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Original Article

Malignant Central Nervous System Tumors Among Adolescents and Young Adults (15-39 Years Old) in 14 Southern-Eastern European Registries and the US Surveillance, Epidemiology, and End Results Program: Mortality and Survival Patterns

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BACKGROUND: Unique features and worse outcomes have been reported for cancers among adolescents and young adults (AYAs; 15-39 years old). The aim of this study was to explore the mortality and survival patterns of malignant central nervous system (CNS) tumors among AYAs in Southern-Eastern Europe (SEE) in comparison with the US Surveillance, Epidemiology, and End Results (SEER) program. **METHODS:** Malignant CNS tumors diagnosed in AYAs during the period spanning 1990-2014 were retrieved from 14 population-based cancer registries in the SEE region (n = 11,438). Age-adjusted mortality rates were calculated and survival patterns were evaluated via Kaplan-Meier curves and Cox regression analyses, and they were compared with respective 1990-2012 figures from SEER (n = 13,573). **RESULTS:** Mortality rates in SEE (range, 11.9-18.5 deaths per million) were higher overall than the SEER rate (9.4 deaths per million), with decreasing trends in both regions. Survival rates increased during a comparable period (2001-2009) in SEE and SEER. The 5-year survival rate was considerably lower in the SEE registries (46%) versus SEER (67%), mainly because of the extremely low rates in Ukraine; this finding was consistent across age groups and diagnostic subtypes. The highest 5-year survival rates were recorded for ependymomas (76% in SEE and 92% in SEER), and the worst were recorded for glioblastomas and anaplastic astrocytomas (28% in SEE and 37% in SEER). Advancing age, male sex, and rural residency at diagnosis adversely affected outcomes in both regions. **CONCLUSIONS:** Despite definite survival gains over the last years, the considerable outcome disparities between the less affluent SEE region and the United States for AYAs with malignant CNS tumors point to health care delivery inequalities. No considerable prognostic deficits for CNS tumors are evident for AYAs versus children. ***Cancer* 2017;000:000-000**. © *2017 American Cancer Society*.

KEYWORDS: adolescents and young adults, brain tumors, central nervous system tumors, epidemiology, mortality, outcome, survival.

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INTRODUCTION

Cancer in adolescents and young adults (AYAs; 15-39 years old) is an entity with distinctive molecular, histopathological, epidemiological, and outcome features in comparison with cancer in children and older adults.[1] It has generally been associated with poorer survival in comparison with cancer in younger patients, with only modest outcome improvements being reported over the last decades.[2,3] AYA cancer patients have been considered a neglected age group by both pediatric and adult oncologists; the worse prognosis has been mainly attributed to the lack of clinical trials and the subsequent lack of specific treatment guidelines.[1,3,4] Likewise, the majority of published studies on cancer epidemiology in AYAs have focused on presenting overall incidence and survival trends rather than decrypting the specific patterns of each cancer subtype. In this context, in 2006, the US National Cancer Institute released specific recommendations for minimizing this gap in prognosis between children and AYAs,[5] and specific initiatives to this end have already been implemented.[6,7]

Malignant central nervous system (CNS) tumors are a group of distinct histopathological entities; they are the most common malignancies among adolescents (15-19 years) and are the third most common malignancies among AYAs overall.[8-10] CNS tumors are the leading cause of cancer mortality among children and the third most common cause of cancer deaths among AYAs; they pose significant challenges to diagnosis, management, and treatment.[11,12] Although the prognosis of CNS tumors has generally improved over the last 40 years, primarily because of technological developments in neuroimaging modalities, the optimization of treatment protocols, and advances in the field of neurosurgery, this improvement is not that obvious among AYAs.[8,13,14] The latest reports from Europe and the United States have documented 5-year survival rates of 57% and 65%, respectively.[3,11] In addition, international variations in outcomes[3,10] indicate room for further improvement and the need to explore the impact of socioeconomic parameters on CNS tumor outcomes among AYAs.

In the current study, we aimed to calculate mortality and survival patterns of malignant CNS tumors by histological subtype, sex, age group, and urbanization status among AYAs in Southern-Eastern Europe (SEE), a region rather underrepresented in the published literature; the data were derived from a network of cancer registries operating since 1990 in 12 countries (Belarus, Croatia, Cyprus, Malta, Montenegro, Poland, Portugal, Romania, Serbia, Slovenia, Turkey, and Ukraine). To explore potential survival disparities with more affluent and developed countries, we also compared the outcomes of malignant CNS tumors among AYAs in the SEE registries and used as a benchmark publicly available data from the US Surveillance, Epidemiology, and End Results (SEER) program.[15-18]

MATERIALS AND METHODS

The SEE cancer registry network,[15-17] established within the context of Europe Against Cancer: Optimisation of the Use of Registries for Scientific Excellence in Research and aimed at presenting cross-country variations and time trend patterns among childhood cancers, was expanded for the current study to AYAs (notably the age range of 15-39 years).[5] A study protocol, a priori defined, was consented by administrators of all participating registries and was approved by the respective institutional committee of each registry. Individual anonymized data on incident CNS tumor cases registered during 1990-2014 were delivered by a total of 14 registries operating in 12 countries (Belarus; Croatia; Cyprus; Malta; Montenegro; greater Poland; central Portugal; northern Portugal; Cluj, Romania; Iasi, Romania; central Serbia; Slovenia; Izmir, Turkey; and Ukraine). In addition, incident data on CNS tumor cases were derived from the SEER network of 18 cancer registries operating in the United States.[8,19] Although SEER provided data for 1973 to 2012, only cases diagnosed in the most recent period (1990-2012) were included in the analyses to enable meaningful comparisons with the SEE registries. CNS tumors cases were considered to be all cases with the following codes from the *International Classification of Diseases, Tenth Revision*: C70.0 to C72.9 and C75.1 to C75.3.[20] For the purposes of this study, only tumors with malignant behavior were considered eligible because 6 of the SEE registries (Cyprus; greater Poland; Iasi, Romania; central Serbia; Izmir, Turkey; and Ukraine) did not systematically record nonmalignant tumors. Malignant tumors were isolated with the behavior codes of the *International Classification of Diseases for Oncology, Third Edition*; in particular, only tumors with behavior code 3 (malignant) were included in analyses.[21] All registries covered the entire age spectrum of 15 to 39 years, except for the childhood cancer registry of Belarus, which was restricted to individuals up to 19 years old.

Diagnostic Classification and Demographic Variables

Barr et al's diagnostic classification for tumors in AYAs was used.[22] Specifically, on the basis of morphology and

topography, CNS tumors were classified as follows: astrocytomas, other gliomas, ependymomas, medulloblastomas and other primitive neuroectodermal tumors (PNETs), other specified intracranial and intraspinal neoplasms, or unspecified intracranial and intraspinal neoplasms. Because of the significant survival discrepancies, astrocytomas were also divided into the subcategories of low-grade astrocytic tumors, glioblastomas and anaplastic astrocytomas, and astrocytomas not otherwise specified (NOS), whereas medulloblastomas and other PNETs were divided into medulloblastomas and supratentorial PNETs (also in accordance with Barr et al's diagnostic classification).

