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Survival of European patients with central nervous system tumors

Milena Sant[1], Pamela Minicozzi[1], Susanna Lagorio[2], Tom Børge Johannesen[3], Rafael Marcos-Gragera[4], Silvia Francisci[2,5] and the EUROCARE Working Group[6]

[1] Analytical Epidemiology Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, Milan, Italy
[2] National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome, Italy
[3] Cancer Registry of Norway, Department of Clinical and Registry-based Research, Institute of Population-based Cancer Research, Fridj of Nansens vei 19, Majorstuen, Oslo, Norway
[4] Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health and Catalan Institute of Oncology, Girona, Spain
[5] Department of Cancer Epidemiology, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome, Italy
[6] See Appendix for EUROCARE Working Group members

We present estimates of population-based 5-year relative survival for adult Europeans diagnosed with central nervous system tumors, by morphology (14 categories based on cell lineage and malignancy grade), sex, age at diagnosis and region (UK and Ireland, Northern, Central, Eastern and Southern Europe) for the most recent period with available data (2000–2002). Sources were 39 EUROCARE cancer registries with continuous data from 1996 to 2002. Survival time trends (1988 to 2002) were estimated from 24 cancer registries with continuous data from 1988. Overall 5-year relative survival was 85.0% for benign, 19.9% for malignant tumors. Benign tumor survival ranged from 90.6% (Northern Europe) to 77.4% (UK and Ireland); for malignant tumors the range was 25.1% (Northern Europe) to 15.6% (UK and Ireland). Survival decreased with age at diagnosis and was slightly better for women (malignant tumors only). For glial tumors, survival varied from 83.5% (ependymoma and choroid plexus) to 2.7% (glioblastoma); and for non-glioma tumors from 96.5% (neurinoma) to 44.9% (primitive neuroectoderm tumor/medulloblastoma). Survival differences between regions narrowed after adjustment for morphology and age, and were mainly attributable to differences in morphology mix; however UK and Ireland and Eastern Europe patients still had 40% and 30% higher excess risk of death, respectively, than Northern Europe patients (reference). Survival for benign tumors increased from 69.3% (1988–1990) to 77.1% (2000–2002); but survival for malignant tumors did not improve indicating no useful advances in treatment over the 14-year study period, notwithstanding major improvement in the diagnosis and treatment of other solid cancers.

Published data on the survival of patients with central nervous system (CNS) tumors are largely based on clinical studies. Some survival studies derived from the population-based data provided by cancer registries (CRs) are available, but the tumors are grouped into broad categories that include disparate morphologies of widely varying prognoses.[1–3] These studies indicate that survival for malignant glial tumors is generally low, and that survival for benign tumors (*e.g.*, meningioma) is considerably better. However, information on benign tumors is collected by relatively few CRs.[1,4,5]

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Correspondence to: Milena Sant, Analytical Epidemiology Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy, Tel: +39 02 23903520; Fax: +39-02-23903516, E-mail: milena.sant@istitutotumori.mi.it

The population-based EUROCARE study (European Cancer Registry-Based Study on Survival and Care of Cancer Patients) on malignant brain tumors diagnosed in Europe between 1985 and 1989 found that age-standardized 5-year relative survival varied little across Europe, but was conspicuously low in Scotland, Estonia and Poland, and varied more in younger patients.[6] The influence of morphology mix or other factors on survival differences across Europe was not investigated. This study also found an overall increase in survival with time (1978 to 1989), which was most marked in younger patients, and mainly confined to 1-year survival in older patients.

By contrast, a population-based SEER study on US patients indicated that the survival of adult and elderly patients with most types of CNS tumors remained substantially stable over the period 1973–2001.[7] However systematic survival comparisons between Europe and US patients with CNS tumors—that might explain this difference—do not appear to be available.

Although survival for selected CNS morphologies was investigated as part of the RARECARE project, based on EUROCARE data,[8–10] we are aware of no systematic studies

Table 1. Number of CNS tumor cases archived by 72 European cancer registries and diagnosed in 1995–2002, by country and European region, with indicators of data quality and age-adjusted incidence rates

European region	Country	Cancer registry	No. of cases without major errors	DCO and autopsy cases (%[1])	Lost cases (%[1])	Cases eligible for survival analysis	MV[2] cases (%)	Benign cases (%)	Censored[3] cases 1995–1998 (%)	Incidence per 100,000 benign cases (95% CI)[4]	Incidence per 100,000 malignant cases (95% CI)[4]
Northern Europe	Denmark	Denmark	4,217	2.2	0.0	4,123	65.0	53.9	0.9	9.9 (9.5–10.3)	8.4 (8.1–8.8)
	Finland	Finland[5]	5,784	7.1	0.0	5,376	88.0	51.4	1.1	8.3 (8.0–8.6)	7.8 (7.5–8.1)
	Iceland	Iceland[5]	252	3.6	0.0	243	86.0	43.2	0.0	7.3 (6.0–8.8)	8.7 (7.3–10.3)
	Norway	Norway[5]	5,499	3.4	0.0	5,310	70.1	48.0	0.0	8.9 (8.5–9.2)	9.5 (9.1–9.8)
	Sweden	Sweden[5]	9,317	5.0	0.1	8,846	93.7	53.7	1.1	8.2 (8.0–8.4)	7.0 (6.8–7.2)
	Total Northern Europe		**25,069**	**4.7**	**0.0**	**23,898**	**82.1**	**51.8**	**0.8**	**8.5 (8.4–8.7)**	**7.9 (7.7–8.0)**
UK and Ireland	Ireland	Ireland[5]	3,053	3.2	0.0	2,954	74.1	32.8	0.7	4.6 (4.3–4.9)	9.5 (9.1–9.9)
	England	East Anglia[5]	2,974	1.2	7.2	2,724	76.8	40.8	29.9	7.3 (6.9–7.7)	8.5 (8.1–8.9)
		Mersey	1,230	8.2	0.0	1,129	69.4	34.4	0.5	4.2 (3.8–4.6)	7.7 (7.1–8.2)
		North Western	2,315	2.3	0.0	2,263	65.1	42.9	0.0	5.4 (5.1–5.8)	7.4 (7.0–7.8)
		Northern and Yorkshire[5]	4,819	1.8	0.0	4,732	72.6	36.6	0.0	4.5 (4.3–4.7)	7.8 (7.5–8.1)
		Oxford[5]	1,454	0.9	0.0	1,441	91.4	1.7	0.3	0.1 (0.1–0.2)	8.1 (7.7–8.5)
		South Western	4,391	8.6	0.0	4,015	62.8	42.6	0.9	6.1 (5.8–6.4)	8.3 (8.0–8.7)
		Thames	6,911	13.3	0.0	5,991	74.6	34.5	0.6	3.9 (3.7–4.1)	8.0 (7.8–8.3)
		Trent	2,857	7.5	0.0	2,643	63.9	37.1	0.0	5.0 (4.7–5.3)	8.5 (8.1–8.9)
		West Midlands[5]	4,507	8.5	0.0	4,125	77.8	40.8	0.0	5.0 (4.8–5.3)	7.1 (6.8–7.4)
	Northern Ireland	Northern Ireland[5]	1,181	1.1	0.0	1,168	54.5	31.1	0.7	3.5 (3.1–3.9)	7.9 (7.3–8.4)
	Scotland	Scotland[5]	3,889	1.5	0.0	3,832	64.7	26.7	0.1	2.8 (2.6–2.9)	7.9 (7.6–8.2)
	Wales	Wales[5]	1,898	8.4	0.0	1,738	45.8	4.6	0.0	0.4 (0.3–0.5)	8.5 (8.1–8.9)
	Total UK and Ireland		**41,479**	**6.1**	**0.5**	**38,755**	**69.9**	**33.8**	**2.1**	**4.1 (4.1–4.2)**	**8.0 (7.9–8.1)**
Central Europe	Austria	Austria[5]	4,486	17.7	0.8	3,660	90.9	1.2	7.7	0.1 (0.0–0.1)	7.9 (7.6–8.1)
	Belgium	Flemish[5]	2,706	0.4	0.0	2,695	91.3	28.1	1.1	2.9 (2.7–3.1)	7.3 (7.0–7.7)
	France	Bas Rhin	168	0.0	0.0	168	71.4	0.0	0.0	na	7.1 (6.1–8.3)
		Calvados	81	0.0	0.0	81	93.8	0.0	0.0	na	5.5 (4.4–6.9)
		Doubs	85	0.0	1.2	84	92.9	0.0	0.0	na	7.4 (5.8–9.1)
		Haut Rhin	121	0.0	0.0	121	93.4	0.0	0.0	na	7.0 (5.8–8.3)
		Hérault	192	0.0	5.7	181	0.0	21.0	0.0	2.2 (1.6–2.9)	6.7 (5.6–7.9)
		Isère	376	0.0	25.3	281	82.9	26.0	0.4	6.7 (5.7–7.8)	8.3 (7.2–9.5)
		Manche	80	0.0	0.0	80	88.8	12.5	0.0	0.8 (0.4–1.5)	5.9 (4.6–7.6)

