

Clinical Study

Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues

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Summary

Neuropsychiatric problems, and how they interact to impact on quality of life (QOL) in brain tumor patients, are generally poorly understood. The objectives of this study were: (1) to document the prevalence of depression, fatigue, emotional distress, and existential issues in a sample of brain tumor patients (2) to examine the interconnectedness of these problems, and (3) to explore their relationship with disease-related variables and QOL. This is a cross-sectional, questionnaire-based survey of 73 patients with primary brain tumors who presented to a neurological clinic at a tertiary cancer centre for ongoing care. Data for 60 participants (29 women, 31 men) who completed validated questionnaires were retained for analysis. Results showed that there was a high burden of depressive symptoms as measured by the Beck Depression Inventory-II (mean score 11.1, SD 7.4), with 38% of the sample scoring in the clinically depressed range. Overall QOL scores for this sample were similar to a reference sample of brain tumor patients. The scores on the existential subscale of the McGill Quality of Life questionnaire were comparable to those of a reference sample of cancer patients receiving ongoing care (mean score 7.2; SD 1.7). Fifty per cent of the sample could be classified as struggling with existential issues. Although scores reflecting depression, fatigue, emotional distress, and existential problems were interrelated, the presence of depressive symptoms was the single most important independent predictor of QOL in this cohort of brain tumor patients. Implications for treatment are discussed.

Introduction

Malignant brain tumors usually result in devastating morbidity for those affected and for their families and typically result in death of the patient within a few years or less [1–3]. For example, even with aggressive radiation and chemotherapy regimens, the median survival for patients with grade 4 astrocytoma (glioblastoma multiforme or GBM) is about 12 months, and for grade 3 gliomas it is about 36 months [4]. Malignant gliomas are considered incurable; less than 2% of GBM patients survive 3 years or more [5]. Further, the treatment itself is often toxic and can result in considerable morbidity. Since treatment regimens have significant toxicities and long-term survival is rare, the quality of life of brain cancer patients is often limited. A better

understanding of the emotional distress experienced by brain tumor patients could lead to more effective interventions, thereby enhancing the ability of patients and families to cope with the illness and enjoy a better quality of life (QOL).

Neuropsychiatric problems in brain tumor patients can arise from the disease process itself, which usually causes focal neurological damage and from radiation therapy and chemotherapy which can cause more diffuse damage [6]. High dose corticosteroids used to control neurologic symptoms in this population also can result in sequelae such as labile affect and behavioral changes. Cognitive changes and negative mood states associated with disease or treatment related neurologic dysfunction are amplified by comorbid psychosocial problems such as reactive

depression, job loss, financial difficulties, and marital strife. Frequently reported neuropsychiatric problems in brain tumor patients include delirium, dementia, depression, anxiety, fatigue, somnolence and disinhibition disorders including restlessness, mania, and aggression [2,7,8].

Disinhibition disorders or marked cognitive impairment are often clinically identifiable and when appropriate, can be at least partially responsive to a variety of medications such as neuroleptics. However, the prevalence and impact of problems such as depression, fatigue, emotional distress, and existential issues are not fully delineated in the brain tumor population. Possibly because of variations in study methodologies and populations, estimates of the prevalence of depression and other forms of emotional distress in brain tumor patient populations vary from 7.9% to 39% [9–12].

Somnolence and fatigue are also described as being common in brain cancer patients. Detailed observations of 19 brain tumor patients led Faithful and Brada [13] to the identification of a somnolence syndrome that follows treatment. Sixteen of the 19 subjects reported symptoms such as excessive drowsiness, lethargy, being mentally slow, difficulties in concentration, and perceived clumsiness. While some questionnaire-based studies identify fatigue as prevalent following chemotherapy or radiation therapy [14–16], others using a reliable measure of fatigue in a study of patients with low-grade glioma, did not find a difference in levels of fatigue between the patients and the ‘normal population’ [17].

