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EPIDEMIOLOGY OF PRIMARY CENTRAL NERVOUS SYSTEM TUMOURS IN ESTONIA FROM 1986 TO 1996

Clinical characteristics, incidence, survival and prognostic factors

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II Liigant A, Haldre S, Õun A, Linnamägi Ü, Saar A, Asser T, Kaasik A. Seizure disorders in Patients with Brain Tumors. Eur Neurol 2001; 45: 46–51.

III Liigant A, Kulla A, Linnamägi Ü, Asser T, Kaasik A. Survival of patients with primary CNS tumours in Estonia. Eur J Cancer 2001; 37: 1895–1903.

IV Liigant A, Asser T, Kaasik A-E. Kesknärvisüsteemi kasvajad. Eesti Arst 2000; 2: 89–95.

ABBREVIATIONS

ASIR	age-adjusted incidence rate
CI	confidence interval
CT	computed tomography
CNS	central nervous system
CR	crude rate
EEG	electroencephalography
ECR	Estonian Cancer Registry
EUROCARE	A population-based survival study of European Cancer Registries
G	tumor grade
ICD-9	International Classification of Diseases 9th revision
ICD-10	International Classification of Diseases 10th revision
ICD-O	International Classification of Diseases for Oncology
IR	incidence rate
IRR	incidence rate ratio
KPS	Karnofsky Performance Status
MRI	magnet resonance imaging
PNET	primitive neuroectodermal tumor
SEER	Surveillance, Epidemiology and End Results
SR	survival rate
ST	survival time
WHO	World Health Organization

INTRODUCTION

The term "brain tumour" refers to a collection of neoplasms, each with its own biology, prognosis and treatment. These tumours are better identified as "intracranial neoplasms", since some do not arise from brain tissue (e.g. meningiomas and lymphomas). However, for most intracranial tumours, the clinical presentation, diagnostic approach, and initial treatment are similar. Brain tumours are characterised by a vast array of different histological types, complexity of clinical presentations and modest success in therapy.

Meningioma was first described in an autopsy report by Felix Plater, 1614, as a round, fleshy, hard tumour full of holes and as large as a medium-sized apple, covered with its own membrane and entwined with veins. The first operation for intracranial tumour was carried out in 1835 by Zanobi Pecchioli. He removed a "fungus of dura matter" presented as a large extra-cranial mass (Green and Stern, 1967). In 1884, Rickman Godlee performed the first recognised resection of a primary brain tumour. The patient died on the 28th post-operative day. The post-mortem examination revealed evidence of meningitis and infarction, but no residual tumour (Kirkpatrick, 1984).

Neuroepithelial tumours, the so-called gliomas of the brain constitute about half of all primary intracranial tumours. All gliomas, particularly the astrocytic neoplasms, are histologically and genetically heterogeneous. Accurate pathological grading is essential because it defines treatment and prognosis. Tumours of meningothelial cells, including all meningiomas, account for approximately 13–20% of all intracranial tumours in men and 24–38% in women (Preston-Martin *et al.*, 1989; Helseth *et al.*, 1989; Longstreth *et al.*, 1993). Meningiomas are benign tumours that rarely invade the substance of the brain. In 1922, Harvey Cushing (Bondy and Ligon, 1996) coined the term "meningioma" to characterise a group of different pathological tumour types arising from the meninges.

Intracranial tumours are an important cause of morbidity and mortality, particularly in relatively young people. According to the data of the Estonian Cancer Registry (Thomson *et al.* 1996; Aareleid and Mägi, 1999), brain tumours have not been among the ten most frequent tumour types diagnosed during recent years. At the same time, it has been recorded as the 9th (in males) and 10th (in females) site among cancers which caused death of patients. In children (0–14 years) and young people (15–29 years), brain tumours rank among the second or the third most common primary sites of cancer, both among males and females. In 1996–1998, the mean annual number of new primary brain tumours reported to the Estonian Cancer Registry was 98, comprising 1.7% of all reported tumours.

Most of the published studies concerning survival of central nervous system (CNS) tumours are hospital-based and restricted to gliomas or their histological subtypes. Few population-based studies, including survival of all primary

benign and malignant tumours, have been published. The range of survival times in brain tumours is broad and may be unpredictable. In children, primary central nervous system tumours are the leading cancer-related cause of death and illness. Epidemiologic data confirm that survival patterns vary by histology. The prognoses of intracranial tumours can be more dependent on tumour location than the benign or malignant nature of the lesion. Cure is not rare in cerebellar astrocytomas in children or adolescents. At the same time, despite aggressive treatment, most patients die of glioblastoma during the first year after diagnosis.

However, little is known about the aetiology of intracranial tumours. Studies of the incidence of disease provide valuable information for health service planning, but they can also enhance research into aetiology. Geographical or secular changes in incidence can highlight potential risk factors for a disease which can then be studied in further detail (Doll *et al.*, 1981).

Meningiomas are found more frequently in women than in men, leading to the speculation that hormones may play a role in their development. Other possible aetiologic factors are head trauma (Preston-Martin *et al.*, 1989), which has yet to be established; both high- and low-dose irradiation, which have several associations with meningiomas; infections including viruses (Davis and McCarthy, 2000), which may act alone or with other mutagens in this formation; and chromosomal abnormalities, deletion of loci on chromosome 22q occurs in approximately 30% of sporadic meningiomas. Genetic alterations discovered in gliomas include p53 mutations reported in approximately 40% of astrocytic tumours of all grades, deletions of chromosome 10 occurring frequently in astrocytic tumours and loss of heterozygosity at 10q23 reported in as many as 70% of glioblastomas (Hill *et al.*, 1999).

The aim of the present study was to evaluate the epidemiological characteristics of primary brain tumours in Estonia; to find out the survival rate of patients with primary CNS tumours diagnosed between 1986 and 1996 and to examine variations in different age and histological groups, evaluating changes in the length of survival that have occurred over these years.

REVIEW OF LITERATURE

1. Histological classification

General aspects

Numerically, gliomas constitute the most important group of intracranial tumours. Their complexity is due to the considerable number of cell types involved in neoplasia. The variations are found both within the major classes of glioma and often in different parts of one individual tumour. Most classifications have reflected a general acceptance of histological tumour types that are based on the identification of reasonably precise cytological features linking neoplastic elements to normal cell types found in the mature and developing CNS (Russell and Rubinstein, 1989). Accurate histological diagnosis is fundamentally important from both clinical and experimental perspectives.

History

The origin of systematic classification of brain tumours can be attributed to Virchow. He described neuroglia and related this to brain tumours. During the second half of the 19th century, he continued to develop tumour classification, separating gliomas from sarcomas of the brain and describing also ependymomas.

Most modern classifications are based upon that of Bailey and Cushing (1926). Having enumerated 20 cell types, they divided brain tumours into 14 main groups including astrocytomas, oligodendrogliomas and ependymomas. Subsequent to the publication of Bailey and Cushing's classification, increasing attention was directed to the frequency with which anaplasia determines the morphological characteristics of tumour cell populations and their diversity in malignant gliomas. The problem was especially applicable in the case of the common glioblastoma and its multiple variants (Russell and Rubinstein, 1989). Later, the concept became accepted that neoplasms derive from mature cells through a process of anaplastic transformation.

In 1949, Kernohan and his co-workers (Kernohan and Sayre, 1952) reduced the glioma types to five main groups by introducing a four-tiered grading system of gliomas, classifying them as grade I (well differentiated) to grade IV (poorly differentiated) according to the histological criteria of (de)differentiation. This resulted in the elimination of several tumour entities, including the glioblastoma multiforme. The validity of the Kernohan grading system of astrocytomas has been questioned ever since its introduction. The system has

been found difficult to apply and its reproducibility has been low because grade is determined according to the degree of presence of multiple features, i.e. anaplasia, cellular and nuclear pleomorphism, hyperchromasia, vascularity, cellularity, necrosis, endothelial proliferation, and mitotic rate and abnormallities, as well as tumour delimitation. Daumas-Duport *et al.* (1988) found that the Kernohan grading system accurately distinguished only two major groups, i.e., those with low-grade ordinary astrocytomas (grades 1 and 2) and those with high-grade neoplasms (grades 3 and 4).

The practice of grading, if used in all tumours of the glioma group, presents considerable problems. Anaplasia is so often a localised development that the prognostic value, to be attached to the grading of biopsies, carries serious limitations. Furthermore, it cannot be assumed that any tumour will be static in its cytology. In practice, and within a particular type of glioma, grading can perhaps most consistently be applied to the diffuse cerebral astrocytomas (Russell and Rubinstein, 1989).

WHO Classifications

The International Classification of Central Nervous System Tumours approved by the World Health Organisation (WHO) (Zülch, 1979) represents a consensus attempting to combine the different approaches to the typing and grading of CNS tumours. It is, in its essential lines, derived from Bailey's and Cushing's classifications. Subsequently, some disagreements have persisted and slightly modified classifications have later been published (Nelson *et al.*, 1983; Zülch, 1986; Russell and Rubinstein, 1989). In 1988, Daumas-Duport *et al.* proposed a grading method for use on astrocytomas. The method is based upon the recognition of the presence or absence of four morphologic criteria: nuclear atypia, mitoses, endothelial proliferation and necrosis resulting in a summary score, which is translated into a grade as follows: 0 criteria = grade 1, 1 criteria = grade 2, 2 criteria = grade 3, 3 or 4 criteria = grade 4.

The revised WHO classification, where several new tumour types have been added, was published (Kleihues, Burger and Scheithauer, 1993) in 1993 (Table 1a). This WHO classification was considered as an international standard to facilitate communication and to avoid current conceptual controversies between different schools of thought. In the first edition of the WHO classification, the biological behaviour of CNS tumours was, in addition to describing histological evidence of differentiation or anaplasia, characterised by assigning a histological grade ranging form I (benign) to IV (malignant). The WHO grading is a malignancy scale ranging across a wide variety of intracranial neoplasms rather than a histological grading system. The vast majority of gliomas are typed according to histological criteria of (de)differentation, by name rather than by number (low-grade, anaplastic and for the most malignant astrocytic tumours, glioblastoma). Specific clinicopathological entities are defined, such as pilocytic

astrocytoma, myxopapillary ependymoma, subependymal giant cell astocytoma and pleomorphic xantoastrocytoma. Yet, the distinction between astrocytomas from oligoastrocytomas and oligodendrogliomas (Krouwer *et al.*, 1997) and an unequivocal interpretation, of certain histological features with respect of definition of the grade of differentation, remains unresolved (Coons *et al.*, 1997).

The latest WHO classification of CNS tumours has been published in 2000 (Table 1b) where some new clinicopathologial entities like chordoid glioma of the third ventricle, cerebellar liponeurocytoma and peripheral neuroblastic tumours, new terms like diffusely infiltrating astrocytomas, have been introduced. New histological variants of meningiomas, which must be recognised by pathologists but most of these have no bearing on clinical outcome, have been included. Remarkable attention has been paid to the molecular and cytogenetics basis in formation and histological diagnosis of brain tumours (Kleihues and Cavenee, 2000).

Table 1 a. WHO 1993 histological typing of tumours of the central nervous system (abbreviated)

I. Tumours of neuroepithelial tissue
A. Astrocytic tumours
1. Astrocytoma (with variants)
2. Anaplastic astocytoma
3. Glioblastoma (with variants)
4. Pilocytic astrocytoma
5. Pleomorphic xanthoastrocytoma
6. Subependymal giant cell astrocytoma
B. Oligodendroglial tumours
1. Oligodendroglioma
2. Anaplastic oligodendroglioma
C. Ependymal tumours
1. Ependymoma (with variants)
2. Anaplastic ependymoma
3. Myxopapillary ependymoma
4. Subependymoma
D. Mixed gliomas
1. Oligo-astrocytoma
2. Anaplastic oligo-astrocytoma
3. Others
E. Chorioid plexus tumours
1. Chorioid plexus papilloma
2. Chorioid plexus carcinoma
F. Neuroepithelial tumours of uncertain origin
1. Astroblastoma
2. Polar spongioblastoma
3. Gliomatosis cerebri
G. Neuronal and mixed neuronal-glial tumours
1. Gangliocytoma
2. Dysplastic gangliocytoma of cerebellum
3. Desmoplastic infantile ganglioglioma
4. Dysembryoplastic neuroepithelial tumour
5. Ganglioglioma
6. Anaplastic ganglioglioma
7. Central neurocytoma
8. Paraganglioma of the filum terminale
9. Olfactory neuroblastoma
H. Pineal parenchymal tumours
1. Pineocytoma
2. Pineoblastoma
3. Mixed/transitional pineal tumours
I. Embryonal tumours
1. Medulloepithelioma
2. Neuroblastoma
3. Ependymoblastoma
4. Primitive neuroectodermal tumours (PNETs)
5. Medulloblastoma (with variants)

II. Tumours of cranial and spinal nerves
A. Schwannoma (with variants)
B. Neurofibroma (with variants)
C. Malignant peripheral nerve sheath tumour (MPNST) (with variants)
III. Tumours of meninges
A. Tumours of meningothelial cells
1. Meningioma (with variants)
2. Atypical meningioma
3. Papillary meningioma
4. Anaplastic meningioma
B. Mesenchymal, non-meningothelial tumours
1. Benign
2. Malignant neoplasms
3. Primary melanocytic lesions
4. Tumours of uncertain histogenesis
IV. Lymphomas and haemopoietic neoplasms
A. Malignant lymphomas
B. Plasmacytoma
C. Granulocytic sarcoma
D. Others
V. Germ cell tumours
A. Germinoma
B. Embryonal carcinoma
C. Yolk sac tumour
D. Choriocarcinoma
E. Teratoma
F. Mixed germ cell tumours
VI. Cysts and tumour-like lesions
VII. Tumours of the sellar region
A. Pituitary adenoma
B. Pituitary carcinoma
C. Cranopharyngioma (with variants)
VIII. Local extensions from regional tumours
IX. Metastatic tumours
X. Unclassified tumours

Table 1 b. WHO classification of CNS tumours, 2000

Tumours of neuroepithelial tissue
Astrocytic tumours
- Diffuse astrocytoma (variants: fibrillary, protoplasmic, gemistocytic)
- Anaplastic astocytoma
- Glioblastoma (variants: giant cell glioblastoma, gliosarcoma)
- Pilocytic astrocytoma
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma

Oligodendroglial tumours
- Oligodendroglioma
- Anaplastic oligodendroglioma

Mixed gliomas
- Oligoastrocytoma
- Anaplastic oligoastrocytoma

Ependymal tumours
- Ependymoma (variants: cellular, papillary, clear cell, tanycytic)
- Anaplastic ependymoma
- Myxopapillary ependymoma
- Subependymoma

Chorioid plexus tumours
- Chorioid plexus papilloma
- Chorioid plexus carcinoma

Glial tumours of uncertain origin
- Astroblastoma
- Gliomatosis cerebri
- Chorioid glioma of the 3rd ventricle

Neuronal and mixed neuronal-glial tumours
- Gangliocytoma
- Dysplastic gangliocytoma of cerebellum
- Desmoplastic infantile astrocytoma/ ganglioglioma
- Dysembryoplastic neuroepithelial tumour
- Ganglioglioma
- Anaplastic ganglioglioma
- Central neurocytoma
- Cerebellar liponeurocytoma
- Paraganglioma of the filum terminale

Neuroblastic tumours
- Olfactory neuroblastoma
- Olfactory neuroepithelioma
- Neuroblastomas of the adrenal gland and sympathetic nervous system

Pineal parenchymal tumours
- Pineocytoma
- Pineoblastoma
- Pineal parenchymal tumour of intermediate differentiation

Embryonal tumours
- Medulloepithelioma
- Ependymoblastoma
- Medulloblastoma (variants: desmoplastic, large cell, medullomyoblastoma, melanotic)
- Supratentorial primitive neuroectodermal tumour (PNETs) (variants: neuroblastoma, ganglioneuroblastoma)
- Atypical teratoid/rhabdoid tumour

Tumours of peripheral nerves
Schwannoma/Neurinoma/Neurilemmoma (variants: cellular, plexiform, melanotic)
Neurofibroma (variants: plexiform)
Perineurioma (variants: intra-neural, soft tissue perineurinoma)
Malignant peripheral nerve sheath tumour (MPNST) (variants: epithelioid, MPNST with divergent mesenchymal and/or epithelial differentation, melanotic, melanotic psammomatous)

Tumours of the meninges
Tumours of meningothelial cells
- Meningioma (variants: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, metaplastic, clear cell, chordoid, atypical, papillary, rhabdoid, anaplastic)

Mesenchymal, non-meningothelial tumours
Primary melanocytic lesions
- Diffuse melanocytosis
- Melanocytoma
- Malignant melanoma
- Meningeal melanomatosis

Tumours of uncertain histogenesis
- Haemangioblastoma

Lymphomas and haemopoietic neoplasms
Malignant lymphomas
Plasmacytoma
Granulocytic sarcoma

Germ cell tumours
Germinoma
Embryonal carcinoma
Yolk sac tumour
Choriocarcinoma
Teratoma (variants: mature, immature, with malignant transformation)
Mixed germ cell tumour

Tumours of the sellar region
Craniopharyngioma (variants: adamantinomatous, papillary)
Granular cell tumour

Metastatic tumours

2. Limitations of using a cancer registry to identify incidence of CNS tumours

National and regional cancer registries routinely collect data on CNS tumours. A few studies, concerning quality control of the tumour registration, have been published. Helseth and co-workers (1988) found that the data from the Norwegian Cancer Registry were sufficiently valid for a thorough study of CNS neoplasms. Under-estimation of brain tumours has been found in Great Britain and Ireland (Pobereskin, 2001; Ogungbo *et al.*, 2002). Counsell, with co-workers (1997), showed that the Scottish Cancer Registry significantly under-estimated the incidence of all primary intracranial tumours and of malignant intracranial tumours. It is apparent that a significant number of tumours, especially benign varieties, are not recorded in cancer registries.

Population-based cancer registries can provide information on a large group of unselected patients with primary CNS tumours relatively quickly. But histological data may not be interpreted directly because diagnostic criteria for histological classification of CNS tumours have not been applied uniformly. This occurs because there is no meaningful link between the ICD coding system used in cancer registries and the WHO classification system used by neuropathologists (Counsell *et al.*, 1997; Davis *et al.*, 1997; Van der Sanden *et al.*, 1998). The original histological diagnosis of the pathologist is coded according to the International Classification of Diseases for Oncology (ICD-O-1 or ICD-O-2) (WHO: International Classification of Diseases for Oncology, 1976; 1990). The ICD-O incorporates the nomenclature of different histological classification systems. This results in an imperfect description of tumour type currently in all population-based brain and CNS tumour databanks. Definition of malignancy within the ICD-O is of limited significance for primary CNS tumours, especially for gliomas (Van der Sanden, *et al.*, 1998). Due to the rarity of many histological types, diagnostic terms, which seem to represent the same group of clinically relevant entities, are usually clustered.

A preliminary integration of the ICD-O and WHO codes has been proposed by Davis *et al.* (1997). They proposed incorporation of site codes recognising all brain and CNS tumours including those that cannot be readily distinguished as benign or malignant to facilitate use of histology groupings consistent with the WHO classification. In 1998, Van der Sanden and co-workers proposed ICD-O gradings for the distinction according to differentiation with less specific histological terms and these were recorded or the grade was not explicitly expressed by name. Astrocytomas were simply divided into low-grade and high-grade astrocytomas. Nevertheless, the need for standard definitions concerning site and morphology codes has been outlined and discussed.

3. Histological distribution of primary CNS tumours

Gliomas constitute 23–39% and spinal tumours 8–12% of all CNS tumours. The most frequent histologies of primary CNS tumours include glioblastoma multiforme (15–30%), astrocytoma (12–26%), meningioma (14–35%), anaplastic astrocytoma (3–5%), pituitary tumours (5–18%), neurinoma (2–9%), oligodendroglioma (1–5%) and medulloblastoma (0.3–4.5%), (Gudmundsson, 1970; Percy *et al.*, 1972; Schoenberg *et al.*, 1976; Mahaley *et al.*, 1989; Kuratsu *et al.*, 1996; Surawicz *et al.*, 1998). Meningiomas constitute 13% of all histologically verified primary intracranial neoplasms among males and 24% among females; 95% of these tumours are histologically benign (Helseth *et al.*, 1988; 1989).

In children, the most common brain tumours are astrocytoma (26–42%), medulloblastoma (11–25%), ependymoma (10–13%), supratentorial primitive neuroectodermal tumours (2–7%) and craniopharyngioma (4–12%) (Lannering *et al.*, 1990; Agerlin *et al.*, 1999; Kuratsu *et al.*, 2001; Kaatsch *et al.*, 2001;).

4. Diagnosis

Clinical presentation

Brain tumours can cause either focal or generalised neurological symptoms. Generalised symptoms reflect increased intracranial pressure and consist of headache and, when the illness is severe, nausea and vomiting. Focal symptoms and signs are caused by local irritation or destruction of brain tissue reflecting the intracranial location of the tumour. The frequency and duration of symptoms vary with the type and location of the tumour.

Headache occurs in about half of all patients with brain tumours. Typically, the headache is diffuse, lasting for hours but not permanent, developing in weeks or months. It can accurately indicate the hemisphere in which the tumour is located in one-third of headache patients and occasionally mimic migraine or even cluster headaches (Forsyth and Posner, 1993). Headache has shown a close relationship with the prevailing edema, but not with the size of the tumour. It has been reported as the most frequent symptom in metastatic brain tumours and different astrocytomas (Pfund *et al.*, 1999).

Other symptoms that reflect the location of tumours, such as hemiparesis, aphasia or some other neurological deficits not associated with seizures, typically have a sub-acute onset and a progressive course. The frequency and duration of symptoms vary with the type of tumour. A rapidly evolving neurological deficit is more typical of a high-grade than low-grade glioma.

Kamiguchi *et al.* (1996) studying 1155 brain tumour patients found 9.5% of tumour patients asymptomatic. Most frequent accidentally diagnosed histologies included meningiomas (mostly convexity and falx location) and pituitary adenomas.

Epileptic seizures

Brain neoplasms account for about 4–5% of all cases with seizure disorders (Hauser *et al.*, 1993; Morris *et al.*, 1989). Of cerebral neoplasms 25 to 50% present with seizures (Shady *et al.*, 1994; Moots *et al.*, 1995). Patients with slowly growing chronic lesions are more likely to have a seizure disorder, with an incidence as high as 75% (Morris and Estes, 1993). Le Blanc and Rasmussen (1974) found the highest seizure incidences in patients with oligodendrogliomas (92%), astrocytomas (70%), meningiomas (67%) and glioblastomas (37%). According to reported data, seizures as the first manifestation of brain tumours are very variable (11–50%) (Le Blanc and Rasmussen, 1974; Ketz, 1974).

Seizures are often reported as being the first and sometimes the only presenting symptom of intracranial tumours (Morris *et al.*, 1993). In a retrospective study of 222 meningiomas, 26.6% of the patients presented epilepsy as their initial symptom (Lieu and Howling, 2000). Lühdorf and co-authors (1986) found seizures to be the first sign of brain tumour in 50% of patients who developed seizures after the age of 60 years.

Several authors have reported the mean interval from onset of seizures to tumour diagnosis or surgery to be from 2 to 11 years with a maximum of more than 20 years (Bartolomei *et al.*, 1997; Hirsch *et al.*, 1989; Smith *et al.*, 1991; Afra *et al.*, 1999). In a study carried out in 6 countries (Schlehofer *et al.*, 1999) including 1,178 glioma and 331 meningioma cases, there was an increased risk associated with epilepsy at least 2 years before brain tumour diagnosis in glioma patients. In epilepsy, of more than 20 years duration, the risk was significantly weaker.

Data on the incidence of seizure activity and patients' age are controversial. The age distribution of cases depends largely on the biological type of the tumours.

The probability of diagnosing an underlying tumour in a patient with epilepsy is related to seizure type, with simple and complex partial seizures being the most common. Many authors consider tumour location the most important factor (Shady *et al.*, 1994; Dam *et al.*, 1985).

Imaging

The standard methods for diagnosing brain tumours during the pre-CT era were plain skull x-rays, angiography, pneumoencephalography, ventriculography for intracranial and myelography for spinal tumours. In Estonia, the first CT was installed in 1983. From this time the number of CT scans has been steadily increased and all bigger centres have now been equipped. An ultra low field MRI scan was introduced in 1993. For several years it was the only scan for the whole republic and during our study period it has not been frequently used for diagnosis of brain tumours.

At the moment, MRI has been considered the best imaging method for diagnosing a brain tumour. CT can miss structural lesions, particularly in the posterior fossa, or non-enhancing tumours such as low-grade gliomas. Therefore, if a brain tumour is a diagnostic consideration, MRI with gadolinium enhancement is the best choice of test.

Histological diagnosis

Relevance of histological diagnosis to patient management is obvious and cannot be underestimated. An incorrect diagnosis may result in inadequate therapy for a high-grade tumour or, worse, harmfully aggressive therapy for low-grade glioma. Several factors affect diagnostic accuracy. Diagnostic errors may be caused by insufficient biopsy size and regional heterogeneity. Significant problems also relate to the interpretation of histological criteria used to classify and grade gliomas. Subjective interpretation promotes inter-observer variation and decrease diagnostic reproducibility among pathologists, resulting in classification and/or grading errors that lead to failure to predict tumour behaviour (Coons *et al.*, 1997). Aldape, and co-workers (2000), has found diagnostic discrepancies in a population-based adult glioma study by speciality training of the original diagnosing pathologist. Clinically significant discrepancies were much more likely to have originated at a hospital without a neuropathologist. This study highlights the importance of the review of brain tumours by a neuropathologist prior to decision-making regarding treatment. Mittler and co-workers (1996) studied the inter-observer and intra-observer reliability of histological grading of astrocytoma specimens obtained using stereotactic biopsy. They found a significantly greater degree of reliability in histopathological diagnosis of low- or high-grade astrocytomas than in those of intermediate-grade astrocytomas. Therefore, the highest variability occurred at the point of clinical decision making (intermediate-grade tumours that may or may not be selected to receive adjuvant therapy).

Problems of classification are most apparent with respect to differentiating astrocytomas from oligodendroglial tumours. In oligodendroglioma the diagnosis is complicated by the fact that many oligodendrogliomas contain an astrocytic component, which may be substantial at times; such mixed tumours are termed oligoastrocytomas. In practice, the distinction of oligodendroglioma from oligoastrocytoma is probably not as important as the distinction between these 2 oligodendroglial lesions and pure astrocytoma, since many oligoastrocytomas, grade for grade, behave clinically and respond to both radiotherapy and chemotherapy in a fashion very similar to pure oligodendrogliomas (Perry *et al.*, 1999). High-grade oligodendrogliomas should not be equated with typical glioblastomas; they may also be chemo-sensitive (Cairncross *et al.*, 1994).

5. Incidence rates

General data

The earliest reports dealing with the frequency of CNS neoplasms have been based on the experience of neurosurgeons, autopsy series and hospital admissions. While providing valuable descriptions of clinical or pathologic experiences, these data do not reflect the real incidence of neoplasms or their frequency by type in the population. It is desirable to have such statistics for various populations, which might disclose trends and population selection of disease providing relevant clues to aetiology. Comparisons can be extended to regional and national population.

Incidence of primary central nervous system neoplasms in a defined population has been reported in a number of studies. It varies from 4.9 to 25.5 per 100,000 population (Table 2), while higher rates are generally found in socio-economically advanced societies with sufficient availability of medical care, better organised registries for data collection and possibly higher autopsy rate. The observed differences in different populations, races and sexes suggest the possible role of environmental, genetic and hormonal factors in the etiology of brain tumours (Bahemuka, 1988).

There are wide variations in the age-standardised incidence of all primary intracranial tumours and the crude incidence of specific tumour types in different studies. Much of this is due to differences in study methodology. Counsell and Grant (1998) found higher incidences of primary tumours in studies that used many methods to identify cases, included a high percentage of asymptomatic patients and did not require histological conformation of the diagnosis. The high number of CNS tumour categories, combined with a relatively low incidence of CNS tumours, hinders the collection of an adequate number of similar tumour types for study.

Studies based solely on existing cancer registries give consistently lower incidences (Percy *et al.*, 1972; Counsell *et al.*, 1997). This was not because the registries were excluding benign tumours but may be because they relied on voluntary registration and routine data collection, which can be incomplete (Davis *et al.* 1996). When interpreting the results of incidence studies it is also important to note whether some patients were excluded on the basis of age, tumour type or lack of histology, and also to know the percentage of asymptomatic patients who were included. Prospective studies have not identified more cases than retrospective studies (Counsell and Grant, 1998).

Most studies confirm that the incidence of primary tumours — especially neuroepithelial and meningeal tumours — increase markedly with age except in the very elderly (Percy *et al.*, 1972; D'Alessandro *et al.*, 1995; Kuratsu *et al.*, 1996; Van der Sanden *et al.*, 1998; Counsell *et al.*, 1996; Fogeholm *et al.*, 1984; Heshmat *et al.*, 1976; Schoenberg *et al.*, 1976). Only a few authors (Barker *et al.*, 1976; Kallio, 1988) confirm that the peak incidence of gliomas occurs in the

Table 2. Incidence rates (per 100,000 population) of CNS tumours

Reference	Region	Period	Gliomas	Meningiomas	All brain tumours
Gudmundsson 1970	Iceland	1954–1963			7.8 (CR)
Leibowitz *et al.* 1971	Israel	1961–1965	3.8 (CR)	2.2 (CR)	12.8 (CR)
Barker *et al.* 1976	Southern England, United Kingdom	1964–1974	M 4.76, F 3.22 (CR)	M 0.6, F 1.8 (CR)	M 7.2, F 6.8 (CR)
Heshmat *et al.* 1976	Washington, DC (Caucasians); US	1960–1969	M 4.4, F 2.5*	M 0.2, F 0.3*	M 5.5, F 3.6*
Schoenberg *et al.* 1976	Connecticut, US	1935–1964		M 0.5, F 0.7*	M 4.9, F 4.0*
Lukas 1979	Estonia, USSR	1951–1970	2.9 (CR)	0.9 (CR)	5.9 (CR)
Fogelholm *et al.* 1984	Central Finland	1975–1982			12.3*
Helseth *et al.* 1988	Norway	1955–1984			M 8.2, F 6.8**
Kallio 1988	Southern Finland	1978–1980	M 6.4, F 4.9*		
Cole et al 1989	Wales (South East)	1981–1987	3.6*	1.3*	5,6*
Rohringer *et al.*1989	Manitoba, Canada	1980–1987		2.3 (CR)	
Preston-Martin 1993	Victoria, Australia	1982–1990	M 5.5, F 3.8***	M 1.3, F 2.6***	M 8.8, F 8.1***
Tola *et al.* 1994	Ferrara, Italy	1986–1991	M 7.0, F 4.0*		
Radhakrishnan 1995	Rochester, Minnesota; US	1950–1989	5.7*	7.8*	19.1*
D'Alessandro *et al.* 1995	Valle d'Aosta, Italy	1986–1991	M 10, F 8.1*	M 5.3, F 13.9*	M 21.7, F 28.1*
Counsell *et al.* 1996	Lothians, Scotland	1989–1990	7.7 (CR)	2.7 (CR)	15.3 (CR)
Davis *et al.* 1996	Connecticut, Missouri, Massachusetts, Utah; US	1985–1989			9.4*
Helseth 1997	Norway	1983–1992		M 1.5, F 2.8**	
Van der Sanden *et al.* 1998	South and East Netherlands	1989–1994			M 6.5, F 4.4***
Surawicz *et al.* 1999	US (11 cancer registries)	1990–1994			M 12.1, F 11.0*
Kuratsu *et al.* 2001	Kumamoto, Japan	1989–1998			M 9.7, F 11.9*
Cordera *et al.* 2002	Valle d'Aosta, Italy	1992–1999	M 10.6, F 8.1*	M 9.8, F 16.7*	25.5*
Christensen *et al.* 2003	Denmark (patients <20 years not included)	1993–1997	3.7***	2.4***	

M=male, F=female, CR=crude rate
Standard population:
* Local
** European
*** World

age group of 50–59 years. The decline in incidence in the elderly probably reflects under-diagnosis. Elderly patients may be less likely to present themselves to a doctor if they have symptoms of an intracranial tumour, and less likely to be referred for a CT scan or to have an autopsy (Asplund *et al.*, 1996). There may also be a diagnostic bias in the very elderly: patients with intracranial symptoms or signs may be diagnosed as having a stroke rather than a tumour, particularly if they did not have a CT.

