

# DEPRESSIVE AND ANXIOUS SYMPTOMATOLOGY IN RELATION TO A PRIMARY BRAIN TUMOR

Prospective study of neurosurgical patients in Northern Finland

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TO A PRIMARY BRAIN TUMOR**

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in Northern Finland

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# **Mainio, Arja, Depressive and anxious symptomatology in relation to a primary brain tumor. Prospective study of neurosurgical patients in Northern Finland**

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## ***Abstract***

The findings on depression and anxiety among brain tumor patients have so far been based on case series and case samples. In Finland, psychiatric research in relation to psychiatric symptoms among patients with different types of brain tumors is lacking.

The study population of this thesis consisted of 101 patients (39 males and 62 females) aged between 20 and 82 years with a solitary primary brain tumor treated surgically at the Oulu Clinic for Neurosurgery, Oulu University Hospital between February 1990 and March 1992. The major histological subgroup consisted of gliomas (40%), and the rest were meningiomas (33%), acoustic neurinomas (13%), pituitary adenomas (8%) and other types (6%).

The psychiatric symptoms of the patients were assessed at three time points, namely before tumor operation as well as at three months and at one year after operation by two valid measurement instruments, the Beck Depression Inventory and the Crown Crisp Experiential Index. In addition, the patients' functional state was evaluated by the Karnofsky Performance Scale and their quality of life according to Sintonen 15 D.

Prevalence of at least mild depression before tumor operation was 30% for males and 38% for females. The mean depressive scores decreased significantly for up to one-year during follow-up for both males and females, but they remained notably high in all patients. Decreased functional status (KPS under 70) in the patients was significantly associated with high depressive scores at all measurement points. The decrease in the mean depressive scores was significant among patients with an anterior tumor and those with a pituitary adenoma.

Five-year survival of the brain tumor patients was found to be mainly associated with the histology of the tumor. Survival time in months (SD) of the patients with high-grade (III–IV) gliomas was shown to be 22.5 (21.4), while it was 50.2 (19.9) for the patients with low-grade (I–II) gliomas, and 58.2 (9.4) for the rest of the patients. Depression among low-grade glioma patients was significantly associated with worse survival at five years follow-up.

The level of anxiety was shown to be significantly higher among patients with a primary brain tumor in the right hemisphere compared to the anxiety scores among patients with left hemispheric tumors. A significant increase was found in the level of obsessiveness over time in the female patients with a brain tumor in the left anterior location of the brain at three months after operation.

The level of quality of life (QOL) was significantly worse among female brain tumor patients compared to males. Depressive females had significantly lower quality of life compared to that of non-depressive females up to one-year follow-up after surgical operation of the tumor.

Depression, anxiety and obsessive-compulsive symptoms have to be recognized and be treated by psychotherapy and pharmacotherapy as soon as possible at every unit where brain tumor patients are followed and encountered.

*Keywords:* acoustic neurinoma, anxiety, depression, functional outcome, glioma, meningioma, obsessiveness, primary brain tumor, prospective study, quality of life, survival



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Oulu, April 2005

Arja Mainio

## Abbreviations

ABS	Affect Balance Scale
ACTH	Adenocorticotrophic hormone
AVP	Arginine vasopressin
BDI	Beck Depression Inventory
CCEI	Crown Crisp Experiential Index
CRH	Corticotropin releasing hormone
CT	Computer tomography
DEP	Depression subscale in CCEI
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECT	Electroconvulsive Therapy
FFA	Free Floating Anxiety subscale in CCEI
FLIC	Functional Living Index-Cancer
GABA	Gamma-aminobutyric acid
GM	Glioblastoma multiforme
HAD	Hospital Anxiety and Depression Scale
HDS	Hamilton Rating Scale for Depression
HPA	Hypothalamic-pituitary-adrenal
HYS	Hysteria subscale in CCEI
5-HT	5-hydroksytryptamine, serotonin
KPS	Karnofsky Performance Scale
MAOIs	Monoamine Oxidase inhibitors
MRI	Magnetic resonance imaging
NASSAs	Noradrenergic and specific serotonergic antidepressants
OBS	Obsessionality subscale in CCEI
OCD	Obsessive compulsive disorder
PET	Positron Emission Tomography
PHO	Phobic anxiety subscale in CCEI
POMS	Profile of Mood States
QOL	Quality of life
SRDS	Self-rating Depression Scale
SNRIs	Serotonin and noradrenaline reuptake inhibitors
SOM	Somatic anxiety subscale in CCEI

SSRIs Selective serotonin reuptake inhibitors  
STAI State-Trait Anxiety Inventory  
WHO World Health Organization

## **List of original publications**

The present thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-V.

- I Mainio A, Hakko H, Niemelä A, Tuurinkoski T, Koivukangas J, Räsänen P (2003) The effect of brain tumour laterality on anxiety levels among neurosurgical patients. *J Neurol Neurosurg Psychiatry* 74: 1278-1282.
- II Mainio A, Hakko H, Niemelä A, Salo J, Koivukangas J, Räsänen P The level of obsessionality among neurosurgical patients with a primary brain tumor. *J Neuropsychiatry Clin Neuroscien* (in press).
- III Mainio A, Hakko H, Niemelä A, Koivukangas J, Räsänen P Depression and functional outcome among brain tumor patients: A population based one year follow-up study (submitted for publication).
- IV Mainio A, Hakko H, Niemelä A, Koivukangas J, Räsänen P Depression in relation to survival among neurosurgical patients with a primary brain tumor: 5-years follow-up study. *Neurosurgery* (in press).
- V Mainio A, Hakko H, Niemelä A, Koivukangas J, Räsänen P Gender difference in relation to depression and quality of life among the patients with a primary brain tumor (submitted for publication).

In addition, some unpublished data have been included in this thesis.



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# 1 Introduction

Primary brain tumor has a great, often dramatic impact on the life of patients and their families (Lovely 1988, Passik *et al.* 1994, Salander *et al.* 1996). Brain tumor, being both a malignancy and a progressive neurodegenerative disease, has a direct effect on the patient's cognitive, neurologic and psychic functions, causing focal cerebral dysfunction at the site of the tumor lesion (Weitzner 1999). Besides, treatment of the tumor, i.e. surgery, radiotherapy, chemotherapy and immunotherapy, may be neurotoxic and cause dysfunction of the subcortical white matter (Scheibel *et al.* 1996).

Main literature in the field of neuropsychiatric symptoms in brain tumor patients has been based on individual case reports and retrospective case series (Weitzner 1999). Besides, studies focusing on psychiatric symptoms in brain tumor patients have been mainly descriptive and the numbers of cases in study populations have been small (Irle *et al.* 1994, Weitzner & Meyers 1997).

The factors suggested to be associated with psychiatric symptoms among brain tumor patients are tumor location, patient's premorbid psychiatric status, tumor-associated cognitive symptoms and adaptive or maladaptive response to stress, usually all in combination (Weitzner 1999). Although psychiatric symptoms are based on location of damage in the brain, psychiatric symptoms in brain tumor patients are different from those of patients with infarct, injury or infection in the brain (Kallio 1993). In stroke patients in whom psychiatric symptoms are more studied, destruction of neurons is seen, while in brain tumor patients deficits are mainly based on the more gradual displacement and plasticity of neuronal structures (Anderson *et al.* 1990, Irle *et al.* 1994). Psychiatric symptoms can be the first and only signs of primary brain tumor, and between 1% and 2% of patients with a psychiatric disorder may have unrecognized brain neoplasms (Price *et al.* 1992).

Quality of life (QOL) in brain tumor patients has not yet been extensively studied; the first studies were initiated as recently as in the 1990s (Aiken 1994, Weitzner *et al.* 1996, Lovely *et al.* 1998). Since many studies of QOL in brain tumor patients are either retrospective or cross-sectional in nature, the effects of tumor characteristics and treatment as well as patients' emotional and cognitive impairments are difficult to estimate over time (Weitzner & Meyers 1996).

In general, a human is a biopsychosocial entity in which psyche, soma and the social environment are in a subtle and complex interrelation between each other. The central nervous system is responsible for the regulation of this entity, and a brain tumor, causing brain dysfunction, has thus a direct, biological impact on all human functions (Weitzner

1999). Patients with a primary brain tumor can experience their disease in a more comprehensive way than indicated by their clinical symptoms due to the tumor (Fox 1998). This is because the serious illness causes a psychological reaction, a typical, individual response in each patient (Weitzner 1999), and malignancy per se causes dysregulation of the hypothalamic-pituitary-adrenal axis and changes in immune system (Spiegel 1996, Horrobin & Bennett 1999).

This study is part of an ongoing project in which quality of life among brain tumor patients is widely evaluated at the Neurosurgery Clinic of Oulu University. The project was initiated after a pilot study of Koivukangas & Koivukangas (1988) among low-grade glioma patients. Thus far, psychiatric research in relation to psychiatric symptoms in patients with different types of brain tumors has been lacking in Finland. The purpose of this study is to examine depressive and anxious symptomatology in relation to tumor characteristics and patients' psychosocial factors among brain tumor patients.

## 2 Review of the literature

Brain tumors comprise an important area in neurosurgery (Nyström 1988). Since patients with brain tumors have multifarious somatic and psychic symptoms, collaboration between units of neurosurgery, radiology, anesthesiology, neurology, oncology and psychiatry is inevitable in diagnostics and therapy (Nyström 1988, Kallio 1993, Peterson 2001).

Primary brain tumors are very different as to their clinical course and expected prognosis. According to their manner of growth they can be classified as extraparenchymal (compressive) and parenchymal (infiltrative) intracranial tumors. Some tumors are histologically benign, such as most meningiomas, acoustic neurinomas and pituitary adenomas, for which surgery is often curative (Peterson 2001). Although histologically benign and extraparenchymal, tumors can without treatment cause the death of the patient by general pressure effect or by local effect on vital brain functions (Kallio 1993). Others, such as grade III-IV gliomas are highly malignant and are very likely to cause death of the patient within a year from initial diagnosis (Peterson 2001). In addition, e.g. grade I pilocytic astrocytoma, although clinically benign, may grow in an infiltrative manner (Kallio 1993).

Despite the development of diagnostic and treatment procedures, i.e. surgery, radiotherapy and chemotherapy, the prognosis of malignant gliomas has remained nearly unchanged (Hulshof *et al.* 2000, Klein *et al.* 2001, Lutterbach *et al.* 2002). During recent years, along with the development of improved diagnostic and treatment regimens, special attention thus also has been focused on psychosocial factors and the quality of life of brain tumor patients during the entire illness period (Weitzner 1999, Peterson 2001, Klein *et al.* 2001, Lutterbach *et al.* 2002, Litofsky *et al.* 2004).

### 2.1 Prevalence of primary brain tumors

The prevalence of primary brain tumors has continuously increased during recent decades, especially among the elderly (Passik *et al.* 1994, Weitzner & Meyers 1997, Helén 2001). The increased prevalence is suggested to be due to new techniques in diagnostics (CT and MRI), lengthened lifetime (the prevalence of primary brain tumors increases in the course of age), and radiological examination for other reasons (findings by chance) (Helén 2001, Jukich *et al.* 2001).

The mean annual numbers of new cases of primary brain tumors in Finland during years 1998-2002 have been 332 for males and 455 for females (Finnish Cancer Registry 2002). At the same time period the age-adjusted incidence rates have been 10.1 for males and 12.0 for females per 100,000 persons (Finnish Cancer Registry 2002). The overall incidence of intracerebral tumors for the years 1969-98 has ranged from 8.4-11.8 for men and 5.8-9.3 for women per 100,000 in Nordic population (Denmark, Sweden, Norway and Finland), while the corresponding incidence rate in USA has been 13.8 per 100,000 (Davis *et al.* 2001, Lonn *et al.* 2004). The proportion of tumors in the central nervous system is about 3% of all cancers in Finland (Salminen *et al.* 1999, Finnish Cancer Registry 2002), while the corresponding proportion in USA is 5-9% (American Cancer Society 2003). In general, half of all brain tumors are malignant by histology, as presented in Table 1 (Helén 2001, Hales *et al.* 1987).

*Table 1. Primary brain tumors according to histological type of tumor.*

Tumor type	% of brain tumors*
Gliomas	40-50
Astrocytomas	10-15
Glioblastomas	20-25
Others	10-15
Meningiomas	10-20
Pituitary adenomas	10
Schwannomas (mainly acoustic neuromas)	5-8
Medulloblastomas and pinealomas	5
Other primary tumors	5

\*The prevalence (%) of specific tumor among all brain tumors (Helén 2001, Hales *et al.* 1987)

## 2.2 Classification and location of brain tumors

The classification of primary brain tumors is based on the histology as well as on the biological behavior of brain tumor (Kleihues *et al.* 1993). The histological classification is primarily based on histological assessment of cell types and tissue patterns recognized by conventional light microscopy (Kleihues *et al.* 1993). The most common histological group consists of gliomas originating from neuroepithelial tissue. The majority of other primary brain tumors are schwannomas, neurofibromas as well as meningiomas originating from cranial and spinal nerves and meninges (Kallio *et al.* 2001, Nyström 1988). The biological behavior of brain tumors is determined by histological evidence of differentiation or anaplasia that is characterized by assigning a histological grade ranging from I (benign) to IV (malignant) (Kleihues *et al.* 1993).

Primary brain tumors are mainly located in posterior fossa covering 30% of all tumors, while 22% are found in both frontal and temporal regions, 12% in the parietal area, 10% in the pituitary, and 4% of tumors are located in the occipital lobes (Lohr & Cadet 1987).

### ***2.2.1 Tumors of neuroepithelial tissue***

The histological typing of gliomas is based on the phenotypical resemblance of tumor cells to normal glia, i.e. astrocytes, oligodendrocytes, or a combination of both. According to the World Health Organization (WHO) classification gliomas are categorized into astrocytic tumors, oligodendrial tumors, ependymal tumors and mixed gliomas (Table 2).

The grading of malignancy is based on the following aspects of tumors: nuclear atypia, mitotic activity, cellularity, vascular proliferation and necrosis (Kleihues & Cavenee 2000). The growth of gliomas is invasive and infiltrative, and an exact line to brain tissue is impossible to find (Giese *et al.* 2001). Therefore total and curative extirpation of the tumor is usually not possible. In addition, these tumors respond poorly to other forms of treatment, such as radiotherapy and chemotherapy (Kleihues & Cavenee 2000, Aronen *et al.* 2000, Giese *et al.* 2001). The degree of invasiveness does not necessarily correlate with the grade of malignancy, and the recurrence of the tumor is common in low-grade and high-grade glioma patients (Gurthie & Laws 1990, Gaspar *et al.* 1992).

*Table 2. Histological grading of neuroepithelial tumors (Kleihues & Cavenee 2000).*

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Tumors of neuroepithelial tissue: gliomas by the WHO classification

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1. Astrocytic tumors	3. Oligodendrial tumors
Pilocytic astrocytoma Grade I	Oligodendroglioma Grade II
Pleomorphic xanthoastrocytoma Grade II	Anaplastic oligodendroglioma Grade III
Subependymal giant cell astrocytoma Grade I	4. Ependymal tumors
Diffuse astrocytoma Grade II	Myxopapillary ependymoma Grade I
Anaplastic astrocytoma Grade III	Subependymoma Grade I
Glioblastoma multiforme Grade IV	Ependymoma Grade II
2. Mixed gliomas	Anaplastic ependymoma Grade II
Oligo-astrocytoma Grade II	5. Choroid plexus tumors
Anaplastic oligo-astrocytoma Grade III	Choroid plexus papilloma Grade II
Others	Choroid plexus carcinoma Grade III

---

### 2.2.2 Tumors of cranial and spinal nerves and meninges

Meningiomas and schwannomas are benign brain tumors that are non-invasive and only displace brain structures instead of infiltrating brain tissue (Aronen *et al.* 2000). The classification according to WHO is presented in Table 3 (Kleihues *et al.* 1993). Successful total extirpation of the tumors usually results in cure of the patients (Sachsenheimer 1992, Aronen *et al.* 2000, Moshnipourly 2001). However, surgical cure is often not possible in those meningiomas involving the skull base or vital neurovascular structures (Sekhar *et al.* 1990, Al Mefty 1990, Kujas 1993).

Median age of diagnosis among meningioma patients is 61 years, and the incidence of meningiomas in women is known to be more than double compared to males (Mahaley *et al.* 1989, McCarthy *et al.* 1998).

Table 3. Tumors of cranial and spinal nerves and meninges by the WHO (Kleihues & Cavenee 2000).

Tumors of cranial and spinal nerves and meninges by the WHO	
1. Tumors of cranial and spinal nerves	2.2 Mesenchymal, non-meningothelial tumors
Schwannoma (Neurilemmoma, Neurinoma)	Hemangiopericytoma
Neurofibroma	Chondrosarcoma
Malignant peripheral nerve sheath tumor (MPNST), Neurogenic sarcoma, Anaplastic neurofibroma, "Malignant schwannoma)	Malignant fibrous histiocytoma
2. Tumors of meninges	Rhabdomyosarcoma
2.1 Tumors of meningotheial cells	Meningeal sarcomatosis
Meningioma	Others
Atypical meningioma	2.3 Primary melanocytic lesions
Papillary meningioma	2.4 Tumors of uncertain histogenesis
Anaplastic (malignant) meningioma	

### **2.3 Prognostic factors for survival among primary brain tumor patients**

The long-term outcome in brain tumor patients is most importantly dependent on tumor type (Kim *et al.* 1990, Detmar *et al.* 2000, Huang *et al.* 2001, Liigant *et al.* 2001). The most aggressive and most common primary brain tumor is glioblastoma multiforme (Peterson 2001). Survival time of patients with glioblastoma is reported to be about one year after initial diagnosis of the tumor (Sneed *et al.* 1998, Aronen *et al.* 2000, Maher *et al.* 2001). In all glioma patients the 5-year survival rate is 20-34% (Kallio 1990, Davis *et al.* 1998), in patients with Grade I and Grade II gliomas 5-year survival is 38-45% (North *et al.* 1990). Survival time for patients with anaplastic astrocytoma and other grade III gliomas varies from three years to five years (Fine *et al.* 1993, Prados *et al.* 1998, Urtasun *et al.* 1996). The 5-year survival rate for meningioma patients lies at 69-91%, declining with patient's age to 56% for patients 65 years of age and older (Mahaley *et al.* 1989, McCarthy *et al.* 1998). In Finnish population survival rates for meningioma patients are found to lie between 81% and 89% at one year and between 71% and 78% at 15 years (Kallio *et al.* 1992, Sankila *et al.* 1992). Prognostic factors for survival according to different studies are summarized in Table 4.

Table 4. Predictors for survival among brain tumor patients in different patient samples.

