NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

MEDICAL SCHOOL

DEPARTMENT OF HYGIENE, EPIDEMIOLOGY AND MEDICAL STATISTICS

THE CONTRIBUTION OF META-ANALYTICAL METHODOLOGY TO THE INVESTIGATION OF PRIMARY CENTRAL NERVOUS SYSTEM TUMORS

DOCTORAL THESIS

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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΕΡΓΑΣΤΗΡΙΟ ΥΓΙΕΙΝΗΣ, ΕΠΙΔΗΜΙΟΛΟΓΙΑΣ ΚΑΙ ΙΑΤΡΙΚΗΣ ΣΤΑΤΙΣΤΙΚΗΣ

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«Η έγκρισις της διδακτορικής διατριβής υπό της Ιατρικής Σχολής του Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών δεν υποδηλοί αποδοχήν των γνωμών του συγγραφέως»

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ΕΚ ΤΟΥ ΙΠΠΟΚΡΑΤΕΙΟΥ ΟΡΚΟΥ

ΚΕΙΜΕΝΟ

« ΟΜΝΥΜΙ ΤΟΝ ΘΕΟΝ ΕΠΙΤΕΛΕΑ ΠΟΙΗΣΕΙΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ ΟΡΚΟΝ ΤΟΝΔΕ ΚΑΙ ΞΥΓΓΡΑΦΗΝ ΤΗΝΔΕ. ΗΓΗΣΕΣΘΑΙ ΜΕΝ ΤΟΝ ΔΙΔΑΞΑΝΤΑ ΜΕ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ ΙΣΑ ΓΕΝΕΤΗΣΙΝ ΕΜΟΙΣΙ. ΔΙΑΙΤΗΜΑΣΙ ΤΕ ΧΡΗΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ ΚΑΜΝΟΝΤΩΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ, ΕΠΙ ΔΗΛΗΣΕΙ ΔΕ ΚΑΙ ΑΔΙΚΙΗ ΕΙΡΞΕΙΝ. ΟΥ ΔΩΣΩ ΔΕ ΟΥΔΕ ΦΑΡΜΑΚΟΝ ΟΥΔΕΝΙ ΑΙΤΗΘΕΙΣ ΘΑΝΑΣΙΜΟΝ. ΟΥΔΕ ΥΦΗΓΗΣΟΜΑΙ ΞΥΜΒΟΥΛΙΗΝ ΤΟΙΗΝΔΕ. ΟΜΟΙΩΣ ΔΕ ΟΥΔΕ ΓΥΝΑΙΚΙ ΠΕΣΣΟΝ ΦΘΟΡΙΟΝ ΔΩΣΩ. ΑΓΝΩΣ ΔΕ ΚΑΙ ΟΣΙΩΣ ΔΙΑΤΗΡΗΣΩ ΒΙΟΝ ΤΟΝ ΕΜΟΝ ΚΑΙ ΤΕΧΝΗΝ ΤΗΝ ΕΜΗΝ. ΕΣ ΟΙΚΙΑΣ ΔΕ ΟΚΟΣΑΣ ΑΝ ΕΣΙΩ, ΕΣΕΛΕΥΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ ΚΑΜΝΟΝΤΩΝ, ΕΚΤΟΣ ΕΩΝ ΠΑΣΗΣ ΑΔΙΚΙΗΣ ΕΚΟΥΣΙΗΣ ΚΑΙ ΦΘΟΡΙΗΣ ΤΗΣ ΤΕ ΑΛΛΗΣ ΚΑΙ ΑΦΡΟΔΙΣΙΩΝ ΕΡΓΩΝ. Α Δ' ΑΝ ΕΝ ΘΕΡΑΠΕΙΗ, Η ΙΔΩ Η ΑΚΟΥΣΩ, Η ΚΑΙ ΑΝΕΥ ΘΕΡΑΠΕΙΗΣ ΚΑΤΑ ΒΙΟΝ ΑΝΘΡΩΠΩΝ, Α ΜΗ ΧΡΗ ΠΟΤΕ ΕΚΛΑΛΕΕΣΘΑΙ ΕΞΩ, ΣΙΓΗΣΟΜΑΙ, ΑΡΡΗΤΑ ΗΓΕΥΜΕΝΟΣ ΕΙΝΑΙ ΤΑ ΤΟΙΑΥΤΑ. ΟΡΚΟΝ ΜΕΝ ΟΥΝ ΜΟΙ ΤΟΝΔΕ ΕΠΙΤΕΛΕΑ ΠΟΙΕΟΝΤΙ ΚΑΙ ΜΗ ΞΥΓΧΕΟΝΤΙ ΕΙΗ ΕΠΑΥΡΑΣΘΑΙ ΚΑΙ ΒΙΟΥ ΚΑΙ ΤΕΧΝΗΣ, ΔΟΞΑΖΟΜΕΝΩ ΠΑΡΑ ΠΑΣΙΝ ΑΝΘΡΩΠΟΙΣ ΕΣ ΤΟΝ ΑΙΕΙ ΧΡΟΝΟΝ. ΠΑΡΑΒΑΙΝΟΝΤΙ ΔΕ ΚΑΙ ΕΠΙΟΡΚΕΟΝΤΙ, ΤΑΝΑΝΤΙΑ ΤΟΥΤΕΩΝ. ΤΑΥΤΗΝ ΤΗΝ ΕΠΑΓΓΕΛΙΑΝ ΕΠΙΤΕΛΟΥΝΤΙ ΕΙΗ ΜΟΙ ΤΟΝ ΘΕΟΝ ΑΡΩΓΟΝ ΚΤΗΣΑΣΘΑΙ ΕΝ ΤΩ ΒΙΩ ».

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1st progress report submission: 12/10/2016

2nd progress report submission: 16/10/2017

3rd progress report submission: 18/07/2019

To my primary and high school teachers

…and to all teachers who promote social mobility

CONTENTS

CURRICULUM VITAE

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Date/place of birth: *Lefkas, Greece, October 31st 1991*
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EDUCATION

10/2017-today	***Doctoral studies (Ph.D.):*** Graduate School of Systemic Neurosciences, LMU, Munich
09/2015-today	***Doctoral studies (D.Sc.):*** Epidemiology, National & Kapodistrian University of Athens
09/2015-09/2017	***Master studies (M.Sc.):*** Neurosciences, National & Kapodistrian University of Athens *Graduation grade: 9.8/10 ("Honors"), top 5% of class*
09/2009-08/2015	***Medical studies (M.D.):*** Medical School, National & Kapodistrian University of Athens *Graduation grade: 8.8/10 ("Honors"), top 10% of class*
09/2003-06/2009	***Secondary education*****:** 1st Gymnasium & 1st Lyceum of Lefkas, Greece *Panhellenic exams grade: 19.47 out of 20 ("Honors")*

RESEARCH EXPERIENCE

10/2017-today	**Doctoral researcher** in Institute for Stroke and Dementia Research, University Hospital of Munich, Ludwig-Maximillian University (LMU), Germany *Supervisor: Prof. Martin Dichgans* *Research focus: Genome-phenome interactions on the pathogenesis of stroke and its subtypes*
06/2013-today	**Doctoral researcher** in Department of Epidemiology, Medical School, National and Kapodistrian University of Athens, Greece *Supervisor: Prof. Eleni Th. Petridou* *Research focus: Epidemiology of neuropsychiatric disorders of the elderly, neuro-oncology*
09/2016-09/2017	**Research fellow (Master thesis student)** in Lab of Neurodegenerative diseases, Bio-academy of Athens, Greece *Supervisor: Prof. Leonidas Stefanis* *Topic: The role of chaperone-mediated autophagy in Parkinson's disease (basic science project)*
09/2015-09/2017	**Research fellow** (long-distance), Department of Women's Health, Uppsala University, Sweden *Employer: Prof. Alkistis Skalkidou* *Research focus: postpartum depression*

AWARDS/ACHIEVEMENTS

05/2019	**Best Poster Award** at 5th European Stroke Organization Conference (ESOC 2019), Milan
10/2018-09/2020	**Scholarship** for Doctoral studies by the Onassis Public Benefit Foundation
10/2018-09/2019	**Research Grant** for Doctoral studies by the German Academic Exchange Service (DAAD)
09/2018	**Travel Award** - Neurepiomics Summer School 2018 in Bordeaux
10/2016	**Best Oral Presentation Award** at 28th Greek Conference of Social Pediatrics and Health Promotion, Trikala
09/2015- 08/2017	**Scholarship** for Master studies by the "Bodossaki Foundation"
09/2015	**Best Poster Award** at 27th Greek Conference of Social Pediatrics and Health Promotion, Sparti-Monemvasia
09/2010-08/2015	**Scholarship** for Medical studies by the legacy of "Antonios Papadakis"
04/2008	**Third Award by Greek Mathematical Society** in national mathematical "Euclid" exams contest as a 2nd year High School student

PUBLICATIONS

48 peer-reviewed publications indexed in PubMed, 1 peer-reviewed publication not indexed in PubMed, 7 manuscripts currently accepted/submitted in peer-reviewed journals

1st author in 32

2nd author in 6

Citations: 370 (Google Scholar, as of 12 September 2019)

h-index: 11

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- Zumel-Marnea A, Kundi M, Castano-Vinyals G, Alguacil J, Petridou ET, **Georgakis MK**, …, Cardis E. Clinical presentation of young people (10-24 years old) with brain tumours: Results from the international MOBI-Kids study. [Submitted]
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- **Georgakis MK,** Gill D, Rannikmäe K, Traylor M, Anderson CD, Lee JM, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, Sudlow CLM, Elhadad MA, Herder C, Koenig W, Peters A, Malik R, Dichgans M. Circulating Monocyte Chemoattractant Protein-1 as a Novel Risk Factor of Stroke. *ESOC 2019: European Stroke Organization Conference*, Milan, Italy, May 2019 [Poster].
- **Georgakis MK,** Gill D, Evangelou E, Elliott P, Dehghan A, Malik R, Tzoulaki I, Dichgans M. Genetically determined blood pressure, blood pressure lowering drugs, and risk of stroke and stroke subtypes: a

Mendelian Randomization study. *ISGC 2019: Investigators Meeting of the International Stroke Genetics Consortium*. Cambridge, UK, April 2019 [Oral Presentation].

- **Georgakis MK.** Cognitive endpoints in DEMDAS: mild cognitive impairment and dementia. *Investigators Meeting of the DEMDAS (Determinant of dementia After Stroke) Study*. Munich, Germany, March 2019 [Invited Speaker].
- **Georgakis MK.** Monocyte chemoattractant protein-1 and risk of stroke: a Mendelian Randomization study followed by validation in a population-based cohort. *XXVII: Symposium "Forschung in der Neurologie"* (Organized by the Neurology Department of the University Hospital of LMU Munich). Munich, Germany, November 2018 [Invited Speaker].
- **Georgakis MK,** Zietemann V, Dondaine T, Müller C, Mendyk AM, Kopczak A, Hénon H, Bombois S, Wollenweber FA, Bordet R, Dichgans M. Early post-admission Montreal Cognitive Assessment predicts long-term cognitive and functional outcome and mortality after stroke Neurology. *VasCog 2018: The 9th International Conference of The International Society of Vascular Behavioural and Cognitive Disorders*. Hong Kong, China, November 2018 [Poster].
- **Georgakis MK.** Genetic variants as instruments for blood pressure lowering: predicting the effect of antihypertensive medication on stroke and stroke subtypes. *Annual Retreat of the Institute for Stroke and Dementia Research*. Munich, Germany, July 2018 [Invited speaker].
- **Georgakis MK,** Xilouri M, Stefanis L. Alpha-synuclein-independent dopaminergic neurodegeneration following *in vivo* inhibition of chaperone-mediated autophagy in mice. *20 YEARS of alpha-synuclein in Parkinson's disease & related synucleionopathies.* Athens, Greece, September 2017 [Poster].
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- **Georgakis MK,** Petridou ET. Genetics of temporal lobe epilepsy. *27th Annual Conference of the Greek Society for Social Pediatrics and Health Promotion*. Monemvasia-Sparti, Greece, October 2016 [Poster].

TEACHING ACTIVITIES

2014- 2017	Supervising of 3rd-year medical students in scientific projects (literature reviews) conducted in the context of their training in the "Epidemiology" core course
11/2016	Lecture series in 3rd -year Medical School students of the University of Athens on "Clinical Epidemiology" in the context of their "Epidemiology" core course
2016-2017	Lectures in 2nd-year Medical School students of the University of Athens on "English terminology in Epidemiology" in the context of the "English Medical Terminology" optional course

INVITED REVIEWER FOR SCIENTIFIC JOURNALS

since 08/2019	Journal of the American College of Cardiology (Impact factor: 18.6)
since 08/2019	Journal of Neurology (Impact factor: 4.2)
since 07/2019	Frontier in Neurology (Impact factor: 2.7)
since 07/2019	Journal of the American Geriatrics Society (Impact factor: 4.4)
since 05/2019	JACC Heart Failure (Impact factor: 8.2)
since 05/2019	Psychoneuroendocrinology (Impact factor: 4.9)
since 04/2019	Journal of Affective Disorders (Impact factor: 3.8)
since 03/2019	Journal of Clinical Medicine (Impact factor: 5.6)
since 10/2018	Neurology (Impact factor: 7.7)
since 03/2018	Journal of Psychiatric Research (Impact factor: 4.5)
since 03/2017	Physiology & Behavior (Impact factor: 2.7)
since 01/2017	Biomedicine & Pharmacotherapy (Impact factor: 2.0)
since 07/2016	Acta Obstetrica et Gynecologica Scandinavica (Impact factor: 2.2)

OTHER ACADEMIC ACTIVITIES

11/2018	Courses on Statistics, Advanced Epidemiology, and Genetic Epidemiology (each 1-month duration) offered by the Master in Epidemiology and Public Health of LMU Munich
09/2018	Neurepiomics Summer School on "Epidemiology of vascular and brain aging in cohorts with large scale imaging and omics data" in Bordeaux, France
01-03/2015	Medical Neuroscience 12-week online course, Duke University, North Carolina, U.S.

OTHER SKILLS

Languages	English (C2 level), German (C1 level), Greek (native)
Computer skills	Statistical analysis software (R, SAS, STATA, SPSS)

PREFACE

Primary central nervous system (CNS) tumors are a diverse group of neoplasms characterized by poor prognosis and highly diverse histopathological features. The annual incidence of malignant primary CNS tumors was estimated to 4.6 per 100,000 individuals worldwide for the year 2016, with notable variations across different geographical regions. Several reports have shown an increase in the incidence of primary CNS tumors over the last decades, but it remains unknown if this increase reflects real increases in disease burden or could be attributed to the development of advanced neuroimaging methods that allow a more accurate detection of the disease. Yet, a detailed documentation of the descriptive epidemiology of CNS tumors has not been achieved in all regions, mainly due to gaps in cancer registration policies. In this aspect, the region of Southern and Eastern Europe including Greece remains among the most underrepresented areas in published literature about CNS tumors.

Primary CNS tumors are among the top causes of deaths due to cancer, especially in younger age groups. Yet, their etiology remains largely unknown, thus halting the progress in the understanding of the pathogenesis of the disease. The only well-established risk factors for primary CNS tumors are specific genetic syndromes predisposing to CNS tumorigenesis and ionizing radiation. However, a number of observations including the peak of specific histological subtypes in early childhood, point to perinatal period and early life, as potential periods of susceptibility for the development of CNS tumors. Thus, several studies have explored whether perinatal and early life exposures could be risk factors for primary CNS tumors in children and adults. These include fetal growth, indices of exposure to infections during the perinatal period, allergies, congenital anomalies, early life exposure to specific chemicals like pesticides, and pregnancy exposures, such as maternal or paternal smoking, alcohol consumption, and administration of pharmaceutical compounds.

Less than a third of patients with malignant primary CNS tumors survive for longer than 5 years, even in countries with the most developed diagnostic and therapeutic tools. However, the prognosis is highly variant, primarily depending on the histopathological features and the location of the tumor in the CNS. For specific tumors like pilocytic astrocytoma, 5-year survival rates might exceed 95%, but for others like glioblastoma, it might be lower than 10%. There are rare forms of CNS tumors, with unique features and very poor prognosis. Among them, gliomatosis cerebri is a glial tumor characterized by the wide infiltration of the CNS and its highly variable clinical and imaging picture that might make its diagnosis challenging. There are only scarce data from case reports and small case series on the epidemiology, the clinical picture, the diagnostic features, the prognostic factors, and the optimal therapeutic approaches for this malignancy.

Thus, additional research is required to systematically record and compare the burden of primary CNS tumors worldwide, identify etiological risk factors that would enable the development of preventive and therapeutic strategies, and figure out prognostic biomarkers that would allow optimization of the current management approaches. Due to the highly heterogeneous histopathological features, many of the current efforts to study the epidemiology of CNS tumors are inherently limited by low sample sizes due to the relatively low incidence of the numerous individual CNS tumor subtypes. To increase analytical power and overcome this limitation, new meta-analytical approaches are required, which would entail pooling of data and collaborative research to maximally exploit available data around the globe.

The aim of the current thesis was to leverage the maximum amount of primary and published data in order to explore features of descriptive, analytical, and clinical epidemiology of primary CNS tumors. Specifically, data were pooled from the Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST), the Greek nationwide case-control study of CNS tumors recruiting cases reported in this registry, a collaborative network of population-based cancer registries in 14 countries in Southern and Eastern Europe including Greece, the database of the Surveillance, Epidemiology, and End Results Program (SEER), which includes data from 18 cancer registries covering 25% of the total US population, meta-analyses of published case-control and cohort studies exploring risk factors for childhood and adult CNS tumors, and a pooled dataset of cases with gliomatosis cerebri created by extracting individual-level data from all case reports and case series that have been published in biomedical literature.

This thesis specifically addresses the following aspects of the epidemiology of primary CNS tumors:

- Estimation of the incidence, time trends, mortality rates, and survival patterns of primary CNS tumors in the specific age group of adolescents and young adults (15-39 years) in the region of Southern and Eastern Europe for the period 1990-2014 and comparisons with figures from the SEER database reflecting the US population. The same features were further explored in the area of Southern-Eastern Europe for childhood pilocytic astrocytoma, the most common solid tumors in the ages 0-14 years.
- Exploration of perinatal and early life risk factors for primary CNS tumors. Specifically, a number of risk factors were examined in a Greek case-control study, whereas the associations of birth weight and other anthropometric measures and risk of CNS tumors were further assessed in large-scale meta-analyses. In a systematic review and a pooled analysis of primary data from the collaborating Southern-Eastern European cancer registries, the associations between seasonality in birth and risk of primary CNS tumors was further examined.
- Systematic analysis of the incidence, age and gender distribution, clinical features, diagnostic findings, histopathological hallmarks, prognostic markers, and optimal therapeutic approaches

for the very rare and fatal malignancy of gliomatosis cerebri. This analysis was based on individual-level data extracted from all case reports and case series that describe cases of gliomatosis cerebri and have been published to date.

