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Relative survival of patients with non-malignant central nervous system tumours: a descriptive study by the Austrian Brain Tumour Registry

A Woehrer*[,1], M Hackl[2], T Waldhör[3], S Weis[4], J Pichler[5], A Olschowski[6], J Buchroithner[6], H Maier[7], G Stockhammer[8], C Thomé[9], J Haybaeck[10], F Payer[11], G von Campe[12], A Kiefer[13], F Würtz[13], G H Vince[14], R Sedivy[15], S Oberndorfer[16], F Marhold[17], K Bordihn[18], W Stiglbauer[19], U Gruber-Mösenbacher[20], R Bauer[21], J Feichtinger[22], A Reiner-Concin[23], W Grisold[24], C Marosi[25], M Preusser[25], K Dieckmann[26], I Slavc[27], B Gatterbauer[28], G Widhalm[28], C Haberler[1] and J A Hainfellner[1] on behalf of the Austrian Brain Tumour Registry

[1]*Institute of Neurology, Medical University of Vienna, Währinger Gürtel 18–20, A-1097 Vienna, Austria;* [2]*Austrian National Cancer Registry, Statistics Austria, Guglgasse 13, A-1110 Vienna, Austria;* [3]*Center for Public Health, Department of Epidemiology, Medical University of Vienna, Währinger Gürtel 18–20, A-1097 Vienna, Austria;* [4]*Department of Pathology and Neuropathology, State Neuropsychiatric Hospital Wagner-Jauregg, Linz, Wagner-Jauregg-Weg 15, A-4020 Linz, Austria;* [5]*Internal Medicine and Neurooncology, State Neuropsychiatric Hospital Wagner-Jauregg, Wagner-Jauregg-Weg 15, A-4020 Linz, Austria;* [6]*Department of Neurosurgery, State Neuropsychiatric Hospital Wagner-Jauregg, Wagner-Jauregg-Weg 15, A-4020 Linz, Austria;* [7]*Department of Neuropathology, Institute of Pathology, Medical University of Innsbruck, Christoph-Probst-Platz Innrain 52, A-6020 Innsbruck, Austria;* [8]*Department of Neurology, Medical University of Innsbruck, Christoph-Probst-Platz Innrain 52, A-6020 Innsbruck, Austria;* [9]*Department of Neurosurgery, Medical University of Innsbruck, Christoph-Probst-Platz Innrain 52, A-6020 Innsbruck, Austria;* [10]*Department of Neuropathology, Institute of Pathology, Medical University of Graz, Auenbruggerplatz 25, A-8036 Graz, Austria;* [11]*Division of General Neurology and Division of Neuroradiology, Medical University of Graz, Auenbruggerplatz 25, A-8036 Graz, Austria;* [12]*Department of Neurosurgery, Medical University of Graz, Auenbruggerplatz 25, A-8036 Graz, Austria;* [13]*Institute of Pathology, State Hospital Klagenfurt, St Veiter Strasse 47, A-9020 Klagenfurt, Austria;* [14]*Department of Neurosurgery, State Hospital Klagenfurt, St Veiter Strasse 47, A-9020 Klagenfurt, Austria;* [15]*Department of Clinical Pathology, General Hospital St Pölten, Probst-Führer-Strasse 4, A-3100 St Pölten, Austria;* [16]*Department of Neurology, General Hospital St Pölten, Probst-Führer-Strasse 4, A-3100 St Pölten, Austria;* [17]*Department of Neurosurgery, General Hospital St Pölten, Probst-Führer-Strasse 4, A-3100 St Pölten, Austria;* [18]*Department of Neurosurgery, Christian Doppler Clinic, Paracelsus Private Medical University, Strubergasse 21, A-5020 Salzburg, Austria;* [19]*Institute of Pathology, General Hospital Wiener Neustadt, Corvinusring 3–5, A-2700 Wiener Neustadt, Austria;* [20]*Department of Pathology, Feldkirch State Hospital, Carinagasse 47, A-6807 Feldkirch, Austria;* [21]*Department of Neurosurgery, Feldkirch State Hospital, Carinagasse 47, A-6807 Feldkirch, Austria;* [22]*Department of Pathology, Krankenanstalt Rudolfstiftung, Juchgasse 25, A-1030 Vienna, Austria;* [23]*Institute of Pathology, Danube Hospital, Langobardenstrasse 122, A-1220 Vienna, Austria;* [24]*Department of Neurology, KFJ-Hospital Vienna, Kundratstrasse 3, A-1100 Vienna, Austria;* [25]*Department of Medicine I, Medical University of Vienna, Währinger Gürtel 18–20, A-1097 Vienna, Austria;* [26]*Department of Radiation Oncology, Medical University of Vienna, Währinger Gürtel 18–20, A-1097 Vienna, Austria;* [27]*Department of Paediatrics, Medical University of Vienna, Währinger Gürtel 18–20, A-1097 Vienna, Austria and* [28]*Department of Neurosurgery, Medical University of Vienna, Währinger Gürtel 18–20, A-1097 Vienna, Austria*

Background: Unlike malignant primary central nervous system (CNS) tumours outcome data on non-malignant CNS tumours are scarce. For patients diagnosed from 1996 to 2002 5-year relative survival of only 85.0% has been reported. We investigated this rate in a contemporary patient cohort to update information on survival.

Methods: We followed a cohort of 3983 cases within the Austrian Brain Tumour Registry. All patients were newly diagnosed from 2005 to 2010 with a histologically confirmed non-malignant CNS tumour. Vital status, cause of death, and population life tables were obtained by 31 December 2011 to calculate relative survival.

Results: Overall 5-year relative survival was 96.1% (95% CI 95.1–97.1%), being significantly lower in tumours of borderline (90.2%, 87.2–92.7%) than benign behaviour (97.4%, 96.3–98.3%). Benign tumour survival ranged from 86.8 for neurofibroma to 99.7% for Schwannoma; for borderline tumours survival rates varied from 83.2 for haemangiopericytoma to 98.4% for myxopapillary ependymoma. Cause of death was directly attributed to the CNS tumour in 39.6%, followed by other cancer (20.4%) and cardiovascular disease (15.8%).

Conclusion: The overall excess mortality in patients with non-malignant CNS tumours is 5.5%, indicating a significant improvement in survival over the last decade. Still, the remaining adverse impact on survival underpins the importance of systematic registration of these tumours.

*Correspondence: A Woehrer; E-mail: adelheid.woehrer@meduniwien.ac.at

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Primary central nervous system (CNS) tumours comprise a large spectrum of distinct entities that differ substantially in terms of histomorphology, tumour biology, and behaviour. According to the third edition of the International Classification of Diseases for Oncology (ICD-O) tumours of benign, borderline, and malignant behaviour are distinguished (Fritz *et al*, 2000). While malignant tumours, that is, 'cancer' (ICD-O3/3) are characterised by the invasion of surrounding tissues and their potential for metastatic spread, benign (ICD-O3/0) and borderline (ICD-O3/1) tumours show restricted local growth without the potential for spread (Fritz *et al*, 2000). Thus, benign and borderline (=non-malignant) tumours are generally considered curable by resection only and usually do not require adjuvant treatment.

