



Original research



Survival of European adolescents and young adults diagnosed with central nervous system tumours and comparison with younger and older age groups: EUROCORE-6 results

Martin McCabe^a, Silvia Rossi^{b,*}, Francesco Cerza^b, Maura Massimino^c,
 Francesca Gianno^d, Ben D. Spycher^e, Rafael Marcos-Gragera^{f,g,h,i}, Damien Bennett^j,
 Paolo Lasalvia^k, Fabio Didonè^k, Noura Jeghalef El Karoui^l, Rosalia Ragusa^m,
 Alexandra Mayer-da-Silvaⁿ, Seyed Mohsen Mousavi^o, Annalisa Trama^k, EUROCORE-6 WG¹

^a Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

^b Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy

^c Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

^d Department of Radiological, Oncological and Anatomic-Pathological Sciences, University Sapienza, Rome, Italy

^e Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

^f CIBER Epidemiology and Public Health CIBERESP ISCIII, Madrid, Spain

^g Epidemiology Unit and Girona Cancer Registry, Catalan Institute of Oncology, Directorate Plan of Oncology, Girona Biomedical Research Institute Dr. Josep Trueta (IDIBGI-CERCA), Girona, Spain

^h Josep Carreras Leukaemia Research Institute, Girona, Spain

ⁱ Department of Medical Sciences, Medical School, University of Girona, Girona, Spain

^j Northern Ireland Cancer Registry (NICR), Queens University Belfast, Centre for Public Health, Mulhouse Building, Belfast, Northern Ireland, UK

^k Evaluative epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

^l Registry of Childhood and Adolescent Tumours of Comunitat Valenciana, Spain

^m Integrated Cancer Registry Ct-Me-En, Azienda Ospedaliera Universitaria Policlinico, Catania, Italy

ⁿ Southern Portugal Cancer Registry, Portuguese Oncology Institute of Lisbon Francisco Gentil, Lisbon, Portugal

^o Cancer Registry of Eastern Switzerland, St. Gallen, Switzerland

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ABSTRACT

Background: Data on the incidence and survival of central nervous system (CNS) tumour entities in adolescents and young adults (15–39 years at cancer diagnosis [AYA]) are scarce. Our objective is to provide incidence, survival and survival trends of CNS tumours in European AYAs and compare with older and younger patients with the same tumours.

Methods: We used the EUROCORE-6 database, calculating incidence rates (IR) per 1000,000 individuals/year in the European population (years of diagnosis: 2006–2013), 1-,2-,3-,4- and 5-year relative survival (RS), 5-year RS conditional to surviving the first year after diagnosis, for the follow-up period 2010–2014 (cases diagnosed in 2006–2013) and changes in survival in the years 2000–2013.

Results: The IR for CNS tumours was around 20 per 1000,000 in AYAs and children and increased with increasing age. In AYAs, adults (40–69 years), and elderly (70+ years), CNS tumours other than gliomas were very rare.

* Correspondence to: Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome 00161, Italy.

E-mail address: silvia.rossi@iss.it (S. Rossi).

¹ The EUROCORE-6 Working Group: Austria: M. Hackl (National CR); Belgium: E. Van Eycken; N. Van Damme (National CR); Bulgaria: Z. Valerianova (National CR); Croatia: M. Sekerija (National CR); Cyprus: I. Gregoriou; A. Demetriou (National CR); Czechia: L. Dusek; D. Krejci (National CR); Denmark: H. Storm (National CR); Estonia: M. Magi; K. Innos[#] (National CR); Finland: J. Pitkanen (National CR); France: M. Velten (Bas Rhin CR); X. Troussard (Basse Normandie, Haematological Malignancies CR); A.M. Bouvier; V. Jooste[#] (Burgundy, Digestive CR); N. Vigneron (Calvados, General CR); G. Launoy (Calvados, Digestive CR); S. Dabakuyo Yonli (Cote d'Or, Gynaecological (Breast) CR); M. Maynadie, A. Guilloteau (Cote d'Or, Haematological Malignancies CR); A.S. Woronoff (Doubs CR); J.B. Nausbaum (Finistere, Digestive CR); G. Coureau (Gironde, General CR); A. Monnereau[#] (Gironde, Haematological Malignancies CR); I. Baldi (Gironde, Central Nervous System CR); K. Hammam (Haut-Rhin CR); B. Tretarre (Haut-Rhin CR); M. Colonna (Isere CR); S. Plouvier (Lille Area CR); T. D'Almeida (Limousin CR); F. Molin; A. Cowppli-Bony (Loire-Atlantique/Vendée CR); S. Bara (Manche CR); A. Debreuve (Marne-Ardenne, Thyroid CR); G. Defossez (Poitou-Charentes CR); B. Lapôtre-Ledoux (Somme CR); S. Lamy; L. Daubisse-Marliac (Tarn CR); Germany: S. Luttmann; A. Eberle (Bremen CR); R. Stabenow (Common CR of 4 Federal States [Brandenburg,

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AYAs had better survival than children for gliomas, ependymomas and medulloblastoma and better survival than adults and elderly for all tumours examined. There was a slight improvement in survival of CNS tumours across age groups in Europe throughout 2000–2013.

Conclusions: Differences in survival between children and AYAs may be due to differences in biology and treatment. The improvement in survival may be due to advances in neuroimaging and neurosurgical techniques, centralization of neurosurgical and neurooncology expertise, and multidisciplinary management. Our findings are relevant for informing patients and clinicians about survival in AYA CNS tumours that are rarely included in clinical trials.

1. Introduction

Central nervous system (CNS) tumours are rare tumours across different age groups [1,2]. National and international estimates of incidence are difficult to interpret due to variations in the CNS tumour types included, particularly the inclusion of specific “benign” and malignant histologies. Most adolescent and young adult (AYA)-focused studies report statistics for all malignant CNS tumours [3–7]; detailed reports of the incidence and survival of specific AYA CNS tumour entities are rare [1,8]. As a group, AYA CNS tumour survival is poor, reported as 62 % in Europe [6] and 71 % in the USA [5].