Study	Study design	Tumor type	Number of cases	Country	Prognostic factors
Kallio <i>et al.</i> 1992	Population-based study of 27 years	Meningioma	935	Finland	For worse survival Incomplete tumor removal, poor pre- and postoperative condition, anaplasia of tumor and hyperostosis
Sankila <i>et al.</i> 1992	Population-based study of 30 years	Meningioma	1986	Finland	Old age, no surgical operation, the period of diagnosis, male gender
Pignatti <i>et al.</i> 2002	Multicenter study	Low-grade glioma	322	United Kingdom	Age > 40, largest diameter of the tumor > 6 cm, tumor crossing the midline, presence of neurologic deficits before surgery
Litofsky <i>et al.</i> 2004	Multicenter, longitudinal	High-grade glioma	598	USA	Postoperative depression
North <i>et al.</i> 1990	Patients series of 10 years	Grade I-II astrocytoma	77	USA	For better survival Young age, female gender, normal preoperative mental status, surgical resection (versus biopsy), tumor involvement of only one lobe
Kallio <i>et al.</i> 1991	Population-based study of 30 years	All gliomas	3857	Finland	Young age, recent diagnosis, both operation and radiation as treatment
Hulshof <i>et al.</i> 2001	Patients with GM of 10 years	Glioblastoma multiforme	198	The Netherlands	Lower age, good neurologic performance, total tumor resection, smaller tumor size post surgery
Ligant <i>et al.</i> 2001	Population based study of 10 years	Primary brain tumor (different histology)	1417	Estonia	Lower age, better clinical condition (KPS > 60), tumor histology meningioma or neurinoma
Lutterbach <i>et al.</i> 2002	Patients with GM of 20 years	Glioblastoma multiforme	432	Germany	Lower age, performance status by KPS > 70, tumor location in hemispheres (not centrally)

## 2.4 Psychiatric symptoms and disorders in patients with a primary brain tumor

Brain tumors are important from a psychiatric point of view for a variety of reasons: an unrecognized brain tumor can present only as psychiatric syndromes, patients with a diagnosed brain tumor may have psychiatric symptoms, or psychiatric symptoms may arise during the illness process (Kallio 1993). Psychiatric symptoms may be the only initial manifestations of primary brain tumors in a significant number of cases occurring in the fifth decade of life and may be difficult to differentiate from primary functional psychiatric disorders (Weitzner 1999, Gupta & Kumar 2004). Such patients must be investigated by brain-imaging studies even if there are no neurological signs or symptoms (Gupta & Kumar 2004). Psychiatric symptoms caused by a tumor may develop slowly. A typical syndrome is called psychomotor asthenia and it can be misleadingly diagnosed as depression: the patient is indifferent, apathetic and irritable, and has memory difficulties, lacking spontaneity and sense of illness (Jarho 1996).

It is estimated that about half of brain tumor patients have psychiatric symptoms at some time during the course of illness (Kallio 1993, Kaplan *et al.* 1994). However, psychological distress may be difficult to distinguish from other cognitive changes directly related to the disease or its treatment. Organic and psychological symptoms occur commonly together and distinction between them may be arbitrary (Peterson 2001).

On the other hand, psychiatric symptoms may not be directly related to raised intracranial pressure, although this has frequently been suggested in earlier studies (Gutmann *et al.* 1990, Lilja & Salford 1997). It is estimated that 99% of patients with an infratentorial tumor have raised intracranial pressure, while psychiatric symptoms occur in 10% of these cases. Besides, the patients with a supratentorial tumor had mental disorders in 50% of the cases, while only 25% of the patients had raised intracranial pressure (Lilja & Salford 1997).

Psychiatric symptoms among brain tumor patients can be classified according to many categories: according to mood state, personality change or cognitive disorders of the patient as well as according to the location of the tumor (Kallio 1993). In its classification of psychiatric disorders in relation to any somatic disease the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) has introduced the phrase “due to a general medical condition” and thus replaced the former classification into two categories i.e. “organic” or “functional”. It is hereby suggested that psychiatric symptoms are part of a syndrome caused by a non-psychiatric medical condition (Kaplan *et al.* 1994). Mental disorders may be caused by a brain tumor, degenerative brain diseases, epilepsy, head trauma, demyelinating disorders and infectious brain diseases as well as by immune, endocrine, metabolic and nutritional disorders (Kaplan *et al.* 1994). Table 5 presents the classification in which each mental disorder is classified under the category that resembles its symptoms.

*Table 5. Mental disorders due to a general medical condition (Kaplan et al. 1994).*

DSM IV Category	Mental disorders due to a general medical condition
Delirium, dementia, amnesic, and other cognitive disorders	Delirium, dementia, and amnesic disorder due to a general medical condition
Schizophrenia and other psychotic disorders	Psychotic disorder due to a general medical condition
Mood disorders	Mood disorder due to a general medical condition
Anxiety disorders	Anxiety disorder due to a general medical condition
Sexual disorders	Sexual dysfunction due to a general medical condition
Sleep disorders	Sleep disorder due to a general medical condition
Mental disorders due to a general medical condition not elsewhere classified	Catatonic disorder, personality change, mental disorder NOS due to a general medical condition.

## 2.4.1 Mood disorders

### 2.4.1.1 Depressive disorders

Depressive symptoms – particularly symptoms such as poor sleep, decreased appetite and fatigue – are commonly associated with many medical conditions. Differential diagnosis as whether symptoms are due to a general medical condition or a specific mood disorder can be difficult (Kaplan *et al.* 1994). Diagnostic criteria of mood disorder according to DSM-IV are presented in Table 6.

*Table 6. Diagnostic criteria for mood disorder due to a general medical condition according to DSM-IV.*

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Mood disorder due to a general medical condition
<p>A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:</p> <ol style="list-style-type: none"> <li>(1) Depressed mood or markedly diminished interest or pleasure in all, or almost all, activities</li> <li>(2) Elevated, expansive, or irritable mood</li> </ol>
<p>B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.</p>
<p>C. The disturbance is not better accounted for by another mental disorder (e.g. adjustment disorder with depressed mood, in response to the stress of having a general medical condition).</p>
<p>D. The disturbance does not occur exclusively during the course of delirium or dementia.</p>
<p>E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</p>
<p>Specify type:</p> <ul style="list-style-type: none"> <li>* with depressive features: if the predominant mood is depressed but the full criteria are not met for a major depressive episode</li> <li>* with major depressive-like episode: if the full criteria are met (except criterion D) for a major depressive episode</li> <li>* with manic features: if the predominant mood is elevated, euphoric, or irritable</li> <li>* with mixed features: if symptoms of both mania and depression are present and neither predominates</li> </ul>

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Depression is frequently related with left hemisphere lesions in brain tumor patients (Belyi 1987, Peterson 2001). Frontal location of tumor has also been a highly significant predictor for a major depressive disorder after tumor operation among patients with a primary brain tumor (Wellisch *et al.* 2002). Likewise, in the study of Irle and colleagues (1994), patients with lesions in the ventral frontal cortex or lesions in the temporoparietal

cortex reported significantly worse mood states postoperatively than those with lesions in other regions of the brain. Thus, in patients with brain tumors the cortical interconnection with limbic structures is suggested to be more important than specific lesion location for the development of neuropsychiatric symptoms (Weitzner 1999).

*There are case reports of patients with frontal lobe tumors (Filley & Kleinschmidt-DeMasters 1995, Peterson 2001), and with a tumor in the posterior fossa region (Pollak et al. 1996) in whom depression had been presented as an initial symptom of brain tumor. High incidence of psychiatric symptoms, especially depression, has been found in patients with corpus callosum tumors compared to those with a tumor restricted to only one hemisphere as reported by Nasrallah & McChesney (1981). They described a report of the psychopathological presentations of patients with corpus callosum tumors, e.g. a 57-year-old female with a glioma in the middle of corpus callosum. Her depressive symptoms fulfilled the diagnostic criteria of depressive disorder before her neoplasm was diagnosed, and she was also treated with tricyclic antidepressants without response. Organic etiology for her depression was suspected, and the tumor was diagnosed and treated.*

The prevalence of depressive symptoms has varied from 15% to 38% in different samples of patients with a primary brain tumor as described in Table 7 (Anderson *et al.* 1999, Pringle *et al.* 1999, Pelletier *et al.* 2002, Wellisch *et al.* 2002, Litofsky *et al.* 2004).

Table 7. Prevalence of depression among brain tumor patients according to different patient samples.

Study	Study design	Number of cases	Histology of tumor	Prevalence of depression	Method in assessment of depression	Time from the surgery
Anderson <i>et al.</i> 1999	Cross-sectional	40	Low-grade glioma, high-grade glioma and meningioma	15%	HDS (17/40)	15-67 weeks after operation
Pringle <i>et al.</i> 1999	Prospective	109	Glioma, meningioma, metastasis	16% preoperatively, 6% postoperatively	HAD (11/14)	Immediately before operation and 7 days after operation
Pelletier <i>et al.</i> 2002	Cross-sectional	73	Glioma, meningioma, other	38%	BDI (14/21)	6 months or longer
Wellisch <i>et al.</i> 2002	Cross-sectional	89	Glioma, meningioma, lymphoma	28%	Major depressive disorder by DSM-IV diagnostic criteria	Not informed
Litofsky <i>et al.</i> 2004	Multicenter, longitudinal	598	High-grade glioma	15% postoperatively 22% at 3 months and 6 months	Depressive disorder by DSM-IV diagnostic criteria	At perioperative period, at 3 months and at 6 months after operation

\*HDS= Hamilton Rating Scale for Depression, HAD= Hospital Anxiety and Depression Scale, BDI= Beck Depression Inventory and their cut-off points for depression in brackets.

The effect of tumor histology on depression among brain tumor patients is not clear, and contradictory findings have been reported. Anderson *et al.* (1999) found that patients with high-grade tumors had a higher level of depression than patients with low-grade gliomas or meningiomas, while Pringle *et al.* (1999) observed that patients with meningiomas had higher scores of depression than patients with gliomas or brain metastases. According to Irle *et al.* (1994) the cause of the tumor, namely meningiomas or low-grade or high-grade gliomas, did not influence the mood states. They suggested that lesions resulting from resection of these tumors had similar effects on the emotional state of the patients. The most common psychopathological signs for Cushing's disease among patients with pituitary adenoma were reported to be excitability and depression (Price *et al.* 1992, Kelly *et al.* 1996, Dorn *et al.* 1997, Flitsch *et al.* 2000). Pituitary adenoma patients in general had a significantly increased risk for major depression during a 12-month period before the time of study (Korali *et al.* 2003). Postoperative depression has been found in female acoustic neuroma patients (Blomstedt *et al.* 1996).

In addition, depressive disorder in brain tumor patients was shown to be significantly associated with the patients' physical disability (Anderson *et al.* 1999) and the level of their fatigue (Pelletier *et al.* 2002). Somatic complications such as deep vein thrombosis, seizures, systemic infection and adverse drug reactions were found to be more common in depressive than in non-depressive glioblastoma patients (Litofsky *et al.* 2004).

#### 2.4.1.2 Manic episodes

Manic state as a mood disorder due to brain tumor has been described in case reports. Brain neoplasms involving different lobes of the right hemisphere, temporolimbic areas, the cerebellum, thalamus or pituitary have presented as manic symptoms (Belyi 1987, Starkstein *et al.* 1988, Filley & Kleinschmidt-DeMasters 1995, Peterson 2001).

*Starkstein et al. (1988) reported of cases with secondary mania after brain injury. The five patients aged 28 years to 63 years (two males and three females) had a brain tumor, four of which were meningiomas and one astrocytoma. None had a personal history of psychiatric illness and they were admitted to psychiatric hospital for the treatment of their manic symptoms such as hyperactivity, irritability, flight of ideas, pressure of speech, hypersexuality or grandiose delusions. The symptoms appeared immediately after or concomitantly with the brain lesion. They reviewed also other studies of case reports and suggested that the mechanism of mania is due to damage in the structures, which are functionally interconnected with the orbitofrontal cortex.*

### 2.4.2 Anxiety disorders

The DSM-IV diagnosis of anxiety disorder due to a general medical condition requires the presence of symptoms of an anxiety disorder as described in Table 8.

*Table 8. Diagnostic criteria for anxiety disorder due to a general medical condition according to DSM-IV.*

---

Anxiety disorder due to a general medical condition
A. Prominent anxiety, panic attacks, or obsessions or compulsions predominate the clinical picture.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
C. The disturbance is not better accounted for by another mental disorder (e.g. adjustment disorder with anxiety, in which the stressor is a serious medical condition).
D. The disturbance does not occur exclusively during the course of delirium.
E. The disturbance causes clinically significant distress or impairment in social occupational, or other important areas of functioning.
Specify if: * with generalized anxiety: if excessive anxiety or worry about a number of events or activities predominates in the clinical presentation * with panic attacks: if panic attacks predominate in the clinical presentation * with obsessive-compulsive symptoms: if obsessions or compulsions predominate in the clinical presentation

---

There are no reported prevalence rates of anxiety disorder among brain tumor patients, although anxiety has been considered to be the most common elevating symptom of a brain tumor (Kallio 1993). Anxiety or panic attacks have been reported to be symptoms of a brain tumor in different case reports (Dietch 1984, Ghadirian *et al.* 1986, Drubach & Kelly 1989, Ko & Kok 1990, Kellner *et al.* 1997, Peterson 2001). Patients with a high-grade glioma may have early symptoms of tumor as organically derived anxiety disorder with a sudden onset, while low-grade glioma is suggested to present as anxiety being epileptiform in origin (Lilja & Salford 1997). Anxiety symptoms have been significantly associated with Cushing's syndrome in pituitary adenoma patients (Dorn *et al.* 1997, Kelly *et al.* 1996). Among brain tumor patients there are only a few case reports of adult patients presenting with obsessional symptoms with a tumor located in the frontal, temporal or parietal regions in the brain (Ward 1988, Paradis *et al.* 1992, John *et al.* 1997), whereas among pediatric patients with a brain tumor there are several case reports with initial presentations of a primary cerebral malignancy as obsessive-compulsive disorder (Moriarty *et al.* 1993, Peterson *et al.* 1996, Mordecai *et al.* 2000, Gamazo-Garran *et al.* 2002).

*Ghadirian et al. (1986) reported about a 69-year-old female teacher who was referred for psychiatric treatment due to anxiety and panic attacks lasting over two years without known history of psychiatric illnesses. During the follow-up she also developed depressive symptoms and was treated with antidepressants and anxiolytics for a period of about one year. About 16 months after the beginning of the psychiatric treatment her depression symptoms decreased but she began to have partial complex seizures. Examination in neurological hospital revealed right lobe temporal meningioma. After tumor surgical operation the patient became again depressive and antidepressant treatment was started. No relapses of anxiety attacks were noted during eight months of follow-up.*

*Dietch (1984) has described a 55-year-old woman with recurrent anxiety attacks with somatic symptoms such as dyspnea, tightness in the throat and palpitations that lasted 3 months. She would also occasionally bite her tongue and fall to the ground without hurting herself. During some attacks her speech was incoherent and her consciousness was disturbed. She became afraid of being alone. Psychiatric diagnosis was agoraphobia with panic attacks. She was given imipramine and the panic attacks stopped; however, the patient developed a right-handed weakness. Neurological examination showed a tumor for which histological diagnosis by surgical biopsy was glioblastoma multiforme. The panic attacks ceased after surgical operation.*

### **2.4.3 Other psychiatric disorders**

Psychotic symptoms and disorders in relation to brain tumor have been described. There are case reports of schizophreniform psychosis in patients with fossa posterior tumors and midline tumors involving thalamic, hypothalamic and periventricular regions (Nasrallah & McChesney 1981, Malamud 1987, Sato *et al.* 1993, Takeuchi *et al.* 1993, Pollak *et al.* 1996). Lesions caused by cerebral tumors in the occipital or temporal areas can cause hallucinations, while with lesions in the temporal or parietal lobe, especially in the right hemisphere, the patients' psychotic symptoms may be delusions (Lohr & Cadet 1987, Kaplan *et al.* 1994). Patients with pituitary adenomas as well as ACTH-producing and prolactin-secreting tumors may have psychotic disorders before the tumor is diagnosed (Melkersson & Hulting 2000, Tran & Elias 2003).

*Lisanby et al. (1998) described the case of a 26-year-old woman with schizophreniform psychosis secondary to a meningioma of the right lateral ventricle with extension into the corpus callosum and periventricular white matter. The symptoms resolved completely after surgical excision of the tumor and the patient remained in remission at over two years of follow-up with no medication.*

Case reports have also described personality changes presenting as a symptom of a brain tumor located in the frontal lobe (Filley & Kleinschmidt-DeMasters 1995), thalamus (Gutmann *et al.* 1990) or in the posterior fossa region (Pollak *et al.* 1996). Pressure in the frontal or temporal lobes and structures within the limbic system can lead to disinhibited,

aggressive or agitated behavior (Passik *et al.* 1994). Besides case reports there are no prevalence rates about psychotic symptoms among brain tumor patients.

## **2.5 Some biological aspects of psychiatric disorders in relation to brain tumor**

As reviewed by Ressler and Nemeroff (2000), there is substantial evidence that serotonin and norepinephrine have fundamental roles in the etiology of depression and anxiety disorders as well as in interactions between these transmitter systems. In the central nervous system, changes in these neurotransmitters and in neurotransmitter metabolite concentrations, reuptake sites, and receptors support the hypothesis of serotonergic and noradrenergic neuronal dysfunction in patients suffering from depression (Nemeroff 2002). There is evidence of underactivation of serotonergic function and complex dysregulation of noradrenergic function in the etiology of depression and anxiety (Ressler & Nemeroff 2000).

Although mechanisms underlying the pathophysiology of various anxiety disorders have not yet been fully clarified, the most widely accepted mediators known to play a central role is the primary inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) (Nemeroff 2003, Millan 2003, Mombereau *et al.* 2004). GABAergic neurotransmission can be divided into fast (GABA<sub>A</sub> and GABA<sub>B</sub> receptors) and slow (GABA<sub>C</sub> receptors) components (Wong *et al.* 2003). The inhibitory influence of GABA on neuronal activity is expressed both via GABA<sub>A</sub> and via GABA<sub>B</sub> receptors in the control of anxious states (Barnard *et al.* 1998, Bowery & Enna 2000). GABAergic pathways also exert an inhibitory influence upon the release of such transmitters as e.g. serotonin and norepinephrine (Millan 2003).