Table 1. Number of CNS tumor cases archived by 72 European cancer registries and diagnosed in 1995–2002, by country and European region, with indicators of data quality and age-adjusted incidence rates (Continued)

European region	Country	Cancer registry	No. of cases without major errors	DCO and autopsy cases (%[1])	Lost cases (%[1])	Cases eligible for survival analysis	MV[2] cases (%)	Benign cases (%)	Censored[3] cases 1995–1998 (%)	Incidence per 100,000 benign cases (95% CI)[4]	Incidence per 100,000 malignant cases (95% CI)[4]
		Somme	88	0.0	2.3	86	74.4	1.2	0.0	0.1 (0.0–0.1)	6.4 (5.1–7.9)
		Tarn	82	0.0	0.0	82	64.6	15.9	0.0	1.2 (0.6–2.1)	6.8 (5.2–8.7)
	Germany	Saarland[5]	1,123	4.9	1.2	1,055	93.6	45.1	15.0	6.3 (5.7–6.9)	7.3 (6.7–7.9)
	Switzerland	Basel	193	0.5	4.2	184	97.8	2.2	1.9	0.1 (0.1–0.2)	6.7 (5.8–7.8)
		Geneva[5]	274	3.7	0.0	264	81.8	14.4	0.0	2.3 (1.9–2.7)	8.0 (7.0–9.1)
		St. Gallen[5]	280	3.2	0.0	271	79.3	4.4	14.9	1.7 (1.4–1.9)	7.6 (6.7–8.6)
		Ticino[5]	162	9.9	0.0	146	78.1	0.0	0.0	na	7.9 (6.7–9.2)
		Valais	58	5.2	0.0	55	83.6	7.3	21.8	0.2 (0.0–0.5)	6.1 (4.6–8.0)
	The Netherlands	Amsterdam[5]	1,365	0.2	1.0	1,348	82.0	1.5	1.0	1.5 (1.1–2.0)	7.4 (7.0–7.8)
		Eindhoven	539	0.0	5.6	509	88.4	19.1	0.0	0.5 (0.3–0.8)	7.5 (6.7–8.2)
		North Netherlands	1,050	1.1	0.0	1,038	84.8	18.6	0.0	0.0 (0.0–0.2)	7.3 (6.8–7.8)
		Twente[5]	535	1.1	0.0	529	78.3	17.2	0.0	0.5 (0.1–1.3)	5.7 (5.2–6.3)
	Total Central Europe		**14,044**	**6.5**	**1.5**	**12,918**	**86.7**	**14.5**	**4.0**	**1.3 (1.2–1.4)**	**7.4 (7.3–7.5)**
Eastern Europe	Czech Republic	West Bohemia[5]	479	12.1	0.6	418	78.7	6.5	7.1	0.5 (0.3–0.7)	7.7 (7.0–8.5)
	Poland	Cracow[5]	434	0.5	0.2	431	51.3	4.9	1.5	0.4 (0.2–0.6)	8.3 (7.5–9.2)
		Kielce[5]	865	0.0	0.0	865	52.0	0.9	0.0	0.1 (0.0–0.2)	11.0 (10.2–11.7)
		Warsaw[5]	1,132	4.2	0.8	1,076	59.7	4.9	0.4	0.4 (0.3–0.6)	9.0 (8.4–9.5)
	Slovakia	Slovakia[5]	2,683	17.4	2.2	2,156	87.5	29.7	0.0	2.2 (2.0–2.3)	6.3 (6.0–6.6)
	Total Eastern Europe		**5,593**	**10.3**	**1.3**	**4,946**	**71.4**	**15.2**	**0.7**	**1.3 (1.2–1.4)**	**7.7 (7.5–7.9)**
Southern Europe	Italy	Alto Adige[5]	276	1.8	0.0	271	67.2	0.0	1.6	na	8.2 (7.3–9.3)
		Biella[5]	240	0.4	0.0	239	54.4	59.4	0.0	8.2 (6.9–9.8)	5.9 (4.7–7.3)
		Ferrara[5]	317	3.2	0.0	307	56.0	0.0	0.0	na	9.7 (8.6–10.9)
		Firenze[5]	2,024	0.6	0.4	2,003	44.3	55.7	2.0	11.0 (10.3–11.7)	8.7 (8.1–9.4)
		Friuli V.G.	825	2.3	0.0	806	60.2	0.0	0.0	na	7.7 (7.1–8.3)
		Genova	1,397	2.0	0.0	1,369	45.3	64.6	0.4	13.6 (12.6–14.6)	7.6 (6.9–8.4)
		Macerata	141	5.0	0.0	134	44.8	0.0	1.7	na	8.8 (7.3–10.4)
		Modena[5]	435	1.6	0.0	428	47.9	0.0	0.0	na	8.3 (7.5–9.1)
		Napoli	203	4.9	0.5	192	59.4	14.6	1.0	1.4 (0.9–2.1)	9.4 (8.1–10.9)