Non-malignant CNS tumours differ from their systemic counterparts with regard to their exclusive location within the CNS rendering them close to eloquent areas. The potential for malignant transformation of some benign tumour types (Evans *et al*, 2006), the occurrence of multiple tumours in the case of genetic tumour syndromes as well as unexpected events in the perioperative course of neurosurgerical procedures (Cornwell *et al*, 2012; Solheim *et al*, 2012) constitute further factors that have an impact on the functional outcome and quality of life of the affected patients. Nevertheless, in contrast to malignant CNS tumours, non-malignant tumours are not consistently reported through cancer registries, thus the population-based experience with these tumours is still limited (McCarthy *et al*, 2009).

Following an initiative of the Central Brain Tumour Registry of the United States (CBTRUS) the registration of non-malignant CNS tumours has become legally mandatory in the United States in 2004 (McCarthy *et al*, 2013). Similarly, selected cancer registries across the Scandinavian countries, the United Kingdom, Japan, and Israel (Sant *et al*, 2012; Shibui, 2012; Israel National Cancer Registray, 2013) as well as specialized brain tumour registries emerging in France and Austria (Bauchet *et al*, 2007; Woehrer 2013) are reporting incidence data on non-malignant CNS tumours, which account for ~50% of all primary CNS tumours (Wohrer *et al*, 2009; Dolecek *et al*, 2012). Yet, with regard to the outcome of these patients population-based data are even scarcer. Probably, the most comprehensive effort, so far, has come from the Eurocare project, which has compiled cancer registry data across different European regions to evaluate patient survival in a pan-European context (Sant *et al*, 2012). Their recent work also included survival data of patients with non-malignant CNS tumours, where they found a 5-year relative survival rate of only 85.0%, thus indicating an alarming excess risk of death (Sant *et al*, 2012). In addition, they observed substantial regional variations with poorest outcome in Eastern Europe (Sant *et al*, 2012). However, the survival analysis was based on a patient cohort diagnosed from 1996 to 2002. Thus, it does not yet reflect the beneficial impact of innovations in the field of neurooncology, which have taken place over the last decade. New diagnostic standards (Louis *et al*, 2007), widely available sophisticated functional imaging techniques (Kuhnt *et al*, 2013) as well as improved neurosurgical techniques (Chen *et al*, 2011; Kuhnt *et al*, 2012) and perioperative patient management (Wong *et al*, 2012) are among the major factors. As up-to-date information on survival serves as an important reference for clinicians and scientists (Talback *et al*, 2004), we readdressed and further scrutinised this issue in a large contemporary cohort of patients with non-malignant CNS tumours diagnosed from 2005 to 2010.

MATERIALS AND METHODS

A consecutive cohort of patients with non-malignant CNS tumours (ICD-O3 behaviour codes/0 benign and/1 borderline) was retrieved from the records of the Austrian Brain Tumour Registry (ABTR, $n=3983$). Austrian Brain Tumour Registry scientific activities have been approved by the local ethics committee and data protection authorities (approval no 550/2005). Persons without permanent Austrian residency were excluded. All cases were newly diagnosed in the time period 2005–2010 across all Austrian neuropathology departments ($n=11$), and had a histologically confirmed diagnosis of a non-malignant CNS tumour. Reported patient parameters included personal identifiers, gender, date of birth, age at diagnosis, histopathological diagnosis, and tumour location. In cooperation with Statistics Austria, the vital status of the patient cohort (Austrian National Cancer Registry, Statistics Austria) as well as life tables of the Austrian population (Social Statistics, Statistics Austria) were obtained with a last up-date by 31 December 2011. In addition, information on cause-specific death according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was available from death certificates (Causes of Death Statistics, Statistics Austria). Cause-specific deaths were grouped into the following reasonable categories: CNS tumour, other cancer, cardiovascular disease, infection, metabolic disease, other CNS-related causes (including CNS trauma and haemorrhage but also dementias), and other non-CNS-related causes.

All statistical analyses were performed using Microsoft Excel, SAS (http://www.pauldickman.com), and SPSS software packages. Group comparisons were assessed with *t*- and χ^2 tests. In order to eliminate the effect of competing causes of mortality relative survival rates were calculated. Relative survival is defined as the ratio of the observed survival in the patient group and the expected survival in a sex- and age-matched disease-free population (Ederer *et al*, 1961). Life table methods were applied to estimate observed survival, and the Ederer II model (Ederer and Heise, 1959) was applied to estimate expected survival using calendar year-, sex-, and age-specific life tables provided by Statistics Austria. In order to warrant comparability with clinical studies overall survival rates are provided along with the relative survival rates, where appropriate. Overall and relative survival rates are not displayed for tumours with less than 10 observations during the study period. Subgroup analyses were performed for gender, tumour location (ICD-O3 topography codes) (Fritz *et al*, 2000), and selected age cohorts (0–18, 19–44, 45–59, 60–74, and 75 years+). Substratifications of tumour type according to gender and age as well as tumour behaviour according to age were performed for tumours with adequately large sample sizes. Confidence intervals are not displayed in the case of insufficient sample size (referred to as asterisk). The study is retrospective and descriptive in nature. *P*-values and confidence intervals should therefore be interpreted as explorative only. No adjustments for multiple tests were applied.

RESULTS

Patient characteristics. The total cohort of non-malignant CNS tumours consisted of 3983 cases, among which 83.0% ($n=3305$) constituted tumours of benign and 17.0% ($n=678$) tumours of borderline behaviour. Within the group of benign brain tumours, females were more commonly affected than males (F/M ratio 1.8), whereas no major gender difference was observed for the group of borderline tumours (F/M ratio 1.1). A detailed distribution of tumour entities per category is provided in Table 1. Among the group of benign CNS tumours, the most common entities were meningioma WHO grade I ($n=1{,}914$, 57.9%), pituitary adenoma ($n=757$, 22.9%), and Schwannoma ($n=544$, 16.5%), whereas meningioma WHO grade II ($n=235$, 34.7%), pilocytic astrocytoma ($n=109$, 16.1%), and haemangioblastoma ($n=76$, 11.2%) constituted the most common tumours of borderline behaviour. Gender distribution was approximately equal for the majority of

tumour types except benign meningioma (WHO grade I), which showed a 2.9-fold female excess. Similarly, subependymoma and myxopapillary ependymoma tended to be more common in females (M/F ratios of 0.6 and 0.7, respectively), whereas central neurocytoma, neurofibroma, dysembryoplastic neuroepithelial tumour, and pilocytic astrocytoma showed a male preference (M/F ratios of 2.7, 1.4, 1.4, and 1.3, respectively). Overall, median age at diagnosis was significantly higher among patients with benign CNS tumours (57.2 years, range 3.6 months–92.0 years) compared with tumours of borderline behaviour (47.0 years, range 4.8 months–84.6 years; $P<0.0001$) but clearly varied according to tumour type (see Table 1) from pilocytic astrocytoma (median age at onset 14.1 years) to meningioma WHO grade II (60.3 years). With regard to tumour topography, 54.0% of tumours were located within the meninges, 19.1% within the pituitary gland, 14.5% occurred within cranial nerves, and 10.2% within the CNS parenchyma.

