

Population-based incidence and survival of central nervous system (CNS) malignancies in Girona (Spain) 1994–2005

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Abstract The purpose of this study was to describe the incidence and survival of primary Central Nervous System (CNS) malignancies using data from the population-based cancer registry for Girona province (north-east Spain).

We included all cases of primary CNS malignancies registered between 1994 and 2005. Pathological diagnoses were reviewed and grouped according to the 2007 WHO Classification. Meningeal, soft tissue tumours, spinal cord

tumours and primary CNS lymphoma were not included. Cases notified only by death certificate were excluded from the survival analysis. Kaplan and Meier survival curves were calculated from date of diagnosis to death or end of study (31 December 2005), as was relative survival. A total of 493 new CNS cancer patients were registered during the study period: 49.3% astrocytic, 3.4% oligodendroglial and oligoastrocytic tumours, 2.6% ependymal tumours, 3.7% embryonal tumours, 0.2% choroid plexus and 41% without histological confirmation. The mean age (in years) for embryonal tumours was 18.17 years, these being the younger patients in the sample, and 66.34 years for those without histological confirmation, the older patients. Overall, the age standardised incidence rate was 5.88 cases/100,000 people/year (men = 6.81; women = 4.99) with an increasing trend by age until the 70–74 age group. Five-year observed survival rates were: 14.6% for astrocytic tumours, 35.7% for oligodendroglial and oligoastrocytic tumours, 41.0% for ependymal tumours, 32.4% for embryonal tumours and 7.5% for those without histological confirmation (log rank test: $P < 0.001$). Five-year observed survival rates for astrocytic tumours were analyzed separately by tumour grading, with 37% for diffuse astrocytoma, 7.1% for anaplastic astrocytoma and 4.7% for glioblastoma (log rank test: $P < 0.001$).

Our results show that astrocytic tumours are most frequently diagnosed and glioblastoma patients have the worst survival figures for the area covered by our population cancer registry.

The high observed incidence of histologically unverified tumours is most probably due to easy access to state of the art CNS imaging in our area.

Keywords Primary brain tumours · Population based · Incidence · Survival

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Background

During the last few years, new developments in the management of central nervous system (CNS) malignancies using different combinations of surgery, radiation therapy and chemotherapy have been translated into better outcomes on selected groups of patients [1–5]. In order to improve the standard of care for patients diagnosed with CNS tumours and evaluate its real impact over the population as a whole, accurate knowledge regarding incidence and any prevailing population trends is essential, as highlighted in a recent paper by the Brain Tumor Epidemiology Consortium [6]. CNS tumour data from population-based cancer registries in Europe are seldom reported, and when they are they tend to come from northern Europe [7–11]. This report provides population-based data regarding descriptive epidemiology and survival rates for CNS malignancies according to histological subtype on the basis of the new 2007 WHO Classification of Central Nervous System Tumours [12] after analysing data taken from a population cancer registry in a Mediterranean region of southern Europe over an 11-year period.

Patients and methods

The Girona Cancer Registry (GCR) is a population-based cancer registry located in north-east Spain. Girona is one of the four provinces of the autonomous region of Catalonia and the GCR covered a population of 553,661 inhabitants in 2001. Information sources for the cancer registry are regional and community hospitals, haematology and pathology departments, and death certificates. Registered tumours are those considered malignant, in situ and borderline. The completeness of the registry is 96.3%.

The vital status of patients is updated yearly by means of a record linkage with the Catalan Mortality Registry and the National Death Index. In order to perform an up-to-date analysis, pathological reports were reviewed and recoded wherever possible to bring them into line with the new 2007 WHO classification [12].

Data selection

Patients were selected who had been diagnosed with a primary brain tumour between 1 January 1994 and 31 December 2005. The following ICD-10 (International Classification of Diseases) classification codes were included: C71–C72 (Table 1). Meningeal tumours, soft tissue tumours and spinal cord tumours were excluded. Patients diagnosed with a primary CNS lymphoma were also excluded from this data set.

Statistical analysis

Incidence was calculated as a crude rate (CR) and also as a world age-standardised rate (ASR). The Mantel–Haenszel test was used to compare ASRw between sexes. Survival status was obtained by active follow-up and was calculated from the date of diagnosis until December 2008 or the last follow-up. Record linkage was performed with the Catalan Mortality Registry in cases of incomplete follow-up. Cases diagnosed by death certificate only (DCO) were excluded for the survival analysis. A total of 79 patients (16%) were alive as of December 2008. The median follow-up time for live patients was 5.50 years (interquartile range: 5.83 years).

