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Descriptive epidemiology of primary malignant and non-malignant central nervous tumors in Spain: Results from the Girona Cancer Registry (1994–2013)

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ABSTRACT

Background: Systematic registration of non-malignant central nervous system (CNS) tumors is a rare practice among European cancer registries. Thus, the real burden of all CNS tumors across Europe is underestimated. The Girona Cancer Registry provides here the first data on CNS tumor incidence and survival trends in Spain for all histological types, including malignant and non-malignant tumors.
Methods: Data on all incident cases of primary CNS tumors notified to the Girona population-based cancer registry from 1994 to 2013 (n = 2,131) were reviewed. Incidences rates (IRs) were standardized to the 2013 European population and annual percentage changes (EAPC) were estimated using a piecewise log linear model. 1- and 5-year observed (OS) and relative survival (RS) were also calculated. Results were expressed by sex, age-group, histological subtype and behavior.
Results: The overall IR was 16.85 and increased across the period of study (EAPC = +2.2%). The proportion and IRs of malignant (50.2%; IR = 9.35) and non-malignant cases (49.8%; IR = 9.14) were similar; however, non-malignant tumors were more frequent in women (sex ratio = 0.63). The most frequently reported histologies were meningioma (27.6%; IR = 5.11) and glioblastoma (22.2%; IR = 4.15), which also accounted for the highest and lowest 5-year RS (80.2%; 3.7%, respectively). Globally, 5-year RS was lower in men (42.6% vs. 58.3%, respectively) and in the elderly (64.9% for 0–14years vs. 23.0% for >74years).
Conclusion: This study presents a comprehensive overview of the epidemiology of malignant and non-malignant CNS primary tumors from the well-established region-wide Girona Cancer Registry (1994–2013). Incidence rates were recovered for all histologies. Survival is still dramatically associated to both age and histological subtype.

Abbreviations: CR, Crude rate; IR, European age-standardized incidence rate; IR_{US}, United States age-standardized incidence rate; IR_W, World age-standardized incidence rate; EAPC, estimated annual percent change; GCR, Girona Cancer Registry; CBTRUS, Central Brain Tumor Registry of the United States; DCO, Death certificate only; MV, microscopical verification; OS, Observed survival; RS, Relative survival.

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1. Introduction

Primary central nervous system (CNS) tumors are a heterogeneous group of diseases involving a wide range of histological features and anatomical structures, including brain, meningeal and peripheral nerves. Their intrinsic complexity has prompted several updates of the histological classification, the 2016 WHO version being the most recent [1]. According to the International Classification of Diseases, third edition (ICD-O3) [2], and based on their biological behavior, brain tumors fall into three broad categories: benign tumors (/0), tumors with intermediate or uncertain behavior (/1), and malignant tumors (/3).

CNS tumors can result in significantly high morbidity and mortality irrespective of their biological behavior, mostly depending on their topography [3]. In addition, as molecular markers are being discovered, it has become clear that certain low grade brain tumors may become malignant over time [4]. Therefore, the underregistration of CNS tumors classified as either 'benign' or of 'uncertain behavior' has become a major concern. Following an initiative of the Central Brain Tumor Registry of the United States (CBTRUS), the registration of non-malignant CNS tumors became mandatory in the United States (US) in 2004 [5]. According to the CBTRUS, between 2009 and 2013 non-malignant tumors represented 68% of all primary CNS tumors in US [6]. In Europe, the European Network of Cancer Registries (ENCR) guidelines [7] recommends the registration of all intracranial and intraspinal cases, irrespective of their behavior. However, only selected cancer registries in the United Kingdom [8,9] and Scandinavia [10–12], as well as specialized brain tumor registries emerging in France [13] and Austria [14], are currently following such guidelines. This, together with the highly heterogeneous incidence rates reported across Europe [15] and the scarce published information on survival [15,16] prompts an underestimation of the real burden of all CNS tumors.

The infra-registry of non-malignant CNS tumors has been confirmed for Southern Europe [17] where this study is set in. In previous reports, we described the epidemiology of malignant CNS tumors in the Girona province [18,19]. In the present study, we sought to estimate population-based incidence and survival of all primary CNS tumors, for the first time in Spain, by sex, age at diagnosis, behavior, and histology, over a 20-year period (1994–2013).

2. Material and methods

2.1. Population

We compiled incident cases of primary malignant and non-malignant CNS tumors reported to the population-based Girona Cancer Registry (GCR) – Northeast of Spain (covering a population of 748,341 inhabitants in 2013) – during 1994–2013 [20]. However, non-malignant CNS tumor registry is not mandatory in our region, and thus, before the study onset, the GCR did not systematically recode non-malignant cases before the study. To overcome this infra-registry, we requested, to all the registry information sources, all benign or uncertain CNS cases diagnosed during the period of study. This approach was incorporated in the routine GCR data collection procedures thereafter. Therefore, we raised the completeness of the GCR for CNS tumors to 96.39%, similar to that reported for all cancer sites (94.91%) [21].

All cases were retrospectively revised in order to classify them according to the 2007 WHO Classification [22]. The following ICD-O-3 codes [2] were considered: brain (C71.0–C71.9), meninges (C70.0–C70.9), spinal cord, cranial nerves, and other parts of the CNS (C72.0–C72.9), pituitary and pineal glands (C75.1–C75.3), olfactory tumors of the nasal cavity [C30.0 (9522–9523)] and lymphomas and leukemia (9590–9989) occurring at any CNS site (Appendix, Tables A1 and A2).

Tumors were categorized by behavior and by histological subtype following the grouping scheme used by the CBTRUS [6] to ensure comparability. The study population was further stratified by sex and grouped by age at diagnosis into five categories: children (<15 y), adolescents (15–24 y), middle-aged adults (25–64 y), and elderly persons (65–84 y and ≥75 y separately).