Death-specific mortality. Of the total cohort, 10.5% ($n=417$) deceased during the observation period. The fraction was significantly higher among patients with CNS tumours of borderline behaviour (15.5%) compared with benign tumour types (9.4%; $P<0.0001$). According to death certificates, in 39.6% of the patients the death was directly attributed to the CNS tumour (34.9% of deaths from benign tumours, 53.3% of deaths from tumours of borderline behaviour, respectively, see Figure 1). Common competing causes of death included other cancer (20.4%) and cardiovascular disease (15.8%), which were both more prevalent among benign CNS tumour patients (22.8% and 19.6%, compared with 13.3% and 4.8%, respectively). The most common other type of cancer was lung cancer, which constituted 21.2% (18 persons) of all cancer-related deaths, whereas other cancer types accounted for less than 5% (4 individuals) each. The time interval from neurosurgical intervention to cause-specific death was shortest for metabolic disease (median 4 months) and infections (median 6.5 months) ranging up to 34.7 months for cardiovascular disease. Central nervous system tumour-related death occurred on average at 16.0 months after diagnosis (s.d. 24.2 months, ranging from 0 to 89.0 months). Detailed information on causes of death and median time to death is provided for brain tumour types with more than five events of death in Table 2. Median CNS-related tumour death was shortest, that is, 1 month after diagnosis, for pituitary adenoma and haemangioblastoma patients.

Relative survival. One- and five-year cumulative relative survival rates (cRSR) for patients with non-malignant CNS tumours are presented in Table 3. There was a small but statistically significant excess mortality in patients with non-malignant CNS tumours compared with the general population. The relative survival rates were significantly lower in patients with tumours of borderline as

Table 1. Cohort of non-malignant primary CNS tumours including histology, gender, and age distribution (Austrian Brain Tumour Registry, 2005–2010)

ICD-O3 morphology	Histology	Total *N*	%	M	F	M/F ratio	Age[a] (s.d.)
ICD-O3 behaviour							
Benign (ICD-O3/0)							
9530/0	Meningioma (WHO grade I)	1.914	57.9	489	1.425	0.3	59.8 (13.5)
8272/0	Pituitary adenoma	757	22.9	407	350	1.2	53.3 (15.9)
9560/0	Schwannoma	544	16.5	256	288	0.9	52.4 (15.7)
9413/0	Dysembryoplastic neuroepithelial tumour	22	0.7	13	9	1.4	27.4 (15.9)
9540/0	Neurofibroma	19	0.6	11	8	1.4	38.8 (16.9)
9390/0	Choroid plexus papilloma	18	0.5	8	10	0.8	42.0 (25.1)
9080/0, 9492/0, 8815/0, 9582/0	Other[b]	31	0.9	16	15	1.1	37.0 (14.3)
	Total	3.305	100.0	1,200	2.105	0.6	57.2 (15.4)
Borderline (ICD-O3/1)							
9539/1, 9538/1	Meningioma (WHO grade II)	235	34.7	102	133	0.8	60.3 (14.9)
9421/1	Astrocytoma pilocytic	109	16.1	61	48	1.3	14.1 (17.2)
9161/1	Haemangioblastoma	76	11.2	40	36	1.1	53.8 (16.9)
9350/1	Craniopharyngioma variants	70	10.3	35	35	1.0	51.1 (22.1)
9505/1	Ganglioglioma	34	5.0	18	16	1.1	24.0 (14.7)
9394/1	Myxopapillary ependymoma	32	4.7	13	19	0.7	42.6 (15.9)
9150/1	Haemangiopericytoma	30	4.4	15	15	1.0	43.8 (15.1)
9383/1	Subependymoma	25	3.7	9	16	0.6	54.2 (14.3)
9752/1, 9753/1	Langerhans cell histiocytosis[c]	20	2.9	11	9	1.2	17.8 (20.3)
9506/1	Central neurocytoma	11	1.6	8	3	2.7	36.2 (10.1)
8680/1	Paraganglioma	11	1.6	5	6	0.8	51.0 (16.0)
9384/1, 9509/1, 9412/1, 9431/1, 9361/1, 8728/1, 9080/1	Other[d]	25	3.8	11	14	0.8	21.8 (16.0)
	Total	678	100.0	328	350	0.9	47.0 (22.4)

Abbreviations: CNS = central nervous system; ICD = International Classification of Diseases.
[a]Median age at diagnosis in years.
[b]Includes cases of mature teratoma, gangliocytoma, solitary fibrous tumour, and granular cell tumour.
[c]Includes eosinophilic granuloma and Hand-Schuller-Christian disease.
[d]Includes cases of subependymal giant cell astrocytoma, rosette-forming glioneuronal tumour of the fourth ventricle, desmoplastic infantile astrocytoma/ganglioglioma, angiocentric glioma, pineocytoma, melanocytoma, and teratoma.

compared with benign behaviour (see also Figure 2). Within behavioural categories, male performed worse compared with female patients, although the gender difference in rates – based on overlapping confidence intervals – did not reach statistical significance.

Tumour type-specific 1- and 5-year cRSR are listed in Table 4. Compared with the general population, all tumour types together showed impaired survival. Whereas some tumour types showed a small but not significant restriction in survival, for example, pituitary adenoma, Schwannoma (WHO grade I), and gangliolioma (WHO grade I/II), the following tumours demonstrated a statistically significant impaired relative survival throughout the entire observation period: meningioma WHO grades I and II, dysembryoplastic neuroepithelial tumour, neurofibroma, pilocytic astrocytoma, haemangioblastoma, craniopharyngioma, haemangiopericytoma, subependymoma, and central neurocytoma. With regard to benign meningioma subtype analysis revealed that impaired survival was enhanced in patients with meningothelial meningiomas in contrast to other subtypes (fibrous, psammomatous, transitional, angiomatous, metaplastic, and microcystic Figure 3). In several tumour types including meningioma a trend towards worse outcome of male patients was noted, although which did not reach statistical significance (Table 4).

Stratification into age cohorts showed worse outcome with increasing age, overall and for individual tumour types (Figure 4). The youngest age cohort (0–18 years, 169 individuals) had a slightly worse outcome as compared with the 19–44 years age cohort (881 individuals); however, this difference was statistically not significant. Among patients above age 75 years an early drop of the survival rate was seen, which was followed by a secondary incline. This dynamic in the rate of elderly patients was mainly due to benign meningioma patients.

Although a considerable fraction of tumours (41.3%) had imprecisely defined topography codes (i.e., C70.9 meninges, not otherwise specified NOS; C72.5 cranial nerve, NOS; C71.0 cerebrum, NOS) (Fritz *et al*, 2000), cRSR demonstrated impaired survival for tumours of the cerebral meninges, optic nerve, craniopharyngeal duct, brain stem, cerebellum, and ventricles (see Table 5). Subgroup analysis according to tumour location showed that patients with pilocytic astrocytomas of the optic tract/chiasm ($n=15$) had worse outcome (5-year cRSR 86.9% (56.5–96.7%)) compared with cerebellar tumours ($n=32$; 5-year cRSR 100.4% (CI contains 1)). Likewise, patients with cerebral meningiomas ($n=714$) performed worse (5-year cRSR 95.2% (92.5–97.4%)) compared with their spinal counterparts ($n=93$; 5-year cRSR 99.0% (89.3–104.8%)). In contrast, the rate for acoustic Schwannoma ($n=195$, 5-year cRSR 100.4% (95.9–102.7%)) corresponded to that for Schwannomas at all other sites ($n=312$, 5-year cRSR 98.7% (95.2–101.0%)).

