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ORIGINAL PAPER

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Decreased quality of life and depression as predictors for shorter survival among patients with low-grade gliomas: a follow-up from 1990 to 2003

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Abstract *Objectives* To assess the long-term survival of brain tumor patients, and in particular to evaluate the relation of quality of life (QOL) to survival among low-grade glioma patients. *Methods* The postoperative survival of 101 brain tumor patients was followed from surgery (1990–1992) until the end of the year 2003. Depression was evaluated by the Beck Depression Inventory (BDI) and QOL with Sintonen's 15D scale before operation and at one year as well as at five years after operation. *Results* The mean survival times in years (SD) were significantly related to tumor malignancy, being the shortest, 1.9 (0.6), for patients with high-grade gliomas, while patients with low-grade gliomas or a benign brain tumor had mean survival times of 9.1 (1.0) and 11.6 (0.5), respectively. At all follow-ups, depressed low-grade glioma patients had a significantly shorter survival time, 3.3–5.8 years, compared to non-depressed low-grade glioma patients, 10.0–11.7 years. A decreased level of QOL in low-grade glioma patients was significantly related to the shorter survival. *Conclusions* The results suggest that depression and decreased QOL among low-grade glioma patients is related to shorter survival at long-term follow-up. Decreased QOL may serve as an indicator for poor prognosis in low-grade glioma patients.

Key words brain tumor · low-grade glioma · survival · depression · quality of life

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Introduction

Man is a complex entity in which the central nervous system, peripheral nerves, the endocrine and the immune system are in continuous and multifarious interconnection with each other [1]. Recent studies of psychoneuroimmunology have shown an accumulating literature concerning the existence of reciprocal communication pathways between nervous, endocrine and immune systems [2–4]. Both stress and depression have been associated with impaired immune function and increased susceptibility of the patient to infectious diseases and cancer. Such dysfunctions as hyperactivity of the hypothalamic-pituitary-adrenal axis, hypersecretion of proinflammatory cytokines and changes in the amount of lymphocytes have been documented to be common for depression and cancer [1, 5–8].

Preoperative depression among brain tumor patients seems to serve as a significant prognostic factor for worse survival among glioblastoma patients [9] and among low-grade glioma patients [10]. In literature, controversial findings of the relation between QOL and survival among cancer patients have been reported [11, 12]. However, as was recently reported by Giovagnoli et al. [13], the overall QOL level of patients with recurrent high-grade glioma is poorer than that of the patients with stable disease.

The aim of the study was to evaluate whether depression is associated with survival among brain tumor patients up to over 10 years after tumor sur-

gery. Secondly, among malignant tumors special attention was given to low-grade glioma patients due to their relatively favorable prognosis after tumor operation. We explore whether the level of QOL among low-grade glioma patients can serve as an estimate of survival time of the patients.

Material and methods

Patients

The study population consisted of 101 patients, 39 males and 62 females, with a solitary primary brain tumor treated surgically at the Clinic for Neurosurgery, Oulu University Hospital, between February 1990 and March 1992, who were followed according to their survival status up to 2003. The mean (SD) age for males was 49.4 (12.9) years and for females 48.8 (13.7) years. The database has been fully documented earlier [14]. Epidemiologically the cohort is a comprehensive and unselected sample of population because the Oulu Clinic for Neurosurgery performs all resections of brain tumors in its catchment area. Geographically this area covers about 49% of Finland.

Tumor characteristics

The radiological diagnosis of the brain tumor was carried out by computer tomography (CT) or magnetic resonance imaging (MRI). There were 34 (35%) patients with the tumor located in the right hemisphere and 45 (46%) patients with the tumor located in the left hemisphere. The tumor was sited bilaterally in 14 (14%) patients, and the location of the tumor was undefined in 4 (4%) cases. Brain CT or MRI was not available in 4 (4%) patients, excluding them from further study. Histological grading was done according to the WHO classification [15]. Tumors were divided into the following classes: grade I–II gliomas (9 males, 10 females), grade III–IV gliomas (14 males, 8 females), meningiomas (7 males, 26 females), pituitary adenomas (5 males, 3 females), acoustic neurinomas (4 males, 9 females) and 6 other tumors (two hemangiopericytomas, malignant lymphoma, craniopharyngeoma and two undefined tumors, all females).