Previous data about Estonia

A previous study of primary brain neoplasms in Estonia carried out between 1951 and 1970 was a retrospective, population-based epidemiological survey using histological classifications proposed by Smirnov and Hominski (Lukas, 1979). However, it included only primary intracranial tumours establishing the crude rate of primary intracranial tumours as 5.9 (6.1 for men and 5.8 for women) per 100,000 population. The incidence rate increased significantly during the study period from 5.0 (1951–1960) to 6.9 (1961–1970). Age-specific incidence rate was the highest in the age groups of 50–59 and 60–69 years (12.5 and 12.3 per 100,000 population, respectively). The most frequent histologies were glioblastoma (21.5%), meningioma (14.7%), astrocytoma (8.8%) and pituitary adenoma (5.9%); unclassified brain tumours consisted 15.8%. Incidence of glioblastoma was 1.29 for men and 1.18 for women, astrocytoma 0.55 for men and 0.47 for women and meningioma 0.62 for men and 1.13 for women.

Data reported by the Estonian Cancer Registry (1994–1996) show the values of 6.2/100,000 for men and 5.6/100,000 for women for brain and other central nervous system (CNS) tumours (Thomson *et al.*, 1996). Recent data show the crude rate of 6.2 (1994–1996) and 8.0 (1996–1998) for males, 5.6 (both time periods) for females. Age-standardised incidence rates were 7.2 (1996) and 6.4 (1998) for males, 5.0 (1996) and 4.5 (1998) for females (Aareleid and Mägi, 1999; 2001).

Histology-, race-, sex- and age-specific incidence rates

The incidence rate of glioblastoma ranges from 1.3 to 2.6 per 100,000 population.

The age-specific incidence rates for glioblastoma are low among children, dip slightly in the ages 10–20, then rise steadily to a peak among those aged 70–74 and decline in the oldest age groups. A male preponderance for the whole glioma group and for glioblastoma has been found in most studies.

Incidence rates for low-grade astocytomas has been reported 0.5–1.4 per 100,000 population (Fleury *et al.*, 1997; Van der Sanden *et al.*, 1998; Kallio

et al., 1991; Preston-Martin *et al.*, 1993; Barker *et al.*, 1976; Davis *et al.*, 1996). In astrocytoma, the rates in the younger age groups are relatively high, astrocytoma is the most common type of brain tumour among children (Polednak and Flannery, 1995; Preston-Martin *et al.*, 1993). Age-specific incidence of low-grade astrocytoma is the highest in the 30–39 years' age group. Considering the sex in astrocytoma, no significant differences has been reported (Tola *et al.*, 1994; Fleury *et al.*, 1997).

Incidence of oligodendroglioma ranges from 0.1 to 0.6 per 100,000 population peaking in the forties and fifties with no significant differences between genders (Fleury *et al.*, 1997)

Medulloblastoma is the second most common type of tumour among children and can be called predominantly a paediatric brain tumour with reported incidence rates of about 0.2–0.5 per 100,000 population (Van der Sanden *et al.*, 1998; McNeil *et al.*, 2002). Age-specific incidence rates have a marked peak at ages 0–4 years in boys but not in girls. The incidence of medulloblastomas falls to zero after 45 years of age.

Incidence rates for ependymoma has been reported about 0.2 per 100,000 population (Birgisson *et al.*, 1992; Davis *et al.*, 1996). Ependymoma shows a peak at age 0–4 years (Polednak and Flannery, 1995), whereas a horizontal age-curve is seen in adulthood.

The reported incidence rates for pituitary tumours is 1.8–2.3 per 100,000 population. In the Japanese study, (Kuratsu *et al.*, 1996), women evidenced two peaks in the incidence of pituitary adenomas in the 20–29 and 60–69-year-old age groups. In males, the rate increased with age. The Scottish study (Counsell *et al.*, 1996) found no obvious relation between age and the incidence of sellar tumours.

The frequency of meningiomas has been the topic of relatively few reports. Population-based studies indicate an overall incidence of 2.3–2.8 per 100,000 population. More females than males are shown to get meningiomas in a number of surveys (Helseth *et al.*, 1988, 1997; Sankila *et al.*, 1992; Kurland *et al.*, 1982; Gudmundsson, 1970). The female predominance has been shown to be age dependent (Helseth, 1997). Below 20 years of age, no gender difference was noted. The sex ratio peaked at 30–39 years of age and fell towards unity among those 80–89 years of age. Several series of studies have shown that the incidence of meningioma increases with age (Longstreth *et al.*, 1993; Rohringer *et al.*, 1989). The increased use of CT and MRI has led to an increase in the detection of asymptomatic meningiomas. Kuratsu and co-workers (2000) found 39% of diagnosed meningiomas asymptomatic. The incidence of asymptomatic meningiomas was significantly higher in individuals older than 70 years. Meningiomas in children are rare and differ from those in adults and other childhood tumours, including a male preponderance, more frequent incidence of intraventricular and posterior fossa meningiomas than in adults. Children meningiomas are characterised by a significantly higher incidence of tumour

calcification, sarcomatous elements and a high recurrence rate (Bondy and Ligon, 1996).

Regarding Caucasians and Africans, African-Americans, and Asians, certain differences have also been noted. The African groups show equal gender distribution or a male preponderance (Bondy and Ligon, 1996). In the Los Angeles County population-based survey, a higher incidence in Africans than in Caucasians was observed. Asians were found to have the lowest rates (Preston-Martin, 1989). The US study including 20,765 cases of primary brain tumours (Surawicz *et al.*, 1999) reported the higher incidence in whites (11.6 per 100,000 population) than blacks (7.8).

Time trend studies

Some investigators have reported that the frequency of primary brain tumours, especially in the elderly, has increased substantially during the past two decades in several countries (Greig *et al.*, 1990; Werner *et al.*, 1995; Polednak, 1996). The results of a Rochester study (Radhakrishan *et al.*, 1995), which had a very high autopsy rate, indicate that the increase in incidence is an element reflecting improvement in diagnostic technology and practice. Helseth (1995) who studied the incidence of primary CNS tumours in Norway before, during and after the introduction of CT found that in the elderly a large part of the three-fold incidence increase from the pre-CT era to the post-CT era can be attributed to improved tumour detection. A similar study carried out in Canada (Desmeules *et al.*, 1992) estimated that modern imaging technology is responsible for the newly seen detection of about 20% of brain tumours in both younger and older patients.

As in different age groups, time trend studies of different histological groups show very controversial results. The Japanese study (Kanako *et al.*, 2002) pointed out 3 patterns of time trends between 1973 and 1993. These were a gradual linear increasing trend before the 1980s followed by a plateau for gliomas and meningioma; a step-up increase before 1980s followed by a plateau in germ cell tumour and pituitary tumour and a linear increasing throughout the study period for lymphoma and neurinoma. Data from US SEER program analysing histology-specific incidence between 1980–1990 (Ahsan *et al.*, 1995) found no significant increase in the incidence of different histological types, except for lymphomas in men. The increase of lymphomas in specific age groups has been supported by other authors (Jukich *et al.*, 2001). In the Canadian study (Hao *et al.*, 1999) no significant increase in lymphomas has been established during the past 20 years. Analysis based on Surveillance, Epidemiology and End Results (SEER) data from 1973–1998 showed that primary CNS lymphomas rates have been decreasing in the majority of demographic groups since the mid-1990s (Kadan-Lottick *et al.*, 2002).

Fleury *et al.* (1997) observed an increasing trend of 5% per year in the incidence of malignant astrocytomas between 1983 and 1990 in the population older than 65 years. Mao and co-workers (1991), has indicated that the increase has been more pronounced for glioblastomas. In a Florida study (Werner *et al.*, 1995) the rise in brain tumour incidence was observed in anaplastic astrocytoma in all ages and in glioblastoma among the elderly. As malignant gliomas are generally easier to diagnose than low-grade astrocytomas, the increased brain cancer rates may not be entirely attributable to improved diagnostic techniques.

In ependymomas, some increase in the population aged 20 to 64 has been reported (Jukich *et al.*, 2001).

In meningiomas, the incidence has markedly increased in Norway from 1963 to 1992 (Helseth, 1997). With the available descriptive data, it has not been possible to determine to what extent the increase was caused by improved case investigation, or was it a real increase, or both? Many old patients have small and asymptomatic meningiomas. It has been established that the case detail discovery, especially for small meningiomas in the elderly, is dependent on the autopsy rate in the population (Kurland *et al.*, 1982). Thus, the complete meningioma incidence will only be detected in populations with high autopsy rates, good health care systems and easy access to CT and MRI without major economic barriers for individual patients (Helseth, 1993; 1997).

6. Survival rates

General data

Most of the published studies, concerning the survival of central nervous system tumours, are hospital-based and restricted to gliomas or their histological subtypes. Very few population-based studies, including survival of all primary benign and malignant tumours, have been published. Increased mortality rates for malignant CNS tumours, particularly among the elderly, have been attributed to improved diagnostic techniques and increased environmental carcinogens (Modan *et al.*, 1992). A study from the Estonian Cancer Registry (Thomson *et al.*, 1996) reported the 5-year relative survival rate among patients of diagnosed CNS tumours in Estonia (1983–1987) 11.2% for males and 24.6% for females and mortality rate (1988–1992) 4.9 and 3.5 per 100,000 population, respectively. In a recent EUROCARE survey (Sant *et al.*, 1998), including malignant CNS tumours diagnosed between 1985 and 1989 in 17 European countries, the mean European age-standardised 5-year relative survival was 17% in men and 20% in women with markedly lower rates in Scotland, Estonia and Poland. In the U.S.A., in 1973–1991, 5-year relative survival of malignant CNS tumours was 20% according to the US SEER program (Davis *et al.*, 1998).

Survival by histological types

In gliomas, the most favourable prognosis includes pilocytic astrocytoma and ependymoma (5 year survival 77–84% and 60–68%, respectively). The worst outcome has patients with glioblastoma, the most common CNS malignancy (5-year survival 1–2.5%). Other histologies of poor outcome include anaplastic astrocytoma, astrocytoma and anaplastic oligodendroglioma (5-year survival 20–40%). Mixed gliomas and anaplastic ependymomas have a slightly better prognosis (5 year survival-about 50%). In oligodendroglioma, a 5-year survival rate has been reported at 45–65%. In medulloblastomas diagnosed during the last 20–30 years, 5-year survival rates show values of 55–60% (Surawicz *et al.*, 1998; Davis *et al.*, 1998). In Victoria, Australia, the survival of benign meningiomas was 94% in women and 87% in men (Preston Martin *et al.*, 1993). The Finnish study reported an overall relative survival of 83% at 1 year, 79% at 5 years and 74% at 10 years for the time period 1953–1984 (Sankila *et al.*, 1992). The results based on the National Cancer Data Base (McCarthy *et al.*, 1998) showed a 5-year survival rate 69% for all meningiomas, 70% for benign and 75% for atypical meningiomas. In Norway, a 5-year relative survival for benign meningiomas was 94% or better for patients below 75 years and 78% for patients 75 years of age or more (Helseth, 1997). For malignant meningiomas, survival prospects are poor, long-term relative survival ranging between 49% and 55% (Helseth, 1997; McCarthy *et al.*, 1998). Survival of another more frequent non-malignant tumour, neurinoma, is even slightly better than the prognosis of meningioma, reaching 85% (Surawicz. *et al.*, 1998)

Time trend studies

Clinically significant improvement in survival of patients with CNS tumours has taken place over the past 25 to 30 years (Sant *et al.*, 1998; Davis *et al.*, 1998; Levin, 1999). Improvement in survival has been histology specific, being more evident in medulloblastoma, astrocytoma and oligodendroglioma. In low-grade astrocytomas, it is not possible to attribute this increased survival to a specific method of management, because the trend has been noted with the use of a variety of treatments.

The SEER program (Davis *et al.*, 1998) found statistically significant improvements in survival rates for patients with astrocytoma, medulloblastoma and oligodendroglioma. Clinically significant improvements in survival rates were not apparent in those patients aged 65 years and older.

The median survival for patients, with anaplastic astrocytoma, has increased from 82 weeks to 4 years and patients with anaplastic oligodendroglioma have a median survival of more than 7 years. For glioblastoma, the most frequent primary CNS tumour, no striking improvement has taken place (Polednak and Flannery, 1995; Paszat *et al.*, 2001).

The prognosis of meningiomas has improved following the introduction of CT. In time-trend studies, both short-term and long-term survival has improved during the last decades. The improved 1-year survival is likely to be caused by improved operative technique and improved post-operative care. Other causes that could account for the increased long-term survival include selection bias reflecting the likelihood that more patients with small meningiomas are diagnosed early since CT became available (Helseth, 1997). Sankila and co-workers. (1992), has reported an increase in long-term mortality for male meningioma patients, which can be explained by more malignant meningiomas among males.

Treatment and survival

The obvious optimal purpose of treatment is to cure the patient by suppressing the disease. This goal in unfortunately very rarely achieved when dealing with cerebral neuroepithelial tumours. In most of these cases, it is necessarily being limited to offering the longest and best quality survival, without producing or further increasing neurological deficits. Within these limitations, respective surgery is generally regarded as the most fruitful means of treatment, even if, in several cases, it is the first step of a multi-modality management. Even if the tumour cannot be completely eradicated, a substantial reduction of its mass can be achieved, thus enhancing the efficacy of other subsequent treatments, such as radiotherapy or chemotherapy. For low-grade gliomas, however, the utility of surgical resection has been questioned. Uncertainties regarding their natural history and the possibility of long survival in untreated cases are at the basis of the controversy. Although natural history of a low-grade astrocytoma may be difficult to predict, once the tumour has changed to an anaplastic lesion, the prognosis becomes predictably poor. Piepmeier with co-workers (1996) suggests that aggressive surgery may delay the time of recurrence and prolong survival.

The role of adjuvant chemotherapy in glioblastomas in unclear. Gundersen with co-workers (1998) observed a markedly increased survival among patients under 55 years of age with anaplastic gliomas, which were receiving adjuvant chemotherapy. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults showed some benefit in some subgroups of patients, particularly in anaplastic astrocytomas, after combined treatment (Fine *et al.*, 1993). Lindegaard with co-workers (1987) suggests that post-operative radiotherapy significantly prolongs the median survival time in oligodendroglioma patients with sub-total surgery.

Consequently, a critical analysis of operative risks versus the risk of the natural course is necessary to answer the question of the benefit of doing operations on meningiomas (Meixensberger *et al.*, 1996). Operative mortality of meningiomas ranges from 4% to 16% (Chan and Thomson, 1984; Cornu *et al.*,

1990). There is a general agreement about the importance of the completeness of surgical resection on tumour recurrence and it is clear that sub-totally removed meningiomas continue to grow (McCarthy *et al.*, 1998; Ayerbe *et al.*, 1999) Some authors emphasise that a balanced strategy is necessary in the treatment of asymptomatic meningiomas in elderly and high risk patients (Meixenberger *et al.*, 1996).

7. Prognostic factors

Patient-related factors

Practically all studies identify age as a strong independent prognostic factor. Generally, in CNS tumours, survival rates are declining with the increasing age at diagnosis. The differences are more pronounced for low-grade than high-grade astrocytomas (Takeuchi *et al.*, 1991). Exceptions to this pattern are noted for meningiomas and two paediatric tumours: medulloblastomas and ependymomas (Surawicz *et al.*, 1998). The survival rates for meningiomas remain relatively constant across the younger age groups with a decline in survival of patients, aged 75 and older. In medulloblastomas the youngest patients (< 5 years) have the lowest survival rate. Younger patients (< 15 years) with ependymomas also have a poorer survival statistic than adults.

Another important patient-related prognostic factor for survival is clinical condition of the patient. Only very few studies have found no significant association of the pre-treatment and post-treatment Karnofsky score with survival in contrast with most of the others (Massimo *et al.*, 1996).

Concerning clinical symptoms before the diagnosis, Scott and Gibberd (1980) found that a young patient who presents epilepsy and has a low histological grade of glioma would have the best prognosis. Earlier diagnosis in the patients, without chronic epilepsy, has been proposed as a potential factor in the extended survival noted in several work series (Piepmeier, 1987; Vertostic *et al.*, 1991).

In most studies in multivariate analysis, gender has been reported to have no significant influence on survival, only a few studies have found a better prognosis in women. In a study based on cancer registries of 17 European countries, (Sant *et al.*, 1998), a better prognosis for women was observed in most countries. The same tendency has been reported in the Finnish study (Kallio *et al.*, 1991). This finding has been explained by the occurrence of higher-grade gliomas and glioblastomas in men. Davis with co-workers (1998) observed modest gender differences in survival in astrocytomas and other gliomas.

Tumour- and treatment-related factors

Histology and anatomical location are important tumour-related agents in estimating survival. Prognosis is worse for grade IV tumours than less malignant tumours. Glioblastomas remain the most fatal of all brain tumours despite other prognostic factors. Some studies have shown that frontal lobe location is associated with improved survival for malignant gliomas. Large variations, in survival by site, are noted for astrocytomas and anaplastic astrocytomas with poorest outcomes associated with tumours located in the supratentorial regions and higher survival rates for tumours in the ventricles and cerebellum (Surawicz *et al.*, 1998).

The influence of pre-operative tumour size in gliomas has not been so far extensively investigated and is still controversial.

Unfortunately, earlier detection of malignant brain tumours, particularly glioblastoma multiforme, has little impact on survival, especially in elderly patients (Lowry *et al.*, 1998). Treatment related prognostic factors include surgery, radiation therapy and chemotherapy, which can improve the survival of patients with favourable histology, tumour location and good performance status (Flowers, 2000).

Prognostic factors in different histologies

In malignant gliomas, age, symptom duration, histology, pre-operative Karnofsky performance status, radiation dose and epilepsy at onset have been considered independent prognostic factors (Salminen *et al.*, 1996; Kowalczuk *et al.*, 1997; Smith *et al.*, 1991; Billiar *et al.*, 1999; Lote *et al.*, 1998). Patients of younger age, longer duration of symptoms, lower tumour grade, better Karnofsky performance status and receiving a higher radiation dose have been reported to have a better prognosis. Aggressive surgical resection does not impart a significant increase in survival time.

In low-grade astrocytomas, younger age, gross-total resection, long duration of pre-operative symptoms, pre-operative neurological deficit and CT-contrast enhancement are associated with longer survival in multivariate analysis (Schuurman *et al.*, 1997). Piepmeier (1996) suggests that low-grade astrocytomas, occurring among patients having relatively short pre-operative symptoms, more commonly transform into anaplastic tumours. Tumours causing chronic epilepsy are much less likely to evolve into anaplastic lesions and more typically behave as "benign" astrocytomas. Scott and Gibberd (1980) confirmed that the prognosis was better if epilepsy had occurred, but epilepsy was not more likely to occur with lower histological grades of tumour. If epilepsy occurs, then it is usually the first symptom, rarely it begins after the diagnosis as been made (except post-operative epilepsy).

In oligodendrogliomas age at surgery, duration of symptoms, tumour calcification, extent of surgical resection, performance status (Karnofsky score) and some immunohistochemical parameters (MIB-1, Labelling Index) are associated with survival. Sex and location has been found to have no statistically significant influence on survival in oligodendrogliomas (Mørk *et al.*, 1985; Ludwig *et al.*, 1986). Generally, oligoastrocytomas have the same outcome and prognostic factors as pure oligodendrogliomas (Schiffer *et al.*, 1997).

In primitive neuroectodermal tumours (PNETs) of the CNS multivariate analysis, using Cox regression, has revealed a significantly worse outcome in those patients with a supratentorial tumour location, advanced metastatic stage (M1–3) and treatment with radiation or chemotherapy alone. Age, sex and the extent of surgical resection did not have significant prognostic value (Janss *et al.*, 1996).

The prognosis for patients with benign, atypical and malignant meningiomas is better for females and depends on the patients age (Preston-Martin *et al.*, 1993; Meixensberger *et al.*, 1996; McCarthy *et al.*, 1998) being more favourable for patients below 60 years. Helseth (1997) analysed benign and malignant meningiomas separately and found that below 60 years of age, females have a better survival prognosis than males. The cause of this difference is unknown. Atypical meningiomas represent a heterogenous prognostic group whose limits with a benign and malignant type remains to be determined (Ayerbe *et al.*, 1999). In benign meningiomas, besides patient age, the outcome is also influenced by poor clinical condition, tumour size and extent of surgery. Additional operative difficulties related to location, vascularisation of the tumour and disturbances of cerebrospinal fluid circulation has been pointed out (Meixensberger *et al.*, 1996). In malignant meningiomas, age at diagnosis, surgery and no radiation treatment in those patients who had survived at least 12 months were estimated as significant predictors of survival time (McCarthy *et al.*, 1998). It has been reported that up to 4% of benign meningiomas show brain invasion (Jääskeläinen *et al.*, 1985). Brain infiltration is difficult to assess and has little prognostic significance by itself (Jellinger and Slowik, 1975).

PURPOSE OF THE STUDY

The general objective of the study was to evaluate the epidemiological characteristics of primary brain tumours in Estonia diagnosed during the period 1986–1996.

The specific objectives were:

1) to analyse in detail the clinical and morphological data of patients with diagnosed brain tumours presented with seizure disorders.
2) to find out age-specific incidence rates of primary brain tumours in specific histological groups.
3) to compare those of investigations, carried out in other populations and with data from the pre-CT diagnostic era (1951–1970) in Estonia, with the aim of assessing the changes in incidence rates in Estonia
4) to find out 1- and 5-year survival of patients with primary CNS tumours, examine variation in different ages and histological groups and evaluate changes in the length of survival that have occurred over these years.
5) to compare survival rates of brain tumours in Estonia with those in other countries
6) to evaluate prognostic factors influencing survival rates using the Cox model
7) to evaluate the reporting of brain tumours in the Estonian Cancer Registry.

PATIENTS AND METHODS

1. Study population and case finding

The study was based on the Estonian population of approximately 1.5 million served by two neurosurgical centres (Tartu University Clinics and Tallinn Mustamäe Hospital), which admit or consult all patients suspected of having CNS tumours. The records of all intracranial and spinal tumours (including suspicious cases and brain metastases) at these hospitals from 1986 to 1996 were retrospectively reviewed. The criteria for inclusion were either histological confirmation, or verification of neoplasms by radiological or clinical methods. To maximise case ascertainment, we obtained material from several sources including hospital records (case histories, autopsy protocols, pathology reports), the Estonian Cancer Registry (founded in 1978) and the Estonian State Statistical Office.

2. The Estonian Cancer Registry

The Estonian Cancer Registry (ECR) is population-based covering the whole of Estonia. The registry was founded in 1978, but its data are retrospective to 1968. Reporting on cancer cases is compulsory by the Decree, issued by the Minister of Social Affairs of Estonia. All treating physicians, pathology and haematology laboratories are requested to report all cases of cancer that come to their attention. The cancer patients are followed by the ECR up to their death or emigration. The Registry links its data with death certificates filed at the Estonian State Statistical Office and with the inpatient data from two major hospitals — Tallinn Mustamäe hospital and Tartu University Clinics. If the hospital files contain information on patients not recorded in the registry, the registry staff performs a trace-back of these patients to their original medical records.

The overall reporting to the Registry is estimated to be 95–98% of all diagnosed cancers. Since meningiomas and other histologically benign brain tumours were not recorded until recently, the registry can be considered complete with regard to malignant brain tumours but incomplete for benign tumours. Since 1998, the Cancer Registry includes information on all primary brain tumours. Improvement of brain tumour reporting in Estonia is important for our understanding of the occurrence of these complex tumours and for our ability to conduct large-scale epidemiologic investigations.

In the registry, the anatomical site and histology of tumours are coded according to the International Classification of Diseases for Oncology (ICD-O, first edition 1976, second edition 1990) by the WHO. For statistical purposes, the ICD-O codes are converted into the International Classification of Diseases

(ICD-9, ICD-10). To maximise case ascertainment and assess the reporting of brain tumours, electronic record linkage of the study population with the cancer registry database was used.

3. Selection of patients

Selection of patients was carried out according to the guidelines of the International Classification of Diseases for Oncology (ICD-O-2) including the following topography codes: C71.0–C71.9 for brain, C70.0 and C70.9 for meninges, C72.2–C72.9 for cranial nerves and other intracranial parts of the CNS, C75.1–C75.3 for pituitary gland, pineal gland and craniopharyngeal duct. Metastatic tumours were also reviewed but included only in the analysis of clinical manifestation and seizure incidence. Cases discovered at autopsy, patients diagnosed with another tumour previously or during the follow-up period and patients of lost to follow-up, (no contacts after diagnosis, not included in the Registry of Inhabitants) were excluded from survival analyses.

4. Classification of tumours

Tumours were classified according to the histopathological type of brain tumour following the scheme approved by the World Health Organization (Kleihues, Burger and Scheithauer, 1993). All histologically obscure cases (with the majority of pathological material having been preserved) were retrospectively overviewed by a neuropathologist. Tumours of the skull and vascular malformations were excluded. Patients were analysed for tumour pathology and grade according to individual WHO histological diagnosis as well as groups. The following categories were used: astrocytoma (low-grade), anaplastic astrocytoma, glioblastoma, oligodendroglioma, ependymoma, mixed glioma, medulloblastoma, neurinoma (schwannoma), meningioma, hemangioblastoma, lymphoma, pituitary adenoma, craniopharyngioma, metastatic tumour and cases without microscopic conformation.

5. Clinical data

The medical records were reviewed for the following information: patient gender, age at diagnosis, patient clinical condition, diagnostic method, histological type, grade and location of a tumour and performed treatment.

Information on tumour location was obtained from CT or MRT and from surgery reports. Additional data of patients with primary and secondary intracranial brain tumours diagnosed between 1991 and 1995 were recorded to

analyse the clinical data of patients with epileptic seizures. These data included nature and duration of signs and symptoms, seizure type, time of the first seizure and the first symptom and seizure incidence.

The study population was divided into 4 age groups: children (≤ 20 years at diagnosis), younger adults (21–44 years), older adults (45–64 years) and the elderly (≥ 65 years), reflecting the fact that CNS tumours have specific characteristics including histology, behaviour, anatomical location depending on age, and survival rates are varying by age at diagnosis.

The clinical functional ability of the patient before therapy was assessed according to the Karnofsky Performance Status scale. Three groups were considered: score 80–100% (no evidence of disease or minor signs and symptoms, normal activity even with effort) 60–70% (unable to carry on normal activity or to do active work, able to care for most of his needs, may require occasional assistance) and less than 60% (disabled, requires assistance and frequent medical or special care, needs hospitalisation) (Karnofsky and Burchenal, 1949).

As clinical data varied in quality and quantity, symptoms were grouped in the simplest way: headache, papilledema (reflecting intracranial hypertension), epileptic seizures, neurological deficit (motor deficit, lesions of cranial nerves, speech disorders, disorders of sensation, ataxia etc) and mental disturbances. A sign or a symptom was recorded if any physician described its presence.

According to seizure types patients were classified as having simple or complex partial and secondarily generalised seizures. When seizures were not described adequately, to be classified according to the guidelines of the International League against Epilepsy (Commission on Classification and Terminology of the International League against Epilepsy, 1981) the term unclassified seizures was used.

Tumour location was analysed as supra (hemispheres)- and infratentorial and by individual sites: lobes, central structures, parasagittal and hypophyseal region.

6. Time periods and follow-up

Our study included CNS tumours diagnosed between 1986 and 1996 in Estonia. Follow-up of vital status was until January 1, 1998. In glioma patients, the follow up period was lengthened until January 1, 2000. Following-up of patients was performed by using case histories, autopsy protocols and pathology reports. Additional information on date and cause of death was received from the Estonian Cancer Registry and the Estonian State Statistical Office.

To estimate potential changes in 1-year survival rates over time in different age and histological groups, three time periods were defined according to the year of diagnosis: 1986 to 1989, 1990 to 1993 and 1994 to 1996. Advances in diagnostic procedures (the introduction of computerised tomography and magnetic resonance imaging) should not affect potential changes in survival, as the

first CT scan was introduced in 1983 in Estonia. Changes in 5-year survival were not estimated because of the too short follow up period.

7. Epidemiological and statistical methods

Average annual incidence rates per 100,000 population for primary CNS neoplasms 1986 through 1996 were computed. Annual age-specific and age-adjusted incidence rates were calculated for all CNS tumours and for each type separately. Population figures were obtained from the annual publications of the Statistical Office of Estonia for each year between 1986 and 1996. Age adjustment was performed by direct standardisation according to the World Standard Population (Waterhouse at al., 1976) and the Estonian Standard Population (1989 census). To compare our data with those of a previous study carried out in Estonia (Lukas, 1979), the 95% confidence limits (95% CI) for incidence rates were estimated assuming a Poisson distribution for the studied cases. The difference in incidence between the CT and pre-CT eras was expressed as the incidence rate ratio and presented with 95% confidence intervals.

Multivariable analysis was used to identify the factors that associate with seizures. The tested categories were patient age at diagnosis, their gender, tumour histology as well as anatomical location of tumour and duration of symptoms. χ^2 and Fisher's Exact Test was used in comparisons involving category variables, and Wilcoxon Rank-Sum test was employed for continuous variables.

Survival time was calculated from date of diagnosis. One- and five-year observed survival rates were estimated overall, by the above-mentioned age groups, for each histological group using life table method with intervals of one month. Kaplan-Meyer estimation was used to compute the median length of survival by gender, age and clinical condition, histology and location of tumour, based on the whole study period. The log-rank-test was used to compare survival in sub-groups. Proportional hazards models (Cox's models with stepwise procedure) were used to determine the effect of different patient (gender, age, clinical condition before treatment) and tumour related (anatomical location, histology) factors on survival. In all analyses, the statistical significance was chosen to be $p<0.05$.

All analyses were performed by using the STATISTICA programme (STATISTICA for Windows operating system 1994) and the SAS Version 6.12 (SAS Institute, Cary, NC).

8. Ethics

The study was approved by the Medical Research Ethics Committee of the University of Tartu.

RESULTS

1. General characteristics

In the period from 1986–1996, 1665 cases (739 males, 926 females) of primary CNS neoplasms and 330 cases (220 males, 110 females) of metastatic neoplasms were identified in the resident population of Estonia. During the same period, 996 patients (179 without histological confirmation) with primary CNS tumours were identified at the Cancer Registry. Mean age at diagnosis was 47 years (45 for males and 49 for females) and median age was 52 years (52 for males and 50 for females; range 1 month to 85 years). Histological verification was available in 1346 (80.8%) cases. This percentage varied depending on tumour site, being lower (58%) in pituitary region tumours and higher in tumours of the cerebral hemisphere and tumours of spinal location (86 and 85%, respectively). Histological confirmation according to tumour location is shown in table 3. Before histological confirmation, the majority, (76%), of tumours were diagnosed by CT or MRI (Table 4). Taking into account the low proportion of autopsies in Estonia, a remarkable number of tumours (5.3%) were diagnosed on autopsy, including both incidental findings and mis-diagnosed cases. Forty-three per cent of cases diagnosed post mortem were identified as glioblastomas, 19% were astrocytomas and only 8% were meningiomas.