Although the existential dimension of brain tumor patients’ distress has not been well studied, there is evidence that existential or spiritual issues are important to cancer patients. Cohen and her collaborators [18,19] have shown that the Existential subscale of the McGill Quality of Life Questionnaire (MQOL) was the only subscale correlating significantly with a single item rating of QOL in palliative patients. Indeed, Brady et al. [20] found that spirituality as measured by the functional assessment of chronic illness therapy-spirituality (FACIT-Sp) correlated with general QOL to the same extent as physical well-being. The significant association between spirituality and general QOL was independent of other possibly confounding variables, and patients who scored higher on spiritual well-being also were more likely to enjoy life in spite of the presence of various symptoms. Holland et al. [21], in a study of religious and spiritual beliefs in melanoma patients, found that their measure of spirituality correlated with

neither QOL nor emotional distress. However, they did document that melanoma patients who relied more extensively on religious and spiritual beliefs also had a more active coping style. Other research [22–24] showed an association among the extent of religious practice, existential distress, and negative mood states in cancer patients.

In summary, there is evidence that fatigue and depression are prevalent clinically important issues in patients with brain tumors. Existential and spiritual well-being are additional domains that contribute to QOL, and could positively or negatively impact emotional distress experienced by brain tumor patients. However, published reports vary widely in the conceptualization and measurement of problems such as depression, fatigue, and spirituality and existential distress. Also, the clinical relationships among fatigue, depression, existential issues, and QOL in brain tumor patients is still poorly understood.

Thus, the purpose of the current study was to examine: (1) the prevalence of depression, fatigue, emotional distress, and existential issues in brain tumor patients; (2) the interconnectedness of these problems; and (3) the relationship between these problems and demographic variables, disease-related variables, and a measure of QOL.

Methods

Ethics

The study protocol received scientific and ethical approval from the Department of Medical Bioethics at the University of Calgary and the Tom Baker Cancer Centre Research Advisory Committee. The research assistants explained the study to all potential participants, who were given the opportunity to ask questions before signing a consent form.

Procedure

This is a cross-sectional, questionnaire-based survey of patients with primary brain tumors who presented to a brain tumor clinic for ongoing care. Seventy-three patients were asked to participate. The clinical characteristics of the patients (including pathologic diagnosis, location of the lesion, hemispheric side, type of treatment, and length of survival from diagnosis) were obtained by chart review. Patients’ social and demographic data were collected by questionnaire.

The participants were asked by a research assistant to complete the questionnaire package that also included:

The Functional Assessment of Cancer Therapy-Brain (FACT-BR) [25]. The FACT-BR is a modular instrument that measures health-related QOL in brain tumor patients. It is composed of a core instrument, the FACT-G, which measures general QOL, and a disease-specific subscale focusing on QOL issues affecting brain tumor patients. In total, the instrument is comprised of 58 questions and yields a total of 8 scores: five subscale scores, a QOL score, a score for the brain cancer module, and a total FACT-BR score. The FACT-BR has good psychometric properties, including good internal consistency (Cronbach's alpha ranges from 0.66 to 0.84 for all subscales), adequate test-retest reliability (ranging from 0.23 to 0.83 for the entire questionnaire and the subscales), and adequate convergent and divergent validity.

The Beck Depression Inventory-II (BDI-II) [26]. The BDI-II is a 21-item self-report questionnaire for measuring the severity of depressive symptoms in adults. The questionnaire was developed to assess symptoms corresponding to diagnostic criteria for depressive disorders listed in the DSM-IV. This questionnaire is a revised and updated version of the Beck Depression Inventory (BDI), which was widely accepted as one of the best screening instruments for depression in both clinical work and in research. The first version of the BDI has been used previously in research with brain tumor patients [11]. The BDI-II has very good internal consistency (Cronbach's alpha = 0.92) and test-retest reliability (0.93), in addition to having well documented content and construct validity. A recent study demonstrated the validity and the usefulness of the BDI-II in the detection of depression in primary care medical patients [27].

The existential well-being subscale of the McGill Quality of Life Questionnaire (MQOL) [18,19,28]. This 7-item subscale is part of the MQOL, a multi-dimensional QOL questionnaire designed for use at all phases of the disease trajectory in patients with life-threatening diseases. The subscale items focus on patients' ability to find meaning in existence, achieve goals, and find life worthwhile. The MQOL has been applied in patients with advanced cancer [29] and in patients with HIV [30]. The internal consistency of the MQOL ranges from 0.81 to 0.91, and the internal

consistency of the existential subscale specifically ranges from 0.75 to 0.82 under various circumstances [28]. The existential subscale has also been found to have adequate test-retest reliability (intraclass coefficient of 0.76) [28] and good convergent and divergent validity [19].