DISCUSSION

In contrast to malignant CNS tumours, outcome data on non-malignant CNS tumours are scarce. This is mainly due to the fact that these tumours are generally not considered as 'cancer' and thus, are frequently not systematically registered (Fritz *et al*, 2000). Outcome analyses for these types of tumours are further hampered as affected individuals are usually not supposed to die due to their CNS tumour but rather due to competing causes of death. This was also an important finding of the present study. Common competing causes of death included cancer and cardiovascular disease, which were both more prevalent among patients with benign than borderline CNS tumours, most likely reflecting the older age at disease onset of patients with benign tumours and the higher prevalence of those diseases with increasing age. In contrast, deaths from metabolic disease (including hepatic and renal failure) and infections occurred relatively early following neurosurgical interventions. These early events might indeed comprise a small fraction of patients, who experience perioperative mortality. Yet, detailed information on the hospital records or autopsy reports of these patients has not been available, and thus the exact prevalence of perioperative mortality remains unclear. Interestingly, however, ~40% of all events of death were directly attributed to the non-malignant CNS tumour. Among the latter median time to death was strikingly short for pituitary adenoma and haemangioblastoma patients—a finding that needs to be cautiously interpreted in the light of small sample sizes but clearly deserves further attention.

Still, the information of cause-specific death has been obtained from death certificates, which carry the inherent problem of considerable inter-rater variability across different centers and practitioners (Burger *et al*, 2012; Sutra *et al*, 2012; Hu *et al*, 2013; Lafrance *et al*, 2013). Thus, cause-specific mortality from death certificates cannot generally be considered as objective outcome measure. Therefore, in order to assess any excess mortality in patients with non-malignant CNS tumours compared with the general population, we calculated relative survival rates, which are considered as gold standard for cause-specific survival analyses. Compared with baseline data from the Eurocare project (5-year RSR from non-malignant brain tumours of only 85.0% based on patients diagnosed from 1996 to 2002) (Sant *et al*, 2012), we found a considerably higher survival rate of up to 96.1% in our large contemporary patient series. The difference in rates might be even slightly enhanced considering the fact that Sant *et al* (2012) used the Hakulinen model to estimate relative survival, which yields comparable results but may lead to overestimation of rates in presence of many censored cases (Cho *et al*, 2011). Nevertheless, the observed increase confirms a trend, which has already been present in the Eurocare data (Sant *et al*, 2012) and may partly correspond to earlier and refined diagnostic procedures including improved and more widely available neuroimaging techniques (Legler *et al*, 1999; Klaeboe *et al*, 2005; Sant *et al*, 2012). Furthermore, a high health status of the Austrian general population and/or a lower threshold to undergo CT and MRI scans for minor complaints need to be taken into account when comparing Austria with a pan-European study which includes less favourable Eastern European countries.

All patients included in this study were diagnosed in specialized Austrian neurooncology centers by neurosurgical resection from 2005 to 2010 and had a histologically confirmed non-malignant CNS tumour, thereby warranting direct comparability with Eurocare data. Although a central histopathology review was not feasible for the present study, all cases were diagnosed by experienced board-certified neuropathologists using WHO consensus criteria for tumour typing, thereby warranting high diagnostic standards across Austria. Information on persons, who did not undergo neurosurgical resection (watchful waiting) due to a number of reasons including poor health condition at perioperative evaluation, are not yet routinely available through ABTR (Wohrer *et al*, 2009). Thus, the herein observed rates might be biased towards optimistic survival, as patients with poor preoperative performance scores were likely to be not included. According to internationally available data, the majority of cancer registries including also cancer registries with experience in reporting benign CNS tumours, report a rate of microscopically verified CNS tumours of more than 85% (Sant *et al*, 2012). Still, the exact prevalence of non-malignant CNS tumour patients, who are on a wait-and-see strategy for various reasons (asymptomatic patients, stable disease, poor performance status, neoadjuvant chemo- or radiotherapy) is largely unknown and more efforts have to be undertaken to register these patients systematically.

Table 2. Competing cause of death by behavioural category and selected histologies (Austrian Brain Tumour Registry, 2005–2010)

				Competing cause of death %													
				CNS tumour		Other cancer		Cardiovascular disease		Infection		Metabolic		Other non -CNS-related cause		Other CNS-related cause	
Histology	Total *N* at risk	*N* (%) deceased	*t*	%	*t*	%	*t*	%	*t*	%	*t*	%	*t*	%	*t*	%	*t*
ICD-O3																	
Benign (ICD-O3/0)																	
All benign	3305	312 (9.4)	23.0	34.9	15.0	22.8	31.0	19.6	31.0	5.8	4.5	2.9	1.0	6.1	31.0	8.0	26.0
Meningioma (WHO grade I)	1914	217 (11.3)	21.0	37.8	14.0	22.6	26.0	18.9	25.0	5.5	2.5	3.7	5.5	5.1	31.0	6.4	17.5
Pituitary adenoma	757	60 (7.9)	31.5	21.7	1.0	23.3	33.0	28.3	38.0	5.0	18.0	1.7	1.0	6.7	37.5	13.3	32.5
Schwannoma	544	27 (5.0)	28.0	33.3	28.0	25.9	21.0	7.4	34.5	7.4	25.5	—	—	14.8	25.5	11.1	18.0
Borderline (ICD-O3/1)																	
All borderline	678	105 (15.5)	21.0	53.3	20.5	13.3	22.0	4.8	47.0	5.7	15.0	5.7	8.5	7.6	26.5	9.5	19.5
Meningioma (WHO grade II)	235	54 (23.0)	22.0	55.6	25.0	13.0	22.0	7.4	39.0	9.3	15.0	3.7	2.5	5.6	25.0	5.6	22.0
Astrocytoma pilocytic	109	9 (8.3)	28.0	33.3	16.0	11.1	58.0	—	—	11.1	33.0	—	—	22.2	37.5	22.2	13.5
Haemangioblastoma	76	12 (15.8)	12.0	41.7	1.0	41.7	10.0	—	—	—	—	—	—	16.7	39.0	—	—
Craniopharyngioma	70	13 (18.6)	23.0	46.2	3.5	—	—	7.7	47.0	—	—	15.4	25.0	7.7	20.0	23.1	26.0
Haemangiopericytoma	30	6 (20.0)	30.5	100.0	30.5	—	—	—	—	—	—	—	—	—	—	—	—
Overall ICD-O 0&1	3983	417 (10.5)	22.0	39.6	16.0	20.4	26.0	15.8	34.7	5.8	6.5	3.6	4.0	6.5	28.0	8.4	22.0

Abbreviations: CNS = central nervous system; ICD = International Classification of Diseases. *t* = median time to death (in months)

Table 3. Cumulative relative and overall survival rates for non-malignant CNS tumours according to ICD-O3 behaviour codes (Austrian Brain Tumour Registry, 2005–2010)