CNS tumours in AYAs comprise multiple entities including malignancies typical of childhood, such as the embryonal tumours, those typical of older adults such as meningiomas and IDH-wildtype glioblastoma, and a smaller number of malignancies whose peak incidence is in AYA, such as CNS germ cell tumours. Diagnostic criteria have changed significantly in the last two decades, becoming increasingly defined by molecular features [9,10] and new entities continue to be described, defined by a combination of molecular and histological features [11,12]. The 2021 World Health Organisation (WHO) classification of CNS tumours radically changed the diagnostic criteria for gliomas, meaning that for all but a small number of glioma histologies, historical and contemporary glioma data are not comparable.

Here, we report the incidence and the survival of the largest cohort of AYA diagnosed with CNS tumours available in Europe and compare AYA data with older and younger patients with the same tumour classes.

2. Methods

We used the EUROCARE-6 database, which contains data from 108 population-based cancer registries (CRs) from 29 European countries [6]. In the EUROCARE-6 dataset the last year of incidence is 2013 and the last year of follow-up is 2014. CRs provided information on the site

and morphology of each diagnosed cancer, coded according to the International Classification of Disease for Oncology, Third Edition, first revision [ICD-O-3] [13]. Only primary tumours coded in ICD-O-3 with a malignant behaviour code were included in the analyses since not all CRs provided non-malignant CNS tumours. We used ICD-O-3 codes to define clinically relevant CNS tumours. Due to the radical redefinition of gliomas in recent years, it was not possible to adequately classify all tumours according to current standards. Histologies whose definitions are still recognisable in WHO 2021 are reported individually (Supplementary Table S1). They are: pleomorphic xanthoastrocytomas (PXA), medulloblastomas, atypical teratoid rhabdoid tumours (AT/RT), other CNS embryonal tumours, germ cell tumours, choroid plexus carcinomas, meningiomas and, ependymomas; the remaining malignant glioma histologies are described as a group named ‘other gliomas’ (i.e. astrocytoma, anaplastic astrocytoma, glioblastoma and gliosarcoma, oligodendroglioma, and anaplastic oligodendroglioma, malignant glioma).

We grouped all these 9 subtypes in one group named “All CNS tumours”.

2.1. Incidence

We calculated crude incidence rates (IR) per 1000,000 per year in the European population from 2006 to 2013. We estimated incidence as the number of new cases diagnosed in 2006–2013 divided by the corresponding total person-years in the general population covered by the contributing CRs. We excluded CRs specialising only in specific tumours groups. A total of 95 CRs contributed to the incidence analyses, covering 57 % of the European population (EU27 and Iceland, Norway, Switzerland, and UK).

In addition to the group of “other gliomas”, we reported the IR for the specific glioma entities included in this group as they were in use prior to the WHO 2021 classification and were reported to CRs. Although these

Footnote continued: Mecklenburg-West Pomerania, Saxony-Anhalt, Thüringen]); A. Nennecke; F. Peters (Hamburg CR); J. Kieschke (Lower Saxony CR); S. Zeissig (Rhineland-Palatinate CR); B. Holleczer (Saarland CR); A. Katalinic[#] (Schleswig-Holstein CR); *Iceland*: H. Birgisson (National CR); *Ireland*: D. Murray; (National CR); *Italy*: G. Mazzoleni; F. Vittadello (Alto Adige CR); F. Cuccaro (Barletta-Andria-Trani CR); R. Galasso (Basilicata CR); G. Sampietro (Bergamo CR); S. Rosso (Biella CR); C. Gasparotti; G. Maifredi (Brescia CR); M. Ferrante; R. Ragusa (Catania-Messina-Enna CR); A. Suter Sardo (Catanzaro CR); M. L. Gambino; M. Lanzoni (Province of Varese and Como CR); P. Ballotari; E. Giacomazzi (Cremona and Mantova CR); S. Ferretti (Ferrara CR); A. Caldarella; G. Manneschi (Firenze-Prato CR); G. Gatta[#]; M. Sant[#]; P. Baili[#]; F. Berrino[#]; L. Botta; A. Trama; R. Lillini; A. Bernasconi; S. Bonfarnuzzo; C. Vener; F. Didonè; P. Lasalvia; L. Buratti; G. Tagliabue (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan); L. Dal Maso; F. Toffolutti (Centro di Riferimento Oncologico, IRCCS, Aviano for the Friuli Venezia Giulia CR); R. Capocaccia[#] (Epidemiologia & Prevenzione Board); R. De Angelis[#]; E. Demuru; F. Cerza; F. Di Mari; C. Di Benedetto; S. Rossi[#]; M. Santaquilani; S. Venanzi; M. Tallon (Istituto Superiore di Sanità, Rome); L. Boni (Genova CR); S. Iacovacci (Latina CR); Genova; L. Benfatto (Liguria, Mesotheliomas CR); A. G. Russo; F. Gervasi (Province of Milan and Lodi CR); G. Spagnoli (Modena CR); L. Cavalieri d'Oro (Monza and Brianza CR); M. Fusco; M. F. Vitale (Naples 3 South CR); P. Pinna (Nuoro CR); W. Mazzucco (Palermo CR); M. Michiara (Parma CR); G. Chiaranda (Piacenza CR); G. Cascone; M. C. Giurdanella (Ragusa CR); L. Mangone (Reggio Emilia CR); F. Falcini (Romagna CR); R. Cavallo (Salerno CR); D. Piras (Sassari CR); A. Madeddu; F. Bella (Siracusa CR); A. C. Fanetti (Sondrio CR); S. Minerba (Taranto CR); G. Candela; T. Scuderi (Trapani CR); W. Mantovani; M. A. Gentilini (Trento CR); F. Stracci (Umbria CR); M. Zorzi; S. Guzzinati (Veneto CR); N. Ferrarini (Viterbo CR); *Latvia*: E. Liepina (National CR); *Lithuania*: G. Smailyte (National CR); *Malta*: M. Azzopardi; N. Calleja (National CR); *Norway*: T. B. Johannesen[#] (National CR); *Poland*: J. Didkowska; U. Wojciechowska (National CR); M. Bielska-Lasota[#]; *Portugal*: A. Pais (Central Portugal CR); M. J. Bento; C. Alves-Rodrigues (Northern Portugal CR); A. Lourenço; A. Mayer (Southern Portugal CR); *Slovakia*: C. Safaei Diba (National CR); *Slovenia*: V. Zadnik; T. Zagar (National CR); *Spain*: P. Ruiz Armengol (Balearic Islands, Mallorca CR); A. Lopez de Munain; M. De-La-Cruz (Basque Country CR); M. Garrido (Canary Islands CR); A. Vizcaino (Castellon CR); R. Marcos-Gragera; A. Sanvisens (Girona CR, CIBERESP); M. J. Sanchez; D. Redondo-Sanchez (Granada CR, EASP, IBS.GRANADA, CIBERESP); M. D. Chirlaque Lopez; A. Sanchez-Gil (Murcia CR, CIBERESP); M. Guevara[#]; E. Ardanaz (Navarra CR, CIBERESP); J. Galceran; M. Carulla (Tarragona CR); *Switzerland*: Y. Bergeron (Fribourg CR); A. Flahault; R. Schaffar (Geneva CR); R. Von Moos (Graubünden and Glarus CR); S. Mohsen Mousavi; M. Blum (Eastern Switzerland CR); A. Bordoni (Ticino CR); *The Netherlands*: O. Visser[#] (National CR); *UK-England*: S. Stevens; J. Broggio (National CR); *UK-Northern Ireland*: D. Bennett (National CR); A. Gavin[#]; *UK-Scotland*: D. Morrison (National CR); *UK-Wales*: D. W. Huws[#]; S. Smits (Welsh Cancer Intelligence and Surveillance - WCISU).[#] = EUROCARE Steering Committee Member.