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European region	Country	Cancer registry	No. of cases without major errors	DCO and autopsy cases (%[1])	Lost cases (%[1])	Cases eligible for survival analysis	MV[2] cases (%)	Benign cases (%)	Censored[3] cases 1995–1998 (%)	Incidence per 100,000 benign cases (95% CI)[4]	Incidence per 100,000 malignant cases (95% CI)[4]
		Parma[5]	678	0.0	0.0	678	59.0	46.8	0.0	8.8 (7.8–9.9)	9.8 (8.7–10.9)
		Ragusa[5]	337	4.2	0.0	323	47.1	45.8	0.0	7.6 (6.4–8.9)	8.4 (7.2–9.8)
		Reggio Emilia[5]	265	0.0	0.0	265	37.4	1.1	0.0	0.1 (0.0–0.4)	8.2 (7.2–9.4)
		Romagna[5]	1,342	2.8	0.0	1,305	67.4	42.4	0.9	6.2 (5.7–6.8)	9.2 (8.5–9.9)
		Salerno	540	5.9	3.5	489	60.1	0.8	0.0	0.1 (0.0–0.2)	9.3 (8.5–10.1)
		Sassari[5]	430	4.9	0.0	409	48.4	23.7	0.0	2.9 (2.4–3.6)	9.6 (8.6–10.7)
		Torino	579	3.3	0.0	560	40.9	0.9	0.0	0.1 (0.0–0.2)	8.2 (7.5–8.9)
		Trento	277	2.9	0.0	269	2.6	0.0	0.0	na	10.4 (9.2–11.8)
		Umbria[5]	668	1.4	0.0	659	58.3	0.0	0.0	na	9.1 (8.4–9.8)
		Varese	349	1.4	0.6	342	61.7	1.8	3.7	0.2 (0.1–0.4)	8.6 (7.7–9.6)
		Veneto	981	2.9	0.0	953	68.6	0.0	0.0	na	8.2 (7.7–8.8)
	Malta	Malta[5]	271	4.4	0.0	259	78.0	41.3	0.9	4.6 (3.8–5.6)	6.8 (5.8–7.9)
	Portugal	South Portugal	528	0.0	0.0	528	91.1	2.3	1.4	0.2 (0.1–0.3)	6.4 (5.9–7.0)
	Slovenia	Slovenia[5]	825	2.7	0.0	803	85.8	3.0	0.0	0.2 (0.1–0.3)	6.0 (5.6–6.5)
	Spain	Basque Country	902	5.9	0.0	849	69.6	1.3	0.0	0.1 (0.1–0.2)	9.1 (8.5–9.7)
		Girona[5]	408	3.9	0.0	392	66.3	13.8	0.0	1.4 (1.0–1.8)	8.7 (7.7–9.7)
		Murcia	247	6.1	0.8	230	61.3	1.3	0.9	0.1 (0.0–0.3)	7.0 (6.1–8.0)
		Navarra	349	4.3	0.6	332	55.4	24.4	0.4	3.5 (2.8–4.3)	10.5 (9.2–11.9)
		Tarragona	284	9.9	0.0	256	63.3	0.8	1.0	0.1 (0.0–0.3)	10.4 (9.2–11.7)
	Total Southern Europe		**16,118**	**2.7**	**0.2**	**15,650**	**58.0**	**23.0**	**0.6**	**2.3 (2.2–2.4)**	**8.1 (7.9–8.2)**
All cases			**102,303**	**5.5**	**0.5**	**96,167**	**73.3**	**33.0**	**1.7**	**3.9 (3.8–3.9)**	**7.9 (7.8–7.9)**

[1]Percentages of cases without major errors. [2]Microscopically verified cases. [3]Less than five years of follow-up. [4]Incidence is age-adjusted with weightings of the European standard population; CI = confidence interval.
[5]Cancer registries contributing to period estimates of five-year relative survival. na: Data not available for benign tumors

on survival trends for European patients diagnosed with CNS tumors.

The first aim of the present study was to estimate 5-year relative survival for adult European patients diagnosed with CNS tumors, by morphology, sex, age at diagnosis and European region, for the most recent period for which population-based data are available (2000–2002).

The second aim was to estimate changes in 5-year relative survival for CNS tumors, overall and by European region, over the period 1988–2002.

Methods

Cases

The source of cases was the EUROCARE-4 dataset of all incident cancers archived by population-based European CRs. A detailed description of the EUROCARE-4 dataset, and its quality control and analytical methods, has been published elsewhere.[11] Briefly, cases were collected according to a standardized protocol, and quality control and statistical analyses were carried out centrally using a uniform methodology.

We were interested in adult patients (age 15 years or more at diagnosis) diagnosed with CNS tumors. We therefore examined the cases from 72 EUROCARE CRs in 24 European countries that collect data on CNS tumors.

Because for most cases, follow-up (vital status information) was only available up to the end of 2003, we used the period approach[12] to estimate 5-year relative survival from follow-up information available for patients who were alive at some point during the period 2000–2002. In this approach, survival for the unavailable years is estimated from the survival experience of patients diagnosed in preceding years[12]; and implies the use of data on patients diagnosed in years before 2000. The approach provides a prediction of what the 5-year survival for patients diagnosed during 2000–2002 will be when sufficient follow-up information is available. Only 39 EUROCARE CRs had continuous survival data from 1996 to 2002, from which it was possible to produce survival estimates by the period approach for cases alive at some point in 2000–2002. Table 1 shows the numbers of cases archived and data quality indicators for the 72 CRs that collected data on CNS tumors, and also identifies the 39 CRs used to produce the period survival estimates.

To estimate time trends in 5-year relative survival we used the data from the 24 EUROCARE CRs that had continuous incident data from 1988 to 2002.

CRs were grouped by country, and countries were grouped into regions: Northern Europe (Denmark, Finland, Iceland, Norway, Sweden), United Kingdom and Ireland (England, Scotland, Wales, Northern Ireland, Republic of Ireland), Central Europe (Austria, Belgium, France, Germany, Switzerland, The Netherlands), Eastern Europe (Czech Republic, Poland, Slovakia) and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain). Age at diagnosis was divided into five categories: 15–44, 45–54, 55–64, 65–74, 75–99 years.

Tumor morphology and topography were coded according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3).[13] The following topography codes were included: C70 (meninges), C71 (brain), C72 (spinal cord, cranial nerves and other parts of the CNS). Morphology codes were grouped into 14 categories based on cell lineage and grade of malignancy, as determined from the nervous system tumor classifications of the World Health Organization[14] and the US Central Brain Tumor Registry.[15] The 14 categories are: ependymoma and choroid plexus tumor (ICD-O-3 codes: 9390–9394); astrocytoma not otherwise specified (NOS) and other subtypes (9400, 9410, 9420, 9424); anaplastic astrocytoma (9401, 9411); pilocytic astrocytoma (9421–9423); glioblastoma (9440–9442); oligodendroglioma (9450); anaplastic oligodendroglioma (9451-9460); other glioma (9380–9384, 9490–9506, 9522–9523); miscellaneous non-glioma CNS tumor; primitive neuroectodermal tumor (PNET) and medulloblastoma (9363–9364, 9413, 9430, 9470–9480); anaplastic, malignant and benign meningioma (9530–9539); neurinoma (9540–9580); blood vessel tumor (9120–9173); and CNS tumor of unspecified morphology (8000–8002).

The category "miscellaneous non-glioma CNS tumor," subsequently referred to as "non-glioma tumor," includes: epithelial tumor (8010–8050, 8260–8530), adenoma and adenocarcinoma (8140–8246), Leydig cell tumor (8680–8711), melanoma (8720–8730), sarcoma (8800–8963, 9180–9240), germ cell tumor (9060–9110, 9508), chraniopharyngioma and pineocytoma (9350–9362), and chordoma (9370–9371). Benign tumors were identified from the fifth digit (0, 1) of the ICD-O-3 morphology code.