2.2. Data analysis

Overall and sex-specific crude incidence rates (CRs) and their 95% confidence intervals (95% CI) were calculated and expressed per 100,000 person-years. Age-standardized incidence rates were calculated using the European (IR), US (IR_{US}), and World (IR_w) reference populations. Time trends related to IRs were assessed through a log-linear model using Joinpoint Software (version 4.3.1.0) and expressed as the estimated annual percent change (EAPC). $P < 0.05$ was considered statistically significant.

Survival analysis was performed on a dataset excluding death certificate only (DCOs) and those cases diagnosed at autopsy. Patients were followed from date of diagnosis to date of last known vital status; i.e. death by any cause, loss of follow-up, or end of follow-up at 31st December 2014, whichever came first. Vital status of patients was obtained by linking records to the Catalan Registry of Mortality and the National Death Index [23]. 1- and 5-year observed survival (OS) was estimated by sex, age-group, histological type, behavior and period (1994–1998, 1999–2003, 2004–2008 and 2009–2013) using the Kaplan-Meier method and statistical differences between curves were estimated using the Log-rank test. We repeated the analysis for relative survival (RS) using the Pohar-Perme method [24].

3. Results

3.1. Population description

During 1994–2013, a total of 2,131 cases of primary CNS tumors were registered. There were 986 men (46.27%) and 1,145 women (53.73%) of whom 1,962 were adults and 117 pediatric patients (0–19 years). The mean age (SD) at diagnosis was 57.89(20.29) years overall, and 66.94(11.86) years when only adults were considered.

Overall, there were 1,417 (66.5%) cases with microscopical verification (MV), whereas only 54 (2.8%) were diagnosed by DCO, 2 (0.1%) at autopsy and in 35 cases (1.8%) the diagnostic method was unknown (data not shown). The percentage of cases that lacked MV (Appendix, Fig. A1) increased progressively with age, moving from a 1.68% in pediatric patients to a 48.88% in patients >74 years old.

3.2. Incidence

The overall CR of CNS tumors was 16.85, corresponding to IR = 18.5 (95% CI:17.70; 19.30). Globally, more women were diagnosed (sex ratio (SR) = 0.95) (Table 1) with an annual average of new cases of 57.25 and 49.3 in women and men, respectively. Age-specific incidence rates by sex are shown in Fig. 1. Incidence was similar across childhood tumors and rose progressively by adolescence, with a marked incidence peak at 70–74 and a drastic decrease ahead of 80 years. Despite women showed a more sharpened distribution of the incidence rates by age, incidence trends were similar for both sexes.

Overall, the proportion of non-malignant and malignant CNS tumors was similar (Table 1); non-malignant tumors constituted 49.8% (IR = 9.14) of all cases; whereas malignant CNS tumors accounted for the remaining 50.2% (IR = 9.35). However, this

distribution differed according to sex with a SR = 0.63 for non-malignant tumors (58.7% and 39.5% for women and men, respectively).

Neuroepithelial tumors constituted the largest group of primary brain tumors (42.7%, IR = 7.83), ahead of the tumors of the meninges (29.6%; IR = 5.61), tumors of the sellar region (9.8%; IR = 1.71), unclassified tumors (9.8%; IR = 1. 87), tumors of the cranial and spinal nerves (4.6%; IR = 0.081), lymphomas and other hematopoietic neoplasms (2.6%; IR = 0.48) and germ cells tumors and cysts (1.0%; IR = 0.18). Together, neuroepithelial and tumors of the meninges accounted for approximately 75% of all CNS tumors. However, this distribution pattern varied according to sex: neuroepithelial tumors represented a 49.6% in men—i.e. the most incident histological type—and a 36.8% in women, being the first and second most incident histological types respectively.

Histological subtypes are presented in more detail in Table 1. The most frequently reported subtype overall was meningioma (28.1%; IR = 5.35) followed by glioblastoma (21.7%; IR = 4.17). The sex distribution differed between the two; the first being more common in women (SR = 0.53) and the second in men (SR = 1.47). None of the other histological subtypes exceeded the 10% of all cases. Overall, meningioma was the most common non-malignant histology; however, we found 6 malignant meningioma cases in our dataset during the 20-year period (1%; IR = 0.051 (0.0; 0.14), data not shown).

3.3. Incidence time trends

Table 2 shows the EAPC for CNS tumors during 1994–2013 by sex, age-group and histology, stratified by behavior. Overall, there was a positive trend for all CNS (EAPC = 2.1) but only due to the contribution of non-malignant tumors (EAPC = 4.1). This pattern was similar in both sexes (EAPCs for non-malignant tumors were 5.32 and 4.0 in men and women, respectively) and was present in all age groups, with the exception of the 15–44 years age-group which showed a stable trend. Interestingly, the >74 years age-group showed the highest increase in the incidence rate of non-malignant tumors (EAPC = 8.1) as well a positive trend in malignant cases (EAPC = 4.1).

Histological groups with insufficient number of patients were excluded of the analysis and results are not presented by behavior due to limited sample size. Tumors of the cranial and spinal nerves and tumors of meninges were the only tumor types with a significant positive incidence trend (EAPC = 5.1 and 6.0, respectively).

3.4. Survival

1- and 5-year OS and RS for patients diagnosed with malignant and non-malignant CNS tumors are presented in Table 3 by sex, age group, histological subtype and behavior. Global 5-year RS was 51%

Table 1
Twenty years total, %, annual average and incidence rates for primary central nervous system tumors by histology and gender. Girona province, 1994–2013.