In addition, the date and basis of the diagnosis (according to the recommendations of the European Network for Cancer Registries[23]), age, sex, and place of residence at diagnosis (classified as urban, semi-urban, or rural according to the recommendations of the national statistical service of each country) were provided by each registry (except for Croatia and Izmir, Turkey) and were also extracted from the SEER data. To facilitate a comparison with the SEER data, the semi-urban and urban categories were merged, and the variable was considered dichotomized in the analyses.

Follow-Up Data

Follow-up data for each registry included the vital status for the longest follow-up period available and the date of last contact. Therefore, based on the date of diagnosis, survival as an endpoint was assessed. Because of the inadequacy of follow-up data for the period before 2007, central Serbia was excluded from all survival analyses. Similarly, death certificate only (DCO) diagnoses and cases lost to follow-up were excluded from survival analyses.

Mortality Data

Data on mortality due to CNS tumors at the regional or national level were provided by the respective national statistical services. The cause of death for CNS tumors was coded according to the *International Classification of Diseases, Tenth Revision*; the codes included C70.0 to C72.9 and C75.1 to C75.3. Official mortality data were not available for the 2 Romanian registries and the Izmir registry; therefore, they were excluded from the mortality analyses. The US mortality data for the total AYA population, provided by the National Center for Health Statistics, were downloaded from the SEER Web site.[24] The participating SEE registries also provided the underlying populations needed to calculate mortality rates for the respective registration years by age group, sex, and calendar year, whereas population data were available online from the SEER database.

Statistical Analysis

On the basis of the number of deaths by age group (15-19, 20-24, 25-29, 30-34, and 35-39 years), crude and age-standardized with the world (Segi) population,[25] mortality rates for malignant CNS tumors were calculated for each registry. Consequently, we estimated annual percent changes in mortality rates with Poisson regression analysis; to identify potential breaks in time trends, a joinpoint regression analysis was additionally implemented.

Kaplan-Meier curves were derived to calculate the cumulative survival for patients with malignant CNS tumors 6 months and 1, 2, 3, 5, and 10 years after their diagnosis with stratification by registry, geographical region, diagnostic subtype, age group, and sex. Further analyses, restricted to the most recently available 10 registration years for each registry, were also performed to preserve comparability among registries with highly heterogeneous study periods. To evaluate temporal changes in the overall survival of patients with malignant CNS tumors in the SEE region, survival rates were calculated for the registration period 2001-2009, which was common in the majority of the largest SEE registries; time trends were evaluated on the basis of survival rates in three 3-year periods (2001-2003, 2004-2006, and 2007-2009). The log-rank test was used for the statistical evaluation of differences in survival rates.

Lastly, Cox proportional hazards models were designed that encompassed the age group, sex, diagnostic period (in 5-year intervals), diagnostic group, and registry. As an alternative to the registry variable, the place of residence was introduced into the model. All analyses were also conducted by geographical region (SEE and SEER); thereafter, subanalyses were performed by age group (15-19 and 20-39 years) and by diagnostic category and were restricted to cases diagnosed within the last 10 registration years for each registry and to cases diagnosed after 2000. Belarusian data were included only in the subanalyses of the 15- to 19-year age group. Statistical analyses were performed with SAS software (version 9.4; SAS Institute, Inc).

RESULTS

Mortality

Table 1 presents the crude and age-standardized mortality rates for AYAs with malignant CNS tumors and also the respective incidence rates to put the mortality rates in context. In addition, the incidence rates by diagnostic group

TABLE 1. CIRs, AIRs, CMRs, and AMRs for Malignant (*ICD-O-3* Behavior Code 3) Central Nervous System Tumors per Million Adolescents and Young Adults (15-39 Years Old), Male-to-Female Ratios, and APCs in SEE Cancer Registries and the United States

	Incidence Analysis										Mortality Analysis									
			CIR by Age Group					AIR (15-39 y)					CMR by Age Group					AMR (15-39 y)		
Registry	Period	Cases, No.	15-19 y	20-24 y	25-29 y	30-34 y	35-39 y	Rate	Male/ Female	APC (95% CI)	Period	Deaths, No.	15-19 y	20-24 y	25-29 y	30-34 y	35-39 y	Rate	Male/ Female	APC (95% CI)
Belarus[a]	1990-2014	239	13.3	—	—	—	—	—	1.2	0.1 (–1.7 to 2.0)	2002-2014	66	7.4	—	—	—	—	—	1	–0.2 (–6.6 to 6.7)
Croatia	2001-2013	608	21.2	21.2	39.0	41.0	46.2	30.8	1.2	–2.5 (–4.6 to –0.4)	1995-2013	460	10.2	8.5	12.0	18.8	31.4	15.1	1.4	–0.1 (–1.8 to 1.5)
Cyprus	1998-2013	85	12.7	12.3	23.1	19.8	23.7	17.8	1.9	–3.9 (–8.2 to 0.6)	2004-2014	7	0.0	2.7	0.0	4.4	3.2	1.8	2.5	–2.1 (–22.8 to 24.2)
Malta	1995-2014	56	10.7	13.7	19.3	34.6	22.0	18.9	2.0	1.2 (–3.3 to 6.0)	1995-2014	40	7.2	12.0	7.0	25.5	20.2	13.3	2	–0.4 (–5.6 to 5.1)
Montenegro[b]	2013	6	22.7	23.4	0.0	89.9	0.0	25.1	0.9	—	2013	0	0.0	0.0	0.0	0.0	0.0	0.0	—	—
Greater Poland	1999-2014	627	23.7	23.1	29.4	37.2	38.3	29.3	1.2	2.7 (0.9 to 4.4)	1999-2014	404	11.6	10.6	18.5	25.0	33.2	18.5	1.5	–0.9 (–3.0 to 1.2)
Central Portugal	1999-2009	233	13.7	18.8	27.7	27.8	40.8	24.5	1.2	2.4 (–1.7 to 6.7)	1999-2009	105	5.2	7.0	10.9	14.9	19.6	11.9	1.4	0.3 (–5.6 to 6.6)
Northern Portugal	1999-2010	385	15.7	20.9	25.0	29.4	40.7	25.1	1.5	3.5 (0.5 to 6.5)	1999-2010	176	9.3	8.1	8.4	15.0	19.5	12.3	1.5	–0.9 (–5.1 to 3.5)
Cluj, Romania[c]	2008-2012	90	2.3	9.1	15.4	24.8	26.5	14.2	1.3	6.2 (–8.2 to 22.9)	—	—	—	—	—	—	—	—	—	—
Iasi, Romania[c]	2008-2011	136	17.6	18.4	19.2	32.2	38.1	23.8	0.8	–7.9 (–21.1 to 7.6)	—	—	—	—	—	—	—	—	—	—
Central Serbia	1999-2013	1216	36.2	35.1	45.8	53.1	58.1	44.3	1.2	–0.4 (–1.7 to 0.9)	1999-2013	451	8.3	9.4	14.7	22.5	29.4	15.6	1.6	–2.4 (–4.5 to –0.3)
Slovenia	1990-2013	391	12.8	14.5	19.1	28.1	35.2	20.6	1.6	0.3 (–1.1 to 1.8)	1990-2015	255	7.2	8.6	8.3	16.4	25.5	12.2	1.8	–2.4 (–4.0 to –0.7)
Izmir, Turkey[c]	1993-2014	891	17.4	18.4	23.0	35.1	42.0	25.7	1.3	2.1 (1.0 to 3.1)	—	—	—	—	—	—	—	—	—	—
Ukraine	2000-2012	6475	19.1	18.6	26.4	36.9	45.7	27.8	1.2	0.7 (0.0 to 1.3)	2005-2012	2339	9.7	9.8	13.5	24.3	29.8	16.2	1.4	–1.3 (–3.0 to 0.5)
US SEER[d]	1990-2012	13,573	15.4	19.4	26.4	31.5	36.7	24.7	1.3	–0.3 (–0.6 to –0.1)	1990-2013	25,158	5.4	5.7	8.3	12.7	18.4	9.4	1.5	–1.6 (–1.8 to –1.4)