The cortisol profile is one of the best-studied indicators of hypothalamic-pituitary-adrenal (HPA) function in depressed populations (Spiegel & Giesel-Davis 2003). Cortisol is a glucocorticoid hormone produced by the adrenal cortex whose circulating levels and circadian rhythm are regulated by the hypothalamus and the pituitary gland. The adrenal axis reacts to stress by increasing the secretion of cortisol (Kaplan *et al.* 1994). As a consequence of intact negative feedback at the pituitary, as plasma cortisol rises, plasma adrenocorticotrophic hormone (ACTH) levels fall in response to glucocorticoid negative feedback, followed by a fall in plasma cortisol; as cortisol falls, there is less glucocorticoid negative feedback at the pituitary, and ACTH rises once again. This phenomenon could lead to an underestimation of the rate of hypercortisolism in depression (Golda *et al.* 2002). Cross-sectional comparisons of depressed and non-depressed individuals have identified elevated 24-hour mean cortisol levels and a flattened circadian cortisol rhythm in depressed subjects (Thompson *et al.* 1992, Yehuda *et al.* 1996, Deuschle *et al.* 1997). It is known that the elevated cortisol induced by stress increases serotonin uptake, under both rest and nerve stimulation, which are overtly expressed in symptoms of depression (Tafet *et al.* 2001). Under chronic stress or depression, the capacity for increase in serotonin transporter has reached its limit due to the chronically elevated blood cortisol level (Tafet *et al.* 2001).

The serotonergic system as well as such stress neuropeptides as arginine vasopressin (AVP), corticotropin-releasing hormone (CRH), somatostatin and oxytocin have been

thought to be highly implicated in the pathophysiology of OCD (Barr *et al.* 1992, Altemus *et al.* 1993, Baumgarten *et al.* 1998).

Expression of 5-hydroxytryptamine (5HT) receptors has been found in human glioma cells and serotonin was found to positively modulate the glioma cell proliferation, migration, and invasion in vitro. Research suggests that 5-HT may play an important role in the control of the biological properties of human glioma cells, and the serotonergic system in brain function may also change (Merzak *et al.* 1996, Noda *et al.* 2003). It has also been reported that most human meningiomas and gliomas have receptors for somatostatin (Reubi *et al.* 1987, Koper *et al.* 1992, Prat *et al.* 1997, Held-Feindt *et al.* 1999, Cavalla & Schiffer 2001).

## **2.6 Quality of life in brain tumor patients**

Quality of life (QOL) is a multidimensional concept, focusing on the impact of illness and treatment on different areas of a patient's functioning reported by the patient himself (Aaronson 1990). The different dimensions of a patient's functioning in QOL consist of physical, psychological, social, functional and family functioning (Aaronson *et al.* 1988, Weitzner 1999, Huang *et al.* 2001). Quality-of-life issues are the core of treatment of all neoplasias. Patients are often equally concerned with the impact of the disease and therapy on their life and daily function as they are with disease-related outcomes (Aiken 1994).

Early studies evaluating QOL among brain tumor patients were focused on external and physical measures (Lieberman *et al.* 1982, Schag *et al.* 1984). Later, in addition to measuring the functional performance state, also cognitive, social and psychological aspects have been taken account in the assessment of QOL among brain tumor patients (Taphoorn *et al.* 1992, Aiken 1994, Giovagnoli *et al.* 1996, Weitzner *et al.* 1996, Weitzner & Meyers 1997, Osoba *et al.* 1997, Lovely *et al.* 1998). Anxiety and depression have an important impact in decreasing the patients' overall QOL through the illness process and they have been studied in recent QOL research (Giovagnoli 1999, Peterson 2001). Table 9 summarizes the findings of QOL studies using brain tumor patient samples.

*Table 9. Recent studies on the association of QOL with psychiatric symptoms among patients with a primary brain tumor.*

Study	No. of cases	Histology of tumor	Assessment of QOL	Assessment of mood state	Impact of mood state on QOL
Taphoorn <i>et al.</i> 1992	14	Low-grade (II) glioma	Clinical interview by psychologist	ABS, POMS	Depression, anger, fatigue, tension and lack of vigor was found in 11 of 13 patients examined, POMS was not analyzed with QOL
Giovagnoli <i>et al.</i> 1996	101	Grade II-IV tumors	FLIC	STAI, SRDS	High FLIC scores correlated higher STAI and higher SRDS scores
Giovagnoli 1999	57	Malignant glioma	FLIC	STAI, SRDS	QOL was significantly associated with depression and state anxiety
Pelletier <i>et al.</i> 2002	73	Grade II-IV gliomas, meningioma, other	McGill Quality of Life Questionnaire	BDI	Presence of depressive symptoms was the single most important predictor for decreased QOL

\* FLIC= Functional Living Index-Cancer, ABS= Affect Balance Scale, POMS= Profile of Mood States, STAI= State-Trait Anxiety Inventory, SRDS= Self-Rating Depression Scale, BDI= Beck Depression Inventory

## 2.7 Psychological reactions to serious somatic disease

In general, intrapsychic or experiential aspect of a patient's response to serious illness refers to one's perceptions, thoughts, imagery and emotions that compose subjective experience of illness ((Lipowski 1985). The emotions evoked by physical illness vary in quality, intensity, duration and temporal sequence (Lipowski 1985). The most common emotions are anxiety, sadness, grief, disgust, shame, guilt, anger, surprise or acceptance varying in intensity and according to the patient's past mood before the onset of illness (Plutchik 1980).

Brain tumor patients face the severe stress of having a neoplasm and thus potentially the danger of one's own death (Weitzner & Meyers 1996). The patients must also come to terms with altered social and family roles, their decreased physical and cognitive status as well as the stigmatizing label of cancer which one has to live with after being diagnosed with a neoplasm (Weitzner & Meyers 1996). There are many theories described by e.g. J Bowlby, CM Parkes, E Lindemann, E Bassuk, and A Birk of how a person can manage the grief and the entire psychological reaction caused by a serious somatic illness involving the danger of death, as reviewed by Kaplan *et al.* 1994. Figure 1 presents the theory of traumatic crisis by the Swedish psychiatrist J Cullberg (Cullberg 1977). He has divided the phases of crisis into four phases: 1 Shock, 2. Reaction, 3. Solving through and 4. Reorganization.

**Shock**

Lasts some days: the person defends reality and may behave normally but his mind all is confused and it is difficult for him to remember what happened and what was talked about. Reaction can be also a drastic burst of emotion.

**Reaction**

Lasts about 2-4 weeks: the person opens his eyes and begins to look at what has happened in a realistic way. He asks again and again: why? He tries to find realistic reasons for the occurrence and he may have feelings of guilt and he is liable to think magically. All his emotions and senses have become more sensitive. He tries to get equilibrium in the changed situation.

**Solving through**

From reaction phase up to a year: the event is analysed in the person's mind. This is the phase of grief and mourning. It is usual that also the human body reacts and the person may have many somatic symptoms such as sleep disturbance, headache and poor appetite. With time he can gradually accept what has happened and begin to turn to the future.

**Reorganization**

This last phase is really never finished. A person continues his life and the traumatic event is with him as a scar in his mind. He may feel that the order of precedence in his life has changed. He can find new interests and challenges. Distressing feelings of what has happened are mild but come to his mind for short periods of time.

**Fig. 1. The course of traumatic crisis according to Cullberg (1977).**

## **2.8 Summary of reviewed literature: what is known and what should be studied?**

Primary brain tumors consist of a heterogenic disease group by etiology, clinical course and expected prognosis. Treatment for histologically benign tumors such as low-grade gliomas, meningiomas, pituitary adenomas and acoustic neuromas is often curative, while the survival time among patients with high-grade gliomas is about one year with all treatment regimens. The proportion of tumors in the central nervous system is about 3% of all cancers in Finland, the annual prevalence being 332 for males and 455 for males during years 1998-2002, and about half of all brain tumors are malignant by histology.

The knowledge about psychopathology due to brain lesion is mainly based on findings of studies among patients with infarct, infection or traumatic lesion in the brain. Psychiatric symptoms in medical condition due to brain tumor may be multifarious. The main factors causing psychiatric symptoms are suggested to be the location of the tumor and the speed and the way of tumor growth. On the other hand, there are no specific psychiatric symptoms typical of brain tumors. There may be several mechanisms at work simultaneously or alone that are responsible for the psychopathology in brain tumor patients. The most important factors are assumed to be the local effect of the tumor on brain function and the biochemical impact of transmitters and neuropeptides to surrounding brain metabolism. It can be suggested, based on earlier literature, that brain tumor increases the risk of having psychiatric disorders involving dysfunction in serotonin metabolism. In addition, a serious, probably fatal disease also induces a psychological crisis.

Research findings on psychiatric symptoms among brain tumor patients are almost totally based on case reports or case series in which the number of subjects studied has been rather low. Methodologically valid population-based studies for prevalence rates of psychiatric disorders among brain tumor patients are mainly lacking. In particular, there are no prospective studies of psychiatric symptoms in brain tumor patients.

Anxiety among brain tumor patients has been shown to be associated with lesions in the right hemisphere, while obsessive-compulsive symptoms are found to relate with frontal lesions, and especially with left-brain lesions. On the one hand, patients with lesions in the left hemisphere, and on the other hand those with lesions in anterior brain regions have been reported to suffer from depression. Lesions caused by cerebral neoplasm in the occipital or temporal areas can cause hallucinations. When lesions are located in the temporal or parietal lobe and particularly in the right hemisphere, patients' psychotic symptoms may be manifested as delusions.

It is recommended that the clinical follow-up of brain tumor patients should last for the remaining lifetime of these patients. Besides the recurrence of the tumor, cognitive, psychic and general coping in their disease should be regularly evaluated. In general, longitudinal studies focusing on the impact of depression on cancer progression have rather consistently shown that depression predicts an adverse outcome in terms of cancer progression and mortality. Unfortunately, corresponding studies among brain tumor patients are mainly lacking. Also, it has not yet been clarified what is the effect of depression and treatment of depression on brain tumor patients' functional state and their quality of life after the primary treatment regimens.

### **3 Aims of the present study**

The purpose of this study was to investigate anxiety, obsessive-compulsive symptoms and depression as psychiatric symptoms as well as the effect of depression on the quality of life among patients with a primary brain tumor by using a population-based study sample of brain tumor patients in Northern Finland. The numbers I -V hereafter refer to the original publications.

The aims of the present study were:

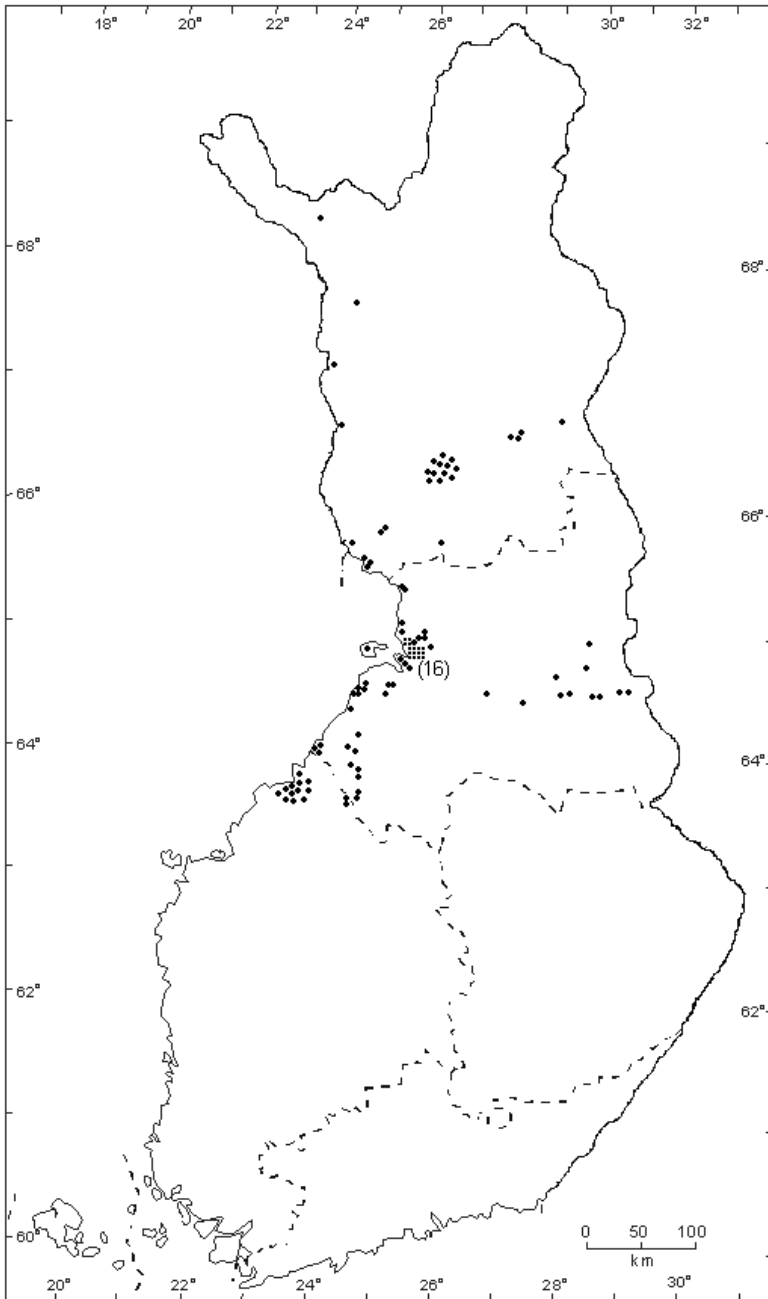
1. To investigate the level of anxiety before the surgical operation of brain tumor as well as three months and one year after the operation, and to evaluate whether anxiety is associated with tumor laterality (I).
2. To study the level of obsessionality among brain tumor patients with preoperative and postoperative measurements by taking also into account the location and histology of the tumor (II).
3. To describe the prevalence of depression among brain tumor patients in relation to their functional state and to the clinical characteristics of the tumor (III).
4. To study the putative association with depression and five-year survival of patients after tumor operation (IV).
5. To study the relationship between the level of depression and the quality of life as well as the functional status among males and females, separately (V).

## **4 Material and methods**

### **4.1 Study population and data collection**

The original study population consisted of 101 patients (39 males and 62 females) aged between 20 and 82 years with a solitary primary brain tumor treated surgically at the Oulu Clinic for Neurosurgery, Oulu University Hospital between February 1990 and March 1992.

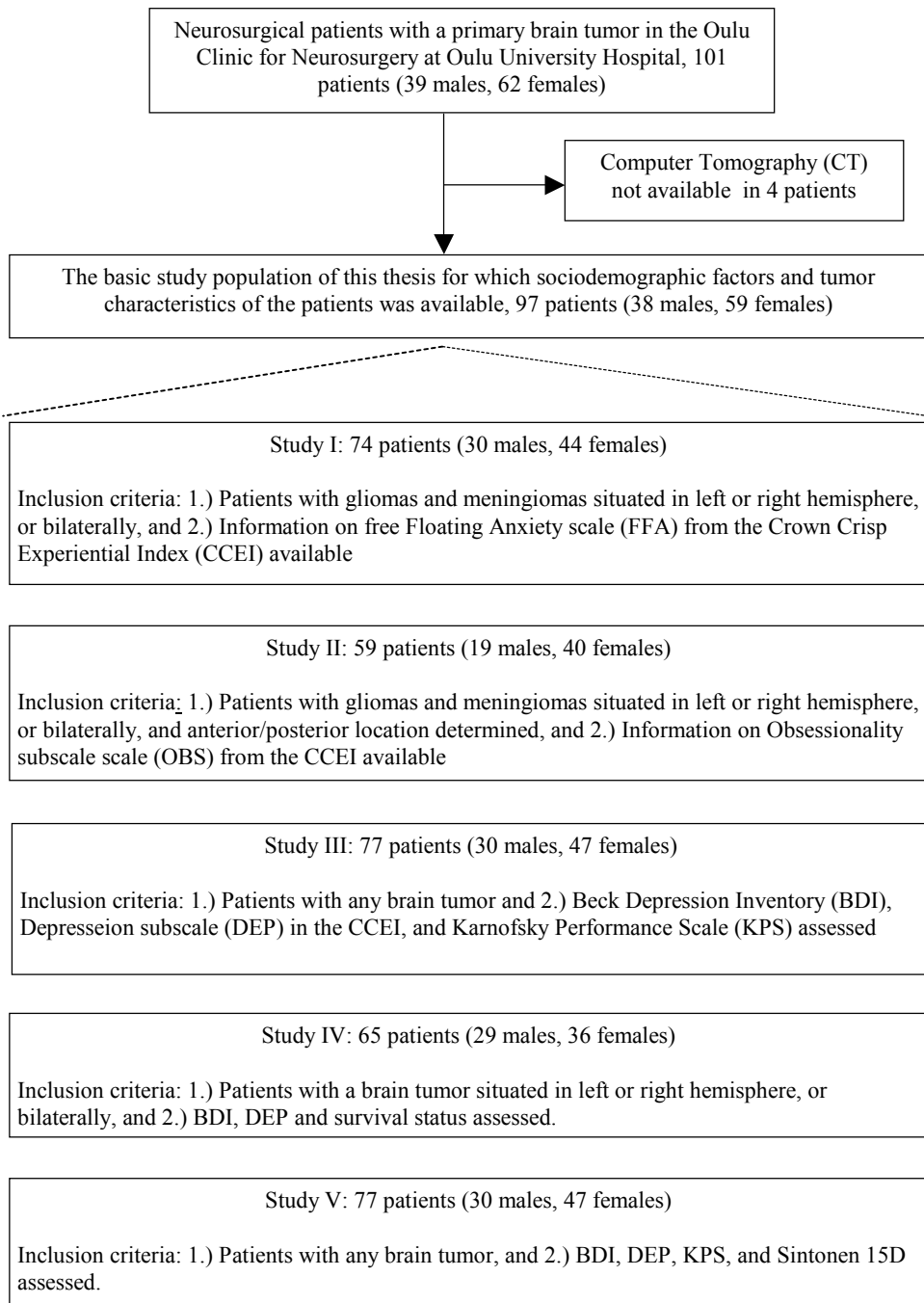
Epidemiologically the cohort is a comprehensive and unselected sample of patients, because the Oulu University Hospital for Neurosurgery performs all resections of brain tumors in its catchments area, and this area covers about 49% of Finland as shown in Figure 2.



**Fig. 2.** Map of the home municipalities of the neurosurgical patients with a primary brain tumor in Northern Finland.

Sociodemographic and clinical information on the patients including the radiological diagnosis of the tumors was collected in two ways. Firstly, the patients' case notes were carefully checked on admission to surgical operation for the tumor. Secondly, a professionally trained physician interviewed the patients. The histological diagnosis of the tumor was analyzed and classified by a trained pathologist at Oulu University Clinic of Pathology. The physician determined the location of each tumor manually from radiological images. The evaluation of psychiatric symptoms was administered by a trained psychologist. The mortality data including the date and the cause-of-death diagnoses were obtained from the National Cause of Death Register provided by Statistics Finland. A detailed description of the study sample and the data has been presented earlier (Salo *et al.* 2002)

The information on the patients' psychiatric symptoms, functional state as well as the level of quality of life was gathered at three time points – before tumor operation as well as three months and one year after the operation – using appropriate structured and standardized instruments, which are described in detail in subsequent chapters. The inclusion criteria for the patients in studies I -V are presented in Figure 3.