Relative survival was calculated as the ratio of the observed survival of patients with cancer to the expected survival of the corresponding sex and age group of the general population using WAERS [13], a web-based application developed by the Catalan Institute of Oncology. This application uses the Hakulinen method to estimate expected survival [14], the Kaplan–Meier method to estimate observed survival and the Greenwood method [15] to estimate confidence intervals. Comparisons between survival curves were tested by means of the log-rank test.

Results

A total of 493 incident cases were reported by the GCR between 1994 and 2005 according to our data selection. The percentage of histological confirmation was 59% for both sexes and the percentage of cases detected only by death certificates (DCO) was 5.5%.

Applying the 2007 WHO classification [12], the histological groups showed the following distribution: astrocytic tumours 243 (49.3%), oligodendroglial tumours and mixed histologies 17 (3.4%), ependymal tumours 13 (2.6%), embryonal tumours 18 (3.7%), choroid plexus tumours 1 (0.2%) and patients without histological confirmation 202 (41%). The most frequent astrocytic tumours were glioblastomas. The mean age of the group without histology was 66.3 years (Table 1).

Incidence

During the period 1994–2005, the annual average number of new cases of CNS malignancies in Girona was 25 in men and 20 in women; CR was 9.21 cases per 100,000 man-years and 7.2 cases per 100,000 woman-years. The annual age-standardised incidence rates (ASRw) were 6.81 and 4.99 per 100,000 person-years, respectively. The gender ratio (M/F) was 1.36 for all CNS tumours as a whole (Table 2).

Table 1 Distribution of neuroepithelial tissue tumours according to the WHO Classification for tumours of the central nervous system [12]

Histology	ICDO-O 3 histology code	Cases, (n)	(%)	Mean age	Min–max
Astrocytic tumours		243	49.3	55.03	(2–86)
Pilomyxoid astrocytoma	9425/3	0	0		
Pleomorphic xanthoastrocytoma	9424/3	1	0.2		
Diffuse astrocytoma	9400/3	64	13.0		
Fibrillary astrocytoma	9420/3	5	1.01		
Gemistocytic astrocytoma	9411/3	2	0.41		
Protoplasmic astrocytoma	9410/3	0	0		
Anaplastic astrocytoma	9401/3	28	5.68		
Glioblastoma	9440/3	134	27.1		
Giant cell glioblastoma	9441/3	2	0.4		
Gliosarcoma	9442/3	2	0.4		
Gliomatosis cerebri	9381/3	5	1.01		
Oligodendroglial tumours		17	3.4	42.76	(28–70)
Oligodendroglioma	9450/3	12	2.4		
Anaplastic oligodendroglioma	9451/3	4	0.8		
Oligoastrocytic tumours		1	0.2	1	(1–1)
Oligoastrocytoma	9382/3	0	0		
Anaplastic Oligoastrocytoma	9382/3	0	0		
Ependymal tumours		13	2.6	32.92	(1–61)
Ependymoma	9391/3	12	2.4		
Cellular	9391/3	0	0		
Papillary	9393/3	0	0		
Clear cell	9391/3	0	0		
Tanycytic	9391/3	0	0		
Anaplastic ependymoma	9392/3	1	0.2		
Embryonal tumours		18	3.7	18.17	(0–40)
Medulloblastoma	9470/3	12	2.4		
Desmoplastic/nodular medulloblastoma	9471/3	1	0.2		
Anaplastic medulloblastoma	9474/3	0	0		
Large cell medulloblastoma	9474/3	0	0		
CNS primitive neuroectodermal tumour	9473/3	5	1.0		
CNS neuroblastoma	9500/3	0	0		
CNS Ganglioneuroblastoma	9490/3	0	0		
Medulloepithelioma	9501/3	0	0		
Ependymoblastoma	9392/3	0	0		
Atypical teratoid/rhabdoid tumour	9508/3	0	0		
CNS without histological confirmation		202	41.0	66.34	(4–92)
Total		493	100.0	57.20	(0–92)

ICDO-O 3 International classification of diseases, third edition

Among pathologically confirmed tumours, the highest incidence was found for the malignant astrocytoma (ASRw: 3.01 per 100,000 person-years), followed by embryonal tumours (0.45 per 100,000 person-years) and the oligodendroglioma and oligoastrocytoma group (0.23 per 100,000 person-years). Incidence of tumours without histological confirmation was 1.91 per 100,000 person-years. With regard to incidence of astrocytic tumours

according to grading, glioblastoma was the most frequent subtype, with an ASRw of 1.59 cases per 100,000 person-years; followed by diffuse astrocytoma (1.03) and anaplastic astrocytoma (0.36) (data not shown).