Histological subtype	Total					Men					Women				
	N	%	IR	95% CI	Mean age	(SD)	N	%	IR	95% CI	N	%	IR	95% CI	SR
Tumors of neuroepithelial tissue	**910**	**42.7**	**7.83**	**(7.32;8.36)**	**54.04**	**(22.38)**	**489**	**49.6**	**8.73**	**(7.96;9.58)**	**421**	**36.8**	**7.09**	**(6.42;7.81)**	**1.23**
Pilocytic astrocytoma	35	1.6	0.28	(0.19;0.39)	22.40	(18.80)	11	1.1	0.17	(0.08;0.33)	24	2.1	0.39	(0.25;0.59)	0.44
Diffuse astrocytoma	113	5.3	0.93	(0.76;1.12)	48.26	(22.35)	53	5.4	0.89	(0.66;1.19)	60	5.2	0.99	(0.75;1.28)	0.90
Anaplastic astrocytoma	56	2.6	0.48	(0.36;0.62)	53.77	(18.01)	30	3.0	0.51	(0.34;0.75)	26	2.3	0.44	(0.28;0.64)	1.16
Unique astrocytoma variants	31	1.5	0.26	(0.18;0.38)	54.61	(21.01)	16	1.6	0.29	(0.16;0.49)	15	1.3	0.24	(0.14;0.41)	1.21
Glioblastomas	463	21.7	4.17	(3.80;4.57)	63.97	(14.60)	265	26.9	5.05	(4.45;5.72)	198	17.3	3.44	(2.97;3.96)	1.47
Oligodendroglioma	21	1.0	0.17	(0.10;0.26)	45.52	(10.53)	8	0.8	0.12	(0.05;0.27)	13	1.1	0.21	(0.11;0.37)	0.57
Anaplastic oligodendroglioma	8	0.4	0.06	(0.03;0.13)	44.50	(10.24)	6	0.6	0.09	(0.03;0.24)	2	0.2	0.03	(0.00;0.12)	3.00
Oligoastrocytic tumors	6	0.3	0.05	(0.02;0.11)	45.83	(9.35)	2	0.2	0.03	(0.00;0.15)	4	0.3	0.07	(0.02;0.18)	0.43
Ependymal tumors	48	2.3	0.38	(0.28;0.51)	39.90	(23.06)	27	2.7	0.43	(0.28;0.65)	21	1.8	0.33	(0.21;0.52)	1.30
Glioma malignant, NOS	56	2.6	0.5	(0.38;0.65)	57.04	(26.79)	29	2.9	0.55	(0.37;0.82)	27	2.4	0.46	(0.30;0.67)	1.20
Choroid plexus tumors	5	0.2	0.04	(0.01;0.09)	8.80	(12.76)	2	0.2	0.03	(0.00;0.15)	3	0.3	0.05	(0.01;0.14)	0.60
Neuronal and mixed neuronal-glial tumors	22	1.0	0.17	(0.11;0.27)	31.77	(23.43)	13	1.3	0.19	(0.10;0.36)	9	0.8	0.15	(0.07;0.29)	1.27
Tumors of the pineal region	13	0.6	0.1	(0.05;0.18)	42.54	(25.79)	6	0.6	0.08	(0.03;0.22)	7	0.6	0.12	(0.05;0.25)	0.67
Embryonal tumors	33	1.5	0.25	(0.17;0.35)	18.82	(16.37)	21	2.1	0.31	(0.19;0.51)	12	1.0	0.18	(0.09;0.32)	1.72
Tumors of cranial and spinal nerves	**97**	**4.6**	**0.81**	**(0.66;0.99)**	**52.28**	**(16.66)**	**40**	**4.1**	**0.7**	**(0.50;0.98)**	**57**	**5.0**	**0.93**	**(0.70;1.22)**	**0.75**
Tumors of meninges	**630**	**29.6**	**5.61**	**(5.18;6.07)**	**63.54**	**(15.61)**	**206**	**20.9**	**3.91**	**(3.39;4.51)**	**424**	**37.0**	**7.13**	**(6.47;7.86)**	**0.55**
Meningioma	599	28.1	5.35	(4.92;5.80)	63.95	(15.38)	189	19.2	3.63	(3.12;4.20)	410	35.8	6.9	(6.25;7.61)	0.53
Mesenchymal tumors	9	0.4	0.08	(0.04;0.15)	60.44	(14.34)	3	0.3	0.06	(0.01;0.20)	6	0.5	0.1	(0.04;0.22)	0.60
Other neoplasms related to meninges	22	1.0	0.18	(0.11;0.28)	53.73	(19.40)	14	1.4	0.23	(0.12;0.41)	8	0.7	0.13	(0.06;0.27)	1.77
Lymphomas and other hematopoietic neoplasms	**55**	**2.6**	**0.48**	**(0.36;0.63)**	**58.93**	**(16.42)**	**31**	**3.1**	**0.54**	**(0.37;0.79)**	**24**	**2.1**	**0.42**	**(0.27;0.63)**	**1.29**
Germ cell tumors and cysts	**22**	**1.0**	**0.18**	**(0.11;0.27)**	**37.41**	**(18.96)**	**11**	**1.1**	**0.18**	**(0.09;0.35)**	**11**	**1.0**	**0.18**	**(0.09;0.32)**	**1.00**
Tumors of sellar region	**208**	**9.8**	**1.71**	**(1.48;1.97)**	**50.40**	**(18.66)**	**94**	**9.5**	**1.67**	**(1.34;2.06)**	**114**	**10.0**	**1.8**	**(1.48;2.16)**	**0.93**
Tumors of the pituitary	191	9.0	1.58	(1.36;1.82)	51.51	(17.86)	83	8.4	1.49	(1.18;1.87)	108	9.4	1.7	(1.39;2.06)	0.88
Craniopharyngioma	17	0.8	0.14	(0.08;0.22)	37.94	(23.18)	11	1.1	0.18	(0.09;0.35)	6	0.5	0.09	(0.03;0.21)	2.00
Unclassified tumors	**209**	**9.8**	**1.87**	**(1.62;2.14)**	**69.54**	**(17.20)**	**115**	**11.7**	**2.4**	**(1.97;2.91)**	**94**	**8.2**	**1.5**	**(1.21;1.85)**	**1.60**
Hemangioma	13	0.6	0.11	(0.06;0.19)	50.38	(12.58)	4	0.4	0.06	(0.02;0.20)	9	0.8	0.15	(0.07;0.29)	0.40
Neoplasm, unspecified	196	9.2	1.76	(1.52;2.03)	70.81	(16.72)	111	11.3	2.34	(1.91;2.84)	85	7.4	1.35	(1.35;1.08)	1.73
Behavior															
Malignant	**1070**	**50.2**	**9.35**	**(8.80;9.94)**	**59.11**	**(20.59)**	**597**	**60.5**	**11.09**	**(10.20;12.05)**	**473**	**41.3**	**7.94**	**(7.24;8.70)**	**1.40**
Non-malignant	**1061**	**49.8**	**9.14**	**(8.59;9.71)**	**56.65**	**(19.91)**	**389**	**39.5**	**7.05**	**(6.35;7.81)**	**672**	**58.7**	**11.11**	**(10.28;12.0)**	**0.63**
Total	**2131**	**100.0**	**18.49**	**(17.70;19.30)**	**57.89**	**(20.29)**	**986**	**100.0**	**18.14**	**(17.00;19.35)**	**1145**	**100.0**	**19.05**	**(17.96;20.20)**	**0.95**