Abbreviation: AIR, age-standardized incidence rate; AMR, age-standardized mortality rate; APC, annual percent change; CI, confidence interval; CIR, crude incidence rate; CMR, crude mortality rate; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; SEE, Southern-Eastern Europe; SEER, Surveillance, Epidemiology, and End Results.

[a] Belarus provided data only for the 15- to 19-year age group.

[b] Because of the unavailability of data, no APC was estimated for Montenegro. Mortality analyses were also not meaningful for Montenegro because there were no central nervous system tumor deaths during the period.

[c] The Izmir registry and the 2 Romanian registries were excluded from the mortality analysis because of the unavailability of data.

[d] The incidence analysis was based on the cases registered in the population covered by SEER, whereas the mortality analysis was based on the total US population.

are presented in Supporting Table 1. Specifically, age-standardized mortality rates ranged from 12.2 (Slovenia) to 18.5 deaths per million (greater Poland) in the SEE countries, except for Cyprus and Montenegro, whose rates may not be reliable on account of the small numbers; overall, the respective rate derived from the US SEER program was considerably lower (9.4 deaths per million). Mortality rates increased by age group in all registries, with deaths among males outnumbering those among females (male/female ratio, 1.4-2.0 in SEE countries and 1.5 in the United States). Declining mortality trends were generally noted in SEE registries and reached statistical significance in Serbia (1999-2013; annual percent change, –2.4%) and Slovenia (1990-2013; annual percent change, –2.4%) without any significant breaks in trends. An annual mortality decrease of 1.6% was also evident in the United States; this was, however, restricted to 1990-2007 and was followed by a stable rate thereafter (2007-2012).

Descriptive Registry Characteristics

A total of 11,438 primary malignant CNS tumors were diagnosed during the registration periods in the areas covered by the SEE registries, whereas 13,573 cases were recorded in SEER during 1990-2012. The descriptive characteristics of the registries along with quality indicators are presented in Table 2. The very low mortality/incidence (M/I) ratios noted in Cyprus (0.1) and Montenegro (0.0) and the very high Maltese rate (0.7) should be interpreted within the context of the very low number of incident cases and deaths in the respective registration periods; on the other hand, central Serbia also had a very low M/I index in comparison with the other registries (0.35), and this can possibly be explained by the very high incidence rate in the region. The M/I ratios for the remaining registries were comparable and ranged from 0.49 (Croatia) to 0.63 (greater Poland). The proportion of DCO diagnoses was <3% in all SEE registries except for Cyprus (5.8%) and the 2 Romanian registries (12.2% and 12.5%); this was notably not significantly different from the proportion in SEER (0.6%). In comparison with SEER (92.3%), the proportion of microscopically verified cases was considerably lower in SEE registries and ranged from 71.4% to 85.1%; at the extremes were the very low microscopically verified proportion in the Croatian registry (57.2%) and the high values in the Slovenian registry (96.4%) and the 2 Portuguese registries (91.9% and 93.5%). The vast majority of the cases (96.5%) had active follow-up with a mean follow-up duration of 6.3 ± 5.9 years.

Survival by Age, Sex, Geographical Region, and Diagnostic Subtype

After the exclusion of DCO diagnoses, cases lost to follow-up, and the central Serbian registry data, a total of 10,078 primary CNS tumor cases from SEE registries and another 13,010 from SEER were included in the survival analyses. As shown in Table 3, the overall 5-year survival rate of AYAs with malignant CNS tumors was 46% in SEE registries; this unfavorable figure is statistically significantly lower than the rate of 67% in SEER ($P < .001$). Although survival was highly variable by histological subtype, SEER data presented more favorable survival across all subtypes and all time intervals examined since diagnosis. In particular, ependymoma was the subtype with the most favorable outcome (5-year survival, 76% in SEE vs 92% in SEER), and it was followed by other specified intracranial and intraspinal neoplasms (71% in SEE vs 84% in SEER), other gliomas (63% in SEE vs 80% in SEER), and low-grade astrocytomas (59% in SEE vs 76% in SEER). Glioblastomas and anaplastic astrocytomas were by far the tumors with the worst prognosis (5-year survival, 28% in SEE vs 37% in SEER). Worth noting is the vast disparity between the SEE registries and SEER regarding survival in the category of unspecified neoplasms (5-year survival, 36% in SEE vs 72% in SEER), which should be interpreted in the context of the much higher proportion of SEE cases lumped in this category (30% vs 2.5% in SEER).

Survival for patients with malignant CNS tumors overall in the individual SEE registries is presented in Supporting Table 2 (see online supporting information). The 5-year survival rate ranged from 52% to 65% but was less than 50% in Ukraine (38%) and Slovenia (49%). In cross-country comparisons during the most recent and rather common (last 5- or 10-year) registration periods, improvements in survival, noted in the majority of the countries, led to diminished differences across the largest registries with the exception of a persistently low survival rate in Ukraine, which influenced the overall SEE performance.

Figure 1 depicts age-specific 5-year survival rates for patients with malignant CNS tumors by the histological subtype in SEE and SEER. Increasing age was associated with worse outcomes for astrocytic tumors (low-grade astrocytomas, glioblastomas and anaplastic astrocytomas, and astrocytomas NOS) and other gliomas in both the SEE registries and SEER ($P < .001$) and for unspecified neoplasms only in the SEE registries. On the contrary, a trend of higher survival with increasing age groups was noted among patients with ependymomas in the SEE registries ($P = .04$).