**Fig. 3. The study population of the brain tumor patients and the total number of subjects used in the original papers I-V in this thesis.**

## 4.2 Variables

### *4.2.1 General characteristics of the data*

On admission to surgical operation of the brain tumor the mean (SD) age for males was 49.4 (12.9) years and for females 48.8 (13.7) years. The majority of the patients (82% of males and 77% of females) were married. Two thirds of the patients had basic educational level (i.e. elementary school or less). The male patients (41%) were employed as often as females (44%), and a quarter of the patients (both males and females) were on sickness leave before tumor operation.

In the whole database the major histological subgroup consisted of gliomas (40%), and the rest were meningiomas (33%), acoustic neurinomas (13%), pituitary adenomas (8%) and other types (6%) as described in Table 10. There was a notable gender difference in the distribution of different types of brain tumors: in the males the main histological diagnosis of tumor was grade III-IV gliomas (36%), while in the females it was meningiomas (42%).

The tumors were more commonly situated in the left (44%) than in the right hemisphere (33%) of the brain, and 14% were located bilaterally. Furthermore, about half of the tumors were located anteriorly. Successful total surgical extirpation was possible in 48% of the tumors; extirpation was possible for 80% of the patients with meningiomas and for 10% of the patients with gliomas (Table 10).

*Table 10. The sociodemographic factors of the patients (n=101) and clinical characteristics of the tumors among the neurosurgical Northern Finnish patients with a primary brain tumor according to the histology of tumors.*

Characteristics	Grade I-II glioma	Grade III-IV glioma	Meningioma	Pituitary adenoma	Acoustic neurinoma	Other
<b>Patients n (%)</b>						
<b>Gender</b>						
Males	9 (47)	14 (64)	7 (21)	5 (62.5)	4 (31)	-
Females	10 (53)	8 (36)	26 (79)	3 (37.5)	9 (69)	6
Mean age (SD)	39.7 (11.6)	49.1 (13.3)	53.6 (12.1)	52.0 (6.7)	49.1 (8.1)	50.0 (21.0)
<b>Marital status</b>						
Married	15 (79)	16 (73)	26 (79)	8 (100)	11 (85)	4 (66)
Unmarried	3 (16)	2 (9)	2 (6)	-	-	1 (17)
Widow(er)	1 (5)	1 (4)	5 (15)	-	1 (8)	1 (17)
Divorced	-	3 (14)	-	-	1 (8)	-
<b>Education</b>						
Elementary	12 (63)	14 (64)	21 (64)	5 (62.5)	8 (62)	3 (50)
Middle school	4 (21)	6 (27)	9 (27)	1 (12.5)	3 (23)	1 (17)
High school	3 (16)	2 (9)	3 (9)	2 (25.0)	2 (15)	2 (33)
<b>Employment</b>						
Employed	10 (53)	9 (41)	13 (39)	1 (12.5)	11 (85)	2 (33)
Unemployed	1 (5)	-	1 (4)	-	-	-
Sickness leave	6 (32)	7 (32)	8 (24)	3 (37.5)	1 (8)	1 (17)
Pensioner	2 (10)	6 (27)	11 (33)	4 (50.0)	1 (8)	3 (50)
<b>Tumors n (%)</b>						
<b>Lateralization</b>						
In left hemisphere	11 (58)	11 (50)	13 (39)	1 (12.5)	7 (54)	2 (33)
In right hemisphere	7 (37)	8 (36)	11 (33)	-	6 (46)	2 (33)
Bilaterally	1 (5)	3 (14)	5 (16)	3 (37.5)	-	2 (33)
Not identified	-	-	4 (12)	4 (50.0)	-	-
<b>Location</b>						
Anteriorly	10 (53)	11 (50)	21 (64)	6 (75.0)	-	4 (66)
Posteriorly	5 (26)	3 (14)	8 (24)	2 (25.0)	13 (100)	1 (17)
Not identified	4 (21)	8 (36)	4 (12)	-	-	1 (17)
<b>Volume</b>						
Under 25 ml	5 (26)	7 (32)	15 (45.5)	6 (75.0)	12 (92)	3 (50)
25 ml or more	14 (74)	15 (68)	15 (45.5)	1 (12.5)	1 (8)	3 (50)
Not identified	-	-	3 (9)	1 (12.5)	-	-
<b>Extent of surgery</b>						
Extirpation	2 (10)	2 (9)	27 (82)	5 (62.5)	11 (85)	1 (17)
Resection	11 (58)	8 (36)	3 (9)	-	2 (15)	3 (50)
Biopsy/ unknown	6 (32)	12 (55)	3 (9)	3 (37.5)	-	2 (33)

\* Others include two hemangiopericytomas, malignant lymphoma, craniopharyngeoma and two undefined tumors

### ***4.2.2 Sociodemographic factors (III-V)***

In addition to the age and the gender of the study subjects, the sociodemographic factors consisted of variables describing the marital, educational and employment status of the patients.

In study III the variables for marital, educational and employment status were used in their original form as described in Table 10. However, the age of the study subjects was categorized into two classes: below 50 years, and age 50 or more.

In study IV the variables for marital and employment status were used as dichotomized, and the age of the study subjects as in study III. Marital status of the patients was assessed preoperatively as being ‘married/cohabiting’ or ‘not married’, and the latter class included the patients being unmarried, divorced or widowed. Employment status was determined as ‘employed’ or otherwise ‘unemployed’ regardless of whether the patients had been working full-time or part-time. The ‘unemployed’ group also included students and pensioners as well as patients on sickness leave.

In study V the age of the patients was analyzed as a continuous variable, determined as mean (SD) age, and marital status as dichotomized, as in study IV. In the variable for employment status, the patients were categorized into three groups according to their working status; ‘employed’, ‘on sickness leave’ and the others (i.e. ‘unemployed’, and pensioners). The educational status of the patients was analyzed using the original classes determined as shown in Table 10.

### ***4.2.3 Tumor characteristics***

In this study, the brain tumors were characterized according to the location, histology and the volume of the tumor. The classifications of these characteristics were based on international practices and were also found to have been used in earlier studies on brain tumor patients as described in the following chapters.

#### ***4.2.3.1 Tumor location (I-V)***

The radiological diagnosis of the brain tumor was carried out by computer tomography (CT) or magnetic resonance imaging (MRI). Matsui’s anatomical location was used in defining the tumor location in the brain (Matsui *et al.* 1977).

Regarding the hemispheric lateralization the tumors were classified into three groups: tumors in the left hemisphere, tumors in the right hemisphere and tumors located bilaterally. Furthermore, if the tumors reached the supratentorial space, the location of the tumor was defined to be ‘anterior’ or ‘posterior’ (Salo *et al.* 2002). The distance of the tumor from the apex of the frontal lobe was determined by calculating from each CT or MRI slice ratio of the distance between the anterior part of the tumor and the apex of the frontal lobe to the anterior-posterior diameter of the whole brain. The mean of these percentages was used to describe the distance from the apex of the frontal lobe to the tumor.

Depending on the aims of studies I-V, the hemispheric lateralization of the tumor (right, left, bilateral) or the location (anterior, posterior) of the tumor or the combination of these variables was used in the statistical analyses.

In study I, the study sample included subjects with a tumor located in either the right or the left hemisphere of the brain. Study V also included patients with a tumor located bilaterally as a separate group. In study IV, the patients were categorized into two groups: patients having a tumor in the hemispheres, and the patients with a tumor located bilaterally.

In study II the study groups were formed according to both hemispheric laterality and the anterior/posterior location of the tumor, simultaneously. Thus, five study groups were formed: tumor location being anteriorly in the left hemisphere, posteriorly in the left hemisphere, anteriorly in the right hemisphere, posteriorly in the right hemisphere, and bilaterally.

In study III the study groups for the tumor location were determined according to anterior or posterior location of the brain tumor.

#### 4.2.3.2 Tumor histology (I-V)

Histological grading of the tumors followed the WHO classification. In this study, the brain tumors of the patients formed six histological groups: grade I-II gliomas (low-grade gliomas), grade III-IV gliomas (high-grade gliomas), meningiomas, acoustic neurinomas, pituitary adenomas and other types of tumors (Kleihues *et al.* 1993).

The original histological grouping, as described in Table 10, was used in study III. In study II the histological groups were combined into three groups: namely gliomas (i.e. grade I-IV gliomas), meningiomas, and others (acoustic neurinomas, pituitary adenomas, and other types). The study sample in paper I included only patients having grade I-II gliomas, grade III-IV gliomas or meningiomas, and these three exclusive groups were used in statistical analyses. In study IV three different histological groups were used: grade I-II gliomas, grade III-IV gliomas and others (meningiomas, acoustic neurinomas, pituitary adenomas and other benign tumors)

In study V tumors were divided into two subgroups for the statistical analyses; gliomas (grade I-IV) and other tumors (meningiomas, acoustic neurinomas, pituitary adenomas and other types).

#### 4.2.3.3 Tumor volume (III, V)

The volume of the tumor was determined manually from the CT or MRI by a trained physician in the neurosurgical ward. The tumors were categorized into two groups according to the tumor volume i.e.  $\leq 25$  ml, and  $> 25$  ml in the study III and V (Salo *et al.* 2002) (Table 10).

### 4.3 Assessment of psychiatric symptoms

Depressive and anxious symptoms of the patients were evaluated at three time points. They were firstly assessed before surgery, i.e. during the admission for the surgical operation of a brain tumor, within 1-3 days before operation. After that, two follow-up measurements for psychiatric symptoms were performed – the first assessment was done after three months and the second after one year from the brain tumor surgery. Psychiatric symptoms were assessed using two structured screening instruments - the Crown-Crisp Experiential Index (CCEI) and the Beck Depression Inventory (BDI). Some cases were missed before operation due to severe dysfunction of patients' somatic condition, e.g. confusion or state of unconsciousness due to raised intracranial pressure, or tumor-induced motor aphasia, and successful measurements were thus not obtained for all the subjects at all times.

#### 4.3.1 Crown Crisp Experiential Index (I-V)

The level of anxiety, obsessive-compulsive symptoms and history of previous depression were assessed using appropriate subscales of Crown-Crisp Experiential Index (CCEI), earlier called the Middlesex Hospital Questionnaire (Crown & Crisp 1966).

According to Crown & Crisp (1966), CCEI has been formulated for three different purposes: to describe normal and deviant groups, to study psychosomatic interrelationships, and as a clinical psychometric test to study personality change following either psychological or somatic therapies. CCEI is a self-rating scale consisting of six different subscales designed to measure neurotic psychopathology: free-floating anxiety (FFA), phobic anxiety (PHO), obsessionality (OBS), somatic anxiety (SOM), depression (DEP) and hysteria (HYS). Each subscale contains eight items and total score in each subscale can vary from 1 to 16 (Crown 1974).

CCEI has frequently been used in studies on patients with psychiatric (Elliot *et al.* 2000) or somatic diseases (Haines *et al.* 2001, Kelly *et al.* 1996) and in studies screening normal population to find neurotic psychopathology (Lindeman & Joukamaa 2002). CCEI has also been validated for Finnish population (Joukamaa 1992). In the present study, the subscales for anxiety (study I), obsessionality (study II) and a history of previous depression (study III-V) were used in statistical analyses. All these subscales have been found to be reliable and valid tools for measuring anxiety, obsessive compulsive and depressive neurotic psychopathology (Crown *et al.* 1970, Crown 1974).

##### 4.3.1.1 The assessment of anxiety

The eight items in the free-floating anxiety (FFA) subscale of the CCEI and their scoring are presented in Table 11. In study I the sum score in the FFA subscale was used as a continuous variable, since in the literature, no standard reference values or cut-off points in FFA scores are given to indicate anxious disorder in a person. Some studies have reported FFA norms for mentally healthy general practice patients and for outpatients with

psychoneurotic illness (Crown & Crisp 1970, Crisp & Priest 1971). FFA norms, i.e. mean score, and SD for middle-aged general practice patients have been shown to be 2.8 (2.8) for males and 5.4 (3.5) for females (Crisp & Priest 1971). For patients suffering from anxious neurotic disorder FFA norms (SD) have been reported to be 9.7 (3.9) for males and 11.0 (3.5) for females (Crown & Crisp 1970).

*Table 11. The items for the free-floating anxiety subscale in the CCEI questionnaire (Crown & Crisp 1966).*

The questions of free-floating anxiety in CCEI	The answers
1. Do you often feel upset for no obvious reason?	No=0, Yes=2
2. Have you felt as though you might faint	Never=0, Occasionally=1, Frequently=2
3. Do you feel uneasy and restless?	Never=0, Occasionally=1, Frequently=2
4. Do you sometimes feel really panicky?	No=0, Yes=2
5. Would you say you were a worrying person?	Not at all=0, Fairly=1, Very=2
6. Do you often feel 'strung-up' inside?	No=0, Yes=2
7. Have you ever had the feeling you were 'going to pieces'?	No=0, Yes=2
8. Do you have bad dreams, which upset you, when you wake up?	Never=0, Sometimes=1, Frequently=2

#### *4.3.1.2 The assessment of obsessionality*

The eight items in the obsessionality subscale (OBS) of the CCEI and their scoring are presented in Table 12. Similarly to the FFA subscale, due to the lack of standard reference values or exact cut-off points for obsessionality the sum score of the OBS subscale was analyzed as a continuous variable in study II. The OBS subscale norms (SD) for general practice patients have been reported to be 6.8 (2.8) for males and 7.4 (2.9) for females (Crisp & Priest 1971). Furthermore, the OBS norms for patients with obsessive-compulsive disorder have been reported to be 8.7 (3.5) for males and 8.2 (3.8) for females (Crown & Crisp 1970).

*Table 12. The items for the obsessionality subscale in the CCEI questionnaire (Crown & Crisp 1966).*

The questions of obsessionality in CCEI	The answers
1. Do people ever say you are too conscientious?	No=0, Yes=2
2. Do you think, “cleanliness is next to godliness”?	No=0, Yes=2
3. Do you think that silly thoughts keep recurring in your mind?	Never=0, Sometimes=1, Frequently=2
4. Are you happiest when you are working?	No=0, Yes=2
5. Are you perfectionist?	No=0, Yes=2
6. Do you have to check things to an unnecessary extent?	No=0, Yes=2
7. Does it irritate you if your normal routine is disturbed?	Not at all=0, A little=1, Greatly=2
8. Do you find yourself worrying unreasonably about things that do not really matter?	Never=0, Sometimes=1, Frequently=2

#### *4.3.1.3 The assessment of history of previous depression*

Information on previous depression was obtained from the depression subscale in the CCEI. The DEP subscale included the question: “Do you experience long periods of sadness?” (Never = 0, Sometimes = 1, and Often = 2). In studies III and IV previous depression was indicated to be present if a patient had reported experiencing long periods of sadness ‘Often’.

#### *4.3.2 Beck Depression Inventory (III, IV, V)*

Depressive symptoms were evaluated by the Beck Depression Inventory (BDI). The BDI is a 21-item self-report rating inventory measuring characteristic attitudes and symptoms of depression (Table 13) (Beck *et al.* 1961). BDI is widely used and accepted as a screening instrument for depressive symptoms corresponding to diagnostic criteria for depressive disorders according to DSM-IV (Beck *et al.* 1988, Groth-Marnat 1990). The BDI is found to be a reliable instrument in evaluating the level of depression in psychiatric and non-psychiatric populations (Beck *et al.* 1988) It is also known to show reliably at recurrent measurements changes in the clinical depth of depression (Beck *et al.* 1961). The BDI has also been used in studies evaluating depressive psychopathology among patients with a primary brain tumor (Pelletier *et al.* 2002, Kaplan & Miner 2000).

Table 13. The items in the Beck Depression Inventory concerning the depressive symptoms of patients for diagnosis of depressive disorder (Groth-Marnat 1990).

The contents of the items in Beck Depression Inventory	
1. Sadness	12. Social withdrawal
2. Pessimism	13. Indecisiveness
3. Sense of failure	14. Change in body image
4. Dissatisfaction	15. Retardation
5. Guilt	16. Insomnia
6. Expectation of punishment	17. Fatigability
7. Dislike of self	18. Loss of appetite
8. Self-accusation	19. Loss of weight
9. Suicidal ideation	20. Somatic preoccupation
10. Episodes of crying	21. Low level of energy
11. Irritability	

Each item (i.e. 1-21) mentioned in Table 13 is scored from 0 to 3. Consequently, the sum score of the total BDI scale can range from 0 to 63. Sum scores 5 - 9 are considered to indicate a normal mood state, while sum scores 10 - 18 indicate mild to moderate depression, sum scores 19-29 moderate to severe depression and sum scores 30-63 indicate severe depression (Beck *et al.* 1988). Furthermore, a sum score below 4 reflects possible denial of depression, and scores over 40 indicate possible exaggeration of depression, e.g. characteristic of histrionic or borderline personality disorders (Groth-Marnat 1990).

The cut-off point for screening depression has been recommended to be 9/10 among medical patients and 12/13 among psychiatric patients (Beck & Beamesderfer 1974). Further, e.g. among patients with Parkinson's disease the cut-off point 8/9 has been shown to be a valid screening instrument for depression with low specificity, while the cut-off score 16/17 has been shown to have high specificity but low sensitivity (Leentjens *et al.* 2000). Among treatment-seeking outpatient-care patients the cut-off 14/15 has been shown to be valid for screening an episode of major depressive disorder (Viinamäki *et al.* 2004).

In studies II-V, depression of the patient was defined to be present if the BDI sum score was 10 or higher. In study IV, the BDI depression was combined with information on the history of previous depression (see 4.4.1.3) and three study groups were formed: 1. Current depression (BDI sum score 10 or higher) 2. Previous depression (patients report having a previous history of depression) 3. No current or previous depression (BDI sum score below 10 and no previous history of depression).

#### 4.4 Assessment of functional state (III, V)

The overall functional state of the patients was assessed by the Karnofsky Performance Scale (KPS) (Karnofsky & Burchenal 1949) before tumor operation as well as three months and one year after surgery (Table 14). This scale is intended to measure the person's ability to work, his physical activity and self-care. The physician-categorized ratings can vary from 0 (dead) to 100 (healthy) at 10-unit intervals. KPS has been used to assess functional status in earlier studies of brain tumor patients (Giovagnoli *et al.* 1996, Weitzner *et al.* 1996).

In study III the patients were categorized into two groups according to their KPS scores: KPS scores over 70 and KPS scores of 70 or lower. In study V, the mean values of KPS scores were used in the statistical analyses.