We used question 1 from the FACT-BR and questions 15 and 20 of the BDI-II to measure low energy and fatigue, and the total score of the emotional well-being subscale of the FACT-BR as a measure of general emotional distress. Participants were also surveyed regarding their preferences concerning their control over their medical treatment using a validated scale recently developed in Canada [31]. Finally, the participants were asked to answer four questions on their use of complementary therapies that were similar to those used in a previous study in this clinic [32]. Results concerning the last two subjects will be part of a different communication.

Results

Sample characteristics

Seven patients declined to participate in the study and three had to be excluded because of spoiled records or wrong diagnosis. We further excluded three patients who were more than 10 years since initial diagnosis as the long-term survivor group was small and we thought it to be an unrepresentative group. Thus, 60 participants constituted the final sample for this study. Table 1 presents the demographic and disease profile of the 60 study participants. Most were 6 months or longer since the diagnosis of brain tumor and had been extensively treated with radiation therapy, chemotherapy, or a combination of both.

Prevalence of depression, quality of life, emotional distress, fatigue, and existential tension

Scores for depressive symptoms, QOL, emotional distress, fatigue, and existential tension revealed a substantial burden of distress and related symptoms in that sample (Table 2). The average BDI-II score was 11.1 (SD = 7.4), which is relatively low. More importantly, we noted that 38% of the sample attained a score of 14 or more, indicating the presence of at least mild depressive symptoms in those participants.

The FACT-BR, which we used to measure general QOL and emotional distress in this study, does

Table 1. Demographic and medical characteristics of sample ($N = 60$)

Characteristics	Mean	SD
Age (yrs)	41.1	10.5
	<i>N</i>	%
Gender		
Male	31	51.7
Female	29	48.3
Education		
Less than high school	3	5.0
High school graduate	9	15.0
Some post-secondary	48	80.0
Married	40	66.7
Employed	16	26.7
Pathologic diagnosis		
Malignant glioma	34	56.7
Low-grade glioma	18	30.0
Meningioma	4	6.7
Others	4	6.7
Time from diagnosis to test (in months)		
0–5	20	33.3
6–12	7	11.7
12–23	8	13.3
24–60	19	31.7
60+	6	10.0
Number of surgeries		
None	6	10
One	49	81.7
Two	5	8.3
Adjuvant treatment		
Radiation only	29	48.3
Chemotherapy only	2	3.3
Radiation and chemotherapy	12	20.0
No radiation or chemotherapy	17	28.3

Table 2. Self-reported ratings of emotional distress, fatigue, use of alternative therapies, depression, and existential tension

Variable	Measure	<i>N</i>	Mean (SD)
Depressive symptoms	BDI-II	58	11.1 (7.4)
Emotional distress	Emotional subscale of FACT-BR	59	15.6 (3.22)
QOL	Total score of FACT-BR	60	136.3 (26.7)
Fatigue	#1 FACT-BR	60	2.0 (1.2)
	#15 + #20 of BDI-II	58	2.1 (1.4)
Existential tension	Existential subscale of MQOL	60	7.2 (1.7)

not have clinical cutoffs. Overall, the results obtained by the patients in this study do not differ significantly from those obtained by FACT-BR normative sample [25] or from the scores obtained by the normative sample for the FACT-G [33] (none of the *t*-tests were

Table 3. Mean and FACT-G total scores and emotional well-being scores for the study participants compared to patients in the FACT-BR and FACT-G standardization from samples

	This study; <i>n</i> = 60	FACT-BR standardization sample [25]; <i>n</i> = 101	FACT-G Standardization sample [33]; <i>n</i> = 466
FACT-G Total score	83.98 (14.56)	86.97 (17.34)	82.06 (15.86)
Emotional well-being subscale score	15.64 (3.22)	5.96 (4.38)	14.82 (3.8)

significant) (Table 3). On average, the participants in this study reported approximately 70% of the maximum QOL scores that could have been reported on the questionnaire.