Men showed a significantly higher incidence of CNS malignancies compared to women ($P < 0.05$). According to the histological subgroup, higher rates were observed for males in malignant astrocytic tumours [male (M)/female

Table 2 Incidence by histological subtype, age and gender according to WHO classification

Histologic type	Men					Women					Both sexes					Gender ratio (M/F)
	<i>n</i>	%	CR	ASR _w	CI (95%)	<i>n</i>	%	CR	ASR _w	CI (95%)	<i>n</i>	%	CR	ASR _w	CI (95%)	
Astrocytic tumours	134	48.7	4.490	3.120	(2.71; 3.92)	109	50	3.600	2.720	(2.14; 3.30)	243	49.3	4.04	3.01	(2.59; 3.43)	1.15
Oligodendro and oligoastro	8	2.9	0.270	0.230	(0.07; 0.39)	9	4.1	0.300	0.230	(0.08; 0.8)	17	3.4	0.28	0.23	(0.12; 0.34)	1.00
Ependymal tumours	8	2.9	0.270	0.380	(0.09; 0.67)	5	2.3	0.170	0.170	(0.01; 0.32)	13	2.6	0.22	0.28	(0.11; 0.44)	2.24
Embryonal tumours	11	4	0.370	0.560	(0.20; 0.92)	7	3.2	0.230	0.340	(0.06; 0.61)	18	3.7	0.30	0.45	(0.22; 0.68)	1.65
Choroid plexus	–	–	–	–	–	1	–	–	–	–	1	0.2	–	–	–	–
Without histological confirmation	114	41.5	3.820	2.330	(1.84; 2.82)	88	40.4	2.910	1.560	(1.13; 1.2)	202	41	3.36	1.91	(1.59; 2.23)	1.49
Total	275	100.0	9.21	6.81	(5.89; 7.73)	218	100.0	7.2	4.99	(4.19; 5.79)	493	100.0	8.20	5.88	(5.27; 6.49)	1.36

n Number of cases, *CR* crude rate (number of cases per 100,000 person-years), *ASR_w* world age-standardised rates, *M* men, *F* women

(F)] ratio of 1.15), ependymal tumours (M/F ratio of 2.24), embryonal tumours (M/F ratio of 1.65) and tumours without histological confirmation (M/F ratio of 1.49) (Table 2).

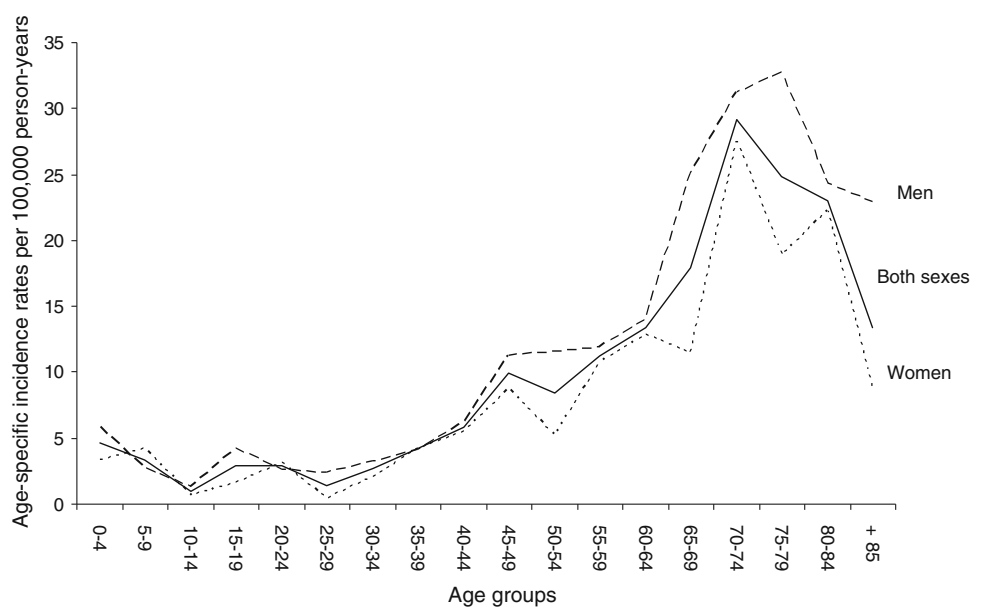
Age distribution and age specific incidence rates according to gender are shown in Fig. 1. The highest incidence in the paediatric population was between 0 and 4 years and, from 25 years old, the number of cases rises progressively, with a peak incidence at 70 years of age. The mean age of the whole group was 57.20 years (range 0–92 years). Incidence rates by age showed an increasing number of cases as the age of the population rises, reaching peak incidence rates at 70 years. Of the total number of