Table 3. Histological confirmation (%) according to tumour location (n=1665)

Tumour location	All cases N	Histologically confirmed cases n (%)
Supratentorial		
Cerebral hemispheres	803	694 (86.3)
Central structures	63	39 (61.9)
Pituitary or pineal region	121	70 (57.8)
Other	162	138 (85.2)
Infratentorial	323	255 (79.0)
Intra-cranial, not localised	55	33 (60.0)
Spinal	138	117 (84.8)
Total	1665	1346 (80.8)

Table 4. Frequency of diagnostic methods before histological confirmation used in verification of primary brain tumours (n=1665)

Method	Number of cases (%)
CT	1085 (65.2)
MRI	176 (10.6)
Autopsy	88 (5.3)
Myelography	81 (4.9)
Angiography	67 (4.0)
Clinical	35 (2.1)
Ventriculography	13 (0.8)
X-rays	11 (0.7)
Histology	4 (0.2)
Pneumoencephalography	6 (0.4)
No diagnostic method recorded	99 (5.9)

2. Histological distribution

Table 5 illustrates the distribution of histologically confirmed cases of neoplasms according to sex and average age at diagnosis. The most common histological type was glioblastoma, which accounted for 29.9% of all brain tumours among males and for 21.2% among females, and meningioma (including both spinal and intracranial), which accounted for 13.1% and 32.8% of cases in males and females, respectively. Fourteen per cent (47 cases) of meningiomas were spinal. The other two most common major histological groups were astrocytoma (12.5% in males, 10.1% in females) and neurinoma (5% in males and 7% in females). Among patients below 20 years of age the most frequent were astrocytoma (25%), medulloblastoma (17%), ependymoma and glioblastoma (both 6%); 42 cases (22%) were not histologically confirmed.

Table 5. Distribution of pathologically confirmed primary brain tumours (n=1346) by histological diagnosis, sex and mean age of patients (Estonia 1986–1996).

Tumour type	ICD-O Morphology Codes	No. of cases (%)			Mean age (years) at diagnosis
		Male	Female	Total	
Neuroepithelial tumours					
Astrocytoma (G1–2)	9400/3, 9410/3, 9411/3, 9420/3, 9421/3	73 (12.5)	77 (10.1)	150 (11.2)	36.4
Anaplastic astrocytoma	9401/3	35 (6.0)	44 (5.8)	79 (5.9)	48.7
Glioblastoma	9440/3, 9441/3, 9442/3	174 (29.9)	162 (21.2)	336 (25.0)	53.4
Oligodendroglioma	9450/3, 9451/3	25 (4.3)	17 (2.2)	42 (3.1)	44.0
Ependymoma	9391/3, 9393/1, 9392/3	24 (4.1)	13 (1.7)	37 (2.8)	34.5
Mixed glioma	9382/3	10 (1.7)	13 (1.7)	23 (1.7)	46.6
Pineal tumours	9361/1, 9362/3	4 (0.7)	0	4 (0.3)	39.8
Medulloblastoma	9470/3, 9471/3, 9472/3	23 (4.0)	19 (2.5)	42 (3.1)	14.8
Tumours of cranial and spinal nerves					
Neurinoma	9560/0	29 (5.0)	53 (7.0)	82 (6.1)	47.8
Neurofibroma	9540/0, 9550/0	2 (0.3)	7 (0.9)	9 (0.7)	38.9
Meningeal tumours					
Meningioma	9530/0, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9530/1, 9538/1	76 (13.1)	250 (32.8)	326 (24.2)	54.6
Anaplastic meningioma	9530/3	5 (0.9)	13 (1.7)	18 (1.3)	56.5
Haemangioblastoma	9161/1	8 (1.4)	14 (1.8)	22 (1.6)	48.4
Malignant lymphomas	9590/3	12 (2.1)	8 (0.9)	20 (1.5)	49.8
Germ cell tumours	9064/3, 9070/3, 9080/1, 9084/3	4 (0.7)	2 (0.3)	6 (0.5)	33.7
Sellar region tumours					
Pituitary adenoma	8140/0	16 (2.6)	20 (2.6)	35 (2.6)	48.7
Craniopharyngioma	9350/1	8 (1.4)	6 (0.8)	14 (1.0)	30.1
Other, specified*	8140/3, 9390/0, 9390/3, 9430/3, 9443/3, 9381/3, 9084/0	55 (9.5)	45 (5.9)	100 (7.4)	40.7
Total specified		583 (100)	763 (100)	1346 (100)	47.4

* due to small number of cases not given separately

3. Seizures in patients with brain tumours

We analysed 721 patients with diagnosed primary and secondary brain tumours. Out of these, 711 patients remained in the study group, while 10 patients were excluded because of incomplete data. 165 (23.2%) patients experienced at least one seizure before their tumour diagnosis, 546 patients had no history of seizures. Mean age in the seizure group was 47.4 years (95% CI 45.0–49.8 years) ranging from 2 to 83 years, in the seizure free group 49.2 years (95% CI 47.4–50.1 years) ranging from 1 to 87 years. Age was associated ($p<0.05$) with the presence of seizures. Occurrence of seizures was remarkably higher in 30 to 39-year ($p<0.005$) and 40 to 49-year ($p=0.001$) age groups (Table 6). The male to female ratio was 1:1.04 in the seizure group and 1:1.2 in those patients without seizures. Gender was not associated with occurrence of seizures.

Table 6. Incidence of seizures and patients age (n=711).

	All patients	Patients with seizures	
	N	N	%
0–9	37	5	13.5
10–19	31	4	12.9
20–29	36	10	27.8
30–39	70	26	37.1*
40–49	123	43	35.0**
50–59	196	39	19.9
60–69	170	30	17.7
70+	48	8	16.7
All	711	165	23.2

*p=0.004
**p=0.001

According to the histological typing, the most common histological types were glioblastoma, meningioma and low-grade astrocytoma (Table 7). Patients with mixed gliomas (62%), oligodendrogliomas (53%), anaplastic astrocytomas (42%), low grade astrocytomas (41%) and meningiomas (37%) experienced seizures most frequently. Association between tumour pathology and seizures at presentation was highly significant ($p<0.001$).

Table 7. Tumour pathology and occurrence of seizures (n=711).

	Number of patients	With seizures	
		N	%
Low-grade astrocytoma	53	22	41.5*
Anaplastic astrocytoma	30	13	43.3**
Glioblastoma	106	27	25.5*
Oligodendroglioma	19	10	52.6**
Ependymoma	8	2	25
Mixed glioma	8	5	62.5***
Medulloblastoma	15	0	0
Schwannoma	27	0	0
Meningioma	124	47	37.9*
Anaplastic meningioma	8	1	12.5
Hemangioblastoma	7	0	0
Lymphoma	6	1	16.7
Metastatic tumour	105	16	15.2***
Without histology	138	17	12.3*

Pathology of 59 tumour patients with very low incidence (<5) is not given.
*$p<0.001$
**$p<0.005$
***$p<0.05$

Tumour location and seizures

Of the 711 tumours, 71% had supratentorial and 21% had infratentorial location, 8% were multilocular; in the seizure group 94% of tumours were supratentorial, 2% were infratentorial and 4% were multilocular. The incidence of seizure occurrence for different lobes was significantly different ($p<0.001$) (Table 8). Higher incidences of seizures were found in tumours involving the frontoparietal (58%), frontotemporal (44%), parasagittal (41%) and temporal (40%) regions. Seizures occurred in only 11% of patients with tumours of the occipital lobe and the multilocular tumours. Only 3 patients out of 148 with infratentorial tumours experienced seizures. Association with seizure occurrence was found for tumours involving the frontal and fronto-parietal, temporal and fronto-temporal, as well as the parietal and parasagittal regions. Seizures as the first manifestation of the tumour had no significant association with tumour location.

Table 8. Tumour location and the incidence of seizures (n=711).

Location	Number of patients	With seizures	
		N	%
Frontal lobe	83	32	38.5*
Frontal and parietal	38	22	57.9*
Frontal and temporal	36	16	44.4**
Frontal, temporal and parietal	11	5	45.4
Parietal lobe	64	22	43.4***
Temporal lobe	52	21	40.4**
Temporal and parietal	49	11	22.5
Occipital lobe	9	1	11.1
Occipital and parietal or temporal	26	4	15.4
Central structures	30	6	20.0
Parasagittal region	29	12	41.4***
Hypophyseal region	46	0	0
Other supratentorial	30	4	13.3
Multilocular	55	6	10.9***
Infratentorial	148	3	2.0*

* $p<0.001$
** $p<0.005$
*** $p<0.05$

Factors predicting seizure occurrence

In multivariable analysis, patients gender and age were not associated with seizures. Categories that influenced the occurrence of seizures were the duration of symptoms, tumour location and histology. Epileptic seizures occurred more frequently in those patients, with a long duration of symptoms (6 months and more), who were diagnosed of astrocytoma, anaplastic astrocytoma, some other glioma or meningioma. Infrequently, seizures occurred in tumours of infratentorial, central or multiple location.

Presentation and duration of epileptic seizures

Epileptic seizures were the single presenting symptom at diagnosis in 44, and the first manifestation in 123, patients; 121 patients presented simultaneously seizures and some other sign or symptom. Patients with seizures showed a significantly lower incidence of neurological deficit, headache ($p=0.001$) and mental disturbances ($p<0.05$) compared with seizure free patients (Table 9). We found no association between occurrence of epileptic seizures and increased intracranial pressure. Table 10 presents the clinical characteristics of seizures. In 26.7% of seizure patients, seizures were their only complaint and in 74.6% were the first manifestation. Thirteen per cent of patients presented only one seizure,

55% presented recurrent seizures and 21% had seizures at diagnosis (the tumour was diagnosed less than one month after presentation). Median time from the first epileptic seizure to diagnosis was 3 months, with a mean of 16 months (range from 0 to 240 months). Most brain tumours (72.8%) were diagnosed during the first year after seizure presentation, while 5 patients had had seizures for more than 10 years (one of them for 20 years). The mean time was different (p=0.02) for seizures as the single presenting sign (mean time 18 months) and for seizures presented with other symptoms (mean time 12 months).

Table 9. Presenting signs and symptoms (n=711)

	Number of patients	
	Without seizures (n=546)	With seizures (n=165)
Seizures with other symptoms		121
Other symptoms		
Headache	367	58*
Papilledema	141	31
Neurological deficit	429	92*
Mental disturbances	126	25**

*p=0.001
**p<0.05

Table 10. Clinical characteristics of seizures.

	N	%	
		Patients with seizures (n=165)	All patients (n=721)
Seizures	165		22.9
As the first manifestation	123	74.6	17.1
As the single presentation	44	26.7	6.1
At diagnosis	35	21.2	4.9
One seizure	22	13.3	3.1
Recurrent (≥2 seizures)	95	57.6	13.2

Seizure types and EEG findings

Seizures could be classified in 91.5% (151 cases) of patients with epilepsy (Table 11). Secondarily generalised and simple partial seizures, existing as the only type in a patient, were the most common and occurred in 51% and 36.5% of patients, respectively. Epileptic seizures were of complex partial type and simple partial type with secondary generalisation in 9.3% of cases. Only 83 (50.3%) of the 165 patients who presented with seizures underwent EEG evaluation (Table 12). Electroencephalography was considered abnormal in

84% of cases. In 12% of cases EEG only lateralised the tumor and in 13% of cases it localised but did not lateralise the tumor. Local manifestations localised exactly the lobe and hemisphere involved by the tumor in 41% of patients.

Table 11. Classification of seizures (n=151)

Seizure type	Number of patients	%
Secondarily generalised	77	51.0
Simple partial		
Without secondary generalisation	41	27.2
With secondary generalisation	14	9.3
Complex partial		
Without secondary generalisation	14	9.3
With secondary generalisation	1	0.7
Both simple partial and complex Partial	1	0.7

Seizures were classifiable in 151 of 164 patients

Table 12. EEG abnormalities in patients with seizures (n=83)

EEG	Number of patients (%)
Focal slow activity	65 (78)
Epileptiform/paroxysmal activity	
Sharp waves	22 (27)
Spikes	7 (8)
Normal	13 (16)

Only 83 of 165 patients with seizures underwent EEG evaluation.

4. Incidence rates

The average annual incidence rate for all primary CNS neoplasms was 9.8 per 100,000 population (9.0 for intracranial tumours and 0.8 for intra-spinal tumours). The age-specific incidence rate of intracranial tumours was much lower in childhood (3.7), increased in the 30- to 39-year age group (6.5), reached a maximum in the age range of 50-69 years (20.6) and then declined abruptly in the elderly (7.6) (Figure 1). Intra-spinal neoplasms revealed a steady increase in incidence up to the age of 60–69 years. Age-specific incidence rates for glioblastoma, astrocytoma, meningioma and tumours without microscopic confirmation, including both intracranial and intra-spinal cases, are shown in figure 2. Some variations of the curves of individual histological types of brain tumours are noteworthy. Specifically, that the annual incidence rate of astrocytoma showed a small peak in childhood (1.0) and a plateau in the age range 30 to 49 years, then increased in the 50- to 69-year age group (2.4), and

fell significantly in those aged 70 and older. Age-specific incidence rate for glioblastoma increased with age, reaching a maximum of 6.1 at the age of 60–69 and declined in the more elderly. Meningioma had a similar pattern with a peak incidence of 6.1 in the age range 60 to 69 year.

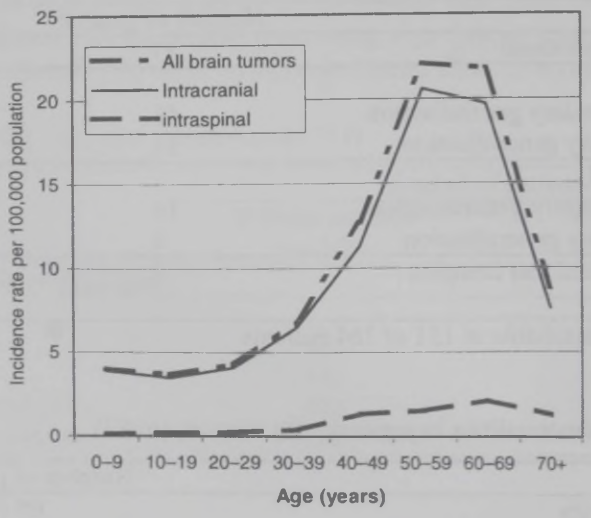

Figure 1. Age-specific incidence rates for intra-cranial and intra-spinal tumours and for all brain tumours in Estonia (1986–1996).

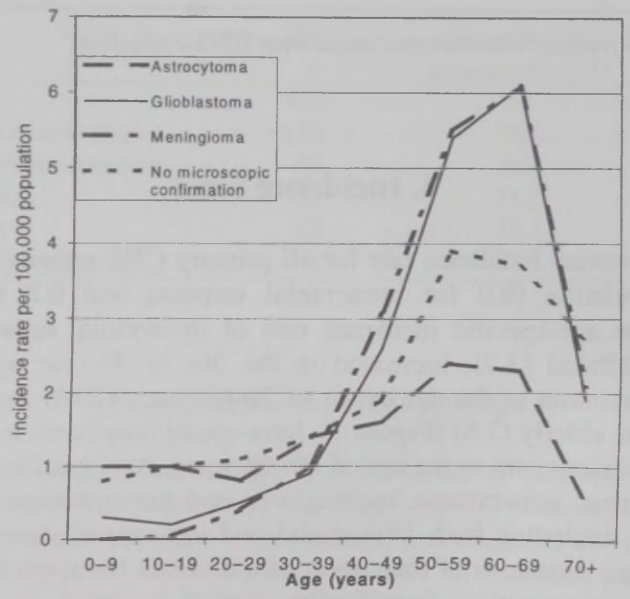

Figure 2. Average annual age-specific incidence rates for astrocytoma, glioblastoma, meningioma and cases without microscopic confirmation. Estonia 1986–1996.

There were no statistically significant differences between the sexes either in the total incidence of tumours, or in the incidence of astrocytomas and glioblastomas (Table 13). However, neuroepithelial tumours ($p<0.01$) and gliomas ($p<0.05$) were more common in males (male/female ratio 1.2), while meningiomas and tumours of cranial and spinal nerves (including neurinomas) were significantly more frequent ($p=0.001$ and <0.005, respectively) in females (male/female ratios 0.35 and 0.59, respectively).

Table 13. Incidence rates (per 100,000 person-years) by histological types and male/female ratios for primary brain tumours in Estonia (1986–1996)

Tumour type	Crude rate (95% CI)		Male/female ratio
	Males	Females	
Neuroepithelial tumours	4.90 (4.41–5.39)	4.01 (3.60–4.42)	1.22[c]
All gliomas	4.32 (3.86–4.78)	3.60 (3.21–3.99)	1.2[b]
Astrocytoma	1.37 (1.11–1.63)	1.34 (1.10–1.58)	1.02
Glioblastoma	2.20 (1.87–2.48)	1.79 (1.51–2.07)	1.23
Oligodendroglioma	0.32 (0.20–0.44)	0.19 (0.10–0.28)	1.68
Ependymoma	0.30 (0.18–0.42)	0.14 (0.06–0.22)	2.14[b]
Mixed glioma	0.13 (0.05–0.21)	0.14 (0.06–0.22)	0.93
Medulloblastoma	0.29 (0.17–0.41)	0.21 (0.11–0.31)	1.38
Tumours of cranial and spinal nerves	0.39 (0.25–0.53)	0.66 (0.49–0.83)	0.59[b]
Neurinoma	0.37 (0.24–0.50)	0.59 (0.43–0.75)	0.63[b]
Meningeal tumours	1.46 (1.19–1.72)	3.32 (2.94–3.70)	0.47[d]
Meningioma	0.96 (0.74–1.18)	2.77 (2.43–3.11)	0.35[d]
Haemangioblastoma	0.10 (0.03–0.17)	0.16 (0.08–0.24)	0.63
Malignant lymphomas	0.15 (0.06–0.24)	0.09 (0.03–0.15)	1.67
Sellar region tumours			
Pituitary adenoma[a]	0.42 (0.28–0.56)	0.44 (0.30–0.58)	0.96
Craniopharyngioma	0.10 (0.03–0.17)	0.07 (0.02–0.12)	1.43
No histological confirmation	1.98 (1.67–2.29)	1.80 (1.52–2.08)	1.10
Intra-cranial tumours	8.62 (7.97–9.27)	9.37 (8.74–10.00)	0.92
Spinal tumours	0.73 (0.54–0.92)	0.89 (0.70–1.08)	0.82
All tumours	9.36 (8.68–10.04)	10.25 (9.59–10.91)	0.91

[a] includes 38 unconfirmed cases of pituitary tumours diagnosed clinically as adenomas
[b] $p<0.05$
[c] $p<0.01$
[d] $p=0.001$

Average annual age-adjusted incidence rates for various histological types of primary brain tumours in Estonia are shown in table 14. Age-adjusted incidence was 3.41 for gliomas, 1.63 for meningiomas and 8.46 for all primary brain tumours. Among gliomas, the most common types were glioblastoma and astrocytoma (incidence rates of 1.58 and 1.27, respectively), oligodendroglioma

and ependymoma being less frequent (incidence rate of 0.22 for both). The incidence rate for cases without microscopic confirmation was 1.63.

Table 14. Age-adjusted incidence rates (ASIR) per 100,000 population for brain tumours by histological types in Estonia 1986–1996.

Tumour type	ASIR[a] (95% CI)
Astrocytoma	1.27 (1.10–1.44)
Glioblastoma	1.58 (1.39–1.77)
Oligodendroglioma	0.22 (0.15–0.29)
Ependymoma	0.22 (0.15–0.29)
Mixed glioma	0.11 (0.06–0.16)
All gliomas	3.41 (3.13–3.69)
Medulloblastoma	0.32 (0.23–0.41)
Neurinoma	0.40 (0.30–0.50)
Meningioma	1.63 (1.44–1.82)
Pituitary adenoma[b]	0.36 (0.27–0.45)
Other specified	0.96 (0.81–1.11)
No microscopic confirmation	1.63 (1.44–1.82)
All tumours	8.46 (8.02–8.90)

[a] rates are age-adjusted to the World Standard Population
[b] includes 38 unconfirmed cases of pituitary tumours diagnosed clinically as adenomas

Changes in incidence

A comparison of current rates with those of a previous study, carried out from 1951 to 1970, suggests that the increase in the incidence rates of intracranial tumours is histology-specific (Table 15). A significant increase was observed in incidence rates for astrocytoma, glioblastoma and meningioma (incidence rate ratios of 1.49, 1.50 and 1.97 respectively, p=0.001). Looking at age-specific incidence rates, a significant increase is evident across all age groups (Table 16), with the increase being most apparent in children, adolescents, and age groups over 50 (incidence rate ratio over 1.5).

Table 15. Changing incidence rates (IR[a]) over time for primary intra-cranial tumours in Estonia during 1951–1970 and 1986–1996

Tumour type	1951–1970 No. of intra-cranial tumours (IR[a])	1986–1996 No. of intra-cranial tumours (IR[a])	Incidence rate ratio (IRR) (95% CI)	P value
Astrocytoma	128 (0.51)	150 (0.76)	1.49 (1.18–1.89)	0.001
Anaplatic astrocytoma	61 (0.25)	78 (0.46)	1.84 (1.32–2.57)	0.001
Glioblastoma	313 (1.30)	336 (1.95)	1.50 (1.29–1.75)	0.001
Oligodendroglioma	45 (0.18)	42 (0.25)	1.39 (0.91–2.12)	0.125
Ependymoma	34 (0.14)	24 (0.15)	1.07 (0.64–1.80)	0.789
All gliomas	678 (2.77)	651 (3.81)	1.38 (1.24–1.54)	0.001
Medulloblastoma	45 (0.18)	42 (0.26)	1.44 (0.95–2.19)	0.083
Neurinoma	76 (0.31)	59 (0.35)	1.13 (0.76–1.65)	0.478
Meningioma	214 (0.87)	297 (1.71)	1.97 (1.65–2.35)	0.001
Pituitary adenoma	86 (0.35)	73 (0.43)	1.23 (0.90–1.68)	0.195
No histological confirmation	229 (0.89)	299 (1.75)	1.97 (1.66–2.34)	0.001
All types	1454 (5.91)	1527 (8.93)	1.51 (1.41–1.62)	0.001

[a] Rates are age-adjusted to the Estonian Standard Population (1989 census)

Table 16. Changing age-specific incidence rates (per 100,000 population) of intra-cranial tumours in Estonia, 1951–1970 and 1986–1996.

Age (years)	1951–1970		1986–1996		Incidence rate ratio (IRR) (95% CI)
	No. of cases	Age-specific incidence	No. of cases	Age-specific incidence	
0–9	95	2.5	96	3.9	1.6 (1.2–2.1)[b]
10–19	74	2.2	83	3.5	1.6 (1.2–2.2)[c]
20–29	119	3.0	97	4.1	1.4 (1.1–1.8)[b]
30–39	204	5.2	164	6.5	1.3 (1.0–1.5)[b]
40–49	277	8.5	241	11.3	1.3 (1.1–1.6)[c]
50–59	340	12.5	422	20.6	1.7 (1.4–1.9)[c]
60–69	270	12.3	322	19.7	1.6 (1.4–1.9)[c]
70+	75	4.4	100	7.6	1.7 (1.3–2.3)[c]
Total	1454	5.9 (5.9[a])	1525	9.0 (8.9[a])	1.5 (1.4–1.6)[c]

[a] Rates are age-adjusted to the Estonian Standard Population (1989 census)
[b] $p<0.005$
[c] $p=0.001$

5. Survival rates

Survival analysis included 1417 patients (628 men and 789 female) with CNS tumours. 88 cases discovered at autopsy, 2 patients with incomplete data, 17 patients diagnosed with another tumour, previously or during the follow-up period, and 141 patients lost to follow-up were excluded from the survival analysis.

The distribution and median survival of patients by gender, age, tumour location and clinical condition are shown in table 17. Univariate analysis found that females (p=0.002), patients of younger age (<45 years, p=0.0001) and better clinical condition before treatment, (p=0.0001) had the highest survival. Concerning tumour location, the worst prognosis was associated with those of central structures or ventricular location and the best prognosis with infratentorial and pituitary location.

Table 17. Median survival time (ST) of 1417 brain tumour patients diagnosed in Estonia from 1986 to 1996

Characteristic	No of patients (%)	No of deaths	Median ST (months)
Gender			
male	628 (44.4)	371	18.6
female	789 (56.6)	396	62.8
			p=0.002
Age group			
0–20	191 (13.5)	90	88.3
21–44	344 (24.3)	140	136.9
45–64	677 (47.8)	401	15.8
65+	205 (14.5)	136	5.7
			p=0.0001
Location			
frontal	164 (11.6)	107	17.8
parietal	113 (8.0)	63	14.7
temporal	108 (7.6)	71	13.9
2 or more lobes	336 (23.7)	231	10.4
central structures and ventricles	58 (4.1)	36	7.3
other supratentorial	175 (12.1)	82	nc
pituitary or pineal	114 (8.1)	28	nc
infratentorial	311 (21.9)	133	nc
location not available	38 (2.7)		
			p=0.0001
Karnofsky PS			
80–100	370 (26.1)	105	nc
60–70	558 (39.4)	289	48.0
<60	321 (22.7)	251	5.3
KPS not available	168 (11.9)		
			p=0.0001

nc = median could not be computed, over 50% survived

In gliomas (566 cases), univariate analysis (Table 18) found no differences between sexes. Patients of a younger age have a very significantly better median survival: in children and adolescents more than 50% of patients survived till the end of the study period so that the median cannot be computed. Among the elderly, the median survival time was only 2.6 months. Concerning the patients' clinical condition before treatment, the higher the Karnofsky Performance Status score was before treatment, the better the survival rate. The distribution of treatment strategy was not homogenous. Most patients underwent only surgery or surgery combined with radiation therapy. Only a few patients received chemotherapy. Median survival was the best in combined treatment groups and the worse in the symptomatic treatment group, which mainly includes patients in a terminal condition. In the surgery group, the survival period was only about 3 months.

Table 18. Median survival time (ST) of 566 glioma patients (Estonia, 1986–1996)

Characteristic	N	Median ST (months)	P value
Gender:			
Male	294	7.8	
Female	272	7.9	ns
Age group (years)			
<21	68	nc	
21–44	142	16.5	
45–64	273	5.8	
>64	83	2.6	<0.0001
KPS (%):			
80–100	108	47.2	
60–70	217	9.5	
<60	170	3.6	
not available	71		<0.0001
Treatment:			
surgery	288	3.3	
radiation	4	6.1	
surgery+radiation	187	16.0	
surgery+chemotherapy	6	8.9	
surgery+radiation+chemotherapy	32	12.0	
symptomatic	19	0.7	
incomplete data	34		<0.0001

nc = median could not be computed, over 50% survived

Survival by histology

One- and five-year survival rates and median survival time by histology are presented in table 19. The overall 1-year survival was 59%, 5-year survival 46% and median survival 33 months. Tumours with the most favourable prognosis included pituitary adenoma (89%, both 1- and 5-year survival), meningioma (1-year survival 86% and 5-year survival 82%) and neurinoma (76%, both). Patients with glioblastoma and anaplastic astrocytoma had the worst outcome (5-year survival 9% and 16%, respectively). In contrast, about half of the low-grade astrocytoma patients survived beyond 5 years. The long-term prognosis for patients with medulloblastoma, ependymoma, oligodendroglioma and mixed glioma appeared similar to each other (23%, 27%, 28% and 28%, respectively), at the same time, median survival was not so homogenous. The prognosis of craniopharyngioma was about the same as astrocytoma.

Table 19. One-year and five-year survival rates (SR) and median survival time (ST) by histology for patients with primary brain tumours in Estonia (1986–1996)

Histology	N	1-year SR (%) (95% CI)	5-year SR (%) (95% CI)	Median ST (months)
Astrocytoma (G1–2)	138	64.5 (60.4–68.6)	49.8 (45.2–54.4)	54.2
Anaplastic astrocytoma	72	36.1 (30.4–41.8)	15.8 (11.3–20.4)	8.3
Glioblastoma	297	28.0 (25.4–30.6)	8.6 (6.8–10.3)	6.2
Ependymoma	22	50.0 (39.3–60.7)	26.9 (16.5–37.4)	10.7
Oligodendroglioma	38	60.5 (52.6–68.5)	28.1 (18.7–37.3)	22.9
Mixed glioma	23	56.5 (46.2–66.9)	28.1 (18.2–37.9)	22.4
Medulloblastoma	39	53.9 (45.9–61.8)	22.5 (15.3–29.7)	12.7
Meningioma	284	85.9 (83.9–88.0)	82.4 (80.0–84.8)	nc
Neurinoma	55	76.4 (70.6–82.1)	76.4 (70.6–82.1)	nc
Pituitary adenoma	37	89.2 (78.4–94.3)	89.2 (78.4–94.3)	nc
Craniopharyngioma	15	73.3 (61.9–84.8)	52.4 (37.4–67.3)	nc
Other specified	119	62.6 (57.9–67.3)	43.8 (38.8–48.8)	36.5
Without histology	278	61.9 (59.0–64.8)	53.8 (50.7–56.8)	nc
Total	1417	59.3 (58.0–60.6)	46.0 (44.6–47.4)	33.2

nc = median could not be computed, over 50% survived

Survival by age at diagnosis

Observed survival rates by age at diagnosis for all CNS tumours and selected histology groups are given in table 20. Including all histological groups, the worst outcome occurred in those patients older than 65 years. Decreased survival associated with older age at diagnosis was observed in all histological groups. Differences were the most evident in the astrocytoma group (1-year survival 17% in the elderly and 87% in children, 5-year survival 7% and 79%, respectively) where survival was decreasing with age.