ICD-O3 behaviour	*N* (%)	1-year cRSR (95% CI)	1-year cOS (95% CI)	*N* (%)	5-year cRSR (95% CI)	5-year cOS (95% CI)
ICD-O3/0&1 non-malignant						
Overall	3983 (100.0)	97.3 (96.7–97.9)	96.3 (95.8–96.8)	3194 (80.2)	96.1 (95.1–97.1)	90.6 (90.1–91.1)
Male	1528 (100.0)	97.1 (95.9–98.0)	95.7 (94.6–96.6)	1194 (78.1)	94.7 (92.8–96.4)	88.1 (86.3–89.6)
Female	2455 (100.0)	97.5 (96.7–98.2)	96.7 (95.9–97.3)	2000 (81.5)	97.0 (95.8–98.0)	92.2 (91.1–93.2)
ICD-O3/0 benign						
Overall	3305 (100.0)	97.8 (97.1–98.3)	96.7 (96.0–97.2)	2660 (80.5)	97.4 (96.3–98.3)	91.5 (90.4–92.4)
Male	1200 (100.0)	97.4 (96.1–98.4)	96.0 (94.7–97.0)	949 (79.1)	96.4 (94.3–98.2)	89.2 (87.3–90.9)
Female	2105 (100.0)	98.0 (97.1–98.6)	97.1 (96.2–97.7)	1.711 (81.3)	97.9 (96.6–99.0)	92.8 (91.6–93.9)
ICD-O3/1 borderline						
Overall	678 (100.0)	95.3 (93.3–96.8)	94.5 (92.5–96.0)	534 (78.8)	90.2 (87.2–92.7)	86.4 (83.5–88.8)
Male	328 (100.0)	95.8 (92.8–97.8)	94.8 (91.8–96.7)	245 (74.7)	88.6 (83.8–92.4)	83.9 (97.4–87.5)
Female	350 (100.0)	94.8 (91.8–96.8)	94.3 (91.3–96.3)	289 (82.6)	91.7 (87.6–94.7)	88.8 (84.9–91.7)

Abbreviations: cRSR = cumulative relative survival rate in %; cOS = cumulative observed survival; CI = confidence interval; ICD = International Classification of Diseases; *n* = alive at start of interval.

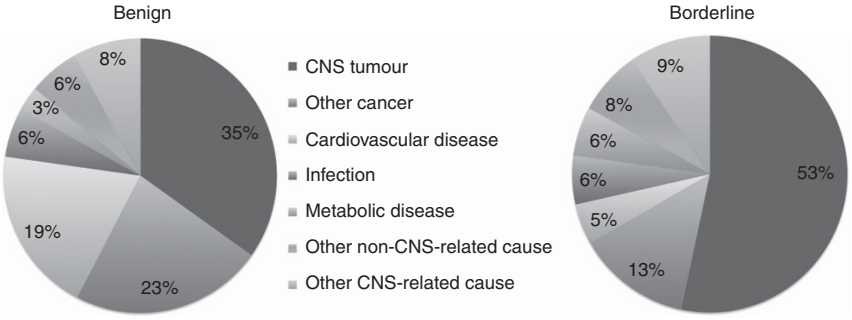

Figure 1. Competing causes of death among patients with benign and borderline CNS tumours (ABTR, 2005–2010). Cause of death in both categories was most commonly directly attributed to the CNS tumour. The fraction was higher among borderline tumours as compared with benign CNS tumours. Common competing causes of death included other cancer and cardiovascular disease, which were more prevalent among benign CNS tumour patients.

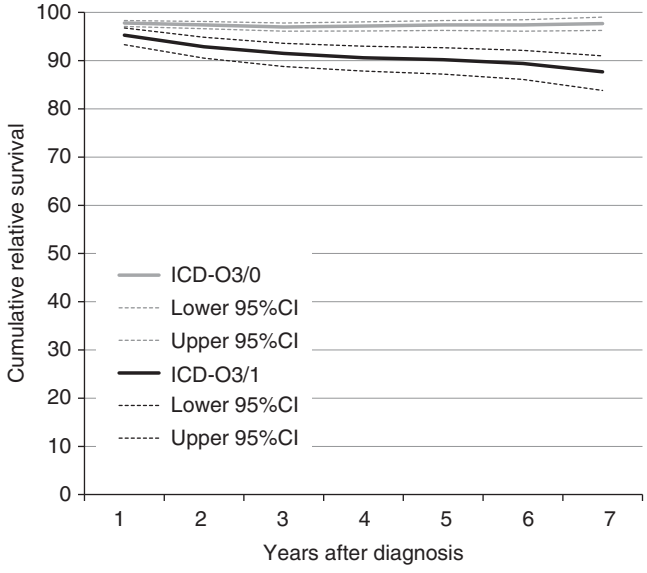

Figure 2. Cumulative relative survival rates of patients with non-malignant CNS tumours over time according to ICD-O3 behaviour codes (ABTR, 2005–2010). Relative survival is inferior in patients with tumours of borderline behaviour (ICD-O3/1) as compared with benign behaviour (ICD-O3/0).

Although neurosurgical resection is considered the standard of care for the majority of non-malignant CNS tumour types, there is also a role for radio- or chemotherapy, hormonal therapy, and stereotactic radiosurgery in the treatment of certain tumour types, for example, pilocytic astrocytoma, subtypes of pituitary adenoma, or atypical meningioma (Zachenhofer *et al*, 2006; Gnekow *et al*, 2012; Vroonen *et al*, 2012; Coskun *et al*, 2013). Thus, detailed information on the outcome of specific tumour entities instead of presenting summary rates on groups of tumours is crucial. This is probably the most relevant aspect of the present study, which covers a huge portfolio of specific non-malignant CNS tumour entities. Herein, survival is first separately assessed for benign and borderline CNS tumours. As expected, lower relative survival rates were observed for tumours of borderline as compared with benign behaviour, reflecting the more aggressive disease course of the former. In line with the Eurocare data, survival decreased with increasing age at diagnosis (Sant *et al*, 2012).

Tumours with least favourable outcome included neurofibroma, craniopharyngioma, and haemangiopericytoma with excess mortalities of above 10%. On the other end of the spectrum were patients with benign meningioma WHO grade I, Schwannoma, and pituitary adenoma, whose favourable outcomes showed almost no difference to the general population. The most common tumour types in our series included meningioma, pituitary adenoma, Schwannoma, and pilocytic astrocytoma.

Table 4. Cumulative relative and overall survival rates for specific CNS tumour types (Austrian Brain Tumour Registry, 2005–2010)