TABLE 2. Registration of Malignant (*ICD-O-3* Behavior Code 3) Central Nervous System Tumors Among Adolescents and Young Adults (15-39 Years Old) in 14 SEE Cancer Registries and the US SEER Program: Characteristics and Quality Indicators

Registry (Registration Period)	Cases, No.	Population Covered (millions)[a]	National Population Coverage, %	DCO, %	MV, %	Unspecified Morphology, %[b]	M/I	Lost to Follow-Up, %	Follow-Up, Mean ± SD, mo	End of Follow-Up
Belarus (1990-2014)[c]	239	18.0	100	0.8	84.5	19.2	0.56	3.5	124 ± 71	3/2016
Croatia (2001-2013)	608	18.6	100	0.7	57.2	31.9	0.49	0.0	90 ± 45	12/2014
Cyprus (1998-2013)	85	4.7	100	5.8	80.5	15.3	0.10	0.0	42 ± 40	3/2016
Malta (1995-2014)	56	2.8	100	1.8	71.4	22.0	0.70	0.0	118 ± 68	12/2015
Montenegro (2013)	6	0.2	100	0.0	83.3	23.2	0.00	0.0	39 ± 2	11/2016
Greater Poland (1999-2014)	627	20.9	10	0.0	79.9	16.7	0.63	5.8	84 ± 52	12/2015
Central Portugal (1999-2009)	233	8.8	23	0.0	91.9	16.3	0.56	0.0	139 ± 39	5/2016
Northern Portugal (1999-2010)	385	14.3	32	0.0	93.5	17.4	0.55	0.0	115 ± 43	12/2015
Cluj, Romania (2008-2012)	90	5.4	13	12.2	72.2	32.2	N/A[d]	0.0	55 ± 15	12/2014
Iasi, Romania (2008-2011)	136	5.4	18	12.5	81.6	26.5	N/A[d]	0.0	28 ± 19	12/2012
Central Serbia (1999-2013)[e]	1216	26.5	76	2.9	78.5	40.3	0.35	N/A[d]	N/A[d]	N/A[d]
Slovenia (1990-2013)	391	17.5	100	0.0	96.4	11.0	0.59	0.5	141 ± 86	6/2016
Izmir, Turkey (1993-2014)	891	33.1	5	1.2	85.1	10.0	N/A[d]	0.1	69 ± 65	2/2016
Ukraine (2000-2012)	6475	223.1	100	1.8	71.4	34.6	0.58	3.7	63 ± 48	12/2015
US SEER (1990-2012)	13,573	520.9	28	0.6	92.3	2.5	0.38	4.3	84 ± 69	12/2012

Abbreviations: DCO, death certificate only; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; M/I, mortality/incidence; MV, microscopically verified; N/A, not available; SD, standard deviation; SEE, Southern-Eastern Europe; SEER, Surveillance, Epidemiology, and End Results.

[a] The population estimates refer to the sum of the annual adolescent and young adult population (15-39 years old) in the area covered by the respective registry during the entire registration period.

[b] The unspecified morphology category includes cases in the sixth diagnostic category (unspecified intracranial and intraspinal neoplasms) of the classification of cancers in adolescents and young adults proposed by Barr et al.[22]

[c] Data from Belarus were available only for the 15- to 19-year age group.

[d] The 2 Romanian registries and the Izmir registry did not have mortality data available.

[e] Serbia was excluded from the survival analysis because of the unavailability of follow-up data for cases diagnosed before 2007.

TABLE 3. Kaplan-Meier–Derived Overall Survival for Adolescents and Young Adults (15-39 Years Old) With Malignant (*ICD-O-3* Behavior Code 3) CNS Tumors 6 Months and 1, 2, 3, 5, and 10 Years After Their Diagnosis by Diagnostic Group in 13 SEE Cancer Registries and the US SEER Program

Diagnostic Group	Overall Survival, % (95% CI)					
	6 mo	1 y	2 y	3 y	5 y	10 y
Specified low-grade astrocytic tumors						
SEE	96 (94-98)	91 (88-93)	84 (81-87)	77 (73-80)	59 (54-63)	42 (37-47)
US SEER	98 (96-98)	96 (94-97)	89 (87-91)	84 (81-86)	76 (72-79)	60 (56-64)
Glioblastomas and anaplastic astrocytomas						
SEE	82 (80-83)	67 (65-69)	48 (46-51)	39 (37-41)	28 (26-30)	16 (15-18)
US SEER	91 (90-92)	80 (78-81)	59 (57-60)	48 (46-49)	37 (35-39)	27 (25-29)
Astrocytomas NOS						
SEE	86 (84-88)	81 (78-82)	72 (70-74)	66 (63-68)	55 (52-57)	38 (35-41)
US SEER	97 (96-98)	94 (93-95)	88 (87-90)	82 (80-84)	72 (69-74)	57 (54-60)
Other gliomas						
SEE	94 (92-95)	89 (87-90)	81 (79-83)	75 (72-77)	63 (60-66)	44 (40-48)
US SEER	98 (98-99)	96 (95-97)	91 (90-92)	87 (86-88)	80 (79-81)	65 (63-67)
Ependymomas						
SEE	93 (90-95)	90 (86-92)	85 (81-88)	80 (76-84)	76 (71-80)	69 (64-74)
US SEER	99 (98-99)	98 (97-99)	96 (94-97)	95 (93-96)	92 (90-94)	90 (87-92)
Medulloblastomas						
SEE	94 (91-97)	89 (84-92)	79 (73-83)	72 (66-77)	57 (50-63)	43 (36-50)
US SEER	96 (94-98)	93 (91-95)	89 (86-92)	85 (82-88)	78 (74-82)	70 (65-74)
Supratentorial PNETs						
SEE	86 (79-90)	79 (71-84)	59 (51-67)	52 (43-60)	41 (33-50)	32 (23-41)
US SEER	95 (92-97)	84 (80-87)	68 (63-72)	58 (53-63)	53 (47-58)	46 (41-52)
Other specified intracranial and intraspinal neoplasms						
SEE	92 (89-94)	87 (84-90)	81 (77-84)	77 (72-80)	71 (66-75)	63 (57-68)
US SEER	96 (93-98)	94 (90-96)	91 (87-94)	88 (84-92)	84 (79-88)	79 (73-84)
Unspecified intracranial and intraspinal neoplasms						
SEE	62 (60-64)	55 (52-55)	46 (44-47)	41 (39-43)	36 (34-38)	29 (27-31)
US SEER	90 (85-93)	86 (81-90)	80 (74-85)	75 (68-80)	72 (65-77)	71 (64-76)
Overall malignant CNS tumors						
SEE	81 (80-81)	72 (71-73)	62 (61-63)	55 (54-56)	46 (45-47)	34 (33-35)
US SEER	96 (95-96)	91 (90-91)	81 (81-82)	75 (75-76)	67 (66-68)	56 (54-57)

Abbreviations: CI, confidence interval; CNS, central nervous system; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor; SEE, Southern-Eastern Europe; SEER, Surveillance, Epidemiology, and End Results.
The classification by diagnostic groups was performed according to the classification of cancers in adolescents and young adults proposed by Barr et al.[22] Serbia was excluded from the survival analysis because of a lack of follow-up data for cases diagnosed before 2007. Belarus was excluded from the overall survival analysis because the childhood registry had data available only for cases within the age range of 15 to 19 years.