Similarly, the maximum possible score for the combined BDI-II questions on fatigue (questions 15 and 20) is 6. Since higher scores on the BDI-II indicate more problems with depressive symptoms, a higher score on these two questions is indicative of greater fatigue. The average score on these questions was 2.0 ($SD = 1.2$). The average score on question 1 of the FACT-BR (lack of energy) was 2.0 ($SD = 1.4$) out of a possible score of 4, with lower scores indicating less energy. Twenty-five (42%) of the participants reported a score of 0 or 1 on question 1 of the FACT-BR, indicating that they felt that their energy was ‘quite a bit low’ or ‘very low’.

The average score on the existential well-being subscale of the MQOL was 7.2 ($SD = 1.7$). Cohen and Mount [28] recently provided normative data for the MQOL by comparing cancer patients in an oncology day centre (rather similar to our ambulatory brain tumor patient cohort) with cancer patients in a palliative care setting. These two groups of patients were asked to complete the MQOL on days they judged to be ‘good’, ‘average’, or ‘bad’. Within the oncology day center sample, patients scored an average of 6.4 on the existential subscale on ‘bad days’, 7.3 on ‘average days’, and 8.2 on ‘good days’. We interpret these data to mean that ambulatory patients who scored 6.4 or less on the existential scale of the MQOL are experiencing moderate or worse existential distress, those who scored between 6.4 and 7.3 (worse than an ‘average’ day) as experiencing discomfort surrounding existential issues, and patients who score 7.3 or more as doing well in the existential domain. By these criteria, 25% of

our ambulatory brain tumor patient study sample were experiencing moderate or worse existential distress at the time of the survey, a further 25% were experiencing some existential problems, and the remainder 50% were apparently doing well.

Contingency analyses

Symptoms of depression, fatigue, emotional distress, and existential concerns correlated significantly with each other, with the exception of emotional distress and fatigue, which were not correlated (Table 4). Among demographic and disease-related variables, patient employment status was strongly related to depression ($r = 300, p = 0.022$), fatigue ($r = 306, p = 0.020$) and existential tension ($r = -308, p = 0.017$). Also, emotional distress as measured by the FACT-BR apparently increased with the length of survival (time since diagnosis) ($r = 0.276, p = 0.034$). Depressive symptoms, fatigue, and existential tension did not correlate

with the length of survival. No other demographic or disease/treatment related variables correlated with the psychosocial indicators chosen for this study.

Hierarchical regression analysis of quality of life

A hierarchical regression was conducted to determine if addition of fatigue or emotional distress variables improved prediction about levels of QOL, independent of depressive symptoms. Depressive symptoms as measured by the BDI-II were the strongest predictors of QOL in our sample. Fatigue and emotional distress were not independent contributors to overall QOL (Table 5).

Discussion

The purpose of this study was to investigate the prevalence of depression, fatigue, emotional distress, and

Table 4. The correlation between age, gender, marital status, employment status, time since diagnosis and depression, existential tension and emotional distress

	Age	Gender	Marital status	Employment	Time since diagnosis
Depression (BDI-II total score)	$r = 0.117$ $p = 0.381$ $N = 58$	$r = 0.044$ $p = 0.745$ $N = 58$	$r = 0.092$ $p = 0.494$ $N = 58$	$r = 0.300$ $p = 0.022^*$ $N = 58$	$r = -0.183$ $p = 0.168$ $N = 58$
Fatigue (BDI-II #15 & 20)	$r = 0.099$ $p = 0.461$ $N = 58$	$r = 0.021$ $p = 0.874$ $N = 58$	$r = 0.062$ $p = 0.643$ $N = 58$	$r = 0.306$ $p = 0.020^*$ $N = 58$	$r = -0.208$ $p = 0.118$ $N = 58$
Existential tension (MQOL total score)	$r = -0.004$ $p = 0.975$ $N = 60$	$r = 0.073$ $p = 0.580$ $N = 60$	$r = -0.166$ $p = 0.205$ $N = 60$	$r = -0.308$ $p = 0.017^*$ $N = 60$	$r = 0.180$ $p = 0.169$ $N = 60$
Emotional distress (FACT-BRR)	$r = -0.136$ $p = 0.303$ $N = 59$	$r = -0.238$ $p = 0.297$ $N = 59$	$r = -0.035$ $p = 0.792$ $N = 59$	$r = -0.236$ $p = 0.072$ $N = 59$	$r = -0.276$ $p = 0.034^*$ $N = 59$

* $p < 0.05$.