Table 2 lists the 14 morphology groupings and proportion of cases in each grouping as a percentage of all microscopically verified (MV) cases for each country.

The survival analysis by morphology was carried out on data from the 38 CRs that had available morphology data coded according to ICD-O-3. The Danish CR was excluded from the analyses by morphology because consent to analyze morphology was not obtained; the Finnish CR was excluded because ICD-O-3 coding had not been adopted by 2002; Hérault (France) and Trento (Italy) were excluded because complete morphology data were not available. Following these exclusions, 67 CRs were included in the descriptive analyses by morphology. The survival analyses by sex, age at diagnosis and European region were carried out on cases from the 39 CRs.

Statistical methods

We used the direct method to estimate incidence per 100,000 person-years, age-standardized to the European standard population, with 95% confidence intervals (CIs) for benign and malignant CNS tumors diagnosed in 1995–2002, by CR.

We also estimated 5-year relative survival by sex, age, European region and morphology grouping for patients with CNS tumors who were alive at some point in 2000–2002,

Table 2. Number of cases and percentage distribution of morphology groupings by country for microscopically verified CNS tumors diagnosed in 1995–2002 by 67[1] European cancer registries

Country	No. of cases	Ependymoma and choroid plexus tumor	Astrocytoma NOS and other subtypes	Anaplastic astro-cytoma	Pilocytic astro-cytoma	Glioblast-oma	Oligo-dendro-glioma	Anaplastic oligodendro-glioma	Other glioma	Non-glioma tumor	PNET and medullo-blastoma	Menin-gioma	Neur-inoma	Blood vessel tumor	Unspecified morphology
Austria	3,328	2.6	15.7	2.4	1.3	52.8	1.3	0.6	5.8	0.4	3.3	9.2	2.6	0.2	1.8
Belgium	2,461	2.8	17.1	5.7	1.7	32.8	4.5	1.5	3.5	0.5	1.0	24.6	0.9	2.9	0.5
Czech Republic	329	0.9	16.1	10.3	1.5	45.3	1.8	1.8	9.8	0.9	0.9	6.7	0.9	2.2	0.9
France	808	1.5	13.8	3.8	1.4	43.6	13.6	1.7	7.4	0.4	1.6	7.9	2.1	0.5	0.7
Germany	987	1.6	3.7	1.0	1.1	35.8	1.8	1.1	6.3	1.5	0.8	36.3	5.7	1.6	1.7
Iceland	209	1.9	10.0	4.8	2.9	30.6	2.4	0.0	1.0	1.0	0.5	39.7	3.8	1.4	0.0
Ireland	2,190	1.8	12.0	9.2	1.6	31.2	2.6	1.2	4.2	0.4	0.9	19.6	12.5	2.2	0.6
Italy	6,355	2.7	9.0	6.7	0.6	39.2	3.9	1.0	6.7	0.6	1.2	23.5	2.7	1.1	1.1
Malta	202	1.5	7.9	7.4	1.0	26.2	1.5	0.5	5.9	1.0	0.5	39.1	4.5	0.5	2.5
The Netherlands	2,850	3.1	31.7	6.5	1.6	29.3	5.3	1.9	5.5	0.5	1.5	10.4	2.0	0.5	0.2
Norway	3,723	2.2	5.8	3.9	1.3	29.3	3.0	1.4	7.0	0.8	1.2	30.9	8.2	2.2	2.8
Poland	1,313	3.0	19.6	5.8	0.6	31.8	3.6	1.8	13.2	0.5	3.1	12.5	0.8	1.3	2.4
Portugal	481	4.2	20.0	4.6	2.3	43.4	6.9	5.2	5.6	0.8	1.2	3.1	0.2	0.6	1.9
Slovakia	1,887	2.8	17.5	14.6	2.1	20.8	3.3	1.6	1.8	0.3	0.6	28.9	4.9	0.3	0.5
Slovenia	689	2.6	5.8	10.2	3.6	57.9	5.5	3.8	3.9	1.0	2.3	2.2	0.3	0.0	0.9
Spain	1,338	4.0	23.8	8.1	2.1	34.3	3.2	0.7	8.6	1.0	2.1	9.7	0.4	0.3	1.7
Sweden	8,289	2.5	5.1	10.6	1.2	18.1	2.2	1.0	5.6	0.7	0.9	35.1	13.1	2.7	1.2
Switzerland	771	2.2	15.3	8.4	2.0	52.1	5.2	2.6	3.9	0.4	1.3	4.9	0.9	0.5	0.3
England	16,523	2.2	11.6	4.2	0.9	33.2	2.9	1.2	7.1	0.6	0.7	21.4	11.2	1.5	1.3
Northern Ireland	637	5.2	22.8	5.8	0.9	24.3	2.2	3.6	7.4	0.9	1.0	14.3	6.3	1.4	3.9
Scotland	2,478	2.3	10.4	5.2	1.5	43.3	3.5	2.2	7.1	0.9	1.1	12.4	5.6	2.6	1.9
Wales	796	1.6	16.2	6.0	0.5	36.7	5.0	0.9	21.6	0.3	2.3	4.2	0.6	0.5	3.6
All cases	58,644	2.5	12.2	6.3	1.2	33.1	3.3	1.3	6.5	0.6	1.2	21.6	7.2	1.6	1.4

[1]Only data from 67 CRs are shown, as morphology data for 5 CRs was either unavailable or of insufficiently high quality (for further details see text).

Table 3. Period estimates of 5-year relative survival for patients with benign and malignant CNS tumors alive in 2000–2002 by sex, age and European region

		Five-year relative survival (95%CI)[1]	
		Benign	Malignant
Sex	Female	**84.9** (83.5–86.2)	**21.7** (20.7–22.7)
	Male	**85.3** (83.4–87.2)	**18.5** (17.6–19.3)
Age (years)	15–44	**95.4** (94.2–96.4)	**49.7** (48.0–51.5)
	45–54	**94.8** (93.4–96.0)	**22.0** (20.4–23.6)
	55–64	**92.2** (90.4–93.8)	**11.9** (10.8–13.4)
	65–74	**78.1** (75.4–80.7)	**7.2** (6.3–8.1)
	75–99	**51.1** (47.2–54.9)	**4.6** (3.8–5.6)
European region	Northern Europe	**90.6** (89.2–91.9)	**25.1** (23.5–26.6)
	UK and Ireland	**77.4** (75.2–79.5)	**15.6** (14.7–16.6)
	Central Europe	**86.6** (80.9–91.2)	**24.9** (23.1–26.8)
	Eastern Europe	**78.2** (72.1–83.4)	**21.8** (19.7–24.2)
	Southern Europe	**84.5** (81.1–87.5)	**16.4** (14.8–18.0)
All cases		**85.0** (83.9–86.7)	**19.9** (19.2–20.6)

[1]95% confidence interval.

using the period approach, in which survival was estimated as the product of interval-specific relative survival values of cohorts of patients diagnosed in previous recent time periods.[12]