tumour entities are no longer used in clinical practice, data are reported to allow comparison with existing literature. We did not report survival of these entities as they are no longer in use.

2.2. Survival

We estimated relative survival (RS), with 95 % confidence intervals, using the period approach [14]. RS (i.e. the ratio of observed to expected survival in the general population of the same age, sex, place of residence, and calendar year) allows for correction for deaths from causes other than the cancer under investigation when the actual cause of death is not available. We estimated expected survival by the Ederer II method [15] from registry-specific lifetables of all-cause mortality stratified by age, sex, and calendar year.

RS was estimated from 1-year to five-year since diagnosis for the follow-up period 2010–2014 (cases diagnosed in 2006–2013). Period survival analysis uses only the most recent interval survival estimate of cases diagnosed in different calendar years (cross-sectional estimate of survival, Supplementary Figure S1). The 2010–2014 period estimation combines the survival of four different three-year cohorts of diagnosis and one four-year cohort of diagnosis for the last period estimate.

Moreover, we estimated conditional survival (5-/1-year CS), which is the probability of surviving four more years given that the patient has already survived one year after the cancer diagnosis, and is calculated as the ratio of 5-year to 1-year RS. 5-/1-year CS provides information on a risk profile that changes over time and can be used to generate hypotheses about possible drivers of survival differences between AYA and other age groups.

RS estimates are based on data from the same 95 CRs used for the IR.

We report incidence and survival for children aged 0–14 years (and separately 0–4 and 5–14 years, infants and older children respectively), AYAs aged 15–39 years, adults aged 40–69 and elderly aged 70 + years. Children under five years are rarely irradiated and are therefore reported separately to older children.

The number of cases (N) is calculated as the average number of people alive at the start of the first interval in the cohorts of diagnosis included in the period survival analysis. A minimum of 30 cases of each CNS tumours was required to compare RS estimates across age groups. Thus, atypical teratoid rhabdoid tumour and choroid plexus carcinoma were excluded from the survival analyses.

2.3. Survival changes over time

We estimated 5-year RS trends between 2000 and 2013 using the period approach for the three follow-up periods: 2004–2006, 2007–09 and 2010–2014, based on cases diagnosed in 2000–2006, 2003–2009, and 2006–2013, respectively (Supplementary Figure S1). We assessed 5-year RS trends by age groups (0–14, 15–39, 40–69 years). It was not possible to provide survival trends for those over 70 because the number of cases was too small.

We selected data from 69 CRs covering at least the years of diagnosis 2001–2010.

Incidence and survival analyses were performed using SEER*Stat software (version 8.4.4) [16].

Z-test was used to assess statistically significant survival differences over time [17].

3. Results

3.1. Incidence

We analysed 6491 children, 16,167 AYAs, 74,236 adults and 34,907 elderly diagnosed with CNS tumours between 2006–2013 (Table 1).

The IR for CNS tumours was 23 per 1000,000 in AYAs and children and increased with increasing age. However, CNS tumours include several types of tumours that differ between age groups. The other

Table 1
Crude incidence rate (IR) of Central Nervous System (CNS) tumours in European adolescents and young adults (aged 15–39 years) and in different age groups by CNS tumours subtypes, in 2006–2013, reported with 95 % confidence intervals (95 %CI) and number of cases (N). IR are x 1000,000 person-years. Males and females, EUROPEAN Pool of 95 registries.