Since central tumor location or tumor expanding into the two hemispheres has in earlier literature been identified as risk factors for shorter survival [16], we categorized the tumors in our study as 1. bilateral tumors, if they located in central regions or reached the two hemispheres (n = 11, 14.3%) and 2. hemispheric tumors (n = 66, 85.7%) if they located only in the left or right hemisphere.

Definition of depression

The patients' depressive symptoms were evaluated by the Beck Depression Inventory (BDI) before they were aware of the histological diagnosis of the tumor and at three months and at one year after tumor operation by a trained psychologist. The depressive status was available in 77 of the patients. BDI is widely accepted as a screening instrument for depressive symptoms corresponding to diagnostic criteria for depressive disorders followed by DSM-IV [17]. Depressive disorder was defined if BDI scores were 10 or higher.

Definition of quality of life (QOL)

The patients' QOL was assessed by Sintonen's 15D scale before tumor operation and at one year after the operation by a physician. The assessment of QOL was determined by sending a questionnaire by mail at five years after operation. Sintonen's 15D scale is a generic, comprehensive, 15-dimensional, standardized, self-administered measure of health-related QOL [18]. It is possible to obtain a sumscore of different dimensions ranging from 0 to 1. The value "0" means that the person has died, and "1" means good QOL of a completely healthy person.

Fig. 1 Survival estimates for survival time after brain tumor operation from 1992 to the end of 2003 among patients with high-grade (III–IV) and low-grade (I–II) gliomas and in patients suffering from benign tumors

Assessment of survival

The survival status and time of each patient was calculated from the date of surgery to the time of death or to the end of the follow-up at the end of the year 2003. The information on the survival (gross survival) was obtained from the Cause of Death Register, provided by Statistics Finland.

Statistical methods

Group differences in continuous variables were tested with Student's t-test, Mann–Whitney U-test and Kruskall–Wallis test. Differences in survival estimates between histological subgroups were tested by Kaplan-Meier (Log rank test). Cox regression model was used to estimate survival curves of different histological groups after controlled for age, gender and tumor laterality. All statistical analyses were performed by using the SPSS statistical software, version 11, and the results in this study were considered statistically significant when the appropriately calculated two-tailed P-value was <0.05.

Results

Figure 1 shows survival curves of the patients with a primary brain tumor. At the end of the follow-up 95.5 % of the patients with a grade III–IV glioma, 63.2 % of the patients with a grade I–II glioma and 23.3% of the patients with a benign brain tumor had died. The corresponding mean survival times in years (SD) were

Table 1 Number (%) of deceased subjects and their survival time after operation among depressive and non-depressive brain tumor patients in each histological group and follow-ups in survival time after tumor operation

Patient's histological group and depression in follow-ups*	Depressive patients		Non-depressive patients		Difference in survival time between depressive and non-depressive patients **
	No. (%) of deaths/ Total N	Survival time (years) after operation Mean (SE)	No. (%) of deaths/ Total N	Survival time (years) after operation Mean (SE)	*P*-value
High-grade gliomas					
Before operation (n = 15)	6/7 (85.7)	3.1 (1.6)	8/8 (100)	2.2 (0.8)	0.746
3 months after operation (n = 11)	4/5 (80.0)	3.9 (2.1)	6/6 (100)	3.0 (1.1)	0.769
12 months after operation (n = 6)	1/1 (100)	2.3 (–)	4/5 (80.0)	6.1 (1.8)	0.247
Low-grade gliomas					
Before operation (n = 16)	5/6 (83.3)	5.8 (1.8)	4/10 (40.0)	11.7 (0.9)	0.021
3 months after operation (n = 18)	2/2 (100)	3.3 (0.4)	9/16 (56.3)	10.4 (0.9)	0.001
12 months after operation (n = 16)	3/3 (100)	5.2 (0.1)	8/13 (61.5)	10.0 (1.1)	0.018
Bening tumors					
Before operation (n = 46)	2/14 (14.3)	12.1 (0.9)	4/32 (12.5)	12.6 (0.5)	0.871
3 months after operation (n = 52)	1/15 (6.7)	13.4 (0.3)	6/37 (16.2)	12.5 (0.5)	0.355
12 months after operation (n = 53)	3/13 (23.1)	12.2 (0.8)	5/40 (12.5)	12.7 (0.5)	0.392

* The number of cases in patient groups varies due to lack of information on the depression status at different measurement points

** Difference in survival estimates between depressed and non-depressed patients was assessed with the long-rank test using the Kaplan–Meier survival analysis controlled for the age and gender of the patients as well as the laterality of the tumors.