Table 20. One- and five-year survival rates (SR) by age at diagnosis for selected histology groups

Histology	Age at diagnosis					
	≤20			21–44		
	N	1-year SR (95%CI)	5-year SR (95%CI)	N	1-year SR (95%CI)	5-year SR (95%CI)
Astrocytoma	46	87.0 (82.0–91.9)	79.3 (73.1–85.6)	43	76.7 (70.3–83.2)	64.6 (56.8–72.5)
Anaplastic astrocytoma	4	*	*	21	52.4 (41.5–63.3)	26.8 (16.8–36.8)
Glioblastoma	12	41.7 (27.5–55.9)	21.6 (8.9–34.3)	55	43.6 (37.0–50.3)	13.8 (8.6–19.0)
Other glioma	13	76.9 (65.2–88.6)	46.2 (30.3–62.0)	30	63.3 (54.5–72.1)	40.8 (30.8–50.8)
Meningioma	3	*	*	58	93.1 (89.8–96.4)	93.1 (89.8–96.4)
Neurinoma	5	*	*	18	88.9 (81.5–96.3)	88.9 (81.5–96.3)
Other specified	65	58.5 (52.4–64.6)	35.6 (29.3–41.8)	53	87.8 (83.1–92.4)	77.1 (70.6–83.6)
Without histology	43	69.8 (62.8–76.8)	55.3 (47.6–62.9)	66	81.8 (77.1–86.6)	72.8 (67.1–78.6)
Total	**191**	**70.2 (66.9–73.5)**	**52.9 (49.1–56.6)**	**344**	**74.7 (72.4–77.1)**	**60.9 (58.1–63.7)**
	45–64			65+		
	N	1-year SR (95%CI)	5-year SR (95%CI)	N	1-year SR (95%CI)	5-year SR (95%CI)
Astrocytoma	37	37.8 (29.9–45.8)	13.2 (6.2–20.3)	12	16.7 (5.9–27.4)	16.7 (5.9–27.4)
Anaplastic astrocytoma	39	25.6 (18.7–32.6)	8.6 (3.6–13.5)	8	*	*
Glioblastoma	173	24.3 (21.0–27.5)	6.3 (4.3–8.3)	57	21.1 (16.6–26.5)	7.0 (3.6–10.4)
Other glioma	31	51.6 (42.6–60.6)	18.3 (11.2–25.4)	9	*	*
Meningioma	182	83.5 (80.8–86.3)	79.8 (76.7–82.9)	41	85.4 (79.9–90.9)	75.0 (66.6–83.4)
Neurinoma	23	73.9 (64.8–83.1)	73.9 (64.8–83.1)	9	*	*
Other specified	79	59.5 (54.0–65.0)	44.8 (38.9–50.6)	13	46.2 (32.4–60.0)	30.8 (18.0–43.6)
Without histology	113	56.6 (52.0–61.3)	49.0 (44.2–53.9)	56	42.9 (36.3–49.5)	39.3 (32.7–45.8)
Total	**677**	**53.5 (51.6–55.4)**	**40.7 (38.7–42.6)**	**205**	**42.4 (39.0–45.9)**	**32.3 (28.9–35.8)**

*Not given due to a very small number (<10) of cases

Changes in survival

Table 21 shows 1-year survival rates for astrocytoma, glioblastoma, meningioma, tumours without histological verification and all tumours by patient age group during three time periods (1986–1989, 1990–1993 and 1994–1996). Comparing the first (1986–1989) and the second (1990–1993) time period a statistically significant decline in 1-year survival for glioblastoma (32.7% and 17.9%, respectively) and all tumours (59.8% and 53.6%, respectively) can be observed. In meningiomas, a similar tendency is evident only between 45 and 64 years. Comparing the first (1986–1989) and the third (1994–1996) time period, no significant changes in survival, neither for meningioma nor

Table 21. 1-year survival rates (SR) by age for patients with low-grade astrocytoma, glioblastoma, meningioma and without histological confirmation and all brain tumours during 3 time periods. Estonia 1986–1996.

Histology	Age group	Year of diagnosis		
		1986–1989 SR (95% CI)	1990–1993 SR (95% CI)	1994–1996 SR (95% CI)
Astrocytoma (G1–2)	0–20	88.2 (80.8–96.1)	81.3 (71.5–91.0)	92.3 (84.9–99.7)
	21–44	76.5 (66.2–86.8)	58.3 (44.1–72.6)	92.9 (86.0–99.7)
	45–64	29.4 (18.4–40.5)	28.6 (16.5–40.6)	83.3 (68.1–98.5)
	65+	25.0 (3.4–46.7)	*	*
	All ages	**61.8 (55.3–68.4)**	**54.6 (47.0–62.1)**	**79.5 (73.0–86.0)**
Glioblastoma	0–20	*	*	*
	21–44	45.0 (33.9–56.1)	22.2 (12.4–32.0)	52.9 (40.8–65.1)
	45–64	27.1 (21.8–32.5)	17.1 (12.6–21.6)	33.3 (25.1–41.5)
	65+	25.0 (14.2–35.8)	9.1 (3.0–15.2)	31.6 (20.9–42.2)
	All ages	**32.7 (28.2–37.2)**	**17.9 (14.2–21.5)**	**36.0 (30.5–41.5)**
Meningioma	0–20	*	*	*
	21–44	90.5 (84.1–96.9)	95.8 (91.7–99.9)	92.3 (84.9–99.7)
	45–64	86.0 (81.4–90.6)	74.6 (69.1–80.1)	90.3 (86.6–94.1)
	65+	*	84.6 (74.6–94.6)	81.8 (73.6–90.0)
	All ages	**88.1 (84.6–91.6)**	**81.2 (77.3–85.1)**	**88.9 (85.7–92.1)**
Without histology	0–20	57.9 (46.6–69.2)	71.4 (58.7–83.5)	90.0 (80.5–99.5)
	21–44	87.5 (80.8–94.3)	83.3 (72.6–94-1)	76.7 (69.0–84.4)
	45–64	52.5 (44.6–60.4)	67.7 (59.3–76.1)	52.4 (44.7–60.1)
	65+	69.2 (56.4–82.0)	31.8 (21.9–41.8)	38.1 (27.5–48.7)
	All ages	**64.6 (59.7–69.5)**	**60.8 (55.3–66.3)**	**60.2 (55.4–65.0)**
Total	0–20	65.7 (59.9–71.5)	72.5 (67.1–77.8)	72.7 (66.7–78.7)
	21–44	78.1 (74.3–81.8)	69.4 (65.0–73.9)	76.1 (72.1–80.1)
	45–64	51.8 (48.6–55.0)	46.0 (40.3–49.2)	64.8 (61.3–68.2)
	65+	47.1 (44.8–54.1)	37.0 (31.3–42.6)	44.4 (38.9–50.0)
	All ages	**59.8 (57.6–62.1)**	**53.6 (51.3–55.9)**	**64.9 (62.7–67.2)**

* Not given due a very small number of cases

glioblastoma, have taken place. There were statistically significant improvements in survival rates comparing the first (1986–1989) and the third (1994–1996) time period for patients with astrocytoma and for all other tumours. Age-specific rates showed that the increase in survival was more evident in older adults, between 45 and 64 years, both, for all tumours (51.8% in 1986 through 1989 and 64.8% in 1994 through 1996) and for astrocytomas (29.4% and 83.3%, respectively). In astrocytomas, a slight, but statistically not significant, improvement can be observed in younger adults, aged between 21 and 44 years.

6. Prognostic factors

In multivariate analysis, older age at diagnosis, the patient's clinical condition (Karnofsky Performance Status <60), tumour histology and period of diagnosis were independent prognostic factors for survival (Table 22). Risk of death was more than eight times greater for glioblastoma (RR 8.31, p=0.0001), about seven times greater for anaplastic astrocytoma (RR 7.22, p=0.0001) and more than five times greater for other gliomas (RR 5.74, p=0.0001). The best prognosis was found in neurinoma, still having significantly greater risk of death (RR=1.87, p=0.04) compared with meningioma.

In multivariate analysis including only gliomas, age, patient clinical condition, tumour histology and treatment were found to be independent prognostic factors (Table 23). The best prognosis had low-grade astrocytoma, oligodendroglioma and ependymoma patients of younger age, better clinical condition which underwent surgery with additional radiation therapy or surgery combined with radiation and chemotherapy. The worst prognosis was found among patients who received only symptomatic treatment.

Table 22. Multivariate analysis (Cox Model). Factors predicting survival in those patients with brain tumours.

Factor	*Variable*	Parameter estimate	*P value*	Risk ratio (in best Cox model)
Gender	Male vs female		ns	
Age	as a continuous variable	0.014	0.0001	1.02
Karnofsky Performance Status				
<60%	60–100% has been taken	0.600	0.0001	1.82
Not specified	as a base category	0.552	0.0001	1.74
Period of diagnosis				
1990–1993	1986–1989 has been ta-		ns	
1994–1996	ken as a base category	–0.190	0.0280	0.83
Histology				
Astrocytoma		1.429	0.0001	4.18
Anaplastic	Meningioma has taken			
astrocytoma	as a base category for all	1.977	0.0001	7.22
Glioblastoma	types	2.117	0.0001	8.31
Other glioma		1.748	0.0001	5.74
Neurinoma		0.624	0.0376	1.87
Other specified		1.497	0.0001	4.47
Without histology		1.166	0.0001	3.21
Localisation				
Hemispheres	Infratentorial location		ns	
Central structures	has been taken as a base		ns	
Other	category		ns	
Not specified		1.461	0.0001	4.31

Table 23. Multivariate analysis (best Cox model). Factors predicting survival in gliomas.

Variable	Parameter estimate	P value	Risk ratio (RR)
Age	0.024	<0.0001	1.03
KPS	0.412	<0.0001	1.51
Histology*			
Astrocytoma (G1–G2)	–1.117	<0.0001	0.33
Ependymoma	–0.742	0.01	0.48
Oligodendroglioma	–0.871	<0.0001	0.42
Mixed glioma	–0.558	0.03	0.57
Treatment**			
Surgery+radiation	–0.821	<0.0001	0.44
Surgery+radiation+chemotherapy	–0.632	0.003	0.53
Symptomatic	1.390	<0.0001	4.02

*Glioblastoma taken as a base category
**Surgery taken as a base category

7. Cancer registration

Of the 1665 patients included in our study, 996 (60%) were identified in the Estonian Cancer Registry as having CNS tumours. Since most gliomas are considered malignant, 98% of them were found in the registry. Differences were revealed in the histological subgroups (Table 24). Over-reported histological types included oligodendroglioma (124%) and astrocytoma (106%), under-reported histological types included glioblastoma (91%) and lymphoma (70%). Reporting of non-malignant CNS tumours was very low: meningiomas (11%) and neurinomas (9%).

Table 24. Reporting of chosen CNS tumour types in the Estonian Cancer Registry (ECR), 1986–1996.

Tumour types	ECR (N)	Estonia 1986–1996 (N)	Reporting %
Astrocytoma (G1-G3)	242	242	106
Glioblastoma	304	336	91
Oligodendroglioma	52	42	124
Ependymoma	38	37	103
Medulloblastoma	42	42	100.
Neurinoma	7	82	9
Neurofibroma	2	9	22
Meningioma	35	326	11
Haemangioblastoma	13	22	59
Malignant lymphomas	14	20	70
Pituitary adenoma	4	35	11
Craniopharyngioma	1	14	7

DISCUSSION

1. Patients and methods

The vast range in incidence rates of primary brain tumours (Table 2) has been explained by differences in inclusion criteria and classification, methods of case researching and the number of patients included rather than on real variations of incidence in different geographical areas and populations. Most authors agree that, besides cancer registration, incidence rates are influenced by the availability of competent medical care, frequency of autopsy and improvement of brain imaging techniques (CT, MRI) (Bahemuka, 1988; Percy *et al.*, 1972). Proceeding from the above evidence, epidemiological studies concerning primary brain tumours should be based both on as such a complete case research study as possible, as well as on clearly defined criteria for different populations and geographical regions. The search strategy used to identify cases has been found to have the greatest influence on results. The more methods that have been used to discover cases, the higher the incidence rates have been reported. Studies that used only a single source to identify patients (e.g. a cancer registry or records from a single hospital) reported incidences that were about 30% lower than studies that used two or four methods (Counsel and Grant, 1998).

Centralised health care and the population-based cancer registration in Estonia markedly facilitated the case finding procedure for our study. We attempted to achieve maximal case discovery by using several sources including different hospital records: patient registration lists, case histories, pathology reports and consulting the databases of the Estonian Cancer Registry. After linkage of our database to the Estonian Cancer Registry, a valuable contact database was established. This enabled the ECR to perform a tracing-back of missing cases to their original medical records to improve the registry. In Estonia, all suspected brain tumours are admitted to neurosurgical departments (Tallinn Mustamäe Hospital and Tartu University Clinics) where specialists make diagnostic and treatment decisions. We had very good co-operation with the neuropathologist who overviewed histologically obscure cases, according to the WHO histological classification of CNS tumours (Kleihues *et al.*, 1993). The possibility was considered that some tumours have been diagnosed in outpatient or children clinics although the centralised system would minimise this. We believe that these few possible missed cases probably did not affect the total incidence numbers considering the number of identified cases. Some problems were caused by the incomplete data of medical records when estimating the clinical characteristics. This shortage is only inevitable in prospective studies. To identify sufficient cases of tumour sub-types the study was conducted on the whole Estonian population of approximately 1.5 million during a period of 11 years (1986–1996).

2. Histological distribution

The distribution of pathologically confirmed cases according to histological types in Estonia is in many respects similar to the distribution reported for other geographic regions (Walker *et al.*, 1985; Cole *et al.*, 1989; Preston-Martin *et al.*, 1993).

In our study, gliomas comprised 50% (including glioblastomas 25%, astrocytomas 17%), meningiomas 24% and neurinomas 6% of all CNS tumours. The U.S. study (Surawicz *et al.*, 1998) based on the National Cancer Data Base (NCDB) has found approximately the same distribution concerning astrocytoma (18.7%) and glioblastoma (29.6%), with a lower occurrence of meningioma (14.3%) and neurinoma (2.5%). Authors suggest that tumours of benign histologies are under-represented in the NCDB because of insufficient diagnostic accuracy and quality of data coding and entry in some institutions. The latest study (Surawicz *et al.*, 1999) based on the Central Brain Tumour Registry of the United States showed that the frequency of meningioma is much higher (24%). A few studies (Percy *et al.*, 1972; the Committee of the Brain Tumour Registry in Japan, 1987; Kuratsu *et al.*, 2001) have revealed lower frequency for gliomas (28–38%) and higher frequency for meningiomas (33–37%). We found that pituitary adenomas accounted for only for 2.6% of cases, which is lower than figures in other studies where they accounted for 6% to 18% (Gudmundsson, 1970; Counsell *et al.*, 1996; D'Alessandro *et al.*, 1995; Kuratsu *et al.*, 2001). The observed difference may be partly due to low histological confirmation (58%), since inclusion of patients with clinically identified adenoma would increase the figure by any figure up to 5.4%. Generally, we suggest that the difference in histological distribution is mostly affected by methods of case ascertaining, the availability of brain imaging techniques and the percentage of histological conformation.

3. Incidence of primary brain tumours

Studies of the incidence patterns of nervous system tumours in adults show a remarkably consistent dependence on age and race as well as on the sex ratio in different population groups (Velema and Walker, 1987). All studies have confirmed that the incidence of primary CNS tumours, especially neuro-epithelial and meningeal tumours, increases with age up to the years of 65–70 (Counsell and Grant, 1998). Data concerning age-specific incidence rates in the elderly are controversial. Several studies (Gudmundsson, 1970; D'Alessandro *et al.*, 1995; Preston-Martin *et al.*, 1993) have found that maximum incidence occurs in the oldest age group. In a Japanese study, (Kuratsu and Ushio, 1997), of 271 intracranial tumours in elderly people, the annual incidence rate was 18.1 per 100,000 population and was significantly higher than in other age groups,

meningioma being the most common type (50.6%). Similar to other studies, (Fogelholm *et al.*, 1984; Helseth *et al.*, 1988; Joensen, 1981; Van der Sandern *et al.*, 1998), the present research shows an increasing incidence from the age of thirty, reaching a maximum in the age-range of 50–69 years and a decline in the elderly, with gliomas as the most frequent type (Greig *et al.*, 1990; Radhakrishnan *et al.*, 1995). The latter trend seems to occur as a result of under diagnosis influenced by autopsy rates (Percy *et al.*, 1972; Preston-Marin *et al.*, 1993), less investigation and diagnostic bias (stroke or dementia being diagnosed more readily than tumour) (Counsell *et al.*, 1996) rather than a real decrease. We agree with Helseth (1993), who suggests that completeness of diagnosis, particularly in the case of the elderly, depend both on the autopsy rate and use of improved imaging techniques. However, like some other authors (Van der Sandern *et al.*, 1998) we do not believe that the decline factor in the elderly is explainable mainly as the result of under-diagnosis. We propose to carry out more prospective epidemiological studies among the elderly, accompanied by neurological examination, using modern imaging techniques in different populations to prevent a missed diagnosis.

Meta-analysis has confirmed that significant differences exist in the incidence of neuroepithelial, meningeal and cranial nerve tumours between males and females and these cannot be explained by age differences (Counsell and Grant, 1998). Some authors have found a higher incidence of primary CNS tumours among males (Van der Sandern *et al.*, 1998). Percy *et al.* (1972) showed that females have meningiomas more frequently, whereas gliomas and most other neoplasms occur at an equal rate in both sexes. In a study, carried out in Central Finland, meningiomas were shown to be eight times more frequent in females than in males (Fogelholm *et al.*, 1984). Our data reveal no significant differences between males and females in the overall incidence of primary CNS tumours. Regarding the incidence rate according to histological types, gliomas were more common in men (with no significant difference when astrocytoma and glioblastoma were treated separately), while meningiomas and tumours of cranial and spinal nerves were more predominant in females as established in most other surveys (Barker *et al.*, 1976; Helseth *et al.*, 1988; Cole *et al.*, 1989; Mahaley *et al.*, 1989).

Spinal tumours constituted 8.3% of all primary tumours with an incidence rate of 0.8 per 100 000 population, which is lower than that presented in the Rochester, Finnish and Icelandic studies (Percy *et al.*, 1972; Gudmundsson, 1970; Fogelholm *et al.*, 1984), and higher than that reported from South East Wales (Cole *et al.*, 1989). Our study shows an age-dependant increase of spinal tumours (Figure 1), similar to all the above mentioned surveys.

The age-adjusted incidence of 8.46 per 100,000 population for all CNS tumours is comparable to the findings of surveys carried out in Iceland, Norway, Victoria (Australia), US (Connecticut, Missouri, Massachusetts, Utah) and Japan (Gudmundsson, 1970; Helseth *et al.*, 1988; Preston-Martin *et al.*, 1993; Davis *et al.*, 1996; Kuratsu *et al.*, 2001). It is higher than that reported

from Washington DC, Wales, Netherlands and England (Heshmat *et al.*, 1976; Cole *et al.*, 1989; Van der Sandern *et al.*, 1998), and lower than that found in Israel, Finland, Rochester (Minnesota), Italy (Valle d'Aosta), Scotland and the US (Leibowitz *et al.*, 1971; Fogelholm et al., 1984; Radhakrishan, 1995; D'Alessandro *et al.*, 1995; Counsell *et al.*, 1996; Surawicz *et al.*, 2001, Cordera *et al.,* 2002). The incidence of two main tumour types, gliomas and meningiomas, was 3.4 and 1.6 respectively, which is comparable with most of the studies, but lower than in Finland, Italy and Scotland (Kallio, 1988; Tola *et al.*, 1994; Cordera *et al.*, 2002). Generally, the incidence of gliomas is about twice as high as that of meningiomas, except in Norway where the incidence ratio of gliomas to meningiomas was 4:1 (Helseth *et al.*, 1988). Higher incidences were found in studies where the incidence of all brain tumours was higher as well. We surmise that a low autopsy rate and a lower overall incidence of CNS tumours in the elderly, influenced by less investigation and diagnostic bias, account for the overall lower incidence of brain tumours in Estonia.

Changes in incidence rates

Comparison of current rates with those of the 1951–1970 study carried out in Estonia, as well as with those of other studies (Schoenberg *et al.*, 1976; Werner *et al.*, 1995; Christensen *et al.*, 2003), suggests that the increase in the incidence rates of intracranial tumours is histology-specific. A significant increase was observed in incidence rates for astrocytoma, glioblastoma and meningioma. In meningiomas and partly also in low grade astrocytomas, our data support the argument that the increase in rates may be due to the fact that some tumours, previously went undetected, are now diagnosed (Helseth, 1993). It is also important to note that the use of different histological classifications in the present and previous Estonian study cannot be disregarded either. Glioblastoma generally presents easily recognisable symptoms, which make diagnosis less dependent on imaging technology. In some works investigators have revealed a higher increase in incidence for meningioma than for glioma (Helseth, 1995; Christensen *et al.*, 2003), while a Connecticut study (Davis *et al.*, 1996) established a higher increase for astrocytoma, meningioma and ependymoma. Analysis of the data of the US Surveillance, Epidemiology and End Results (SEER) Program (Ahsan *et al.*, 1995) showed a statistically significant increase only for lymphoma in men. In Estonia, 59% (126 cases) of meningiomas were diagnosed at autopsy (with an autopsy rate of 30%) from 1951 to 1970, i. e. in the period before dramatic changes in diagnostic technology had taken place. In our study, most cases (70%) diagnosed, post mortem, were identified as gliomas and only 8% (7 cases) were meningiomas (at the same time the autopsy rate has decreased significantly). Evidently, most of these tumours had been misdiagnosed like other CNS diseases, and only a small part was incidental findings. Taking into account the low proportion of autopsies in Estonia, silent tumours

are likely to be underestimated. Comparing the age-specific incidence rates of our study with those of the previous Estonian study, a significant increase is evident in all age groups. The same tendency has been found in Denmark (Christensen *et al.*, 2003). Whereas studies performed in Norway (Helseth *et al.*, 1988), Connecticut (Polednak, 1991) and France (Fleury *et al.*, 1997) revealed a significant increase only in the over 60 age group. This suggests that some of the increase can be accounted for by recent medical interest in, and better understanding of, neurological disorders in the elderly, as well as by improvement in diagnostic procedures. Desmeules *et al.* (1992) has demonstrated that new imaging technology is responsible for detection of about 20% of brain tumours in both younger and older patients. Proceeding from our data, one cannot exclude that some part of the increased incidence in all ages and in some histological types (glioblastoma) is the consequence of environmental effects or some etiological factors. The increase across all age groups suggests a real increase in parallel with the increase related to more effective detection owing to improved case ascertaining with new imaging technology. However further studies are required to define whether this increase is real and continuous in Estonia. For the sake of better comparability of data, we agree with Counsell and Grant (1998) who suggest the use of unified methodology and who have worked out provisional guidelines for further research into incidence of primary brain tumours.

4. Cancer registration

The incidence rates of primary CNS tumours are higher in our study compared with the figures reported by the Estonian Cancer Registry (ECR). Until recently, the ECR recorded only histologically malignant brain tumours excluding meningiomas, neurinomas, pituitary and other benign tumours. The traditional distinction with respect to malignancy is clinically not specific to brain tumours as benign tumours of intracranial location may have as poor a prognosis as malignant tumours. Of the 1665 patients included in our study, 996 (60%) were identified in the Estonian Cancer Registry as having CNS tumours. Since most gliomas are considered malignant, 98% of them were found in the registry. Differences were revealed in the histological sub-groups of gliomas: some types were over-reported (oligodendroglioma 124%, astrocytoma 106%) or under-reported (glioblastoma 91%). Probably classification errors were not caused by incorrect reporting. As other authors (Counsell *et al.*, 1997; Davis *et al.*, 1997; Van der Sanden *et al.*, 1998), we suggest that classification errors occur because there is no meaningful link between the ICD-O coding system used in cancer registries and the WHO classification system used by neuropathologists. The problem can be solved by better collaboration between clinicists, pathologists and the cancer registry. Since, according to the ECR, the proportion of

meningiomas and neurinomas was very low (11% and 9%, respectively), this means that the total incidence of CNS tumours is significantly underestimated. We compared our data with those reported from Scotland (50% of all primary tumours and 85% of malignant tumours identified in the Scottish Cancer Registry) (Counsell *et al.*, 1997) and Norway (errors in overall incidence rates and rates for main tumour groups accounting for 0.3% of the total) (Helseth *et al.*, 1988). A recent study carried out in Devon and Cornwall revealed under registration of more benign tumours in younger patients. Better registration included patients over 60 years of age and having a tumour requiring operation and radiotherapy (Pobereskin, 2001). Unfortunately our study didn't analyse registration in different age groups and by the performed treatment. It becomes evident that the accuracy of registration of brain tumours in the ECR depends on tumour histology. Therefore, there may be limitations in using the cancer registry to identify incidence of primary brain tumours.

5. Epileptic seizures in brain tumours

Brain neoplasms account for about 4–5% of all cases with seizure disorders (Morris *et al.*, 1989; Hauser *et al.*, 1993). Concerning previous medical history in gliomas there has been found an increased risk associated with epilepsy (Schlehofer *et al.*, 1999). The association has been considered weaker for epilepsy of more than 20 years duration. The presence of a tumour should always be considered in those patients with seizure disorders, especially in case of simple partial and secondarily generalised seizure types. Other symptoms, some of which may be of a diagnostic value, will appear several months or years later, whereas in a remarkable proportion of patients they are totally lacking.

Of cerebral neoplasms, 25 to 50% appear with seizures (Morris *et al.*, 1993; Shady *et al.*, 1994; Moots *et al.*, 1995). Seizures are often reported as being the first and sometimes the only presenting symptom of intracranial tumours (Morris *et al.*, 1993; Moots *et al.*, 1995). In meningiomas, 27% of the patients have been reported to have epileptic seizures as their initial symptom (Lieu and Howng, 2000). Lühdorf *et al.* (1986) found seizures to be the first sign of brain tumour in 50% of patients who developed seizures after the age of 60 years. In our study, only 17% of all tumour patients had seizures as their first complaint. The difference may be caused by the retrospective design of this study including mistakes in the chronology of symptoms. The diagnosis of brain tumour is often made after years from the onset of seizures. Several authors have reported the mean interval from onset of seizures to tumour diagnosis or surgery to be from 2 to 11 years with a maximum of more than 20 years (Hirsch *et al.*, 1989; Smith *et al.*, 1991; Bartolomei *et al.*, 1997; Afra *et al.*, 1999). In a study carried out in 6 countries, (Schlehofer *et al.*, 1999) including 1,178 glioma and 331

meningioma cases, there was an increased risk associated with epilepsy at least 2 years before brain tumour diagnosis in glioma patients. In epilepsy of more than 20 years' duration, the risk was significantly weaker. No association between meningioma and previous epilepsy history was observed. In our study, the mean time from the first epileptic seizure to tumour diagnosis was 16 months, ranging from several days to 20 years, while it was significantly longer in patients whose only presented complaint was seizures (18 months), compared with patients who had seizures accompanying other symptoms and signs (12 months). Shorter duration in our examination period may be due to the fact that our study group included patients with both acute and chronic epilepsy. The exact cause for the long duration of seizures prior to tumour diagnosis is still unclear.

Data on the incidence of seizure activity and patients' age are controversial. The age distribution of cases depends largely on the biological type of the tumours (Ketz *et al.*, 1974). Shady *et al.* (1994) found the 50% seizure incidence to have no correlation between age at diagnosis and seizure activity in children with supratentorial astroglial neoplasms. In their study of 3291 children with brain tumours, Gilles *et al.* (1992) reported that 14% of them experienced seizures, while the incidence increased monotonically throughout childhood. In adults with malignant gliomas, seizures at presentation were found more commonly in those patients younger than 50 years (Moots *et al.*, 1995). In a study of 1028 gliomas, the frequency of epilepsy at presentation decreased with age in high-grade glioma patients and increased with age in low-grade glioma patients to a plateau in the fourth decade of life (Lote *et al.*, 1998). In our study of all intracranial tumours, there was no significant difference between children and young adults compared with seizure and seizure free patients. Seizures were significantly more common in the third and fourth decades of life.

Concerning tumour pathology, seizures are reported most frequently in those patients with low-grade, slowly growing tumours and tumours involving the cerebral cortex. The most common tumour types are low-grade astrocytomas, mixed gliomas and oligodendrogliomas. Pace *et al.* (1998) found preoperative seizures even in 83% of supratentorial low-grade astrocytomas. Gangliogliomas are found with a surprisingly higher frequency than could be expected (Morris *et al.*, 1989, 1993; Shady *et al.*, 1994). In our study, the most common tumour types were mixed gliomas (63%), oligodendrogliomas (53%) and astrocytomas (42%) which is comparable with the results obtained by other authors. There was no significant difference in the incidence of low grade astrocytomas (41.5%) and anaplastic astrocytomas (43%). In the case of glioblastomas seizure, the incidence was low (26%); these patients experience other symptoms and signs more commonly. Incidence of seizures was the lowest for metastatic tumours (15%) and in cases without histological confirmation (12%). Seizures at presentation were significantly correlated with tumour pathology and location.

With regard to tumour location, seizures have been reported to occur in 22–68% of patients with supratentorial tumours involving most commonly the temporal and frontal lobes (Morris and Estes, 1993; Moots *et al.*, 1995) and in only 1–6% of patients with infratentorial lesions (Shady *et al.*, 1994). Superficial tumours involving the isocortex without known deep extension were associated with the highest rate of seizures significantly more often than if the tumour had a deep extension (Gilles *et al.*, 1992). Seizure rates associated with frontal or temporal tumours were also significantly reduced in the presence of deep extensions of the tumour. In supratentorial, convex meningiomas, evidence of severe peritumoural edema significantly contributed to that of pre-operative epilepsy (Lieu and Howng, 2000). In our series, the higher incidence of seizures involving the frontoparietal, frontotemporal, parasagittal and temporal regions was evident. We did not take into account peritumoural edema or cortical location of a tumour as data concerning these entities were not sufficient. A prospective study design is more appropriate to evaluate these parameters.

The reported incidences of neurological findings in seizure patients are quite different. Most commonly, patients with low-grade tumours and chronic epilepsy have normal findings on neurological examination. In their series of chronic epilepsy, Morris and colleagues (1993) found 97% of patients without neurological signs. Spencer *et al.* (1984) described neurological abnormality in 12 of 19 neoplasm patients with intractable partial epilepsy. In our series of 165 patients, 44 (27%) had seizures as the single symptom and 123 (75%) as the first manifestation. Controversy between these data may be due to the differences between study groups. In our study group, 121 (73%) patients experienced at least one other symptom; among them, 58 (35%) had headache, 31 (19%) papilledema, 92 (56%) neurological deficit and 25 (15% 9 mental disturbances. Occurrence of neurological deficit, headache and mental disorders was remarkably higher in those patients without seizures. Comparison of seizure and seizure-free patients revealed no difference in the incidence of increased intracranial pressure, which is supported by other authors (Gilles *et al.*, 1992).

The probability of diagnosing an underlying tumour in a patient with epilepsy is related to seizure type, with simple and complex partial seizures being the most common (Le Blanc and Rasmussen, 1974; Lote *et al.*, 1998). The authors who have compared several seizure etiologies and seizure types have found only simple partial seizures to be significantly related to tumour etiology (Spencer *et al.*, 1984). Tumour location has been considered the most important factor. In our series, all patients with classifiable seizures had partial seizures with or without secondary generalisation, 37% had simple partial, 10% had complex partial and 51% had secondary generalised seizures.

Patients with seizures caused by brain tumours reveal normal EEG only infrequently. Expediency of EEG recording in localisation of underlying brain tumours is debatable. Blume *et al.* (1982) found that focal delta activity has a higher tumour-localising value than spikes, and showed that multifocal spikes

are associated with the unifocal tumour, including discharges arising from the opposite hemisphere. Several studies have shown a significant association between focal slow (delta) activity and brain tumours (75–80%) while paroxysmal activity has been seen more seldom (Blume *et al.*, 1982; Dam *et al.*, 1985). However, in these studies the patient population was too small to consider the result significant. In a study of 98 children with supratentorial astroglial tumours (Shady *et al.*, 1994), 88% of EEG abnormalities lateralised the tumour exactly and 56% localised the tumour to a specific lobe. In another study (Spencer *et al.*, 1984) of 19 tumour patients with intractable partial epilepsy, 37% of EEGs localised the lobe and 21% lateralised the tumour. In the present study, 16% of patients had normal EEG, 78% had focal slow activity and 35% revealed paroxysmal activity. EEG findings allowed exact localisation of the lobe and hemisphere in 41% of patients, which is comparable with other authors. Focal delta activity in EEG may be of diagnostic value in case of brain tumours, but the use of EEG is debatable in localisation of an underlying neoplasm, especially when MRI and CT are available.

6. Survival and prognostic factors associated with survival of primary brain tumours

Most studies concerning survival of CNS tumours are hospital based or restricted to histological subtypes of gliomas. Different study designs make the comparison of data very problematic. Our analysis provides population-based survival estimates for both histologically benign and malignant CNS tumours in Estonia. Observed one- and five-year survival, the prognostic importance of patient- and tumour-related factors were analysed in 1417 patients with CNS tumours.