In the first part of the thesis (Introduction), I provide a synopsis for the epidemiology of primary CNS tumors. In particular, I describe the latest consensus of the World Health Organization and the International Classification of Childhood Cancer for the histopathological classification of primary CNS tumors, provide an overview of the risk factors for primary CNS tumors with an emphasis on perinatal and early life risk factors, and summarize data on the incidence, mortality, and survival of the disease. Furthermore, I make a synopsis of available data regarding the epidemiological and clinical features of the gliomatosis cerebri. Finally, I provide a remark on meta-analytical methodology and what it could offer in modern epidemiology.

The second and main part of the thesis focuses specifically on each of the included projects. There is an overview of the specific aims that the current thesis attempted to address, a comprehensive description of the sources used and the methodology that was followed for each of the included projects, a detailed presentation of the results derived after the analysis of the data, a commentary section discussing the interpretation of the findings along with potential limitations, and the concluding remarks along with future research guidelines. Finally, three appendices are included (referenced in the main text) providing additional data.

Towards the end of this journey, I would like to acknowledge the contribution of a number of people without whom the completion of this thesis would not have been possible. First, I would like to express my gratitude to my doctorate supervisor Prof. Eleni Petridou for offering me the opportunity to conduct my thesis in the Department of Epidemiology in the University of Athens, to work on the current project, and to use primary data from the NARECHEM-ST database, which she directs. Her genuine scientific curiosity, her generous willingness for guidance and teaching, her tireless attitude to work, her multi-tasking working style, and her goal-oriented behavior even under the most unfavorable conditions have provided for me a bright source of inspiration and have ultimately framed me as a researcher.

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I further owe special thanks to Dr. Nick Dessypris, the biostatistician of our team, for supporting me before and during the entire duration of my doctoral studies. Being the one who believed in me in the first place, Nick encouraged and supervised my first steps in research and showed me the way

for the current thesis. He introduced me to statistical analysis and offered me scientific and personal guidance that has been valuable ever since.

I would further like to acknowledge the personnel working for the NARECHEM-ST, and specifically Mrs. Evdoxia and Panagiota Bouka for the cumbersome collection of data for the Greek case-control study of CNS tumors and the registration of cases in the database. Without their hard work, this thesis would not have been possible. Along with them, I would like to thank all the directors and handling statisticians of the collaborating cancer registries in the Southern and Eastern European countries for their dedication in running the registry processes and for kindly providing their data to perform the collaborative analyses presented in this thesis. I would also like to acknowledge Surveillance, Epidemiology, and End Results officials for their kind responsiveness and assistance.

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ABSTRACT

Primary central nervous system (CNS) tumors are among the top causes of deaths due to cancer in younger age groups and are associated with poor prognosis. However, effective treatments to halt the progression of the disease are missing. Thus, additional research is required to systematically record and compare the burden of primary CNS tumors worldwide, identify etiological risk factors that would enable the development of preventive and therapeutic strategies, and figure out prognostic biomarkers that would allow optimization of the current management approaches. Primary CNS tumors comprise a highly heterogeneous group of diseases with different etiology, pathology, clinical presentation, and prognosis. Many of the efforts to study the epidemiology of CNS tumors are inherently limited by low sample sizes due to the relatively low incidence of the numerous individual CNS tumor subtypes. To increase analytical power and overcome this limitation, new approaches are required, which would entail pooling of data and collaborative research to maximally exploit available data around the globe.

In the current thesis we leveraged data in different levels of analyses with the objectives to explore features of descriptive, analytical, and clinical epidemiology of primary CNS tumors. Specifically, we pooled data from a collaborative network of population-based cancer registries in 14 countries in Southern and Eastern Europe (SEE) and the US (Surveillance, Epidemiology, and End Results Program, SEER) to explore the incidence, time trends, mortality, and survival patterns of primary CNS tumors and specific subtypes among children (0-14 years), as well as adolescents and young adults (AYAs). We further analyzed data from a Greek nationwide case-control study of CNS tumors recruiting cases from the Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST) and performed systematic reviews and meta-analyses to explore associations of perinatal and early risk factors with the risk of primary CNS tumors. Finally, we recorded data from all case reports and case series that have to date been published and performed an individual participant data meta-analysis of all described cases of gliomatosis cerebri, a very rare CNS tumor with a widely infiltrating pattern and very poor prognosis.

Within SEE (1990-2014) and SEER registries (1990-2012), diagnoses of 11,438 and 13,573 incident malignant CNS tumors in AYAs were retrieved, respectively. The overall age-adjusted incidence rate of malignant CNS tumors was statistically significantly higher in SEE (28.1/million) compared to SEER (24.7/million). Increasing temporal trends in incidence were documented in 4 SEE registries vs. a rather stable rate in SEER. Mortality rates in SEE (range: 11.8-18.5 deaths/million) were overall higher compared to the overall US population (9.4/million) with rather decreasing trends in both regions. Respectively, survival rates were increasing during a comparable period (2001-2009) in SEE and SEER. Five-year survival was considerably lower in the SEE registries (46%) vs. SEER (67%), a

finding consistent across age groups and diagnostic subtypes. Highest 5-year survival was recorded for ependymoma (SEE:76% vs. SEER:92%) and worst for glioblastoma and anaplastic astrocytoma (SEE:28% vs. SEER:37%). Advancing age, male gender and rural residency at diagnosis adversely impacted on outcome in both regions. Childhood pilocytic astrocytomas, comprising the most common CNS tumor in childhood, were also retrieved from SEE registries (N=552) and SEER (N=2,723). The age-adjusted incidence rate of childhood pilocytic astrocytoma during 1990-2012 in SEE was 4.2/million, but much higher in SEER (8.2/million). Increasing trends, more prominent during earlier registration years, were recorded in both regions. Cerebellum comprised the most common location, apart from infants in whom supratentorial locations prevailed. Ten-year survival was 87% in SEE and 96% in SEER. Significant outcome predictors were age<1 year at diagnosis (HR [95%CI]: 3.96, [2.28-6.90]), female gender (HR: 1.38, [1.01-1.88]), residence in SEE (HR: 4.07, [2.95-5.61]) and rural areas (HR: 2.23, [1.53-3.27]), whereas non-cerebellar locations were associated with a 9- to 12-fold increase in risk of death.

In the Greek case-control study (203 cases and 406 age-, and sex-matched controls) instrument-assisted delivery was associated with increased (OR: 7.82, [2.18-28.03]), whereas caesarean delivery with decreased (OR: 0.67, [0.45-0.99]) risk of childhood CNS tumors, as compared to spontaneous vaginal delivery. Maternal alcohol consumption during pregnancy (OR: 2.35, [1.45-3.81]) and history of living in a farm (OR: 4.98, [2.40-10.32]) were associated with higher odds of childhood CNS tumors. Conversely, higher birth order was associated with decreased odds (OR for 2nd vs. 1st child: 0.60, [0.40-0.89] and OR for 3rd vs. 1st: 0.34, [0.18-0.63]). Birth weight did not show a significant association with CNS tumors in this sample (OR per 500 g increment: 1.15, [0.92-1.44]). In a systematic review, after screening >5,000 articles, we identified 41 studies, encompassing 53,167 CNS tumor cases, which explored the association between birth anthropometrics and risk of primary CNS tumors. In the meta-analysis, birth weight >4,000 g was associated with increased risk of childhood CNS tumors (OR: 1.14, [1.08-1.20]). The risk was higher for astrocytomas and embryonal tumors. Increased odds for CNS tumors were also noted among large-for-gestational-age children (OR: 1.12, [1.03-1.22]). In a systematic review, we further explored the association between birth seasonality and risk CNS tumors. Eight out of 10 studies in children vs. 4 out of 8 in adults showed some statistically significant associations between birth seasonality and CNS tumors or tumor subtype occurrence, pointing to a clustering of births mostly in fall and winter months, albeit no consistent pattern was identified by histological subtype. To further explore this question, primary incident CNS tumor cases (N=6014) were retrieved from the SEE cancer registries (1983-2015). Children born during winter were at slightly increased risk of CNS tumors overall and specifically of embryonal histology (IRR: 1.13, [1.01-1.27]). The winter peak of embryonal tumors was higher among boys (IRR: 1.24, [1.05-1.46]), and especially in the course of the first five years of life (IRR: 1.33[1.03-1.71]).

We explored the incidence patterns and survival rates of gliomatosis cerebri in a population-based registration sample from the SEER database (176 cases over the period 1973-2012). The annual age-adjusted incidence rate was estimated to 0.1/million. Gliomatosis cerebri was diagnosed in the entire age spectrum (range 1-98 years), but higher incidence (0.43/million) was noted among the elderly (≥65 years). A slight male preponderance was observed. Median overall survival was 9 months with a 5-year survival rate of 18%. Increasing age, primary tumor location not restricted to the cerebral hemispheres and rural residence at diagnosis were identified as negative prognostic factors. We further performed a systematic literature search for published case reports and case series on patients with histologically confirmed gliomatosis cerebri and extracted clinical, diagnostic, neuroimaging, histopathological, molecular, and survival data on individual patient level. A total of 274 studies were identified, including 1,648 patients (59% males, mean age 43.6 years). Seizures (50%) were the most common presenting symptom followed by headache (36%), cognitive decline (32%), and focal motor deficits (32%). There was bilateral hemisphere involvement in 65%, infratentorial infiltration in 30% and a focal contrast-enhanced mass (type II) in 31% of cases. Magnetic resonance imaging (MRI, extensive hyperintensities in T2/FLAIR sequences) and MR spectroscopy (elevated choline, creatinine, and myoinositol levels; decreased NAA levels) showed highly consistent diagnostic findings. Low-grade and anaplastic astrocytoma were the most prevalent diagnostic categories, but features of any histology (astrocytic, oligodendroglial, oligoastrocytic) and grade (II-IV) were reported. Among molecular aberrations, IDH mutation and MGMT promoter methylation were the most commonly reported. Median overall and progression-free survival were 13 and 10 months, with 5-year rates of 18% and 13%, respectively. Age ≥65 years at diagnosis, high-grade tumor, type II gliomatosis cerebri, more CNS regions involved, focal neurological deficits, cerebellar symptoms, higher burden of presenting symptoms, Karnofsky performance scale score <70, MRI contrast enhancement, symmetric bilateral CNS invasion, and high proliferation index (Ki67 >5) were independent predictors of poor outcome. Conversely, seizure occurrence, IDH mutation, and MGMT promoter methylation, were associated with prolonged survival. Chemotherapy and surgical resection were associated with improved outcome, whereas radiotherapy either as monotherapy or combined with chemotherapy was not superior to chemotherapy alone. Among 182 children with gliomatosis cerebri (0-18 years, 63% males), MGMT promoter methylation, IDH mutations, and codeletion of 1p/19q were less common molecular aberrations, as compared to adult gliomatosis cerebri, whereas age at diagnosis >4 years, extended CNS infiltration, coordination abnormalities, and cognitive decline were predictors of poor outcome in children. Exploring the association between seizure occurrence and improved survival, we found IDH mutations, a favorable prognostic marker, to be associated with a higher seizure occurrence at presentation, in accordance with other gliomas.

In conclusion, by exploiting national, European, and international population-based cancer registry data, in-house resources, data from published case-control and cohort studies, as well as individual-level data from case reports and case series, with this thesis we were able to address research questions related to all aspects of the epidemiology of primary CNS tumors. We provided the overview of the incidence and survival of malignant CNS tumors in the age group 15-39 years in Southern Eastern Europe and comparisons with the US, explored the epidemiology of pilocytic astrocytoma, the most common primary CNS tumor in childhood, evaluated the role of a series of perinatal and early-life risk factors in the etiology of childhood and adult primary CNS tumors, and finally documented the diagnostic and prognostic features of gliomatosis cerebri, an extremely rare fatal primary CNS tumor with to-date unknown etiology and features.

ΕΛΛΗΝΙΚΗ ΠΕΡΙΛΗΨΗ

Οι πρωτοπαθείς όγκοι του κεντρικού νευρικού συστήματος (ΚΝΣ) ανήκου στις πρώτες αιτίες θανάτου λόγω καρκίνου μεταξύ των μικρότερων ηλικιακών ομάδων. Παρά την εξαιρετικά δυσμενή τους πρόγνωση, δεν υπάρχουν αποτελεσματικές θεραπείες που να σταματούν την πρόοδο της νόσου. Επομένως, κρίνεται αναγκαία η συστηματική καταγραφή της επίπτωσής τους παγκοσμίως, η αναγνώριση αιτιολογικών παραγόντων κινδύνου, καθώς επίσης και η αναγνώριση παραγόντων που επηρεάζουν την πρόγνωση και θα βοηθούσαν στην βελτιστοποίηση της χρήσης των υπαρχόντων θεραπευτικών επιλογών. Οι πρωτοπαθείς όγκοι του ΚΝΣ αποτελούν μία ετερογενή ομάδα νεοπλασμάτων με διαφορετική αιτιολογία, ιστοπαθολογία, κλινική εικόνα και πρόγνωση. Οι περισσότερες προσπάθειες για την συστηματική μελέτη της επιδημιολογίας των πρωτοπαθών όγκων του ΚΝΣ περιορίζονται εγγενώς από μικρά μεγέθη δείγματος λόγω της σχετικά μικρής επίπτωσης καθενός από τους πολυάριθμους διαφορετικούς ιστοπαθολογικούς υποτύπους. Για να αυξηθεί η στατιστική ισχύς των αναλύσεων και να ξεπεραστεί αυτός ο περιορισμός, απαιτούνται νέες προσεγγίσεις, οι οποίες θα περιλαμβάνουν μετα-αναλυτικές μεθοδολογίες και τη συνεργατική εκμετάλλευση όλων των υπάρχοντων δεδομένων σε παγκόσμιο επίπεδο.

Στη παρούσα διατριβή συγκεντρώθηκαν δεδομένα από ποικίλες πηγές με σκοπό σε διαφορετικά επίπεδα αναλύσεων να διερευνηθούν χαρακτηριστικά που σχετίζονται με την περιγραφική, την αναλυτική και την κλινική επιδημιολογία των πρωτοπαθών όγκων του ΚΝΣ. Συγκεκριμένα, μετα-αναλύθηκαν δεδομένα από ένα διεθνές δίκτυο βάσεων καταγραφής νεοπλασμάτων σε 14 χώρες της Νοτιανατολικής Ευρώπης, συμπεριλαμβανομένης της Ελλάδας, καθώς και από το πρόγραμμα SEER (Surveillance, Epidemiology, and End Results Program) στις ΗΠΑ, με στόχο να υπολογιστούν η επίπτωση, οι διαχρονικές τάσεις, η θνησιμότητα και η επιβίωση των πρωτοπαθών όγκων του ΚΝΣ σε διαφορετικές ηλικιακές ομάδες, οι οποίες περιλαμβάνουν τα παιδιά (0-14 ετών) και τους έφηβους και νέους ενήλικες (15-39 ετών). Επιπλέον, αναλύσαμε δεδομένα μίας Ελληνικής μελέτης ασθενών-μαρτύρων η οποία βασίζεται σε παιδιά (0-14 ετών) με όγκους ΚΝΣ που καταγράφονται στο Πανελλήνιο Αρχείο Καταγραφής Παιδιατρικών Αιματολογικών Κακοηθειών και Συμπαγών Όγκών (Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors, NARECHEM-ST) και μετα-αναλύσαμε δεδομένα της διεθνούς δημοσιευμένης βιβλιογραφίας, με σκοπό τη διερεύνηση συσχετίσεων μεταξύ πιθανών παραγόντων κινδύνου της περιγεννητικής περιόδου και της πρώιμης παιδικής ηλικίας και του κινδύνου εμφάνισης όγκων του ΚΝΣ σε παιδιά. Τέλος, κατεγράφησαν δεδομένα από όλες τις περιγραφές περιστατικών και τις σειρές ασθενών με εγκεφαλική γλοιωμάτωση, ενός σπανιότατου όγκου του ΚΝΣ με δυσμενέστατη πρόγνωση, που έχουν δημοσιευθεί στη βιοϊατρική βιβλιογραφία και πραγματοποιήθηκαν μετα-αναλύσεις σε επίπεδο ατομικών δεδομένων.