IR, European age-standarized incidencerate; NOS, not otherwise specified; SR, sex ratio; SD: standard deviation.

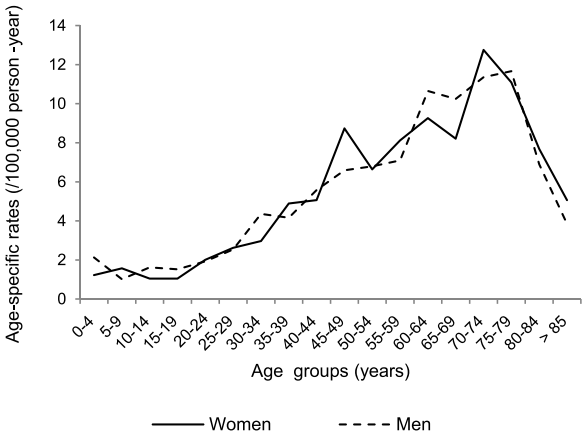

Fig. 1. Age-specific incidence rates of primary central nervous system tumors by gender. Girona province, 1994–2013.

Table 2
Estimated annual percentage change of primary central nervous system tumors overall and by sex, age-groups, histological subtype and behavior. Girona province, 1994–2013.

	Total		Malignant		Non-malignant	
	EAPC	Period	EAPC	Period	EAPC	Period
Total	2.1 (1.6; 2.7)*	1994–2013	0,2 (−0,7; 1,2)	1994–2013	4,1 (3,2; 5,1)*	1994–2013
Sex						
Men	1.7 (0.9; 2.5)*	1994–2013	0,8 (−1,7; 3,4)	1994–2013	5,32 (2,4; 8,3)*	1994–2013
Women	2.6 (1.6; 3.5)*	1994–2013	0,9 (−2,2; 4,0)	1994–2013	4,0 (2,0; 6,0)*	1994–2013
Age-group						
0-14 years	−0,30 (3.9; 3.4)	1994–2013	−2,9 (-8,0; 2,6)	1994–2013	4,3 (0,2; 8,5)*	1994–2013
15–44 years	−2,9 (-5.5; −0.2)*	1994–2013	−2,1 (-5,1; 1,1)	1994–2013	0,4 (−2,7; 3,5)	1994–2013
45–64 years	1,4 (0,2; 2.7)*	1994–2013	−0,5 (-3,7; 2,8)	1994–2013	2,8 (0,2; 5,4)*	1994–2013
65–74 years	9.2 (1.8; 17.1)*	1994–2001	0,3 (−2,2; 2,9)	1994–2013	5,3 (2,2; 8,6)*	1994–2013
	0.4 (−1.8; 2.6)	2001–2013				
>74 years	9.5(5.7; 13.5)*	1994–2013	4,1 (0,6; 7,8)*	1994–2013	8,1 (5,1; 11,2)*	1994–2013
Histological subtype						
Tumors of neuroepithelial tissue	0.4 (−0.5; 1.4)	1994–2013	–	–	–	–
Tumors of cranial and spinal nerves	5.1 (1.6; 8.7)*	1994–2013	–	–	–	–
Tumors of meninges	6.0 (4.9; 7.1)*	1994–2013	–	–	–	–
Lymphoma and other hematopoieteic neoplasms	–		–	–	–	–
Germ cell tumors and cysts	–		–	–	–	–
Tumors of sellar region	7.8 (−1.1; 2.9)	1994–2013	–	–	–	–
NOS	-0.8 (-5.7; 4.4)	1994–2013	–	–	–	–

EAPC, estimated annual percentage change (using European age-standarized incidencerate rates); NOS, not otherwise specified; * statistically significant.

(95% CI: 48.7; 53.5), higher in women than men (Table 3). 1-year RS decreased gradually with age. Similarly, 5-year RS showed a decreasing pattern from 64.9% for the 0–14 age group to 23.0% for the >74 age group, with a peak in survival for the 15–24 age group (70.0%, 95% CI: 59.8; 81.9) (Table 3).

Tumors of the sellar region, tumors of the cranial and spinal nerves and tumors of the meninges had the highest 5-year RS (94.1%, 93.5% and 80.5%, respectively). On the contrary, unclassified tumors, lymphomas and other hematopoietic neoplasms and tumors of the neuroepithelial tissue had a particularly low RS (15.2%, 17.2% and 24.3%, respectively) (Table 3).