		Overall			Male		Female	
Histology	**Time**	***N*** **(%)**[a]	**cRSR (95% CI)**	**cOS (95% CI)**	***N*** **(%)**[a]	**cRSR (95% CI)**	***N*** **(%)**[a]	**cRSR (95% CI)**
ICD-O3 behaviour								
Benign (ICD-O3/0)								
Meningioma (WHO grade I)	1-year	1914 (100.0)	97.0 (96.0–97.8)	95.8 (94.8–96.6)	489 (100.0)	95.7 (93.1–97.5)	1425 (100.0)	97.4 (96.3–98.3)
	5-year	1525 (79.7)	96.0 (94.4–97.4)	89.6 (88.1–90.9)	368 (75.3)	93.4 (89.4–96.8)	1157 (81.2)	96.9 (95.2–98.4)
Pituitary adenoma	1-year	757 (100.0)	98.6 (97.3–99.5)	97.6 (96.3–98.5)	407 (100.0)	97.8 (95.5–99.2)	350 (100.0)	99.6 (97.6–100.4)
	5-year	628 (83.0)	99.6 (97.4–101.2)	93.8 (91.8–95.4)	331 (81.3)	98.0 (94.5–100.6)	297 (84.9)	101.4 (98.7–102.9)
Schwannoma	1-year	544 (100.0)	99.2 (97.7–99.9)	98.3 (96.8–99.1)	255 (100.0)	99.8 (97.4–100.6)	288 (100.0)	98.6 (96.1–99.8)
	5-year	433 (79.6)	99.7 (97.3–101.3)	95.1 (92.8–96.7)	212 (83.1)	101.3 (97.7–103.3)	221 (76.7)	98.2 (94.5–100.5)
Dysembryoplastic neuroepithelial tumour	1-year	22 (100.0)	95.6 (71.0–99.7)	95.2 (70.7–99.3)	12 (100.0)	92.2 (54.2–99.3)	9 (100.0)	100.1 (–)[b]
	5-year	18 (81.8)	91.1 (67.5–98.3)	90.5 (67.0–97.5)	9 (75.0)	84.1 (48.6–96.4)	9 (100.0)	100.5 (–)[b]
Neurofibroma	1-year	19 (100.0)	95.2 (68.4–99.7)	94.7 (68.1–99.2)	11 (100.0)	100.7 (–)[b]	8 (100.0)	87.6 (38.8–98.3)
	5-year	14 (73.7)	86.8 (59.9–97.7)	83.9 (57.9–94.5)	8 (72.7)	85.6 (45.9–99.9)	6 (75.0)	88.1 (39.0–98.9)
Choroid plexus papilloma	1-year	18 (100.0)	100.4 (–)[b]	100.0 (–)[b]	8 (100.0)	100.6 (–)[b]	10 (100.0)	100.3 (–)[b]
	5-year	15 (83.3)	96.1 (67.8–100.9)	94.4 (66.6–99.2)	7 (87.5)	90.0 (39.8–101.0)	8 (80.0)	101.0 (–)[b]
Borderline (ICD-O3/1)								
Meningioma (WHO grade II)	1-year	235 (100.0)	95.0 (90.9–97.5)	93.6 (89.6–96.1)	102 (100.0)	94.1 (86.7–98.0)	133 (100.0)	95.7 (90.1–98.4)
	5-year	180 (76.6)	86.9 (80.7–91.8)	80.6 (74.8–85.1)	71 (69.6)	80.1 (69.2–88.6)	109 (82.0)	92.0 (84.4–97.0)
Astrocytoma pilocytic	1-year	109 (100.0)	98.4 (93.0–99.7)	98.2 (92.9–99.5)	61 (100.0)	100.3 (–)[b]	48 (100.0)	95.9 (84.4–99.0)
	5-year	92 (84.4)	92.5 (85.2–96.6)	91.5 (84.3–95.5)	49 (80.3)	93.0 (81.6–98.1)	43 (89.6)	91.8 (79.5–97.0)
Haemangioblastoma	1-year	76 (100.0)	93.1 (84.2–97.4)	92.1 (83.3–96.4)	40 (100.0)	91.2 (76.5–97.4)	36 (100.0)	95.2 (80.2–99.4)
	5-year	58 (76.3)	91.7 (80.8–98.2)	86.4 (76.1–92.5)	28 (70.0)	89.1 (72.1–98.6)	30 (83.3)	94.6 (76.6–101.1)
Craniopharyngioma	1-year	70 (100.0)	95.0 (86.2–98.6)	94.3 (85.5–97.8)	35 (100.0)	98.3 (82.4–100.8)	35 (100.0)	91.8 (76.0–97.5)
	5-year	53 (75.7)	85.8 (73.8–93.4)	82.3 (70.8–89.6)	25 (71.4)	88.2 (69.8–98.0)	28 (80.0)	83.8 (65.6–93.4)
Ganglioglioma	1-year	34 (100.0)	97.2 (81.0–99.7)	97.1 (80.9–99.6)	18 (100.0)	100.2 (–)[b]	16 (100.0)	93.8 (63.3–99.2)
	5-year	30 (88.2)	97.8 (81.5–100.3)	97.1 (80.9–99.6)	16 (88.9)	101.2 (–)[b]	14 (87.5)	94.1 (63.5–99.5)
Myxopapillary ependymoma	1-year	32 (100.0)	97.2 (80.1–99.8)	96.9 (79.8–99.6)	13 (100.0)	92.7 (56.9–99.3)	19 (100.0)	100.2 (–)[b]
	5-year	28 (87.5)	98.4 (81.1–101.1)	96.9 (79.8–99.6)	11 (84.6)	94.4 (57.9–101.1)	17 (89.5)	101.2 (–)[b]
Haemangiopericytoma	1-year	30 (100.0)	93.8 (76.2–98.7)	93.3 (75.9–98.3)	15 (100.0)	93.8 (61.6–99.5)	15 (100.0)	93.7 (61.5–99.4)
	5-year	20 (66.7)	83.2 (61.4–94.2)	81.2 (59.8–91.9)	9 (60.0)	81.0 (49.2–95.0)	11 (73.3)	84.6 (45.2–98.2)
Subependymoma	1-year	25 (100.0)	92.7 (72.2–98.7)	92.0 (71.6–97.9)	9 (100.0)	100.7 (–)[b]	16 (100.0)	88.3 (59.1–97.6)
	5-year	21 (84.0)	91.4 (69.9–99.7)	88.0 (67.3–96.0)	9 (100.0)	104.3 (–)[b]	12 (75.0)	84.2 (54.3–96.9)
Langerhans cell histiocytosis	1-year	20 (100.0)	95.1 (69.6–99.4)	95.0 (69.5–99.3)	11 (100.0)	100.1 (–)[b]	9 (100.0)	89.1 (43.4–98.6)
	5-year	16 (80.0)	95.6 (69.9–99.9)	95.0 (69.5–99.3)	10 (90.9)	100.5 (–)[b]	6 (66.7)	89.6 (43.7–99.2)
Central neurocytoma	1-year	11 (100.0)	91.1 (50.9–98.8)	90.9 (50.8–98.7)	8 (100.0)	87.7 (38.8–98.3)	3 (100.0)	100.1 (–)[b]
	5-year	8 (72.7)	91.9 (51.4–99.8)	90.9 (50.8–98.7)	5 (62.5)	88.7 (39.2–99.5)	2 (66.7)	100.5 (–)[b]
Paraganglioma	1-year	11 (100.0)	91.3 (51.1–99.1)	90.9 (50.8–98.7)	5 (100.0)	100.6 (–)[b]	6 (100.0)	83.7 (27.4–97.9)
	5-year	9 (81.8)	93.0 (52.0–100.9)	90.9 (50.8–98.7)	4 (80.0)	102.6 (–)[b]	5 (83.3)	84.3 (27.6–98.5)

Abbreviations: cRSR = cumulative relative survival rate; cOS = cumulative overall survival; 95% CI = confidence interval; ICD = International Classification of Diseases; *n* = alive at start of interval.

[a]Percentage within each category.

[b]Confidence interval not calculated due to insufficient sample size.