Data on gender differences are controversial. Most authors report no association between the prognosis and patient gender in malignant CNS tumours (Mørk *et al.*, 1985; Salminen *et al.*, 1996). A study based on 45 European population-based cancer registries reported the higher survival of women in all countries except Switzerland and Austria (Sant *et al.*, 1998). Gender differences have previously been reported for non-malignant CNS tumours (Helseth, 1997; Preston-Martin *et al.*, 1993; McCarthy *et al.*, 1998). The prognosis for patients with benign meningiomas is better for females below 60 years (Sankila *et al.*, 1992; McCarthy *et al.*, 1998). The cause of this difference is unknown.

In our series including all CNS tumours, survival is considerably longer among females: median survival 62.8 months compared with only 18.6 among males. This difference can be explained by the variations in the histologial distribution in men and women. There is a higher incidence of benign meningiomas in females, together with a better prognosis for this type of

tumour. The poorer survival of men is attributable to the relatively greater frequency among men of more aggressive tumour types. In multivariate analysis, no difference in prognosis could be detected for male and female patients.

The importance of age in predicting the survival from CNS tumours has been well documented in studies from the U.S. (Mahaley *et al.*, 1989; Chandler *et al.*, 1993; Salcman *et al.*, 1994; Barker *et al.*, 1996; Davis *et al.*, 1998; McCarthy *et al.*, 1998; Bunin *et al.*, 1998) as well as from other countries (Kallio, 1993; Preston-Martin *et al.*, 1993; Salminen*et al.*, 1993; Lowry *et al.*, 1998; Billiar *et al.*, 1999). Generally, survival rates are declining with increasing decades of age at diagnosis both in benign and malignant tumours. A similar pattern was found in our study. In our series both, univariate and multivariate analyses show better survival in those patients below 45 years, being the most favourable in children and adolescents. The survival pattern of patients aged 45 to 64 years resembles more closely that of older rather than younger patients. However, some authors suggest that influence of age is overestimated (Shaw *et al.*, 1994).

The prognosis of glioma patients, in general, is considered to be poor. In low-grade astrocytomas, the median survival time is about 5 years. Our study shows the similar result of 4.5 years. Long-term survival at 5 years is rather different ranging between 30% and 60% (Preston-Martin *et al.*, 1993; Kreth *et al.* 1997), depending primarily on the inclusion criteria and study design. A hospital-based study of the NCDB (Surawicz *et al.*, 1998) including over 60,000 patients with a CNS tumour, found 5-year survival of 30.3% for astrocytoma and 77.4% for pilocytic astrocytoma. Our data show 5-year survival of 49.8% for low-grade astrocytomas depending significantly on patient age. Both, one- and five-year survival of patients under 20 years is 3–4 times better than those of over 65 years.

The overall median survival of grade 3 and 4 astrocytomas is less than 1 year. Salcman with colleagues (1994) suggests that the median survival of grade 3 and 4 astrocytomas for patients less than 40 years of age, who receive some form of therapy beyond surgery and radiation, is more than 2 years. Younger patients with grade 3 astrocytomas have generally better survival extending over 4 years (Silverstein *et al.*, 1996). The Finnish study (Salminen *et al.*, 1996) reported the median survival of grade 3 and 4 gliomas, 24.0 and 7.7 months, respectively. Barker with co-authors (1996) found the median survival of glioblastoma 11.2 months, the 1- and 5-year survival, 48% and 4%, respectively. Our study found similar median survival for glioblastoma (6.2 months) and anaplastic astrocytoma (8.3 months), 1-year survival 28.0% and 36.1% and 5-year survival 8.6% and 15.8%, respectively. These data show poorer outcome than in other studies, especially concerning anaplastic astrocytoma. The relative poor median survival of patients with anaplastic astrocytoma may be explained by difficulties in making the histological diagnosis. The biggest divergence between neuropathologists lies in the making of the diagnosis of anaplastic

astrocytoma. We suggest that other reasons for poor outcome are being caused by the lack of treatment strategies and oncological systems concerning brain tumours in Estonia. Many patients get lost in "the system" between neurosurgeons and oncologists. There is not a final consensus as to who should perform the following-up of patients: oncologists, neurosurgeons or neurologists.

In oligodendrogliomas the median survival time is between 3 and 8 years (Mørk *et al.*, 1985; Ludwig *et al.*, 1986; Lindegaard *et al.*, 1987). Our data show the survival of 2 years, which is significantly lower, but comparable with the median survival of non-irradiated patients (26.5 months) in the Norwegian study (Lindegaard *et al.*, 1987).

Although patients with benign tumours have a more favourable prognosis compared with patients with malignant ones there is still significant mortality associated with these histologies. Many studies give only observed survival rates (Cornu *et al.*, 1990; Surawicz *et al.*, 1998; McCarthy *et al.*, 1998), which do not consider mortality due to other causes. This fact may have a certain impact on survival rates, especially in older people and one must consider it when comparing different studies. In our study, only observed survival rates were estimated and were not adjusted for deaths due to other causes. According to our results both, 1-year and 5-year survival of meningiomas is about the same as in the Finnish study (Sankila *et al.* 1992) (83% and 79%, respectively). The Norwegian study reported survival of benign meningiomas 93% at 1 year and 95% at 5 year (Helseth, 1997). The U.S. study (McCarthy *et al.*, 1998) based on 9000 meningioma cases found the 5-year survival rate 69% in meningiomas.

The clinical functional ability or Karnofsky score of the CNS tumour patient is known to be a strong predictor of outcome in most of the studies (Mahaley *et al.*, 1989; Shaw *et al.*, 1994; Barker *et al.*, 1996; Van Veelen *et al.*, 1998). In our study, the clinical condition occurred as a statistically significant prognostic factor in both the univariate and multivariate analyses.

Of course, appropriate therapies are among the main determinants of prognosis. The better outcome in socio-economically advanced societies is due to earlier diagnosis and the combined effect of more effective therapies including centralisation of treatment and dissemination of effective therapeutic protocols. Several authors have found the extent of surgical resection one of the most relevant factors affecting survival in both low-and high-grade gliomas (Piepmeier *et al.*, 1996; Scerrati *et al.*, 1996; Barker *et al.*, 1996; Davies *et al.*, 1996). The majority of the reports confirm that combined treatment by surgery and irradiation may give a distinctly longer median survival time than treatment by surgery alone (Shaw *et al.*, 1994; van Veelen *et al.*, 1998). The favourable association of radiation dose and tumour grade with prolonged survival has been confirmed (Salcman *et al.*, 1994; Salminen *et al.*, 1996). In anaplastic glioma an adjuvant chemotherapy among patients < 55 years of age has been reported to increase survival markedly (Gundersen *et al.*, 1998). In glioblastomas, no post-operative adjuvant therapy, whether radiation therapy or chemotherapy or a combination thereof, has appeared to be more effective than

any other practice (Chandler *et al.*, 1993; Gundersen et al., 1998). We didn't investigate the extent of surgical resection and recurrence rate. We suppose that, possibly in most cases, a gross total resection was used. Postoperative radiation therapy and adjuvant chemotherapy or a combination is, for certain reasons (e.g. the lack of defined treatment protocols and insufficient co-operation between surgeons and oncologists), not so widely used in Estonia (Table 18). Most patients (51%) received only surgical treatment, 33% of patients were operated followed by radiation. In both, univariate and multivariate analysis treatment was found to be a significant prognostic factor. Multivariate analysis revealed a small but significant difference between treatment strategies and outcome in gliomas. Our series suggest that in multivariate analysis age, patient clinical condition, tumour histology and treatment are independent prognostic factors for gliomas. Low-grade astrocytoma, oligodendroglioma and ependymoma patients, of a younger age, had better clinical condition when they underwent surgery with additional radiation therapy or surgery combined with radiation and chemotherapy and had the best prognosis. The worst prognosis was found in those patients who had received only symptomatic treatment.

Changes in survival rates

During the last decades, an overall slight increase in survival of malignant tumours for all patients has been found both in the European (EUROCARE) study (Sant *et al.*, 1998) and the US study (SEER programme) (Davis *et al.*, 1998). Most improvement is confined to the first year after diagnosis. Age-specific rates show that the increase is more evident in younger patients, up to 54 years of age. Concerning tumour histology the improvement is evident in medulloblastoma, in adults with astrocytoma and oligodendroglioma (Piepmeier *et al.*, 1996). The survival improvements reflect improvements in the therapy and treatment, taking place at an earlier stage of disease, whereas the newer and better diagnostic techniques help in identifying tumours earlier.

In meningiomas, both short-term and long-term survival has improved during the last decades (Helseth, 1997). The improved 1-year survival is likely to be caused by improved operative technique and improved post-operative care. The increased long-term survival may reflect the likelihood that more patients with small meningiomas are diagnosed early since CT became available. In benign meningiomas, a small tumour size is one of the factors independently associated with increased survival time (McCarthy *et al.*, 1998).

Our survey follows the example of above-mentioned studies and statistically significant improvements in 1-year survival rates were found for all tumours and low-grade astrocytoma comparing the first and the third time period. Age-specific rates showed that the increase was more evident between 45 and 64 years. Decline in survival during the second period (1990–1993) is statistically significant for all tumours, but the most striking decrease took place in

glioblastoma. This discrepancy may reflect the economic condition and reorganisation of the health care system at the beginning of the nineties. It was the period of extensive changes in Estonia, both in political and economical systems including that of health care. Delay at diagnosis, especially in rural areas where availability of medical care has not been so good, may also cause a poorer outcome during the second period. Older patients are rather diagnosed with dementia or vascular disease by family doctors than suspected of CNS tumours and are sent to the neurologist.

CONCLUSIONS

1. In the period 1986–1996, 1665 cases (739 males, 926 females) of primary CNS neoplasms were identified in the resident population of Estonia. Histological verification was available in 81% of cases. The most common histological types were glioblastoma (25%) and meningioma, low-grade astrocytoma (11%), anaplastic astrocytoma (6%) and neurinoma (6%). The distribution of pathologically confirmed cases according to histologic types in Estonia is in many respects similar to the distribution reported for other geographic regions.
2. Categories that influenced the occurrence of seizures in brain tumour patients were the duration of symptoms, tumour location and histology. Epileptic seizures occurred more frequently in those patients with long duration of symptoms (6 months and more) who were diagnosed of astrocytoma, anaplastic astrocytoma, some other glioma or meningioma. Focal delta activity in EEG may be of diagnostic value in case of brain tumours, but the use of EEG is debatable in localisation of an underlying neoplasm, especially when MRI and CT are available.
3. The age-specific incidence rate was much lower in childhood, increased from the age of thirty, reaching a maximum in the age-range of 50–69 years, and declined abruptly in the elderly. The pattern of age-specific incidence rate for glioblastoma and meningioma were similar increasing with age and reaching a maximum at the age of 60–69. Astrocytoma showed a small peak in childhood, a plateau in middle age and an increase between 50 and 70 years.
4. The age-adjusted incidence of 8.46 per 100,000 population for all CNS tumours is comparable to the findings of surveys carried out in Iceland, Norway, Australia and Japan. It is higher than that reported from Washington DC, Wales, Netherlands and England and lower than that found in Israel, Finland, Minnesota, Italy and Scotland. The incidence of two main tumour types, gliomas and meningiomas, was 3.4 and 1.6, respectively which is comparable with most of the studies, but lower than in Finland, Italy and Scotland. Gliomas occurred more commonly in males, while meningiomas and tumours of cranial and spinal nerves were significantly more frequent in females as established in most other surveys.
5. A comparison of current incidence rates with those of a previous study carried out from 1951 to 1970 suggests that the increase in the incidence rates of intracranial tumours is histology-specific. A significant increase was observed in incidence rates for astrocytoma, glioblastoma and meningioma. Looking at age-specific incidence rates, a significant increase is evident across all age groups. The same tendency has been found in Denmark.
6. The overall 1-year survival was 59% ranging from 89%in pituitary adenoma to 28% in glioblastoma. Five-year survival rates were very poor in

gliomastama (9%) and anaplastic astrocytoma (16%). In gliomas, patients of younger age had a very significantly better survival compared with the elderly. Comparing the first (1986–1989) and the third (1994–1996) time period, statistically significant improvements in survival for patients with astrocytoma and for all tumours has taken place. Age-specific rates showed that the increase in survival was more evident in older adults.

7. Compared with other studies, the outcome of CNS tumours in Estonia, especially in anaplastic astrocytoma, is somewhat worse.
8. In multivariate analysis, older age at diagnosis, patient clinical condition, tumour histology and period of diagnosis were independent prognostic factors for survival. Risk of death was more than eight times greater for glioblastoma, about seven times greater for anaplastic astrocytoma and more than five times greater for other gliomas compared with meningioma. The best prognosis was found in neurinoma, still having a significantly greater risk of death compared with meningioma. In glioma patients, the best prognosis had low-grade astrocytoma, oligodendroglioma and ependymoma patients of younger age, better clinical condition for those who underwent surgery with additional radiation therapy or surgery combined with radiation and chemotherapy.
9. Of the 1665 patients included in our study, 996 (60%) were identified in the Estonian Cancer Registry as having CNS tumours. Ninety eight per cent of malignant tumours were represented in the registry. Differences were revealed in the histological subgroups of gliomas: some types were over-reported (oligodendroglioma, astrocytoma) or under-reported (glioblastoma). Since according to the ECR the proportion of meningiomas and neurinomas was very low, this means that the total incidence of CNS tumours is significantly underestimated. It is evident that the accuracy of registration of brain tumours in the ECR depends on tumour histology. Therefore there may be limitations in using the cancer registry to identify the incidence of primary brain tumours.

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SUMMARY IN ESTONIAN

KESKNÄRVISÜSTEEMI KASVAJATE EPIDEMIOLOOGIA EESTIS 1986-1996: kliinik, haigestumus, elulemus, ja prognoos

Kesknärvisüsteemi kasvajate haigestumuse näitajad kõiguvad erinevates populatsioonides ja geograafilistes piirkondades küllalt suurtes piirides: 4–16 100 000 inimaasta kohta (Schoenberg *et al.*, 1976; Cole *et al.*, 1989; Counsell *et al.*, 1996; Surawicz *et al.*, 1999; Kuratsu *et al.*, 2001), Põhja Itaalias isegi kuni 25 (Cordera *et al.*, 2002). Eesti Vähiregistri andmetel ei kuulu aju ja kesknärvisüsteemi kasvajad Eestis ei naiste ega meeste seas kümne sagedamini esineva vähipaikme hulka (Thomson *et al.*, 1996; Aareleid ja Mägi, 1999). Erandiks on alla kolmekümne aastaste vanuserühm, kellel on ajukasvajad sageduselt 2.–3. kohal. Suremuse statistikale toetudes on ajukasvajad vähkide seas Eestis 9.–10. kohal. Elulemus on pahaloomuliste ajukasvajate korral ühtviisi madal kõikides uuringutes. Siiski on leitud, et alates 1970-ndatest aastatest, kui hakati laialdasemalt kasutama radio- ja kemoteraapiat, on elulemus mõningate harvem esinevate kasvajavormide (medulloblastoom) osas paranenud.

Eestis on haigestumust primaarsetesse intrakraniaalsetesse kasvajatesse uurinud Virve Lukas (1979), kelle andmetel oli vastav näitaja ajavahemikus 1951–1969 5,9/100 000. Haigestumus näitas tõusutendentsi, olles esimesel kümnendil 5,0 ja teisel kümnendil 6,7.

Uurimuse eesmärgid

1. Leida primaarsetesse KNS kasvajatesse haigestumus Eestis 1986–1996 ja võrrelda saadud tulemusi teiste uuringute andmetega
2. Analüüsida haigestumuse võimalikke muutusi võrreldes eelmise, 1951–1970 aastal, Eestis läbiviidud uuringuga.
3. Analüüsida epileptiliste hoogudega patsientide kliinilisi ja morfoloogilisi andmeid
4. Välja selgitada KNS kasvajate elulemus, hinnata selle muutumist uuritavate aastate jooksul ning võrrelda saadud tulemusi teiste uuringute andmetega.
5. Leida patsientide prognoosi mõjutavad faktorid
6. Hinnata KNS kasvajate registreerimise kvaliteeti Eesti Vähiregistris

Patsiendid ja meetodid

Registreeriti Eestis ajavahemikul 1986 kuni 1996 diagnoositud kesknärvisüsteemi kasvaja juhud. Retrospektiivselt vaadati läbi Tartu Ülikooli Närvikliiniku ja Tallinna Mustamäe Haigla neurokirurgia osakondade meditsiinilised dokumendid (vastuvõtu nimekirjad, komputeriseeritud andmebaasid, haiguslood, lahangu ning histoloogilise uuringu protokollid). Lisaandmeid koguti Eesti Vähiregistri andmebaasist kasutades elektroonset linkimist. Uuringusse kaasamise kriteeriumiteks oli histoloogiline diagnoos või kasvaja diagnoosimine radioloogilis-kliiniliste meetoditega. Patsientide selektsioon toimus vastavalt Rahvusvahelisele Onkoloogiliste Haiguste klassifikatsiooni (ICD-O-2) topograafilistele koodidele (aju, ajukelmed, kraniaalnärvid, hüpofüüsi ning käbinäärme piirkond ja teised KNS osad). Registreeriti ka metastaatilised kasvajad, mida kasutati ainult epileptiliste krampide esinemissageduse analüüsis. Elulemuse analüüsist arvati välja lahangul diagnoositud haigusjuhud, ning juhud, kus eelnevalt või jälgimise käigus diagnoositi mõni teine pahaloomuline kasvaja. Kasvajate klassifitseerimine toimus vastavalt Maailma Tervishoiuorganisatsiooni ajukasvajate histoloogilisele klassifikatsioonile (1993). Ebaselged histoloogilised diagnoosid vaadati üle neuropatoloogi poolt. Patsientide jälgimine toimus kuni 1. jaanuarini 1998. aastal, glioomi diagnoosiga patsientidel kuni 1. jaanuarini 2000. aastal.

Arvutati standarditud haigestumuskordajad 100 000 inimaasta kohta erinevates histoloogilistes gruppides ja haigestumuse vanuskordajad. Standardimisel kasutati maailma ja Eesti standardrahvastikku. Elulemuse analüüsil arvutati tegelik 1- ja 5-aasta elulemusmäär kasutades elutabeli meetodit. Prognostilised faktorid leiti hulgitunnusanalüüsil Coxi regressioonimudeli järgi. Uuringu läbiviimiseks saadi kinnitus Tartu Ülikooli Inimuuringute Eetika Komisjonilt.

Tulemused ja järeldused

Kokku registreeriti 1665 primaarse KNS kasvaja juhtu, neist 739 meestel ja 926 naistel. Metastaatilisi ajukasvajaid esines 330 juhul, 220 mehel ja 110 naisel. Samal ajavahemikul registreeriti Eesti Vähiregistris 996 KNS kasvaja juhtu. Keskmine vanus kasvaja diagnoosimise ajal oli 47 aastat (meestel 45 ja naistel 49). Kasvaja histoloogia tehti kindlaks 81%-l patsientidest. Kõikidest juhtudest 5.3% diagnoositi lahangul.

Kõige sagedasemateks histoloogilisteks tüüpideks oli glioblastoom (30% meestel ja 21% naistel) ning meningioom (13% meestel ja 33% naistel), järgnesid astrotsütoom ja neurinoom (vastavalt 11 ja 6%). Alla 20-aastastel esines kõige sagedamini astrotsütoomi (25%) ja medulloblastoomi (17%). Kesknärvisüsteemi kasvajate histoloogiline jaotuvus Eestis on üldjoontes võrreldav teistes sarnastes uuringutes tooduga. Oluliselt väiksem hüpofüüsi adenoomide hulk (2,6%) on seostatav nende madala histoloogilise tõestatusega (58%) meie

uuringus. Kliinilis-radioloogiliselt diagnoositud hüpofüüsi piirkonna kasvaja juhtude liitmine histoloogiliselt tõestatud juhtudega suurendab hüpofüüsi piirkonna kasvajate hulka oluliselt.

Kahekümne kolmel protsendil patsientidest esines enne kasvaja diagnoosimist vähemalt 1 epileptiline hoog. Epileptilise sündroomiga patsientidel esines histoloogilistest tüüpidest kõige sagedamini segatüüpi glioomi (62%), oligodendroglioomi (53%), anaplastilist astrotsütoomi (42%) ja diferentseerunud astrotsütoomi (42%). Keskmine aeg esimesest epileptilisest hoost kuni diagnoosini oli 16 kuud. Seitsmekümne viiel protsendil epilepsiaga patsientidest oli krambihoog esmaseks haigus-sümptomiks ja 26%-l patsientidest ka ainsaks kaebuseks. Epileptiliste krampide teke oli seotud kasvaja histoloogia ja lokalisatsiooniga. Sagedamini esines krampe kasvaja frontoparietaalse, frontotemporaalse, parasagitaalse ja temporaalse lokalisatsiooni korral. Kirjanduse andmeil on oluline ka kasvajat ümbritseva turse suurus ning ajukoore haaratus, kuid kuna tegemist oli retrospektiivse uuringuga ei olnud võimalik nimetatud parameetreid hinnata. Hulgitunnusanalüüs näitas, et epileptiliste hoogude teket mõjutavad oluliselt sümptomite kestus enne kasvaja diagnoosi, kasvaja asukoht ja histoloogia. Sarnaselt teiste uuringutega oli 41%-l patsientidest EEG-uuringuga võimalik lokaliseerida kasvaja asukoht.

Ajavahemikul 1986–1996 Eestis diagnoositud kesknärvisüsteemi kasvajate haigestumuskordaja oli 9,8/100 000, meestel 9,4 ja naistel 10,3. Sarnaselt teiste uuringutega esinesid neuroepiteliaalsed kasvajad ja glioomid sagedamini meestel (meeste ja naiste suhe 1,2). Meningioomi ja neurinoomi diagnoositi sagedamini naistel (suhe vastavalt 0,4 ja 0,6).

Haigestumuse vanuskordaja oli kõige väiksem lastel (3,7/100 000), tõusis alates 30-ndast eluaastast jõudes kõrgeimale tasemele (20,6/100 000) 50–69-aastaste vanusgrupis ja langes seejärel kiiresti vanemaealistel. Sarnaselt meie tulemustele leiab üks osa uurijaid, et vanemaealistel haigestumus langeb. Teised autorid väidavad, et 65-aastaste ja vanemate hulgas haigestumus pigem tõuseb ja seda just histoloogiliste healoomuliste meningioomide sageduse tõusu tõttu. Madalamate haigestumusnäitajate üheks põhjuseks on ebapiisav tähelepanu vanurite piltdiagnostilisele uurimisele, samuti lahangute väike arv.

Vanuse järgi standarditud haigestumuskordaja oli 8,5/100 000, glioomil 3,4 ja meningioomil 1,6. Reeglina on haigestumus kõrgem sotsiaalmajanduslikult paremini arenenud piirkondades, kus on hea tehnilise varustusega (kompuutertomograafia, magnetresonantstomograafia) ja kättesaadav meditsiiniline abi, väljakujunenud ja korralikult töötav registerteenistus (vähiregistrid) ning suurem lahangute arv. Samuti mõjutab haigestumuse näitajaid läbiviidud epidemioloogiliste uuringute metoodika: sissearvamiskriteeriumid, haigusjuhtude arv ja kogumisviis, kasutatavad klassifikatsioonid. Meie uuringu tulemused lubavad oletada, et suhteliselt madala haigestumuse põhjuseks Eestis on võimalik aladiagnoosimine, eriti vanemaealistel, kellel diagnoositakse pigem dementsust või vaskulaarse tekkepõhjusega haigust kui mõeldakse ajukasvaja peale. Samuti mõjutavad haigestumusnäitajaid väike lahangute arv ja eriti

maapiirkondades piiratud uurimisvõimalused. Seitsekümmend protsenti lahangul diagnoositud juhtudest olid glioomid ja ainult 8% meningioomid. Nimetatud suhe lubab oletada, et enamasti diagnoositi mõnda teist närvisüsteemi haigust ning juhuleidude hulk oli väike.

Uuringu tulemuste võrdlemisel Eestis aastatel 1951–1970 läbiviidud uuringu tulemustega selgus, et haigestumuse kasv oli erinevates histoloogilistes gruppides erinev. Statistiliselt oluline haigestumuse suurenemine esines astrotsütoomi (suhteline risk RR=1,5), glioblastoomi (RR=1,5) ja meningioomi (RR=2,0) grupis. Haigestumuse vanuskordaja suurenes kõikides vanusrühmades, kõige enam aga laste, noorukite ja üle 50-aastaste vanusrühmas (suhteline risk üle 1,5). Sarnane trend on iseloomulik ka teistes populatsioonides läbiviidud uuringutele. Osaliselt on haigestumuse kasvu põhjuseks (eriti astrotsütoomide ja meningioomide korral) kindlasti diagnostika paranemine. Silmas pidades haigestumuse suurenemist kõikides vanusegruppides ja maliigsete glioomide hulgas, ei saa eitada ka mõne teise etioloogilise faktori või keskkonna toimet.

Kesknärvisüsteemi kasvajate 1 aasta tegelik elulemusmäär oli 59% ja 5 aasta elulemusmäär 46%. Kõige parem elulemus oli hüpofüüsi adenoomiga ja meningioomiga patsientidel (1 aasta elulemusmäär vastavalt 89 ja 86%). Glioblastoomiga patsientide 1 aasta elulemus oli 28% ja 5 aasta elulemus 9%, anaplastilise astrotsütoomiga patsientidel vastavalt 36 ja 16%. Kõikides histoloogilistes gruppides sõltus elulemus patsientide vanusest: mida vanem oli patsient, seda halvem oli elulemus. Teiste riikidega võrreldes on Eestis elulemusnäitajad mõnevõrra halvemad, eriti anaplastiliste astrotsütoomide osas. Selle põhjuseks on ilmselt teatud probleemid histoloogilises diagnostikas, samuti puudujäägid onkoloogilises süsteemis ja kindlate ravijuhiste puudumine. Enamusel (51%) glioomiga patsientidest rakendati ainult operatiivset ravi, ainult 40% patsientidest said kombineeritud ravi. Osad patsiendid "kadusid" teel neurokirurgi juurest oknoloogi juurde. Samuti puudub lõplik otsus selle suhtes, kelle järelvalve alla jäävad patsiendid peale operatsiooni ja adjuvantravi. Nimetatud probleemid on enam aktuaalsed maapiirkondades, kus arstiabi kättesaadavus on halvem kui linnades.

Hulgitunnusanalüüsil Coxi regressioonmudeli järgi, kus võeti arvesse patsientide soo, vanuse, operatsioonieelse seisundi, kasvaja diagnoosimise aasta, histoloogia ning lokalisatsiooni seoseid, olid patsiendi vanus, operatsioonieelne seisund ning kasvaja histoloogia oluliselt seotud prognoosiga.

Eesti Vähiregistrisse oli kantud 60% patsientidest: glioomidest 98%, meningioomidest 11% ja neurinoomidest 9%. Registreerimine oli histoloogilistes gruppides erinev: võrreldes käesoleva uuringuga oli ülehinnatud oligodendroglioomiga (124%) ning astrotsütoomiga (106%), alahinnatud glioblastoomiga (91%) ning lümfoomiga (70%) patsientide arv. Nimetatud lahknevuse põhjuseks on ilmselt erinevate klassifikatsioonide kasutamine.

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PUBLICATIONS

I

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Epidemiology of Primary Central Nervous System Tumors in Estonia

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Key Words

Central nervous system neoplasm · Incidence · Cancer registry · Estonia

Abstract

During the period from 1986 to 1996, 1,665 cases of primary central nervous system (CNS) tumors were identified in the resident population of Estonia. Histological verification was available in 81% of the cases. Gliomas were more common in men, while meningiomas and neurinomas were more common in women. No significant difference was observed between the sexes for all primary CNS tumors. The age-specific incidence increased from the age of 30, reached a maximum in the age range of 50–69 years and declined in the elderly which may reflect under-diagnosis. The age-adjusted incidence rate for CNS tumors was 8.5/100,000 population. A comparison of our results with those of a previous study carried out in Estonia revealed a significant histology-specific increase in incidence in all age groups.

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Introduction

The incidence of primary central nervous system (CNS) neoplasms in a defined population has been reported in a number of studies. It varies from 4.9 to 15.7/100,000/year, while higher rates are generally found in socioeconomically advanced societies where medical care is both available and competent, and where better organized registries for data collection and possibly higher autopsy rates exist. The observed differences in populations, races and sexes suggest the possible role of environmental, genetic and hormonal factors in the etiology of brain tumors [1]. Some investigators have reported that the frequency of primary brain tumors, especially in the elderly, has increased substantially during the past two decades [2, 3]. The results of a Rochester study, which had a very high autopsy rate, indicate that the increase in incidence is an artifact reflecting improvement in diagnostic technology and practice [4]. A previous study of primary intracranial neoplasms in Estonia, carried out from 1951 to 1970, estab-

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lished the crude rate of primary intracranial tumors as 5.9 (6.1 for men and 5.8 for women) per 100,000 population [5]. Recent data (1994–1996) reported by the Estonian Cancer Registry (ECR) show 6.2/100,000 for men and 5.6/100,000 for women [6] for brain and other CNS tumors. The ECR was founded in 1978, but retrospective data are available that date back to 1968. The ECR includes data from all hospitals and laboratories in Estonia and death certificates from the Estonian State Statistical Office. Since meningiomas and other histologically benign brain tumors were not recorded until recently, the registry can be considered complete with regard to malignant brain tumors but incomplete for benign tumors. Since 1998, the ECT includes information on all primary brain tumors according to the World Health Organization classification of CNS tumors [7].

The aim of this study was to evaluate the epidemiological characteristics of primary brain tumors in Estonia during the period 1986–1996. In Estonia the first CT scan was introduced in 1983. The results of the study were compared with those of investigations carried out in other populations and with data from the pre-CT diagnostic era (1951–1970) in Estonia with the aim to assess the changes in incidence rates in Estonia and the reporting of brain tumors in the ECR.

Patients and Methods

The study was based on the Estonian population of 1.5 million who are served by two neurosurgical centers (Tartu Maarjamõisa Hospital and Tallinn Mustamäe Hospital) which admit all patients suspected of having CNS tumors. To maximize case ascertainment we obtained material from several sources including hospital records (case histories, autopsy protocols, pathology reports), the ECR and the Estonian State Statistical Office. The records of all intracranial and spinal tumors (including suspicious cases and brain metastases) at these hospitals from 1986 to 1996 were reviewed. The criteria for inclusion were either histological confirmation or verification of neoplasms by radiological or clinical methods. Data collected for each case included age, sex, histological type, diagnostic methods and tumor location. Selection of patients was carried out according to the guidelines of the International Classification of Diseases for Oncology (ICD-O-2) including the codes C70, C71, C72, C75.1, C75.2 and C75.3. Tumors were classified according to the histopathological type of brain tumor following the scheme approved by the World Health Organization. All histologically obscure cases (with the majority of pathological material having been preserved) were retrospectively overviewed by a neuropathologist. Metastatic tumors, tumors of the skull and vascular malformations were excluded. Average annual incidence rates per 100,000 population for primary CNS neoplasms from 1986 to 1996 were computed. Annual age-specific and age-adjusted incidence rates were calculated for all CNS tumors and for each type separately. Population figures were obtained from the annual publications of the Statistical Office of Estonia for each year between 1986 and 1996. Age adjustment was performed by direct standardization according to the World Standard Population and the Estonian Standard Population. The 95% confidence intervals (95% CI) for incidence rates were estimated assuming a Poisson distribution for the studied cases. The difference in incidence between the CT and pre-CT eras was expressed as the incidence rate ratio and with 95% CI.