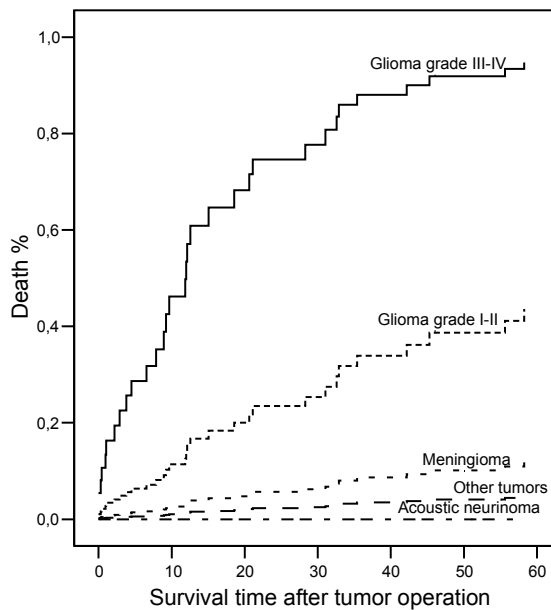
*Table 14. The definition criteria for the Karnofsky Performance Scale (Schag et al. 1984).*

Functional state	Rating value	Definition of the rating criteria
Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

#### 4.5 Assessment of the survival time (IV)

The exact date of death was obtained from the national Cause of Death Register provided by Statistics Finland. The survival time of the patients was calculated from the date of the brain tumor surgery to the date of death or to the date of the end of follow-up time (five years).

Survival curves of the patients after 60 months of surgery according to different histological diagnosis of the tumors (i.e. grade I-II gliomas, grade III-IV gliomas, meningiomas, acoustic neurinomas and others) are presented in Figure 4. At five years after tumor surgery 86% of the patients with a grade III-IV glioma, 32% of the patients with a grade I-II glioma, 18% of the patients with a meningioma and 7% of the patients with “other” tumor had died. All patients with an acoustic neurinoma survived at five years after the tumor surgery.



**Fig. 4.** The survival curves of the neurosurgical patients (n=101) according to the histological diagnosis of their primary brain tumors at five years after tumor surgery,  $p < 0.001$  Kaplan-Meier survival analysis.

In study IV, the survival status and survival time of each patient was assessed 60 months after surgery. If the patient was alive at that time, his/her survival time was determined to be 60 months. Otherwise, the survival time was the time between the surgery and the death of the patient.

#### 4.6 Assessment of quality of life (V)

The assessment of quality of life of the patients was performed using Sintonen's 15D. The patients' QOL was assessed by Sintonen's 15D scale before tumor operation as well as at three months and at one year after the operation by a trained physician. Sintonen's 15D scale is a generic, comprehensive, 15-dimensional, standardized, self-administered measure of health-related quality of life (Sintonen 2001) (Table 15). Each item is categorized into five levels. The higher the score, the better the functioning of that item. It is possible to obtain a sum score 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. The 15D instrument has also been used in previous studies assessing QOL among cancer patients and depressive patients (Lönnqvist *et al.* 1995, Rönkä *et al.* 2004).

*Table 15. The 15 different dimensions of Sintonen's 15D scale for assessing a person's quality of life (Sintonen 2001).*

The items in the Quality of Life Questionnaire (15D)	
1. Mobility	10. Mental functions
2. Vision	11. Discomfort and symptoms
3. Hearing	12. Depression
4. Breathing	13. Distress
5. Sleeping	14. Vitality
6. Eating	15. Sexual activity
7. Speech	
8. Elimination	
9. Usual activities	

## 4.7 Statistical methods

In the studies included in this thesis group differences in categorical variables were assessed with Pearson's Chi-square test or Fisher's Exact test. In continuous variables group differences were investigated with Student's t-test or Mann-Whitney U-test (two independent samples) or Kruskal-Wallis test (more than two independent groups), whichever appropriate. The differences between repeated measurements were analyzed with Wilcoxon signed rank test (two repeated measurements) or Friedman's test (three or more repeated measurements). Spearman rank order correlation was used when evaluating linear relationship between two variables.

In study IV Cox proportional hazard model was used to determine the relative risk between each independent variable and the outcome variable (survival time) after adjustment for the effect of all other variables in the model. In study V the analysis of covariance (ANCOVA) was used to assess the group difference (depressed vs. non-depressed patients) in QOL and functional state after adjusting for age and tumor histology (type, volume and location of the tumor), psychosocial variables (a history of previous depression, marital and employment status, educational state) and treatment modalities in three models for male and female patients, separately.

All statistical analyses were performed by using the SPSS statistical software, version 10 or 11, and the results in this study were considered statistically significant when the appropriately calculated two-tailed p-value was  $<0.05$ .

## 4.8 Ethical considerations and personal involvement

The Ethics Committee of Oulu University Hospital has approved the study protocol. This permission by the Ethics Committee of the Faculty of Medicine covers the present study as well. Written informed permission was available from all the patients. The database complies with present scientific demands of the Data Protection Act. In the scientific articles only group analyses are presented, and personal information of the patients cannot be identified.

The study design in this thesis has been accepted by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu on 4 March 2004. Since 2002, the author has participated as a researcher in the Project of Quality of Life among Patients with a Primary Brain Tumor at the Neurosurgery Clinic of Oulu University. The author has been accorded permission to use data and has participated in design, data analysis and reporting the results in all original papers I-V.

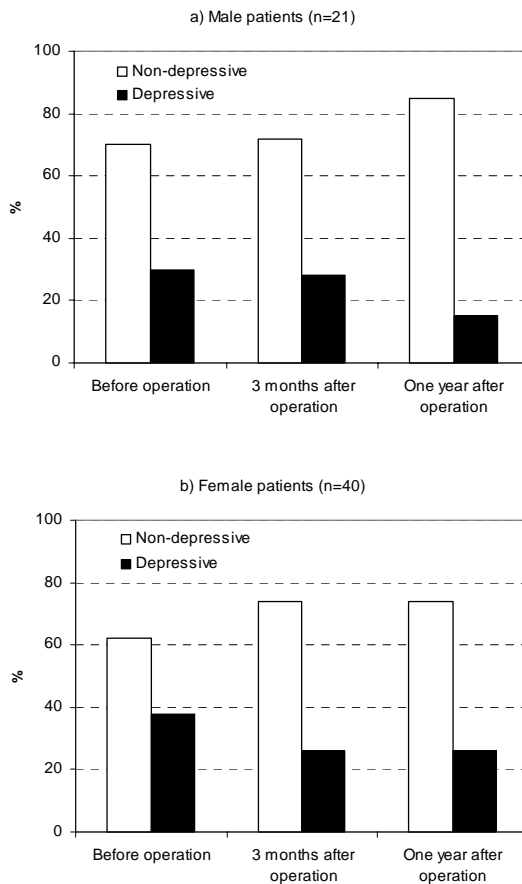
## **5 Results**

### **5.1 General description of depressive and anxious symptoms**

The prevalence of depressive symptoms assessed with Beck Depression Inventory (BDI), the level of anxiety according to the Free Floating Anxiousness (FFA) in the Crown Crisp Experiential Index (CCEI) and the level of obsessive-compulsive symptoms (OBS) in the CCEI for male and female patients, separately, in a total study sample are demonstrated in Figures 5–7.

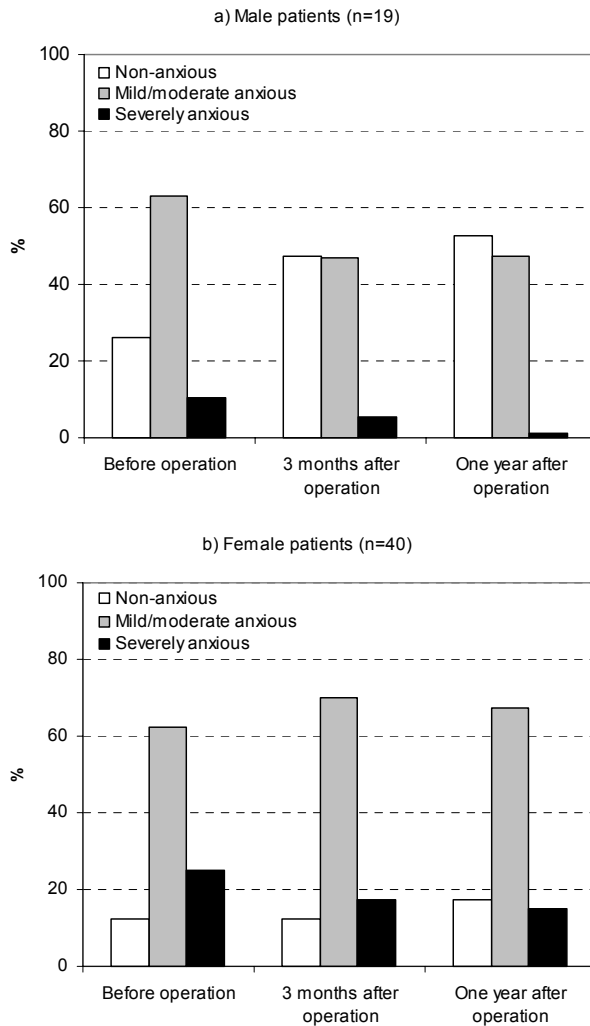
As shown in Figure 5, in the male patients the prevalence of at least mild depression (BDI) before operation was 30%, while it was 28% and 15% at three months and at one year after operation, respectively. In the female patients, 38% of patients were shown to be at least mildly depressed before tumor operation. Furthermore, at three months as well as at one year after operation 26% of females were found to have at least mild depression. The prevalence of depressive symptoms before operation and in two follow-up assessments did not differ statistically significantly between genders.

Before tumor operation the prevalence of major depression (BDI scores 14 or over) was 10% for males and 19% for females. At three months and at one year after operation the prevalence of major depression was 13% and 7% for males, and the corresponding prevalences for females were 6% and 15%.



**Figure 5. The prevalence of depressive and non-depressive subjects before operation and in the two follow-up assessments among a) male, and b) female patients with a primary brain tumor. Diagnostic groups: non-depressive = sum score in the Beck Depression Inventory (BDI) scale below 10, depressive = sum score in the BDI 10 or higher.**

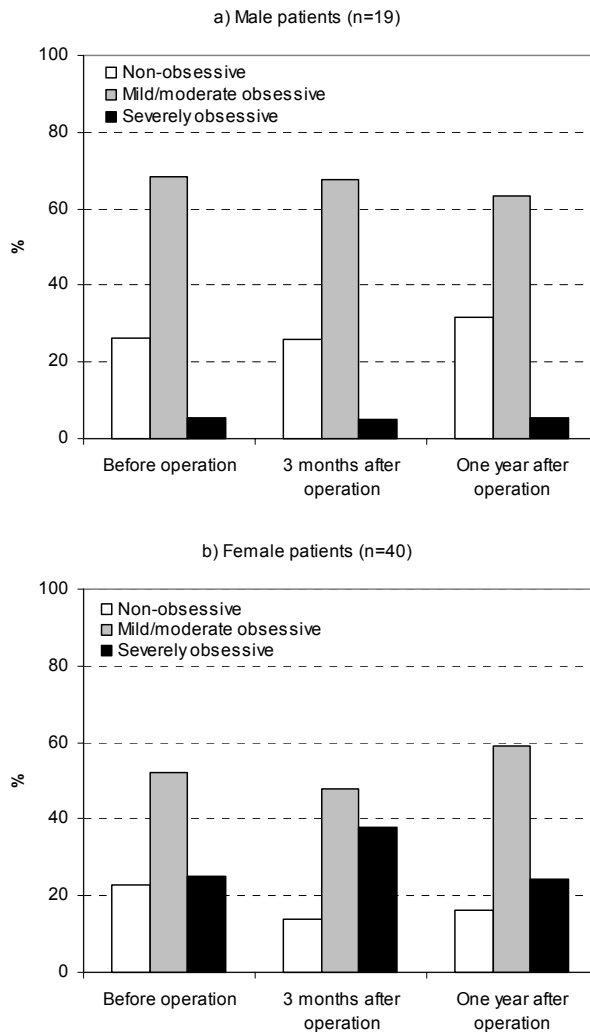
Figure 6 shows that before tumor operation 14% of the male patients were severely anxious (FFA), while the corresponding proportions were 7% at three months after operation, and 4% at one year after operation in the males. In the female patients, 27% of the subjects had reported to be severely anxious before tumor operation. The corresponding proportions for severely anxious females were 18% at three months and 14% at one year after operation. The level of anxiety differed statistically significantly between the genders at three months ( $p=0.015$   $\chi^2$ -test) and at one year ( $p=0.037$ ,  $\chi^2$ -test) after tumor operation, but not before tumor operation.



**Fig. 6. The level of anxiety (FFA) before operation and at two follow-up assessments among a) male, and b) female patients with a primary brain tumor. Diagnostics groups: Free Floating Anxiety (FFA) subscale in Crown Crisp Experiential Index: non-anxious = FFA sum score 0-1, mild/moderate anxious = sum score 2-6, severely anxious = FFA sum score 7 or higher.**

As seen in Figure 7, 14% of the males were severely obsessive (OBS) before tumor operation. However, the proportion of severely obsessive males decreased to 9% at three months and further to 7% at one year after tumor operation. Among females the prevalence of severe obsessiveness was 25% before tumor operation, and it increased at three months after tumor operation up to 38%, decreasing back to a proportion of 25% of severely obsessive females at one year from operation. The gender difference in

obsessionality groups was found to be statistically significant only at three months after operation ( $p= 0.022$ ,  $\chi^2$ -test).



**Fig. 7. The level of obsessionality (OBS) before operation and in two follow-up assessments among a) male, and b) female patients with a primary brain tumor. Diagnostic groups: Obsessionality subscale (OBS) in Crown Crisp Experiential Index: non-obsessive OBS sum score 0-4, mild/moderate obsessive = OBS sum score 5-9, severely obsessive = OBS sum score 10 or higher**

## 5.2 Psychiatric symptoms and brain tumor location (I-III)

### 5.2.1 Anxiety and brain tumor lateralization (I)

In study I the main focus was on the prevalence of anxiety in relation to tumor laterality. Regarding the anxiety level according to CCEI assessed before tumor operation, the patients with a tumor in the right hemisphere were shown to have substantially higher anxiety scores (mean 5.75, SD 3.32) compared to those with a tumor located in the left hemisphere (mean 3.59, SD 3.12) ( $p = 0.032$ , Mann Whitney U-test,  $Z=-2.14$ ) as seen in Figure 8. (I: Figure 1) Corresponding differences in the level of anxiety were not found after three months and after one year from the operation. Furthermore, a statistically significant decline in anxiety levels from brain surgery to the follow-up assessments was found in patients with a right hemisphere tumor ( $p = 0.015$ , Friedmann test for repeated measures,  $\chi^2= 8.40$ ,  $df=2$ ), while no significant difference between measurements was observed among patients with left hemisphere tumors.

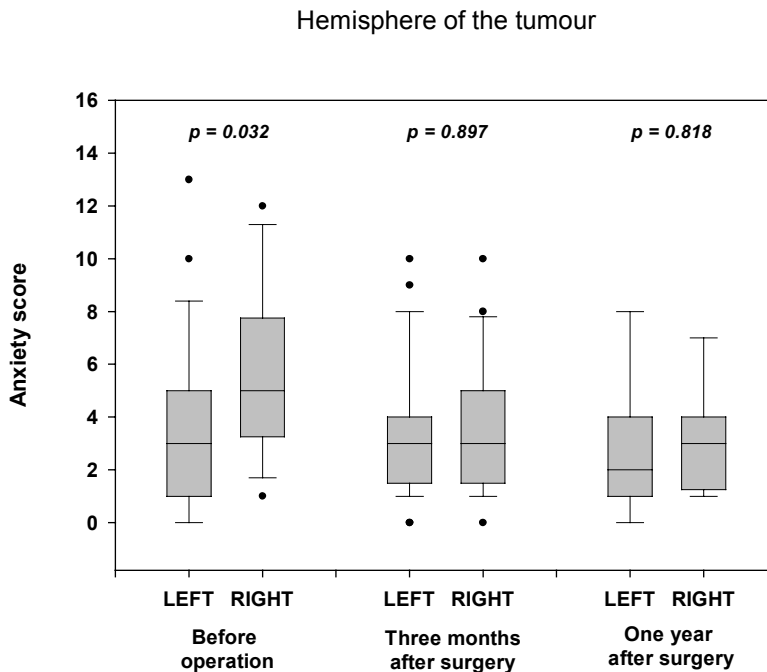


Fig. 8. The mean anxiety scores (CCEI) according to brain laterality at preoperative, three-month and one-year measurements among brain tumor patients from northern Finland (I: Figure 1).

### ***5.2.2 Obsessive compulsive symptoms and brain tumor location (II)***

In study II, the changes over time in the level of obsessionality (OBS) by the CCEI were investigated according to lateralization and anterior/posterior location of the tumor. In the female patients having a primary brain tumor in the left anterior hemisphere there was a statistically significant increase in the level of obsessionality between preoperative and three-month postoperative measurements ( $p=0.007$ , Wilcoxon signed rank test). No corresponding increase in the level of obsessionality was found in females if the tumor was located in any other region of the brain, nor in any males. Further, no significant changes in the mean obsessionality scores were found at the measurements between three months and one year after operation, or at the measurements between preoperative measurements and one year after the operation in any defined brain region in males or females (II: Table 2).

Another finding, as seen in Figure 9, was that at preoperative measurements the level of obsessionality was notably high among patients with the tumor in the right anterior hemisphere (right anterior vs. left anterior  $p=0.021$ , right anterior vs. right posterior  $p=0.055$ , Mann-Whitney U-test), and it remained notably high (the mean obsessionality scores  $> 8.0$ ) also in subsequent measurements.

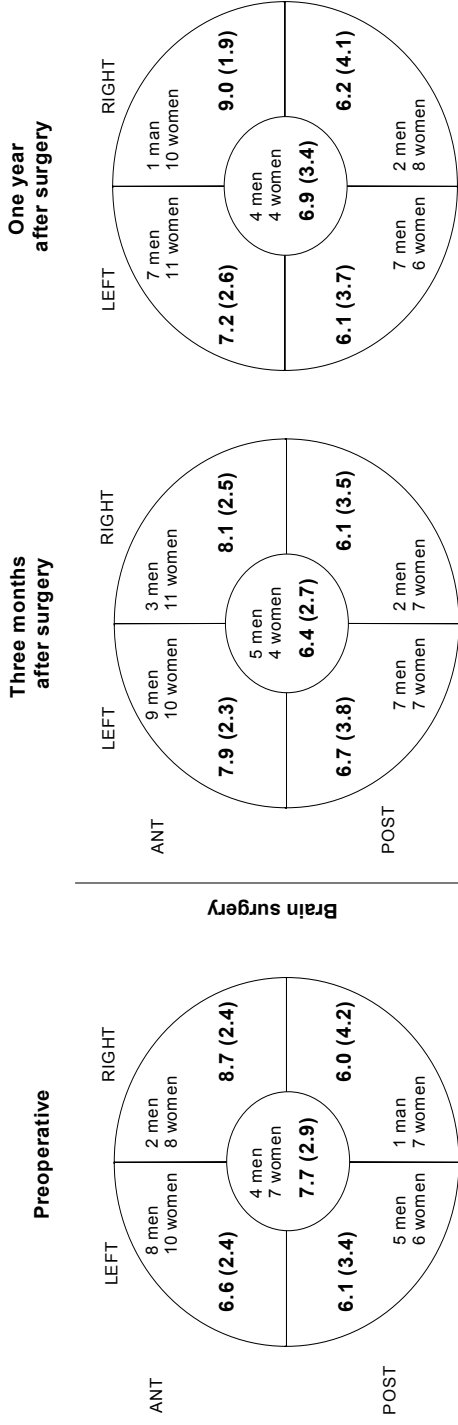


Fig. 9. The mean obsessiveness scores (OBS) by Crown Crisp Experiential Index according to the location of the tumor in male and female brain tumor patients before the operation and at two follow-up measurements after the operation.