Στις βάσεις καταγραφής των χωρών της Νοτιοανατολικής Ευρώπης (1990-2014) και στην βάση δεδομένων της SEER (1990-2012), εντοπίστηκαν 11 438 και 13 573 περιπτώσεις πρωτοπαθών κακοήθων όγκων του ΚΝΣ, αντίστοιχα, στην ηλικιακή ομάδα των εφήβων και ενηλίκων. Η συνολική σταθμισμένη κατά ηλικία ετήσια επίπτωση των κακοήθων πρωτοπαθών όγκων του ΚΝΣ ήταν στατιστικά σημαντικά υψηλότερη στη Νοτιοανατολική Ευρώπη (28,1/εκατομμύριο), σε σύγκριση με την βάση του SEER στις ΗΠΑ (24,7/εκατομμύριο). Αυξανόμενες διαχρονικές τάσεις στην επίπτωση εντοπίστηκαν σε 4 βάσεις καταγραφής στη Νοτιοανατολική Ευρώπη, έναντι μίας σχετικά σταθερής επίπτωσης στη βάση του SEER. Οι δείκτες θνησιμότητας λόγω όγκων του ΚΝΣ ήταν επίσης υψηλότεροι στη Νοτιοανατολική Ευρώπη (εύρος: 11,8-18,5 θάνατοι/εκατομμύριο), συγκριτικά με τις ΗΠΑ (9,4/εκατομμύριο) με σχετικά πρωτικές τάσεις και στις δύο περιοχές. Αντιστοίχως, η επιβίωση έδειξε αυξανόμενες τάσεις κατά το διάστημα 2001-2009 τόσο στις βάσεις καταγραφής της Νοτιοανατολικής Ευρώπης, όσο και στη βάση SEER. Η 5-ετής επιβίωση ήταν εμφανώς χαμηλότερη στις βάσεις της Νοτιοανατολικής Ευρώπης (46%, έναντι 67% στη SEER), ένα έυρημα σταθερό ανεξάρτητα από την εξεταζόμενη ηλικιακή υπο-ομάδα ή τους ιστοπαθολογικούς υποτύπους. Η υψηλότερη 5-ετής επιβίωση κατεγράφη για το επενδύμωμα (76% στη Νοτιοανατολική Ευρώπη και 92% στη SEER) και η χειρότερη για το γλοιοβλάστωμα και το αναπλαστικό αστροκύτωμα (28% στη Νοτιοανατολική Ευρώπη και 37% στη SEER). Η αυξανόμενη ηλικία, το ανδρικό φύλο και η διαμονή σε αγροτικές περιοχές κατά τη διάγνωση συσχετίστηκαν με δυσμενή έκβαση και στις δύο περιοχές. Στοιχεία για τα πιλοκυτταρικά αστροκυτώματα της παιδικής ηλικίας, τα οποία αποτελούν τον πιο κοινό όγκο του ΚΝΣ στα παιδιά, εξήχθησαν επίσης από τα αρχεία καταγραφής των χωρών της Νοτιοανατολικής Ευρώπης (N=552) και τη SEER (N=2 723). Η σταθμισμένη κατά ηλικία επίπτωση των παιδικών πιλοκυτταρικών αστροκυττωμάτων κατά την περίοδο 1990-2012 υπολογίστηκε σε 4,2 νέες περιτώσεις/εκατομμύριο στη Νοτιοανατολική Ευρώπη, αλλά πολύ υψηλότερη στην περιοχή καταγραφής της SEER (8,2/εκατομμύριο). Αυξανόμενες τάσεις, εμφανέστερες κατά τα πρώτα έτη καταγραφής, παρατηρήθηκαν και στις δύο περιοχές. Η παρεγκεφαλίδα αποτελούσε την συνηθέστερη περιοχή εντόπισης των πιλοκυτταρικών αστροκυττωμάτων, εκτός από τα βρέφη (<1 έτους) όπου επικρατούσαν οι υπερσκηνιδιακές εντοπίσεις. Η 10-ετής επιβίωση ήταν 87% στη Νοτιοανατολική Ευρώπη και 96% στην βάση του SEER. Οι σημαντικότεροι αρνητικοί προγνωστικοί παράγοντες ήταν η ηλικία <1 έτους στη διάγνωση (HR: 95% CI: 3.96, [2,28-6,90]), το θήλυ φύλο (HR: 1,38, [1,01-1,88]) και η διαμονή σε αγροτικές περιοχές (HR: 2,23, [1,53-3,27]), ενώ οι μη παρεγκεφαλιδικές εντοπίσεις συσχετίστηκαν με 9 έως 12 φορές αυξημένο κίνδυνο θανάτου.

Στην ελληνική μελέτη ασθενών-μαρτύρων (203 περιπτώσεις παιδιατρικών πρωτοπαθών όγκων ΚΝΣ και 406 μάρτυρες σταθμισμένοι κατά ηλικία και φύλο), ο υποβοηθούμενος με εμβρυουλκία τοκετός συσχετίστηκε με αυξημένο (OR: 7,82, [2,18-28,03]), ενώ η καισαρική τομή με μειωμένο (OR: 0,67 , [0,45-0,99]) κινδύνο για όγκους ΚΝΣ παιδικής ηλικίας, σε σύγκριση με τον φυσιολογικό

αυθόρμητο κολπικό τοκετό. Η μητρική κατανάλωση κατανάλωση αλκοόλ κατά τη διάρκεια της εγκυμοσύνης (OR: 2,35, [1,45-3,81]) και το ιστορικό διαβίωσης σε φάρμα (OR: 4,98, [2,40-10,32]) συσχετίστηκαν με υψηλότερες πιθανότητες εμφάνισης παιδικών όγκων του ΚΝΣ. Αντίθετα, η αυξανόμενη σειρά γέννησης του παιδιού συσχετίστηκε με μειωμένο κίνδυνο (OR για το 2ο έναντι του 1ου παιδιού: 0,60, [0,40-0,89] και OR για 3ο έναντι 1ου: 0,34, [0,18-0,63]). Το βάρος κατά τη γέννηση δεν έδειξε στατιστικά σημαντική συσχέτιση με τους όγκους του ΚΝΣ σε αυτό το δείγμα (OR ανά 500 g: 1,15, [0,92-1,44]). Σε συστηματική ανασκόπηση, κατά την οποία πραγματοποιήθηκε διαλογή> 5 000 άρθρων, εντοπίσαμε 41 μελέτες (N=53 167 περιπτώσεις όγκων του ΚΝΣ), οι οποίες διερευνούσαν τη συσχέτιση μεταξύ ανθρωπομετρικών μετρήσεων κατά τη γέννηση και κινδύνου πρωτοπαθών όγκων του ΚΝΣ. Στην μετα-ανάλυση, το βάρος γέννησης> 4 000 γρ. συσχετίστηκε με αυξημένο κίνδυνο παιδικών όγκων του ΚΝΣ (OR: 1,14, [1,08-1,20]). Ο κίνδυνος ήταν υψηλότερος για τα αστροκυττώματα και τους εμβρυϊκούς όγκους. Αυξημένος κίνδυνος για όγκους ΚΝΣ παρατηρήθηκε επίσης μεταξύ των παιδιών που γεννήθηκαν με μεγάλο για την ηλικία κύησης βάρος (OR: 1,12, [1,03-1,22]). Ακόμη, σε μια συστηματική ανασκόπηση, διερευνήσαμε τη συσχέτιση μεταξύ της εποχικότητας των γεννήσεων και του κινδύνου εμφάνισης όγκων του ΚΝΣ. Οκτώ από τις 10 μελέτες σε παιδιά έναντι 4 από τις 8 στους ενήλικες έδειξαν κάποιες στατιστικά σημαντικές συσχετίσεις μεταξύ της εποχικότητας των γεννήσεων και όγκων του ΚΝΣ, δείχνοντας μια συσσώρευση γεννήσεων κυρίως κατά τους φθινοπωρινούς και χειμερινούς μήνες. Για να διερευνήσουμε περαιτέρω αυτό το ερώτημα, δεδομένα από περιστατικά πρωτοπαθών όγκων του ΚΝΣ (N=6 014) εξήχθησαν από τα αρχεία καταγραφής νεοπλασμάτων στις βάσεις της Νοτιοανατολικής Ευρώπης (1983-2015). Τα παιδιά που γεννήθηκαν κατά τη διάρκεια του χειμώνα παρουσίασαν ελαφρώς αυξημένο κίνδυνο εμφάνισης όγκων του ΚΝΣ, και συγκεκριμένα όγκων εμβρυϊκής προέλευσης (IRR: 1,13, [1,01-1,27]). Το εύρημα αυτό ήταν υσχυρότερο μεταξύ των αγοριών (IRR: 1,24, [1,05-1,46]), και ειδικά για όγκους που διαγιγνώστηκαν κατά τη διάρκεια των πρώτων 5 ετών ζωής (IRR: 1,33 [1,03-1,71]).

Εξετάστηκαν ακόμη οι δείκτες επίπτωσης και επιβίωσης της εγκεφαλικής γλοιωμάτωσης με βάση τα δεδομένα από την πληθυσμιακή βάση καταγραφής του SEER, που λειτουργεί στις ΗΠΑ (176 περιπτώσεις κατά την περίοδο 1973-2012). Η ετήσια σταθμισμένη κατά ηλικία επίπτωση της εγκεφαλικής γλοιωμάτωσης σε αυτόν τον πληθυσμό υπολογίστηκε σε 0,1 περιπτώσεις/ εκατομμύριο. Η εγκεφαλική γλοιομάτωση εμφανίζονταν σε ολόκληρο το ηλικιακό φάσμα (εύρος 1-98 ετών), αλλά παρατηρήθηκε υψηλότερη επίπτωση (0,43/εκατομμύριο) στους ηλικιωμένους (≥65 ετών). Παρατηρήθηκε μια ελαφρά υπεροχή της επίπτωσης στους άνδρες. Η μέση συνολική επιβίωση ήταν 9 μήνες και η 5-ετής επιβίωση 18%. Η αύξηση της ηλικίας, ο μη περιορισμός του αρχικού όγκου στα εγκεφαλικά ημισφαίρια και η αγροτική κατοικία κατά τη διάγνωση, αναγνωρίστηκαν ως αρνητικοί προγνωστικοί παράγοντες. Διενεργήθηκε επίσης μια συστηματική βιβλιογραφική ανασκόπηση για δημοσιευμένες αναφορές περιστατικών και σειρές ασθενών με ιστολογικά

επιβεβαιωμένη εγκεφαλική γλοιωμάτωση και πραγματοποιήσαμε εξαγωγή κλινικών, διαγνωστικών, νευροαπεικονιστικών, ιστοπαθολογικών, μοριακών δεδομένων και δεδομένων επιβίωσης σε ατομικό επίπεδο ανά ασθενή. Συνολικά εντοπίστηκαν 274 μελέτες, οι οποίες περιελάμβαναν δεδομένα για 1 648 ασθενείς (59% άνδρες, μέση ηλικία 43,6 ετών). Οι επιληπτικές κρίσεις (50%) ήταν το συνηθέστερα αναφερόμενο σύμπτωμα κατά τη διάγνωση, ακολουθούμενες από την κεφαλαλγία (36%), την έκπτωση νοητικών λειτουργιών (32%) και τα εστιακά κινητικά ελλείμματα (32%). Παρατηρήθηκε αμφοτερόπλευρη συμμετοχή των δύο ημισφαιρίων στο 65%, διήθηση των υποσκηνιδιακών περιοχών στο 30% και η παρουσία εστιακής μάζας που προσλαμβάνει σκιαγραφικό στη μαγνητική τομογραφία (MRI, τύπος II) στο 31% των περιπτώσεων. Η απεικόνιση με MRI (εκτεταμένες αλλιοώσεις σήματος αυξημένης έντασης σε αλληλουχίες T2/FLAIR) και η μαγνητική φασματοσκοπία (αυξημένα επίπεδα χολίνης, κρεατινίνης και μυοϊνοσιτόλης, μειωμένα επίπεδα N-ακετυλασπαρτικού οξέος) έδειξαν εξαιρετικά σταθερά διαγνωστικά ευρήματα. Τα χαμηλού βαθμού και αναπλαστικά αστροκυττώματα ήταν οι πλέον διαδεδομένοι διαγνωστικοί υπότυποι, αλλά αναφέρθηκαν χαρακτηριστικά οποιασδήποτε ιστολογίας (αστροκυτταρική, ολιγοδενδρογλοιακή, ολιγοαστροκυτταρική) και βαθμού (II-IV). Μεταξύ των μοριακών αλλοιώσεων, η μετάλλαξη του IDH και η μεθυλίωση του υποκινητική του MGMT ήταν οι συχνότερα αναφερθείσες. Η μέση συνολική επιβίωση και η ελεύθερη πρόοδου νόσου επιβίωση ήταν 13 και 10 μήνες, αντίστοιχα. Η 5-ετής συνολική και ελεύθερη πρόοδου νόσου επιβίωση υπολογίστηκαν σε 18% και 13%, αντίστοιχα. Ηλικία ≥65 ετών στη διάγνωση, όγκος υψηλού βαθμού κακοήθειας, τύπου II εγκεφαλική γλοιωμάτωση, μεγαλύτερο εύρος συμπτωμάτων κατά τη διάγνωση, εστιακά νευρολογικά ελλείμματα, σημεία παρεγκεφαλιδικής προσβολής, απεικονιστική εκτεταμένη διήθηση του ΚΝΣ, βαθμολογία <70 στην κλίμακα λειτουργικότητας του Karnofsky, πρόσληψη σκιαγραφικού στην MRI, η συμμετρική αμφοτερόπλευρη προσβολή του ΚΝΣ και αυξημένος δείκτης κυτταρικού πολλαπλασιασμού (Ki67> 5%) ήταν ανεξάρτητοι παράγοντες αυξημένου κινδύνου για χειρότερη πρόγνωση. Αντίθετα, η εμφάνιση επιληπτικών κρίσεων κατά τη διάγνωση, η παρουσία της μετάλλαξης του IDH στα κύτταρα του όγκου και η μεθυλίωση του υποκινητή του MGMT συσχετίστηκαν με παρατεταμένη επιβίωση. Η χημειοθεραπεία και η χειρουργική εκτομή συνδέθηκαν με βελτιωμένη έκβαση, ενώ η ακτινοθεραπεία είτε ως μονοθεραπεία είτε σε συνδυασμό με χημειοθεραπεία δεν ήταν ανώτερη από την αποκλειστική χημειοθεραπεία. Μεταξύ 182 παιδιών με εγκεφαλική γλοιομάτωση (0-18 ετών, 63% αγόρια), η μεθυλίωση του υποκινητή του MGMT, οι μεταλλάξεις του IDH και η συν-διαγραφή των χρωμοσωμικών περιοχών 1p/19q ήταν λιγότερο συνηθισμένες μοριακές αλλοιώσεις, σε σύγκριση με την εγκεφαλική γλοιωμάτωση των ενηλίκων. Στην παιδική εγκεφαλική γλοιωμάτωση, η ηλικία >4 ετών στη διάγνωση, η εκτεταμένη διείσδυση του ΚΝΣ στην απεικόνιση, συμπτώματα συμβατά με ελλείμματα συντονισμού και η έκπτωση των γνωσιακών λειτουργιών ήταν παράγοντες που συσχετίστηκα ανεξάρτητα με χειρότερη πρόγνωση. Εξετάζοντας τη συσχέτιση μεταξύ εμφάνισης επιληπτικών κρίσεων κατά τη διάγνωση και της

βελτιωμένης επιβίωσης, διαπιστώθηκε ότι οι μεταλλάξεις του IDH, ένας ευνοϊκός προγνωστικός δείκτης, συσχετίζονται με αυξημένη επίπτωση επιληπτικών κρίσεων, ένα εύρημα συμβατό με τη βιβλιογραφία για άλλα γλοιώματα.

Συμπερασματικά, με την αξιοποίηση δεδομένων από πληθυσμιακές βάσεις καταγραφής νεοπλασμάτων στη Νοτιοανατολική Ευρώπη και τις ΗΠΑ, πρωτογενών δεδομένων από μελέτες στον Ελληνικό πληθυσμό, δεδομένων από δημοσιευμένες προοπτικές μελέτες και μελέτες ασθενών-μαρτύρων, καθώς και δεδομένων από αναφορές περιπτώσεων και σειρές ασθενών, με αυτή τη διατριβή επιχειρήθηκε η διερεύνηση ζητημάτων σχετικών με όλες τις πτυχές της επιδημιολογίας των πρωτοπαθών όγκων του ΚΝΣ. Παρουσιάστηκε η συνολική εικόνα της επίπτωσης και της επιβίωσης των κακοήθων όγκων του ΚΝΣ στην ηλικιακή ομάδα 15-39 ετών στη Νότιαοανατολική Ευρώπη και συγκρίσεις με τις ΗΠΑ, καθώς και η επιδημιολογία του παιδικού πιλοκυτταρικού αστροκυττώματος, του συχνότερου πρωτοπαθούς όγκου του ΚΝΣ στην παιδική ηλικία. Εντοπίστηκαν συσχετίσεις μιας σειράς περιγεννητικών και πρώιμων παραγόντων κινδύνου με την εμφάνιση πρωτοπαθών όγκων ΚΝΣ στα παιδιά και τους ενήλικες. Τέλος, πραγματοποιήθηκε η πρώτη συστηματική καταγραφή της περιγραφικής επιδημιολογίας, καθώς και των διαγνωστικών και προγνωστικών χαρακτηριστικών της εγκεφαλικής γλοιωμάτωσης, ενός εξαιρετικά σπάνιου, επιθετικού και θανατηφόρου όγκου του ΚΝΣ με μέχρι στιγμής άγνωστη αιτιολογία και κλινική συμπεριφορά.

LIST OF PUBLICATIONS IN THE CURRENT THESIS

1. **Georgakis MK,** Panagopoulou P, Papathoma P, Tragiannidis A, Ryzhov A, Zivkovic-Perisic S, Eser S, Taraszkiewicz Ł, Sekerija M, Žagar T, Antunes L, Zborovskaya A, Bastos J, Florea M, Coza D, Demetriou A, Agius D, Strahinja RM, Sfakianos G, Nikas I, Kosmidis S, Razis E, Pourtsidis A, Kantzanou M, Dessypris N, Petridou ET. Central nervous system tumours among adolescents and young adults (15-39 years) in Southern and Eastern Europe: Registration improvements reveal higher incidence rates compared to the US. Eur J Cancer. 2017 Nov; 86:46-58. doi: 10.1016/j.ejca.2017.08.030.

2. **Georgakis MK,** Papathoma P, Ryzhov A, Zivkovic-Perisic S, Eser S, Taraszkiewicz Ł, Sekerija M, Žagar T, Antunes L, Zborovskaya A, Bastos J, Florea M, Coza D, Demetriou A, Agius D, Strahinja RM, Themistocleous M, Tolia M, Tzanis S, Alexiou GA, Papanikolaou PG, Nomikos P, Kantzanou M, Dessypris N, Pourtsidis A, Petridou ET. 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. Cancer. 2017 Nov 15;123(22):4458-4471. doi: 10.1002/cncr.30884.

3. **Georgakis MK,** Karalexi MA, Kalogirou EI, Ryzhov A, Zborovskaya A, Dimitrova N, Eser S, Antunes L, Sekerija M, Zagar T, Bastos J, Agius D, Florea M, Coza D, Bouka E, Bourgioti C, Dana H, Hatzipantelis E, Moschovi M, Papadopoulos S, Sfakianos G, Papakonstantinou E, Polychronopoulou S, Sgouros S, Stefanaki K, Stiakaki E, Strantzia K, Zountsas B, Pourtsidis A, Patsouris E, Petridou ET. Incidence, time trends and survival patterns of childhood pilocytic astrocytomas in Southern-Eastern Europe and SEER, US. J Neurooncol. 2017 Jan;131(1):163-175. doi: 10.1007/s11060-016-2284-9.

4. **Georgakis MK,** Kalogirou EI, Liaskas A, Karalexi MA, Papathoma P, Ladopoulou K, Kantzanou M, Tsivgoulis G; NARECHEM-BT Working Group, Petridou ET. Anthropometrics at birth and risk of a primary central nervous system tumour: A systematic review and meta-analysis. Eur J Cancer. 2017 Apr;75:117-131. doi: 10.1016/j.ejca.2016.12.033.