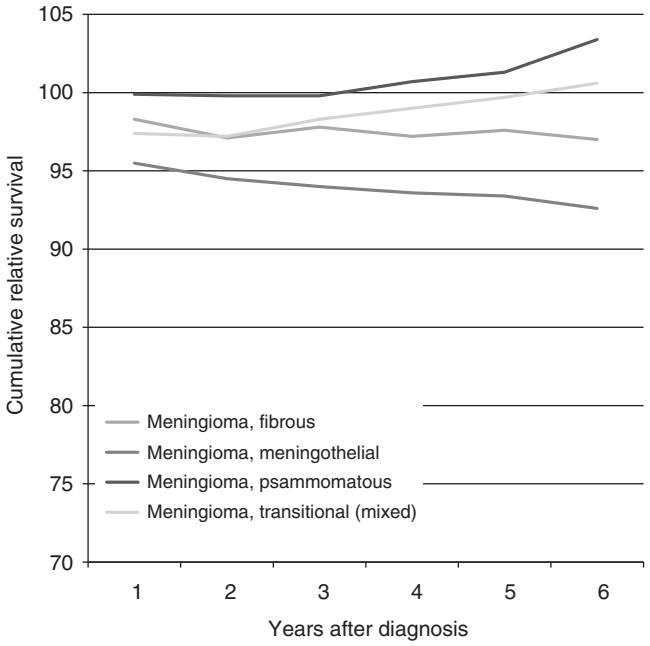

Figure 3. Cumulative relative survival rates for WHO grade I meningioma patients according to histopathological subtype (ABTR, 2005–2010). Patients with meningothelial subtype meningiomas show worse outcome as compared with other common meningioma subtypes (difference not statistically significant).

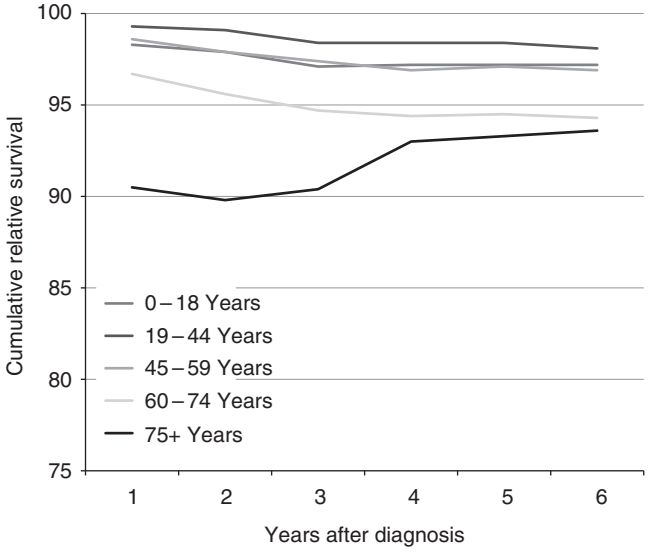

Figure 4. Cumulative relative survival rates of patients with non-malignant CNS tumours according to age cohorts (ABTR, 2005–2010). Subgroup analysis according to age cohorts shows decreasing survival with increasing age. In elderly patients (75 + years) an early drop of the rate is present, which is followed by a secondary incline. This pattern is not seen in other age cohorts.

With regard to benign meningioma (WHO grade I) impaired survival has been previously implicated by data of the Swedish Cancer Registry, based on a patient cohort diagnosed from 1960 to 1998 (Talback *et al*, 2004). Similarly, Eurocare found a 5-year relative survival for meningioma of 88.7%, ranging from 79.5% in Eastern Europe to 93.4% in Northern Europe (Sant *et al*, 2012). However, their data included both benign and borderline meningioma variants. Considering only benign meningioma, a large, retrospective analysis of 205 patients from 1985 to 2003 found 5-year relative survival rates of 92%, which is slightly below the herein observed rate (van Alkemade *et al*, 2012). Of note, by reporting longer follow-up times (exceeding 5 years), they were able to demonstrate a prolonged continuous decline in survival, indicating a significant long-term mortality from these tumours. However, neither Eurocare data nor the study by van Alkemade *et al* (2012) observed gender-specific differences in survival, which contrasts the herein observed trend towards worse outcome for male patients. Improved survival of females has already been described for many cancers and has been attributed to fewer comorbidities and higher clinical performance of females (Cook *et al*, 2009; Sant *et al*, 2012). As ABTR data are based on accurate histopathological diagnoses, our data first allowed for subgroup analysis of histopathological meningioma subtypes, and interestingly, we observed increased excess mortality for patients with meningothelial meningiomas. The reason for this observation remains obscure on basis of our data. One possible explanation might be a higher likelihood of this meningioma variant for infiltration of surrounding tissues, for example, the skull base.

Atypical meningiomas differ from benign meningiomas in several aspects including their lower incidence, little if any gender predominance, and a considerably worse prognosis, which lies between benign and anaplastic meningiomas (Louis *et al*, 2007). They carry a two-fold increased risk of death at 3–5 years (Perry *et al*, 2004; Louis *et al*, 2007). Single studies based on small cohorts of 17–42 patients diagnosed in the 1940–90s, have reported 5-year overall survival rates of 91–95% (Palma *et al*, 1997; Goyal *et al*, 2000). Interestingly, these rates are considerably higher compared with the herein observed overall survival rate of 80.6%. This discrepancy might be due to several reasons: first, small patient series are prone to selection bias; indeed, the patient cohorts then were on average younger (median age 55 compared with 60 years). Second, diagnostic criteria have changed from first introduction to the WHO classification in 1993 to the 2000 and 2007 WHO criteria, which have become more objective and reproducible (Kleihues *et al*, 1993; Kleihues and Cavanee, 2000; Louis *et al*, 2007). Thus, a caveat remains for atypical meningioma patients diagnosed before 2005. In 2009, Boskos *et al* (2009) published cause-specific survival data on 19 atypical meningioma patients and found a 5-year survival rate of 80%, which is well in line with the present rate.

On the basis of a single-center series of 248 patients with *pituitary adenomas* (non-functioning and corticotrophs), an excess mortality of 41% compared with the general population was reported (Dekkers *et al*, 2007). Excess mortality was particularly enhanced in corticotroph adenomas (Cushing's disease), especially in patients with persistent Cushing's disease after operation. Even though stratification according to hormone production was not feasible within the present study, our data indicate a trend towards impaired survival of patients with pituitary adenomas. The implicated difference in survival between hormone-producing subtypes remains to be readdressed in further large scale studies. So far, Eurocare data did not list pituitary adenomas among benign CNS tumour types (Sant *et al*, 2012). Another important issue, which has been raised by Dekkers *et al* (2007) highlights the considerable neurological comorbidity of patients with pituitary adenoma, which was not only due to local tumour growth but also due to hormonal derangements. Therefore, survival may not be the only accurate outcome measure, but clearly needs to be considered together with quality of life data.