### ***5.2.3 Depression and brain tumor location (III)***

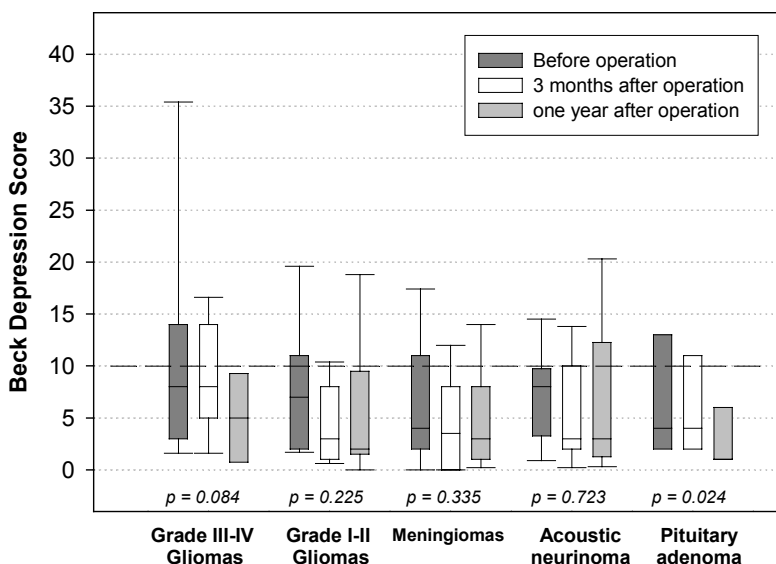
While assessing the association of depression with tumor location in study III the patients with a tumor located anteriorly in the hemispheres had a trend for higher depression (BDI) scores (mean 9.4, SD 8.7) before tumor operation compared to those with a tumor in posterior regions of the brain (mean 5.7, SD 6.0) ( $p=0.057$ , Mann-Whitney U-test) (III: Table 3). This difference in the level of depression was, however, not found at three months and at one year after the surgery.

The level of depression decreased statistically significantly from the mean (SD) scores 9.4 (8.7) before surgery to the scores 6.1 (5.2) at three months after the operation among the patients with an anterior tumor ( $p= 0.049$ , Wilcoxon Signed Rank test). A corresponding decrease between preoperative and postoperative measurements was not found if the tumor was located in the posterior regions of the brain.

## **5.3 Tumor histology and psychiatric symptoms (I, III)**

The level of anxiety in study I and the level of depression in study III was investigated in relation to histology of the tumor in the patients. Results of study I showed that in the patients with a high-grade glioma in the right hemisphere the anxiety scores (FFA) by CCEI (mean 4.7 SD 2.0) declined statistically significantly between measurements before tumor operation and at three months after the operation (mean 2.4 SD 1.5) ( $p=0.018$ , Wilcoxon signed rank test) (I: Table 2). No differences in the level of anxiety were found in the patients with a glioma (low-grade or high-grade), with a meningioma in the left hemisphere or in the patients with a meningioma in the right hemisphere (I: Table 2).

Also, as seen in Figure 10 (III: Figure 2), the level of depression did not differ between the histological subgroups, being thus independent on the malignant or benign status of the tumor. However, a change over time in the depression level was observed in the patients with a pituitary adenoma (PA), whose depression scores decreased significantly during the follow-up from 6.7 (5.6) to 2.4 (2.8), ( $p=0.019$ , Friedman Test for repeated measurements).



**Fig. 10.** The mean Beck scores in the brain tumor patients according to the histology of the tumor before operation and at three months and at one year from surgery.

## 5.4 Depression in brain tumor patients (III-V)

The prevalence of depression was studied in paper III. The mean (SD) BDI scores for males were 6.9 (6.9), the corresponding scores for females being 8.9 (7.9). At three months after tumor operation the mean depressive scores were statistically significantly decreased in the whole database ( $p=0.031$ ,  $z=-2.157$  Wilcoxon Signed Rank Test).

The mean depressive scores in the male patients decreased statistically significantly ( $p=0.047$ ,  $z=-1.989$ , Mann-Whitney U-test) by 12 months after tumor operation, while among the females the scores decreased statistically significantly ( $p=0.046$ ,  $z=-1.995$ , Mann-Whitney U-test) already at three months after tumor surgery (III: Figure 1).

### 5.4.1 Depression and survival of the patients (IV)

In the five-year follow-up of the patients, survival time of the patients with high-grade (III-IV) gliomas was shown to be 22.5 (SD 21.4) months while it was 50.2 (19.9) months for the patients with low-grade (I-II) gliomas, and 58.2 (9.4) months for the patients with

meningiomas, pituitary adenomas, and acoustic neurinomas ( $p < 0.001$ , difference between groups, Kruskal-Wallis test) (IV: Table 1). Furthermore, as shown in Table 18 in the subgroup of patients with low-grade gliomas, depressive patients were found to have a significantly shorter survival (median 51.7 (0-60) months) compared to non-depressive subjects (60 (0-60) months) ( $p = 0.031$ , Kaplan Meier survival analysis, log-rank=4.67, df=1) (IV: Table 2). A corresponding difference between depressive and non-depressive subjects was not found in the subgroups of patients with high-grade gliomas or benign tumors.

*Table 18. Equality of survival distributions for depression groups by diagnostic groups according to histology of tumor in patients with primary brain tumor.*

Depression status by the histology of the tumor <sup>a</sup>	Total number of cases	Proportions of subjects alive at the end of follow-up	Survival time after surgery Med (min-max)	Equality of survival distributions for depression groups <sup>b</sup>		
				Overall difference, log-rank (df=2) <sup>c</sup>	p-value	Pairwise
Gliomas grade III-IV	15	20.0		0.39	0.824	
No depression	6	33.3	12.3 (1-60)			
Previous depression	2	0	15.2 (9-21)			
Current depression	7	14.3	15.1 (1-60)			
Gliomas grade I-II	16	68.7		5.55	0.063	0.031
No depression	5	100.0	60.0 (60-60)			(log-rank =
Previous depression	5	80.0	60.0 (5-60)			4.67,
Current depression	6	33.3	51.7 (0-60)			df= 1)
Benign tumors	44	95.4				
No depression	15	100.0	60.0 (60-60)	1.06	0.588	
Previous depression	15	93.3	58.2 (33-60)			
Current depression	14	92.9	60.0 (3-60)			
Overall	75	74.7				

<sup>a</sup> No depression = no life-time depression, previous depression = a history of depressive periods, but not currently depressive, current depression = depression according to BDI assessed before operation

<sup>b</sup> Survival estimates and equality of survival distributions are calculated using Kaplan-Meier survival analysis

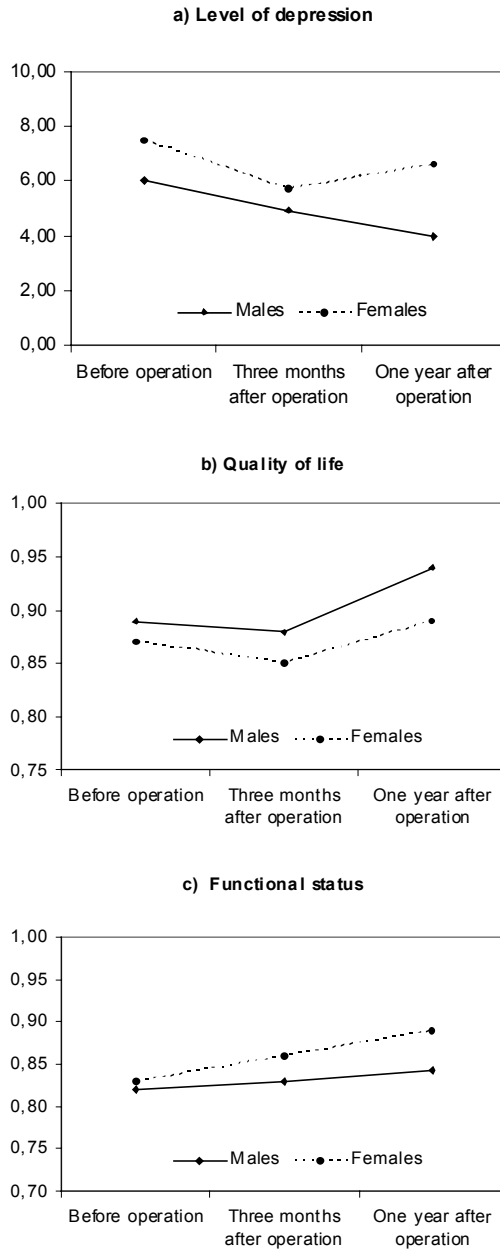
<sup>c</sup> Only significant differences in pairwise comparisons (no depression versus current depression) are reported

### ***5.4.2 Depression, functional outcome and quality of life (III, V)***

Before tumor operation, 50% (n=13) of the patients with decreased functional status (KPS < 70) had depression, while only 27% (n=14) of those with KPS scores over 70 were depressed ( $p= 0.022$ , Chi-Square Test) (III: Table 1). Decreased functional status (KPS under 70) among the patients was also significantly correlated with increased depression on both follow-up measurements at three months and at one year after operation ( $r= -0.140$ ,  $p< 0.001$  and  $r= -0.545$ ,  $p< 0.001$ , respectively) (III: Table 2).

Figure 11 (V: Figure 1) shows that females had lower QOL in all measurements compared to males ( $p=0.054$ ). In males, a statistically significant increase in QOL was observed between pre-operative measurements and those made one year after the operation ( $p=0.046$ , Wilcoxon signed ranks test) as well as between postoperative measurements three months and one year after the operation ( $p=0.001$ , Wilcoxon signed ranks test).

The level of QOL measured before tumor operation was found to be statistically significantly lower in depressed patients compared to non-depressed ones in both genders. The mean difference between depressed and non-depressed patients in QOL and functional state remained statistically significant in all follow-up measurements in female, but not in male patients. (V: Table 2)



**Fig. 11.** The change over time in the level of depression, functional outcome and quality of life among male and female patients with a primary brain tumor. Scales used: Beck Depression Inventory (BDI) for depression, Sintonen's 15D for quality of life, Karnofsky Performance Scale (KPR) for functional state.

## **6 Discussion**

### **6.1 Overview of the results**

Depressive symptoms as well as anxious and obsessive psychopathology were shown to be prevalent signs among neurosurgical patients with a primary brain tumor in Northern Finland; the prevalence of at least mild depression before tumor operation was as high as 30% for males and 38% for females. Although the proportion of depressed patients decreased significantly after tumor operation, the prevalence of at least mild depression was still notably high, i.e. 15% for males and 26% for females at one year after the tumor operation. Before tumor operation, severe anxious as well as severe obsessive-compulsive symptoms were present in 14% of males. In females 29% of the subjects had reported to have severe anxiousness and 25% severe obsessive symptoms. The prevalence of severe anxiousness, however, decreased during follow-up both in females to 14% and in males to 4%. On contrary to anxiety symptoms, the prevalence of severe obsessionality in female patients increased significantly up to the three-month measurement point, while in males it decreased during follow-ups. Above all, the level of severe obsessionality among patients was high at the one-year follow-up, especially in females.

The study on the association of tumor lateralization with the anxiety of patients showed that before tumor operation the level of anxiety was substantially higher in the patients with a tumor in the right hemisphere compared to those with a left hemispheric tumor. Furthermore, the level of anxiety decreased significantly after three months from tumor operation in the patients with a right hemispheric tumor.

While investigating the level of obsessionality in relation to tumor location it was found that in the female patients with a tumor in the left anterior region of the brain the obsessionality scores were significantly increased at three months after operation. However, in the patients with a tumor in right anterior location severe obsessionality was already present before tumor operation as well as at two follow-ups.

The association of depression with tumor location and with the patients' functional outcome was also investigated. The anterior location of the tumor of the patients was found to be associated with higher preoperative depressive scores compared to the scores of the patients suffering from a posterior location of the tumor. In addition, depression in the patients was found to significantly correlated with the patients' decreased functional outcome before tumor operation and at both follow-ups.

The five-year survival time after the tumor operation for the patients with a primary brain tumor was shown to vary significantly and was dependent on the malignancy of the tumor. The higher the malignancy of the tumor, the shorter was the survival of patients. Further, the survival time for depressive low-grade glioma patients was significantly shorter compared to non-depressive subjects with a low-grade glioma.

The study examining the association of depression with the patients' quality of life revealed that the scores indicating the quality of life of the patients were lower in females compared to males at all measurement points. Decreased quality of life was found in particular among depressive female patients compared to non-depressed ones at all three measurements.

## 6.2 Discussion of the results

Depression among patients with a primary brain tumor was shown to be a major psychiatric symptom, and in all likelihood it complicated the course of the disease before and after operation. In addition, obsessive and compulsive symptoms in females appeared to increase as early as at three months after operation among those with a tumor in left anterior location of the brain. Severe obsessiveness was found especially in female patients with a tumor in right anterior location of the brain at all measurement points.

In earlier literature, depression among cancer patients was considered to be a normal psychological reaction to a serious illness (Spiegel 1996). Nowadays, there is growing evidence that depression in cancer patients is not merely an appropriate psychological reaction, but that it also has a biological and biochemical basis (Horrobin & Bennett 1999). The pathophysiology behind the depression in relation to cancer of the patients is, in any case, most probably multifactorial in its origin. As suggested by several researchers, dysregulation of the hypothalamic-pituitary-adrenal axis and changes in cytokine levels in the brain may lie behind the association between depression and cancer (Spiegel 1996, Horrobin & Bennett 1999). Further, depression in cancer patients complicates coping with the disease, causes worsening of quality of life and interferes with adherence to medical treatment (Spiegel & Giese-Davis 2003).

The prognosis of cancer patients may worsen particularly due to depression, since depression often prevents patients from complying with treatment regimens and other health-promoting behaviors (Evans & Charney 2003). Both obsessive-compulsive symptoms and depression are known to decrease the quality of life of the patients (Hollander *et al.* 1996, Pelletier *et al.* 2002).

## ***6.2.1 The prevalence of depressive, anxious and obsessive psychopathology***

### *6.2.1.1 Depression among brain tumor patients*

The findings of the studies in this thesis showed that the prevalence of at least mild depression in brain tumor patients before tumor operation was remarkably high, being 30% for males and 38% for females. The prevalence of depression indicating an episode of major depression was 10% for males and 19% for females at diagnosis of brain tumor. The 12-month prevalence of any depressive disorder in Finnish general adult population has been found to be 4.5% for males and 8.2% for females (Pirkola *et al.* 2005). The prevalence of major depressive disorder has not been changed over the years in Finland, being 3% in males and 7% in females (Lehtinen *et al.* 1993, Pirkola *et al.* 2002). In Finnish health center patient population the prevalence of depression has shown to be 10% (Salokangas *et al.* 1996). In clinical patient samples, among patients with a meningioma or a glioma the prevalence of depression before operation has been reported to be 16% (Pringle *et al.* 1999), while after tumor operation it has varied from 15% to 38% (Anderson *et al.* 1999, Pelletier *et al.* 2002, Wellisch *et al.* 2002, Litofsky *et al.* 2004). Thus, the findings of this thesis regarding the high prevalence of depression are in line with earlier studies. What is notable in this thesis is that the prevalence of at least mild depression remained at a high level also at one year after tumor operation. In addition, the level of depression indicating an episode of major depressive disorder in this study was two-fold for both males and females at one year after operation compared to the prevalence of major depression in Finnish general population (Pirkola *et al.* 2002).

Depression in medically ill patients is difficult to determine because somatic symptoms themselves can cause over-diagnosis of depression. Anorexia, weight loss, sleep disturbance, psychomotor changes, fatigue, loss of energy, decreased sexual drive and decreased concentration diagnosis are common symptoms in physically ill patients (Cavanaugh 1983). On the other hand, overemphasized somatic symptoms might in fact differentiate depressed physically ill patients from non-depressed ones, since physically ill patients with symptoms of clinical depression have been found to be characterized by overwhelming somatic symptoms in contrast to physically ill patients without any signs of depression (Emmons *et al.* 1987).

The literature on psychiatric disorders among patients with a primary brain tumor has been divided as regards the conceptualization and measurement of depression (Pelletier *et al.* 2002). Also, it is not yet known well enough whether the mood symptoms of patients are due to direct effects of the tumor or whether they are psychological reactions in adapting to the diagnosis of severe disease (Pringle *et al.* 1999). In conclusion, earlier literature (Spiegel 1996) and the findings of this thesis firmly suggest that depression in cancer patients has been underdiagnosed and undertreated, probably mainly due to the belief that depression is a normal and universal reaction to serious illness.

### 6.2.1.2 Anxiety and obsessionality in brain tumor patients

The prevalence of severe anxious symptoms in the patients before tumor operation was about three-fold for males and 2.5-fold for females compared to the prevalence of anxious disorder in Finnish general population. The prevalence of anxious disorder has been reported to be from 3.7% to 6% in males and from 4.8% to 12% in females in the general Finnish population (Lehtinen *et al.* 1993, Pirkola *et al.* 2005).

Among glioma and meningioma patients, the prevalence of anxiety symptoms before tumor operation has been reported to be 15% for males and 50% for females (Pringle *et al.* 1999). Furthermore, 5% of the patients with a glioma or meningioma had been found to show clinically significant levels of anxiety 16 months after operation (Anderson *et al.* 1999). Consequently, the findings in this study are in line with earlier studies concerning high level of anxiety before tumor operation and lower level of anxiety about one year after operation. In fact, the level of severe anxiousness up to one year after the tumor operation reached the level of anxious disorder observed in the general population in both males and females. The gender difference in anxiety found in this study seemed to represent well the gender difference existing in the prevalence of anxiety in general Finnish population.

The prevalence of severe obsessionality in males, indicating obsessive compulsive neurosis, before tumor operation was about six times higher compared to the rates in the general population. Although the proportions of obsessive males decreased up to the one-year follow-up, the prevalence remained about three times higher compared to general population. In females, however, the prevalence of severe obsessionality after tumor operation was about ten times higher than in the general population. It increased from preoperative 25% to 38% at three months after operation. In international studies, the prevalence of obsessive-compulsive neurosis is reported to vary between 2-3% in general population (Karno *et al.* 1988, Wells *et al.* 1989).