Relative survival is defined as the ratio of the observed survival of patients with cancer to the expected survival of persons of the same sex and age in the general population. The expected survival was estimated by the Hakulinen method[16] using CR area-specific official mortality data. To account for differences in the age structure of the different populations, relative survival was adjusted for age using the international standard for cancer survival analysis.[17]

For time trends, we estimated the 5-year relative survival of patients diagnosed in five consecutive 3-year periods (1988–1990, 1991–1993, 1994–1996, 1997–1999, 2000–2002). For those diagnosed in the first four periods survival was estimated by the cohort approach[16]; for those alive in 2000–2002, survival was estimated by the period approach.[12]

We also estimated the relative excess risks (RERs) of death[18] within 5 years of diagnosis (with 95%CI), for MV cases diagnosed in 1995–1999 (cases with full 5-year follow-up) using generalized linear models adjusted by European region, age at diagnosis, and morphological grouping. The models assumed that the observed number of deaths followed a Poisson distribution. The analyses were carried out using STATA[19]; the SEER*STAT software[20] was used to calculate the registry-specific age-standardized incidence of benign and malignant cancers.

Results

Data quality indicators

As shown in Table 1, 5.5% of cases overall were diagnosed from the death certificate only (DCO) or at autopsy, with generally high percentages—indicating poorer data quality—in the CRs of Eastern Europe, and low percentages in Southern Europe. Overall only 0.5% of cases were lost to follow-up, with satisfyingly low percentages in most individual CRs.

Overall 1.7% of cases diagnosed in 1995–1998 had less than 5 years of follow-up, ranging from 0.6% in Southern Europe to 4.0% in Central Europe. Overall 73.3% of cases were MV, ranging from 58.0% in Southern Europe to 86.7% in Central Europe. France and Switzerland were characterized by considerable within-country MV variation. Low MV figures also characterized most Eastern European CRs.

Overall 33.0% cases were benign, with highest percentages in Northern Europe (51.8%), followed by UK and Ireland (33.8%), Southern Europe (23.0%), Eastern Europe (15.2%) and Central Europe (14.5%). Several French and Italian CRs, as well as Ticino (Switzerland), do not register benign tumors and had no benign cases.

The last columns of Table 1 show incidence rates age-standardized to the European standard population. The overall incidence of malignant CNS tumors diagnosed in 1995–2002 was 7.9 per 100,000 person-years and was fairly uniform across areas. By contrast, regional variation in the incidence of benign tumors was marked, with overall incidence of 3.9 per 100,000 person-years, ranging from 1.3 (Central and Eastern Europe) to 8.5 (Northern Europe).

Distribution of morphology groupings

Table 2 shows the distribution of morphology groupings in each country for MV cases diagnosed in 1995–2002, in the 67 CRs with available information on morphology. Glioblastoma and astrocytoma NOS and other subtypes, formed the highest proportions of glial tumors overall. For most countries, glioblastomas constituted over 30% of CNS tumors.

Anaplastic astrocytoma constituted 6.3% and pilocytic astrocytoma 1.2% of CNS tumors overall. Oligodendroglioma, anaplastic oligodendroglioma and ependymoma and choroid plexus tumors were less common. The "other glioma" subtype constituted 6.5% of overall cases, with marked variation between countries; PNET and medulloblastoma were around 1%.

Meningioma was most common non-glioma tumor and second most common CNS tumor overall (21.6%; after glioblastoma), followed by neurinoma and blood vessel tumors. For these benign tumors, the proportion varied markedly with country, since many CRs did not register them systematically.[1,4,5]

Overall, 1.4% of all MV cases had unspecified morphology, with highest proportions in Northern Ireland and Wales, and lowest proportions in Belgium, Iceland, Ireland, The Netherlands, Slovakia and Switzerland.

Table 4. Period estimates of 5-year relative survival for patients with CNS tumors alive in 2000–2002 by morphological groupings and European region

	Period estimates of 5-year relative survival (95% confidence interval)					
Morphology grouping	Northern Europe	UK and Ireland	Central Europe	Eastern Europe	Southern Europe	All cases
Ependymoma and choroid plexus tumor	**86.3** (77.5–92.3)	**84.8** (77.0–90.5)	**83.8** (69.5–92.7)	**66.5** (47.6–80.5)	**88.1** (74.7–95.6)	**83.5** (79.0–87.3)
Astrocytoma NOS and other subtypes	**49.4** (42.7–55.8)	**39.0** (34.7–43.3)	**35.4** (29.9–40.9)	**28.0** (22.5–33.8)	**42.6** (33.9–51.1)	**38.5** (35.9–41.1)
Anaplastic astrocytoma	**10.8** (7.8–14.4)	**17.6** (13.5–22.2)	**28.8** (19.3–39.0)	**11.7** (7.1–17.4)	**18.1** (11.8–25.4)	**15.8** (13.6–18.2)
Pilocytic astrocytoma	**81.9** (68.4–90.3)	**80.6** (68.4–88.6)	**79.7** (62.6–89.9)	**57.3** (33.5–75.8)	**97.3** (74.7–100.0)	**80.5** (74.1–85.6)
Glioblastoma	**1.9** (1.2–2.9)	**2.2** (1.6–2.9)	**4.4** (3.2–5.9)	**2.2** (1.0–4.4)	**2.8** (1.8–4.3)	**2.7** (2.3–3.2)
Oligodendroglioma	**74.1** (64.4–81.8)	**65.8** (57.5–73.0)	**75.5** (61.8–85.2)	**47.8** (32.4–62.0)	**63.8** (51.4–74.1)	**67.2** (62.5–71.6)
Anaplastic oligodendroglioma	**35.1** (21.2–49.5)	**35.5** (24.4–46.9)	**29.7** (13.4–48.3)	**6.1** (1.3–16.6)	**33.3** (14.7–53.6)	**31.5** (25.0–38.3)
Other glioma	**46.6** (40.5–52.6)	**39.4** (34.2–44.7)	**38.5** (30.4–46.7)	**20.9** (12.6–30.9)	**27.0** (18.3–36.6)	**38.5** (35.4–41.7)
Non-glioma tumor	**88.1** (66.8–97.7)	**54.5** (36.2–70.2)	**51.7** (24.9–74.7)	**51.1** (10.4–83.8)	**69.5** (35.6–91.1)	**64.0** (53.0–73.5)
PNET and medulloblastoma	**48.9** (33.7–62.7)	**53.1** (37.8–66.4)	**53.2** (37.6–67.1)	**11.8** (2.7–28.2)	**30.7** (13.9–49.4)	**44.9** (37.6–52.0)
Meningioma	**93.4** (91.3–95.2)	**85.9** (82.8–88.7)	**89.0** (83.6–93.5)	**79.5** (73.1–85.0)	**84.2** (79.7–88.2)	**88.7** (87.2–90.0)
Neurinoma	**98.3** (95.7–100.0)	**97.6** (94.6–99.7)	**90.0** (76.5–97.8)	**80.2** (63.1–91.3)	**89.1** (75.4–96.9)	**96.5** (94.7–98.0)
Blood vessel tumor	**95.8** (88.5–99.6)	**93.5** (85.1–98.5)	**75.7** (22.1–97.1)	**52.2** (21.7–77.3)	**100.0** (–)	**93.1** (88.2–96.6)
Unspecified morphology	**70.7** (55.3–82.5)	**22.3** (12.5–34.4)	**35.0** (19.3–51.9)	**12.4** (2.8–30.4)	**40.4** (21.9–59.0)	**38.7** (31.5–45.9)

Survival, cases alive in 2000–2002

Table 3 shows 5-year relative survival for benign and malignant CNS tumors for patients alive at some point in 2000–2002, by sex, age and European region. Survival for benign tumors was similar in women (84.9%) and men (85.3%), whereas survival for malignant tumors was slightly better in women (21.7% *vs*.18.5%).