5. **Georgakis MK,** Dessypris N, Papadakis V, Tragiannidis A, Bouka E, Hatzipantelis E, Moschovi M, Papakonstantinou E, Polychronopoulou S, Sgouros S, Stiakaki E, Pourtsidis A, Psaltopoulou T, Petridou ET; NARECHEM-ST CNS tumors Working Group. Perinatal and

early life risk factors for childhood CNS tumors: Is instrument-assisted delivery associated with higher risk? Cancer Epidemiol. 2019 Apr;59:178-184. doi: 10.1016/j.canep.2019.01.017.

6. **Georgakis MK,** Ntinopoulou E, Chatzopoulou D, Petridou ET. Season of birth and primary central nervous system tumors: a systematic review of the literature with critical appraisal of underlying mechanisms. Ann Epidemiol. 2017 Sep;27(9):593-602.e3. doi: 10.1016/j.annepidem.2017.08.016.

7. Karalexi MA, Dessypris N, **Georgakis MK,** Ryzhov A, Jakab Z, Zborovskaya A, Dimitrova N, Zivkovic S, Trojanowski M, Sekerija M , Antunes L, Zagar T, Eser S, Bastos J, Demetriou A, Agius D, Coza D, Gheorghiu R, NARECHEM-BT Working Group, Kantzanou M, Ntzani EE, Petridou ET Birth seasonality patterns of childhood central nervous system tumors: analysis of 6000 cases from 16 Southern-Eastern European population-based cancer registries. [Paper submitted].

8. **Georgakis MK,** Spinos D, Pourtsidis A, Psyrri A, Panourias IG, Sgouros S, Petridou ET. Incidence and survival of gliomatosis cerebri: a population-based cancer registration study. J Neurooncol. 2018 Jun;138(2):341-349. doi: 10.1007/s11060-018-2802-z.

9. **Georgakis MK,** Tsivgoulis G, Spinos D, Dimitriou NG, Kyritsis AP, Herrlinger U, Petridou ET. Clinical, neuroimaging and histopathological features of gliomatosis cerebri: a systematic review based on synthesis of published individual patient data. J Neurooncol. 2018 Nov;140(2):467-475. doi: 10.1007/s11060-018-2976-4.

10. **Georgakis MK,** Tsivgoulis G, Spinos D, Liaskas A, Herrlinger U, Petridou ET. Prognostic Factors and Survival of Gliomatosis Cerebri: A Systematic Review and Meta-Analysis. World Neurosurg. 2018 Dec;120:e818-e854. doi: 10.1016/j.wneu.2018.08.173.

11. **Georgakis MK,** Tsivgoulis G, Pourtsidis A, Petridou ET. Gliomatosis Cerebri Among Children and Adolescents: An Individual-Patient Data Meta-analysis of 182 Patients. J Child Neurol. 2019 Mar 19:883073819836551. doi: 10.1177/0883073819836551.

12. **Georgakis MK** *et al*. IDH Mutations as predictors of seizure occurrence in gliomatosis cerebri and other gliomas. [Manuscript under preparation].

LIST OF ABBREVIATIONS

AIR	Age-adjusted Incidence Rate
APC	Annual Percent Change
AYAs	Adolescents and Young Adults
CBTRUS	Central Brain Tumor Registry of the United States
CIR	Crude Incidence Rate
CNS	Central Nervous System
CT	Computed Tomography
GC	Gliomatosis Cerebri
ICCC	International Classification of Childhood Cancer
ICD-10	International Classification of Diseases (10th Edition)
ICD-O-3	International Classification of Diseases for Oncology (3rd Edition)
IDH	Isocitrate Dehydrogenase
MGMT	O^{6}-methylguanine DNA methyltransferase
MOOSE	Meta-analyses Of Observational Studies in Epidemiology ...
MRI	Magnetic Resonance Imaging
NARECHEM-ST	Nationwide Registry of Childhood Hematological Malignancies and Solid Tumors
NF1	Neurofibromatosis type I
NF2	Neurofibromatosis type II
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PNET	Primitive Neuroectodermal Tumor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SEE	Southern and Eastern Europe
SEER	Surveillance, Epidemiology, and End Results
WHO	World Health Organization

INTRODUCTION

Primary central nervous system (CNS) tumors comprise a diverse group of neoplasms that affect both adults and children and are diagnosed in all anatomical regions of the CNS, with >90% occurring in the brain and the remainder in the meninges, the spinal cord, and the cranial nerves. CNS tumors may arise from different cells in the CNS and thus include a number of histological subtypes with markedly different tumor growth rates. Gliomas comprise by far the most common histological type of CNS tumors both in adults and children representing >75% of primary malignant CNS tumors [1]. They are of neuroectodermal origin arising from glial or precursor cells and include astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma [2]. Other primary CNS tumors of non-neuroepithelial origin include meningiomas, tumors of cranial and paraspinal nerves, lymphomas and hematopoietic neoplasms of the CNS, germ cell tumors, and tumors of the sellar region [3]. Malignant CNS tumors remain among the most difficult cancers to treat and are associated with 5-year survival rates of ≤35% [1]. Their clinical presentation is diverse ranging in the entire spectrum of neurological deficits and their accurate diagnosis even with the use of the most advanced neuroimaging methods remains challenging [2].

Histopathological classification of primary central nervous system tumors

Two main classification systems are used to categorize CNS tumors: the World Health Organization (WHO) classification is based on tumor histology and molecular parameters and is universally used for the grouping of CNS tumors in adults and children; and the International Classification of Childhood Cancer (ICCC), which is a classification specific for childhood CNS tumors that is primarily based on primary tumor site and morphology.

The WHO classification for CNS tumors was first published in 1979 and subsequently revised four times, most recently in 2016 [3]. The most updated 2016 WHO classification is based not only on histopathologic appearance, but also on well-established molecular parameters separating for example astrocytomas to isocitrate dehydrogenase (IDH)-mutant and IDH-wild type tumors [3]. The histological classification is presented in **Table 1**.

Table 1. The 2016 World Health Organization Classification of Tumors of the Central Nervous System.

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

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Table 1. The 2016 World Health Organization Classification of Tumors of the Central Nervous System (*continue*).

Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {742A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
Italics: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

Furthermore, tumors in the WHO classification are histologically graded on severity based on histological features in a grading scale ranging I-IV [3], as follows:

- Grade I: Tumors do not meet any of the criteria. These tumors are slow growing, nonmalignant, and associated with long-term survival
- Grade II: Tumors meet only one criterion, i.e., only cytological atypia. These tumors are slow growing but recur as higher-grade tumors. They can be malignant or non-malignant
- Grade III: Tumors meet two criteria, i.e., anaplasia and mitotic activity. These tumors are malignant and often recur as higher-grade tumors
- Grade IV: Tumors meet three or four of the criteria, i.e., showing anaplasia, mitotic activity with microvascular proliferation, and/or necrosis. These tumors reproduce rapidly and are very aggressive malignant tumors.

The grading of the most common CNS tumor subtypes according to the WHO classification system is presented in **Table 2**.

Table 2. Histological grading of the most common central nervous system (CNS) tumors according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System.

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

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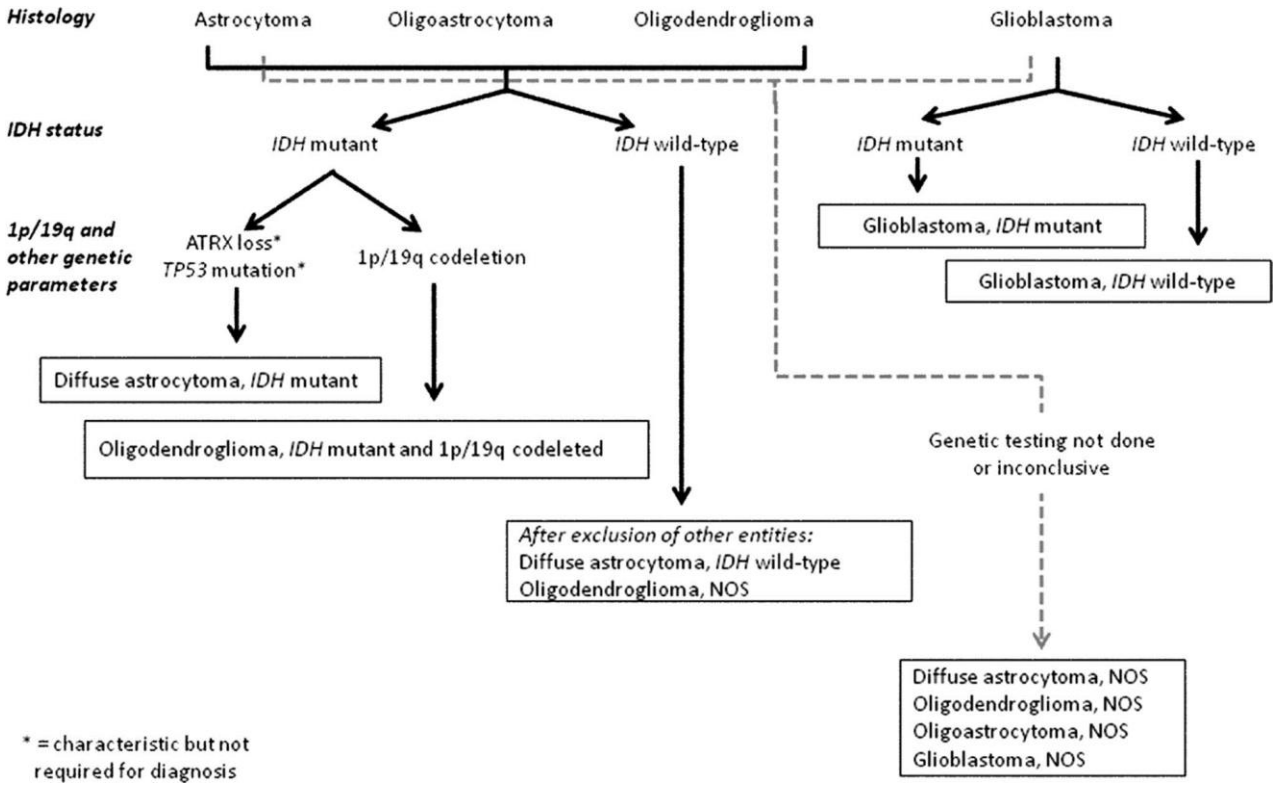
Diffuse astrocytic and oligodendroglial tumors: The 2016 WHO classification system as opposed to prior versions classifies astrocytic and oligodendroglial tumors on the basis of molecular alterations, mainly the isocitrate dehydrogenase (IDH) mutation status, rather than strictly by histopathologic features (**Figure 1**) [3].

Figure 1. Algorithm for the diagnosis of diffuse astrocytic and oligodendroglial tumors based on the 2016 World Health Organization Classification of Tumors of the Central Nervous System.



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Abbreviations: ATRX, ATP-dependent transcriptional regulator X-linked helicase; IDH, isocitrate dehydrogenase; NOS, not otherwise specified

Most grade II and III diffuse astrocytomas and essentially all oligodendrogliomas show IDH mutations, whereas the majority of glioblastomas are IDH-wildtype. This classification improves prognostication. Three general groups of diffuse gliomas with different prognosis can be established based on molecular alterations included in this classification: good-prognosis IDH-mutant, 1p/19q-codeleted tumors (oligodendroglioma histology); intermediate-prognosis tumors with loss of ATP-dependent transcriptional regulator X-linked helicase (ATRX) expression, and poor-prognosis IDH-wildtype tumors (primarily glioblastoma or anaplastic astrocytoma) [4-8].

Astrocytic tumors are characterized by cells with elongated or irregular, hyperchromatic nuclei and eosinophilic cytoplasm, which is positive for glial fibrillary acidic protein (GFAP). Oligodendroglioma consists of cells with rounded nuclei, often with perinuclear halos, calcification, and delicate, branching blood vessels [3]. Despite the significant regional heterogeneity, the tumors are histologically graded according to their most anaplastic-appearing areas. Nuclear atypia and increased mitotic activity characterize anaplastic, grade III tumors, while microvascular proliferation and necrosis define grade IV tumors. Yet, evidence suggests that traditional histological grading criteria may not improve prognostic power on top of the presence of IDH mutations [9].

Other astrocytic tumors: Other astrocytic gliomas are more circumscribed and have a less malignant natural history, as compared to diffuse gliomas. These include pilocytic astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma [3]. Pilocytic astrocytomas are, slow-growing, and well-demarcated tumors. They occur predominantly in children and young adults, comprising the most common CNS tumor in childhood [10,11]. Pilocytic astrocytomas most frequently arise in the posterior fossa, and especially in the cerebellum and around the third ventricle [12-15]. Pilocytic astrocytomas comprise of elongated cells with long processes forming a densely fibrillary background, alternating with regions of loose and microcystic appearances. Rosenthal fibers are a pathologic hallmark of the disease and differentiate pilocytic astrocytomas from other astrocytic gliomas. A specific molecular alteration associated with the histopathology of pilocytic astrocytoma is a tandem duplication of chromosome 7q34, which is associated with a BRAF-KIAA fusion gene [16,17].

Ependymal tumors: Ependymomas consist of cells that resemble the ependymal cells that line the ventricular system and form small tubules and larger spaces lined by these cells. Ependymomas tend to appear alongside the cerebral ventricles. Ependymomas are generally considered grade II tumors, but high cellularity and mitotic activity characterize grade III anaplastic ependymoma. Location is a powerful prognostic marker for ependymoma. A subset of childhood ependymomas in supratentorial locations are molecularly characterized by a RELA fusion chromosome that is associated with poor prognosis, whereas childhood posterior fossa ependymomas are associated with an intermediate prognosis. Based on genetic and methylation profiling ependymomas of posterior fossa, may be further divided into two groups with different invasive and metastatic potential and prognosis [18].

Neuronal and mixed neuronal-glial tumors: A heterogeneous groups of less common primary CNS tumors are of neuronal or mixed neuronal-glial origin. They mainly comprise well-circumscribed tumors of good prognosis that are often only surgically treated. The most common of these tumors is ganglioglioma, an often partially cystic, well-demarcated tumor of low-grade astrocytic component accompanied by collections of neoplastic ganglion cells. Their behavior most commonly corresponds to WHO grade I [19].

Embryonal tumors: This groups includes medulloblastomas, CNS primitive neuroectodermal tumors (PNET), and atypical teratoid rhabdoid tumors. These tumors have been classified as PNET due to the hypothesis that they share a common progenitor cell. Yet, cytogenetic and molecular evidence suggests medulloblastoma, occurring in cerebellum, to be a separate and distinct histologic entity.

Tumors of the sellar region: Tumors of the sellar region include pituitary tumors and craniopharyngiomas. These tumors are generally located in the suprasellar area and arise from remnants of Rathke pouch.

Tumors of cranial and paraspinal nerves: Tumors of cranial and paraspinal nerves include schwannomas, neurofibromas, and malignant peripheral nerve sheath tumors.

Germ cell tumors: Germ cell tumors include germinoma, embryonal carcinoma, yolk sac tumor (endodermal sinus tumors), choriocarcinoma, and teratoma. Approximately two-thirds of these tumors occur in the pineal and suprasellar areas, and the remaining occur in the supratentorial region.

Meningiomas: Tumors of the meninges arise from the arachnoid cap cell in the arachnoid membrane and have varying degrees of malignancy.

Lymphomas: Lymphoma and hemopoietic neoplasms account for a very small proportion of CNS tumors.

Unclassified tumors: Unclassified tumors may include hemangiomas and other unspecified neoplasms.

The histologic types of CNS tumors vary with age and may in children differ from those that present in adults [1]. In children, primary CNS tumors predominate over metastases from tumors of other origin, and approximately 30-50% are located in the posterior fossa, as opposed to adults where most tumors are located in the cerebral hemispheres [1]. These differences translate to differences in clinical presentation between pediatric and adult malignant CNS tumors. For this reason, there is a separate CNS tumor classification specific for children, which takes these differences into account. The ICCC-3 is based not only on histological morphology, but also on primary tumor site aiming to identify groups, which more accurately reflect differences in prognosis [20]. **Table 3** presents the classification for CNS tumors.

Table 3. The International Classification of Childhood Cancer, Third Edition (ICCC-3): Main Classification Table for primary central nervous system (CNS) tumors.

	ICD-O-3 code(s)[10]	
Diagnostic group	**Morphology**	**Topography**
III. CNS and miscellaneous intracranial and intraspinal neoplasms		
a. Ependymomas and choroid plexus tumor	9383, 9390–9394[a]	
b. Astrocytomas	9380[a]	C72.3
	9384, 9400–9411, 9420, 9421–9424, 9440–9442[a]	
c. Intracranial and intraspinal embryonal tumors	9470–9474, 9480, 9508[a]	
	9501–9504[a]	C70.0–C72.9
d. Other gliomas	9380[a]	C70.0–C72.2, C72.4–C72.9, C75.1, C75.3
	9381, 9382, 9430, 9444, 9450, 9451, 9460[a]	
e. Other specified intracranial and intraspinal neoplasms	8270–8281, 8300, 9350–9352, 9360–9362, 9412, 9413, 9492, 9493, 9505–9507, 9530–9539, 9582[a]	

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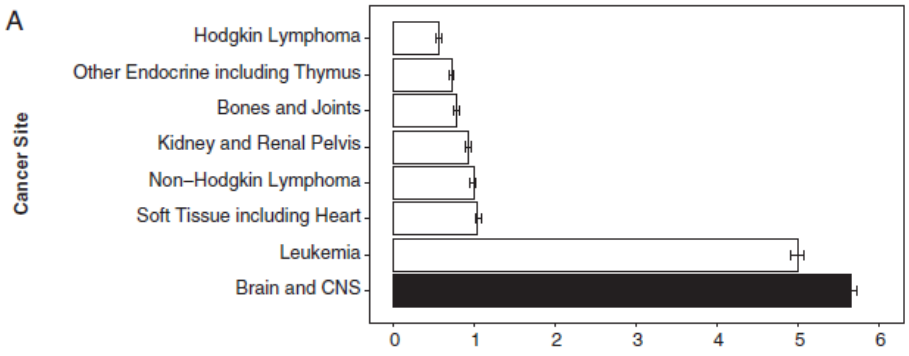
[a] Tumors with nonmalignant behavior are included for all morphology codes on the line.
Abbreviations: ICD-O-3: International Classification of Diseases for Oncology, third edition.