1.9 (0.6), 9.1 (1.0) and 11.6 (0.5), ($P < 0.001$, log-rank = 85.0, df = 2 Kaplan–Meier survival analysis).

The total number of deceased patients at the end of the follow-up was 48 (47.5%), 24 of whom (50%) were males and 24 (50%) females. The mean (SD) age in years at time of death among the deceased subjects was 54.5 (11.0) for males and 55.7 (17) for females, ($P = 0.779$, df = 45, t-test). The cause of death diagnosis was related to brain tumor in 81% of the patients, while 13% of the patients had died from cardiac disease and 6% from other somatic diseases. One patient had committed suicide.

As seen in Table 1, after controlling for age, gender and tumor laterality, the depressed low-grade glioma patients had statistically significantly shorter survival time compared to non-depressed low-grade glioma patients. A corresponding difference was not seen among the patients with a high-grade glioma or a benign brain tumor (meningiomas, acoustic neurinoma or pituitary adenoma).

Table 2 presents the case description of each low-grade glioma patient and the level of QOL in relation to their survival. The mean (SD) age in years before operation did not differ between the study groups, being 44.1 (15.2) among patients who survived less than five years, 39.9 (8.3) for the patients who survived up to ten years, and 35.0 (11.0) for those still alive at the end of the follow-up, ($P = 0.636$ df = 2, Kruskall–Wallis test).

Figure 2 shows that the better the level of QOL of the patients, the longer their survival during the following five-year period.

Discussion

In the present study, long-term postoperative survival of the brain tumor patients was studied. It has been documented earlier that outcome in brain tumor patients depends most on tumor type [16, 19, 20]. The most aggressive and common primary brain tumor is glioblastoma multiforme; survival time is reported to vary from less than one year to three years after initial diagnosis of tumor, and patients usually have tumor recurrence, often within a year after completion of first-line therapy [19, 20]. In all glioma patients the 5-year survival is found to be from 20% to 34% [21, 22], while in patients with grade I and II gliomas 5-year survival is 38%–45% [16]. Recently, Claus and Black (2006) reported that the long-term clinical course of low-grade glioma patients might be favorable among patients with female gender, younger age, white race, better histology and later year of diagnosis. In the best conditions the 5-year survival has been shown to be up to 59.9%, and correspondingly, the 20-year survival up to 26.0 % [23]. The 5-year survival rate for meningioma patients lies at 69–91%, declining with patient's age to 56% for patients 65 years of

Table 2 The case series of low-grade glioma patients according to age, gender, survival time, and their level of quality of life at the follow-ups before and after tumor operation

The patients (n = 19) with a low-grade glioma					
Gender	Age (years) before operation	Survival time in months	Sintonen 15 D before operation	Sintonen 15 D at one year after operation	Sintonen 15 D at five years after operation
Patients surviving up to five years after operation					
female	27	<1	0.85	–	
male	56	5	0.81	–	
male	67	31	0.85	0.95	
female	32	35	0.78	0.90	
male	46	45	0.81	0.77	
female	37	58	0.64	0.74	
Patients surviving five to ten years after operation					
female	31	77	0.87	0.84	0.68
female	41	86	0.95	0.87	0.90
male	53	98	0.96	0.90	0.70
female	40	114	0.98	1.00	0.91
male	32	120	0.94	0.98	0.95
female	48	130	0.95	1.00	0.89
male	34	135	0.93	0.94	0.88
Patients surviving up to ten years follow-up					
male	20		0.82	0.98	1.00
female	23		0.93	0.90	0.88
female	36		0.97	0.98	0.98
male	42		0.95	0.92	0.95
female	43		0.85	0.98	0.95
male	46		0.92	0.98	0.93

