of brain tumor diagnoses and treatments. Additionally, little is known about specific risk factors and effective treatments for PTSD in patients with CNS cancers. Cancer patients in general who have PTSD can benefit from CBT and other psychotherapies, as well as palliative care interventions that address both physical and psychological distress (2,77,87-95).

Conclusions

Depression, anxiety, adjustment, and PTSDs are prevalent in cancer patients and can significantly reduce their quality of life. Individuals with brain tumors are particularly susceptible to psychiatric morbidities as a result of their disease. Screening for psychiatric morbidities should take place across the cancer care continuum, and palliative care settings are uniquely suited to differentiate and treat these conditions. Ultimately, more research is needed to fully understand and address the needs of brain tumor patients with psychiatric disorders.

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