Table 5. Hierarchical regression of depression, fatigue, and emotional distress on QOL

Variables	QOL (DV)	Depression	Fatigue	Emotional distress	B	B	sr2 (Incremental)
Depression	-0.73				-0.73	-2.6	0.54**
Fatigue	-0.62	-0.63			0.27	6.0	0.04**
Emotional distress	0.42	-0.63	0.23		0.30	2.6	0.03**
Means	136.3	11.1	5.0	15.6			
SD	26.7	7.4	2.1	3.2			
$R^2 = 0.63$							
Adjusted $R^2 = 0.61$							
$R = 0.80^{**}$							

* $p < 0.01$.

existential tension in patients with brain tumor. We also wanted to identify the correlation between these problems and their influence on overall QOL, with a view to finding treatable symptoms that could potentially impact on QOL. Based on our results, further research should be designed to directly test the hypothesis that QOL can be improved in brain tumor patients by therapeutic interventions for depression, fatigue, emotional distress, or existential tension.

The prevalence of depression, emotional distress, fatigue, and existential tension

Almost 40% of participants had clinically significant symptoms of depression, similar to or higher than the prevalence found in brain tumor patients by other investigators. Comparatively, the point prevalence rate for depression in the general adult population is approximately 6% [34]; 15–30% of individuals with major medical conditions develop a depressive disorder at some time during the course of their physical illness [34,35], and an estimated 6–15% of cancer patients can be expected to experience some level of depression [36]. Thus, the results of this study affirm that depressive symptoms are a prevalent and serious clinical issue for brain tumor patients. The high prevalence of clinically significant symptoms of depression in brain tumor patients may be due to the complexity of the journey they must endure: a sense of hopelessness and loss that may accompany a diagnosis of brain tumor (especially given the generally poor prognoses); the worry about existential issues (i.e., trying to find meaning in a life-threatening situation); the decrease in levels of social and occupational functioning; symptoms of the illness that may mimic or exacerbate depression symptoms (e.g., fatigue, cognitive problems); and lastly, side effects of treatment regimens for brain tumors, including chemotherapy, radiation therapy, and other interventions [37–39].

The emotional well-being scores and, generally speaking, the FACT-BR general and subscale scores are more difficult to interpret because of the absence of clinical cutoff scores. However, the study shows that at the time of the survey, this sample of brain tumor patients enjoyed on average as good a general QOL as another sample of brain tumor patients and as a sample of cancer patients with a mix of diagnoses. They also enjoyed a very similar level of emotional well-being.

The levels of fatigue reported by study participants were considerable, with the average score indicating

that many participants endorsed the following BDI-II items: ‘I don’t have enough energy to do very much’ and ‘I am too tired or fatigued to do a lot of the things I used to do’. It is difficult to predict the main causes of fatigue because there were several contributing factors for fatigue in the study sample, including medical (effects of the illness and treatment, other co-morbid physical disorders) [37], psychological (depression and existential) and other factors.

Lastly, existential tension was a problem for 25% of our sample, and it was probably a source of difficulties for 50% of our sample. This result points to the immense stress experienced by patients with brain tumor who try to make sense of, and find meaning in their present life situation. This very human component of suffering is one that has often been neglected but we postulate could be an area of therapeutic activity to improve QOL in brain tumor patients.