Survival differences by sex were also evident (Supporting Fig. 1 [see online supporting information]). In particular, female sex was associated with higher survival rates for astrocytomas NOS and other gliomas in both the SEE registries ($P = .003$ and $P = .03$, respectively) and SEER ($P < .001$ for both subtypes), for low-grade astrocytomas ($P < .001$), glioblastomas and anaplastic astrocytomas ($P < .001$), and unspecified neoplasms ($P = .01$) in SEER, and for other specified neoplasms in SEE ($P = .008$).

Temporal Trends in Survival

Figure 2 depicts Kaplan-Meier–derived 5-year survival curves for 2001-2003, 2004-2006, and 2007-2009 for the 9 SEE registries that contributed data for this period and for the US SEER program. Improving trends in survival ($P < .001$) were recorded in both regions, with 5-year survival rates increasing from 41% to 46% in SEE and from 65% to 72% in SEER. The low number of cases did not allow further comparisons by diagnostic subtype to evaluate whether these improvements pertained to specific histologies.

Cox Analysis: Prognostic Factors

The unadjusted Kaplan-Meier–derived trends were replicated in multivariate Cox models (Table 4); notably, the diagnosis for older age groups (vs 15- to 19-year-olds) and male sex were inversely associated with the outcome. All other diagnostic subtypes were associated with worse survival in comparison with ependymomas, whereas

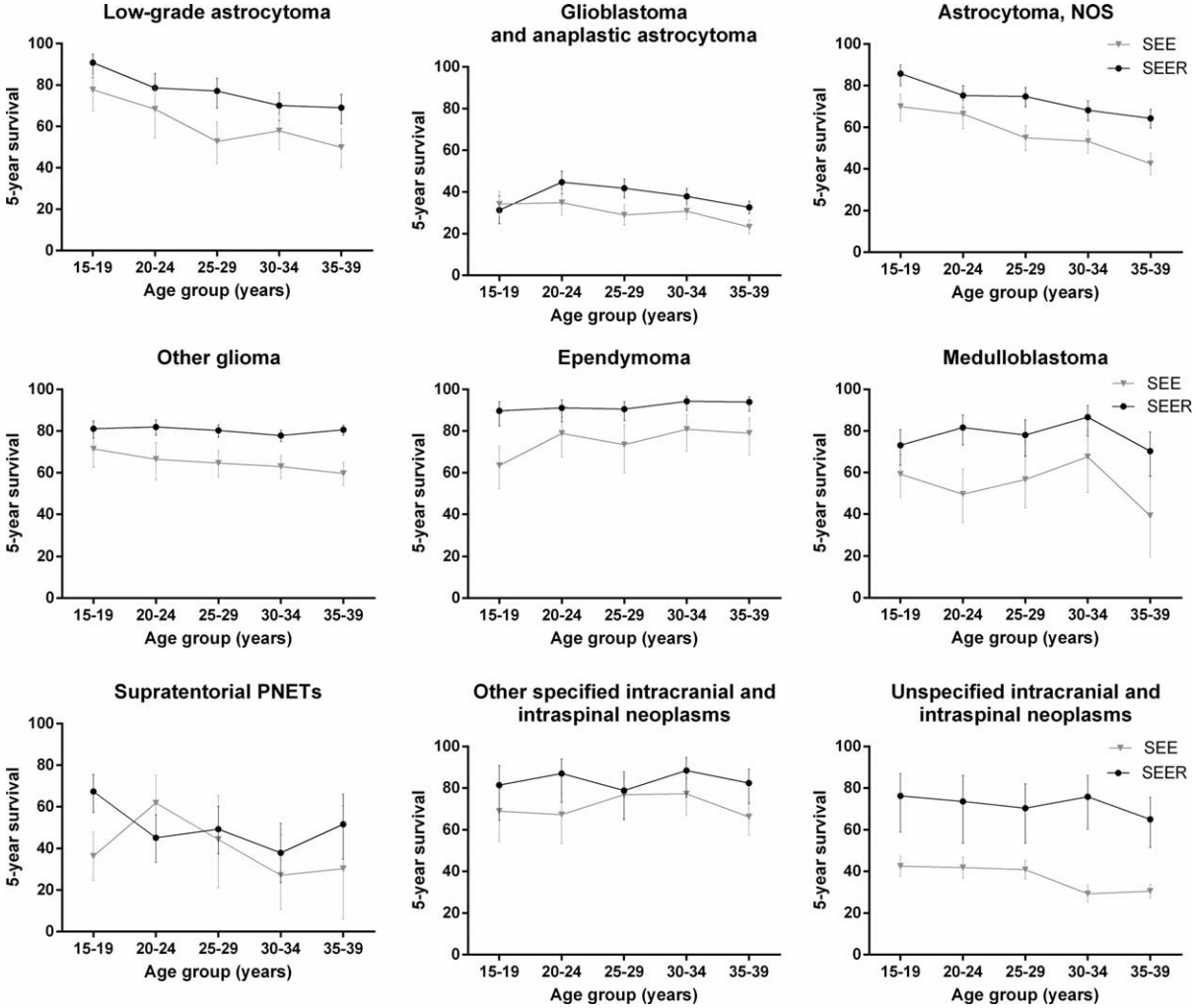

Figure 1. Age-specific 5-year overall survival for adolescents and young adults (15-39 years old) with malignant (*ICD-O-3* behavior code 3) central nervous system tumors in 13 SEE cancer registries and the US SEER program by diagnostic group. The diagnostic classification was performed in accordance with Barr et al.[22] The error bars correspond to the 95% confidence intervals. Central Serbia was excluded from the survival analyses because of the unavailability of follow-up data for cases diagnosed before 2007. Belarus was included only in the analysis of the 15- to 19-year age group. *ICD-O-3* indicates *International Classification of Diseases for Oncology, Third Edition*; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor; SEE, Southern-Eastern Europe; SEER, Surveillance, Epidemiology, and End Results.

glioblastoma and anaplastic astrocytoma patients and patients diagnosed with supratentorial PNETs were at highest risk for death (7- and 5-fold, respectively, in comparison with ependymoma patients). In comparison with SEER, a significantly increased risk of death was noted for malignant CNS tumors in all SEE registries besides the Croatian, Montenegrin, greater Poland, and 2 Romanian registries. Interestingly, CNS tumor patients residing at the time of diagnosis in rural areas had a 36% increased risk of death in comparison with individuals residing in urban or semi-urban areas.

