Depression screening in patients with brain tumors: a review

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Practice points

- Depression is a common complication in patients with established brain tumor diagnosis, and should be actively sought and managed.
- Recognition of depressed brain tumor remains poor and can be improved with depression screening scales.
- Current evidence suggest that the Hospital Anxiety and Depression scale–Depression subscale and Patient Health Questionnaire-9 have adequate psychometric properties for depression screening purposes.
- Due to high false-positive rate of depression screening, all patients screened positive for depression should be referred for detailed psychiatric evaluation prior to initiating treatment.
- Methodologically rigorous studies evaluating psychometric properties of depression scales are strongly encouraged.
- Randomized trials of antidepressant treatment efficacy in brain tumor patients are lacking.
- Potential value of depression biomarkers in neuro-oncology setting should be evaluated.

SUMMARY Brain tumor (BT) is often a devastating disease associated with poor prognosis. Depression is a common complication in BT patients that often remains under-recognized and untreated. Implementation of reliable depression screening algorithms in routine neuro-oncology setting could potentially improve recognition of depression. The Hospital Anxiety and Depression scale–Depression subscale and Patient Health Questionnaire-9 demonstrated adequate psychometric properties for depressive disorder screening in glioma patients. Patients screened positive for depression should be referred for detailed psychiatric assessment prior to initiating anti-depressive treatment. Further methodologically rigorous studies investigating psychometric properties of single-item and multiple-item depression scales are urgently warranted. Studies evaluating anti-depressive treatments' efficacy and clinical value of depression biomarkers are important avenues for future research endeavors in BT patients.

Primary brain tumor (BT) is a rare disease affecting approximately seven out of 100,000 persons worldwide [1]. Prognosis of patients affected by malignant primary BT often remains dismal, with only one quarter of glioblastoma multiforme patients surviving beyond 2 years after the diagnosis even when multimodality treatment is used [2]. Furthermore, tumor- and treatment-related factors, such as progressive neurological impairment due to BT invasion and treatment side effects, contribute toward progressive deterioration. Patient-centered outcomes, including symptoms of psychological distress, are becoming increasingly used as secondary outcome measured in clinical trials

KEYWORDS

- brain tumors • depression
- diagnostic accuracy
- screening

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and should be considered when guiding individual patient treatment [3,4]. Therefore, accurate identification of BT patients suffering from psychological distress is becoming increasingly important in clinical practice and in research studies. Assessment of psychological distress was recently identified as priority research area in psycho-oncology [5].

From a clinical perspective, elevated symptoms of psychological distress and mental disorders should be considered as separate entities of the same continuum. According to the National Comprehensive Cancer Network (NCCN) distress is defined as a multifactorial unpleasant emotional experience in psychological, social and/or spiritual domains that can impair effective coping with cancer [6]. At its most severe form, psychological distress can manifest as a mental disorder and significantly disrupt patient functioning. Thus, major depressive disorder (MDD) is the most severe form of psychological distress spectrum that is characterized by sadness or reduced interest in pleasure activities and impairment in social functioning that is accompanied by psychomotor abnormalities (e.g., fatigue and psychomotor retardation) [7].

Depression is a common complication in patients with BT. It has been estimated that up to 50% of primary BT patients suffer from elevated depressive symptoms as evaluated by using self-rating depressive symptom scales [8,9]. MDD is more common in BT patients when compared with the general population [10]. Reported prevalence rate of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria was 28% in ambulatory BT patients [11]. Recent meta-analysis of Krebber and colleagues revealed that depression rates in BT patients are one of the highest when compared with other forms of cancer [12].

Depression carries serious health risks in BT patients. For example, it has been shown that greater depressive symptom severity predicts shorter overall survival of BT patients [13,14]. In addition, depressive symptoms were linked to impairment across numerous aspects of health-related quality of life of BT patients and this association was independent from patients' age, functional status and BT histological type [15]. Furthermore, depression predicts cognitive impairment [16] and puts BT survivors at increased risk for suicide ideation [17]. Therefore, depression should be actively sought and managed in patients with established diagnosis of BT.

However, depression often remains under-diagnosed and untreated in cancer patients [18]. Litofsky with colleagues have reported significant dis-concordance between patient-reported (Short Form-36 health survey and a three question survey for major depression) and physician (DSM criteria) reported depression rates in a longitudinal study of 598 high-grade glioma patients [9]. Specifically, 93% of patients reported symptoms consistent with depression, while less than 22% of patients were classified as depressed by physicians [9].