For both benign and malignant tumors, 5-year relative survival decreased with advancing age at diagnosis, however the decline was most marked for malignant tumors (from 49.7% at 15–44 years to 4.6% at 75–99 years).

When the youngest age class was split into 15–29 year and 30–44 year categories, 5-year relative survival was 95.6 and 95.4% for benign tumors, and 59.4 and 45.5% for malignant tumors, respectively (data not shown in tables).

As regards regional survival differences, these were marked for benign tumors, varying from 90.6% in Northern Europe to 77.4% in UK and Ireland. For malignant tumors, survival variation across Europe was more constrained, ranging from 25.1% in Northern Europe to 15.6% in UK and Ireland.

Survival by morphology

Table 4 shows period estimates of 5-year relative survival for patients followed-up to 2000–2002 according to morphological grouping and European region. Among tumors of glial origin, ependymoma and pilocytic astrocytoma had best (>80%) and glioblastoma had worst (2.7%) survival. Survival varied with malignancy grade: 38.5% for astrocytoma NOS and other subtypes; 15.8% for anaplastic astrocytoma; 67.2% for oligodendroglioma and 31.5% for anaplastic oligodendroglioma.

The most common benign CNS tumor was meningioma (5-year relative survival 88.7%). Malignant meningioma constituted 8.8% (1,110 cases) of all meningiomas, for which 5-year relative survival was 72.7% (data not shown in tables).

For most morphological groupings, survival was best in Northern Europe, significantly so for "other glioma" and meningioma (compared to overall). In Eastern Europe, survival was significantly lower than overall for astrocytoma NOS and other subtypes, oligodendroglioma, anaplastic oligodendroglioma, other glioma, meningioma, neurinoma and blood vessel tumors.

Relative excess risk of death

Table 5 shows the results of the multivariable analyses of MV cases diagnosed in 1995–1999 to estimate the relative excess risk (RER) of dying 5-years after diagnosis, in each European region, in each age category, and according to morphology, in comparison with the appropriate reference category (RER = 1, by definition). We present three models: Model 1 (crude); Model 2 adjusted by age at diagnosis; and Model 3 adjusted by age at diagnosis and morphology grouping. From Model 3, it is evident that patients diagnosed in UK and Ireland, Central Europe and Eastern Europe had 40%, 20% and 30% greater mortality, respectively, than patients diagnosed in Northern Europe (reference area), after adjusting for

Table 5. Multivariable regression estimates of relative excess risk (RER) of death within 5 years of diagnosis for microscopically verified CNS tumors diagnosed in 1995–1999

		No. of cases	Model 1 RER (95% CI)[1]	Model 2 RER (95% CI)[1]	Model 3 RER (95% CI)[1]
European region	Northern Europe	7,654	1 (reference)	1 (reference)	1 (reference)
	UK and Ireland	15,765	1.7 (1.66–1.80)	1.8 (1.75–1.90)	1.4 (1.33–1.44)
	Central Europe	7,137	2.1 (2.03–2.23)	2.2 (2.12–2.32)	1.2 (1.11–1.22)
	Eastern Europe	2,142	1.8 (1.71–1.95)	2.1 (1.96–2.24)	1.3 (1.26–1.44)
	Southern Europe	6,455	2.0 (1.93–2.13)	2.0 (1.87–2.06)	1.1 (1.02–1.12)
Age (years)	15–44	9,727		1 (reference)	1 (reference)
	45–54	7,944		1.8 (1.72–1.88)	2.0 (1.95–2.14)
	55–64	9,392		2.7 (2.56–2.78)	3.0 (2.90–3.17)
	65–74	8,933		3.5 (3.36–3.66)	4.5 (4.28–4.69)
	75–99	3,157		4.0 (3.75–4.18)	7.1 (6.70–7.53)
Morphology	Meningioma	8,097			1 (reference)
	Ependymoma and choroid plexus tumor	962			2.9 (2.48–3.40)
	Astrocytoma NOS and other subtypes	5,364			14.3 (13.18–15.48)
	Anaplastic astrocytoma	2,522			19.8 (18.20–21.57)
	Pilocytic astrocytoma	477			3.9 (3.15–4.85)
	Glioblastoma	12,639			25.8 (23.92–27.83)
	Oligodendroglioma	1,367			5.6 (4.97–6.24)
	Anaplastic oligodendroglioma	471			9.8 (8.54–11.22)
	Other glioma	2,647			13.6 (12.51–14.88)
	Non-glioma tumor	222			4.2 (3.26–5.30)
	PNET and medulloblastoma	478			12.4 (10.69–14.34)
	Neurinoma	2,742			0.3 (0.25–0.43)
	Blood vessel tumor	582			1.4 (1.08–1.82)
	Unspecified morphology	583			7.8 (6.77–8.88)

[1]95% confidence interval.

differences in age at diagnosis, and distribution of tumor morphology between regions. These excess risks of death were statistically significant (*i.e.*, the 95% CI does not include the risk (=1) for the reference category). By contrast, RERs of death in Southern Europe and Northern Europe did not differ significantly from reference. RER of death increased significantly with advancing age at diagnosis and was at a maximum in the oldest age category.

All morphological groupings except neurinoma had significantly greater RERs of death than meningioma (reference), after adjusting for age and region (Model 3). Neurinoma had significantly lower risk of death than reference. Glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma had the highest RERs of death.

Time trends in 5-year relative survival

Figure 1 shows 5-year age-adjusted relative survival for the five 3-year periods from 1988 to 2002, by European region, for malignant and benign CNS tumors. For benign tumors, overall (all regions together) survival varied from 69.3% in 1988–1990 to 77.1% in 2000–2002. In Northern and Central Europe most of this survival increase occurred from 1988 to 1999, with no changes in the last study years. In UK and Ireland and in Southern Europe the survival increase was evident throughout the study period. Survival declined slightly from 1997–1999 to 2000–2002 in Eastern Europe.

For malignant tumors, overall survival decreased from 14.3% to 12.1% in the period 1988–2002 and also decreased in three of the five regions, remaining stable in Southern Europe, and more or less stable in Central Europe.

We also analyzed changes in survival with time according to age at diagnosis: the survival increase for benign CNS tumors was greater in younger than older patients, increasing from 90.0% to 95.3% over the study period in patients of 15–54 years; from 83.9% to 92.3% in patients of 55–65 years; and from 62.3% to 67.2% in patients of 65–99 years (data not shown).