In analyses stratified by age group (15-19 and 20-39 years; see Table 4), males seemed to have worse outcomes only in the older age group, whereas disparities in survival by histological subtype were generally narrower in the 15- to 19-year age group. In particular, in contrast to older individuals, patients aged 15 to 19 years with low-grade astrocytomas, astrocytomas NOS, other gliomas, and other specified intracranial and intraspinal neoplasms were not at increased risk of death in comparison with ependymoma patients. Conversely, the negative effect of rural residency was clearly evident in both age groups.

The findings were similar when SEE data were analyzed separately from SEER data (Supporting Table 3 [see online supporting information]). The effect estimates for age groups, histological subtypes, and rural residency at

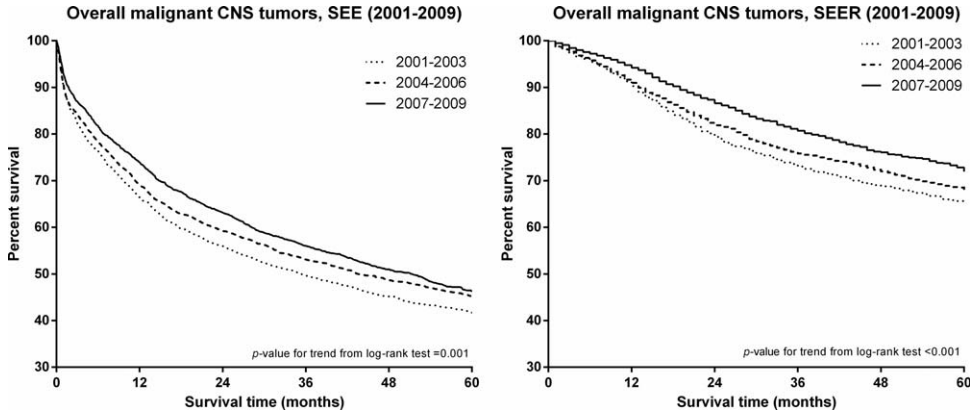

Figure 2. Kaplan-Meier–derived 5-year survival curves for malignant (*ICD-O-3* behavior code 3) CNS tumors diagnosed among adolescents and young adults (15-39 years old) in 9 SEE registries and the US SEER program during 2001-2009 in 3-year intervals. Registries providing data for the entire 2001-2009 time period included Croatia, Cyprus, Malta, greater Poland, central Portugal, northern Portugal, Slovenia, Izmir (Turkey), and Ukraine. CNS indicates central nervous system; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; SEE, Southern-Eastern Europe; SEER, Surveillance, Epidemiology, and End Results.

diagnosis were identical for the 2 geographical regions, although the effect estimate for male sex was higher in SEER (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.19-1.34) versus SEE (HR, 1.08; 95% CI, 1.02-1.13). The analyses by registry, where meaningful, showed similar results for age, histological diagnosis, and rural residency across the registries, whereas the aggravating male effect was statistically significant only in some of the large registries (Croatia, northern Portugal, Slovenia, and Ukraine); however, the effect size was in the same direction for all of them (data not shown). Restricting the analyses to the last 10 registration years for each registry and to all cases diagnosed after 2000 did not materially change the findings (data not shown).

To identify potential histology-specific determinants of outcomes, the Cox analysis was repeated by histological subtype (data not shown). Interestingly, male sex was an independent negative predictor of outcome for all astrocytic tumors (low-grade astrocytomas, glioblastomas and anaplastic astrocytomas, and astrocytomas NOS), other gliomas, and other specified intracranial and intraspinal neoplasms, but it had no impact on ependymomas, embryonal tumors (medulloblastomas and supratentorial PNETs), and unspecified neoplasms. The negative impact of increasing age was clearly evident for low-grade astrocytomas, astrocytomas NOS, and unspecified neoplasms, although this was more prominent in the former (HR for 35-39 vs 15-19 years, 3.16; 95% CI, 2.24-4.46). Among glioblastoma and anaplastic astrocytoma patients, although no trend effect was evident, subjects in the oldest group (35-39 years) were also at increased risk for death (HR, 1.21; 95% CI, 1.08-1.37). Similarly, in comparison with 15- to 19-year-olds, the diagnosis of supratentorial PNETs at 30 to 34 years was also associated with a higher risk of death. Conversely, increasing age seemed to have a positive effect on ependymoma outcomes; ependymoma patients diagnosed at the ages of 30 to 34 and 34 to 39 years had almost half the risk of death in comparison with 15- to 19-year-old individuals (HRs, 0.51 [95% CI, 0.33-0.78] and 0.58 [95% CI, 0.39-0.89]).

DISCUSSION

This study is the first comprehensive overview of mortality and survival patterns of malignant CNS tumors in the distinct age group of AYAs (15-39 years old) derived from several SEE registries. Higher mortality rates and, inversely, lower survival rates in comparison with the respective US rates (assessed from publicly available SEER data) were found across all age groups and tumor subtypes. Survival gains were reflected in the declining mortality rates in the majority of the SEE registries (1990-2014) and the increasing survival rates in 2001-2009. Glioblastoma and anaplastic astrocytoma patients still had the worst prognosis. Increasing age and male sex were identified as independent negative predictors, although the patterns varied by tumor subtype; in line with findings for other types of cancer, there seemed to be persistent inequalities in prognosis and health care delivery, as reflected in worse prognoses for those residing in rural areas and less financially privileged countries.

As expected, our findings from the US SEER 18 data analyses approximated those recently reported by the

TABLE 4. Cox Proportional Hazards Modeling–Derived HRs and 95% CIs for Death Among AYAs (15-39 Years Old) With Malignant (*ICD-O-3* Behavior Code 3) Central Nervous System Tumors in 13 SEE Registries and the US SEER Program by Study Variables