CNS tumours	0–4 years			5–14 years			0–14 years			15–39 years			40–69 years			70 +		
	N	IR	95 % CI	N	IR	95 % CI	N	IR	95 % CI	N	IR	95 % CI	N	IR	95 % CI	N	IR	95 % CI
Pleomorphic xanthoastrocytoma (PXA)	7	0.06	0.02	0.13	54	0.24	0.18	0.31	0.18	0.14	0.23	0.156	0.22	0.19	0.16	0.14	0.19	0.14
Other gliomas	970	8.60	8.07	9.16	1879	8.38	8.00	8.77	2849	8.45	8.15	8.77	12,976	18.52	18.20	18.84	69,265	84.90
Astrocytoma	325	2.88	2.58	3.21	537	2.39	2.20	2.61	862	2.56	2.39	2.73	4395	6.27	6.09	6.46	6438	7.89
Anaplastic astrocytoma	74	0.66	0.52	0.82	182	0.81	0.70	0.94	256	0.67	0.67	0.86	1767	2.52	2.41	2.64	4450	5.45
Glioblastoma and Gliosarcoma	113	1.00	0.83	1.20	378	1.69	1.52	1.86	491	1.46	1.33	1.59	3643	5.20	5.03	5.37	50,026	61.32
Oligodendroglioma and anaplastic oligodendroglioma	41	0.36	0.26	0.49	117	0.52	0.43	0.63	158	0.47	0.40	0.55	2316	3.30	3.17	3.44	5233	6.41
Malignant glioma	417	3.70	3.35	4.07	665	2.97	2.74	3.20	1082	3.21	3.02	3.41	855	1.22	1.14	1.30	3118	3.82
CNS embryonal tumours	298	2.64	2.35	2.96	193	0.86	0.74	0.99	491	1.46	1.33	1.59	318	0.45	0.41	0.51	249	0.31
Ependymoma	462	4.10	3.73	4.49	367	1.64	1.47	1.81	829	2.46	2.29	2.63	1243	1.77	1.68	1.88	2280	2.79
Medulloblastoma	558	4.95	4.54	5.37	1070	4.77	4.49	5.07	1628	4.83	4.60	5.07	697	0.99	0.92	1.07	161	0.20
Meningiomas	5	0.04	0.01	0.10	7	0.03	0.01	0.06	12	0.04	0.02	0.06	270	0.39	0.34	0.43	2031	2.49
Germ cell tumours	41	0.36	0.26	0.49	313	1.40	1.25	1.56	354	1.05	0.94	1.17	475	0.68	0.62	0.74	76	0.09
Atypical Teratoid Rhabdoid Tumor (AT/RT)	148	1.31	1.11	1.54	21	0.09	0.06	0.14	169	0.50	0.43	0.58	14	0.02	0.01	0.03	3	0.00
Choroid plexus carcinoma	83	0.74	0.59	0.91	15	0.07	0.04	0.11	98	0.29	0.24	0.35	18	0.03	0.02	0.04	37	0.05
All CNS tumours*	2572	22.80	21.93	23.70	3919	17.48	16.93	18.03	6491	19.26	18.79	19.73	16,167	23.07	22.71	23.43	74,236	91.00

*including: PXA, Other gliomas, CNS embryonal tumours, Ependymoma, Medulloblastoma, Meningiomas, Germ cell tumours, AT/RT, Choroid plexus carcinoma as defined in this table

Table 2

One to five-year relative survival (RS, %) and 5-year to one year conditional survival [5-/1-year CS] for Central Nervous System (CNS) tumours in European adolescents and young adults (aged 15–39 years), children (0–4, 5–14 and 0–14 years), adults (40–69 years) and elderly (70 + years) by CNS tumour subtype common to each age group being compared, reported with 95 % confidence intervals (95 %CI) and number of cases (N). Follow-up period 2010–2014, based on cases diagnosed in 2006–2013. Males and females, EUROPEAN Pool of 95 registries.