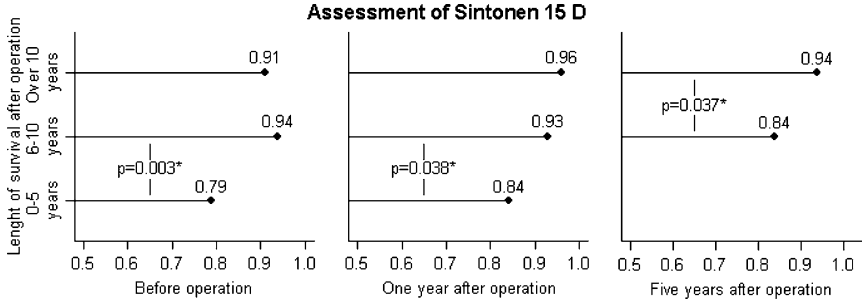

Fig. 2 The mean levels of quality of life among patients with a low-grade glioma at three follow-ups according to their survival times. *Mann–Whitney *U*-test

age and older [24, 25]. The follow-up over ten years in the present study was in line with earlier studies. The larger proportion of females who survived in this study is suggested to be due to the major proportion of female patients in the subgroups of meningiomas and acoustic neurinomas.

The present study confirms our earlier findings that depression has a long-term effect on survival among the patients with a low-grade glioma [10]. However, there are other studies in which depression has had no significant association with cancer survival [26, 27]. From a psychological perspective there is a popular belief that a depressive person with cancer may concede and "give" his life to cancer. In a recent study, there was some evidence suggesting that among breast cancer patients such psychological responses as being helpless/hopeless after primary diagnosis were related to adverse impact on disease-free survival [27].

However, it has been proposed that depression is not only a psychological reaction to the cancer, but that the association between these disorders has biochemical roots [4, 6]. The pathophysiology behind the patients' depression in relation to cancer is in any case most probably multifactorial in its origin. Dysregulation of the hypothalamic-pituitary-adrenal axis and changes in cytokine levels in the brain may lie behind the association between depression and cancer [2, 4]. Further, depression in cancer patients complicates coping with the disease, hampering their everyday life and adherence to medical treatment [4]. The prognosis among cancer patients may worsen particularly due to depression, since depression often prevents patients from complying with treatment regimens and other health-promoting behaviors.

Earlier studies among depressive cancer patients have reported that treatment of depression increased their survival [28–30]. However, in the study of

Litofsky et al. [9] treatment of depression did not have any impact on survival among high-grade glioma patients. Therefore, it is especially important to examine related–related depression in order to find the patients whose depression can be treated, as well as to find out what is the appropriate treatment of choice for depression in brain tumor patients. The right timing, type or duration of psychotherapeutic interventions as well as how the survival of brain tumor patients is affected by the treatment of depression are also issues worth studying.

In the present study we could also take into account the effect of QOL in the patients on their survival time. The multidimensional assessment of health-related QOL was in relation to survival among low-grade glioma patients in this study. The decreased level of QOL was positively correlated with shorter survival already during the five-year period before their death. Recently, Giovagnoli et al. [21] found a relation between poor QOL and recurrent high-grade glioma. In the prospective study of Brown et al significant declines were found between baseline QOL measurements and follow-up measurements among newly diagnosed high-grade glioma patients [31]. They also reported that decreased performance status was closely related to decreased level of QOL in the patients. Besides, it has been noticed that increased fatigue in high-grade glioma patients serves as an independent predictor for their overall poorer survival [32].

Small sample size was one of the reasons why we had to use a non-parametric approach when selecting statistical methods. Despite this, it is possible that some findings may appear statistically significant by chance. On the other hand, the possibility of a type II error to detect small differences cannot be excluded either. Although our study was underpowered, we believe that our findings are important and suggest a replication in larger databases.

Formerly, the level of QOL has been found to serve as a good estimate for survival among other cancer patients [11] and to indicate recurrence of disease among high-grade glioma patients [13]. The finding in our study that decreased QOL was associated with shorter survival among low-grade glioma patients is novel, and it is remarkable also due to the fact that assessment of QOL was performed using a questionnaire both by a trained physician and by mail at five year after the operation. The pattern of health-related QOL may serve as an easy and cost-effective indicator to recognize changes in the subjective condition of the patients, which is probably in relation to progression of their disease or their survival.

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