Variable	All AYAs, 15-39 y (n = 22,856)				Adolescents, 15-19 y (n = 2999)				Young Adults, 20-39 y (n = 20,086)			
	Deaths, %	HR	95% CI	*P*	Deaths, %	HR	95% CI	*P*	Deaths, %	HR	95% CI	*P*
Age group												
15-19 y	35.6	Reference								N/A		
20-24 y	39.1	1.15	1.06-1.25	.001					39.1	Reference		
25-29 y	43.1	1.29	1.19-1.39	<.001					43.1	1.12	1.04-1.20	.002
30-34 y	45.2	1.40	1.30-1.50	<.001					45.2	1.22	1.14-1.31	<.001
35-39 y	51.3	1.57	1.46-1.69	<.001					51.3	1.38	1.29-1.47	<.001
Sex												
Male	46.9	1.15	1.10-1.20	<.001	37.5	0.94	0.83-1.06	.31	48.4	1.17	1.12-1.22	<.001
Female	41.5	Reference			36.2	Reference			42.4	Reference		
Diagnostic period (5-y increment)		0.92	0.90-0.94	<.001		0.92	0.86-0.97	.005		0.92	0.90-0.94	<.001
Diagnostic group[a]												
Astrocytomas												
Specified low-grade astrocytic tumors	36.5	2.66	2.25-3.14	<.001	19.2	0.75	0.50-1.13	.17	39.4	3.26	2.72-3.92	<.001
Glioblastomas and anaplastic astrocytomas	63.0	6.61	5.72-7.64	<.001	61.5	3.72	2.77-4.99	<.001	63.2	7.51	6.37-8.84	<.001
Astrocytomas NOS	42.2	3.00	2.59-3.49	<.001	23.0	0.92	0.66-1.29	.65	44.9	3.62	3.06-4.29	<.001
Other gliomas	31.5	2.38	2.05-2.76	<.001	22.7	1.11	0.80-1.53	.54	32.3	2.74	2.31-3.24	<.001
Ependymomas	14.0	Reference			21.3	Reference			12.8	Reference		
Medulloblastomas and other PNETs												
Medulloblastomas	31.6	2.49	2.07-3.00	<.001	34.5	1.61	1.14-2.29	.008	31.6	2.68	2.17-3.31	<.001
Supratentorial PNETs	48.0	5.13	4.27-6.18	<.001	43.9	2.29	1.62-3.23	<.001	51.2	6.29	5.08-7.79	<.001
Other specified intracranial and intraspinal neoplasms	25.2	1.65	1.38-2.02	<.001	29.0	1.24	0.79-1.94	.35	24.7	1.79	1.44-2.23	<.001
Unspecified intracranial and intraspinal neoplasms	60.3	5.46	4.70-6.34	<.001	54.6	2.73	2.01-3.71	<.001	61.8	6.39	5.40-7.58	<.001
Registry												
Belarus[b]		N/A			52.2	1.84	1.49-2.27	<.001		N/A		
Croatia	41.9	1.03	0.90-1.18	.68	35.7	0.98	0.65-1.49	.94	42.7	1.03	0.89-1.19	.70
Cyprus	52.0	2.14	1.56-2.94	<.001	63.6	2.89	1.36-6.10	.006	50.0	2.03	1.43-2.88	<.001
Malta	58.2	1.45	1.02-2.06	.04	66.7	2.33	0.86-6.27	.09	57.1	1.33	0.92-1.94	.13
Montenegro	16.7	0.53	0.08-3.77	.53		N/A			20.0	0.67	0.09-4.77	.69
Greater Poland	37.2	1.07	0.94-1.23	.32	30.2	1.02	0.69-1.49	.93	38.5	1.07	0.92-1.23	.38
Central Portugal	56.5	1.30	1.09-1.55	.003	52.4	1.72	0.94-3.16	.08	58.9	1.26	1.05-1.51	.01
Northern Portugal	55.9	1.56	1.36-1.80	<.001	55.3	1.91	1.23-2.98	.004	56.0	1.51	1.30-1.75	<.001
Cluj, Romania	31.7	0.90	0.61-1.34	.60		N/A			32.5	0.93	0.63-1.38	.72
Iasi, Romania	15.7	0.76	0.48-1.22	.26	18.8	0.85	0.27-2.66	.78	15.2	0.73	0.44-1.22	.23
Slovenia	65.2	1.49	1.31-1.69	<.001	50.0	1.68	1.07-2.64	.02	67.0	1.49	1.31-1.70	<.001
Izmir, Turkey	37.4	1.29	1.15-1.45	<.001	29.1	1.22	0.85-1.76	.28	38.6	1.31	1.16-1.48	<.001
Ukraine	62.5	2.34	2.23-2.46	<.001	53.5	2.19	1.88-2.56	<.001	63.9	2.35	2.23-2.48	<.001
SEER	35.7	Reference			25.3	Reference			37.1	Reference		
Place of residence[c]												
Rural	56.1	1.36	1.30-1.43	<.001	50.3	1.45	1.26-1.67	<.001	57.2	1.35	1.28-1.43	<.001
Urban/semi-urban	42.8	Reference			34.4	Reference			44.1	Reference		

Abbreviations: AYA, adolescent and young adult; CI, confidence interval; HR, hazard ratio; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; N/A, not available; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor; SEE, Southern-Eastern Europe; SEER, Surveillance, Epidemiology, and End Results.

Serbia was excluded from the survival analyses because of the unavailability of follow-up data for cases diagnosed before 2007.

[a] The classification by diagnostic groups was performed according to the classification of cancers in adolescents and young adults proposed by Barr et al.[22]

[b] Belarus was included only in the analysis of the 15- to 19-year age group and not in the analysis of the 20- to 39- year age group or the all AYAs analysis.

[c] The place of residence was introduced as an alternative to the registry variable. After the exclusion of cases with an unknown place of residence, the n value was 21,291 for the total data set analysis, 2810 for the analysis of the 15- to 19-year age group, and 18,713 for the analysis of the 20- to 39-year age group.

Central Brain Tumor Registry of the United States,[9] which includes the whole US population; likewise, the population-based analyses conducted in the context of the EUROCARE, a large collaborative cancer registry project, operating in the overall European region (2000-2007) showed an outcome rate (5-year survival, 57%) for AYAs with malignant CNS tumors rather intermediate between those we calculated for SEE and SEER.[3] Notably, there are wide variations within the European region; indeed, the survival patterns derived from German data (2002-2006) for the age groups of 15 to 29, 30 to 39, and 40 to 49 years were similar to those from SEER for low-grade astrocytomas, glioblastomas and anaplastic astrocytomas, astrocytomas NOS, and other gliomas.[26] Comparisons of the most recent UK findings (5-year survival [2001-2005], 82% and 71% for individuals aged 13-24 and 25-49 years, respectively) with our data are not feasible because they also included nonmalignant CNS tumors.[7] In accordance with previous studies of childhood CNS tumors[15,17] and other childhood and adult cancers,[27-29] rural residence was also associated with a worse prognosis; this indicates the important role of socioeconomic status and health care delivery in outcomes and that there is room for further improvements at a population level.

Besides the definite role of socioeconomic differences in the observed prognosis disparities between SEE and the United States, other parameters should also be taken into account. In particular, access to the health care system, the availability of specified neuro-oncological centers in the United States, the improved neurosurgical outcomes in the United States, the vast difference in the proportion of patients included in clinical trials (which affect survival), and the differences in treatment-related factors, including the type of adjuvant therapy, the aggressiveness of relapse treatment, and supportive care, could partly explain the discrepancies.[30,31] Furthermore, the availability of temozolomide and the possible delay in its incorporation into clinical practice in the SEE countries could also play a role in the observed disparities, especially for high-grade gliomas.[32] However, the completeness of registration is an additional important factor; in particular, if less aggressive tumors are more likely to slip registration in SEE registries because of their management in non-oncology departments, then a phenomenally lower survival rate might emerge. Lastly, the variable ethnic distribution in the US population could have had an impact on the higher survival and lower mortality rates (in comparison with SEE) that were observed in the study.