There are numerous potential patient-related, physician-related and system-related barriers that prevent timely recognition of mental disorders. Time constraints [19], inadequate training and knowledge about recognition and treatment of mental disorders [20], and lack of evidence-based diagnostic algorithms [21,22] can be considered important and preventable barriers stemming from healthcare systems and physicians. Mental disorders can be diagnosed by trained mental health specialists using structured clinical interviews. However, administration of psychiatric interviews can be time-consuming and imposes significant burden to healthcare settings and patients. Toward this end, it has been shown that recognition of depression can be significantly improved by administering self-rating depression screening scales that evaluate depressive symptom severity as experienced by a patient [23]. Patients reporting depressive symptoms should be considered high-risk and referred for more detailed psychiatric assessment. However, a recent survey has shown that less than 10% of oncologists employed validated self-rating instruments to screen for symptoms of psychological distress [24].

Thus, this article aims to review current knowledge regarding diagnostic accuracy of self-rating depressive symptom scales for identifying depressive disorders diagnosed using structured psychiatric interview according to the DSM criteria in patients with established diagnosis of BT.

Instruments investigated for depression screening in BT patients

We have identified three published studies that have investigated diagnostic accuracy of self-rating depressive symptom scales for identifying MDD, diagnosed using structured psychiatric interview according to the DSM criteria, in patients with established diagnosis of primary BTs. The distress thermometer (DT) [25], Patient Health Questionnaire-9 (PHQ-9) [26]

and Hospital Anxiety and Depression Scale–Depression subscale (HADS-D) [27] have been tested for MDD screening purposes in BT patients (Table 1). The DT was developed by the NCCN in order to improve recognition of distressed cancer patients and comprises Likert-type distress scale with possible answers ranging from 0 (extreme distress) to 10 (no distress) and subscales intended to report practical, family, emotional, spiritual/religious, physical and other problems experienced by a patient. The HADS comprises two seven-item subscales of depression (HADS-D) and anxiety (HADS-A) that are designed for assessment of depressive and anxiety symptoms, respectively, in somatic patients, thus somatic symptoms of depression/anxiety were excluded for the scale. The PHQ-9 includes nine cardinal symptoms of MDD that are rated on a four-point Likert-type scale. The HADS and DT are concerned with symptom severity during the past week while the PHQ-9 inquires about depressive symptom severity in the past 2 weeks that meets the MDD symptom duration criteria according to the DSM definition.

Diagnostic accuracy of self-rating scales

Two of the reviewed studies have been performed in Scotland and one in Germany (Table 2). Sample sizes were small to moderate ranging from 29 to 154 patients. Two studies included only glioma patients (both high grade and low grade) while one study included patients irrespective of histological BT type. Diagnosis of current MDD was established according to the Structured Clinical Interview for DSM-IV (SCID) in all studies.

Ronney with colleagues have provided with the most robust findings to date with respect to diagnostic accuracy of depression self-rating scales for MDD screening in BT patients [28]. In 154 patients with established diagnosis of glioma

they investigated sensitivity, specificity and positive-predictive value (PPV) of the DT, HADS and PHQ-9 for MDD diagnosis at three time points: during primary radiotherapy, 3 months later and 6 months later. The HADS-D (range from 0.89 to 0.98) and PHQ-9 (range from 0.89 to 0.94) had superior areas under the receiver operating characteristic curve values across the three study visits when compared with the DT (range from 0.78 to 0.90). At optimal cut-off values the HADS-D (cut-off value of ≥ 7) has demonstrated slightly superior but comparable values of sensitivity, specificity and PPVs relative to the PHQ-9 (cut-off of ≥ 10). In another publication by the same group it has been reported that the PHQ-9 at cut-off value of ≥ 9 had unacceptable sensitivity (57%) and moderate specificity (80%) for MDD in 41 high-grade and low-grade glioma patients [29]. Finally, a study from Germany in a small sample ($n = 26$) of patients with various BTs has reported excellent sensitivity (100%) but poor specificity (30%) of the DT at cut-off value of ≥ 5 for MDD [30]. In the latter study, the HADS-D at cut-off value ≥ 11 had poor sensitivity (18%) for MDD.