With regard to Schwannoma Eurocare data showed highly favourable outcome with an overall relative survival rate of 96.5% (98.3% in Northern Europe) (Sant *et al*, 2012), which is well in line with our recent findings. However, their data did not allow for further stratification according to tumour location. Within our data set, we were first able to show that patients with acoustic Schwannomas have comparable outcome to those at all other cranial nerves. On the basis of hospital discharge data, McClelland

Table 5. Cumulative relative and overall survival rates according to tumour location (Austrian Brain Tumour Registry, 2005–2010)

ICD-O3 topography			1-year			5-year	
		N (%)[a]	cRSR (95% CI)	cOS (95% CI)	*N* (%)[b]	cRSR (95% CI)	cOS (95% CI)
C70.9	Meninges, NOS	1204 (30.3)	97.1 (95.8–98.1)	95.9 (94.7–96.9)	933 (77.5)	94.7 (92.5–96.6)	88.3 (86.3–90.1)
C70.0	Cerebral meninges	843 (21.2)	96.0 (94.3–97.4)	94.9 (93.2–96.2)	682 (80.9)	94.5 (92.0–96.6)	88.7 (86.3–90.7)
C70.1	Spinal meninges	98 (2.5)	95.8 (88.7–99.2)	93.9 (96.9–97.2)	73 (74.5)	98.5 (88.8–104.5)	87.3 (78.6–92.6)
C72.5	Cranial nerve, NOS	334 (8.4)	98.7 (96.4–99.8)	97.9 (95.7–99.0)	271 (81.1)	98.1 (94.6–100.4)	93.7 (90.4–95.9)
C72.4	Acoustic nerve	198 (5.0)	98.8 (95.5–100.1)	98.0 (94.7–99.2)	151 (76.3)	100.4 (95.9–102.7)	95.6 (91.4–97.8)
C72.2	Olfactory nerve	17 (0.4)	101.6 (–)[c]	100.0 (–)[c]	17 (100.0)	102.7 (66.4–109.2)	93.1 (60.2–99.0)
C72.3	Optic nerve	28 (0.7)	96.6 (77.4–99.7)	96.4 (77.2–99.5)	21 (75.0)	89.3 (67.9–97.3)	88.1 (67.0–96.1)
C75.1	Pituitary gland	762 (19.1)	98.7 (97.3–99.5)	97.6 (96.3–98.5)	631 (82.8)	99.6 (97.4–101.2)	93.9 (91.9–95.4)
C75.2	Craniopharyngeal duct	72 (1.8)	95.2 (86.5–98.6)	94.4 (85.9–97.9)	55 (76.4)	86.2 (74.6–93.6)	82.8 (71.6–89.8)
C75.3	Pineal gland	6 (0.2)	100.2 (–)[c]	100.0 (–)[c]	6 (100.0)	100.8 (–)[c]	100.0 (–)[c]
C71.0	Cerebrum, NOS	102 (2.6)	96.4 (89.7–99.1)	95.7 (89.1–98.2)	75 (73.5)	90.3 (81.1–96.0)	86.9 (78.1–92.4)
C71.1	Frontal lobe	19 (0.5)	95.2 (68.4–99.7)	94.7 (68.1–99.2)	17 (89.5)	96.7 (69.5–101.3)	94.7 (68.1–99.2)
C71.3	Parietal lobe	8 (0.2)	87.8 (38.8–98.5)	87.5 (38.7–98.1)	6 (75.0)	89.3 (39.5–100.1)	87.5 (38.7–98.1)
C71.2	Temporal lobe	27 (0.7)	96.7 (76.8–99.8)	96.3 (76.5–99.5)	25 (92.6)	97.6 (77.5–100.8)	96.3 (76.5–99.5)
C71.4	Occipital lobe	13 (0.3)	100.2 (–)[c]	100.0 (–)[c]	11 (84.6)	93.4 (57.3–100.0)	92.3 (56.7–98.9)
C71.8	Overlapping lesion of brain	2 (0.1)	100.3 (–)[c]	100.0 (–)[c]	2 (100.0)	101.4 (–)[c]	100.0 (–)[c]
C71.7	Brain stem	7 (0.2)	100.3 (–)[c]	100.0 (–)[c]	7 (100.0)	87.1 (33.9–99.4)	85.7 (33.4–97.9)
C71.6	Cerebellum, NOS	70 (1.8)	96.2 (87.8–99.1)	95.7 (87.3–98.6)	58 (82.9)	95.4 (86.0–99.6)	92.9 (83.7–97.0)
C71.5	Ventricle, NOS	171 (1.8)	96.2 (87.9–99.1)	95.8 (87.5–98.6)	56 (32.7)	93.7 (84.1–98.3)	91.5 (82.2–96.1)
C72.0	Spinal cord	49 (1.2)	96.6 (85.3–99.7)	95.9 (84.7–99.0)	41 (83.7)	97.6 (85.4–101.8)	93.9–82.2–98.0)
C72.1	Cauda equina	30 (0.8)	100.2 (–)[c]	100.0 (–)[c]	27 (90.0)	101.4 (–)[c]	100.0 (–)[c]
C41.0	Calvarium	17 (0.4)	100.1 (–)[c]	100.0 (–)[c]	15 (88.2)	100.7 (–)[c]	100.0 (–)[c]

Abbreviations: 95%CI = confidence interval; cRSR = cumulative relative survival rate (in %); cOS = cumulative overall survival; ICD = International Classification of Diseases. ICD-O3 topographies C75.3 (pineal gland), C71.3 (parietal lobe), C71.8 (overlapping lesion of the brain), C71.7 (brain stem), C72.0 (spinal cord) contain less than 10 observations each and rates may be unstable.

[a]Percentage of total number of cases.

[b]Percentage within category.

[c]Confidence interval not calculated due to insufficient sample size.

et al (2011) described a postoperative mortality of patients with acoustic Schwannoma in the United States of 0.5% (22/4886 patients). Interestingly, mortality was higher in African Americans compared with Caucasians, and lower with high-caseload surgeons, private insurance, younger age, and lower overall morbidity (McClelland *et al*, 2011). Indeed, these findings on sociodemographic disparities are alerting and deserve further consideration in a European setting.

Pilocytic astrocytomas constitute the only exception, as CBTRUS groups them together with other malignant tumours and routinely reports relative survival rates (Dolecek *et al*, 2012). According to latest CBTRUS findings, 5-year relative survival from pilocytic astrocytoma is 94.1% (93.8–95.6), a rate which is similar—even slightly higher compared with the present rate of 92.5% (Dolecek *et al*, 2012). In addition, Eurocare data indicate favourable outcome from pilocytic astrocytoma with a 5-year relative survival rate of 97.3% in those registries, which include also paediatric cases, whereas the overall rate across all age cohorts remained considerably lower with only 80.5% (Sant *et al*, 2012). When analysing individual age groups, we observed the same trend with 5-year relative survival of 95.6% (86.9–98.6%) in younger patients (0–18 years) but only 74.1% (27.5–94.6%) in the age group 45–59 years. However, the relatively small sample sizes per category prevented us from drawing definite conclusions.

This study does have limitations including its retrospective nature as well as its lack of therapy-related data. So far, ABTR constitutes an incidence, mortality and survival database for CNS tumour patients (Wohrer *et al*, 2009). In the near future, ABTR will transform into a follow-up registry with input of therapy-related data through members of the Austrian Society of Neurooncology (www.sano.co.at). This will enable assessment of different patterns of care across Austrian neurooncology centers thereby serving as a national and international benchmark system.

In summary, we present relative survival rates of patients with non-malignant CNS tumours in a large contemporary patient cohort. A significant increase in rates indicates improved patient outcome due to advances in the field of neurooncology over the last decades, but underlines the necessity of systematic registration of these types of tumours at the same time. Moreover, relevant issues addressing quality of life, sociodemographic disparities, and differences in patterns of care remain unanswered and need to be addressed in further studies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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