patients, 180 patients (36.5%) were older than 70. A higher incidence can be observed among men.

Survival

Median survival after compiling all histological groups was 5 months (Fig. 2). Patients showing the best survival rates were those diagnosed with ependymal tumours. Tumours with unknown histologies showed the worst median survival. However, when astrocytomas are analysed by subgroup, glioblastoma patients have the poorest survival.

Fig. 1 Age-specific incidence rates (male and female) of primary brain tumours (Girona, Spain, 1994–2005)



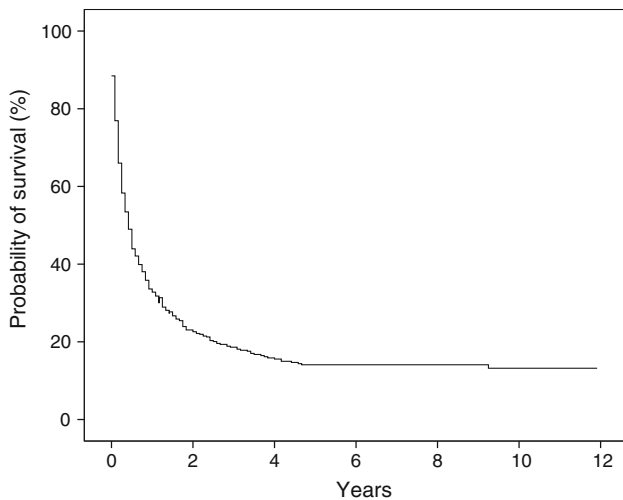
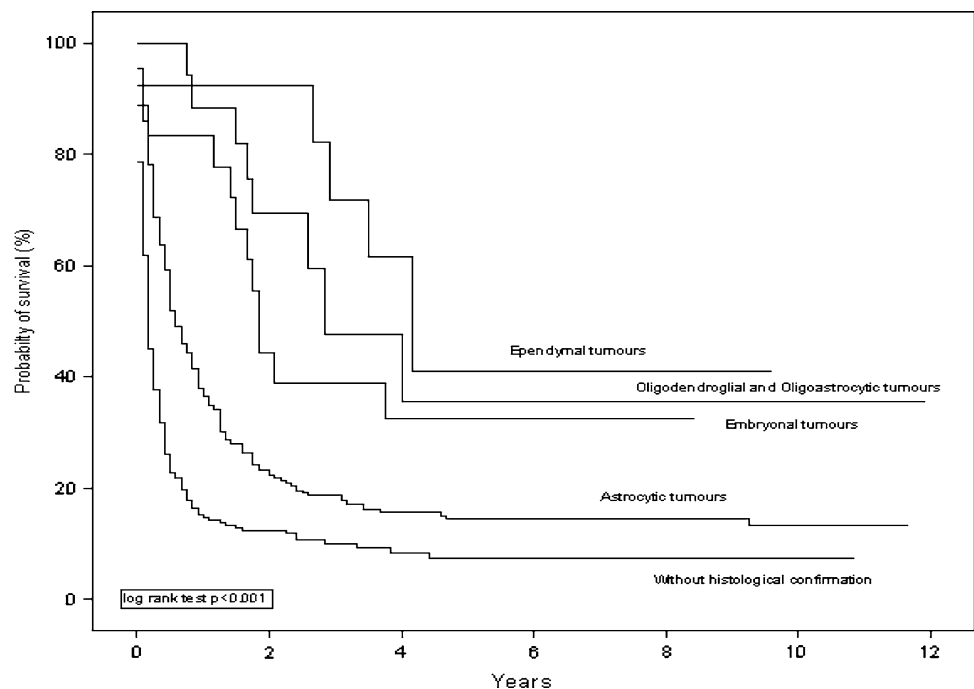