CNS tumours	Years from diagnosis	0–4 years			5–14 years			0–14 years			15–39 years			40–69 years			70 +								
		N [§]	RS	95 % CI	N [§]	RS	95 % CI	N [§]	RS	95 % CI	N [§]	RS	95 % CI	N [§]	RS	95 % CI	N [§]	RS	95 % CI						
Pleomorphic xanthoastrocytoma (PXA)	1 yr				26	100.0	0.0	0.0	30	100.0	0.0	0.0	73	95.8	87.3	98.6	69	72.1	59.5	81.3	-				
	2 yr				30	96.9	79.7	99.6	34	97.2	81.3	99.6	82	91.2	82.3	95.8	70	52.0	39.5	63.1					
	3 yr				30	93.7	76.9	98.4	34	94.1	78.4	98.5	82	90.0	80.9	95.0	71	46.7	34.5	58.0					
	4 yr				30	93.7	76.9	98.4	34	94.1	78.4	98.5	82	84.7	74.4	91.1	72	42.6	30.7	54.0					
	5 yr				30	93.7	76.9	98.4	34	94.1	78.4	98.5	82	81.5	70.4	88.7	70	33.8	21.9	46.0					
	5-/1-year CS				31	93.7	76.9	98.4	33	94.1	78.4	98.5	79	85.1	74.3	91.6	50	46.9	30.9	61.3					
Other gliomas	1 yr	573	82.4	78.9	85.3	925	73.9	70.9	76.7	1284	77.5	75.0	79.7	5836	86.4	85.5	87.3	32,446	51.6	51.1	52.2	16,139	17.7	17.2	18.4
	2 yr	621	70.5	66.6	74.0	990	56.8	53.6	59.8	1376	63.0	60.3	65.5	6127	73.9	72.8	75.0	34,010	26.7	26.2	27.2	16,727	6.5	6.2	7.0
	3 yr	630	68.6	64.7	72.2	1000	52.4	49.2	55.5	1388	59.5	56.8	62.1	6269	65.6	64.4	66.8	34,515	18.8	18.4	19.2	16,763	4.0	3.8	4.4
	4 yr	638	66.9	63.0	70.5	1031	50.9	47.7	54.0	1426	57.9	55.2	60.4	6378	59.5	58.2	60.7	34,633	15.1	14.7	15.5	16,763	3.0	2.8	3.4
	5 yr	638	66.3	62.3	69.9	1031	49.8	46.6	52.9	1426	56.9	54.2	59.5	6429	54.8	53.5	56.0	34,633	13.1	12.8	13.5	16,624	2.6	2.4	2.9
	5-/1-year CS	538	80.5	76.8	83.6	815	67.4	63.9	70.6	1172	73.5	70.8	76.0	5742	63.4	62.1	64.7	18,092	25.5	24.8	26.1	2737	14.7	13.4	16.4
CNS embryonal tumours	1 yr	133	71.9	63.2	78.9	81	80.7	70.1	87.9	214	75.2	68.7	80.6	124	80.0	71.7	86.2	103	58.1	47.8	67.1	41	35.9	21.0	51.0
	2 yr	146	52.4	43.8	60.4	90	62.8	51.6	72.2	235	56.4	49.6	62.6	137	61.5	52.5	69.2	114	35.8	26.9	44.9	38	27.9	14.6	42.8
	3 yr	151	51.3	42.7	59.2	91	56.3	45.2	66.0	242	53.3	46.6	59.6	143	49.2	40.6	57.2	114	30.2	21.8	38.9	38	25.7	12.8	40.8
	4 yr	151	50.0	41.5	58.0	97	55.3	44.2	65.0	243	52.1	45.4	58.4	149	43.8	35.6	51.7	114	25.4	17.7	33.7	38	23.6	10.9	39.1
	5 yr	151	50.0	41.5	58.0	97	52.4	41.4	62.2	243	51.0	44.3	57.2	157	40.9	32.9	48.8	123	21.5	14.5	29.3	38	20.9	8.4	37.1
	5-/1-year CS	116	69.6	60.0	77.3	82	64.8	52.8	74.5	193	67.7	60.4	74.0	132	51.2	42.0	59.6	77	36.9	25.8	48.1	11	58.2	21.0	82.9
Ependymoma	1 yr	224	89.5	84.6	92.9	173	96.5	92.3	98.4	397	92.6	89.4	94.8	580	96.0	94.0	97.3	1084	88.6	86.5	90.5	208	72.2	65.0	78.1
	2 yr	228	85.7	80.2	89.7	184	89.0	83.5	92.8	412	87.0	83.2	90.0	609	92.6	90.1	94.5	1148	83.9	81.5	86.0	214	66.9	59.2	73.4
	3 yr	228	80.3	74.3	85.1	187	83.1	76.9	87.8	414	81.4	77.2	84.9	611	90.7	88.0	92.8	1150	81.2	78.6	83.5	214	65.4	57.4	72.3
	4 yr	228	74.8	68.2	80.2	196	80.7	74.3	85.7	420	77.6	73.1	81.4	629	89.2	86.3	91.5	1152	79.2	76.5	81.6	214	62.2	53.8	69.5
	5 yr	230	67.5	60.5	73.6	196	79.0	72.4	84.2	420	73.1	68.3	77.2	629	87.4	84.4	89.8	1152	77.5	74.7	80.0	214	58.7	49.8	66.5
	5-/1-year CS	192	75.5	68.2	81.3	200	81.9	75.5	86.8	390	79.0	74.3	82.9	615	91.0	88.3	93.1	1040	87.4	85.0	89.5	146	81.1	70.1	88.4
Medulloblastoma	1 yr	262	74.5	68.7	79.4	507	91.5	88.7	93.6	769	85.7	83.0	88.0	319	91.8	88.2	94.4	78	75.7	64.3	83.8	-			
	2 yr	274	66.4	60.2	71.8	530	81.8	78.1	84.8	804	76.5	73.4	79.4	341	85.4	81.1	88.8	81	66.4	54.7	75.7				
	3 yr	282	60.6	54.4	66.3	544	74.9	71.0	78.4	825	70.1	66.7	73.2	353	80.2	75.5	84.1	81	60.0	48.1	69.9				
	4 yr	282	57.3	51.1	63.1	545	69.5	65.4	73.2	825	65.3	61.9	68.6	356	76.3	71.4	80.5	81	60.0	48.1	69.9				
	5 yr	282	55.5	49.2	61.3	545	65.6	61.4	69.5	825	62.2	58.7	65.4	356	72.1	67.0	76.5	81	60.0	48.1	69.9				
	5-/1-year CS	215	74.5	67.8	80.0	515	71.7	67.5	75.5	730	72.5	69.0	75.7	336	78.5	73.6	82.6	61	79.2	66.4	87.6				
Meningiomas	1 yr													124	91.8	85.3	95.5	887	86.6	84.0	88.8	599	61.6	57.2	65.7
	2 yr													134	84.4	76.8	89.7	919	79.7	76.7	82.3	619	50.8	46.2	55.2
	3 yr													134	80.7	72.6	86.5	952	74.5	71.4	77.4	637	44.2	39.6	48.7
	4 yr													134	74.6	66.0	81.3	983	71.5	68.2	74.5	640	40.4	35.8	45.0
	5 yr													134	69.8	61.1	76.9	1001	69.7	66.3	72.7	640	37.5	32.9	42.2
	5-/1-year CS													130	76.0	67.3	82.6	871	80.4	77.2	83.2	386	60.9	54.3	66.9
Germ cell tumours	1 yr	16	56.4	29.6	76.4	152	97.3	92.9	99.0	168	93.4	88.3	96.3	219	93.1	88.8	95.8	34	67.5	48.6	80.8	-			
	2 yr	18	51.7	26.3	72.2	158	94.2	89.1	96.9	176	90.0	84.5	93.7	229	90.5	85.7	93.7	39	49.7	32.4	64.8				
	3 yr	18	51.7	26.3	72.2	161	92.4	86.9	95.6	179	88.4	82.5	92.4	231	89.2	84.2	92.6	42	41.1	25.4	56.2				
	4 yr	18	51.7	26.3	72.2	161	92.4	86.9	95.6	179	88.4	82.5	92.4	233	88.4	83.3	92.0	42	38.2	22.9	53.5				
	5 yr	18	51.7	26.3	72.2	161	91.0	85.2	94.6	179	87.1	81.1	91.4	235	87.9	82.8	91.6	42	35.9	21.0	51.1				
	5-/1-year CS	9	91.7	53.8	98.8	159	93.5	88.2	96.5	169	93.3	88.2	96.3	226	94.5	90.2	96.9	26	53.2	32.7	70.0				
All CNS tumours*	1 yr	1205	79.3	76.9	81.6	1796	83.6	81.7	85.2	3001	81.9	80.4	83.2	7286	87.7	86.9	88.4	34,716	53.8	53.3	54.3	17,002	19.9	19.3	20.5
	2 yr	1272	69.6	66.9	72.2	1909	70.8	68.6	72.8	3181	70.3	68.6	71.9	7670	76.5	75.5	77.5	36,396	30.0	29.5	30.5	17,617	8.8	8.3	9.2
	3 yr	1283	66.2	63.5	68.8	1939	65.9	63.7	68.0	3222	65.9	64.2	67.6	7831	69.1	68.0	70.1	36,935	22.4	21.9	22.8	17,669	6.2	5.8	6.6
	4 yr	1285	63.4	60.6	66.0	1978	63.3	61.1	65.4	3263	63.3	61.6	65.0	7968	63.6	62.5	64.6	37,089	18.8	18.4	19.2	17,669	5.1	4.8	5.5
	5 yr	1285	61.4	58.6	64.1	1978	61.4	59.1	63.5	3263	61.3	59.6	63.0	8011	59.3	58.2	60.4	37,089	16.8	16.4	17.2	17,568	4.6	4.2	4.9
	5-/1-year CS	1035	77.4	74.6	79.9	1740	73.4	71.2	75.5	2776	74.9	73.2	76.5	7257	67.6	66.5	68.7	20,256	31.2	30.5	31.8	3295	22.9	21.3	24.5