A previous study of CNS tumors in Estonia was carried out from 1951 to 1970; however, it included only primary intracranial tumors. It was a retrospective, population-based epidemiological survey using histological classifications proposed by Smirnov and Hominski [5].

Results

General Characteristics

In the period 1986–1996, 1,665 cases (739 men, 926 women) of primary CNS neoplasms were identified in the resident population of Estonia. During the same period, 996 patients (179 without histological confirmation) were identified in the ECR. The mean age at diagnosis was 47 years (45 for men and 49 for women), and the median age was 52 years (52 for men and 50 for women; range: 1 month to

Table 1. Histological confirmation (%) according to tumor location (n = 1,665)

Tumor location	All cases	Histologically confirmed cases	
		n	%
Supratentorial			
Cerebral hemispheres	803	693	86.3
Central structures	63	39	61.9
Pituitary or pineal region	121	70	57.8
Other	162	138	85.2
Infratentorial	323	255	79.0
Intracranial, not localized	55	33	60.0
Spinal	138	117	84.8
Total	1,665	1,345	80.8

Table 2. Frequency of diagnostic methods before histological confirmation to verify brain tumors (n = 1,665)

Method	Cases	
	n	%
CT	1,085	65.2
MRI	176	10.6
Autopsy	88	5.3
Myelography	81	4.9
Angiography	67	4.0
Clinical examination	35	2.1
Ventriculography	13	0.8
X-rays	11	0.7
Histology	4	0.2
Pneumoencephalography	6	0.4
No diagnostic method recorded	99	5.9

85 years). Histological verification was available in 1,346 (80.8%) cases. This percentage varied depending on the tumor site, being lower (58%) in pituitary region tumors and higher in tumors of the cerebral hemisphere and tumors of spinal location (86 and 85%, respectively). Histological confirmation according to tumor location is shown in table 1. Before histological confirmation, the majority (76%) of tumors were diagnosed by CT or MRI (table 2). Taking into account the low proportion of autopsies in Estonia, a remarkable number of tumors (5.3%) were diagnosed at autopsy, including both incidental findings and misdiagnosed cases. Forty-three percent of cases diagnosed post mortem were identified as glioblastoms, 19% were astrocytomas and only 8% were meningiomas.

Table 3 illustrates the distribution of histologically confirmed cases of neoplasms according to sex and average age at diagnosis. The most common histological type was glioblastoma, which accounted for 29.9% of all brain tumors among men and 21.2% among women, and meningioma (including both spinal and intracranial), which accounted for 13.1 and 32.8% of cases in men and women, respectively. Fourteen percent (47 cases) of meningiomas were spinal. The other two most common major histological groups were astrocytoma (12.5% in men, 10.1% in women) and neurinoma (5% in men and 7% in women). Among patients under 20 years of age, the most frequent were astrocytoma (25%), medulloblastoma (17%), ependymoma and glioblastoma (both 6%). Forty-two cases (22%) were not histologically confirmed.

Table 3. Distribution of pathologically confirmed brain tumors (n = 1,346) by histological diagnosis, sex and mean age of patients (Estonia 1986–1996)

Tumor type	Cases			Mean age at diagnosis years
	men	women	total	
Neuroepithelial tumors				
Astrocytoma (G_{1-2})	73 (12.5)	77 (10.1)	150 (11.2)	36.4
Anaplastic astrocytoma	35 (6.0)	44 (5.8)	79 (5.9)	48.7
Glioblastoma	174 (29.9)	162 (21.2)	336 (25.0)	53.4
Oligodendroglioma	25 (4.3)	17 (2.2)	42 (3.1)	44.0
Ependymoma	24 (4.1)	13 (1.7)	37 (2.8)	34.5
Mixed glioma	10 (1.7)	13 (1.7)	23 (1.7)	46.6
Pineal tumors	4 (0.7)	–	4 (0.3)	39.8
Medulloblastoma	23 (4.0)	19 (2.5)	42 (3.1)	14.8
Tumors of cranial and spinal nerves				
Neurinoma	29 (5.0)	53 (7.0)	82 (6.1)	47.8
Neurofibroma	2 (0.3)	7 (0.9)	9 (0.7)	38.9
Meningeal tumors				
Meningioma	76 (13.1)	250 (32.8)	326 (24.2)	54.6
Anaplastic meningioma	5 (0.9)	13 (1.7)	18 (1.3)	56.5
Hemangioblastoma	8 (1.4)	14 (1.8)	22 (1.6)	48.4
Malignant lymphomas	12 (2.1)	8 (0.9)	20 (1.5)	49.8
Germ cell tumors	4 (0.7)	2 (0.3)	6 (0.5)	33.7
Sellar region tumors				
Pituitary adenoma	16 (2.6)	20 (2.6)	35 (2.6)	48.7
Craniopharyngioma	8 (1.4)	6 (0.8)	14 (1.0)	30.1
Other, specified	55 (9.5)	45 (5.9)	100 (7.4)	40.7
Total specified	583 (100)	763 (100)	1,346 (100)	47.4

Figures in parentheses indicate percentages.

Incidence Rates

The average annual incidence rate for all primary CNS neoplasms was 9.8/100,000/year (9.0 for intracranial tumors and 0.8 for intraspinal tumors). The age-specific incidence rate of intracranial tumors was much lower in childhood (3.7), increased in the 30- to 39-year age group (6.5), reached a maximum in the age range of 50–69 years (20.6) and then declined abruptly in the elderly (7.6; fig. 1). Intraspinal neoplasms revealed a steady increase in incidence up to the age of 60–69 years. Age-specific incidence rates for glioblastoma, astrocytoma, meningioma and tumors without microscopic confirmation, including both intracranial and intraspinal cases, are shown in figure 2. Some variations of the curves of individual histological types of brain tumors are noteworthy. Specifically, the annual incidence rate of astrocytoma showed a small peak in childhood (1.0) and a plateau in the age range from 30 to 49 years, then increased in the 50- to 69-year age group (2.4) and fell significantly in those aged 70 and older. The age-specific incidence rate for glioblastoma increased with age, reaching a

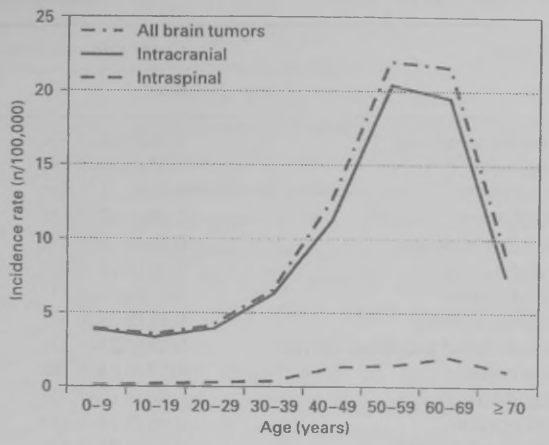

Fig. 1. Age-specific incidence rates for intracranial and intraspinal tumors and for all brain tumors in Estonia (1986–1996).

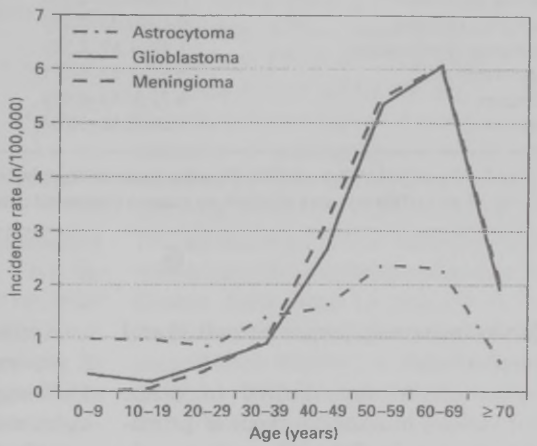

Fig. 2. Average annual age-specific incidence rates for astrocytoma, glioblastoma, and meningioma cases in Estonia 1986–1996.

maximum of 6.1 at the age of 60–69 and declined in the elderly. Meningioma had a similar pattern with a peak incidence of 6.1 in the age range from 60 to 69 years.

There were no statistically significant differences between the sexes either in the total incidence of tumors or in the incidence of astrocytomas and glioblastomas (table 4). However, neuroepithelial tumors ($p < 0.01$) and gliomas ($p < 0.05$) were more common in men (male/female ratio 1.2), while meningiomas and tumors of cranial and spinal nerves (including neurinomas) were significantly more frequent ($p = 0.001$ and < 0.005, respec-

Table 4. Incidence rates (per 100,000 population) by histological types and male/female ratio for primary brain tumors in Estonia (1986–1996)

Tumor type	Crude rate		Male/female ratio
	men	women	
Neuroepithelial tumors	4.90 (4.41–5.39)	4.01 (3.60–4.42)	1.22**
All gliomas	4.32 (3.86–4.78)	3.60 (3.21–3.99)	1.2*
Astrocytoma	1.37 (1.11–1.63)	1.34 (1.10–1.58)	1.02
Glioblastoma	2.20 (1.87–2.48)	1.79 (1.51–2.07)	1.23
Oligodendroglioma	0.32 (0.20–0.44)	0.19 (0.10–0.28)	1.68
Ependymoma	0.30 (0.18–0.42)	0.14 (0.06–0.22)	2.14*
Mixed glioma	0.13 (0.05–0.21)	0.14 (0.06–0.22)	0.93
Medulloblastoma	0.29 (0.17–0.41)	0.21 (0.11–0.31)	1.38
Tumors of cranial and spinal nerves	0.39 (0.25–0.53)	0.66 (0.49–0.83)	0.59*
Neurinoma	0.37 (0.24–0.50)	0.59 (0.43–0.75)	0.63*
Meningeal tumors	1.46 (1.19–1.72)	3.32 (2.94–3.70)	0.47***
Meningioma	0.96 (0.74–1.18)	2.77 (2.43–3.11)	0.35***
Hemangioblastoma	0.10 (0.03–0.17)	0.16 (0.08–0.24)	0.63
Malignant lymphomas	0.15 (0.06–0.24)	0.09 (0.03–0.15)	1.67
Sellar region tumors			
Pituitary adenoma[1]	0.42 (0.28–0.56)	0.44 (0.30–0.58)	0.96
Craniopharyngioma	0.10 (0.03–0.17)	0.07 (0.02–0.12)	1.43
No histological confirmation	1.98 (1.67–2.29)	1.80 (1.52–2.08)	1.10
Intracranial tumors	8.62 (7.97–9.27)	9.37 (8.74–10.00)	0.92
Spinal tumors	0.73 (0.54–0.92)	0.89 (0.70–1.08)	0.82
All tumors	9.36 (8.68–10.04)	10.25 (9.59–10.91)	0.91

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Figures in parentheses indicate 95% CI.

[1] Includes 38 unconfirmed cases of pituitary tumors diagnosed clinically as adenomas.

tively) in women (male/female ratios 0.35 and 0.59, respectively).

Average annual age-adjusted incidence rates for various histological types of primary brain tumors in Estonia are shown in table 5. The age-adjusted incidence was 3.41 for gliomas, 1.63 for meningiomas and 8.46 for all primary brain tumors. Among gliomas the most common types were glioblastoma and astrocytoma (incidence rates of 1.58 and 1.27, respectively), oligodendroglioma and ependymoma being less frequent (incidence rate of 0.22 for both). The incidence rate for cases without microscopic confirmation was 1.63.

A comparison of current rates with those of a previous study carried out from 1951 to 1970 suggests that the increase in the incidence rates of intracranial tumors is histology specific (table 6). A significant increase was observed in incidence rates for astrocytoma, glioblastoma and meningioma (incidence rate ratios of 1.49, 1.50 and 1.97, respectively; $p = 0.001$). For age-specific incidence rates, a significant increase is evident across all age groups (table 7), with the increase being most apparent in children, adolescents and age groups over 50 (incidence rate ratio over 1.5).

Table 5. Age-adjusted incidence rates (ASIR) per 100,000 population for brain tumors by histological types in Estonia 1986–1996

Tumor type	ASIR
Astrocytoma	1.27 (1.10–1.44)
Glioblastoma	1.58 (1.39–1.77)
Oligodendroglioma	0.22 (0.15–0.29)
Ependymoma	0.22 (0.15–0.29)
Mixed glioma	0.11 (0.06–0.16)
All gliomas	3.41 (3.13–3.69)
Medulloblastoma	0.32 (0.23–0.41)
Neurinoma	0.40 (0.30–0.50)
Meningioma	1.63 (1.44–1.82)
Pituitary adenoma[1]	0.36 (0.27–0.45)
Other specified	0.96 (0.81–1.11)
No microscopic confirmation	1.63 (1.44–1.82)
All tumors	8.46 (8.02–8.90)

Rates are age-adjusted to the World Standard Population. Figures in parentheses indicate 95% CI.

[1] Includes 38 unconfirmed cases of pituitary tumors diagnosed clinically as adenomas.

Discussion

According to the epidemiological literature [8–15] incidence rates for primary CNS tumors vary greatly (from 4.9 to 15.7/100,000/year, and in Northern Italy 26). This vast range may be explained by differences in inclusion criteria and classification, methods of case ascertainment and the number of patients included, rather than on real variations of incidence in different geographical areas and populations. While most authors agree that incidence rates are influenced by availability of competent medical care, frequency of autopsy, cancer registration level and improvement of brain imaging techniques (CT, MRI) [1, 14], a study of the incidence patterns of nervous system tumors in adults still shows a remarkably consistent dependence on age and race as well as on the sex ratio in different population groups [16]. Proceeding from the above evidence, it appears necessary to carry out epidemiological studies based both on as complete a case ascertainment as possible as well as on clearly defined criteria for different populations and geographical regions.

This study was conducted on the Estonian population of approximately 1.5 million during 11 years (1986–1996), and although we attempted to achieve maximal case ascertainment by using several sources, it must be noted that some cases were most likely missed.

The distribution of pathologically confirmed cases according to histological types in Estonia is in many respects similar to the distribution reported for other geographic regions [15, 17, 18]. In our study gliomas comprised 50% (including glioblastomas 25%, astrocytomas 17%), meningiomas 24% and neurinomas 6% of all CNS tumors. A recent US study [19] based on the National Cancer Data Base shows approximately the same distribution of astrocytoma (18.7%) and glioblastoma (29.6%), with a lower occurrence of meningioma (14.3%) and neurinoma (2.5%). The authors suggest that tumors of benign histologies are underrepresented in the National Cancer Data Base because of insufficient diagnostic accuracy and quality of data coding and entry in some institutions. Some studies [9, 14, 20] have revealed a lower frequency for gliomas (28–38%) and a higher frequency for meningiomas (35–37%). We found that pituitary adenomas accounted for only 2.6% of cases, which is lower than figures in other studies where they accounted for 6–14% [8, 9, 21]. The observed difference may be partly due to low histological confirmation (58%), since inclusion of patients with clinically identified adenoma would increase the figure up to 5.4%.

All studies have confirmed that the incidence of primary tumors, especially neuroepi-

Table 6. Changing incidence rates (IR) over time for primary intracranial tumors in Estonia during 1951–1970 and 1986–1996

Tumor type	1951–1970 intracranial tumors		1986–1996 intracranial tumors		Incidence rate ratio	p value
	n	IR	n	IR		
Astrocytoma	128	0.51	150	0.76	1.49 (1.18–1.89)	0.001
Anaplastic astrocytoma	61	0.25	78	0.46	1.84 (1.32–2.57)	0.001
Glioblastoma	313	1.30	336	1.95	1.50 (1.29–1.75)	0.001
Oligodendroglioma	45	0.18	42	0.25	1.39 (0.91–2.12)	0.125
Ependymoma	34	0.14	24	0.15	1.07 (0.64–1.80)	0.789
All gliomas	678	2.77	651	3.81	1.38 (1.24–1.54)	0.001
Medulloblastoma	45	0.18	42	0.26	1.44 (0.95–2.19)	0.083
Neurinoma	76	0.31	59	0.35	1.13 (0.76–1.65)	0.478
Meningioma	214	0.87	297	1.71	1.97 (1.65–2.35)	0.001
Pituitary adenoma	86	0.35	73	0.43	1.23 (0.90–1.68)	0.195
No histological confirmation	229	0.89	299	1.75	1.97 (1.66–2.34)	0.001
All types	1,454	5.91	1,527	8.93	1.51 (1.41–1.62)	0.001

Rates are age-adjusted to the Estonian Standard Population (1989 census). Figures in parentheses indicate 95% CI.

Table 7. Changing age-specific incidence rates per 100,000 population of intracranial tumors in Estonia 1951–1970 and 1986–1996

Age years	1951–1970		1986–1996		Incidence rate ratio
	cases	age-specific incidence	cases	age-specific incidence	
0–9	95	2.5	96	3.9	1.6 (1.2–2.1)*
10–19	74	2.2	83	3.5	1.6 (1.2–2.2)**
20–29	119	3.0	97	4.1	1.4 (1.1–1.8)*
30–39	204	5.2	164	6.5	1.3 (1.0–1.5)*
40–49	277	8.5	241	11.3	1.3 (1.1–1.6)**
50–59	340	12.5	422	20.6	1.7 (1.4–1.9)**
60–69	270	12.3	322	19.7	1.6 (1.4–1.9)**
≥70	75	4.4	100	7.6	1.7 (1.3–2.3)**
Total	1,454	5.9 (5.9[1])	1,525	9.0 (8.9[1])	1.5 (1.4–1.6)**

* $p < 0.005$, ** $p < 0.001$. Figures in parentheses indicate 95% CI.

[1] Rates were age-adjusted to the Estonian Standard Population (1989 census).

thelial and meningeal tumors, increases with age up to 65 or 70 years [22]. Data concerning the age-specific incidence rate in the elderly are controversial. Several studies [9, 14, 15, 21] have found that maximum incidence occurs in the oldest age group. In a Japanese study [23] of 271 intracranial tumors in elderly people, the incidence rate was 18.1/100,000/year which was significantly higher than in other age groups, meningioma being the most common type (50.6%). Other studies [11, 12, 24, 25] as well as the present research reveal an increasing incidence from the age of 30, reaching a maximum in the age range of 50–69 years, and a decline in the elderly, with gliomas as the most frequent type [2, 4]. The latter trend seems to be an artifact of underdiagnosis influenced by autopsy rates [14, 15], less investigation and diagnostic bias (stroke or dementia being diagnosed more readily than tumor) [8] rather than a real decrease. Helseth [26], suggests that completeness of diagnosis, particularly in the case of the elderly, depends both on autopsy rate and use of imaging techniques. Still, like some other authors [25], we do not believe that the decline in brain tumors in the elderly is explainable mainly as the result of underdiagnosis. Meta-analysis has confirmed that significant differences exist in the incidence of neuroepithelial, meningeal and cranial nerve tumors between men and women, and these cannot be explained by age differences [22]. Some authors have found a higher incidence of primary CNS tumors among men [25]. Percy et al. [14] showed that women have meningiomas more frequently, whereas gliomas and most other neoplasms occur at an equal rate in both sexes. In a study carried out in Central Finland, meningiomas were shown to be 8 times more frequent in women than in men [11]. Our data reveal no significant differences between men and women in the overall incidence of primary CNS tumors. Regarding the incidence rate according to histological types, gliomas were more common in men (with no significant difference when astrocytoma and glioblastoma were treated separately), while meningiomas and tumors of cranial and spinal nerves were more predominant in women as established in most other surveys [12, 17, 27, 28].

Spinal tumors constituted 8.3% of all primary tumors with an incidence rate of 0.8/100,000, which is lower than that presented in the Rochester, Finnish and Icelandic studies [11, 14, 21] and higher than that reported from South East Wales [17]. Spinal tumors show an age-dependent increase in all surveys.

The age-adjusted incidence of 8.46/100,000 for all CNS tumors is comparable to the findings of surveys carried out in Norway, Iceland and Victoria (Australia). This is higher than that reported from the eastern Netherlands, southern England (children were excluded) and Washington, D.C., and lower than that found in Finland, Rochester, Minn., and the Lothian region of Scotland [8, 13, 15, 21, 25, 27, 29]. The incidence of two main tumor types, gliomas and meningiomas, was 3.4 and 1.6, respectively. Generally, the incidence of gliomas is about twice as high as that of meningiomas (except in Norway where the incidence ratio of gliomas to meningiomas was 4:1), with higher incidences found in studies where the incidence of all brain tumors was higher as well. We surmise that a low autopsy rate and a lower overall incidence of CNS tumors in the elderly, influenced by less investigation and diagnostic bias, account for the overall lower incidence of brain tumors in Estonia.

Cancer Registration

The incidence rates of primary CNS tumors are higher in our study compared with the figures reported by the ECR. Until recent-

ly the ECR has recorded only histologically malignant brain tumors excluding meningiomas, neurinomas, pituitary and other benign tumors. The traditional distinction with respect to malignancy is clinically not specific to brain tumors as benign tumors of intracranial location may have as poor a prognosis as malignant tumors. Of the 1,665 patients included in our study, 996 (60%) were identified in the ECR as having CNS tumors. Since most gliomas are considered malignant, 98% of them were found in the registry. Differences were revealed in the histological subgroups of gliomas: some types were overreported (oligodendroglioma 124%, astrocytoma 106%) or underreported (glioblastoma 91%), which was probably caused by classification errors and can be solved by collaboration between clinicians, pathologists and the cancer registry personnel [10]. Since according to the ECR the proportion of meningiomas and neurinomas was very low (11 and 9%, respectively), this means that the total incidence of CNS tumors is significantly underestimated. We compared our data with those reported from Scotland (50% of all primary tumors and 85% of malignant tumors identified in the Scottish Cancer Registry) [30] and Norway (errors in overall incidence rates and for main tumor groups accounting for 0.3% of the total) [31]. It becomes evident that the accuracy of registration is different; therefore, there may be limitations in using a cancer registry to identify incidence of primary brain tumors.

Changes in Incidence Rates

Comparison of current rates with those of the 1951–1970 study carried out in Estonia as well as with those of other studies [3, 32] suggests that the increase in the incidence rates of intracranial tumors is histology specific. A significant increase was observed in incidence rates for astrocytoma, glioblastoma and meningioma. In meningiomas and partly also in low-grade astrocytomas, these data support the argument that the increase in rates may be due to the fact that some tumors that previously went undetected are now diagnosed [26]. It is also important to note that the use of different histological classifications cannot be disregarded either. Glioblastoma generally presents easily recognizable symptoms which makes diagnosis less dependent on imaging technology. In his series Helseth [33] revealed a higher increase in incidence for meningioma than for glioma, while a Connecticut study [10] established a higher increase for astrocytoma, meningioma and ependymoma. Analysis of the data of the US Surveillance, Epidemiology and End Results Program [34] showed a statistically significant increase only for lymphoma in men. In Estonia, 59% (126 cases) of meningiomas were diagnosed at autopsy (with an autopsy rate of 30%) from 1951 to 1970, i.e. in the period before dramatic changes in diagnostic technology had taken place. In our study, most cases (70%) diagnosed post mortem were identified as gliomas and only 8% (7 cases) were meningiomas (at the same time the autopsy rate has decreased). Evidently, most of these tumors had been misdiagnosed like other CNS diseases, and only a small part were incidental findings. Taking into account the low proportion of autopsies in Estonia, silent tumors are likely to be underestimated. Comparing the age-specific incidence rates of our study with those of a previous Estonian study, a significant increase is evident in all age groups, whereas studies performed in Norway [12], Connecticut [35] and France [36] revealed a significant increase only in the over 60 age group. This suggests that some of the increase can be accounted for by recent medical interest in and better understanding of neurological disorders in the elderly, as well as by improvement in diagnostic procedures. Desmeules et

al. [37] have demonstrated that new imaging technology is responsible for detection of about 20% of brain tumors in both younger and older patients. Proceeding from our data, one cannot exclude that some part of the increased incidence in all ages and in some histological types (glioblastoma) is the consequence of environmental effects or some etiological factors. The increase across all age groups suggests a real increase in parallel with the increase related to more effective detection owing to improved case ascertainment with new imaging technology. However, further studies are required to define whether this increase is real and continuous in Estonia. For the sake of better comparability of data, we agree with Counsell and Grant [22] who suggest the use of unified methodology and who have worked out provisional guidelines for further research into the incidence of primary brain tumors.

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Seizure Disorders in Patients with Brain Tumors

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Key Words
Seizures · Brain tumor · Clinical manifestations · Pathology · Location

Abstract
The aim of this study was to analyze the clinical data of patients with epileptic seizures and diagnosed brain tumors. Analysis included 711 patients with primary and secondary brain tumors. 165 (23%) patients had experienced at least one seizure before tumor diagnosis. The mean time from the first epileptic seizure to tumor diagnosis was 16 months. The patient's age, location and pathology of tumor were associated with occurrence of seizures. Seizures were more common in patients aged 30–50 years. Tumors involving the frontal, frontoparietal, temporal and frontotemporal lobes were associated with occurrence of seizures. According to the histological diagnosis, patients with mixed gliomas (62%), oligodendrogliomas (53%) and astrocytomas (42%) experienced seizures most frequently.

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Introduction

The incidence of epilepsy in patients with brain tumors is approximately 30% [1]. Patients with slowly growing chronic lesions are more likely to have a seizure disorder, with an incidence as high as 75% [1]. Le Blanc and Rasmussen [2] found the highest seizure incidences in patients with oligodendrogliomas (92%), astrocytomas (70%), meningiomas (67%) and glioblastomas (37%). According to reported data, seizures as the first manifestation of brain tumors are very variable (11–50%) [2, 3]. The aim of our study was to analyze the clinical data of patients with epileptic seizures and diagnosed brain tumors.

Patients and Methods

We analyzed retrospectively 721 patients with primary and secondary intracranial brain tumors diagnosed between 1991 and 1995, in Estonia. Data were collected from the medical records of the neurosurgical departments of Tartu Maarjamõisa Hospital and Tallinn Mustamäe Hospital (the only two specialized neurosurgical departments in Estonia). Additional material was obtained from the Estonian Cancer Registry (founded in 1978). The medical records were reviewed for the following information: patient gender, age at diagnosis, nature and duration of signs and symptoms (e.g. time of the first seizure and the first symptom), histology, grade and location of

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the tumor. A sign or a symptom was recorded if any physician described its presence. As clinical data varied in quality and quantity, they were grouped in the simplest way: headache, papilledema, neurological deficit and mental disturbances. Seizure types were classified as simple or complex partial, secondarily generalized and unclassified (seizures were not described adequately to be classified according to the guidelines of the International League against Epilepsy) [4]. Information on tumor location was obtained from CT or MRT and from surgery reports. Tumor location was analyzed by individual sites and as supra- and infratentorial.

Classification of Tumors

Histological classification was drawn up using the histological classification of brain tumors approved by the World Health Organization (WHO) [5]. Patients were analyzed for tumor pathology and grade according to individual WHO histological diagnosis as well as groups. The following categories were used: low-grade astrocytoma, anaplastic astrocytoma, glioblastoma and other gliomas; meningioma; other primary brain tumors; metastatic tumors; cases without a microscopically confirmed diagnosis.

Multivariable analysis was used to identify the factors that associate with seizures. The tested categories were patient age at diagnosis, gender, tumor histology as well as anatomical location of tumor and duration of symptoms. χ^2 and Fisher's exact tests were used in comparisons involving category variables, and the Wilcoxon rank-sum test was employed for continuous variables. All analyses were performed by using a PC. SAS Version 6.12 (SAS Institute, Cary, N.C., USA).

Results

General

We analyzed 721 patients with diagnosed brain tumors. Out of these, 711 patients remained in the study group, while 10 patients were excluded because of incomplete data. 71% of tumors were revealed by CT and 14% were revealed by MRI scans. 165 (23.2%) patients experienced at least one seizure before their tumor diagnosis, 546 patients had no history of seizures. The mean age in the seizure group was 47.4 years (95% CI 45.0–49.8 years) ranging from 2 to 83 years, in the seizure-free group 49.2 years (95% CI 47.4–50.1 years) ranging from 1 to 87 years. Age was associated ($p < 0.05$) with the presence of seizures. The occurrence of seizures was remarkably higher in the 30- to 39-year ($p < 0.005$) and 40- to 49-year ($p = 0.001$) age groups (table 1). The male-to-female ratio was 1:1.04 in the seizure group and 1:1.2 in patients without seizures. Gender was not associated with occurrence of seizures.

Presentation and Duration

Epileptic seizures were the single presenting symptom at diagnosis in 44 and the first manifestation in 123 patients; 121 patients presented simultaneously seizures and some other sign or symptom (table 2). Patients with seizures showed a significantly lower incidence of neurological deficit, headache ($p = 0.001$) and mental disturbances ($p < 0.05$) compared with seizure-free patients (table 3). We found no association between occurrence of epileptic seizures and increased intracranial pressure. In

Table 1. Incidence of seizures and patients' ages (n = 711)

Age	All patients	Patients with seizures	
		n	%
0–9 years	37	5	13.5
10–19 years	31	4	12.9
20–29 years	36	10	27.8
30–39 years	70	26	37.1*
40–49 years	123	43	35.0**
50–59 years	196	39	19.9
60–69 years	170	30	17.7
≥ 70 years	48	8	16.7
Total	711	165	23.2

* $p = 0.004$, ** $p = 0.001$.

Table 2. Clinical characteristics of seizures (22.9% of all patients)

Seizures	n	Patients with seizures (n = 165), %	Of all patients (n = 721), %
As the first manifestation	123	74.6	17.1
As the single presentation	44	26.7	6.1
At diagnosis	35	21.2	4.9
One seizure	22	13.3	3.1
Recurrent (≥ 2 seizures)	95	57.6	13.2

Table 3. Presenting signs and symptoms (n = 711)

Other symptoms	Without seizures (n = 546)	With seizures (n = 165)
Headache	367	58**
Papilledema	141	31
Neurological deficit	429	92**
Mental disturbances	126	25*

* $p < 0.05$, ** $p = 0.001$. Seizures with other symptoms: n = 121. Patients could have more than one symptom.

Table 4. Tumor pathology and occurrence of seizures (n = 711)

	Patients	With seizures	
		n	%
Low-grade astrocytoma	53	22	41.5***
Anaplastic astrocytoma	30	13	43.3**
Glioblastoma	106	27	25.5***
Oligodendroglioma	19	10	52.6**
Ependymoma	8	2	25
Mixed glioma	8	5	62.5*
Medulloblastoma	15	0	0
Schwannoma	27	0	0
Meningioma	124	47	37.9***
Anaplastic meningioma	8	1	12.5
Hemangioblastoma	7	0	0
Lymphoma	6	1	16.7
Metastatic tumor	105	16	15.2*
Without histology	138	17	12.3***

The pathology of 59 tumor patients with very low incidence (<5) is not given.

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

Table 6. Tumor location and the incidence of seizures (n = 711)

Location	Patients	With seizures	
		n	%
Frontal lobe only	83	32	38.5***
Frontal and parietal	38	22	57.9***
Frontal and temporal	36	16	44.4**
Frontal, temporal and parietal	11	5	45.4
Parietal lobe only	64	22	43.4*
Temporal lobe only	52	21	40.4**
Temporal and parietal	49	11	22.5
Occipital lobe only	9	1	11.1
Occipital and parietal or temporal	26	4	15.4
Central structures	30	6	20.0
Parasagittal region	29	12	41.4*
Hypophyseal region	46	0	0
Other supratentorial	30	4	13.3
Multilocular	55	6	10.9*
Infratentorial	148	3	2.0***

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

Table 5. Classification of seizures (n = 151)

Seizure type	Patients	
	n	%
Secondarily generalized	77	51.0
Simple partial		
Without secondary generalization	41	27.2
With secondary generalization	14	9.3
Complex partial		
Without secondary generalization	14	9.3
With secondary generalization	1	0.7
Both simple partial and complex partial	1	0.7

Seizures were classifiable in 151 of 164 patients.