Fig. 2 Kaplan–Meier estimates of overall observed survival curves for patients diagnosed with a CNS tumour (Girona, Spain, 1994–2005)

Five-year observed survival rates were as follows: astrocytic tumours 15%; oligodendroglial and oligoastrocytic tumours 41.2%; ependymal tumours 42.2%; embryonal tumours 33.3%; and CNS malignancies without histological confirmation 7.8%. Survival by histological group is represented in Fig. 3 and Table 3. Differences between survival curves were statistically significant (log rank test; $P < 0.001$). Taking into account the grading of astrocytic tumours, 5-year survival was better for diffuse astrocytoma (37.0%) in comparison with anaplastic astrocytoma (7.1%)

Fig. 3 Kaplan–Meier survival curves of histological groups according to WHO classification (Girona, Spain, 1994–2005)



and glioblastoma (4.7%), log rank test, $P < 0.001$, as shown in Fig. 4.

The mean 5-year relative survival of patients diagnosed with CNS tumours (1994–2005) was 15.3%, higher in women (16.5%) than in men (14.3%). According to histological subtype, 5-year relative survival for astrocytic tumours was 15.5% (12.0% in men, 19.6% in women), for oligodendroglial and oligoastrocytic tumours 41.6% (50.5% in men, 48.1% in women), for ependymal tumours 42.7% (53.2% in men and 25.3% in women), and for embryonal tumours 33.4% (36.5% in men and 28.6% in women). CNS tumours without histological confirmation present a 5-year relative survival rate of 8.7% (8.9% in men and 7.7% in women). According to grading, 5-year relative survival for astrocytic tumours was 38.4% for diffuse astrocytoma (47.2% in women and 30.2% in men), for anaplastic astrocytoma 14.5% (14.5% in women and 14.5% in men) and for glioblastoma 5.2% (4.6% in men and 7.5% in women) (data not shown).

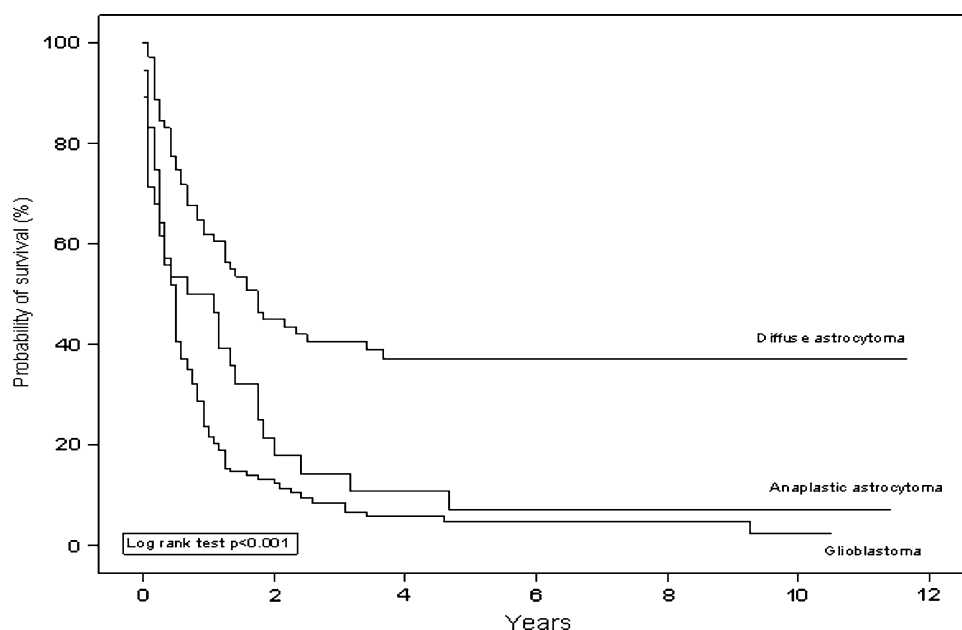
Discussion

Population-based cancer registries are extremely valuable tools for providing useful and reliable information regarding incidence and survival of central nervous system tumours. Reports publishing incidence and mortality in these groups of tumours in Europe are infrequent and spread over time [7–11]. To the best of our knowledge, this paper is the first to present epidemiological data for