In previous literature, obsessive-compulsive symptoms have frequently been associated with different types of brain dysfunction or brain damage of the patients (McKeon *et al.* 1984, Cheyette *et al.* 1995, Berthier *et al.* 2001, Stengler-Wenzke & Müller 2002). Surprisingly, case reports have only been published in brain tumor patient samples describing feelings of compulsions or the onset of obsessive-compulsive symptoms presented as a symptom of brain tumor (Ward 1988, Paradis *et al.* 1992, John *et al.* 1997). Thus, the finding of this thesis indicating a high prevalence of severe obsessionality among brain tumor patients with a tumor anteriorly in the brain is important and it is also worth confirming in other databases for brain tumor patients. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) anxiety disorder due to a general medical condition also contains the category "Anxiety disorder with obsessive-compulsive symptoms: if obsessions or compulsions predominate in the clinical presentation" (American Psychiatric Association 2000). Thus, obsessive-compulsive symptoms may represent anxiety symptoms among patients with a brain tumor.

## ***6.2.2 Psychiatric symptoms in relation to tumor location and the change over time***

Any lesion, e.g. brain infarct, injury, or tumor that destroys or disturbs brain structures can be expected to have an effect on a person's motor, sensory or neurobehavioral functioning (Filey & Kleinschmidt-Demasters 1995). Brain lesions caused by tumors are not so discrete and clearly defined as are for example cerebrovascular lesions, and therefore it is often not possible to notice a precise correlation between lesion location and behavioral change (Filey & Kleinschmidt-Demasters 1995). Moreover, the effect of tumor location on psychopathology among brain tumor patients has shown to be different before tumor operation on the one hand and after operation on the other hand (Irle *et al.* 1994, Pringle *et al.* 1999).

### ***6.2.2.1 Depression and brain tumor location***

The level of depression in the patients with an anterior brain tumor was higher compared to the patients with a posterior tumor as described in original publication III. The mean depression scores of the patients were significantly decreased at three months after tumor operation in the patients with an anterior tumor, being at the same level as in the patients with a tumor posteriorly in the brain. In literature the findings reporting the relation of depression to brain lesion location have been contradictory. Studies on stroke patients have reported an association of frontal lesion location with depression (Vataja *et al.* 2004, Narushima *et al.* 2003). Carson and colleagues (2000) systematically reviewed 48 studies of stroke patients and noted no support for the hypothesis of depression and lesion location. Also, a recent review of a total of 3,668 stroke patients in 52 studies pointed out that there was only a weak relationship between post-stroke depression and right hemisphere lesion (Yu *et al.* 2004). Ligand binding studies using positron emission tomography (PET) have shown alterations in serotonin transport sites in the frontal cortical regions and in cingulate cortices in depressive patients with no brain lesions, suggesting that these areas are associated with pathophysiology of depression (Reivich *et al.* 2004).

The finding in this thesis of an association of anterior tumor location with increased level of depression before tumor operation is in line with previous studies among brain tumor patient samples. In a cross-sectional study the frontal location of tumor has shown to be a highly significant predictor for a major depressive disorder after tumor operation among patients with a glioma or meningioma (Wellisch *et al.* 2002). Also, in the study of Irle and colleagues (1994), brain tumor patients with lesions in the ventral frontal cortex or lesions in the temporoparietal cortex reported significantly worse mood states immediately after operation than those with lesions in other regions of the brain.

### 6.2.2.2 Anxiety and brain tumor lateralization

The results in original publication I showed that before tumor operation the level of anxiety in patients with the tumor in the right hemisphere was significantly higher compared to the level of anxiety in patients with a left hemispheric tumor. Anxiety in brain tumor patients has been sparsely studied, and only a few case reports have so far focused on anxiety and right lateralization of the tumor in brain tumor patients (Ghadrian *et al.* 1986, Kellner *et al.* 1996, Lilja & Salford 1997). However, hemispheric right laterality in patients with brain lesions in general has been documented in earlier studies, and the findings of this study are thus in line with the earlier findings (Castillo *et al.* 1993, Cummings 1997, Paradiso & Robinson 1999, Wasserstein & Stefanatos 2000).

### 6.2.2.3 The change over time in depressive and anxious psychopathology

As shown in studies I and III, both the level of anxiety in the patients with right hemispheric tumor and the level of depression in the patients with anterior tumor decreased significantly after tumor operation. These findings accord with earlier ones. It has already been shown that if patients with brain tumors had affective symptoms before operation these symptoms decreased after the resection of the tumor (Irle *et al.* 1994, Pringle *et al.* 1999).

If anxiety and depression were only patients' psychological reactions to their serious illness, the presence of anxiety and depressive symptoms would appear in equal magnitude in patients having tumors in different locations of the brain. However, earlier findings and the one in the present thesis give support to the explanation that there is a biological basis of anxiety and depression mimicking psychological disorders, and this biological impact is specifically associated with lesion location. Also, some authors have put forward the idea that psychiatric symptoms are mainly related to the location of the tumor (Kallio 1993, Armstrong *et al.* 2004). Furthermore, the cortical interconnection with limbic structures is proposed to be more important for the development of neuropsychiatric symptoms than specific lesion location (Weitzner 1999). As noted earlier, the development of psychiatric symptoms most probably originates from frontal and/or limbic release or inhibition system dysregulation through diaschisis, i.e. due to their sudden disconnection from the damaged area, or through disconnection syndromes (Lezak 1975, Reggia 2004). This complex regulation system is mediated by different neurotransmitters involved in the pathophysiology of depression and anxiety such as serotonin, norepinephrine, dopamine, and  $\gamma$ -aminobutyric acid (Kaplan *et al.* 1994, Owens & Nemeroff 1994, Cummings 1997).

#### 6.2.2.4 *Obsessionality in relation to brain tumor location and the change over time*

The increase in the level of obsessionality was outstanding in females if the tumor was located in the left anterior hemisphere as investigated in study II. Previous case reports in male and female patients have stated that obsessions or compulsions were linked with lesions caused by a brain tumor in frontal regions of the brain (Ward 1988, John *et al.* 1997). Our results support these case reports in relation to obsessionality and neuroanatomic brain location of the tumors. Ward (1988) suggested that a focal cerebral disturbance could cause obsessive-compulsive disorder (OCD) that had earlier been considered to be purely psychological in etiology. Nowadays OCD is associated with different types of brain damage or dysfunction, and it is considered to be a neuropsychiatric disorder in which altered function in the prefrontal-basal ganglia-thalamic-prefrontal circuits is particularly important (Insel 1992). Tot and colleagues (2002) found that patients with OCD, especially female ones, had left frontotemporal dysfunction recorded by quantitative electroencephalography. Further, functional imaging studies have also demonstrated that OCD is characterized by increased activity in the orbitofrontal cortex and in basal ganglia at rest and especially during exposure to feared stimuli (Rauch & Savage 1997).

Another finding regarding obsessionality and brain tumor location in the study was that patients with a tumor in the right anterior hemisphere had mean obsessionality scores which reached the reference values of clinically psychoneurotic patients both pre- and postoperatively (Crown 1974). The level of obsessionality remained notably high until one year after operation. In previous case reports the onset of OCD has been observed after mild, moderate or severe head injury in frontal or right anterior regions of the brain (McKeon *et al.* 1984, Berthier *et al.* 2001, Stengler-Wenzke & Müller 2002). Thus, it is justified to suggest that the increased obsessionality might be related to the brain lesion that is caused by the tumor itself.

A gender difference in the increase of obsessionality was also observed in study II. The level of obsessionality three months after the operation among patients with a brain tumor situated left anteriorly was significantly higher in females compared to males. In epidemiological studies the prevalence of OCD is reported to be roughly equal in males and females (Karno *et al.* 1988, Wells *et al.* 1989, Stein 2002). Zohar *et al.* (1999), however, reported about sexual dimorphism of OCD with the explanation that OCD is differently expressed in the two sexes, and that the etiology of OCD might be different in the two genders. Gender-related differences of response to pharmacotherapy have also been documented among patients with OCD (Mundo *et al.* 2002). Thus, the gender difference in obsessionality reported in this thesis is a novel and important finding, and further studies on this topic are needed.

#### 6.2.3 *The association of psychiatric symptoms with tumor histology*

The finding of a decline in the level of anxiety scores after brain tumor operation indicated that the decline was significant in the patients with gliomas in the right hemisphere, but not in patients with meningioma, and no decrease at all was seen in the patients with any type of tumor located in the left hemisphere. Thus, gliomas might

preoperatively have more serious effects than meningiomas on brain function in the etiology of anxiety. Furthermore, an increased level of obsessive-compulsive symptoms in the patients with both a benign and malignant tumor suggested that the tumor itself, regardless of its histology, is associated with the obsessionality in the patients.

The association of depression with the histology of the tumor in brain tumor patients adds some interesting points to previous literature. After tumor operation the level of depression in the patients with a pituitary adenoma decreased significantly up to the one-year measurement point. An increased incidence of affective disorders has been found in patients with different types of pituitary adenomas (Dorn *et al.* 1997, Sobrinho 1998). The theory of hypothalamic-pituitary-adrenal axis in the etiology of depression might explain at least in part the finding of the study in this thesis (Parker *et al.* 2003). In the study sample of this thesis, the patients with gliomas, meningiomas or acoustic neurinomas showed no difference in the level of depression between these histological subgroups or between different measurement points. In earlier studies, it has been suggested that patients with meningiomas had preoperatively higher levels of anxiety and depression compared to patients with other types of brain tumors (Pringle *et al.* 1999). However, Irle and colleagues (1994) found that lesions resulting from resection of different histological types of tumors had similar effects on the emotional state of patients.

## ***6.2.4 Depression in relation to the survival, functional outcome and quality of life***

### ***6.2.4.1 Depression in relation to the survival***

The survival time after tumor operation among the brain tumor patients varied significantly according to the histology of the tumor. In the study the mean survival time for the patients with a high-grade glioma was about two years, which was in line with recent literature. Also, in earlier literature it is noted that the main predictor for survival among patients with a primary brain tumor is the malignancy of the tumor, and the prognosis of high-grade gliomas has not improved in spite of the new treatment maneuvers introduced during recent decades (Hulshof *et al.* 2000, Liigant *et al.* 2001). The survival after tumor operation of patients with a low-grade glioma was observed to be about four years in this study. The survival of patients with low-grade gliomas after tumor surgery has been reported to be very heterogeneous by clinical behavior and survival time, varying from three years to over five years (Pignatti *et al.* 2002).

Depressed patients with a low-grade glioma had a significantly shorter survival time compared to non-depressive subjects after tumor operation. A corresponding difference was not found in patients with a high-grade glioma or those with a benign tumor. Depression as a significant predictor for shorter survival among brain tumor patients has been recently shown in patients with high-grade gliomas (Litofsky *et al.* 2004).

The finding of this thesis that depression significantly shortened the survival explicitly in the patients with a low-grade glioma is remarkable. Since the prognosis for these patients is in general over five years at its best, it can be suggested that depressed low-

grade glioma patients have such psychological or biological factors that have an adverse impact on their prognosis.

#### *6.2.4.2 Depression in relation to functional outcome and quality of life of the patients*

Depression was significantly associated with worse functional outcome in the patients not only before tumor operation but also during follow-ups. The findings are in line with earlier studies (Anderson *et al.* 1999, Weitzner 1999). But, as reviewed by Huang and co-authors (2001), only few studies have so far focused especially on functional outcomes in brain tumor patients. Further studies are needed to investigate the effect of depression on the whole rehabilitation process in brain tumor patients.

The level of quality of life (QOL) in depressive females was lower compared to non-depressive females up to one year of follow-up after surgical operation of the tumor. A corresponding difference was not found postoperatively between depressive and non-depressive males. In the entire database, the level of QOL among females was lower than among males during the one-year follow-up. The gender difference in the level of QOL has also been found in other follow up studies among patients with different somatic diseases such as chronic lymphocytic leukemia (Holzner *et al.* 2004), inflammatory bowel disease (Bernklev *et al.* 2004), chronic arterial disease (Norris *et al.* 2004) and a myocardial infarct (Agewall *et al.* 2004). The findings in this thesis were similar to those reported by Weitzner and colleagues (1996) that female patients with a primary brain tumor had higher levels of psychological distress compared to males, and at the same time their overall QOL was lower than among males. The findings of this thesis are, however, the first so far in which a gender difference has been found in the level of QOL among brain tumor patients using a one-year follow-up and both pre- and postoperative measurements.

Female cancer patients are in general likely to use many of their friends/relatives and their partner to provide social support during their cancer crisis, while male cancer patients are more likely to have only one confidante (Harrison *et al.* 1995). Since one main symptom of depressive disorder is withdrawal from social connections, it is probable that depressive females with a primary brain tumor cannot utilize their social network, and thus cannot gain mastery over their lives in spite of the prognosis of their disease. Furthermore, brain tumor patients are known to exhibit increased emotional reactivity and lowered tolerance for stressful situations (Taphoorn *et al.* 1992). It can be suggested that depressive females with these problems can experience their normal daily events as being highly distressing, reflecting on their QOL.

## 6.3 Theoretical considerations

### 6.3.1 Biological explanations

Since the location of tumor has shown to be the main impact on psychiatric symptoms among brain tumor patients it can be assumed that a biological mechanism exists behind the patients' psychopathology. Cummings (1997) suggested that psycho-organic syndromes caused by brain damage could be explained by the fact that the two hemispheres have different concentrations of transmitters as well as different behavioral functions, and therefore lesions in the brain could cause different hemispheric-specific syndromes.

#### 6.3.1.1 The serotonin metabolism

There is evidence that alterations in central serotonin (5-HT) systems may play a key role in the pathophysiology of depression (Owens & Nemeroff 1994). A decrease of 5-HT metabolism has been ascertained in the brain of a subgroup of depressive patients, and this phenomenon is associated with heightened anxiety in patients (Van Praag 2004). Lowered cerebrospinal concentrations of 5-HIAA (the major degradation product of 5-HT) in depression were shown to correlate positively with increased anxiety as well (Van Praag 1988). In addition, 5-HT receptor disturbances may be observed in depressive and anxious patients (Van Praag 2004). The so-called tryptophan-depletion theory also strengthens the major role of 5-HT in depression (Delgado *et al.* 1989). It is known that serotonin metabolism is also dysfunctional in patients with OCD (Barr *et al.* 1992, Hollander 1998).

Whittle (1992) noted that dysregulation in transmitter metabolism among brain tumor patients may be behind the neurophysiologic dysfunction of patients. Animal studies have also focused on increased serotonergic function in peritumoral areas of brain tumors as well as the association of serotonergic excess in the right amygdale with anxiety behavior (Andersen & Tiecher 1999, Whittle & Kelly 2001). Patterns of tryptophan hypercatabolism have been noticed among glioma patients (Ravikumar *et al.* 2000), although the interrelationship between patients' psychiatric symptoms and elevated concentration of tryptophan, serotonin and 5-HIAA in the plasma has not yet been studied.

### 6.3.1.2 *The stress system*

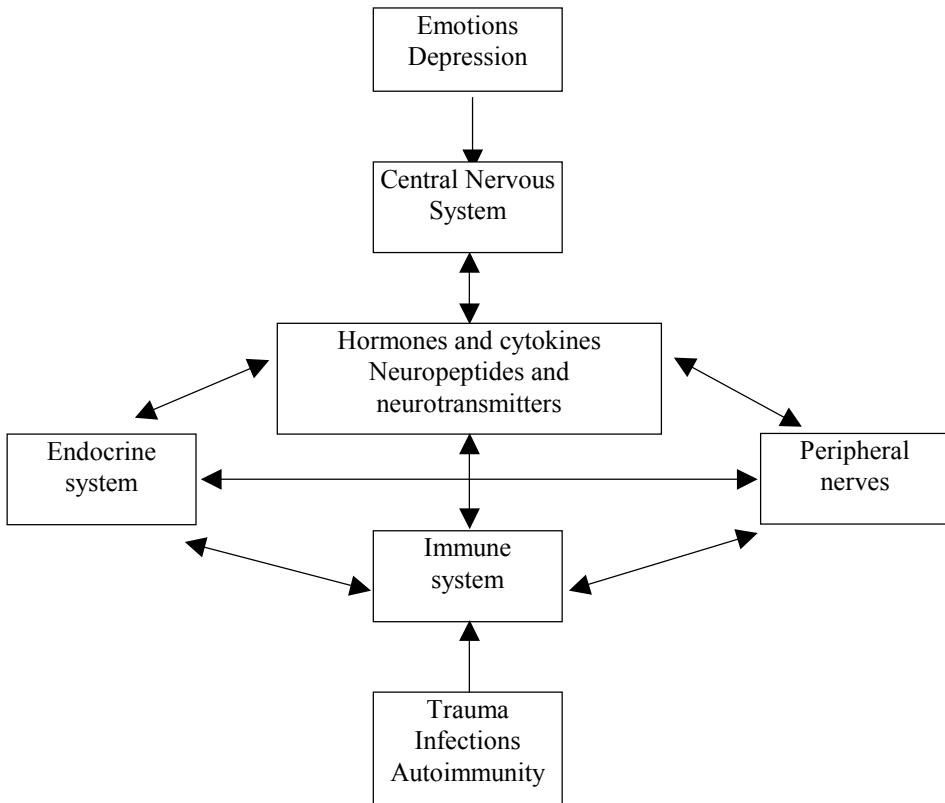
In addition to the 5-HT theory in the etiology of depression, the association between stress and depression may highlight the great prevalence of psychiatric symptoms in this sample of brain tumor patients. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is thought to play an important role in the etiology of depression (Holsboer 2000, Parker *et al.* 2003, Peeters *et al.* 2004). Furthermore, abnormalities in HPA function have been reported among cancer patients (Touitou *et al.* 1996, van der Pompe *et al.* 1996).

Differences in the HPA system may be due to disease- or treatment-related effects on endocrine regulation or due to the psychological challenges that cancer patients must deal with in their daily lives (Cruess *et al.* 2000). It is suggested that disturbances in the HPA axis are categorically non-specific and possibly related to disturbances in specific psychic regulation mechanisms across psychiatric diagnoses (Van Praag 2004). However, several lines of evidence point to stress hormones as depressogenic variables (Young *et al.* 2000, Van Praag 2004).

The disturbances in stress hormones are also suggested to be associated with OCD. Baumgarten and colleagues (1998) suggested that serotonin not only has a primary pathogenetic role in obsessive-compulsive disorder, but that OCD should be viewed within the context of elevated cerebrospinal fluid stress neuropeptides such as arginine vasopressin, somatostatin and corticotrophin releasing hormone (Altemus *et al.* 1992, Altemus *et al.* 1993). However, there are a few studies about transmitters or neuropeptides related to brain tumors. Some animal studies had linked serotonin and somatostatin with gliomas and meningiomas; the studies have reported that high levels of somatostatin receptors located in meningiomas and gliomas, expressing that somatostatin is associated with these tumors (Dutour *et al.* 1998, Held-Feindt *et al.* 1999, Cavalla & Schiffer 2001).