26.7% of seizure patients, seizures were their only complaint and in 74.6% as the first manifestation. 13% of patients presented only one seizure, 55% presented recurrent seizures and 21% had seizures at diagnosis (tumor was diagnosed less than 1 month after presentation). The median time from the first epileptic seizure to diagnosis was 3 months, with a mean of 16 months (range from 0 to 240 months). Most brain tumors (72.8%) were diagnosed during the first year after seizure presentation, while 5 patients had had seizures for more than 10 years (one of them for 20 years). Mean time was different ($p = 0.02$) for seizures as the single presenting sign (mean time 18 months) and for seizures presenting with other symptoms (mean time 12 months).

Pathology

According to the histological typing, the most common histological types were glioblastoma, meningioma and low-grade astrocytoma (table 4). Patients with mixed gliomas (62%), oligodendrogliomas (53%), anaplastic astrocytomas (42%), low-grade astrocytomas (41%) and meningiomas (37%) experienced seizures most frequently. The association between tumor pathology and seizures at presentation was highly significant ($p < 0.001$).

Seizure Types

Seizures could be classified in 91.5% (151 cases) of patients with epilepsy (table 5). Secondarily generalized and simple partial seizures, existing as the only type in a patient were the most common. Epileptic seizures were of complex partial type and simple partial type with secondary generalization in 9.3% of cases.

Location

Of the 711 tumors, 71% had supratentorial and 21% had infratentorial location, 8% were multilocular; in the seizure group 94% of tumors were supratentorial, 2%

were infratentorial and 4% were multilocular. The incidence of seizure occurrence for different lobes differed significantly ($p < 0.001$; table 6). Higher incidence of seizures were found in tumors involving the frontoparietal (58%), frontotemporal (44%), parasagittal (41%) and temporal (40%) regions. Seizures occurred in only 11% of patients with tumors of the occipital lobe and the multilocular tumors. Only 3 patients out of 148 with infratentorial tumors experienced seizures. Association with seizure occurrence was found for tumors involving the frontal and frontoparietal, temporal and frontotemporal, as well as the parietal and parasagittal regions. Seizures as the first manifestation of the tumor had no significant association with tumor location.

Multivariable Analysis

In multivariable analysis, patient gender and age were not associated with seizures. Categories that influenced the occurrence of seizures were the duration of symptoms, tumor location and histology. Epileptic seizures occurred more frequently in patients with long duration of symptoms (6 months and more) who were diagnosed as having astrocytoma, anaplastic astrocytoma, some other glioma or meningioma. Infrequently seizures occurred in tumors of infratentorial, central or multiple location.

Discussion

Brain neoplasms account for about 4–5% of all cases with seizure disorders [6, 7]. Of cerebral neoplasms 25–50% present with seizures [7–9]. Seizures are often reported as being the first and sometimes the only presenting symptom of intracranial tumors [8–10]. In meningiomas 27% of the patients have been reported to have epileptic seizures as their initial symptom [11]. Lühdorf et al. [12] found seizures to be the first sign of brain tumor in 50% of patients who developed seizures after the age of 60 years. In our study, only 17% of all tumor patients had seizures as their first complaint. This difference may be caused by the retrospective design of this study including mistakes in the chronology of symptoms. The diagnosis of brain tumor is often made after years from onset of seizures. Several authors have reported the mean interval from onset of seizures to tumor diagnosis or surgery to be from 2 to 11 years with a maximum of more than 20 years [13–16]. In a study carried out in 6 countries [17] including 1,178 glioma and 331 meningioma cases, there was an increased risk associated with epilepsy at least 2 years before brain tumor diagnosis in glioma patients. In epilepsy of more than 20 years' duration, the risk was significantly weaker. No association between meningioma and previous epilepsy history was observed. In our series, the mean time from the first epileptic seizure to tumor diagnosis was 16 months, ranging from several days to 20 years, while it was significantly longer in patients whose only presenting complaint was seizures (18 months) compared with patients who had seizures plus other symptoms and signs (12 months). Shorter duration in our series may be due to the fact that our study group included patients with both acute and chronic epilepsy. The exact cause for the long duration of seizures prior to tumor diagnosis is still unclear.

Data on the incidence of seizure activity and patients' age are controversial. The age distribution of cases depends largely on the biological type of the tumors [3]. Shady et al. [8] found the 50% seizure incidence with no association between age at diagnosis and seizure activity in children with supratentorial astroglial neoplasms. In their study of 3,291 children with brain tumors, Gilles et al. [18] reported that 14% of them experienced seizures, while the incidence increased monotonically throughout childhood. In adults with malignant gliomas, seizures at presentation were found more commonly in patients younger than 50 years [9]. In a study of 1,028 gliomas, the frequency of epilepsy at presentation decreased with age in high-grade glioma patients and increased with age in low-grade glioma patients to a plateau in the fourth decade of life [19]. In our study of all intracranial tumors, there was no significant difference between children and young adults compared with seizure and seizure-free patients. Seizures were significantly more common in the third and fourth decades of life.

Concerning tumor pathology, seizures are reported most frequently in patients with low-grade, slowly growing tumors and tumors involving the cerebral cortex. The most common tumor types are low-grade astrocytomas, mixed gliomas and oligodendrogliomas. Pace et al. [20] found preoperative seizures even in 83% of supratentorial low-grade astrocytomas. Gangliogliomas are found with a surprisingly higher frequency than could be expected [7, 8, 10]. In our series, the most common tumor types were mixed gliomas (63%), oligodendrogliomas (53%) and astrocytomas (42%) which is comparable with the results obtained by other authors. There was no significant difference in the incidence of low-grade astrocytomas (41.5%) and anaplastic astrocytomas (43%). In case of glioblastomas seizure incidence was low (26%); these patients experience other symptoms and signs more commonly. The incidence of seizures was the lowest for metastatic tumors

(15%) and in cases without histological confirmation (12%).

With regard to tumor location, seizures have been reported to occur in 22–68% of patients with supratentorial tumors involving most commonly the temporal and frontal lobes [1, 9, 10] and in only 1–6% of patients with infratentorial lesions [8, 18]. Superficial tumors involving the isocortex without known deep extension were associated with the highest rate of seizures significantly more often than if the tumor had a deep extension [18]. Seizure rates associated with frontal or temporal tumors were also significantly reduced in the presence of deep extensions of the tumor.

In supratentorial, convex meningiomas, evidence of severe peritumoral edema significantly contributes to preoperative epilepsy [11]. In our series, the higher incidence of seizures involving the frontoparietal, frontotemporal, parasagittal and temporal regions was evident. We did not take into account peritumoral edema or cortical location of a tumor as data concerning these entities were not sufficient.

The reported incidences of neurological findings in seizure patients are quite different. Most commonly, patients with low-grade tumors and chronic epilepsy have normal findings on neurological examination. In their series of chronic epilepsy, Morris et al. [10] found 97% of patients without neurological signs. Spencer et al. [21] described neurological abnormality in 12 of 19 neoplasm patients with intractable partial epilepsy. In our series of 165 patients, 44 (27%) had seizures as the single symptom and 123 (75%) as the first manifestation. Controversy between these data may be due to the difference between study groups. In our study group, 121 (73%) patients experienced at least one other symptom; among them, 58 (35%) had headache, 31 (19%) papilledema, 92 (56%) neurological deficit and 25 (15%) mental disturbances. Occurrence of neurological deficit, headache and mental disorders was remarkably higher in patients without seizures. Comparison of seizure and seizure-free patients revealed no difference in the incidence of increased intracranial pressure, which is supported by other authors [18].

The probability of diagnosing an underlying tumor in a patient with epilepsy is related to seizure type, with simple and complex partial seizures being the most common [2, 8, 9, 21]. The authors who have compared several seizure etiologies and seizure types have found only simple partial seizures to be significantly related to tumor etiology [21, 22]. Many authors consider tumor location the most important factor [3]. In our series, all patients with classifiable seizures had partial seizures with or without secondary generalization, 37% had simple partial, 10% had complex partial and 51% had secondarily generalized seizures.

In conclusion, the presence of a tumor should always be considered in patients with seizure disorders, especially in case of simple partial and secondarily generalized seizure types. Other symptoms, which may be of diagnostic value, may appear several months or years later, whereas in a remarkable proportion of patients they are lacking completely. Seizures at presentation are significantly correlated with tumor pathology and location.

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III

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Survival of patients with primary CNS tumours in Estonia

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Abstract

We studied a population-based survey that included 1417 patients with a primary central nervous system (CNS) tumour diagnosed in Estonia between 1986 and 1996. Survival rates at 1 and 5 years and median survival by histology and patient's age at diagnosis were estimated. Median survival time for all tumours was 33.2 months and 1- and 5-year survival rates were 59.3 and 46.0%, respectively. In multivariate analysis, younger age, better clinical condition (i.e. a Karnofsky Performance Status (KPS) score of 60 and more) and tumour histology were all dependent prognostic factors for better survival. Risk of death was more than 8 times greater for glioblastoma (Risk Ratio (RR) 8.31) and approximately seven times greater for anaplastic astrocytoma (RR 7.22) and other gliomas (RR 5.74) compared with meningiomas. Comparing the first (1986–1989) and the third (1994–1996) time periods, statistically significant improvements in survival occurred for all tumours and astrocytomas. Declines in survival during the second period (1990–1993) were statistically significant for all the tumour groups, but the most striking decrease took place in patients with glioblastoma. Age-specific rates showed that the increase in survival was more evident for patients aged between 45 and 64 years. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Survival; CNS tumours; Estonia; Prognostic factors

1. Introduction

Most of the published studies concerning survival of central nervous system (CNS) tumours are hospital-based and restricted to gliomas or their histological subtypes. Very few population-based studies including survival of all primary benign and malignant tumours have been published. Increased mortality rates for malignant CNS tumours, particularly among the elderly, have been attributed to improved diagnostic techniques and increased environmental carcinogens [1]. A study from the Estonian Cancer Registry [2] reported the 5-year relative survival rate among patients of diagnosed CNS tumours in Estonia (1983–1987) as 11.2% for males and 24.6% for females and the mortality rate (1988–1992) as 4.9 and 3.5 per 100 000 population, respectively. Since meningiomas and other histologically benign CNS tumours were not recorded until 1998, the registry can be considered complete with regard to malignant tumours, but incomplete concerning benign tumours. In the recent EUROCARE survey [3], including malignant CNS tumours diagnosed between 1985 and 1989 in 17 European countries, the mean European age-standardised 5-year relative survival was 17% in men and 20% in women with markedly lower rates in Scotland, Estonia and Poland. In the USA in 1986–1991, 5-year relative survival of malignant CNS tumours was 20% according to the Surveillance, Epidemiology and End Results (SEER) data [4].

Generally, in CNS tumours, survival rates decline with increasing age at diagnosis. Other patient-related prognostic factors for survival are gender and the clinical condition of the patient. Histology and anatomical location are important tumour-related agents in estimating survival. The prognosis for patients with benign meningiomas is better for females and depends on the patient's age [5,6], being more favourable for patients below 60 years.

Clinically significant improvements in the survival of patients with CNS tumours has taken place over the last two decades [3,4]. Improvements in survival have been histology-specific, being more evident in medullo-

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blastomas, astrocytomas and oligodendrogliomas. For glioblastomas, the most frequent primary CNS tumour, no striking improvement has taken place.

The aim of this study was to determine the relative 1- and 5-year survival rates of patients with primary CNS tumours diagnosed in Estonia between 1986 and 1996, to examine variations in the different age and histological groups and evaluate changes in the length of survival that have occurred over recent years.

2. Patients and methods

2.1. Data collection and selection

The study was based on the Estonian population of approximately 1.5 million served by two neurosurgical centres (Tartu University Clinics and Tallinn Mustamäe Hospital) which admit all patients suspected of intracranial tumours. Our data included all cases of primary CNS tumours diagnosed at these hospitals from 1986 to 1996. We obtained information about patient's gender, age at diagnosis, clinical condition, tumour location, histological type and follow-up results from case histories, autopsy protocols and pathology reports. Additional information on date and cause of death was received from the Estonian Cancer Registry and the Estonian State Statistical Office.

We selected 1524 patients diagnosed between 1986 and 1996 with CNS tumours by using the International Classification of Diseases for Oncology (ICDO) [7] including the following topography codes: C71.0–C71.9 for brain, C70.0 and C70.9 for meninges, C72.2–C72.9 for cranial nerves and other intracranial parts of the CNS, C75.1–C75.3 for pituitary gland, pineal gland and craniopharyngeal duct. 88 cases discovered at autopsy, 2 patients of incomplete data and 17 patients diagnosed with another tumour previously or during the follow-up period were excluded.

2.2. Data classification

The remaining 1417 tumours were classified according to the histopathological type of the CNS tumour following the scheme approved by the World Health Organization (WHO) [8]. All histologically obscure cases (with the majority of pathological material having been preserved) were retrospectively overviewed by a neuropathologist. The study population was divided into four age groups: children ($\leqslant 20$ years at diagnosis), younger adults (21–44 years), older adults (45–64 years) and the elderly ($\geqslant 65$ years), reflecting the fact that CNS tumours have specific characteristics including histology, behaviour, anatomical location depending on age, and survival rates are varying by age at diagnosis. The clinical functional ability of the patient before therapy was assessed according to the Karnofsky Performance Status scale. Three groups were considered: score 80–100, 60–70 and less than 60.

2.3. Time periods

Our study included CNS tumours diagnosed in Estonia between 1986 and 1996. Follow-up of vital status was until 1 January 1998. Follow-up was based on the data of the Estonian Cancer Registry and the Estonian State Statistical Office.

To estimate potential changes in 1-year survival rates over time in the different age and histological groups, three time periods were defined according to the year of diagnosis: 1986–1989, 1990–1993 and 1994–1996. Advances in diagnostic procedures (the introduction of computerised tomography (CT) and magnetic resonance imaging (MRI)) should not affect potential changes in survival, as the first CT scan was introduced in 1983 in Estonia. Changes in 5-year survival were not estimated because of too short a follow-up period.

2.4. Data analysis

Survival time was calculated from the date of diagnosis. One- and 5-year survival rates were estimated overall, by the above-mentioned age groups, for each histological group using the life table method with intervals of 1 month. Kaplan–Meier estimation was used to compute the median length of survival by gender, age and clinical condition, histology and location of tumour, based on the whole study period. The logrank-test was used to compare survival in the subgroups. Proportional hazards models (Cox's models) were used to determine the effect of different patient (gender, age, clinical condition before treatment) and tumour-related (anatomical location, histology) factors on survival. All analyses were performed by using PC: SAS Version 6.12 (SAS Institute, Cary, NC, USA).

3. Results

3.1. General data

The 1417 patients included 628 men and 789 female with CNS tumours. The median age at referral was 49 years (range 1–83 years) for men and 52 years (range 4 months–84 years) for women.

The distribution and median survival of patients by gender, age, tumour location and clinical condition are shown in Table 1. Univariate analysis found that females ($P=0.002$), patients of younger age (<45 years, $P=0.0001$) and better clinical condition before treatment ($P=0.0001$) had the highest survival. Concerning tumour location, the worst prognosis was associated with those

Table 1
Characteristics of 1417 brain tumour patients diagnosed in Estonia from 1986 to 1996

Characteristic	Patients *n* (%)	*n* Deaths	Median survival (months)
Gender			
Male	629 (44.4)	371	18.6
Female	788 (55.6)	396	62.8
			$P=0.002$
Age group (years)			
≤20	191 (13.5)	90	88.3
21–44	344 (24.3)	140	136.9
45–64	677 (47.8)	401	15.8
≥65	205 (14.5)	136	5.7
			$P=0.0001$
Location			
Frontal	164 (11.6)	107	17.8
Parietal	113 (8.0)	63	14.7
Temporal	108 (7.6)	71	13.9
Two or more lobes	336 (23.7)	231	10.4
Central structures and ventricles	58 (4.1)	36	7.3
Other supratentorial	175 (12.4)	82	nc
Pituitary or pineal	114 (8.0)	28	nc
Infratentorial	311 (21.9)	133	nc
<Location not available	38 (2.7)		
			$P=0.0001$
KPS			
80–100	370 (26.1)	105	nc
60–70	558 (39.4)	289	48.0
<60	321 (22.7)	251	5.3
KPS not available	168 (11.9)		
			$P=0.0001$

nc, median could not be computed, over 50% survived; KPS, Karnofsky Performance Status.

of central structures or ventricular location and the best prognosis with infratentorial and pituitary location.

3.2. Distribution by histology

The distribution of tumours by histology according to the WHO classification of CNS tumours with the corresponding ICDO morphology codes are presented in Table 2. The most frequently reported histologies were glioblastoma (21.0%), meningioma (18.8%) and astrocytoma (9.2%).

3.3. Survival by histology

One- and 5-year survival rates and median survival time by histology are presented in Table 3. The overall 1-year survival was 59.3%, 5-year survival 46.0% and median survival 33.2 months. Tumours with the most favourable prognosis included pituitary adenoma (89.2%, both 1- and 5-year survival rates), meningioma (1-year survival 85.9% and 5-year survival 82.4%) and neurinoma (76.4%, both survival rates). Patients with glioblastoma and anaplastic astrocytoma had the worst outcome (5-year survival 8.6 and 15.8%, respectively). In contrast, approximately half of the low-grade astrocytoma patients (49.8%) survived beyond 5 years. The long-term prognosis for patients with medulloblastoma, ependymoma, oligodendroglioma and mixed gliomas appeared similar to each other (22.5, 26.9, 28.1 and 28.1%, respectively), while median survival was not so homogenous.

3.4. Survival by age at diagnosis

Survival rates by age at diagnosis for all CNS tumours and selected histology groups are given in Table 4. Including all histological groups, the worst outcome occurred in patients aged 65 years or older. Decreased survival associated with older age at diagnosis was generally observed in all histological groups. Differences were the most evident in the astrocytoma group (1-year survival 16.7% in the elderly and 87.0% in children, 5-year survival rates of 16.7 and 79.3%, respectively), where survival decreased with age.

3.5. Comparison of 1-year survival rates in the three time periods

Table 5 shows the 1-year survival rates for astrocytoma, glioblastoma, meningioma, tumours without histological verification and all tumours by patient age group during the three time periods (1986–1989,

Table 2
Distribution of CNS tumours by histology in Estonia (1986–1996)

Histology by WHO	ICDO Morphology Codes	Cases		
		n (%)	Male (%)	Female (%)
Tumours of neuroepithelial tissue				
Astrocytoma (G1–2)	9400/3, 9410/3, 9411/3, 9420/3, 9421/3	138 (9.2)	64 (10.2)	66 (8.4)
Anaplastic astrocytoma	9401/3	72 (5.6)	36 (5.7)	44 (5.6)
Glioblastoma	9440/3, 9441/3, 9442/3	297 (21.0)	159 (25.3)	138 (17.5)
Oligodendroglioma	9450/3	24 (1.7)	16 (2.5)	8 (1.0)
Anaplastic oligodendroglioma	9451/3	14 (0.9)	6 (1.0)	8 (1.0)
Ependymoma	9391/3, 9393/1	12 (0.8)	7 (1.1)	5 (0.6)
Anaplastic ependymoma	9392/3	10 (0.7)	6 (1.0)	4 (0.5)
Mixed gliomas	9382/3	23 (1.6)	11 (1.8)	12 (1.5)
Choroid plexus tumours	9390/0, 9390/3	9 (0.6)	6 (1.0)	3 (0.4)
Neuroepithelial tumours of uncertain origin	9430/3, 9443/3, 9381/3	12 (0.8)	4 (0.6)	8 (1.0)
Pineal tumours	9361/1, 9362/3	3 (0.2)	3 (0.5)	0 (0.0)
Medulloblastoma	9470/3, 9471/3, 9472/3	39 (2.8)	20 (3.2)	19 (2.4)
Tumours of cranial and spinal nerves				
Neurinoma	9560/0	55 (3.9)	18 (2.9)	37 (4.7)
Neurofibroma	9540, 9550/0	4 (0.3)	1 (0.2)	3 (0.4)
Tumours of the meninges				
Meningioma	9530/0, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9530/1, 9538/1	267 (18.8)	62 (9.9)	205 (26.0)
Anaplastic meningioma	9530/3	17 (1.2)	4 (0.6)	13 (1.6)
Haemangioblastoma	9161/3	21 (1.5)	8 (1.3)	13 (1.6)
Malignant lymphomas	9590/3	18 (1.3)	10 (1.6)	8 (1.0)
Germ cell tumours	9064/3, 9070/3, 9080/1, 9084/3	4 (0.3)	2 (0.3)	2 (0.3)
Cysts and tumour-like lesions	9084/0	9 (0.6)	7 (1.1)	2 (0.3)
Pituitary adenoma	8140/0	35 (2.5)	15 (2.4)	20 (2.5)
Pituitary carcinoma	8140/3	3 (0.2)	2 (0.3)	1 (0.1)
Craniopharyngioma	9350/1	15 (1.1)	8 (1.3)	7 (0.9)
All others	[a]	38 (2.7)	20 (3.2)	18 (2.3)
Unclassified tumours (no histological verification)	8000/0, 8010, 8000/1, 8001/1, 8000/3, 8001/3, 8002, 8003	278 (19.6)	134 (21.3)	144 (18.3)
Total		1417 (100)	628 (100)	789 (100)

WHO, World Health Organization.
[a] Amount of cases in each histological group was very small, morphology codes are not given.

Table 3
One- and 5-year survival rates (SR), and median survival time (ST) by histology for patients with primary brain tumours in Estonia (1986–1996)

Histology	*n*	1-year SR (%) (95% CI)	5-year SR (%) (95% CI)	Median ST (months)
Astrocytoma (G1–2)	138	64.5 (60.4–68.6)	49.8 (45.2–54.4)	54.2
Anaplastic astrocytoma	72	36.1 (30.4–41.8)	15.8 (11.3–20.4)	8.3
Glioblastoma	297	28.0 (25.4–30.6)	8.6 (6.8–10.3)	6.2
Ependymoma	22	50.0 (39.3–60.7)	26.9 (16.5–37.4)	10.7
Oligodendroglioma	38	60.5 (52.6–68.5)	28.1 (18.7–37.3)	22.9
Mixed gliomas	23	56.5 (46.2–66.9)	28.1 (18.2–37.9)	22.4
Medulloblastoma	39	53.9 (45.9–61.8)	22.5 (15.3–29.7)	12.7
Meningioma	284	85.9 (83.9–88.0)	82.4 (80.0–84.8)	nc
Neurinoma	55	76.4 (70.6–82.1)	76.4 (70.6–82.1)	nc
Pituitary adenoma	35	89.2 (78.4–94.3)	89.2 (78.4–94.3)	nc
Craniopharyngioma	15	73.3 (61.9–84.8)	52.4 (37.4–67.3)	nc
Other specified	121	62.6 (57.9–67.3)	43.8 (38.8–48.8)	36.5
Without histology	278	61.9 (59.0–64.8)	53.8 (50.7–56.8)	nc
Total	1417	59.3 (58.0–60.6)	46.0 (44.6–47.4)	33.2

95% CI, 95% confidence interval; nc, median could not be computed, over 50% survived.

1990–1993 and 1994–1996). Comparing the first (1986–1989) and the second (1990–1993) time periods, a statistically significant decline in the 1-year survival rate for glioblastoma (32.7 and 17.9%, respectively) and for all tumours (59.8 and 53.6%, respectively) was observed. In meningiomas, a similar result was evident only for those aged between 45 and 64 years. Comparing the first (1986–1989) and the third (1994–1996) time periods no significant changes in survival, either for meningioma or glioblastoma, have taken place. There were statistically significant improvements in the survival rates comparing the first (1986–1989) and the third (1994–1996) time periods for patients with astrocytoma and for all tumours. Age-specific rates showed that the increase in survival was more evident in the older adults, between 45 and 64 years, both, for all tumours (51.8% in 1986 through to 1989 and 64.8% in 1994 through to 1996) and for astrocytomas (29.4 and 83.3%, respectively). In patients with astrocytomas, a slight, but statistically not significant improvement can be observed in the younger adults, aged between 21 and 44 years.

3.6. Multivariate analysis

In multivariate analysis, older age at diagnosis, patient's clinical condition (Karnofsky Performance Status <60), tumour histology and period of diagnosis were independent prognostic factors for survival (Table 6). Risk of death was more than 8 times greater for glioblastoma (Risk Ratio (RR) 8.31, $P=0.0001$), about seven times greater for anaplastic astrocytoma (RR 7.22, $P=0.0001$) and more than 5 times greater for other gliomas (RR 5.74, $P=0.0001$). The best prognosis was found for those with neurinomas, but these patients still had a significantly greater risk of death (RR = 1.87, $P=0.0376$) compared with those with meningiomas.

4. Discussion

This analysis provides population-based survival estimates for both histologically benign and malignant CNS tumours in Estonia. One- and 5-year survival rates and the prognostic importance of patient- and tumour-related factors were analysed in 1417 patients with CNS tumours. The distribution of pathologically-confirmed cases according to histological type in Estonia is in many respects similar to the distribution reported for other geographical regions [6,9]. In our study, gliomas comprised 50% (including glioblastoma 21.0%, astrocytoma 14.8%), meningioma 20.0% and neurinoma 3.9% of all CNS tumours. A recent US study [10] based on the National Cancer Data Base (NCDB), a data set that is limited to hospital reporting, has found approxi-

Table 4
One- and 5-year survival rates (SR) by age at diagnosis for selected histology groups

Histology	Age at diagnosis					
	≤20			21–44		
	n	1-year SR (95% CI)	5-year SR (95% CI)	*n*	1-year SR (95% CI)	5-year SR (95% CI)
Astrocytoma (GI–2)	46	87.0 (82.0–91.9)	79.3 (73.1–85.6)	43	76.7 (70.3–83.2)	64.6 (56.8–72.5)
Anaplastic astrocytoma	4	[a]	[a]	21	52.4 (41.5–63.3)	26.8 (16.8–36.8)
Glioblastoma	12	41.7 (27.5–55.9)	21.6 (8.9–34.3)	55	43.6 (37.0–50.3)	13.8 (8.6–19.0)
Other glioma	13	76.9 (65.2–88.6)	46.2 (30.3–62.0)	30	63.3 (54.5–72.1)	40.8 (30.8–50.8)
Meningioma	3	[a]	[a]	58	93.1 (89.8–96.4)	93.1 (89.8–96.4)
Neurinoma	5	[a]	[a]	18	88.9 (81.5–96.3)	88.9 (81.5–96.3)
Other specified	65	58.5 (52.4–64.6)	35.6 (29.3–41.8)	53	87.8 (83.1–92.4)	77.1 (70.6–83.6)
Without histology	43	69.8 (62.8–76.8)	55.3 (47.6–62.9)	66	81.8 (77.1–86.6)	72.8 (67.1–78.6)
Total	191	70.2 (66.9–73.5)	52.9 (49.1–56.6)	344	74.7 (72.4–77.1)	60.9 (58.1–63.7)
	45–64			≥65		
	n	1-year SR (95% CI)	5-year SR (95% CI)	*n*	1-year SR (95% CI)	5-year SR (95% CI)
Astrocytoma (G1–2)	37	37.8 (29.9–45.8)	13.2 (6.2–20.3)	12	16.7 (5.9–27.4)	16.7 (5.9–27.4)
Anaplastic astrocytoma	39	25.6 (18.7–32.6)	8.6 (3.6–13.5)	8	[a]	[a]
Glioblastoma	173	24.3 (21.0–27.5)	6.3 (4.3–8.3)	57	21.1 (16.6–26.5)	7.0 (3.6–10.4)
Other glioma	31	51.6 (42.6–60.6)	18.3 (11.2–25.4)	9	[a]	[a]
Meningioma	182	83.5 (80.8–86.3)	79.8 (76.7–82.9)	41	85.4 (79.9–90.9)	75.0 (66.6–83.4)
Neurinoma	23	73.9 (64.8–83.1)	73.9 (64.8–83.1)	9	[a]	[a]
Other specified	79	59.5 (54.0—65.0)	44.8 (38.9–50.6)	13	46.2 (32.4–60.0)	30.8 (18.0–43.6)
Without histology	113	56.6 (52.0–61.3)	49.0 (44.2–53.9)	56	42.9 (36.3–49.5)	39.3 (32.7–45.8)
Total	677	53.5 (51.6–55.4)	40.7 (38.7–42.6)	205	42.4 (39.0–45.9)	32.3 (28.9–35.8)

95% CI, 95% confidence interval.
[a] Not given due to a very small number (<10) of cases.

Table 5
1-year survival rates (SR) by age for patients with low-grade astrocytoma, glioblastoma, meningioma and without histological confirmation and all brain tumours during the three time periods. Estonia 1986–1996

Histology	Age group (years)	Year of diagnosis		
		1986–1989 SR (95% CI)	1990–1993 SR (95% CI)	1994–1996 SR (95% CI)
Astrocytoma (G1–2)	⩽20	88.2 (80.8–96.1)	81.3 (71.5–91.0)	92.3 (84.9–99.7)
	21–44	76.5 (66.2–86.8)	58.3 (44.1–72.6)	92.9 (86.0–99.7)
	45–64	29.4 (18.4–40.5)	28.6 (16.5–40.6)	83.3 (68.1–98.5)
	⩾65	25.0 (3.4–46.7)	[a]	[a]
	All ages	61.8 (55.3–68.4)	54.6 (47.0–62.1)	79.5 (73.0–86.0)
Glioblastoma	⩽20	[a]	[a]	[a]
	21–44	45.0 (33.9–56.1)	22.2 (12.4–32.0)	52.9 (40.8–65.1)
	45–64	27.1 (21.8–32.5)	17.1 (12.6–21.6)	33.3 (25.1–41.5)
	⩾65	25.0 (14.2–35.8)	9.1 (3.0–15.2)	31.6 (20.9–42.2)
	All ages	32.7 (28.2–37.2)	17.9 (14.2–21.5)	36.0 (30.5–41.5)
Meningioma	⩽20	[a]	[a]	[a]
	21–44	90.5 (84.1–96.9)	95.8 (91.7–99.9)	92.3 (84.9–99.7)
	45–64	86.0 (81.4–90.6)	74.6 (69.1–80.1)	90.3 (86.6–94.1)
	⩾65	[a]	84.6 (74.6–94.6)	81.8 (73.6–90.0)
	All ages	88.1 (84.6–91.6)	81.2 (77.3–85.1)	88.9 (85.7–92.1)
Without histology	⩽20	57.9 (46.6–69.2)	71.4 (58.7–83.5)	90.0 (80.5–99.5)
	21–44	87.5 (80.8–94.3)	83.3 (72.6–94–1)	76.7 (69.0–84.4)
	45–64	52.5 (44.6–60.4)	67.7 (59.3–76.1)	52.4 (44.7–60.1)
	⩾65	69.2 (56.4–82.0)	31.8 (21.9–41.8)	38.1 (27.5–48.7)
	All ages	64.6 (59.7–69.5)	60.8 (55.3–66.3)	60.2 (55.4–65.0)
Total	⩽20	65.7 (59.9–71.5)	72.5 (67.1–77.8)	72.7 (66.7–78.7)
	21–44	78.1 (74.3–81.8)	69.4 (65.0–73.9)	76.1 (72.1–80.1)
	45–64	51.8 (48.6–55.0)	46.0 (40.3–49.2)	64.8 (61.3–68.2)
	⩾65	47.1 (44.8–54.1)	37.0 (31.3–42.6)	44.4 (38.9–50.0)
	All ages	59.8 (57.6–62.1)	53.6 (51.3–55.9)	64.9 (62.7–67.2)

95% CI, 95% confidence interval.
[a] Not given due a very small number of cases.