Correlations between depression, fatigue, emotional distress, and existential tension

With the exception of emotional distress and fatigue, depressive symptoms, fatigue, emotional distress, and existential tension were all significantly correlated with each other. Perhaps the most striking finding was that depressive symptomatology was so strongly correlated with all of these other measures. It is also interesting that in this sample, a significant relationship could not be found between depressive symptoms and pathological diagnosis, the location of the tumor, or the type of treatment. One interpretation for these results is that depressive symptoms, as measured by the BDI-II, do not constitute an isolated construct but instead are a response to impaired physical, psychological or social functions that are themselves affected by medical conditions (e.g., changes in appetite, sleep, energy levels, sociability). A second possibility is that biological depression is, in fact, highly prevalent as a primary event in brain tumor patients and that impaired physical, psychological or social functions are made worse by it. In either case, impairment in all these domains is prevalent in brain tumor patients and because of it, QOL is often poor.

Quality of life: prevalence and correlations

Detailed analyses of QOL scores were difficult to interpret because clinical cutoffs have not been well established for some of these scales. Nonetheless,

QOL scores were highly correlated with depressive symptomatology, fatigue, emotional distress, and existential tension. All measures of compromised psychological and emotional functioning were correlated with QOL. Moreover, in regression analyses depression scores alone accounted for more than half of all variance in QOL scores. We conclude from these findings that impaired QOL is often of paramount importance to patients and that depressive symptomatology, although itself complex, is among the largest single contributing factor to poor QOL.

Improving quality of life in brain tumor patients

The clinical implications of this study are clear: QOL is often poor in brain tumor patients, and could potentially be improved if depression can be identified and managed. According to our preliminary results, it appears that the presence of depression should be investigated in every brain tumor patient, and if it is identified, it should be treated as early as possible.

Depression may be closely correlated with fatigue, emotional distress, and unaddressed existential issues, and specific interventions for each of these problems are often readily available. Antidepressant medications and psychotherapy (particularly cognitive behavior therapy) have been shown to be of comparable effectiveness in the treatment of major depression, although the studies available so far have been conducted mostly with populations from which major depression with psychotic features or problematic medical conditions were excluded [40–42]. Our knowledge of the effectiveness of psychotherapy for depression in brain tumor patients or other neurologically impaired populations remains limited, but cognitive behavior therapy has been identified as worthy of additional investigation [43,44]. Also, participation in support groups whenever possible may be helpful for many patients and their partners [43,45]. Although for many brain tumor patients, treating depression with psychotherapy may present a welcome relief from the use of medications, those who also experience significant fatigue or who may have limitations preventing them from benefiting from psychotherapy may do better with antidepressant medication or with psychostimulants such as methylphenidate [46,47]. Similarly, brain tumor patients may benefit from recently developed pastoral or psychotherapeutic interventions designed to help people come to terms with existential and spiritual concerns [48,49].

Strengths, limitations, and future research

This is one of only a few studies that investigated the prevalence and intercorrelation of important psychosocial problems (depression, emotional distress, fatigue, existential tension) and QOL in brain tumor patients. It is also one of relatively few studies which looks at existential issues experienced by cancer patients in active treatment, and specifically by brain tumor patients. This is important because of the relatively high prevalence of existential tension in this population, and its correlation with QOL. The significance of our findings can be summed up by Aiken's [50] statement that 'quality of life is an important concern to patients, possibly more important than the [cancer] treatment'.

There are several limitations to this study. First, this study was based on a cross-sectional design and conducted with a relatively small, heterogeneous sample of brain tumor patients. Consequently, this study is limited in terms of the specificity of the findings and provides only limited information as to how the psychosocial status of brain tumor patients might evolve over time. Second, the use of a more specific measure of fatigue would have allowed for a more detailed evaluation of this problem. Finally, many of the measures we used did not have clinical cutoffs, which would have facilitated clinical interpretation of the extent of psychosocial problems for this population.

More research is needed to acquire a better understanding of the correlates of depression and existential tension in brain tumor patients, with the view of arriving eventually at treatments that could be more specifically tailored for this population. Other QOL issues, such as sense of control over treatment, the use of alternative/complementary therapies, and the relationship between the QOL of caregivers and the QOL of patients need to be explored. Finally, it is becoming increasingly obvious that the assessment and treatment of patients' psychosocial issues such as emotional distress, fatigue, and existential problems need to be integrated to the medical treatment in order to provide optimum care to brain tumor patients.

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