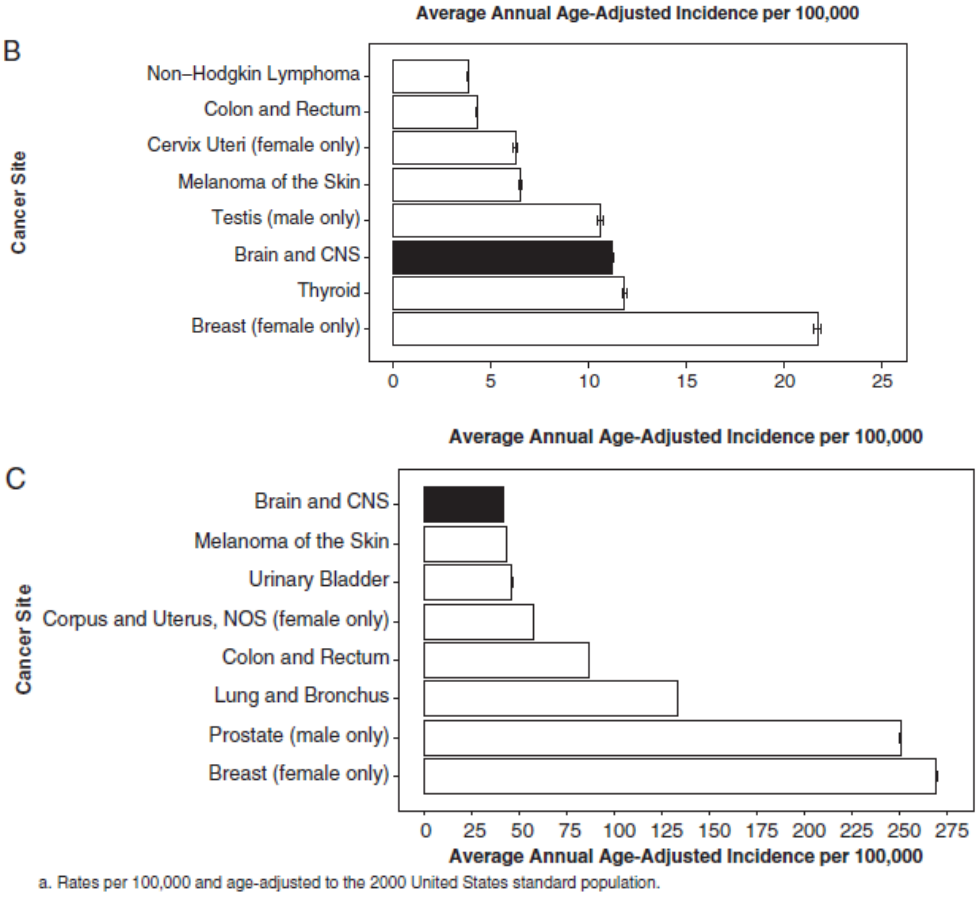
Descriptive epidemiology of primary central nervous system tumors

Incidence and time trends

The incidence rate for primary CNS system tumors varies by the geographical region under study, either because of differences related to the registration methodologies of the examined cancer registries or due to real differences related to genetic and environmental susceptibility. In the United States, according to data coming from the Central Brain Tumor Registry of the United States (CBTRUS) for the period 2011-2015, the overall incidence of primary CNS tumors (malignant and non-malignant) in adults (aged 20 years or older) was estimated to 29.9 per 100,000 individuals [1]. One third of the tumors were malignant and the remainder were benign or of borderline malignancy [1]. The incidence rate for children and adolescents (aged 0 to 19 years) was much lower (5.9 per 100,000 children), although more primary CNS tumors in children were malignant (around 60%), when compared with adults [1]. As depicted in **Figure 2**, According to these data, primary CNS tumors (both malignant and non-malignant) were the most common malignancy among children (0-14 years), the third most common malignancy in the groups of adolescents and young adults (AYAs, 15-39 years), and the eighth most common malignancy in older adults (40 years or more).

Figure 2. Average annual age-adjusted incidence rates of all primary central nervous system (CNS) tumors in comparison to the most common malignancies in the age groups of (A) children aged 0–14 years; (B) adolescents and young adults aged 15–39 years, and (C) older adults aged ≥40 years.





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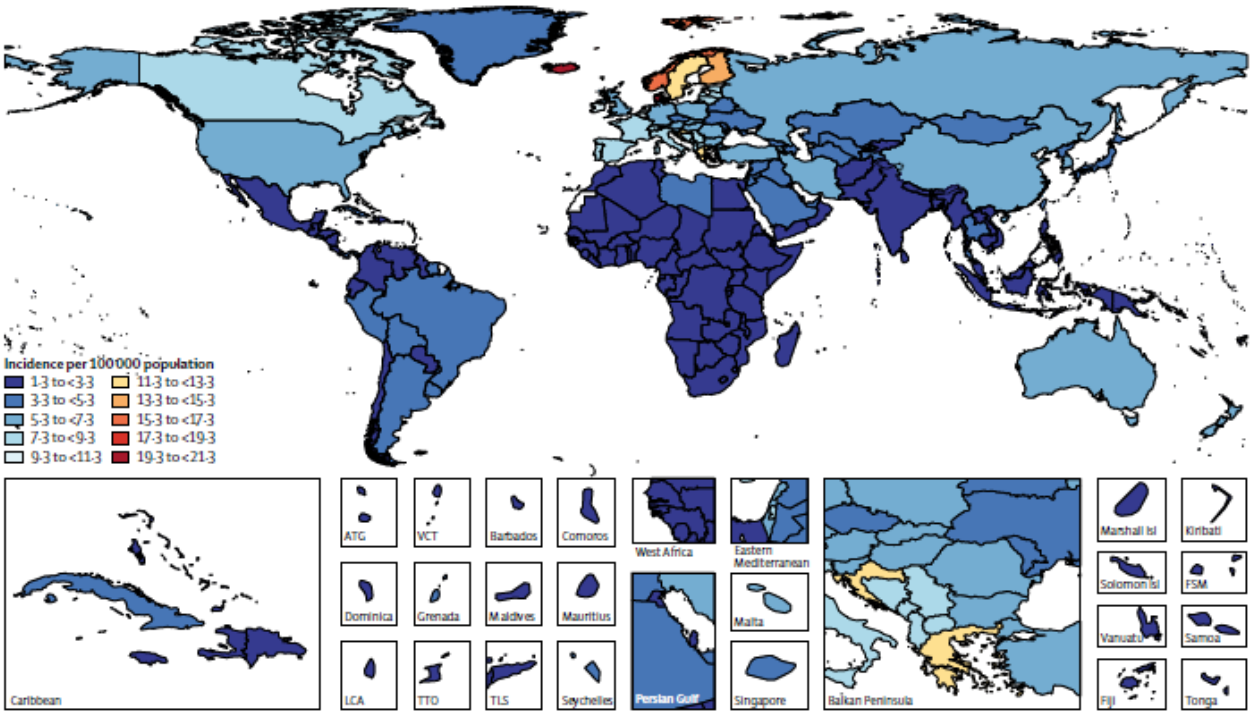
Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report: National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology, and End Results Program (SEER) 2011–2015, United States Cancer Statistics (USCS) 2011–2015.
Abbreviations: NOS, not otherwise specified.

Yet, the worldwide incidence of primary CNS tumors varies widely between countries. According to the statistics from the 2016 Global Burden of Disease Study [21], the overall annual incidence rate of malignant primary CNS tumors was 4.6 per 100,000 persons ranging from 1.3 to 21.3 cases per 100,000 individuals, as depicted in **Figure 3**.

Figure 3. Age-adjusted incidence rates of malignant central nervous system tumors per 100,000 population for both sexes, 2016. Global Burden of Disease (GBD) Study 2016.



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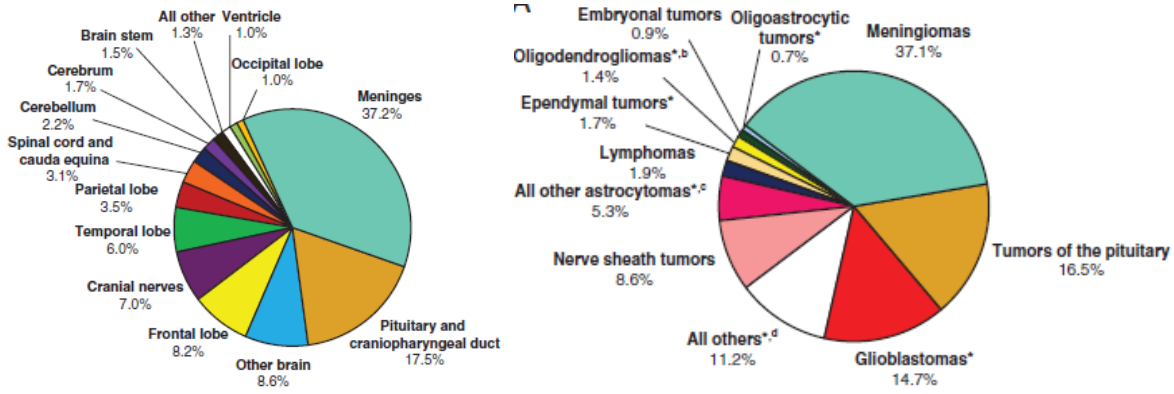
Multiple studies have documented rising incidence rates for CNS tumors in the second half of the 20th century in industrialized countries, mainly among older adults, with no clear ethnic, gender, or geographic differences [22,23]. Although it was considered that incidence rates have generally remained stable over the last several decades, the most recent 2016 Global Burden of Disease Study showed an increase in the incidence of malignant primary CNS tumors by 17% in the period 1990-2016 [21]. The factors underlying this increase in CNS tumor incidence remain unclear. Most researchers interpreted the observed increase as a result of a more complete case ascertainment with improved diagnostic technology mainly due to the advances in neuroimaging [24,25]. However, improved diagnostic utility cannot fully account for the magnitude of the observed increase in CNS tumor incidence [24]. These data, in conjunction with the evidence suggesting the increase is occurring for many decades and may be ongoing, leave open the possibility that an environmental exposure may account for part of the increasing incidence of CNS tumors.

Distribution by age, sex, tumor site, and histology

The distribution of primary CNS tumors by tumor site and histological subtype is depicted in **Figure 4**. The most common histological subtype is meningiomas, and after the meninges and the sellar region (mainly represent non-malignant CNS tumors), the most common tumor locations are the cerebellar hemispheres. However, when considering only malignant CNS tumors, the most common histological subtypes are diffuse gliomas, especially glioblastoma.

Figure 4. Distribution of primary CNS tumors (both non-malignant and malignant) by tumor site and histological subtypes by a) site and b) histology subtypes.



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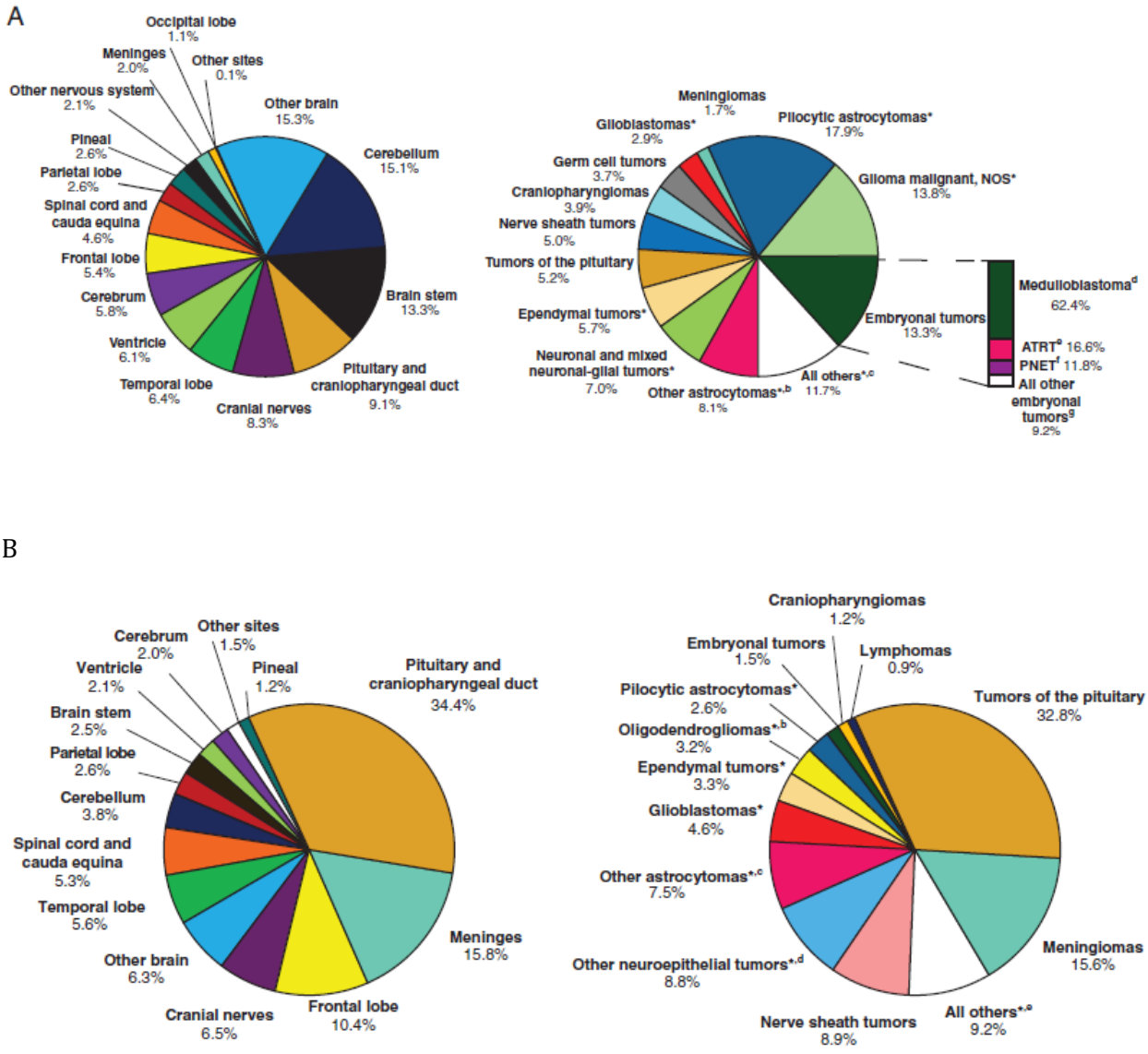
Yet, even these features differ by age. In children (0-14 years) and AYAs, the distributions are different. Posterior fossa locations and particularly the cerebellum and the brainstem are the most common tumor locations in children due to the higher frequency of pilocytic astrocytomas and embryonal tumors that comprise the most common histological subtypes in this age group, which tend to appear in the cerebellum [1]. The picture in AYAs is similar to the one of adults. The detailed distributions by tumor site and histology are presented in **Figure 5**.

Figure 5. Distributions by tumor site and histological subtypes of primary CNS tumors (non-malignant and malignant) in (A) children (age 0-14 years) and (B) adolescents and young adults (aged 15-39 years).



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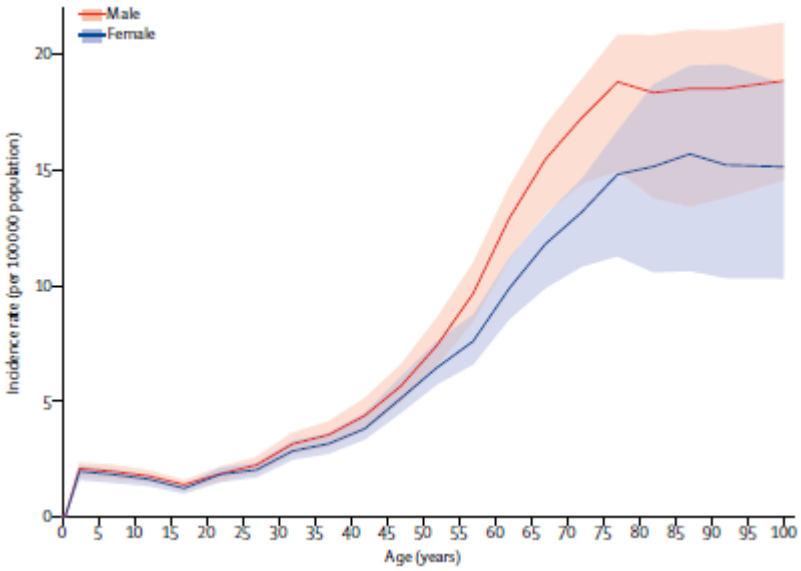
The overall incidence of primary malignant CNS tumors by age and sex is presented in **Figure 6**. There is a slight male predominance in the incidence of primary malignant CNS tumors over the life course, mainly due to differences in older ages (>50 years) [1,21]. However, when both malignant and benign tumor types are examined, males account for only around 40% of the cases due to the much higher incidence of meningiomas, which are usually non-malignant, in females [1]. The incidence of CNS tumors increases considerably with age.

Figure 6. Global age-adjusted incidence rates per 100,000 population of malignant central nervous system tumors by age and sex. Global Burden of Disease (GBD) Study 2016.