*Including: PXA, Other gliomas, CNS embryonal tumours, Ependymoma, Medulloblastoma, Meningiomas, Germ cell tumours, AT/RT, Choroid plexus carcinoma as defined in this table

§N is the average number of people alive at the start of the first interval in the cohorts of diagnosis included in the period survival analysis

gliomas were the most common CNS tumour across all age groups, but within gliomas, astrocytomas, glioblastoma, and oligodendrogliomas had a higher IR in AYAs and adults compared to children (Table 1). By contrast, compared to AYA and adults, children had a higher IR for medulloblastoma, embryonal and germ cell tumours. The IRs of ependymomas and embryonal tumours were highest among children younger than 4 years while germ cell tumours had the highest IR in children aged 5–14 years. In AYAs, adults, and elderly, CNS tumours other than gliomas were very rare with IRs less than 3 per 1000,000 for most tumours.

3.2. Survival

Table 2 reports the 1-, 2-, 3-, 4-, and 5-year RS and 5-/1-year CS for CNS tumours in different age groups. Overall, CNS tumours survival was lower in adults and elderly (40–69 and 70+ years, respectively) than in AYAs and children.

In detail, AYAs and children with PXA had a very good prognosis (>80%) although the difference between 1-year and 5-year RS was smaller in children than in AYAs. Adults with PXA had worse survival than AYA.

For other gliomas, 1-year RS was higher in AYAs than in infants and older children, and 2-, 3-, 4- and 5-year RS were higher in AYAs than older children. AYA had similar 2- and 3- year RS to infants but worse 4- and 5-year RS. 5-/1-year CS was lower in AYA than both infants and older children. AYAs with other gliomas had far better RS than adults and elderly at all time points and better 5-/1-year CS.

For other CNS embryonal tumours, no important differences were observed between children and AYA in the RS at 1, 2, 3, 4 and 5 years. No difference was also observed between 0 and 4 and 5–14 years. However, AYA RS declined faster with years since diagnosis than childhood RS. 5-/1-year CS was worse in AYA than in infants and older children. Survival was worse at all time points in adults and elderly than in AYA.

For ependymomas, 3-, 4-, and 5-year RS and 5-/1-year CS were higher in AYAs than in children and no differences in RS or CS were found between infants and older children.

For medulloblastoma, 1-, 2-, 3-, 4-, and 5-year RS were higher in AYAs than in both infants and older children and also higher than adults. Infants with medulloblastoma had the worst RS, but 5-/1-year CS was similar across infants, older children, AYA and adults.

For meningioma no major differences were observed between AYA and adults, but 1-, 2-, 3-, 4-, and 5-year RS were considerably lower in elderly.

Regarding CNS germ cell tumours, no substantial differences in 1-, 2-, 3-, 4-, and 5-year RS were found between children and AYAs but both RS at all time points and 5-/1-year CS were worse in adults than in AYA and children.

3.3. Survival changes over time

In AYAs, 5-year RS increased only for PXA between the periods 2007–2009 and 2010–2014 and for other gliomas and ependymomas between the periods 2004–2006 and 2010–2014. There were also increases, but non-significant, in CNS embryonal tumours, medulloblastomas and germ cell tumours over all study periods (Fig. 1, Table 3).

In children the only significant increase in 5-year RS was for patients with ependymoma between 2007 and 2009 and 2010–2014 (Fig. 1, Table 3).

For adults aged 40–69 years the only significant increase in 5-year RS was for patients with other gliomas between 2007 and 2009 and 2010–2014 (Fig. 1, Table 3).

Supplementary Table S2 provides more information on the results (i.e., number of cases included in the analyses, 95 % confidence interval, and p-values of the trends).

4. Discussion

This is the largest and most up-to-date study providing real-world data on CNS tumours across age groups in Europe. Our results show an incidence rate (IR) of 23 per 1000,000 for children and AYA, which increases with increasing age, and a 5-year RS of 75 % and 68 % in children and AYA, respectively, which decreases in adults and the elderly.

Our results also show several differences in RS between age groups.

For many CNS tumours, differences in tumour biology and the avoidance of radiotherapy in early childhood are likely to be the major drivers of the observed differences in survival. Of particular note, molecular glioma diagnoses vary significantly with age, exemplified by NTRK fusions in infants, PedRTK methylation subclass gliomas in older children, H3G34 and IDH mutations in AYAs and IDH wildtype GBMs in AYAs and adults [18]. In medulloblastomas, age is intrinsically linked to molecular subgroup and prognosis [19], with a predominance of SHH subtype δ tumours in AYA and adults, compared to SHH subtype β and γ in infants and WNT, group 3 and group 4 tumours in older children. Similarly, ependymoma molecular subgroup defines outcome but varies significantly in frequency with age [20]. Subtype PFB tumours predominate in the posterior fossa in AYA, and have significantly better prognosis than the PFA tumours that arise more frequently in children. In fact, the most common ependymoma subgroup in AYA is myxopapillary ependymoma but they were excluded from this analysis on the basis of having a benign behaviour code in ICD-O-3. Of note, although AYAs with medulloblastoma had better survival than both children and adults, the age-related differences were no longer evident for 5-/1-year CS, demonstrating that medulloblastoma deaths outside of the AYA age range were more likely to occur within the first year after diagnosis while late relapses are more common in AYA and adults [21]. For ependymoma, despite equivalent early survival at 1 year after diagnosis between children and AYA, children had progressively worse survival, resulting in significantly worse 5-/1-year CS in children than in AYA. In contrast, despite equivalent early survival between children and AYAs for non-medulloblastoma embryonal tumours and better survival for the other gliomas group, AYAs had progressively worse survival thereafter and significantly worse 5-/1-year CS demonstrating that early mortality was not the primary cause of death.