Discussion

This study provides the most recently available population-based analysis of the survival of European patients diagnosed

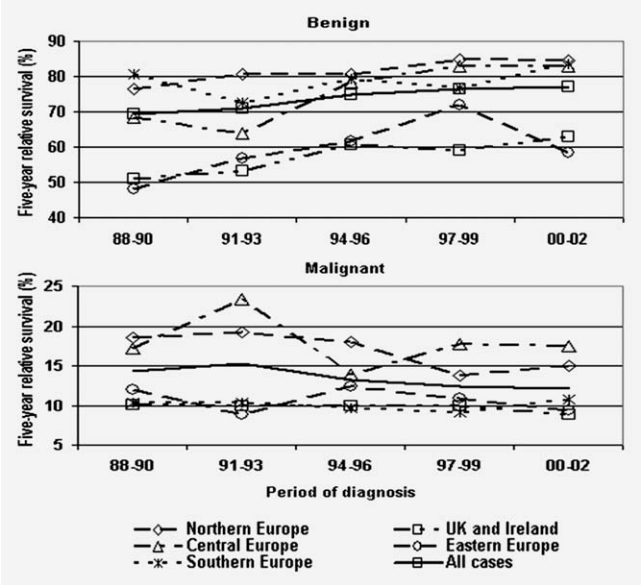

Figure 1. Age-adjusted trends in 5-year relative survival for benign and malignant CNS tumors over five 3-year periods spanning 1988–2002. Survival estimated on 24 CRs with continuous incident data from 1988 to 2002.

with CNS tumors. We chose a long study period (late 1980s to 2002) so as to be able to analyze survival changes over time. In a previous study we investigated survival for malignant brain tumors from 1978 to 1989,[6] however morphology information was incomplete partly because not all participating CRs coded their cases according to ICD-O-3, so survival analysis by morphology was not possible. Most European CRs have now adopted ICD-O-3 making it possible to analyze survival in relation to morphology.

The previous EUROCARE analysis was on malignant tumors only, whereas the present study also analyzed benign tumors. Previous analyses indicated that the EUROCARE databank is complete as regards malignant tumors[21] and the homogeneous incidence of malignant CNS tumors in the present study provides support for that conclusion. However not all CRs systematically register benign CNS tumors. Therefore much of the between CR and between country variation in the frequency of benign CNS tumors (meningioma, neurinoma and blood vessel tumor) is likely to be due to variations in registration practice. This bias is likely to be particularly important for meningioma as it is the most common CNS tumor in elderly people, and—depending on location—may be asymptomatic and only discovered incidentally or at autopsy.[22] Although our survival estimates for benign CNS tumors are not therefore complete we considered it important to present them since survival data on such cancers are scarce for Europe. The forthcoming EUROCARE-5 study will seek to remedy this situation by systematically including survival data for benign CNS tumors.

The variations in the proportion of morphology types across European regions and CRs suggest variations in coding practice, more than real differences in incidence. There was considerable between country variation in the proportion of unspecified morphology cases (from 0% to nearly 4%; Table 2). This is a data quality indicator, with lower percentage suggesting higher quality diagnostic ascertainment. Notwithstanding this problem, the variation of survival with morphology that we found is consistent with previous population-based findings. In particular, glioblastoma and anaplastic astrocytoma had worst survival, whereas ependymoma had relatively good survival.[2] However, 5-year relative survival for ependymoma was considerably higher (83.5%) in the present study than in a SEER study (70%) over a similar study period, although comparison is not straightforward because the SEER data were not age-adjusted, and included children, who have better survival than adults.[23]

The 5-year relative survival we found for glioblastoma (2.7%) is closely similar to that reported in the US,[24] Canada[25] and a study on the population of the Canton of Zurich that investigated genetic alterations in gliomas.[26]

We found excellent survival (about 80%) for pilocytic astrocytoma. The better survival (96% at 10 years) reported in the Canton of Zurich[26] is likely to be mainly due to the inclusion of childhood tumors, whose prognosis is considerably better than that of adults.

Studies analyzing tumor grade[27–30] and genetic alterations[26] report survival figures for anaplastic astrocytoma in line with ours, *i.e.*, somewhat better than for glioblastoma[31–33] but still poor.

We found that survival for oligodendroglioma was generally higher than for other glial tumors, and decreased with grade. A French clinical study reported 5-year survival at 88% for low grade, 64% for medium grade and 16% for high grade oligodendroglioma.[34]

We found that meningioma had excellent survival, in line with the 90% 5-year relative survival for cases diagnosed in 2001 reported by a Swedish population-based study.[35]

Our multivariable analysis, adjusted for age and European region, also showed that morphology was a major independent determinant of survival. The multivariable analysis also suggested a regional effect, with survival significantly higher in Northern Europe than other regions.

Adjustment for age and morphology markedly reduced these regional differences in survival, but in all regions except Southern Europe, the RER of death remained significantly higher than Northern Europe (reference).

Increasingly poorer survival for CNS tumors with advancing age at diagnosis has been reported by many population-based and clinical studies.[1,3,6,30,31,33] In addition to performance status, extent of surgery and intensity of treatment, age is a well-established prognostic determinant for glioblastoma[32,36,37] and meningioma.[38]

We found slightly better survival for women than men only for malignant tumors. For many cancers women survive longer than men, and this has been attributed to lower prevalence of comorbidities in women as well as better performance status (allowing full application of effective surgical and adjuvant treatments) and also to better "resistance" to disease.[39]

As well as depending on grade and morphology, survival for many CNS tumors is crucially dependent on anatomic location, since this is the main factor dictating whether radical excision is

possible, as exemplified in a study on meningioma.[22] We were unable to access reliable information on tumor location, or type of treatment in the present study and this hampers the interpretation of survival differences between regions.

We found that survival for benign CNS tumors increased in all regions, however survival for malignant tumors did not increase, in fact there was a small but consistent decline over the three most recent periods (1994–1996, 1997–1999, 2000–2002) compared to the previous period (1991–1993). Substantially stable survival for malignant CNS tumors has been reported by other studies,[40] and shows that no useful advances in the treatment of these tumors occurred over the study period, notwithstanding the major developments in the diagnosis and treatment of other solid cancers that occurred over this time, and which plausibly contributed to the documented survival improvements for several important non-CNS solid tumors.[41]

The survival increase over time for benign tumors is likely to be mainly due to earlier and more refined diagnosis than in the past as a result of improving imaging techniques.[4,40] Improved diagnostic imaging allows better identification of tumor type and extent than in the past, facilitating refinement of the surgical approach.[42] Some meningiomas are asymptomatic and diagnosed incidentally, thus their inclusion in survival series could inflate survival. However, rising meningioma incidence has also been suggested as related to increased use of hormone therapy (in women) and to environmental factors, such as exposure to electromagnetic fields.[4] Cranial irradiation may also be a risk factor for meningioma.[43] Innovative neurosurgical techniques are also likely to have contributed to a real increase in survival for benign and malignant CNS tumors, since complete resection would be easier and sequelae less for smaller tumors.[44] Improved diagnostic imaging also makes it possible to recognize benign or vascular lesions that in the past might have been confused with malignant lesions.