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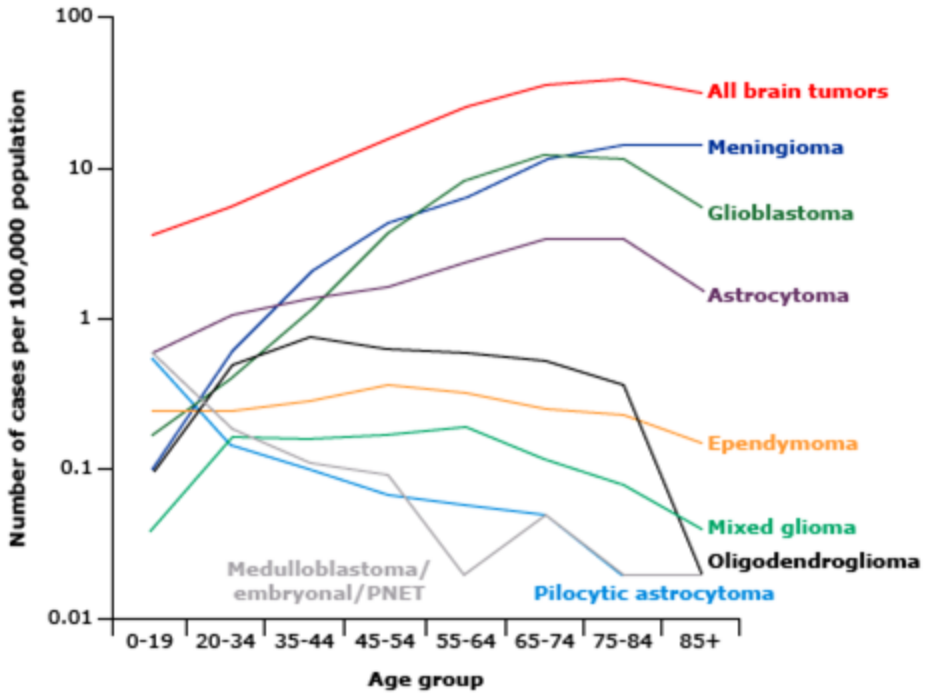
The incidence of primary CNS tumors further varies by age and histological subtype (**Figure 7**). Data from several cancer registries suggest that the incidence rates of astrocytomas (grades II and III), glioblastoma, and meningiomas increase substantially with age, and account for most of the increase in incidence observed for overall CNS tumors. On the contrary, pilocytic astrocytomas and embryonal tumors are more common in childhood (0-14 years) and decrease in older age. Ependymomas show a rather stable incidence rate over lifetime [1,26].

Figure 7. Incidence rates per 100,000 population of primary CNS tumors by age group and histological subtype.



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Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report: National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology, and End Results Program (SEER) 2011–2015, United States Cancer Statistics (USCS) 2011–2015.

Risk factors for primary central nervous system tumors

Several cohort and case-control studies have explored the associations between a number of environmental risk factors in associations with the risk of primary CNS tumors in children and in adults. Yet, despite the breakthrough in the elucidation of their molecular pathogenesis over the last decades [27], their etiologic factors remain largely unknown; only ionizing radiation and specific genetic syndromes have been implicated as causes of CNS tumorigenesis [28]. The high incidence of primary CNS tumor in childhood, however, rationally points to prenatal and perinatal factors potentially impacting on the etiology.

Environmental risk factors

Ionizing radiation: Exposure to ionizing radiation, mainly in the context of therapeutic radiation therapy or among atomic bomb survivors, has been established as a cause of primary CNS tumors including meningiomas, gliomas, and nerve sheath tumors [29]. The latency period between irradiation and the CNS tumorigenesis may be as short as five years or as long as many decades. The risk appears to be higher for meningioma, as compared to glioma and is stronger for younger ages of exposure [29]. Cranial radiation in the context of a childhood neoplasms has been also associated with a higher risk of CNS tumors, especially meningiomas [30]. The risk follows a dose-response pattern and does not appear to plateau over time [30]. Diagnostic cranial computed tomography (CT) scans in childhood delivering radiations doses of about 60 mGy have been further associated with a 3-fold increased risk of CNS tumors [31].

Electromagnetic radiation: Cancer was first associated with exposure to electromagnetic fields in 1979 when it was reported that in Colorado, children dying from cancer resided more often in homes exposed to higher current-flows than healthy control children [32]. Yet, other studies have cast doubt on the possibility that electromagnetic radiation causes CNS tumors. Biologic plausibility has not established, subsequent studies have reported conflicting results, and the probable roles of bias and confounding in these earlier studies have been emphasized. Many of the first studies have used wire configuration around houses as a surrogate for direct electromagnetic field exposure measurements. However, studies using more rigorous methodology, including direct, in-home measurement of electromagnetic radiation, have concluded that a large effect of this type of radiation on the risk of adult CNS tumors can be excluded [33]. Similarly, there is no evidence that exposure of children or pregnant women to magnetic fields from high current lines, electric heating sources, or electric appliances associates with the subsequent occurrence of CNS tumors in children [34-36]. Analyses of

occupational exposure to magnetic fields have also not shown an association with the risk of CNS tumors [37].

Mobile telephones and radiofrequency radiation: Mobile phones comprise a source of radiofrequency radiation and their wide use over the last decades, along with the proximity of the head to the exposure, have raised concerns as potential risk factors for primary CNS tumors. Other sources of radiofrequency radiation exposure include microwave and radar equipment and occupational exposures (sealers, plastic welders, amateur radio operators, medical personnel, and telecommunications workers). Exposures to radiofrequency energy are difficult to quantify, even under laboratory conditions [38-40]. A meta-analysis of 22 case-control series concluded that ever use of a mobile phone, as compared to never or rarely use was not associated with a higher risk for CNS tumors [41]. However, there was an increase of 18% in the risk for individuals reporting an exposure to mobile phone use for >10 years [41]. An international collaboration, the INTERPHONE case-control study pooling data to increase power found no higher risk for either glioma or meningioma, except for some indications for a higher risk of glioma at higher exposures [42]. A cohort study further provided evidence for a specific associations with a higher risk of acoustic neuroma [43], however this was not confirmed in the INTERPHONE study [44]. The WHO and the International Agency for Research on Cancer classify radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B) [45].

Occupational exposures: Several studies have examined whether occupational exposures are associated with the risk of CNS tumors. Although several positive associations have been reported, they are inconsistent and the results are often difficult to interpret because of number of methodological issues. Agricultural occupation and specifically exposure to herbicides and pesticides has been associated with a higher risk of CNS tumors, especially meningiomas [46]. Furthermore, paternal exposure to pesticides during the perinatal period has been associated with a higher risk of malignant CNS tumors in the offspring, according to a meta-analysis of 40 studies [47]. For exposure to rubber, and petroleum, early studies had reported a higher risk, but later meta-analyses summarizing risk estimates showed no excess CNS tumor mortality rates [48,49].

Head trauma: Despite the presence of anecdotal descriptions for CNS tumors arising after head trauma date back to 1922 [50], whether head trauma is a causal risk factor for CNS tumors still remains controversial. In a cohort study of 228,055 individuals from the Danish national registries, increases in the risk of CNS tumors were identified, which reached statistical significance for the subtypes of hemangioblastoma and hemangioma reaching significance [51]. Furthermore, childhood CNS tumors have been found to be higher among firstborn children, among whom birth trauma is more frequent, as well as in children with documented history of birth trauma (including forceps delivery, prolonged labor, and cesarean section) [52]. However, other studies have not found

consistent results and have identified methodological obstacles that may confound these associations in previous publications [53].

Allergies: A number of epidemiological studies have shown significant associations between history of allergy and a lower risk of primary CNS tumors, as summarized in a meta-analysis of 8 observational studies [54]. This meta-analysis showed a decrease in the incidence of glioma in patients with a history of any form of allergy (RR 0.61, 95% CI 0.55-0.67). Statistically significantly lower risk of glioma, but not meningioma, was observed among individuals with either asthma or eczema [54]. Several large epidemiologic studies have further explored the association between serum levels of immunoglobulin E (IgE) and the risk of malignant CNS tumors [55-58]. In the largest study, samples from 594 blood donors who subsequently developed a glioma were compared with 1177 paired controls [57]. An inverse relationship was present for total IgE and risk of glioma among men and women, which was present for more than 20 years before the diagnosis of glioma. Increased immune surveillance in patients with allergies has been suggested as a possible mechanism underlying these observations [54].

N-nitroso compounds and cured meat intake: N-nitroso compounds have been reported as potent carcinogens, especially with regards to the neural tissue in animal models. The major exogenous sources of population exposures to N-nitroso compounds include tobacco smoke, cosmetics, automobile interiors, cured meats, rubber products, and some drugs like antihistamines, diuretics, oral hypoglycemic agents, antibiotics, tranquilizers, and opiates. Although a meta-analysis of nine case-control studies reported a higher relative risk of adult glioma among individuals with a higher intake of cured meat [59], more recent prospective cohort studies found no associations with meat intake or dietary N-nitroso compounds [60,61], thus raising doubts about their importance in gliomagenesis.

Antioxidants, fruits, and vegetables: Indirect support for the N-nitroso compounds hypothesis includes the observation that certain inhibitors of the nitrosation process, and specifically vitamins C and E, appear to reduce CNS tumor risk in adults and children [62-64]. Dietary studies have demonstrated an inverse association between a diet rich in fruits and vegetables and reduced risk of childhood CNS tumors and adult gliomas [65]. Prenatal vitamin supplementation (including vitamins A and C and folate) and increased maternal intake of vegetables have been relatively consistently associated with a lower risk of CNS tumors in the offspring [66,67].

Smoking and alcohol consumption: The presence of nitrosamines in tobacco stimulated the interest in tobacco exposure as a potential risk factor for CNS tumors. Yet, there is only little evidence that either active or passive smoking are significant risk factor for CNS tumors with most case-control and prospective cohort studies yielding conflicting results [68,69], as have also studies exploring the associations between maternal smoking during pregnancy and the risk of childhood

CNS tumors [70]. Yet, there is weak evidence that paternal smoking during pregnancy might be associated with a higher risk of childhood CNS tumors, especially astrocytomas [71,72]. No consistent association between consumption of different types of alcoholic beverages and the risk of adult or childhood (after exposure during pregnancy) CNS tumors has been found [72,73], although data remain scarce.

Infections: There is a large number of reported associations between specific infections or markers of exposure to infection and risk of CNS tumors, but they are relatively inconsistent. Earlier studies of markers of infection and risk of childhood CNS tumors had yielded mixed results [74-76]. However, more recently, a higher risk of CNS tumors among first-born children vs. those with higher birth order and lower risks among those who attended daycare as an infant was reported. A study based on the Swedish Cancer Registry compared the incidence of CNS tumors based on number of siblings, number of older siblings, and number of younger siblings [77]. When compared to cases diagnosed <15 years old with no siblings, the relative risk for cases with ≥3 younger siblings was higher for astrocytoma, medulloblastoma, ependymoma, and meningioma. Another case-controls study reported that the risk of childhood CNS tumors was increased for children having siblings (OR: 1.4; 95% CI 0.9-2.3) and for those being at least second born (OR: 1.7; 95% CI 1.2-2.4) [78]. Harding *et al*. reported that children who had no social contact with other infants in the first year of life displayed a higher risk of CNS tumors, particularly medulloblastomas, as compared to those who had such early exposures (OR: 1.37; 95%CI 1.08-1.75) [79]. In addition, children who attended informal (OR: 0.86; 95%CI: 0.68-1.09) or formal (OR: 0.93; 95%CI 0.68-1.26) daycare showed slightly reduced risks, when compared to those reporting social contact only. Shaw *et al*. reported that the risk of CNS tumors was reduced for subjects who attended daycare for >1 year or were breastfed [78], whereas Harding *et al*. found no association between breastfeeding and childhood CNS tumors [80]. Most recently, a case-control study showed that cases of childhood glioma (OR: 2.93; 95%CI: 1.57-5.50) and embryonal tumor (OR: 4.21; 95%CI: 1.24-14.30) had more frequent sick days with infections in the first 6 years of life than controls [81].

Regarding specific exposures, prior infection with tuberculosis has been suggested as a possible risk factor for glioma in one study [84] but not in another [82,83]. In one large study, subjects who reported a history of clinically manifest infectious diseases, compared with those reporting none, had a lower risk of glioma (RR: 0.72, 95%CI: 0.61-0.85) [84]. Other proposed infectious risk factors include the polyoma virus, simian virus 40 (SV40), neonatal viral infections, and infection with Toxoplasma gondii.

Simian Virus 40 (SV40): Interest in SV40 was stimulated by animal studies documenting CNS tumor development after intracerebral inoculation with SV40 and by human studies which isolated SV40 from CNS tumor tissue [85]. It was unclear, however, if SV40 contributed significantly to malignant

transformation or whether certain tumors provided a microenvironment that favored replication in patients with latent SV40 infection. Poliomyelitis vaccine administered between 1955 and 1962 was contaminated with SV40, and vaccination cohorts have been the subject of study over subsequent decades [86,87]. However, elevated CNS tumor rates have not been observed in these cohorts. In a nested case-control study, no significant association was reported between antibodies to SV40 as measured in pre-diagnostic serum and incident primary malignant CNS tumors [88].

Cytomegalovirus (CMV): Data concerning a possible etiologic role for CMV are conflicting and controversial. While several studies have reported that a high percentage of gliomas are infected with CMV [89,90], other groups have not been able to be replicate these findings [91-93].

In utero viral exposure: Whether exposure to maternal viral infection while in utero is a risk factor for CNS tumors is unclear. A large case-control study found an increased risk for all types of CNS tumors after different maternal and perinatal infections [94]. In addition, an association between influenza infection in pregnant women and childhood CNS tumors was suggested in a study in which mothers of 94 children with CNS tumors or neuroblastomas and 210 controls were interviewed [95]. However, others have failed to confirm an increased risk of CNS tumors in the offspring of mothers infected with varicella, rubella, or mumps during pregnancy [96].

Varicella zoster virus (VZV): By contrast, a protective role for antecedent infection with varicella zoster was suggested by an analysis of 229 adults with glioma and 289 controls from the San Francisco Bay Area Adult Glioma Study [97]. Individuals with gliomas were significantly less likely than controls to have a self-reported history of chickenpox and they also had lower levels of immunoglobulins directed against varicella-zoster. A similar inverse association was observed for self-report of history of chickenpox in a case-control study of 325 adult glioma and 600 controls [98]. Statistically significant inverse associations also were observed for reported infections with other herpesviruses (Epstein-Barr virus, CMV, and herpes simplex virus) in that study [98], but no association had been found for those three herpesviruses in the first study [95].

Toxoplasma infection: Infection with Toxoplasma gondii has been associated with an increased risk of astrocytoma and meningioma in two case-control studies [99,100]. In one, a significantly increased risk of meningioma, but not glioma, was associated with the presence of IgG antibodies to T. gondii as measured by enzyme-linked immunosorbent assay (ELISA) [100]. Although this parasite has a propensity to infect the nervous system, it has not been established as a major risk factor for CNS tumors.

Congenital Anomalies: Among large studies, 45,200 children with congenital anomalies were identified in the Canadian Congenital Anomalies Surveillance System and matched to 45,200 healthy controls identified from the Ontario birth registry. The Ontario Cancer Registry was then used to identify 212 newly-diagnosed cancers in the matched cohorts. The authors observed a 2.5-fold

increased risk of childhood CNS tumors in association with congenital anomalies that was stronger for children < 1 year old (5-fold higher risk). Those with nervous system anomalies had an approximate 6-fold higher risk of primary CNS tumors [101]. Using two population-based national birth registries in Sweden and Norway and linkage to cancer registry a study found children with nervous system malformations to be at a higher risk of CNS tumors in both countries [102]. Furthermore, in a study linking data from the California Cancer Registry to the Birth Defects Monitoring System for the period 1988–2004 among children aged 0–14 years [103], children with non-chromosomal and chromosomal anomalies were found to be at 1.87 (95%CI: 0.60–5.79) and 1.80 (95%CI: 1.28–2.53) fold elevated risks of CNS tumors, respectively. A second study linking data from the California Cancer Registry to California birth certificates examined birth anomalies and CNS tumor risk among children aged 0–14 years old between 1988–2006 [104]. In this study, birth defects were associated with a higher risk of embryonal tumors, with age-stratified analyses revealing relatively stronger risks for younger children [104].

Birth Characteristics: In one of the largest to-date studies examining fetal growth in relation to cancer development, a prospective nested case-control study gathered data from Nordic children born between 1967–2010 using population-based birth registries [105]. A total of 17,698 cases were matched to 172,422 controls. Both higher birth weight (RR for ≥4500 g vs. 3000–3499 g: 1.3; 95%CI: 1.1-1.3) and increasing head circumference (RR for 39–45cm vs. 33–36 cm: 1.7; 95%CI: 1.2-2.3 were associated with a higher risk of childhood CNS tumors, and specifically embryonal (RR: 1.8; 95%CI: 1.2-2.8) tumors, but not other subtypes [105]. Another prospective study examined the relationship between fetal growth measured as proportion of optimal birth weight or length and risk of CNS tumors, as diagnosed between 1980–2004 in children aged 0–14 years [106]. Among >600,000 live births, 183 pediatric CNS tumors were identified and no statistically significant associations between fetal growth factors and CNS tumor risk were observed [106]. In another study based on linkage between cancer and birth registration, MacLean *et al*. matched each child with a CNS tumor (N=3733) to four controls identified through the California birth certificate database, resulting in 14,932 controls [107]. There was an increased risk of childhood CNS tumors, and specifically high-grade gliomas in the highest birth weight category (>4000 g), whereas a low birth weight (<2500 g) was associated with a lower risk of low-grade gliomas [107]. Finally, in a 2008 meta-analysis of 8 case-control studies, high birth weight was associated with a higher risk of childhood astrocytoma and medulloblastoma [108].

Genetic risk factors

Genetic syndromes: Approximately 20% of primary CNS tumors are due to genetic syndromes that confer an increased risk of developing tumors of the nervous system (**Table 4**) [28,109].

Neurofibromatosis type I (NF1) occurs in 1 of 3000 persons and is linked to a gene on chromosome 17. The *NF1* gene encodes a protein called neurofibromin that restricts cell proliferation by activating guanosine triphosphate (GTP) hydrolysis on Ras proteins [110]. Multiple neurofibromas are seen and some undergo malignant change to neurofibrosarcoma. Other malignancies that develop in up to 5 to 10 percent of patients with NF1 include other malignant nerve sheath tumors such as malignant schwannomas and astrocytomas. The astrocytomas are usually low grade and frequently have a pilocytic histology. These lesions have a predilection for the optic pathways, hypothalamus, and cerebellum. It has been proposed that malignant degeneration in NF1 reflects the two-hit hypothesis in which one allele is constitutionally inactivated in the germline while the other allele undergoes somatic inactivation (the second hit) [110]. Animal models are consistent with this hypothesis but suggest that the second hit can be a mutation in the p53 gene [111,112].

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder predisposing to multiple neoplastic lesions. This disorder is due to a mutation in the NF2 gene, a tumor suppressor gene on chromosome 22 that encodes a membrane cytoskeletal protein called merlin or schwannomin [113] that appears to be involved in actin-cytoskeleton organization [114]. The pathognomonic findings are bilateral vestibular schwannomas (acoustic neuromas). Vestibular schwannomas are seen in 90 to 95 percent of patients with NF2 and generally develop by 30 years of age. Other types of CNS tumors are also seen, the most frequent of which are meningiomas. Approximately one-half of individuals with NF2 have meningiomas, and multiple meningiomas are often present [115]. The incidence of meningioma increases with age, and the lifetime risk may be as high as 75% [116]. Patients with NF2 tend to develop meningiomas at an earlier age than those with sporadic meningiomas. The meningiomas seen in patients with NF2 are more frequently atypical or anaplastic compared with sporadic tumors [117,118].