Nevertheless, outcome differences for malignant CNS tumors were also evident when comparisons were made across the SEE registries. In particular, Croatia, greater Poland, Cluj, and Izmir reported 5-year survival rates higher than 60%, which were comparable to the SEER rate (67%), with the remaining registries reporting somewhat lower rates between 50% and 60%. The gap between the SEE region and SEER was, however, exaggerated because of the extremely low 5-year overall survival rate in Ukraine (38%), which contributed more than half of the SEE cases. In addition to the economic disadvantages of the country (the only one participating that was classified as a lower middle income country[33]), this low rate should be interpreted in the context of incidence, mortality, and registration issues. In particular, the overall mortality rate in Ukraine did not seem to be higher than the rates in the other SEE countries. Concurrently the increasing incidence over the registration period along with the high proportion of histologically unspecified cases possibly indicated incomplete registration in the first active years of this nationwide registry. Because the cases most easily slipping registration were the ones with the best prognosis and could also have been treated outside collaborating oncology departments, this could have led to a recording of cases with a phenomenally worse average prognosis.

Despite these disparities, survival gains in SEER, as previously reported,[9,34] and in the SEE region over the period 2001-2009 should be noted; they were also evident in declining mortality trends in the majority of the SEE registries and reached statistical significance in Serbia and Slovenia. Similar increases in 5-year survival or declining mortality trends have also been reported over the last years in the overall European region,[3] Australia,[35] the United Kingdom,[36] and Brazil,[37] and this indicates that AYAs seem to also enjoy as time progresses the previously reported advancements in children and older adults with CNS cancer.

Besides the disease type and the effects of socioeconomic variables, however, nonmodifiable demographic factors seem to independently affect outcomes and shape the international variation of rates. In line with the literature,[3,9] increasing age among AYAs diagnosed with malignant CNS tumors is a negative prognostic factor. This was confirmed in our findings for both the SEE region and SEER, and the impact was furthermore quantified by tumor subtype; this allowed the identification of specific patterns by disease subtype. Specifically, increasing age was more detrimental for all astrocytic tumors, other gliomas, and supratentorial PNETs but had an inverse positive effect for ependymomas.

Survival differences by sex have also been previously described along with an overall higher incidence of specific subtypes of CNS tumors in males.[9,38] Our study also showed that male sex was independently associated with a worse prognosis, especially among older individuals and those diagnosed with astrocytomas, other gliomas, and other unspecified neoplasms. In contrast, in our previous studies of SEE data focusing on children, no sex difference in survival was identified for malignant CNS tumors[17]; an even better prognosis for males was noted with nonmalignant childhood pilocytic astrocytoma.[15] Several mechanisms have been implicated as contributing to the overall male vulnerability to CNS carcinogenesis.[39] Interestingly, sex disparities in CNS tumor incidence and survival are also evident across different molecular subtypes of the same histological diagnosis.[40] This finding highlights the need for a more comprehensive and subtype-specific focus to better clarify the underlying mechanisms of sex differences in CNS tumorigenesis.

The overall prognosis of AYAs with malignant CNS tumors in the SEE region (5-year survival, 46%) does not actually differ from the overall prognosis that we recently reported for children residing in SEE (5-year survival, 47%)[17]; this lack of a survival gap between the 2 age groups is in line with the recent EUROCARE report from Europe[3] and the Central Brain Tumor Registry of the United States report from the United States.[9] Valid comparisons between children and AYAs, however, should take into account the differential epidemiology of CNS tumors. Because the proposed classifications for children[41] and AYAs[6] are almost identical, when we examined the differences across the diagnostic subcategories, higher 5-year survival rates with ependymal (76% vs 51%) and embryonal tumors (52% vs 41%) were evident among AYAs versus children, but the rates were lower with astrocytomas (41% vs 61%) and other specified intracranial and intraspinal neoplasms (36% vs 58%). The worse outcomes of children with embryonal tumors and ependymomas have been reported in the past and could be attributed to the aggressiveness of these tumors in infants and young children.[42,43] On the other hand, the decreasing survival rates observed for astrocytomas with increasing age could at least partially be explained by the increasing incidence of high-grade astrocytic tumors as age advances. Therefore, despite the worse cancer outcomes reported among AYAs versus children, these specific findings as well as the weight of the different histological types in shaping the overall survival figures should be taken into account to determine whether survival among children largely differs from survival among AYAs with respect to CNS tumors.[7]

The variable study periods across the SEE registries could have affected our findings for SEE as well as the comparisons with the SEER data because of the temporal diagnostic and therapeutic improvements in the management of CNS tumors. Among the registry quality indicators, the DCO percentages were low, but the low proportion of morphologically verified cases, leading to a high percentage of cases of unspecified histology in the SEE registries, should be taken into account when one is interpreting the results pertaining to specific diagnostic subtypes. Most importantly, because of the extremely low survival rates of this diagnostic category in SEE (the 5-year survival rate was 36% and was higher only than the rate for the glioblastoma/anaplastic astrocytoma category), if they were correctly classified in the respective categories, it is possible that this would lead to a widening of the gap in prognosis between the SEE region and the United States. What should also be considered are the difficulties associated with the neuropathological diagnosis of CNS tumors; because of the unavailability of modern facilities for evaluating specific molecular and genetic characteristics of some tumor subtypes, especially in less affluent SEE countries, the proper histological classification of tumors can be very challenging.[44] The consequent misclassifications, which seem to also be supported by the high proportion of unspecified cases in SEE, necessitate the careful interpretation of findings by tumor subtypes. Moreover, the fact that only the vital status was available (so the relative survival rates could not be estimated) and the fact that more detailed individual clinical data were not unavailable are among the inherent limitations; as for the former, it could not be excluded that differences in mortality due to other causes between SEE and SEER could at least partially explain the observed vast disparities. Lastly, the unavailability of and nonpublic access to primary data from the European region, which would probably constitute a reference population closer to SEE in comparison with SEER, are considered a drawback of our study. In this context, the heterogeneity of the actual health care systems, the medical approaches, and the genetic compositions of the populations in SEE and the United States should be taken into account. On the positive side, the large sample size, the in-depth analysis of the available data by CNS tumor subtypes, and the availability of the primary SEER data for comparison are the main strengths of the study.

In conclusion, this study has identified considerable outcome discrepancies between the less affluent SEE

registries and the US SEER program for malignant CNS tumors in the age group of AYAs (15-39 years), which indicate international inequalities in health care delivery systems. Nevertheless, the declining mortality rates and the patterns of increasing survival in both geographical regions during the examined time periods probably reflect the diagnostic and therapeutic advancements of the last decades in the management of these fatal malignancies. In contrast to other cancer types, no significant differences in prognosis were identified between AYAs and the younger age group (0-14 years). Nonmodifiable factors, including age and sex, independently affect outcomes, and this points to the need for potentially targeted treatment modalities by age group and sex. The optimization of cancer registration policies and the further recording of clinical and molecular data will allow us to explore the identified discrepancies by disease subtype at a population level.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

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