We demonstrate that there was a slight improvement in survival of AYA CNS tumours in Europe during the study period. Where differences were observed, there are several possible explanations that might apply across all tumour types, including advances in neuroimaging and neurosurgical techniques, specifically the improved tumour delineation afforded by 5-aminolevulinic acid (5-ALA) during neurosurgical resections for gliomas and some other histologies [22], centralisation of neurosurgical and neurooncology expertise and multidisciplinary management, and the development of national multidisciplinary teams for some sites in some countries. There has also been an increasing trend in the last two decades to treat AYA medulloblastoma with chemoradiotherapy rather than radiotherapy alone, driven by paediatric practice, and some evidence of efficacy [23], subsequently substantiated by a large meta-analysis that showed improved survival with chemoradiotherapy [24].

National [25,26] and international estimates of incidence and survival are difficult to compare due to variations in the methodologies, definition of CNS tumour types included of AYA etc. The most comprehensive comparator paper is the report of the Central Brain Tumour Registry of the United States (CBTRUS) [1]. The IRs of the embryonal tumour medulloblastoma was comparable in both cohorts. However, our cohort had higher IRs of embryonal tumours overall and of the tumours previously classified as diffuse astrocytomas, but a lower IR of ependymomas, germ cell tumours, grade 2 and 3 oligodendrogliomas and glioblastomas, as well as the entities previously known as anaplastic astrocytomas and malignant gliomas not otherwise specified (NOS). These differences may be due to the different definition in

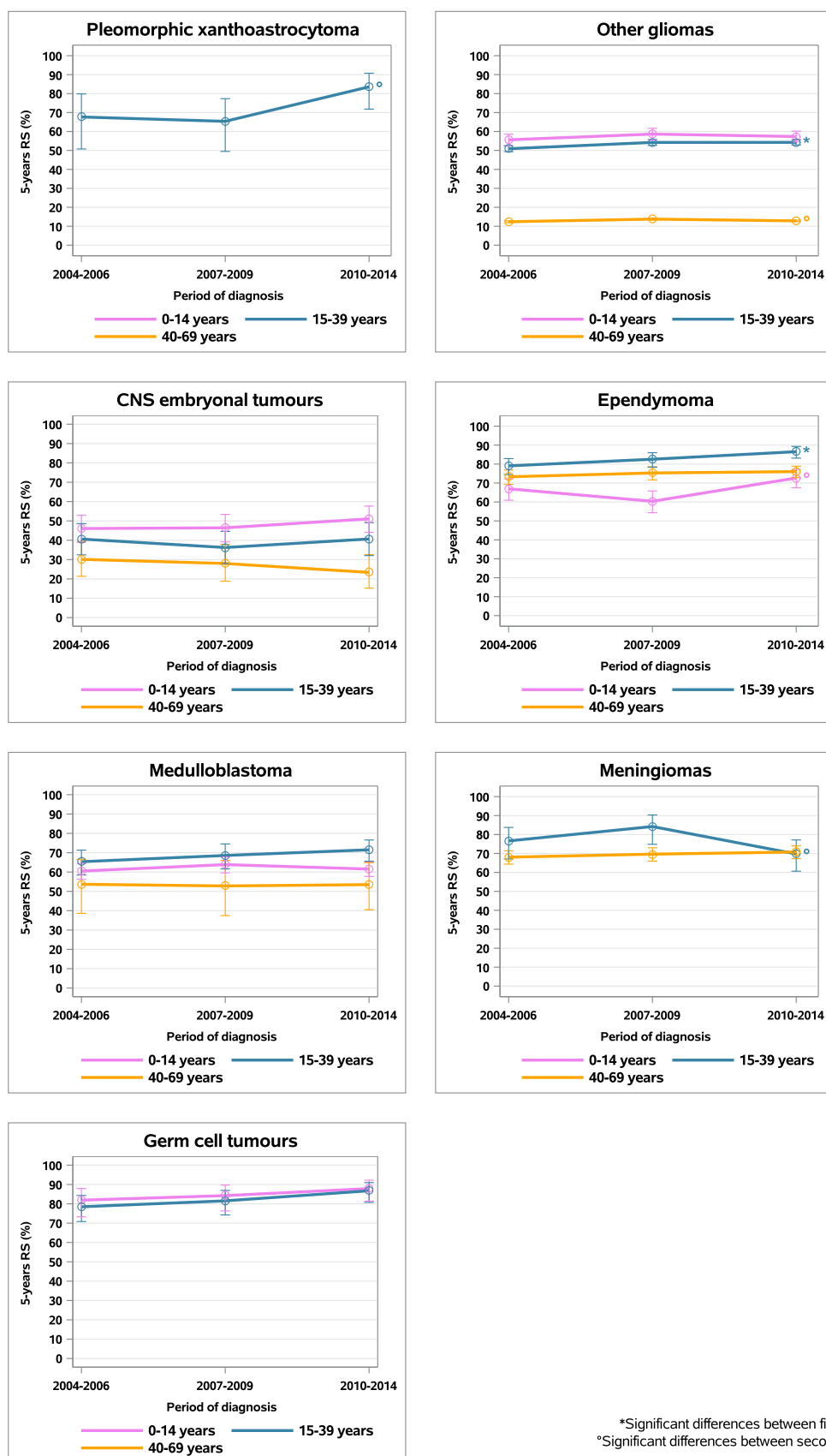


Fig. 1. Trends over time in 5-yr Relative Survival (RS) for patients diagnosed with Central Nervous System (CNS) tumours by subtype and age groups (0–14, 15–39, 40–69 years). Period estimates 2004–2006, 2007–2009 and 2010–2014. Males and females, EUROPEAN Pool of 69 registries.

Table 3

Five-year relative survival (RS, %) trends for Central Nervous System (CNS) tumours by subtype and age groups (0–14, 15–39, 40–69 years), reported with 95 % confidence intervals (95 %CI) and p-value: period estimates 2004–2006, 2007–2009 and 2010–2014. Males and females, EUROPEAN Pool of 69 registries. In bold significant differences, p-value < 0.05.