The von Hippel-Lindau syndrome is an autosomal dominant disorder associated with hemangioblastomas, pancreatic cysts and neuroendocrine tumors, renal tumors, and pheochromocytomas. The gene on chromosome 3p25 normally functions as a tumor suppressor gene [119]. The Li-Fraumeni syndrome is inherited as an autosomal dominant trait and is usually associated with a germline mutation in the TP53 gene [120]. Li-Fraumeni syndrome is primarily characterized by sarcomas, breast cancer, leukemia, and adrenocortical cancer occurring before the age of 45. Other tumors are also seen in the Li-Fraumeni syndrome, including CNS tumors. Of particular note, a high percentage of choroid plexus carcinomas are associated with germline mutations in TP53 even in the absence of another cancer or a positive family history [120].

Table 4. Genetic syndromes predisposing to primary central nervous system (CNS) tumors.

Syndrome	Chromosome	Inheritance	CNS tumors
NF I	17q1	AD	Glioma, meningiomas
NF II	22q	AD	Acoustic neuroma, optic glioma, meningioma, ependymoma
Tuberous sclerosis	9q32-34	AD	Ependymoma, astrocytoma, ganglioneuroma
Von Hippel-Lindau	3p25-26 3p13, 14	AD	Hemangioblastoma

Abbreviations: AD, autosomal dominant.

Genetic susceptibility: Several genome-wide association studies (GWAS) have examined the risk of CNS tumors and identified genetic polymorphisms associated with glioma. The currently identified loci from a meta-analysis of these studies (12,496 cases and 18,190 controls) include: *RAVER2*, *MDM4*, *AKT3*, *IDH1*, *LRIG1*, *OBFC1*, *MAML2*, *AKAP6*, *MPG*, *LMF1*, *HEATR3*, *SLC16A8*, *TERC*, *TERT*, *EGFR*, *CCDC26*, *CDKN2A/B*, *VTI1A*, *ZBTB16*, *PHLTB1*, *POLR3B*, *ETFA*, *TP53*, and *RTEL1* [121]. Furthermore, a meta-analysis of two GWAS studies on meningioma identified two susceptibility loci at 10p12.31 and 11p15.5 including with the closest genes including *MLLT10* and *RIC8A*, respectively [122]. Finally, a transcriptome-wide association study confirmed the several of these associations at the levels of the gene expression levels and further identified associations at new locus including the *GALNT6* gene [123].

Prognosis of primary central nervous system tumors

Although CNS tumors account for only 2% of all cancers, they account for a disproportionate share of cancer morbidity and mortality. According to the latest data, the annual age-adjusted mortality rate for CNS tumors in the US (2011-2015) is 4.4 per 100,000 individuals, being higher for males than females (5.3 vs. 3.5 per 100,000 individuals) [1]. The mortality rates have been reported to be higher in other countries with reporting variations by geography and access to public health, as assessed by the place of residence (rural vs. urban). Furthermore, the mortality rates are different by age, and they comprise the most common cause of death in children (0-14 years) [1].

Overall survival (OS) in patients with CNS tumors is highly variable highly depending on histology, behavior, tumor location, and geographical setting. In the US, the overall 5-year survival was estimated to 35% for malignant and 91% for non-malignant CNS tumors for the time period 2000-2014. The worst survival rates were reported for glioblastoma (6% in all ages) and much higher (>80%) for low-grade gliomas, oligodendrogliomas, and ependymal tumors. Yet, survival rates are also highly variant by age of the patients: the OS rates among malignant CNS tumors were 73% for children (0-14 years), 68% for AYAs (15-39 years), and 20% for older adults (≥40 years) [1].

Gliomatosis cerebri

Gliomatosis cerebri (GC) is a tumor characterized by a diffuse infiltrating pattern of the CNS and extremely poor prognosis [124-126]. GC usually affects the CNS both hemispheres without affecting the normal architecture of the brain parenchyma and commonly extends to deeper structures, infratentorially or to the spinal cord [124,125,127,128]. GC is a very rare neoplasm with an annual incidence rate of 1.5 cases per 10 million individuals, corresponding to ~1 out of 500 malignant CNS tumors, as recently reported in the SEER dataset during the 2003 to 2012 [129]. Despite its known aggressive behavior, there are many controversies regarding the clinical, histopathological and molecular hallmarks of GC. Until recently GC was considered a separate entity of a diffuse CNS tumor affecting at least 3 cerebral lobes [130], but the 2016 WHO classification recognizes GC only as a special widespread and invasive growth pattern of the category of diffuse glioma [3], because of the lack of data supporting a distinct genetic profile [131,132].

GC diffusely infiltrates the CNS, may affect any region and is characterized by very poor prognosis. Clinical studies report 5-year survival rates of 25-30% with a median survival around 20 months [132-142]. Particularly, 50% 1-year and 20% 5-year survival rates were found with a median survival of only 9 months [129]. The histopathology of GC might correspond to grade II to IV astrocytomas, oligodendrogliomas or mixed tumors, but prognosis is poorer compared to other gliomas of the same grade [132,142]. Although the tumor was first described in 1938, the cause for its uniquely aggressive behavior remains to be explored [143]. Due to its rarity, data on prognostic factors and management, as a rule, are based on small case series with restricted numbers of patients [132-142]. Particularly, there is no consensus on a standard of care for GC, as GC patients have been traditionally excluded from glioma trials [125].

Diagnostic features

GC spans across all age groups but is more common in adults. The median age at diagnosis ranges from 46 to 53 years [132,144,145] with a slight male predominance (sex ratio, 1.4) [144]. Clinical presentation is variable and typically insidious, often delaying the diagnosis by months or years. Common presenting symptoms may be location dependent and include focal weakness, sensory loss, seizure, progressive headache or manifestations of increased intracranial pressure, memory deficit with “dementia-like” features, and other constitutional symptoms [140,142,146,147]. Common clinical signs include corticospinal tract, spinocerebellar, sensory-motor and visual field deficits, cranial neuropathies, papilledema, and myelopathy [146,148]. Children commonly present with seizures, developmental delay, increased intracranial pressure, and cognitive changes [149,150]. On examination, hemiparesis, ataxia, cranial neuropathies, altered mental status, tremor, and ataxia are

observed [149]. There are no classical symptoms or signs of GC owing to the extensive and unpredictable invasion of tumor cells into cerebral hemispheres and deep midline structures. Before the magnetic resonance imaging (MRI) era, many patients with GC died without an established diagnosis and GC was determined at autopsy. Currently, GC is diagnosed radiographically by MRI along with histopathologic confirmation of an astrocytic process [128,131]. Brain MRI shows a T1-weighted hypo- or iso-intensity and T2-weighted or FLAIR hyperintensity in the involved areas. There may be diffuse infiltration of the cortex, poor gray-white matter delineation, enlargement of affected cerebral structures and thickened gyri [151,152]. Enhancement patterns are variable, with focal, multifocal, or nodular gadolinium-enhancement in 16–56% patients [132,142]. Radiographic differential diagnoses include multiple sclerosis, progressive multifocal leukoencephalopathy, Behcet's disease, ischemia, viral encephalitis, vasculitis, subacute sclerosing panencephalitis, ischemia, and other CNS inflammatory diseases [128,142]. In children, GC can be misdiagnosed as encephalitis, acute disseminated meningoencephalitis, idiopathic intracranial hypertension, acute disseminated encephalomyelitis, tubercular encephalitis, leukodystrophy and primary progressive multiple sclerosis [125,153]. On MR spectroscopy, the choline-to-creatine ratio is increased and the N-acetylaspartate (NAA)-to-creatinine ratio is decreased, as observed in other malignant CNS tumors [151,154]. MR spectroscopy cannot reliably differentiate GC from encephalitis, demyelinating disease, progressive multifocal leukoencephalopathy, or hemorrhage [155,156]. Perfusion MR findings typically demonstrate lack of elevation of mean relative cerebral blood volume [157], corresponding to a relative lack of vascular angiogenesis. Fludeoxyglucose-positron emission tomography (FDG-PET) is not particularly useful for initial diagnosis as hypometabolism [158] or hypermetabolism [159] is seen in areas with infiltration; however, FDG-PET can be of value in following patients longitudinally for the extent of tumor involvement and treatment response assessment.

Histopathological and molecular characterization

Most GC tumors are astrocytic, although oligodendroglial and mixed phenotype can rarely be seen. The gross anatomy remains intact, but affected areas appear firm, edematous, with flattened gyri and loss of gray-white distinction [160]. Though histological grading encompasses gliomas from grades II through IV, the clinical behavior of the tumor is consistent with an aggressive malignancy. GC classically has a diffuse, irregular parenchymal infiltration of glial cells, in contrast to the destructive, necrotic pattern seen in high-grade gliomas. Histologic exam reveals small, astrocytic cells with elongated fusiform nuclei, readily identified by staining for GFAP [149]. In contrast to high-grade gliomas, neovascularization, significant mitotic activity and necrosis are not common [149]. Because most tissue is obtained from a small biopsy specimen, the degree of intratumor heterogeneity is

unknown. Our clinical and genetic understanding of many CNS tumors are now refined by genomic studies and epigenome-wide methylation profiling, which have unraveled molecular subgroups in tumors such as glioblastoma, medulloblastoma, and ependymoma [161-164]. However, application of these studies has not been insightful for GC. Surprisingly, molecular and methylation profiling showed that in both adults and children, there are no characteristic histologic features or molecular subgroups exclusive to this diagnosis. In a study of 25 adults with GC, patients were found to have IDH mutant astrocytoma, IDH mutant and 1p/19q codeleted oligodendroglioma or IDH wild type glioblastoma [132]. Likewise, when Broniscer et al. analyzed 32 pediatric and adolescent patients with types I and II GC, their DNA methylation profile corresponded with known pediatric glioma molecular subgroups, including IDH mutant (17%), G34 (22%), mesenchymal (17%), and receptor tyrosine kinase (RTK) I (44%) [131]. All tumors were astrocytic and no codeletion of 1p and 19q was observed. No K27 mutation subgroup of pediatric high-grade glioma was identified, despite the fact that four patients had symmetrical bi-thalamic gliomas, which are typically associated with H3K27M mutation [162]. As expected, molecular differences were seen between pediatric and adult GC; the IDH subgroup was less common and no oligodendroglioma or RTK II subgroup was observed in children [132,150,165].

Management and treatment: surgery, chemotherapy, and radiation

There is no standard treatment for patients with GC. While a long indolent course and prolonged survival are rarely observed [166], the disease more typically progresses rapidly, with a median survival of <1 year in patients not receiving antitumor therapy [140,142]. All patients in whom GC is radiographically suspected should have a histopathologic confirmation. Given the diffuse involvement of a large brain volume, the role of surgery primarily lies in securing a tissue diagnosis. Some patients undergo partial resection of an area of T2-signal abnormality or T1 contrast-enhancement to secure sufficient amount of tissue to overcome sampling error. When patients are symptomatic due to edema and mass effect, partial resection can be done with an aim of tumor debulking. It is unclear if extent of surgical resection provides any survival benefit. Perkins *et al*. reported outcomes in 30 GC patients of which 19 received biopsy and 11 had a partial resection [133]. The median survival (21 vs. 18 months, p=0.96) did not reach statistical significance.

The use of radiation therapy in GC is challenging due to the large field involved and the apparent radio-resistance of GC. Anecdotal evidence suggests stabilization of disease and resolution of neurological symptoms for a period of time in patients treated with radiation therapy alone [167-169]. As GC histopathologically mirrors other gliomas, many institutions treat adult patients as high-grade glioma, with upfront radiation or chemo-radiation therapy. This approach raises concern in children given the large tumor volumes involved, the absence of a standard of care for children with

high-grade gliomas, and the disputed evidence of efficacy of chemoradiation in pediatric malignant glioma [170]. It is unclear whether radiation volume and/or dose correlates with outcome. Radiation therapy protocols have delivered radiation to involved field only, whole brain, or whole brain with a cone done to the involved field [149,168]. Whole brain radiotherapy doses ranging from 20 to 59 Gy [133,144,145,168] and regional radiotherapy doses from 54 to 66 GY have been administered [133,144]. Chen *et al*. utilized a median radiation dose of 54.90 Gy and did not find any correlation between the total dose of radiation and survival [144]. Four retrospective studies have reported a clinical response in 58% of patients and a radiographic response in 31% of patients [133,145,168,171]. Taillibert *et al*. reviewed a historic cohort of 296 patients and found that OS curves did not differ according to radiation treatment ($p = 0.3$) [142]. In contrast, Chen *et al*. found the OS was significantly different ($p<0.01$) in patients treated with (27.5 months) or without (6.5 months) radiation therapy [144]. Despite clinical and radiographic improvement in many cases, response to radiation therapy is not durable and the evidence for its impact on OS is, at best, ambivalent.

Patients with GC usually receive chemotherapy alone or in conjunction with radiation. However, no study has demonstrated significant efficacy of chemotherapy in this disease. NOA-05 is the only prospective clinical trial published to analyze the efficacy of primary chemotherapy in GC [172]. This study was a phase II single arm study in which 35 patients with GC were treated with procarbazine and lomustine as upfront therapy. The median progression-free survival (PFS) was 14 months and median OS was 30 months. Although it is difficult to draw conclusions about superiority of upfront radiation versus chemotherapy regimen when comparing results of this study to retrospective historical cohorts who received radiotherapy only (median OS 11.4–38.4 months) [133,145,168,171], the NOA-05 trial results suggest that initial treatment with procarbazine and lomustine may have potential clinical benefit for patients with GC. Temozolomide is widely used for treatment of adult malignant gliomas and is often used in treatment of GC. Samson *et al*. retrospectively compared response rate to procarbazine, vincristine and lomustine (PCV) versus temozolomide in a series of 63 patients with GC. No significant difference was observed in the PCV and temozolomide groups in PFS (15.8 versus 16 months) or OS (25.6 versus 26.4 months), but increased toxicity was noted in the PCV group. Retrospective studies have demonstrated that temozolomide can be used in the treatment of GC, both as initial therapy and at progression with a median PFS and OS ranging from 9 to 18 and 14 to 37.7 months, respectively [139,140,147]. A report from Levin *et al*. suggested that temozolomide may also be used after initial tumor progression with PCV treatment [147]. Of 2 patients whose treatment was changed from PCV to temozolomide, one had continued disease progression but the other was stable for 12 months. Given the variability in PFS and OS in historical cohorts of patients with GC, randomized phase II studies may better elucidate the roles of chemotherapy in this disease. Patients with GC who have oligodendroglial

pathology and 1p/19q codeletions have a higher radiographic response rate, PFS, and OS when treated with temozolomide as compared to patients with non-oligodendroglial GC [140,173]. These data are not surprising given our current knowledge about the chemosensitive nature of oligodendroglial tumors and longer overall patient survival when compared with those with astrocytic tumors. Similar evidence of chemosensitivity can be found from some case reports and studies where nitrosourea-based regimens were used upfront [140,172,174,175]. From current literature, it appears that both temozolomide- and nitrosourea-based regimens may be useful for initial treatment of adult patients with oligodendroglial GC, yet no conclusion can be drawn about the superiority of one treatment over another. As most cases of GC show a lack of contrast-enhancement on MRI and CT, neovascularization is considered to be rare or absent in this disease [176]. In contrast to this assumption, a study found strong VEGF expression in 5 of 6 patients and COX2 expression in 4 of 5 patients despite the absence of contrast-enhancement on MRI. Additionally, histopathology and CD31 antibody studies demonstrated vascular proliferation in GC areas. Patients in this non-randomized study were treated with a combination of low-dose temozolomide and celecoxib and had PFS of 6–18 months [177]. While new treatment paradigms using immunotherapy are being developed for high-grade gliomas, these have not formally evaluated in patients with GC. Generally, tumor cells survive by dysregulating the body's immune checkpoints by overexpressing immunosuppressive surface ligands such as programmed cell death-1 (PD-1) and cytotoxic lymphocyte-associated protein-4 (CTLA-4). Immune checkpoint inhibitors such as nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), and ipilimumab (anti-CTLA-4) are being investigated for CNS tumors, including glioblastoma. With their success in various solid tumors like melanoma and non-small cell lung cancer [178,179], they may be of potential benefit in a heterogeneous disease entity such as GC and thus need to be investigated. Additionally, clinical trials (NCT02746081) are underway to test IDH inhibitors in gliomas [180,181] as the IDH mutation can be found in 17–48% of adults with GC [131,132,172]. Little is known about metabolism and metabolic defects in GC. However, a major issue in evaluating efficacy of chemotherapeutic agents for GC patients is inconsistent inclusion in clinical trials, lack of GC-specific cohorts, and variable definitions of GC for eligibility.

The role of meta-analytical methodology in modern epidemiology

The techniques that are currently used for systematic reviews and meta-analyses comprise useful tools for a standardized and systematic assessment of the available evidence on different topics. Given the accumulation of data in the latest decades, these tools have gradually earned an important place in biomedical research [182]. Meta-analyses have been described as the "epidemiology of the results of independent studies" [183] or as "observational studies of the evidence" [184], where the subjects are independent studies, just as in ecological designs the group replaces the individual as the unit of analysis. In Modern Epidemiology, Greenland and O'Rourke [182] parallel meta-analyses to primary studies reporting that "meta-analysis can be viewed as the transference of good analytic practice from the single-study to the multiple-study context". They further recognize that the search for eligible studies, data abstraction, and analysis of data from different studies "is similar to the need of single studies to identify eligible subjects, abstract their information, and analyze the resulting data by summarizing information across subjects".

Systematic review/meta-analysis vs. traditional reviews

The aims and scope of systematic reviews are distinct from those of meta-analyses, and the two methods may be used independently from each other, although both provide tools useful in the process of summarizing evidence. Systematic review may be defined as "the application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic", while meta-analysis is "a statistical analysis of the results from separate studies, examining sources of differences in results among studies, and leading to a quantitative summary of the results if the results are judged sufficiently similar to support such synthesis" [185]. To perform a meta-analysis, a weighted average of the results from individual studies needs to be computed [186]. The weights vary with the method selected for meta-analysis (mainly random- or fixed-effects models), but the studies with larger samples and more precise estimates are generally assigned higher weights [186].