Among tumors of the neuroepithelial tissue, pilocytic astrocytoma was the histological subtype with the highest 5-year RS (94.4%, 95% CI: 86.7; 100) followed by ependymal tumors (52.1%, 95% CI: 38.5; 70.6). 5-year RS for glioblastoma was the lowest within the neuroepithelial tissue tumors (3.7%, 95% CI: 2.3; 6.2) together with anaplastic astrocytoma (8.6%, 95% CI: 3.7; 20.2). Overall, tumors of the pituitary were the histological subtype with the highest 5-year RS (95%, 95% CI: 89.5; 100) followed by meningioma (80.2%, 95% CI: 75.9; 84.7).

Malignant tumors had a steeper decrease in survival with longer time after diagnosis whereas non-malignant tumors had a less steep trend (Table 3) for both sexes. Overall, no significant differences were found for survival by period, neither in malignant nor in non-malignant tumors (i.e. $p = 0.744$ and $p = 0.058$, respectively, data not shown).

4. Discussion

Herein, we present the first data on CNS tumor incidence and survival rates and 20-year trends in Spain for all histological types, including benign, uncertain and malignant tumors.

4.1. Incidence

Completeness of non-malignant CNS tumor data requires accurate diagnosis, reporting and registration. The EUROCARE project evidenced a lack of systematic registration of non-malignant CNS tumor among European registries in 2012, when the first report on CNS tumors epidemiology in Europe was presented [17]. While the overall IR of malignant CNS tumors was 7.9 and uniform across the continent, there was a marked regional variability in the IR of non-malignant tumors, ranging from 1.3 in Central and Eastern Europe to 8.5 in Northern Europe. With this

Table 3
Twenty years total and 5-year observed survival for primary central nervous system tumors by sex, age-group, histological subtype, and behavior. Girona province, 1994–2013.

	n	1-y OS	95% CI	5-y OS	95% CI	1-y RS	95% CI	5-y RS	95% CI
Total	2131	62.8	(60.7; 64.9)	47.8	(45.6; 50.0)	63.8	(61.8; 66.0)	51.0	(48.7; 53.5)
Sex									
Men	986	57.3	(54.2; 60.5)	39.7	(36.6; 43.0)	58.3	(55.2; 61.5)	42.6	(39.2; 46.2)
Women	1145	67.4	(64.7; 70.2)	54.7	(51.8; 57.8)	68.6	(65.9; 71.4)	58.3	(55.1; 61.7)
Age-group									
0-14 years	91	91.2	(85.6; 97.2)	64.8	(55.3; 75.9)	91.2	(85.6; 97.2)	64.9	(55.5; 75.9)
15–44 years	411	82.4	(73.8; 91.9)	69.8	(59.5; 81.9)	82.4	(73.9; 91.9)	70.0	(59.8; 81.9)
45–64 years	682	75.5	(72.9; 78.2)	60.8	(57.8; 64.0)	76.2	(73.6; 78.9)	62.2	(59.1; 65.4)
65–74 years	453	45.6	(42.3; 49.2)	31.7	(28.6; 35.2)	46.9	(43.6; 50.6)	37.1	(33.3; 41.2)
>74 years	494	30.6	(22.2; 42.1)	9.8	(4.7; 20.5)	35.2	(25.7; 48.3)	23.0	(11.5; 46.2)
Histological subtype									
Tumors of neuroepithelial tissue	**910**	**45.1**	**(42.0; 48.5)**	**23.6**	**(21.0; 25.7)**	**45.6**	**(42.4; 48.9)**	**24.3**	**(21.5; 27.4)**
Pilocytic astrocytoma	35	97.1	(91.8; 100)	94.0	(86.3; 100)	97.2	(91.9; 100)	94.4	(86.7; 100)
Diffuse astrocytoma	113	60.2	(51.8; 69.9)	44.3	(35.9; 54.6)	60.9	(52.5; 70.7)	44.9	(36.4; 55.5)
Anaplastic astrocytoma	56	50.0	38.5; 65.0)	8.5	(3.4; 21.2)	50.2	(38.8; 65.1)	8.6	(3.7; 20.2)
Unique astrocytoma variants	31	48.4	(33.6; 69.6)	29.3	(16.4; 52.3)	48.8	(34.3; 69.6)	30.3	(16.1; 57.2)
Glioblastoma	463	24.0	(20.4; 28.3)	3.3	(2.0; 5.6)	24.4	(20.8; 28.7)	3.7	(2.3; 6.2)
Oligodendroglioma	21	95.2	(86.6; 100)	69.1	(51.2; 93.3)	95.4	(86.9; 100)	69.9	(52.3; 93.6)
Ependymal tumors	48	79.2	(68.5; 91.5)	50.2	(36.8; 68.6)	79.6	(68.9; 91.9)	52.1	(38.5; 70.6)
Glioma malignant, NOS	56	39.3	(28.4; 54.5)	23.2	(14.4; 37.4)	39.4	(28.6; 54.5)	24.0	(15.1; 38.1)
Neuronal and mixed neuronal-glialtumors	22	90.9	(79.7; 100)	75.3	(58.5; 96.9)	86.5	(73.3; 100)	75.9	(59.3; 97.1)
Embryonal tumors	33	78.8	(66.0; 94.0)	37.6	(24.0; 59.0)	78.8	(66.2; 93.8)	37.7	(24.4; 58.5)
Tumors of cranial and spinal nerves	**97**	**92.8**	**(87.8; 98.1)**	**88.7**	**(82.3; 95.7)**	**94.2**	**(89.5; 99.1)**	**93.5**	**(86.9; 100)**
Tumors of meninges	**630**	**86.1**	**(83.5; 88.9)**	**73.4**	**(69.8; 77.1)**	**87.9**	**(85.2; 90.7)**	**80.5**	**(76.4; 84.9)**
Meningioma	599	86.1	(83.3; 88.9)	73.0	(69.3; 76.9)	87.9	(85.1; 90.8)	80.2	(75.9; 84.7)
Other neoplasms related to meninges	22	86.4	(73.2; 100)	86.4	(73.2; 100)	86.9	(75.2; 100)	86.9	(75.2; 100)
Lymphomas and oher hematopoietic neoplasms	**55**	**29.6**	**(19.6; 44.7)**	**16.5**	**(8.8; 31.1)**	**29.8**	**(19.9; 44.6)**	**17.2**	**(9.3; 31.7)**
Germ cell tumors and cysts	**22**	**77.3**	**(61.6; 96.9)**	**72.7**	**(56.3; 93.9)**	**77.4**	**(61.9; 96.7)**	**73.2**	**(57.0; 94.1)**
Tumors of sellar region	**208**	**96.2**	**(93.6; 98.8)**	**90.0**	**(85.8; 94.4)**	**96.5**	**(93.9; 99.2)**	**94.1**	**(88.7; 99.7)**
Tumors of the Pituitary	191	97.4	(95.1; 99.7)	90.7	(86.4; 95.2)	97.7	(95.5; 100)	95.0	(89.5; 100)
Craniopharyngioma	17	82.4	(66.1; 100)	82.4	(66.1; 100)	82.4	(66.6; 100)	83.2	(67.2; 100)
Unclassified tumors	**209**	**19.3**	**(14.0; 26.4)**	**13.9**	**(9.4; 20.5)**	**20.2**	**(14.7; 27.7)**	**15.2**	**(10.2; 22.6)**
Behavior									
Malignant	1070	36.2	(33.3; 39.2)	16.1	(13.9; 18.6)	36.7	(33.9; 39.9)	16.9	(14.6; 19.5)
Non-malignant	1061	88.8	(87.0; 90.8)	79.2	(76.6; 81.8)	90.3	(88.4; 92.2)	84.8	(81.8; 87.8)