Table 3 Distribution by gender of 5-year observed (5-OS) and relative survival (5-RS) with 5-RS, with 95% confidence interval of patients diagnosed with SNC tumours from 1994 to 2005, Girona (Spain)

Histological type	Men				Women				Both sexes			
	n	5-OS	5-RS	CI (95%)	n	5-OS	5-RS	CI (95%)	n	5-OS	5-RS	CI (95%)
Astrocytic tumours	134	11.5	12.0	(7.4; 19.5)	109	19.2	19.6	(13.2; 29.2)	243	15	15.5	(11.3; 21.1)
Oligodendroglial and oligoastrocytics	8	50	50.5	(25.2; 100.9)	9	47.6	48.1	(22.3; 101.0)	17	41.2	41.6	(20.0; 86.5)
Ependymal tumours	8	52.5	53.2	(24.8; 101.4)	5	25	25.3	(4.6; 101.1)	13	42.2	42.7	(20.6; 88.6)
Embryonal tumours	11	36.4	36.5	(16.7; 79.7)	7	28.6	28.6	(8.9; 92.2)	18	33.3	33.4	(17.4; 64.2)
Choroid plexus	–	–	–	–	1	–	–	–	–	–	–	–
Without histological confirmation	114	7.8	8.9	(4.0; 19.9)	88	6.6	7.7	(3.2; 15.6)	202	7.8	8.7	(5.2; 14.7)
Total	275	13.2	14.3	(10.3; 19.8)	218	15.9	16.5	(12.0; 22.6)	493	14.6	15.30	(12.2; 19.1)

5-OS 5-year observed survival, 5-RS 5-year relative survival

Fig. 4 Kaplan–Meier survival curves of astrocytic tumours according to grades (Girona, Spain, 1994–2005)

CNS malignancies from one of the population-based cancer registries in Spain. It should be borne in mind, however, that older reports might register lower incidences due to histological classifications having changed several times over the years and diagnostic imaging techniques having improved dramatically since the first European report, carried out in Iceland for the period 1954–1963 [11].

More recently published series showed an incidence of non-histologically verified cases of 18.9%, corresponding to the French report of 1983–1990 [7], far lower than the 41% of our series. It is important to note, however, that our group of patients is taken from the period 1994–2005, when magnetic resonance imaging was widely available in our area. According to Helseth et al. [16], improvements in neuroimaging have resulted in an increased rate of CNS tumour diagnosis in older patients and a decrease in

histological verification, which appears to be the trend for the years to come.

Survival of CNS tumour patients is strongly dependent on histological typing and grading. Since the first classification published by Bailey and Cushing [17], several more have been published with the aim of reaching a more accurate prognostic value of histology. As a result, the WHO has proposed an amended version of the previous 2000 classification: the fourth edition was published in 2007. Key modifications for glial tumours were the inclusion of *gliomatosis cerebrii* among the high grade tumours along with the incompatibility of necrosis and microvascular proliferation with diagnoses other than glioblastoma multiforme [12]. We have decided to reclassify our patients, moving *gliomatosis cerebrii* to the high-grade gliomas (astrocytic group) and pilocytic astrocytomas to the low-grade group.

A pathological review of high-grade gliomas to reclassify them according to the presence or not of microvascular proliferation was not carried out due to the fact that even the most renowned neuropathologists strongly disagree when reviewing pathological samples [18]. It was therefore decided to make groupings according to main histological subtypes. Our study showed that survival for ependymal and oligodendroglial tumours was more favourable in comparison to other tumour types, which was also consistent with previously published data [6].

There were very low survival figures among the group of patients with CNS malignancies without histological confirmation. We think this finding is the consequence of a more conservative attitude in the management of older or frail patients, basing diagnoses on imaging and avoiding invasive procedures. As a general clinical practice in our area we do not treat histologically unverified patients with radiation or chemotherapy, and we therefore assume that this group of patients only received supporting care. Unfortunately, however, our data do not allow us to analyse clinical management. Whether elderly or frail patients should be subject to histological verification is a matter of debate that does not fall within the scope of our report.

In summary, from our data we can conclude that there is a tendency towards an increasing number of primary CNS cases by age, and that better diagnosis imaging is most probably the cause of an increasing number of patients without histological verification.

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Conflict of interest statement None declared.

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