CNS tumours	Follow-up period	0–14 years					15–39 years					40–69 years				
		N [§]	5-yr RS	95 % CI	p-value 2010-14 vs.2004-06	p-value 2010-14 vs.2007-09	N [§]	5-yr RS	95 % CI	p-value 2010-14 vs.2004-06	p-value 2010-14 vs.2007-09	N [§]	5-yr RS	95 % CI	p-value 2010-14 vs.2004-06	p-value 2010-14 vs.2007-09
Pleomorphicxanthoastrocytoma	2004–2006	.	.	.	.	.	40	67.7	50.8–79.8	.	.	.	.	.	.	.
	2007–2009	.	.	.	.	.	50	65.4	49.5–77.3	.	.	30	14.3	1.30–41.7	.	.
	2010–2014	.	.	.	.	.	73	83.6	71.8–90.7	0.070	0.033	57	32.6	19.7–46.2	.	0.167
Other gliomas	2004–2006	1006	55.6	52.5–58.6	.	.	4262	50.9	49.4–52.4	.	.	18,783	12.4	11.9–12.9	.	.
	2007–2009	996	58.6	55.5–61.7	.	.	4383	54.2	52.7–55.7	.	.	20,794	13.8	13.3–14.3	.	.
	2010–2014	1202	57.3	54.4–60.2	0.414	0.548	5423	54.3	52.9–55.6	0.001	0.975	28,017	12.8	12.4–13.2	0.166	0.005
CNS embryonal tumours	2004–2006	204	46.1	38.9–52.9	.	.	129	40.6	32.4–48.6	.	.	98	30.1	21.3–39.4	.	.
	2007–2009	190	46.4	39.1–53.4	.	.	130	36.2	27.9–44.6	.	.	94	28.0	18.8–37.8	.	.
	2010–2014	221	51.1	44.0–57.7	0.317	0.360	136	40.7	32.1–49.1	0.993	0.469	99	23.4	15.2–32.5	0.296	0.489
Ependymoma	2004–2006	277	66.9	60.9–72.2	.	.	372	79.0	74.5–82.9	.	.	568	73.3	69.3–76.8	.	.
	2007–2009	275	60.3	54.3–65.8	.	.	396	82.5	78.4–86.0	.	.	672	75.3	71.6–78.6	.	.
	2010–2014	355	72.7	67.5–77.2	0.132	0.001	516	86.5	83.1–89.3	0.005	0.108	916	76.0	72.8–78.9	0.267	0.761
Medulloblastoma	2004–2006	553	60.5	56.3–64.4	.	.	214	65.3	58.5–71.3	.	.	46	53.7	38.6–66.6	.	.
	2007–2009	536	63.9	59.6–67.8	.	.	207	68.6	61.6–74.5	.	.	47	52.8	37.5–66.0	.	.
	2010–2014	700	61.5	57.7–65.1	0.710	0.411	270	71.5	65.6–76.6	0.153	0.498	65	53.5	40.5–64.9	0.985	0.943
Meningiomas	2004–2006	.	.	.	.	.	103	76.6	67.1–83.7	.	.	787	68.0	64.4–71.4	.	.
	2007–2009	.	.	.	.	.	96	84.2	74.8–90.3	.	.	779	69.6	66.0–73.0	.	.
	2010–2014	.	.	.	.	.	125	69.7	60.6–77.1	0.248	0.011	914	70.8	67.3–74.0	0.270	0.645
Germ cell tumours	2004–2006	108	81.9	73.3–87.9	.	.	134	78.5	70.8–84.3	.	.	.	.	.	.	.
	2007–2009	117	84.2	76.3–89.7	.	.	148	81.5	74.2–86.9	.	.	.	.	.	.	.
	2010–2014	156	87.9	81.4–92.2	0.191	0.398	190	86.7	80.7–91.0	0.053	0.206	38	30.6	16.4–46.0	.	.

§N is the average number of people alive at the start of the first interval in the cohorts of diagnosis included in the period survival analysis

terms of both morphologies and topographies in the 2 studies and the inclusion of benign and borderline lesion in the USA registry but not in our data. Certain tumour types were reported in one but not both cohorts and could not be compared. For instance, we specifically examined the incidence of AT/RT and PXA, neither of which were explicitly reported by CBTRUS. Several additional morphologies were reported by CBTRUS but not by us, either due to low case numbers or because they have a non-malignant behavior. Finally, for CNS tumours that can only be diagnosed radiologically (e.g. meningiomas, diffuse intrinsic pontine glioma) we cannot exclude that the different access to data sources across CRs for case ascertainment may also have played a role.

Our study has some limitations, including the lack of details on molecular characterization and treatments received and the lack of non-malignant CNS tumours. An additional limitation includes the relatively old diagnostic period. Finally, the quality of a CR inevitably depends on the local healthcare environment. Inappropriate pathological diagnoses will result in misclassification in CRs.

In summary, we demonstrate important differences in both the incidence and survival of AYA with that in children and adults and discuss possible reasons for the observed differences. Biological differences are a major factor but we also suggest that differences in treatment between children and AYA may contribute to observed outcomes, and highlight certain time trends that may relate to advances in therapeutic management. The data we present represent an important dataset to inform patients and clinicians of survival in these rare AYA CNS tumours that are seldom the subject of well-powered clinical trials and act as a European baseline comparator for subsequent analyses that use the 2021 classification.

CRedit authorship contribution statement

Damien Bennett: Writing – review & editing. **Paolo Lasalvia:** Writing – review & editing. **Ben D Spycher:** Writing – review & editing. **Rafael Marcos-Gragera:** Writing – review & editing. **Annalisa Trama:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Maura Massimino:** Writing – review & editing, Conceptualization. **Francesca Gianno:** Writing – review & editing. **Alexandra Mayer-da-Silva:** Writing – review & editing. **Silvia Rossi:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Seyed Mohsen Mousavi:** Writing – review & editing. **Francesco Cerza:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Noura Jeghalef El Karoui:** Writing – review & editing. **Rosalia Ragusa:** Writing – review & editing. **Martin McCabe:** Writing – review & editing, Writing – original draft, Conceptualization. **Fabio Didonè:** Writing – review & editing.

Ethics approval

We analysed pseudonymized data collected from 108 population-based cancer registries, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT 73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analysis agreed on in the EUROcare-6 protocol, available at <http://www.iss.it/en/eurocare-6>.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data access

Annalisa Trama, Silvia Rossi and Francesco Cerza had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2025.115661](https://doi.org/10.1016/j.ejca.2025.115661).

Data availability

We are not permitted to share individual data. Aggregated-level data, in the form of counts, rates or survival proportions, can only be shared upon express permission from the participating registries. These data should be requested by contacting the corresponding author or Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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