OS, observed survival; RS, relative survival.

analysis, we recovered non-malignant CNS primary tumors for the period 1994–2013 in Girona and raised the incidence of non-malignant tumors reported in the EUROCARE study [17] from 1.4 (95% CI: 1.0; 1.8) to 9.14 (95% CI: 8.56; 9.71). These data illustrate the degree to which primary CNS tumor incidence is underestimated when case registration is limited to malignant neoplasms. Likewise, before the registration of non-malignant tumors was mandatory in the US, Gurney GJ et al. found an increase of 28% in the overall incidence rate of CNS tumors in children when non-malignancies were considered [3]. Standardizing by US reference population, our non-malignant incidence rate resembles to that reported by the Austrian Brain Tumor Registry [13], but yet is far from that reported by the CBTRUS (IR_{US} = 15.18) [6] (Appendix, Table A1). Overall, the IR of all CNS tumors in our region was found to be similar to that reported by Gironde in 2000–2007 [13], slightly lower compared to Austria [14] and still markedly lower in comparison with the CBTRUS [6] data (Appendix, Table A1). By contrast, our incidence was higher to that reported by UK (IR_W = 9.21) [8] or Norway (IR_W = 9.53) [12] cancer registries

The 66.5% of MV present in this study (65.1% and 68.4% for malignant and non-malignant tumors, respectively) was remarkably lower than that reported by the Gironde registry (79.3%). In addition, the proportion of cases without MV increased over the time (EAPC = 3.9, 95% CI: 2.4; 5.4) and with advanced age (Appendix, Fig. A1), in contrast to what was found in the RARECARE project [25], especially among the elderly. We hypothesize that, due to the highly developed imaging departments in our area and the frail health status of the elderly, clinicians and neuro-surgeons show a more conservative attitude toward prescribing an invasive diagnostic procedure.

Overall incidence increased over the 20-year study period (EAPC = 2.1%), mainly driven by an increase in the incidence of tumors of the meninges and tumors of cranial and spinal nerves. In addition, this increase was more pronounced in women and in elderly, especially in patients over 74 years, consistent with the literature [6,13,14]. Not only improvements in registration, diagnosis, and clinical practice, but also changes in potential risk factors may explain such trends [9]. Moreover, evidence show that the incidence of other cancers, usually associated with brain metastases, is greater among the elderly [13], so misclassification of some secondary tumors could be suspected, especially in the absence of MV. The debate about the increase in CNS tumors in most countries and especially in elderly persons is still open and thus, a more extensive follow up of complete and reviewed CNS data is needed.

4.2. Survival

The 5-year RS was higher in women—attributed to lower comorbidities and better performance [17]—and in younger people, consistent with previous literature [6,16]. Evidence places age as a major prognostic factor with a relative excess risk of death (RER) 6.1 times higher for patients over 75 years old compared to patients aged 15–44 years old considering only MV tumors of the CNS [17]. Worse response to radiotherapy and chemotherapy, comorbidities and higher risk of complications have been suggested as age-associated risk factors contributing to this trend [26].

According to our results, histology subtype and grade are important prognostic factors, especially for 5-year survival. This is supported by the high variability in survival between

Table A1
Central nervous system tumors histology groupings used by the Central Brain Tumor Registry of the United States (CBTRUS) [6].