Discussion

We have identified three published studies investigating diagnostic accuracy of the DT, HADS and PHQ-9 for MDD screening purposes in patients with established BT diagnosis. One study that was performed in moderate sample of glioma patients has found that the HADS-D and PHQ-9 had superior psychometric properties relative to the DT. Two other reviewed studies were performed in small samples of BT patients and their findings should be interpreted with caution. Thus, based on current knowledge, the HADS-D and PHQ-9 can be recommended for MDD screening in patients with cerebral gliomas.

Table 1. Self-rating instruments evaluated for depression screening in patients with brain tumors.

Instrument	Number of items/subscales/time frame	Studies in brain tumor patients
Hospital Anxiety and Depression Scale	14 items/anxiety and depression/past week	[28,30]
National Comprehensive Cancer Network's Distress Thermometer	Single-item 11-point visual analog scale/psychological distress/past week	[28,30]
Patient Health Questionnaire-9	Nine core symptoms of major depressive disorder/depressive symptoms/previous 2 weeks	[28,29]

In the most methodologically robust study performed in the largest sample of BT patients to date, Rooney with colleagues have demonstrated that multiple-item HADS-D and PHQ-9 scales had acceptable sensitivity (80–93% and 67–80%, respectively), specificity (88–91% and 83–89%, respectively) and PPV (31–59% and 25–56%) for MDD in glioma patients across treatment periods [28]. Another two reviewed studies that investigated psychometric characteristics of the DT, HADS-D and PHQ-9 were performed in substantially smaller patient samples [29,30]. Therefore, the HADS-D and PHQ-9 should be considered for depression screening in BT patients and patients scoring ≥ 7 and ≥ 10 on respective scales should be considered for detailed psychiatric consultation. When available, the HADS-D should be preferred since it has greater sensitivity for MDD, relative to the PHQ-9.

It should be recalled that PPVs of depression screening scales rarely exceeded 50%, indicating that approximately half of BT patients with positive depression screening results met the DSM diagnostic criteria for MDD [28]. PPV is a proportion of patients with positive screening results that are truly positive according to the ‘gold standard’ criteria. Low PPVs indicate that self-rating depression scales are overly inclusive in BT patient population. A large proportion of BT patients screened positively for depression will not meet the DSM criteria for MDD on subsequent psychiatric evaluation, thus healthcare providers should not rely on screening results only. Therefore, it is important to emphasize that patients who screen positive for depression using self-rating scales should be referred for more rigorous psychiatric assessment prior to initiation of antidepressant therapy. Low PPVs of depression screening scales can lead to an overburden of available healthcare resources and may cause unnecessary anti-depressive treatment. Although some evidence exist that cancer patients with depressive symptoms not meeting clinical criteria of depression may benefit from anti-depressive treatment [31], it is still unclear how much these findings might be generalized for BT patients. Possible disadvantages of unnecessary anti-depressive treatment of BT patients include potentially serious side effects, such as decreased seizure threshold, impaired cognitive functioning and fatigue; risks for drug–drug interactions of antidepressants with antiepileptic medication and chemotherapeutic agents; and additional healthcare costs [31–33].

Also, none of the reviewed studies have reported negative-predictive values (NPV) of depression screening. NPV indicates a proportion of patients with negative screening results that are truly negative. From a clinical perspective, this psychometric measure indicates diagnostic accuracy of depression screening scale to correctly classify not-depressed patients. Thus, it remains unclear if additional testing is warranted in BT patients with negative depression screening results to prevent under-recognition of depression. Subsequent studies on diagnostic accuracy of depression screening scales should provide with all psychometric properties, including NPVs and PPVs.

Conclusion & future perspective

Important questions pertaining to depression screening in neuro-oncology setting and subsequent management of depressed BT patients remain to be answered in future studies (Box 1). First, optimal depression screening algorithm should be validated in well-designed studies prior to recommending universal implementation of depression screening protocol in BT patients. Toward this end, we strongly recommend researchers planning depression screening studies to refer to the Standards for the Reporting of Diagnostic (STARD) accuracy studies statement. The STARD checklist was specifically developed to improve quality of reporting of diagnostic accuracy studies [34]. Valuable depression screening instruments in clinical setting should be feasible (i.e., do not impose significant time constraints) and reliable (i.e., be highly sensitive across different BT patient populations). Toward this end, the single-item DT was specifically developed by the NCCN for screening of distress in cancer patients. A recent review of the DT validation studies across cancer patient populations has found that DT cut-off values varied as a function of clinical setting, patient population studied, country and language [35]. Also, the majority of authors have employed the HADS (or other self-rating scales) as established criterion for DT screening results. Therefore, diagnostic accuracy of the DT against the DSM diagnosis of MDD warrants further research. The PHQ-9 and HADS-D has demonstrated superior diagnostic characteristics for MDD screening purposes in BT patients. The PHQ-9 is currently recommended for depression screening in patients with coronary artery disease and