### 6.3.1.3 The association of stress, depression, and immune system

Man is a complex entity in which the central nervous system, peripheral nervous systems, endocrine and immune systems are in continuous and multifarious interconnection with each other as demonstrated in Figure 12 (Reiche *et al.* 2004).



**Fig. 12. The scheme of bidirectional communication between central nervous system, peripheral nervous system, endocrine, and immune systems (Reiche *et al.* 2004).**

Both stress and depression have been associated with impaired immune function and increased susceptibility of the patient to infectious diseases and cancer. The human immune system generates a range of cytokines, including interferons and interleukins, and activation of these responses is also associated with depression (Horrobin & Bennett 1999). It is known that cytokines can act as mediators between the immune system and the brain (Kronfol & Remick 2000). Interactions between emotions and immune functions might underlie the increased clinical susceptibility to malignant tumors (Reiche *et al.* 2004). Immune responses are also induced to antigens in the brain expressed by cerebral malignancies (Walker *et al.* 2003). Interleukin-1beta (IL-1 beta) is the principal pro-inflammatory cytokine participating in the initiation of acute phase response in stress and

infection (Yu *et al.* 2003). IL-1 beta is suggested to have a role in the pathogenesis of major depressive disorder (Yu *et al.* 2003). Interleukins are also suggested to have the capacity to induce “a sickness syndrome”, arising within the context of chronic immune activation and resembling major depressive disorder with symptoms of insomnia, anorexia and fatigue (Raison & Miller 2003). Cytokines are also positively correlated with depression and poor quality of life in cancer patients (Allen-Mersch *et al.* 1998).

Depression is thought to be associated with activation of some aspects of cellular immunity resulting in the hypersecretion of proinflammatory cytokines and the hyperactivity of the hypothalamic-pituitary-adrenal axis (Holden 1998). Both stressors and depression are associated with the decreased cytotoxic T-cell and natural-killer-cell activities that affect immune surveillance of tumors (Reiche *et al.* 2004). Stress and depression can foster tumor progression by means of inhibiting the expression of major histocompatibility complex molecules (malignant cells escape immune surveillance) and through the reduction of natural killer cell activity (Holden 1998).

### ***6.3.2 Psychological considerations***

The experience of having a brain tumor is emotionally arousing. The uncertainty of the prognosis can cause the patient to experience overwhelming anxiety and usually fear of death (Lepola *et al.* 2001). The worries are the same as experienced generally by cancer patients: Can I resume my work? Where can I get support? Where do I find the energy to maintain look after my general health? How can I control my mood fluctuations? (Lovely 1988, Lindvall 1997). Brain tumor patients are faced with uncertainty regarding prognosis and further neurological impairment with consequences on functional capacity (Newton & Mateo 1994). One of the most usual psychological defenses in brain tumor patients is denial (Amato 1991). It is therefore a very challenging task for medical staff to find a delicate balance between breaking down denial and giving information of disease and its treatment (Amato 1991). The information on disease is important, since patients who were more aware of the nature and likely course of their disease seemed to be less distressed than those who were less aware (Amato 1991).

#### ***6.3.2.1 Coping with illness***

Coping has been determined as the actions taken by a sick person with respect to one's illness (Lipowski 1985). From a psychological perspective coping is defined as the strategies for dealing with threat (Lazarus 1966). Two modes of coping are distinguished: 1) direct actions, i.e. active preparation against harm, and 2) intrapsychic processes (psychic defenses), i.e. aiming at withdrawing attention from threat, minimizing it and seeking relief from it in fantasy (Lazarus 1966, Lazarus 1974). From a sociological perspective coping is defined as the instrumental behavior and problem-solving capacities of a person in meeting life demands and goals, i.e. application of skills, techniques and knowledge of a person (Mechanic 1978). As a synthesis of these perspectives Lipowski (1970) has proposed the following definition of coping: “Coping refers to all cognitive and psychomotor activities that a sick person employs to safeguard bodily and psychic

integrity, to recover reversibly impaired function, and to compensate for and adjust to permanent disability". In the coping process the need of information is profound (Strang & Strang 2001). When unrealistic interpretations of disease have been cleared, chaos is relieved in the patient's mind and a sense of comprehensibility increases (Antonovsky 1987). Comprehensibility includes such coping mechanisms as information-seeking, intellectualization, redefinition and rationalization (Amato 1991, Strang & Strang 2001). In order to increase manageability, meaning that one's own resources are available to meet demands, such coping mechanisms as distancing, self-controlling, seeking social support, accepting responsibility, planful problem-solving, and positive reappraisal are used (Lazarus 1993). When a patient's past coping styles have included healthy optimism, the use of prior successful coping strategies increases the ability to cope with the stress of cancer (Goldberg & Cullen 1985).

It is commonly thought that such attitudes as fighting spirit or helplessness/hopelessness might have an impact on cancer patients' survival and recurrence of disease. However, Petticrew and colleagues (2002) showed that there is little consistent evidence that psychological coping styles play an important part in survival from or recurrence of cancer.

Many brain tumors have a poor prognosis and the patients may experience many losses over varying lengths of time; grief and mourning are thus central coping challenges facing patients and their close people (Passik *et al.* 1994). In the course of disease, maintenance of hope in spite of a poor prognosis is an important coping strategy (Salander *et al.* 1996).

## **6.4 Psychiatric treatment in brain tumor patients**

Psychological assessments and symptom management during cancer treatment is important. Brain tumor patients, in spite of their psychological mood states, were very likely to talk about their illness, after-care, and personal future, as well as about the emotional arousal brought on by the illness and its treatment (Kan 1998, Timonen & Sihvonen 1998, Lepola *et al.* 2001).

Psychosocial interventions for brain tumor patients should consist of psychotherapy and pharmacotherapy (Weitzner 1999). Previous studies have demonstrated reduction of depression in cancer patients through psychosocial intervention (Antoni *et al.* 2001, Goodwin *et al.* 2001) as well as psychopharmacological treatment (Berney *et al.* 2000). Furthermore, earlier studies among depressive cancer patients have reported that treatment of depression increased their survival (Spiegel *et al.* 1989, Richardson *et al.* 1990, McCorkle *et al.* 2000). However, in the study of Litofsky *et al.* (2004) treatment of depression did not have any impact on survival among high-grade glioma patients.

### **6.4.1 Psychotherapy**

In view of the character of brain tumors as described earlier in this thesis, the understandable psychic reaction to disease is a psychic crisis. Thus, in individual therapy the main psychological methods have to consist of crisis therapy with supportive elements

and psychoeducational techniques (Passik *et al.* 1994). By supportive therapy the patient's productive coping strategies are strengthened (Weitzner 1999). In a dynamic approach of individual psychotherapy the patient is helped to bring meaning to the illness (Weitzner 1999). Stress management programs and neuropsychological rehabilitation techniques could be also beneficial (Lilja & Salford 1997). It is important to provide protection and hope for the brain tumor patients as well as their spouses and all family members using various cognitive and family therapeutic maneuvers (Salander *et al.* 1996, Weitzner 1999). Brain tumor patients may benefit from individual counseling, support groups and spiritual counseling (Horowitz *et al.* 1996, Peterson 2001).

Support groups for patients and their families facilitated by professionals such as nurses or social workers have been recommended. Members to such groups are likely to be chosen homogeneously by diagnoses (Amato 1991). While supporting patients' families it is essential to give time to the psychic process brought on by the illness. It is important to use open speech and real terms when talking about the disease and death (Siltala 1987). When patients become unable to speak it is necessary to interpret moods, movements, sounds and looks in order to facilitate survival (Amato 1991). Through the group modality, people – both patients and their close relatives – can share experiences, thus preventing isolation. Information is shared along with mutual support and group members can experience normalcy of their reactions to the illness (Newton & Mateo 1994). Coping skills in the groups may be strengthened, developed and improved. Psychological intervention methods should be employed to boost ego strength, to improve coping abilities and to unlearn inadequate adaptive reaction patterns.

Among psychosocial therapy, cognitive psychotherapy, interpersonal psychotherapy and brief dynamic psychotherapy are the treatments of choice in patients with clinical depression (Pelletier *et al.* 2002, Käypä hoito –suositus 2004). Regarding obsessive-compulsive disorder behavioral and cognitive-behavioral therapy may lead to substantial improvement for patients as reviewed by Eddy and his colleagues (2004).

#### **6.4.2 Pharmacotherapy**

The importance of depression treatment as soon as depression has been diagnosed in a brain tumor patient has been emphasized (Pelletier *et al.* 2002). The valid pharmacotherapeutic treatment of depression consists of medical care, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline uptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) or atypical antidepressants and noradrenergic and specific serotonergic antidepressants (NASSAs) (Williams *et al.* 2000, Käypä hoito –suositus 2004). There are also case reports on the efficacy of electroconvulsive therapy (ECT) in the treatment of depression associated with a brain tumor (Gursky *et al.* 2000, Kohler & Burock 2001). According to a recent meta-analysis of 15 clinical trials, clomipramine and other serotonin reuptake inhibitors have been found to be effective pharmacotherapy for obsessive-compulsive disorder (Eddy *et al.* 2004).

## 6.5 Methodological considerations

### 6.5.1 Strengths of the study

The database of this thesis consisted of a representative sample of neurosurgical patients with a primary brain tumor from the large geographical area of Northern Finland. 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 catchments area. Geographically the study area covers about half of Finland.

The accuracy of data from case reports at the Clinic of Neurosurgery in Oulu University Hospital was considered to be good, since the Finnish Hospital Discharge Register has in general been shown to be a reliable source for information for scientific research (Keskimäki & Aro 1991). The information on the survival status and survival time provided by the Cause of Death Register by Statistics Finland was also reliable, since the Finnish death certification practices and cause of death validation procedure have been reported to serve appropriately the coding of causes of death for mortality statistics (Lahti & Penttilä 2001). The histological grading of the tumors followed the WHO classification (Kleihues *et al.* 1993) and it was thoroughly determined by a specialist in pathology. Furthermore, the tumors consisted of both benign and malignant brain tumors, which gave the opportunity to compare the effect of tumor malignancy on psychiatric symptoms.

The major strength of the present thesis was the prospective study design with repeated measurements. The psychopathology as well as the functional outcome and quality of life of the patients were assessed at three time points: before tumor operation as well as at three months and at one year after operation. As far as is known, there are no previous Finnish studies in which psychiatric symptoms among brain tumor patients have been assessed so extensively using measurements before tumor operation and a follow-up covering up to one year after surgery.

The patients were personally and carefully interviewed by a trained psychologist and by a trained physician at each measurement point. The study protocol consisted of standardized and structured instruments measuring widely different aspects of the patients' outcome used in this thesis: psychiatric symptoms were assessed by Beck Depression Inventory and the Free Floating Anxiety subscale and the Obsessionality subscale from the Crown Crisp Experiential Index) (Beck *et al.* 1961, Crown & Crisp 1966), functional state was measured according to the Karnofsky Performance Scale (Karnofsky & Burchenal 1949), and the level of the patients' quality of life by Sintonen 15D (Sintonen 2001).

### ***6.5.2 Limitations of the study***

From a psychiatric point of view it was unfortunate that the study protocol did not include any structured psychiatric diagnostic interviews. The existence of the patients' psychiatric symptoms was based on self-administered questionnaires. In addition, no information was available concerning the patients' previous history of psychiatric disorders, psychiatric treatment, family history of psychiatric diseases or corticosteroid therapy during data collection.

The Beck Depression Inventory includes items concerning bodily change, difficulty with working, sleep problems, fatigue, appetite and weight loss, concern about health, and change of interest in sex. Thus, although only eight of the 21 items could be directly attributable to physical symptoms of the patients, BDI may have caused overestimation of depression among this database with somatic disease, and thus a cut-off point 12/13 might have had higher specificity for screening depressive disorder (Lasa *et al.* 2000). However, the BDI has commonly been shown to exhibit good internal consistency and re-test reliability in assessing the level of depression among different types of study samples (Beck & Steer 1984, Coles *et al.* 2001).

It must be mentioned as a limitation of the CCEI questionnaire that no standard cut-off points or border values exist for the subscales of FFA (Free Floating Anxiety) or OBS (Obsessionality), with which the respective values observed in the studies of this thesis could have directly been compared. Nevertheless, it is reported that CCEI is a valid instrument for evaluating psychiatric, neurotic psychopathology in psychiatric patients and somatically ill patients (Alderman *et al.* 1983) as well as personality change following either psychological or somatic therapies (Crown & Crisp 1966).

Further, some cases were missed during the follow-up due to severe dysfunction of the patients' somatic condition (e.g. confusion or state of unconsciousness due to raised intracranial pressure or tumor-induced motor aphasia) or due to death of a patient. This has caused variation in the number of cases used in different studies and statistical analyses.

The radiological diagnoses of the tumors were mainly based on Computer Tomography (CT), which was the main tool in diagnostic practice used at the time when the study sample was formed and data were gathered. Only a few patients were examined by Magnetic Resonance Imaging (MRI). Because of this diagnostic technique no data were available on functional imaging, the contents of main neurotransmitters or measurements of corresponding receptors.

## **7 Conclusions**

### **7.1 Main conclusions of results**

Depressive and anxious symptomatology of neurosurgical patients having a primary brain tumor have been evaluated and investigated in the studies of the present thesis.

Right laterality in anxiety symptoms among glioma and meningioma patients before tumor operation was shown. The hypothesis of different levels of transmitters in the two hemispheres is suggested to explain the theory of hemisphere-specific psychiatric syndromes.

An increase in the level of obsessive-compulsive symptoms after tumor operation was found in the female patients with a glioma or meningioma in the left anterior location of the brain. Disturbance in the transmitter metabolism in this area caused by the tumor itself or by the surgical operation of the tumor is suggested to be behind the increased level of obsessionality.

The main predictors of depressive symptoms in the patients before tumor operation were shown to be anterior location of the tumor, previous history of depression and patients' decreased functional status. In this thesis depressive symptoms in brain tumor patients were observed to be equally frequent regardless of whether the histology of the tumor was benign or malignant.

Further, depression had an adverse impact on survival time after tumor operation among the patients with a low-grade glioma. Interconnection between dysregulation of the serotonin system, hypothalamic-pituitary-adrenal (HPA) axis and the immune system is suggested to cause association between depression and cancer progression.

The quality of life of the female patients was found to be lower than that in males at each measurement point. Depressive females with a brain tumor might have difficulties in social relations and in coping with a psychological crisis.

## 7.2 Clinical implications

The present thesis brings an important addition to earlier literature. The findings of the studies reported in this thesis highlight the significance of clinical evaluation and follow-up of psychiatric symptoms being present among brain tumor patients before and after tumor operation.

Generally, the adaptive reaction of a patient is to be shocked or sad when confronted with such a serious disease as a brain tumor. The patient is suddenly faced with a real threat of death. From a psychological point of view, tumor surgery itself is a very oppressive and mystifying chain of events for the patient. It can be a traumatic experience for patients to know that their skull will be opened and sensitive areas in their brain are handled and operated on. Regardless of the malignancy level of the tumor, all patients having a primary brain tumor as well as the families of these patients would benefit from psycho-education concerning normal human psychological reactions following a diagnosis of a serious illness and, thus, from supportive intervention.

Based on the findings of this thesis, anxiety symptoms in brain tumor patients seem already to be present before tumor operation, particularly in patients with a brain tumor situated in the right hemisphere. However, the level of anxiety was shown to decrease when the tumor was surgically operated. In clinical practice, it can be recommended that the possibility for the existence of anxiety symptoms among patients with a brain tumor should be evaluated during the perioperative period at neurosurgical units, and the need for pharmacotherapy and psychotherapy with crisis elements in treatment for anxiety must be carefully considered.

On contrary to anxiety, the level of obsessiveness among patients was found to increase after the removal of the brain tumor. This was seen most clearly in female patients whose tumor was located in the left anterior region. Thus, in clinical work it seems to be important that possible obsessive and compulsive symptoms among brain tumor patients are evaluated and subsequently treated in outpatient clinics where these patients are usually followed after the tumor operation. Furthermore, regular screening for obsessive and compulsive symptoms is important, since the patients are frequently aware of the fact that their thoughts and behavior are strange; they feel ashamed and thus try to hide their obsessions and compulsions and may not tell about them spontaneously.

Depressive symptoms, which are commonly reported to be present among physically ill patients and in those suffering from cancer, was shown to be notably prevailing in the study sample of this thesis. It can be suggested that diagnosed depression of a brain tumor patient must be treated with antidepressants and appropriate psychotherapy as soon as possible when he/she has been admitted to care for the brain tumor. It must be noted that the treatment of depression among the patients with grade I-II gliomas might have a favorable impact on their prognosis.

Preventive elements for depression would consist of both pharmacotherapy and supportive psychotherapy. Special attention in relation to prevention and treatment of depression is emphasized in the case of patients having a previous history of depression as well as those with decreased functional outcome.

In conclusion, the physical, functional, emotional, and social needs of brain tumor patients can be best taken into account by adoption of a holistic approach on the part of the professional team. Thus, closer communication between neurosurgeons, oncologists, neurologists and psychiatrists can help create a modern chain of treatment and rehabilitation for this patient population.

### **7.3 Implications for future research**

In future research, it is recommended that psychopathology of brain tumor patients is evaluated using structured methods for psychiatric disorders, such as DSM IV-TR (American Psychiatry Association 2000). Furthermore, increased evidence has indicated that dysfunction in serotonin metabolism, hypothalamus-pituitary-adrenal cortex (HPA) axis and interleukin secretion plays an important role in pathophysiology of psychiatric disorders. Therefore, more research is needed to examine whether specific transmitters as well as endocrine and immunologic changes are especially typical of depression due to the medical condition of brain tumor of patients. With regard on cytokine secretion, further studies are needed to evaluate its association with the development of depression among brain tumor patients.

Among brain tumor patients, Positron Emission Tomography (PET) has already been used in diagnosis of tumor before operation and in follow-up when evaluating treatment response in patients, as recently reviewed by Schaller (2004). In future research PET could serve as an important tool in evaluating temporal association of the level of depression as well as anxiety and obsessionality with functional changes in both tumor area and its surrounding brain tissue.

The impact of the extent of brain tumor surgery on patients' psychiatric symptoms and their quality of life is also worth being investigated. For example, a study setting in which patients with stereotactic biopsy are compared to those with craniotomy could test the hypothesis that more aggressive intervention gives patients more hope and leads to better outcome.

It is especially important to examine tumor-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. What is the right timing, type or duration of psychotherapeutic interventions as well as how the treatment of depression affects the quality of life of brain tumor patients are also issues worth studying.

Further, it should be examined whether and to what extent depression of patients is a cause or a consequence of decreased physical outcome. Additional studies are needed to determine the relationship between functional outcome and QOL in brain tumor patients.

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