Histology	ICD-O−3[a] Histology Code
Tumors of neuroepithelial tissue	
Pilocytic astrocytoma	9421, 9425[b]
Diffuse astrocytoma	9400, 9410, 9411, 9420
Anaplastic astrocytoma	9401
Unique astrocytoma variants	9381, 9384, 9424
Glioblastoma	9440, 9441, 9442[c]
Oligodendroglioma	9450
Anaplastic oligodendroglioma	9451, 9460
Oligoastrocytic tumors	9382
Ependymal tumors	9383, 9391, 9392, 9393, 9394
Glioma malignant, NOS	9380, 9431c, 9432c
Choroid plexus tumors	9390
Other neuroepithelial tumors	9363, 9423, 9430, 9444
Neuronal and mixed neronal; glial tumors	8680, 8681, 8690, 8693, 9412, 9413, 9442[d], 9492 (excluding site C75.1), 9493, 9505, 9506, 9522, 9523
Tumors of the pineal region	9360, 9361, 9362, 9395
Embryonal tumors	8963, 9364, 9470, 9471, 9472, 9473, 9474,9480, 9490, 9500, 9501, 9502, 9508
Tumors of cranial and spinal nerves	
Nerve sheath tumors	9540, 9541, 9550, 9560, 9561, 9570, 9571
Other tumors of cranial and spinal nerves	9562
Tumors of meninges	
Meningioma	9530, 9531, 9532, 9533, 9534, 9537, 9538, 9539
Mesenchymal tumors	8324, 8800, 8801, 8802, 8803, 8804, 8805, 8806, 8810, 8815, 8824, 8830,8831, 8835, 8836, 8850, 8851, 8852, 8853, 8854, 8857, 8861, 8870, 8880,8890, 8897, 8900, 8901, 8902, 8910, 8912, 8920, 8921, 8935, 8990, 9040, 9136,9150, 9170, 9180, 9210, 9241, 9260, 9373
Primary melanocytic lesions	8720, 8728, 8770, 8771
Other neoplasms related to meninges	9161, 9220, 9231, 9240, 9243, 9370, 9371, 9372, 9535
Lymphomas and other hematopoietic neoplasms	
Lymphoma	9590, 9591, 9596, 9650, 9651, 9652, 9653, 9654, 9655, 9659, 9661,9662, 9663, 9664, 9665, 9667, 9670, 9671, 9673, 9675, 9680, 9684,9687, 9690, 9691, 9695, 9698, 9699, 9701, 9702, 9705, 9714, 9719,9728, 9729
Other hemopoietic neoplasms	9727, 9731, 9733, 9734, 9740, 9741, 9750, 9751, 9752, 9753, 9754, 9755,9756, 9757, 9758, 9760, 9766, 9823, 9826, 9827, 9832, 9837, 9860, 9861, 9866, 9930, 9970
Germ cell tumors and cysts	
Germ cell tumors, cysts and heterotopias	8020, 8440, 9060, 9061, 9064, 9065, 9070, 9071, 9072, 9080, 9081, 9082,9083, 9084, 9085, 9100, 9101
Tumors of sellar region	
Tumors of the Pituitary	8040, 8140, 8146, 8246, 8260, 8270, 8271, 8272,8280, 8281, 8290, 8300, 8310, 8323, 9492 (Site C75.1 only), 9582
Craniopharyngioma	8280, 8281, 8290, 8300, 8310, 8323, 9492 (Site C75.1 only), 9582, 9350, 9351, 9352
Unclassified tumors	
Hemaningioma	9120, 9121, 9122, 9123, 9125, 9130, 9131, 9133, 9140
Neoplasm, unspecified	8000, 8001, 8002, 8003, 8004, 8005, 8010, 8021
All other	8320, 8452, 8710, 8711, 8713, 8811, 8840, 8896, 8980, 9173, 9503, 9580

NOS, not otherwise specified.
[a] International Classification of Disease for Oncology, 3rd Edition, 2000. World Health Organization, Geneva, Switzerland.
[b] Morphology 9442/3 only.
[c] Morphology 9442/1 only.

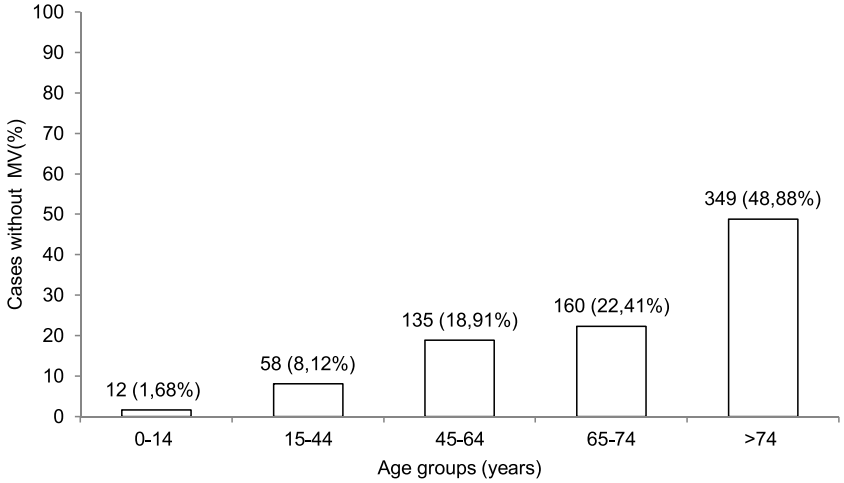

Fig. A1. Primary central nervous system tumors without microscopical verification (%) by age-group in the Girona province (1994–2013).

morphological sub-groupings reported for Europe [17] and illustrated in this present study. Neuroepithelial tumors, the most incident group, showed a 5-year RS of 24.3% (95% CI: 21.5; 27.4), significantly higher than that reported for Spain by the EUROCARE-5 for the period 2000–2007 (17.0%, 95% CI: 14.2; 18.9) [15]. The recovery of most non-malignant CNS primary tumors by GCR and the high variability in the registration of non-malignant tumors by different European registries [17] may contribute to such disparities.