We found that survival differences between European regions were to a large extent explained by differences in morphology mix (and hence prognosis). Thus, after adjustment for morphology, the excess risk of death in Southern Europe disappeared and reduced markedly for Central Europe (still significant). Nevertheless, significantly higher RER of death risk persisted in UK and Ireland and Eastern Europe. Poor survival in Eastern Europe is plausibly due to lower expenditure on health in relation to smaller Gross Domestic Product compared to more wealthy European countries, suggesting inadequate treatment facilities.[45] For the UK, poorer outcomes for most solid cancers compared to European countries of comparable economic status seem to be mainly due to more advanced disease at diagnosis.[46] Although stage at diagnosis is not as important for CNS tumors as for other solid cancers, more refined diagnosis may increase survival for CNS tumors, either artificially by anticipating diagnosis (lead-time bias) or because more effective treatment can be applied if the diagnosis is precise.

To conclude, our study highlights the major influence of morphology on survival for CNS tumors and indicates that most survival differences between European regions, over the study period, were attributable to differences in morphology mix. An important and disquieting finding of this study is that survival for malignant CNS tumors did not improve over the 14-year study period. Nevertheless the introduction of new treatments (*e.g.*, temozolomide) after 2002, now used in many centers in Europe, gives grounds for hope that survival for many malignant brain cancers may have improved in recent years. New studies are required to assess the real (population-based) impact of the new treatments on survival.

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APPENDIX

EUROCARE-4 Working Group: Austria: W Oberaigner (Tyrol Cancer Registry); M Hackl (Austrian National Cancer Registry). Belgium: E Van Eycken; Martine Verstreken (Flemish Cancer Registry). Czech Republic: J Holub, L Jurickova (West Bohemia Cancer Registry). Denmark: HH Storm; G Engholm (Danish Cancer Society, Department of Cancer Prevention and Documentation). Finland: T Hakulinen (Finnish Cancer Registry). France: A Belot (FRANCIM); G Hédelin, M Velten (Bas-Rhin Cancer Registry); AV Guizard (Calvados General Cancer Registry); A Danzon (Doubs Cancer Registry); A Buemi (Haut-Rhin Cancer Registry); B Tretarre (Hérault Cancer Registry); M Colonna (Isère Cancer Registry); S Bara (Manche Cancer Registry); O Ganry (Somme Cancer Registry); P Grosclaude (Tarn Cancer Registry). Germany: H Ziegler (Saarland Cancer Registry). Iceland: L Tryggvadottir (Icelandic Cancer Registry). Ireland: H Comber (National Cancer Registry of Ireland). Italy: F Berrino (Project Leader), C Allemani, P Baili, R Ciampichini, L Ciccolallo, G Gatta, C Margutti, A Micheli, P Minicozzi, M Sant, S Sowe, C Tereanu, G Zigon (Fondazione IRCCS; "Istituto Nazionale dei Tumori"); G Tagliabue, P Contiero (Cancer Registry Unit—Varese Cancer Registry, Fondazione IRCCS, Istituto Nazionale dei Tumori); F Bellù (Registro Tumori Adige/Tumor register Südtirol); A Giacomin (Biella Cancer Registry); S Ferretti (Ferrara Cancer Registry); D Serraino L Dal Maso, M De Dottori, A De Paoli, L Zanier (Friuli Venezia Giulia Cancer Registry, Udine); M Vercelli, MA Orengo, C Casella, A. Quaglia (Liguria Cancer Registry, IST/Università di Genova); F Pannelli (Macerata Province Cancer Registry, Childhood Cancer Registry of Marche); M Federico, I Rashid, C Cirilli (Modena Cancer Registry); M Fusco (Napoli Cancer Registry); V De Lisi, F Bozzani (Parma Cancer Registry); R Tumino, MG La Rosa, E Spata, A Sigona (Cancer Registry Azienda Ospedaliera "Civile M.P.Arezzo" Ragusa, Italy); L Mangone (Reggio Emilia Cancer Registry); F Falcini, F Foca, S.Giorgetti (Romagna Cancer Registry-I.R.S.T); G Senatore, A Iannelli (Salerno Cancer Registry); M Budroni (Sassari Cancer Registry); R Zanetti, S Patriarca, S Rosso (Torino Cancer Registry); S Piffer, S Franchini (Trento Cancer Registry); E Paci, E Crocetti (Tuscany Cancer Registry); F La Rosa, F Stracci, T Cassetti (Umbria Cancer Registry); P Zambon, S Guzzinati (Veneto Cancer Registry, Istituto Oncologico Veneto—IRCCS, Padova); M Caldora, R Capocaccia, E Carrani, R De Angelis, S Francisci, E Grande, R Inghelmann, H Lenz, L Martina, P Roazzi, M Santaquilani, A Simonetti, A Tavilla, A Verdecchia (Centro Nazionale di Epidemiologia, Istituto Superiore di Sanità, Roma). Malta: M Dalmas (Malta National Cancer Registry). Norway: F Langmark, F Bray, TB Johannesen (Cancer Registry of Norway). Poland: J Rachtan (Cracow Cancer Registry), S Góźdź, U Siudowska, R Mezyk (Holycross Cancer Centre); M Bielska-Lasota (Independent Unit of Oncological Education, M. Sklodowska-Curie Cancer Centre, Warsaw); M Zwierko (Warsaw Cancer Registry). Portugal: A Miranda (Southern Portugal Cancer Registry). Slovakia: Chakameh Safaei Diba (National Cancer Registry of the Slovak Republic). Slovenia: M Primic-Źakelj (Cancer Registry of Slovenia). Spain: I Izarzugaza (Basque Country Cancer Registry); R Marcos-Gragera, ML Vilardell, A Izquierdo (Girona Cancer Registry); C Navarro, MD Chirlaque (Murcia Cancer Registry and CIBER Epidemiología y Salud Pública, CIBERESP); E Ardanaz, C Moreno (Navarra Cancer Registry and CIBERESP); J Galceran (Tarragona Cancer Registry). Sweden: Å Klint, M Talbäck (Cancer Registry of Sweden). Switzerland: G Jundt (Basel Cancer Registry); M Usel (Geneva Cancer Registry); SM Ess (St. Gall Cancer Registry); A Bordoni (Ticino Cancer Registry); JC Luthi, I Konzelmann (Valais Cancer Registry); JM Lutz, P Pury (Co-ordinating Centre). The Netherlands: O Visser (Amsterdam Cancer Registry); R Otter, S Siesling, JM van der Zwan, M Schaapveld (Comprehensive Cancer Centre-Groningen/Enschede, the Netherlands); JWW Coebergh, ML Janssen-Heijnen, Louis van der Heijden (Eindhoven Cancer Registry). UK—England: DC Greenberg (Eastern Cancer Registration and Information Centre); MP Coleman, Laura Woods (London School of Hygiene and Tropical Medicine); T Moran (North West Cancer Intelligence Service); D Forman (Northern and Yorkshire Cancer Registry and Information Service); N Cooper (Office for National Statistics); M Roche, (Oxford Cancer Intelligence Unit); J Verne (South West Cancer Intelligence Services); H Møller (Thames Cancer Registry); D Meechan, J Poole (Trent Cancer Registry); G Lawrence (West Midlands Cancer Intelligence Unit). UK—Northern Ireland: A Gavin (Northern Ireland Cancer Registry). UK—Scotland: RJ Black, DH Brewster (Scottish Cancer Registry). UK—Wales: JA Steward (Welsh Cancer Intelligence and Surveillance Unit).