Table 6
Multivariate analysis (Cox model). Factors predicting survival in patients with brain tumours

Factor	Variable	Parameter estimate	*P* value	Risk ratio (in best Cox model)
Gender	Male versus female		ns	1.02
Age (years)	as a continuous variable	0.014	0.0001	
Karnofsky Performance Status				
<60%	60–100% taken as a base category	0.600	0.0001	1.82
Not specified		0.552	0.0001	1.74
Period of diagnosis				
1990–1993	1986–1989 taken as a base category		ns	
1994–1996		0.190	0.0280	0.83
Histology				
Astrocytoma	Meningioma taken as a base	1.429	0.0001	4.18
Anaplastic astrocytoma	category for all types	1.977	0.0001	7.22
Glioblastoma		2.117	0.0001	8.31
Other gliomas		1.748	0.0001	5.74
Neurinoma		0.624	0.0376	1.87
Other specified		1.497	0.0001	4.47
Without histology		1.166	0.0001	3.21
Localisation				
Hemispheres	Infratentorial location taken as		ns	
Central structures	a base category		ns	
Other			ns	
Not specified		1.461	0.0001	4.31

ns, non significant.

mately the same distribution concerning astrocytoma (18.7%), with a lower occurrence of meningioma (15.5%) and higher occurrence of glioblastoma (29.6%).

Gender differences in survival have previously been reported for non-malignant CNS tumours [5,6,11]. The prognosis for patients with benign meningiomas is better for females below 60 years of age [11,12]. The cause of this difference is unknown.

Most authors report no association between prognosis and patient gender in malignant CNS tumours [13,14].

In our series, including all CNS tumours, survival is considerably longer among females: median survival 62.8 months compared with only 18.6 months for males. This difference can be explained by the variations in the histologial distribution in men and women. There is a higher incidence of benign meningiomas in females together with a better prognosis for this type of tumour. The poorer survival of men is attributable to the relatively greater frequency among men of the more aggressive tumour types. In multivariate analysis, no difference in prognosis could be detected for male and female patients.

The importance of age and histology in predicting the survival from CNS tumours has been well documented in studies from the US [4,11,15–19], as well as studies from other countries [6,13,20,21]. Generally, survival rates decline with increasing age at diagnosis, both in benign and malignant tumours. A similar pattern was found in our study. The survival pattern of patients aged 45–64 years has been reported to resemble more closely that of older rather than younger patients [22]. However, some authors suggest that the influence of age is overestimated. Shaw and colleagues [23] suggest that the patient's age is not correlated with an improved survival in mixed gliomas.

In low-grade astrocytomas, the median survival time is reported to be approximately 5 years, similar to our result of 4.5 years (54.2 months). Long-term survival rates at 5 years have been documented as ranging between 30 and 60% [6,10,24], depending primarily on the inclusion criteria and study design. A hospital-based study of the NCDB [10] including over 60 000 patients with a CNS tumour, found 5-year survival rates of 30.3% for astrocytoma and 77.4% for pilocytic astrocytoma. Our data show 5-year survival rates of 49.8% for low-grade astrocytomas.

The overall median survival of grade 3 and 4 astrocytomas in our study was less than 1 year. However, Salcman and colleagues [17] reported that the median survival of grade 3 and 4 astrocytomas for patients less than 40 years of age, who received some form of therapy beyond surgery and radiation, was more than 2 years. Furthermore, younger patients with grade 3 astrocytomas generally have a better survival, extending over 4 years [25]. A Finnish study [13] reported the median survival of grade 3 and 4 gliomas to be 24.0 and 7.7 months, respectively. Barker and co-authors [15] reported a median survival rate of glioblastoma patients of 11.2 months, and 1- and 5-year survival rates of 48 and 4%, respectively. Our study determined a similar median survival rate for glioblastoma of 6.2 months and for anaplastic astrocytoma of 8.3 months, together with 1-year survival rates of 28.0 and 36.1% and 5-year survival rates of 8.6 and 15.8%, respectively. These data suggest patients had a poorer outcome than in other studies, especially those with anaplastic astrocytomas. The relative poor median survival of patients with anaplastic astrocytoma may be explained by difficulties in making this histological diagnosis. The biggest divergence in the results of neuropathologists lies in the diagnosis of anaplastic astrocytoma.

In oligodendrogliomas, the median survival time has been reported to be between 3 and 8 years [14,26,27]. Our data show patients had a survival rate of approximately 2 years, which is significantly lower, but comparable with the median survival of non-irradiated patients (26.5 months) in a Norwegian study [26]. Although patients with benign tumours have a more favourable prognosis compared with patients with malignant tumours, there is still significant mortality associated with these histologies. In our study, both the 1- and 5-year survival rates for meningiomas was approximately the same as those reported in the Finnish study [12] (83 and 79%, respectively). The Norwegian study reported survival following the dignosis of benign meningiomas to be 93% at 1 year and 95% at 5 years [5]. The US study [11], based on 9000 meningioma cases, found a 5-year survival rate of 69%. The clinical functional ability or Karnofsky score of the CNS tumour patient has been shown to be a strong predictor of outcome in most studies [14–16,18,23,28]. In our study, the patient's clinical condition was a statistically significant prognostic factor in both univariate and multivariate analyses.

Of course, appropriate therapies are among the main determinants of prognosis. The better outcome in the socio-economically advanced societies is due to earlier diagnosis and the combined effect of more effective therapies, including centralisation of treatment and dissemination of effective therapeutic protocols. In Estonia, the first CT scan was introduced in 1983 and MRI scans in early 1990s. Up to the present day, joint treatment protocols for patients with CNS tumours are lacking in Estonia. In this study, we did not investigate the association between treatment strategies and outcome. We suppose that in most cases only surgery, possibly a gross total resection was used. Post-operative radiation therapy and adjuvant chemotherapy or a combination is for certain reasons (e.g. the lack of defined treatment protocols and insufficient co-operation between surgeons and oncologists) not so widely used in Estonia.

4.1. Changes in incidence rates

During the last 20 years an overall slight increase in survival of patients with malignant tumours has been found both in EUROCARE study [3] and SEER programme [4]. Most improvement is confined to the first year after diagnosis. Age-specific rates show that the increase is more evident in younger patients, up to 54 years of age. Concerning tumour histology, the improvement is evident in medulloblastomas, in adults with astrocytomas and oligodendrogliomas [29]. The improvements in survival reflect improvements in therapy and the treatment taking place at an earlier stage of disease, where new and better diagnostic techniques have helped in identifying the tumours earlier.

In meningiomas, both short-term and long-term survival has recently improved [5]. The improved 1-year survival rate is likely to be caused by improved operative techniques and postoperative care. The increased long-term survival may reflect the likelihood that more patients with small meningiomas are being diagnosed early since CT became available. In benign meningiomas, a small tumour size is one of the factors independently associated with an increased survival time [11].

Our survey follows the example of above-mentioned studies, statistically significant improvements in 1-year survival rates were found for all tumours and low-grade astrocytoma comparing the first and the third time periods. Age-specific rates showed that the increase was more evident in patients aged between 45 and 64 years. A decline in survival during the second period (1990–1993) is statistically significant for all tumours, but the most striking decrease took place for patients with glioblastoma. This discrepancy may reflect economic factors and the reorganisation of the health care system at the beginning of the 1990s. It was a period of extensive change in Estonia, in both the political and economical systems, including healthcare. Delays in diagnosis, especially in rural areas where availability of medical care was limited, may also have caused the poorer outcome during the second period. Older patients are also more likely to be diagnosed as having dementia or vascular disease by their family doctors than as having CNS tumours.

In conclusion, the outcome of CNS tumours in Estonia, especially malignant tumours, is somewhat worse compared with other studies. The causes of such a tendency, especially with regard to treatment strategies, deserves further investigation.

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IV

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Kesknärvisüsteemi kasvajad

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Aive Liigant, Toomas Asser, Ain-Elmar Kaasik – *Tartu Ülikooli Närvikliinik*

kesknärvisüsteemi kasvajad, klassifikatsioon, haigestumus, elulemus, prognoos

Kesknärvisüsteemi (KNS) kasvajaid iseloomus-tab histoloogiliste vormide mitmekesisus, kliiniliste avalduste kompleksus ja sõltuvalt kasvaja histoloogilisest struktuurist ning lokalisatsioonist head või tagasihoidlikud ravitulemused. See kõik on tekitanud segadust ja nihilismi nii arstide kui ka patsientide hulgas. Eesti Vähiregistri andmetel (28) ei kuulu aju- ja kesknärvisüsteemi kasvajad Eestis ei naiste ega meeste seas kümne sagedamini esineva vähipaikme hulka. Erandiks on alla kolmekümneaastaste vanuserühm, kellel on ajukasvajad sageduselt 2.–3. kohal. Suremuse statistikale toetudes on ajukasvajad vähkkasvajate seas 9.–10. kohal. Eesti

Vähiregister registreeris kuni 1998. aastani ainult histoloogiliselt pahaloomulisi kasvajavorme, mistõttu registri statistikas ei kajastu oluline hulk histoloogiliselt healoomulisi kasvajaid (meningioomid, neurinoomid, hüpofüüsi adenoomid). Traditsiooniline kasvajate jagamine hea- ja pahaloomulisteks on ajukasvajate suhtes kliinilisest aspektist sobimatu, kuna sõltuvalt oma lokalisatsioonist võivad ka intrakraniaalsed healoomulised kasvajad sarnaselt pahaloomulistega olla tõsise prognoosiga. Nagu eespool mainitud, on ajukasvajate histogeneetiline struktuur väga mitmekesine, olles seotud patsiendi soo ja vanuse ning kasvaja lokalisatsiooni ja prognoosiga. Näiteks lapse- ja noorukieas esineva väikeaju astrotsütoomi ravi annab reeglina häid tulemusi ja prognoos on hea, samal ajal kui glioblastoomiga patsient elab ravist sõltumata harva üle ühe aasta.

Klassifikatsioonid

Esmakordne püüe ajukasvajaid süstematiseerida pärineb 19. sajandist, kui Virchow eraldas glioomid sarkoomidest ja kirjeldas mõningaid glioome (ependümoom). Kaasaegne klassifikatsioon põhineb Bailey ja Cushingi (1926) töödel. Bailey ja Cushing uurisid KNS-i erinevate rakuliste komponentide embrüogeneesi, püüdes seejärel klassifitseerida kasvajaid vastavalt morfoloogilistele staadiumitele, mille need rakud läbivad ontogeneesis. Nende klassifikatsioon sisaldas 14 kasvajatüüpi, mis enamjaolt on esindatud ka tänapäevastes klassifikatsioonides. Eesmärgiga lihtsustada klassifikatsiooni ja võtta arvesse anaplaasia olemasolu viis Kernohan koos kaastöötajatega (1949) sisse glioomide 4-järgulise maliigsuse hindamise süsteemi (sobis eelkõige astrotsütoomile ja ependümoomile), kus I staadium oli kõige healoomulisem ja IV staadium kõige pahaloomulisem. Kernohani süsteemil olid aga eelkõige prognostilisest küljest oma puudused: kuna anaplaasia on sageli väga lokaalne ja kasvaja areng dünaamiline (võimalik on üleminek ühest staadiumist teise), siis ei pruugi kasvaja biopsia peegeldada kogu kasvaja struktuuri, samuti ei arvestatud süsteemi tegemisel kasvaja lokalisatsiooni (22). Patsiendi prognoos ei sõltu mitte ainult kasvaja morfoloogilisest ehitusest ja selle maliigsuse astmest, vaid oluline on arvesse võtta ka kliinilisi aspekte ja seda igal üksikul juhul eraldi (27).

Esimene rahvusvaheline Maailma Tervishoiuorganisatsiooni (MTO) poolt heaks kiidetud KNS-i kasvajate histoloogiline klassifikatsioon (26) avaldati 1979. aastal. See klassifikatsioon on konsensus, mis on saavutatud aastaid kestnud uuringute ja mitmete koolkondade vahelise diskussiooni tulemusel. 1993. aastal ilmus selle klassifikatsiooni parandatud variant (15), mis on lühendatult ära toodud tabelis 1.

Histogeneetiline struktuur

Kõige sagedasem ajukasvajate rühm on glioomid, moodustades erinevatel andmetel 40–67% (nendest pool kuni 2/3 on glioblastoomid) kõikidest primaarsetest ajukasvajatest, järgnevad meningioomid (9–35%), neurinoomid (1–11%) ja hüpofüüsi adenoomid (5–18%) (18, 25). Enamikus uuringutes on glioomide ja meningioomide suhe 2 : 1 või 3 : 1 glioomide kasuks. Rochesteri uuringus (18), kus oli suur lahangute hulk (70%), leiti 57% kõikidest meningioomidest lahangul ja vastav suhe oli 0,8 : 1 meningioomide kasuks. See viitab meningioomide elupuhusele aladiagnoosimisele. Metastaasid moodustavad kuni 41% kõikidest KNS-i kasvajatest, kusjuures on alust arvata (toetudes lahanguleidudele), et märkimisväärne hulk metastaasidest jääb kliiniliselt diagnoosimata (18, 22). Lastel vanuses alla 15 eluaasta moodustavad glioomid 70–85% kõikidest KNS-i kasvajatest, sagedamini esinevad astrotsütoom (22–36%), medulloblastoom (15–17%), kraniofarügioom (6–13%) ja ependümoom (3–14%) (27). Harva on lastel meningioomi, neurinoomi ja hüpofüüsi adenoomi.

Haigestumus

Vastavalt kirjanduse andmetele kõiguvad haigestumuse näitajad erinevates populatsioonides ja geograafilistes piirkondades küllalt suurtes piirides: 4–16 juhtu 100 000 elaniku kohta aastas (2, 3, 6, 8, 10, 19, 20, 29), Põhja-Itaalias (5) isegi kuni 26 juhtu (vt tabel 2). Reeglina on haigestumus suurem sotsiaalmajanduslikult paremini arenenud piirkondades, kus on hea tehniline varustus (kompuutertomograafia, magnetresonantstomograafia) ja kättesaadav meditsiiniline abi, väljakujunenud ja korralikult töötav registerteenistus (vähiregistrid) ning suurem lahangute arv (1, 18). Samuti mõjutab haigestumuse näitajaid läbiviidud epidemioloogiliste uuringute metoodika: sissearvamiskriteeriumid, haigusjuhtude arv ja kogumisviis, kasutatavad klassifikatsioonid. Etnilised, rassilised ja soolised erinevused viitavad võimalikule hormonaalsete, geneetiliste ja keskkonna faktorite toimele ajukasvajate tekkes. On leitud (1), et valgetel on üldiselt suurem risk haigestuda ajukasvajatesse kui mustanahalistel. USA-s erinevatel rassidel läbiviidud uuringud (13) on näidanud, et afroameeriklastel esineb võrreldes valgetega rohkem meningioome ja hüpofüüsi kasvajaid ning vähem glioome. Haigestumuse soolise erinevuse ilmekaks näiteks on glioomide sagedam esinemine meestel ja meningioomide ülekaal naistel. Spetsiifiliste hormonaalsete häirete seost primaarsete ajukasvajate tekkega ei ole aga õnnestunud siiani tõestada. Teadaolevalt sõltub haigestumus ajukasvajatesse patsientide vanusest. Haigestumus on suhteliselt stabiilne lapse- ja noorukieas, langeb pisut 30. eluaastates, alates 40. aastatest hakkab aga kiiresti tõusma, saavutades maksimumi 50. ja 70. eluaasta vahel. Andmed haigestumuse kohta vanemaealistel on vastuolulised. Üks osa uurijaid (9, 20) väidab, et

Tabel 1. **Kesknärvisüsteemi kasvajate histoloogiline klassifikatsioon (MTO, 1993)**

1. Neuroepiteliaalsed kasvajad	1. Ajukelmete kasvajad
1.1. Astrotsütaarsed kasvajad	1.1. Meningoteliaalsed
1.1.1. Astrotsütoom	1.1.1. Meningioom (11 varianti)
1.1.2. Pahaloomuline astrotsütoom	1.1.2. Pahaloomuline meningioom
1.1.3. Glioblastoom	1.2. Mesenhümaalsed mittemeningoteliaalsed kasvajad
1.2. Oligodendrogliaalsed kasvajad	1.3. Primaarsed melanotsütaarsed kasvajad
1.2.1. Oligodendroglioom	1.4. Ebaselge histogeneesiga kasvajad
1.2.2. Pahaloomuline oligodendroglioom	2. Lümfoomid ja hemopoeetilise koe kasvajad
1.3. Ependümaalsed kasvajad	3. Idurakkudest pärinevad kasvajad
1.3.1. Ependümoom	4. Tsüstid ja tuumorilaadsed moodustised
1.3.2. Pahaloomuline ependümoom	5. Türgi sadula piirkonna kasvajad
1.4. Segatüüpi glioomid	5.1. Hüpofüüsi adenoom
1.5. Soonpõimiku kasvajad	5.2. Kraniofarüngioom
1.6. Ebaselge päritoluga neuroepiteliaalsed kasvajad	6. Regionaalsete kasvajate lokaalsed ekstensioonid
1.7. Neuronaalsed ja segatüüpi neuronaalgliaalsed kasvajad	7. Metastaatilised kasvajad
1.8. Käbikeha kasvajad	8. Klassifitseerimata kasvajad
1.9. Embrüonaalsed kasvajad	
2. Kraniaal- ja spinaalnärvide kasvajad	
2.1. Neurinoom	
2.2. Neurofibroom	

vanemaealistel haigestumus väheneb, kusjuures kõige sagedasemaks histoloogiliseks tüübiks on glioom. Teised autorid (5, 18, 16) leiavad, et 65-aastaste ja vanemate hulgas haigestumus pigem suureneb ja peamiseks tüübiks on meningioom. Arvatakse, et väiksemate haigestumusnäitajate üheks põhjuseks on, et ei pöörata piisavalt tähelepanu vanurite piltdiagnostilisele uurimisele, kuna traditsiooniliselt diagnoositakse neil

Tabel 2. **Primaarsete KNS-i kasvajate haigestumuskordajad (100 000 elaniku kohta) erinevates epidemioloogilistes uuringutes**

	Piirkond	Uuringu aeg	Haigestumuskordaja
Davis 1996	Connecticut, Utah, Massachusetts, Missouri	1985-1989	9,4*
Helseth 1988	Norra	1955-1984	M 8,2 N 6,8**
Counsell 1996	Lothian, Šotimaa	1989-1990	15,3
Van der Sanden 1998	Holland (kesk-, idaosa)	1989-1994	M 6,5 N 4,4***
Preston-Martin 1993	Victoria, Austraalia	1982-1990	M 8,8 N 8,1***
Radhakrishnan 1995	Rochester, Minnesota	1970-1989	12,5*
D'Alessandro 1995	Valle d'Aosta, Itaalia	1986-1991	M 21,6 N 28,1*
Fogelholm 1984	Kesk-Soome	1975-1982	13,6*
Cole 1989	Wales (kaguosa)	1981-1987	5,6
Standardimiseks kasutatud rahvastikud:	** kohaliku riigi standardrahvastik*	*** Euroopa standardrahvastik*	**** maailma standardrahvastik*

pigem dementsust või insulti kui ajukasvajat.

Trendiuuringud on näidanud, et viimastel aastakümnetel on haigestumus ajukasvajatesse oluliselt suurenenud. Siiani käivad vaidlused selle üle, kas tegemist on tõelise haigestumuse tõusu või diagnostika paranemisest tingitud artefaktiga. Rochesteri uuringus (20) leitakse, et suurenenud on ainult magnetresonants- ja kompuutertomograafilisel uuringul juhuleidudena diagnoositud ajukasvajate hulk. Desmeules koos kaastöötajatega (7) näitab, et piltdiagnostika tehnilise külje paranemine mõjutab haigestumusenäitajaid ainult 20% ulatuses. Tõus on kõige ilmsem üle 65-aastaste patsientide vanusegrupis, osaliselt põhjendatakse seda paranenud diagnostikaga selles vanusegrupis. Samuti on leitud, et haigestumuse tõus erineb histoloogiliste tüüpide osas. Sõltuvalt uuringust esineb suurim tõus kas meningioomide (12) või glioomide (k.a glioblastoom) rühmas (9). Samas on glioomide, eriti nende maliigsete vormide diagnoosimine vähem sõltuv hea tehnoloogia olemasolust, kuna kliiniline leid ilmneb haiguse varasemas staadiumis.

Haigestumus Eestis

Eestis on haigestumust primaarsetesse intrakraniaalsetesse kasvajatesse uurinud Virve Lukas, kelle andmetel oli ajavahemikus 1951 – 1969 vastav näitaja 5,9 juhtu 100 000 elaniku kohta aastas (17). Haigestumus näitas suurenemistendentsi, olles esimesel kümnendil 5,0 ja teisel kümnendil 6,7. Kõige sagedasemaks histoloogiliseks tüübiks oli glioblastoom (haigestumus 1,3), järgnesid meningioom ja atrotsütoom (haigestumus vastavalt 0,9 ja 0,5). Eesti Vähiregistri andmetel põhinevad uuringud (28) annavad kesknärvisüsteemi kasvajate haigestumuskordajaks 100 000 inimese kohta ajavahemikus 1988 – 1992 meestel 5,5 ja naistel 4,4, kusjuures arvesse ei ole võetud healoomulisi kasvajaid. Tartu Ülikooli Kliinikumi Närvikliiniku praegune uurimisprojekt hõlmab Eestis ajavahemikus 1986 – 1996 diagnoositud intrakraniaalseid ja -spinaalseid kasvajajuhte. Haigestumus primaarsetesse kesknärvisüsteemi kasvajatesse 100 000 elaniku kohta on meestel 9,4 ja naistel 10,3; glioomide korral on vastavad näitajad 4,3 ja 3,6 ning meningioomide korral 1,0 ja 2,8. Viimaste andmete võrdlusel V. Lukase poolt toodud haigestumusega (arvestatud on ainult primaarseid intrakraniaalseid kasvajaid, näitajad on standarditud vastavalt Eesti standardrahvastikule 1989. a) ilmneb statistiliselt oluline haigestumuse suurenemine kõikides vanusegruppides ja mõningates histoloogilistes gruppides (astrostütoom, glioblastoom ja meningioom). Samal ajal on haigestumus ependümoomi, medulloblastoomi, neurinoomi ja hüpofüüsi adenoomi püsinud suhteliselt stabiilsena. Osaliselt on haigestumuse tõusu põhjuseks (eriti astrotsütoomide ja meningioomide korral) kindlasti diagnostika paranemine. Seda näitab asjaolu, et V. Lukase uuringus moodustasid enamuse lahangul diagnoositud juhtudest meningioomid, käesolevas uuringus aga glioomid. Võttes arvesse haigestumuse suurenemist kõikides vanusegruppides ja maliigsete glioomide hulga kasvamist, ei saa eitada ka

mõne teise etioloogilise faktori või keskkonna toimet haigestumuse tõusule.

Elulemus ja seda mõjutavad tegurid

Ajukasvajate korral on elulemust oluliselt vähem uuritud kui haigestumust. Kõige laiaulatuslikumad ja põhjalikumad on Euroopa 45 vähiregistril põhineva EUROCARE ja USA-s SEER (*Surveillance, Epidemiology and End Results*) programmi raames läbiviidud uuringud (21, 23). Vaatamata suurtele piirkondlikele erinevustele haigestumuses, on elulemus pahaloomuliste ajukasvajate korral ühtviisi madal kõikides uuringutes. Siiski on leitud, et alates 70. aastatest, kui hakati laialdasemalt kasutama radio- ja kemoteraapiat, on elulemus mõningate harvem esinevate kasvajavormide (medulloblastoom) osas paranenud. Teiste, sagedamini esinevate histoloogiliste tüüpide, nagu glioblastoom, vastav näitaja on aga jäänud praktiliselt muutumatuks. Mõningast elulemuse paranemist põhjendatakse varasema ja paranenud diagnostikaga ning efektiivsema raviga (eriti nooremate patsientidel). Vastavalt EUROCARE programmi tulemustele (sisaldab ainult maliigseid ajukasvaja vorme) oli ajavahemikus 1985-1989 Euroopa keskmine 5 aasta suhteline elulemusmäär meestel 17% ja naistel 20%. Kõige kõrgem oli meeste elulemus Soomes (21%) ja naiste elulemus Saksamaal (26%), madalaimad näitajad olid meestel Eestis ja Poolas (vastavalt 8% ja 10%) ning naistel Šotimaal (13%). Trendiuuringud on näidanud vähest elulemuse paranemist, seda just esimesel aastal pärast diagnoosimist. Sarnane positiivne trend esineb ka nooremates vanusegruppides. Patsientide vanust peetakse üheks oluliseks ajukasvajate prognostiliseks faktoriks. Teadaolevalt on vanus omakorda oluliselt seotud ajukasvajate histoloogiliste tüüpide esinemissagedusega. Nooremas eas esineb sagedamini kõrgemalt diferentseerunud gliialähtega kasvajaid, samuti alluvad mõningad selles vanusegrupis sagedamini esinevad maliigsed vormid (medulloblastoom) paremini radio- ja kemoteraapiale. Uuringud on näidanud, et elulemus pahaloomuliste ajukasvajate korral on meestel mõnevõrra halvem kui naistel (14, 21). Seda seletatakse bioloogiliselt agressiivsemate kasvajavormide sagedasema esinemisega meestel, samuti naiste parema bioloogilise vastupanuga haigustele. Ravi suhtes on andmed vastuolulised, kuna selles vallas puuduvad siiani prospektiivsed randomiseeritud uuringud, mis tõestaksid ühe või teise ravimeetodi statistiliselt olulist mõju elulemusele. Mõned autorid (14) on siiski näidanud, et postoperatiivset kiiritusravi saanutel on esimese aasta prognoos parem kui teistel patsientidel. Pahaloomuliste ajukasvajate kõige olulisemateks prognostilisteks faktoriteks peetakse haige vanust ja kliinilist seisundit ning kasvaja histoloogilist tüüpi.

Elulemust meningioomide korral on uuritud veelgi vähem. Norras aastatel 1975-1992 läbiviidud uuringul (11) oli viie aasta suhteline elulemusmäär 95% (maliigsetel vormidel 49%), Soomes aastatel 1953-1984 oli vastav näitaja kõikidel vormidel kokku 79% (24). Viimati mainitud uuringud näitavad, et elulemus on meningioomide korral viimastel aastakümnetel seoses kompuutertomograafia ja magnetresonantstomograafia kasutusele võtmisega oluliselt suurenenud, sõltudes kasvaja histoloogiast, patsiendi vanusest ning kliinilisest seisundist ja kasvaja eemaldamise ulatusest operatsioonil. Prognoos on reeglina hea alla 75-aastastel kliiniliselt heas seisundis ja operatsioonil täielikult eemaldatud kasvajaga meningioomihaigetel. Maliigseid meningioome esineb harva (erinevatel andmetel 1-10%), sagedamini nooremas eas meestel ning nende prognoos on oluliselt halvem kui teistel vormidel. Meningioomi lokalisatsiooni otsest seost elulemusega leitud ei ole (14).

Kokkuvõte

KNS-i kasvajate haigestumuse ajaliste, geograafiliste, vanuseliste ja sooliste erinevuste olemuse väljaselgitamiseks on tehtud rida metanalüüse (1, 4), mis näitavad uurimismetoodika olulist mõju tulemustele. Siiani ei ole lõplikku selgust haigestumuse suurenemise põhjustes. Edaspidiste ajaliste muutuste hindamiseks on vajalik jätkata pikema ajavahemiku jooksul ja võimalikult sarnase metoodikaga läbiviidud epidemioloogilisi uuringuid.

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Summary
Tumours of the central nervous system

The most modern classifications of brain tumours are based upon that of Bailey and Cushing. The first World Health Organization classification was published in 1979. Subsequently some disagreements have persisted and slightly modified classifications have been published later (the last classification in 1993). Incidence rates for primary brain tumours vary in a wide range (4-16/100,000/ year), while higher rates are generally found in socioeconomically advanced societies with good availability of medical care, better organized registries of data collection and possibly higher autopsy rate. The frequency of primary brain tumours, especially in the elderly, has increased substantially during the past two decades.

Comparison of the data of two epidemiological studies carried out in Estonia suggests that increase in the incidence rates of primary intracranial tumours has occurred from the fifties till the nineties. Increase in incidence rates is histology-specific and is evident in all age groups. Survival in case of primary malignant brain tumours is very low in all countries. The mean European 5-year relative survival rate is 17% for men and 20% for women. Better prognosis has been found in younger patients, which can be attributed to particular histotypes occurring mostly in this age. Other important prognostic factors are the clinical condition of a patient and the histological type of tumour. The 5-year relative survival rate of meningiomas is between 80 and 90% depending on the histological type and the extent of resection of tumour, as well as on the patient`s age and clinical condition.

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One child, born in 1990
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Education

1971–1983	Tartu M. Härma Secondary School
1983–1989	Medical Faculty of the University of Tartu
1989–1991	Internship in neurology at the Department of Neurology and Neurosurgery, Maarjamõisa Hospital
1994–2000	Postgraduate student at the Department of Neurology and Neurosurgery, University of Tartu

Special courses

1998	Salzburg Cornell Seminar in neurology
2000	European Cooperation Neurology Workshop

Professional employment

1991–1999	Jõgeva County Hospital, neurologist
1998–1998	Jõgeva County Hospital, chief of the neurological department
1994–1997	Tartu University, Department of Neurology and Neurosurgery, laboratory assistent
2000–	University of Tartu, Department of Neurology and Neurosurgery, clinical assistant
2000–	Tartu University Clinics, Department of Neurology, neurologist

Scientific work

Research fields: epidemiology of central nervous system tumours
Total: 19 publications, 9 presentations in international scientific conferences.
Membership: L. Puusepp Society of Neurologists and Neurosurgeons, World Federation of Neurology, European Federation of Neurological Societies.

ELULOOKIRJELDUS

Aive Liigant

Kodakondsus:	Eesti
Sünd:	18. Novembril 1964 Tartus
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Haridus

1971–1983	M. Härma nim. Tartu 2. Keskkool
1983–1989	Tartu Ülikooli arstiteaduskond, ravi eriala
1989–1991	internatuur Tartu Maarjamõisa Haigla neuroloogia ja neurokirurgia osakonnas
1994–2000	doktorantuur Tartu Ülikooli Närvikliinikus

Erialane täiendus

1998	Cornelli neuroloogiaalane seminar Salzburgis
2000	EFNS-i poolt korraldatud neuroloogia töötuba

Erialane teenistuskäik

1991–1999	Jõgeva Haigla, neuroloog
1998–1998	Jõgeva Haigla, osakonnajuhataja
1994–1997	TÜ Närvikliinik vanemlaborant
2000–	Tartu Ülikooli Närvikliinik, assistent
2000–	Tartu Ülikooli Kliinikum, Närvikliinik, arst-õppejõud

Teadustegevus

Peamiseks uurimisvaldkonnaks on kesknärvisüsteemi kasvajate epidemioloogia. Ilmunud on 19 publikatsiooni, 9 ettekannet rahvusvahelistel konverentsidel.
L. Puusepa nim. Eesti Neuroloogide ja Neurokirurgide Seltsi liige, Maailma Neuroloogide Föderatsiooni liige, Euroopa Neuroloogia Seltside Assotsiatsiooni liige

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