Tumor subtypes with favorable survival included, pilocytic astrocytoma (94.4%) and meningioma (80.2%). However, meningioma survival was found to be lower than in other European regions [17]. We attribute these disparities to variations in the registration or reporting practice. The classification used in this current study considers benign (/0), uncertain (/1) and malignant (/3) meningioma as a sole group. In contrast, some brain tumor registries evaluate these variants separately, showing 5-year RS of 96.0% (95% CI: 94.4; 97.4) [6], 86.9% (95% CI: 80.7; 91.8) [16], and 65.2% (95% CI: 61.8; 68.4) for benign, uncertain and malign meningioma, respectively [6]. Both uncertain and malignant meningioma have been associated to a 5- to 10-fold greater progression risk and significant lower survival expectations, usually associated to higher rates of cause-specific mortality and less response to treatment[27]. This is supported by the great variability found in the 5-year RS between European regions (from 93.4 in Northern Europe to 79.5 in Eastern Europe) [15,17].

Tumors with the least favorable outcome included glioblastoma, with a 5-year RS of 3.7% (95% CI: 2.3; 6.2), similar to the EUROCARE figures [15]. A phase III randomized trial [28] reported significantly better OS, specially short-term, for patients with WHO grade IV glioblastoma receiving radiotherapy with concomitant and six-cycles of adjuvant temozolomide instead of radiotherapy alone (2-year OS 27.2% and 10.9%, respectively). In previous reports, we found an increase in the survival of glioblastoma patients by 2005, after the introduction of temozolomide in Spain [19]. However, despite these concrete improvements, survival for all CNS tumors did not improve in our region in consonance with international literature [15,17]. This indicates the absence of any remarkable advance in the treatment with a significant impact on the overall survival of patients diagnosed with a CNS primary over the 20-year period of study, notwithstanding major developments in diagnosis and management of other solid cancers [17].

4.3. Strengths and weaknesses

This study did have some limitations including the retrospective nature of the study and the regionalism of the data used. As it can be expected, access to early data could not always be granted, slightly raveling the reliability of early data. In addition, we did not have access to private medical clinics and consequently, although few, those cases could not be evaluated. However, the use of real-world data, the big sample size (N = 2,131) and the long follow-up period provided further reliability to the results. The use of a decentralized method for cancer registration was a potential source of variability due. Nevertheless, a laborious recovery of non-malignant tumors, as well as the retrospective revision and classification according to the 2007 WHO classification of all existing cases by a working group of clinicians added an extra value to this study.

5. Conclusion

In summary, we present a large, comprehensive, and up-to-date analysis of incidence and survival data of malignant and non-malignant primary CNS tumors in Girona (Spain) obtained from a high-quality cancer registration system. To the authors knowledge this is the first population-based study in Spain—the second in Southern Europe—to analyze both tumor incidence and survival of all primary CNS tumors regardless of behavior. This information will contribute to estimate the real burden of CNS tumors in Europe and will serve as a baseline for future analysis, allowing comparison with other registries' data.

Conflicts of interest

None.

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Appenidx A

Table A2
Central nervous system tumors site groupings used by the Central Brain Tumor Registry of the United States (CBTRUS) [6].

Site	ICD-O−3[a] Site Code
Cerebrum	C71.0
Frontal lobe of brain.	C71.1
Temporal lobe of brain	C71.2
Parietal lobe of brain	C71.3
Occipital lobe of brain	C71.4
Ventricle	C71.5
Cerebellum	C71.6
Brain stem	C71.7
Other brain	C71.8-C71.9
Overlapping lesion of brain	C71.8
Brain, NOS	C71.9
Spinal cord and cauda equina	C72.0-C72.1
Spinal cord	C72.0
Cauda equina	C72.1
Cranial nerves	C72.2-C72.5
Olfactory nerve	C72.2
Optic nerve	C72.3
Acoustic nerve	C72.4
Cranial nerve, NOS	C72.5
Other nervous system	C72.8-C72.9
Overlapping lesion of brain and central nervous system	C72.8
Nervous system, NOS	C72.9
Meninges (cerebral & spinal)	C70.0-C70.1, C70.9
Cerebral meninges	C70.0
Spinal meninges	C70.1
Meninges, NOS	C70.9
Pituitary and craniopharyngeal duct	C75.1-C75.2
Pituitary gland	C75.1
Craniopharyngeal duct	C75.2
Pineal gland	C75.3
Olfactory tumors of the nasal cavity[b]	C30.0

NOS, not otherwise specified.
[a] International Classification of Disease for Oncology, 3rd Edition, 2000. World Health Organization, Geneva, Switzerland.
[b] ICD-O-3 histology codes 9522–9523 only.

Table A3
Girona province (1994–2013) incidence rates of primary central nervous tumors by sex and behavior. Comparison with United States (CBTRUS) [6], Gironde [13] and Austria (ABTR) [14] specialized brain tumor registries.

	GCR 1994–2013 IR_{US}	GCR 2009–2013 IR_{US}	CBTRUS 2009–2013 IR_{US}	Austria 2005 IR_{US}	Gironde 2000–2007 IR_{US}
Male	14.40 (13.5;15.3)	15.61 (13.9; 17.4)	20.10 (20.0; 20.2)	17.80 (16.8; 18.9)	14.92
Female	15.51 (14.6;16;4)	17.74 (15.9; 19.6)	24.46 (24.4; 24.6)	18.60 (17.6; 19.7)	16.94
Malignant	7.42 (7.0;7.9)	7.13 (6.3; 8.0)	7.18 (7.1; 7.2)	8.80 (8.3; 9.3)	–
Non-malignant	7.45 (7.0;7.9)	9.49 (8.6; 10.5)	15.18 (15.1;15.2)	Benign: 7.4 (7.0;7.9) Uncertain: 2.0 (1.7; 2.2)	–
Total	14.49 (14.2;15.5)	16.63 (15.4; 17.9)	22.36 (22.3;22.4)	18.10 (17.4;18.9)	15.95

GCR, Girona Cancer Registry; CBTRUS, Cancer Brain Tumor Registry United States.
IR_{US}, United States age-standardized incidence rate.

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