Table 2. Overview of the reviewed studies evaluating diagnostic accuracy of screening tools for major depressive disorder in patients with brain tumors.

Source; Country	No. of patients (% male); BT histology; setting	Mean age (years)	Depression criterion	Depression prevalence rate (%)	Instrument and optimal cut-off score	Diagnostic characteristics		
						Sensitivity (%)	Specificity (%)	Positive-predictive value (%)
Germany [30]	26 (50%); various; in-patient	59.04	MDD, DSM-IV; SCID interview	4	DT ≥ 5	100	30	
					HADS-D ≥ 11	18		
Scotland [†] [28]	154 (57%); high-grade and low-grade gliomas; outpatient	54.2 $\pm$ 12.3	MDD; DSM-IV; SCID interview	14/15/7	DT ≥ 5	80/81/67	84/80/82	42/45/22
	133; high-grade and low-grade gliomas; outpatient				HADS-D ≥ 7	93/100/80	91/88/88	56/59/31
	129; high-grade and low-grade gliomas; outpatient				PHQ-9 ≥ 10	80/71/67	86/89/83	43/56/25
Scotland [29]	41 (71%); high-grade and low-grade gliomas; outpatient	57.9 $\pm$ 8.5	MDD; DSM-IV; SCID interview	17	PHQ-9 ≥ 9	57	80	

[†]Patients were evaluated at three time points: during primary radiotherapy, 3 months later and 6 months later.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV; DT: Distress thermometer; HADS-D: Hospital Anxiety and Depression scale-Depression subscale; MDD: Major depressive disorder; PHQ-9: Patient Health Questionnaire-9; SCID: Structured Clinical Interview for DSM Disorders.

has been studied for MDD screening in cancer patients. For example, a recent study in a heterogeneous sample of 4264 cancer patient has reported high sensitivity (93%) of the PHQ-9 at cut-off value ≥ 8 for MDD [36]. The HADS includes both depressive and anxiety symptom subscales and has been reported as reliable and valuable scale for depression and anxiety screening purposes across different populations of somatic patients [37]. Diagnostic value of the HADS anxiety scale remains to be evaluated for screening of anxiety disorders that are also common in BT patients [38,39].

Diagnostic properties of other commonly used depression screening scales, such as the two-item Patient Health Questionnaire-2 (PHQ-2) and multiple-item Beck Depression Inventory-II (BDI-II), remain to be explored in neuro-oncology setting. A recent study in 227 patients with various histological types of BTs has shown that the PHQ-2 had acceptable sensitivity, specificity and NPVs with low PPVs for identifying moderate-severe depressive symptom severity according to the HADS-D

(score ≥ 11) and BDI-II (score ≥ 20) [8]. However, another recent study has reported significantly worse sensitivity of the PHQ-2 (cut-off score ≥ 2 ; sensitivity = 32%) relative to the DT (cut-off score ≥ 2 , sensitivity = 96%) for depression determined with the PHQ-9 (cut-off score ≥ 5) in 123 patients with advanced cancer [40]. With regards to BDI-II, a study in 46 patients with advanced cancer has reported significantly better psychometric properties of the BDI-II (cut-off score ≥ 16 ; sensitivity = 90% and specificity = 69%) relative to the single screening question 'Are you feeling depressed?' (sensitivity = 50% and specificity = 94%) for PRIME-MD diagnoses of depressive disorder [41]. However, diagnostic accuracy of the BDI-II yet remains to be defined in BT patient population. Toward this end, diagnostic properties of the PHQ-2 and BDI-II for MDD diagnoses in BT patient population should to be explored. Also, studies comparing diagnostic accuracy of depression screening scale in the same cohort of BT patients would allow head-to-head comparison of depression screening instruments.

Box 1. Important questions that remain to be answered in patients with brain tumors.

- Which scale and which cut-off score should be used for depression screening purposes?
- What is the optimal depression screening algorithm?
- Can brain tumor histological type, cerebral location and previously received treatment(s) impact depression screening results?
- Can integration of biomarkers improve recognition of depression?
- How should depressed brain tumor patients be treated?

The American Heart Association currently recommends two-step depression screening algorithm in CAD patients [42]. Patients with positive screening results with the PHQ-2 should be further investigated using the PHQ-9, and patients with positive PHQ-9 screening results should be referred for detailed psychiatric assessment. Two-step screening algorithm can improve patient selection for psychiatric consultation thus reducing costs for healthcare setting. However, diagnostic accuracy of a two-step depression screening algorithm remains to be investigated in BT patients.

Disease- and treatment-related factors can impact depression screening results and should be considered in patients with BTs. For example, depression can develop due to direct compression of neural structures by BT [43]. In addition, major life stress associated with life-threatening diagnosis of BT can put patients at increased risk for depression [44]. Furthermore, debilitating side effects (e.g., anorexia and fatigue) of non-surgical treatments of BT can mask depressive symptoms and interfere with psychiatric assessment [45,46]. Therefore, depression screening results should be interpreted with caution in the context of BT location, temporal association with BT diagnosis, and current and/or previously received treatments for BT. In order to raise clinician's index of suspicion for depression in cancer patients, McDaniel with colleagues have recommended to consider somatic depressive symptoms, such as fatigue and anorexia, as depression-related, even if they could have potentially been caused by cancer treatment [47].

A substantial body of research has attempted to identify neuroendocrine, metabolic, genetic and imaging biomarkers of depression (for detailed review, see [48,49]). Integration of depression biomarkers in neuro-oncology setting has a potential to significantly improve recognition of depressed BT patients and monitor treatment response. However, the importance of biomarkers remains under-studied in BT patients. It was recently shown that lower serum concentration of tri-iodothyronine (thyroid hormone) was associated with greater depressive symptom severity before BT surgery and worse functional outcomes at discharge independently from demographic and clinical factors [50], suggesting that thyroid hormones can provide with valuable additional information regarding patient mental health and somatic health status.

Finally, it is important to learn if depression screening intervention can improve functional and patient-oriented outcomes and what is the optimal management strategy of depressed BT patients. BT patients with established diagnosis of MDD should be considered for antidepressant treatment in order to reduce depressive symptom severity and improve quality of life. However, evidence regarding safety and efficacy of antidepressant treatment in patients with BTs is lacking, since there are no randomized controlled trials investigating safety and efficacy of antidepressant treatment in depressed BT patients. For more detailed information on clinical trials for depression treatment in BT patients, please see a recent review by Rooney and Grant [33]. However, there have been a few attempts to investigate changes of mood symptoms in response to treatment with psychotropic medication. For example, treatment with methylphenidate (psychostimulant) [51], donepezil (reversible acetylcholinesterase inhibitor) [52] and bupropion (antidepressant) [53] reduced depressive symptom severity of BT patients. However, these studies were not specifically designed to investigate antidepressant treatment efficacy in BT patients with established diagnosis of depressive disorder. Instead, depressive symptom severity was considered as a secondary outcome measure. Consequentially, there are no evidence-based recommendations regarding the most optimal management strategy of depressed BT patients. Clinicians caring of depressed BT patients should be cautious when selecting antidepressant medication, since certain antidepressants can lower seizure threshold, impair cognitive functioning and increase fatigue that should be considered as important side effects in neuro-oncology setting.

To conclude, depression is a common complication in patients with established BT diagnosis that often remains under-diagnosed and untreated. Identification of depressed BT patients can be challenging. The PHQ-9 and HADS-D scales can be recommended for depressive disorder screening purposes in neuro-oncology setting. However, due to high false-positive rate antidepressant treatment should not be initiated based solely on screening results and all patients who screened positive for depression should undergo detailed psychiatric assessment. Further methodologically rigorous studies should focus toward evaluating diagnostic accuracy of other depression screening scales and

two-step depression screening algorithm in BT patients. Treatment of depressive disorders and potential clinical value of depression biomarkers in BT patient population are important avenues for future research endeavors.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial

involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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