Meta-analysis is ideally used to summarize the study data collected through a systematic review, which is expected to yield an unbiased sample of the evidence available on a topic. The quantitative synthesis provides therefore a summary estimate usually interpreted as the state of the art on that specific subject. A large proportion of the published systematic reviews do not include a meta-analysis, either because the statistical synthesis of the results would not be meaningful, when the study methods or the results are highly heterogeneous, or because the synthesis is not feasible when the needed information is not available or is provided in different formats across the studies. Some

studies further use meta-analysis to summarize results not obtained from systematic reviews, which reflects the fact that these statistical techniques may be used in any set of individual studies considered “combinable”, even if the units of analysis are not obtained from a literature review, as is the case for meta-analyses of results from different centers of multi-center studies [186].

Despite an element of subjectivity in defining the criteria to determine the eligibility of the studies for the review, systematic reviews are based on a transparent process, as long as all decisions are specified clearly, and it is possible to estimate the extent to which systematic reviews may yield biased conclusions. In contrast, it is often impossible to judge whether traditional or narrative reviews are trustworthy, as the definition of the objectives is often ambiguous and the methods opaque. It should also be kept in mind that although the rigorous framework of a systematic review is expected to contribute to limit some of the biases that may affect literature searches, by itself it cannot ensure the quality of the review, or the validity of its conclusions. The result of the systematic review is always dependent on the quality of the original studies, and a systematic review cannot improve the quality of primary sources that are methodologically flawed. A relatively large proportion of systematic reviews has been reported to have suboptimal quality and caution is needed in their interpretation, as for any other type of epidemiological study [187,188].

Despite the potential for improvement in the conduct and reporting of systematic reviews and meta-analysis, they comprise the optimal method of a qualitative or quantitative synthesis of evidence, on the basis of transparency and reproducibility. This is especially important when the research questions are focused on the evaluation of complex interventions. There is also room for narrative reviews or essays addressing broader questions, providing essential information on relevant concepts or theory, or discussing key studies in detail, which may contribute to place the evidence into context and recommend new research directions.

General structure and procedures for conducting a systematic review

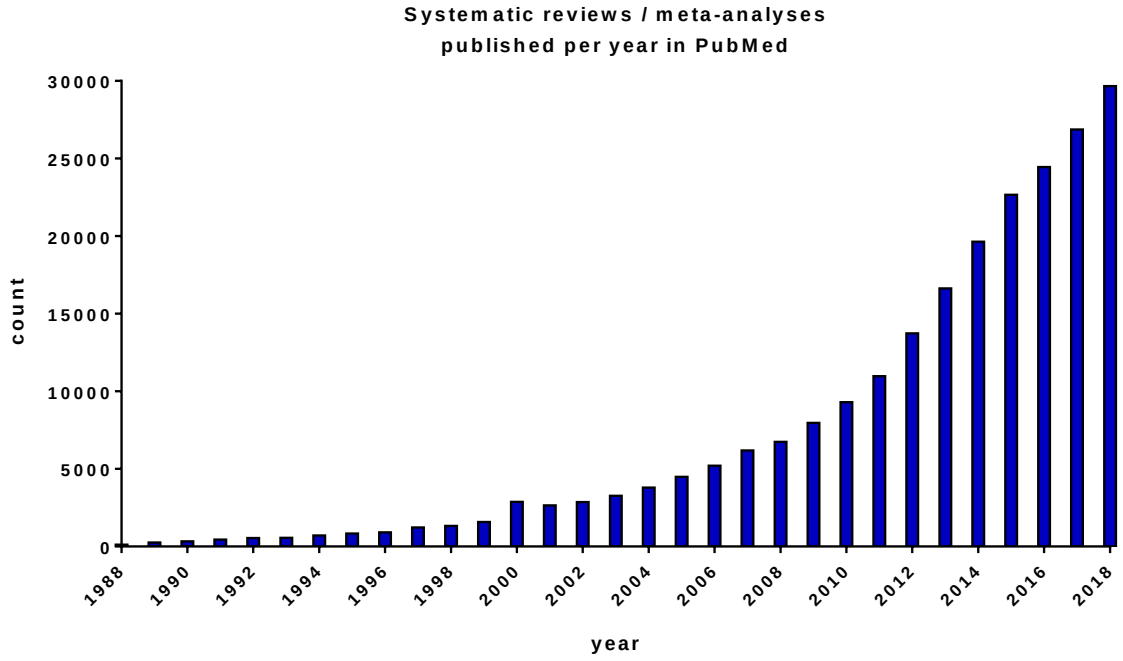
The systematic methodology that was gradually developed for systematic reviews aims to limit the potential biases related with literature reviews. The first step for any systematic review is the *a priori* development of a protocol, with the detailed description of the methods to be used. The detailed predefined description of the whole process allows the assessment of the quality of the reviews and validity of their conclusions.

Definition of a research question

The whole review builds upon the research question being targeted, which largely determines the impact of the conclusions and how smooth the review process will be. We may identify two major determinants of accomplishing this step successfully. First, setting up of a relevant research question depends primarily on how well the researchers know the topic under study, from the biological, clinical and epidemiological viewpoints, as applicable. Second, the precision of the objectives defined for the review will influence the amount of work required and the external validity of the conclusions. Research questions with a broad scope are probably more appealing to a general audience and also more likely to generate conclusions that apply to different contexts or settings. However, these are also more likely to result in a quantity of information unmanageable in a reasonable time.

The number of systematic reviews and meta-analyses being published has increased substantially in the last years (**Figure 8**) and it is not surprising that several research questions have been reviewed before by other authors. However, a new systematic review on a topic that has been previously addressed with these methods is not necessarily redundant, and frequently is necessary. Several strategies, techniques or statistical methods have been developed to support different aspects of the updating of systematic reviews and meta-analyses [189-191]. The identification of systematic reviews/meta-analyses conducted before should probably be the first step of any new review.

Figure 8. Number of systematic reviews or meta-analyses published in peer-reviewed journals registered in the database PubMed (Medline).



Identification and selection of original studies

Ideally, systematic reviews would be based on the assessment of all the evidence available on a given topic. Although this may be possible, when the eligibility criteria restrict the search to a small number of investigations or when reviewing clinical trials, which may be identified in registries of this type of studies, it is virtually impossible otherwise, and an unbiased sample of the evidence is usually the aim to be targeted. The search strategy should be as comprehensive as necessary to minimize bias. The decision on the number and type of the data sources to be included is influenced by the researchers understanding of the topic under study and the available time and resources. The publications from journals indexed in electronic databases such as Medline are easily available (e.g. through PubMed), while unpublished material may only be obtained from the authors and therefore its retrieval tends to be a much more difficult and time-consuming task. Electronic databases are the source of the largest number of articles included in any systematic review on health-related topics, which reflects both the easy access to these resources, and their wide coverage. However, the inclusion of data sources with different characteristics, namely those that include unpublished results or publications with a more limited circulation may be essential to overcome selection bias, as the probability of a study being published or the place where it is published may depend on the nature of the results and their statistical significance.

Regardless of the sources of data selected, a decision has to be made on the eligibility of studies written in different languages; the impact of language restrictions in the comprehensiveness of the search and the potential for selection bias depends primarily on the subject of the review. On the one hand, language restrictions may lead to the exclusion of a large proportion of the available studies when the outcomes or the exposures being studied have a geographical distribution that makes likely the publication of a large number of articles in a language other than English. On the other hand, studies not published in English, predominantly in journals with a more limited circulation, are more likely to have non-statistically significant results or “negative” findings, and therefore language restrictions may contribute to biased samples of studies to be reviewed.

When conducting searches over several electronic database, it should be taken into account that each of them may have different search fields and key-words for indexation of the articles, which requires that the search expressions are adjusted to the specificities of each source. Therefore, a detailed description of the search expression used in each database is essential for the systematic review to be replicable by others. The indexation of the articles in the electronic databases is known to be imperfect, and a hand-search may be used to increase sensitivity. Citation searching is usually one of the components of any search strategy, namely through the identification of the articles cited by those included in the systematic review (“snowball procedure”). Citation searching may also be useful when defining the search strategy, as it may be used as an independent source of references

that provides valuable information to estimate the completeness of the main database searches, to improve the search expressions and the overall search strategy.

The glossary of the Cochrane collaboration [192] refers to "grey literature" as "the kind of material that is not published in easily accessible journals or databases" and it is expected to include "things like conference proceedings that include the abstracts of the research presented at conferences, unpublished theses, and so on". A large number of internet resources may be used to locate the so-called grey literature [193]. However, each of them has a different scope and relatively limited coverage, in addition to specific modes of functioning, which results in the need of using several of these resources to answer a specific research question. It should be taken into account that the different sources of data may yield quite heterogeneous results regarding the quality of the investigations and the detail of the reporting. A large number of reports that may be classified as "grey literature" are not peer reviewed, which may translate into a larger heterogeneity of the studies identified in these sources as well as a lower average quality of the studies and their reporting.

The ideal search strategy should maximize sensitivity, as this is likely to be necessary to avoid selection bias. However, a high sensitivity comes with a high number of non-eligible references that need to be read. If one assumes that the gold-standard is an optimized search of all available resources, a search strategy with a high sensitivity [a/(a+c)], i.e., that misses a small proportion of all eligible reports (c), is likely to have a low positive predictive value [a/(a+b)], i.e., from all the studies identified only a small proportion is eligible for the review, which corresponds to a low precision and a high "number needed to read" [(a+b)/a] [194]. Comprehensive searches of multiple sources are usually necessary to ensure that the systematic review is based on an unbiased sample of the available evidence.

In systematic reviews, the number of eligible studies is usually relatively small and the search strategy is designed to minimize bias instead of aiming a specific number of reports. On the one hand, the assessment of a small sample of studies in a systematic review does not compromise its potential to provide a valid summary of the best available evidence. On the other hand, the assessment of a high proportion of all the eligible studies does not correspond necessarily to an unbiased sample, as the studies missed may be substantially different from those included in the review. This reasoning finds a parallelism with the interpretation of the participation rates in an epidemiological study, as even a high participation may correspond to a differential participation. The screening of the reference lists obtained from different sources should be based in clear and sound criteria defined a priori, and an independent assessment of the references by more than one researcher may contribute to reliable results in this phase of the review.

Arbitrarily defined eligibility criteria may compromise the validity of the reviews and it is not surprising that decisions driven by the results end up in meaningless or biased conclusions. It may be more appropriate to have broad inclusion criteria and to conduct stratified analyses than to restrict the analysis to a highly selected group of studies, which may result in missing important information.

Data extraction

From each study included in the systematic review it is necessary to collect information for the assessment of the study quality, as well as the effect measures to be summarized and the respective uncertainty estimates, or the information needed to compute them. The overall quality of a systematic review/meta-analysis depends on the quality of the studies being reviewed. The synthesis of biased or confounded effect estimates yields equally invalid conclusions, and therefore the assessment of the quality of the original studies is an important component of any systematic review. Several instruments have been developed to produce summary scores of the characteristics of the studies that may influence the validity of the results, but the assessment of the impact of the relevant methodological aspects individually is the most appropriate way of dealing with the information on the quality of the primary sources [195].

A large inter-observer variation in data extraction and consequent decision on the studies to include in the review may be observed, due to different choices and errors [196]. Many reports provide several results potentially eligible for extraction and in different forms, requiring accurate decisions on those to be selected, and frequently is necessary to express all the extracted data in the same format, which may easily originate conversion errors. A study on data extraction errors assessed 27 meta-analyses that used standardized mean differences and showed that a high proportion had errors. The authors concluded that data extraction is prone to errors that can impact the findings of the study [197]. Another investigation addressed the inter-observer variation in the extraction of continuous and numerical rating scale data from trial reports for use in meta-analyses and compared experienced methodologists with PhD students [196]. The agreement was somewhat higher among the former, but disagreements were generally common and often larger than the effect of commonly used treatments [196].

Data extraction is a demanding task and a great deal of effort is needed to ensure the validity and reliability of this procedure. It should be conducted following a previously defined protocol, to limit the potential for different judgements to result in different choices about the data to extract. Although there is some margin for adjustments taking into account unexpected observations, a proper understanding of the topic under study together with experience in the conduct of systematic reviews and meta-analyses should allow the definition of a protocol that requires only minor changes

throughout data extraction. Most of the variability in the methodologies and reporting of data can be anticipated and taken into account in the protocol.

Data synthesis

The extent to which systematic reviews provide relevant answers to their objectives depends on the accomplishment of a sound synthesis of the results, in addition to the detailed description of each original study being reviewed. Meta-analysis should be conducted only when the individual studies are homogeneous regarding their methodological characteristics, to the extent necessary for the weighted average of the results from the individual studies to be meaningful, which tends to occur more frequently among experimental studies than in those with observational designs. However, the fulfillment of this condition is not sufficient, and the homogeneity of the effect measures is also required. There are several methods available to identify and quantify heterogeneity [198,199]. Under the abovementioned circumstances, meta-analysis may be a valuable option to summarize the evidence, contributing to overcome the statistical power limitations of the individual investigations.

The improvement in the statistical power may be illustrated by a meta-analysis on the cardiovascular adverse effects of rofecoxib [200], in which the authors conclude that the drug should have been withdrawn several years earlier. An earlier meta-analysis would have probably resulted in a more efficient use of resources and healthcare [200]. This shows the importance of using meta-analysis to obtain more precise estimates of an effect that is estimated with a very low precision in each of the individual studies because the outcome is too rare, which frequently occurs when dealing with adverse drug reactions.

When the participants' characteristics, study designs, exposures/interventions, or measurement of outcomes differ meaningfully across a set of studies, or when the results differ beyond the expected due solely to the play of chance, the combined estimates are likely to be meaningless, and an analytical rather than a synthetic approach is required. The methods adopted throughout the whole process should aim the reduction of bias, but this may be accomplished to different extents in different systematic reviews, and the readers should be able to assess this, as in any other research design. Even when the number of studies is small and heterogeneous, and neither more precise summary estimates nor an important contribution to the understanding of heterogeneity are possible, the thorough description of the materials and methods allow its replication by others. If no other reason persists for opting for a resource and time-consuming systematic review, its transparency should suffice.

There is a large consensus regarding the importance of having sound and transparent syntheses of the literature for health care providers, policy makers and researchers to be able to integrate the

unmanageable amounts of biomedical information that is constantly being produced. The objectives of systematic reviews/meta-analyses may be primarily synthetic, when aiming more precise average estimates, or analytic, when concerned with understanding the different results observed across studies, even if some overlap between these two pathways may occur, depending on the homogeneity of the original sources of data. These approaches may be placed on the top of each one of the two hierarchies of study designs, corresponding, respectively, to the confirmation of hypotheses when the a priori probability is high and to "discovery and explanation". Understanding the place of systematic reviews/meta-analyses in modern epidemiology, and the determinants of the option between predominantly synthetic or analytic approaches for data synthesis, are crucial for a proper utilization of these resources.

AIMS OF THE THESIS

Malignant CNS tumors are top causes of deaths due to cancer in younger age groups; they are associated with poor prognosis, and effective treatments to halt the progression of the disease are missing. Thus, additional research is required to systematically record and compare the burden of primary CNS tumors worldwide, identify etiological risk factors that would enable the development of preventive and therapeutic strategies, and figure out prognostic biomarkers that would allow optimization of the current management approaches.

However, CNS tumors comprise a highly heterogeneous group of diseases with different etiology, pathology, clinical presentation, and prognosis. Thus, current efforts to study the epidemiology of CNS tumors are inherently limited by low sample sizes due to the relatively low incidence of the numerous individual CNS tumor subtypes. To increase analytical power and overcome this limitation we need collaborative research and methodologies to maximally exploit available data around the globe.

With the current thesis we leveraged data in different levels of analyses with the objectives to explore features of descriptive, analytical, and clinical epidemiology of primary CNS tumors in children, AYAs, and older adults. Specifically, in the context of the research programs of the Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST) of the Department of Hygiene, Epidemiology, and Medical Statistics of the Medical School of the University of Athens, we pooled data from the following sources:

- NARECHEM-ST, which records all primary CNS tumors occurring in children aged 0-14 years since 2009 in Greece (http://narechem.gr/node/24)
- the Greek nationwide case-control study of CNS tumors recruiting cases from the abovementioned registry and matching them individually by age and sex with controls hospitalized in the surgical departments of the participating university hospitals (ratio: 1 case to 2 controls)
- the collaborative network of population-based cancer registries in 14 countries in Southern and Eastern Europe (SEE; Belarus, Bulgaria, Croatia, Cyprus, Greece, Hungary, Malta, Poland, Portugal, Romania, Serbia, Slovenia, Turkey, Ukraine), where cases of CNS tumors are recorded for variable time periods starting since 1990
- the database of the Surveillance, Epidemiology, and End Results Program (SEER), which includes data from 18 cancer registries running since 1973 and covering around 25% of the total US population

- published case-control and cohort studies exploring risk factors for childhood and adult CNS tumors, which were pooled in meta-analyses
- a dataset of cases with GC created in the context of the current thesis by extracting data on an individual-level basis from all case reports and case series that have been published on this tumor in the biomedical literature.

The objectives of this thesis are summarized as follows:

B. We used data from the NARECHEM-ST, the collaborative network of registries in the SEE region, and the SEER database to explore questions related to the descriptive epidemiology of primary CNS tumors. Specifically, we aimed to:
    - explore the incidence and time trends of primary malignant CNS tumors in the specific age group of AYAs in the SEE region for the period 1990-2014 and compare the figures with those from the SEER database reflecting the US population
    - examine the mortality rates and survival patterns by histological subtype, gender, age group and urbanization of primary malignant CNS tumors in the same age group in the SEE region
    - estimate incidence and survival rates, explore the distribution of basic demographic and clinical features, and identify prognostic factors for pilocytic astrocytoma in children, the most common CNS tumor in this age group by leveraging the largest ever sample size for this tumor

C. We explored perinatal and early-life risk factors for primary CNS tumors by leveraging data from the Greek case-control, the network of cancer registries in the SEE countries and by meta-analyzing data from published literature. Specifically, we aimed to:
    - analyze data from the Greek case-control study regarding the associations between a number of perinatal and early-life risk factors (anthropometrics at birth, mode of delivery, maternal exposures during pregnancy, birth order and other markers of exposure to infections during early life, other early-life exposures) and risk of childhood CNS tumors
    - pool data from case-control and cohort studies in the published literature to examine the association of birth weight and other birth anthropometric markers of fetal growth with the risk of primary CNS tumors in children and adults
    - perform a systematic review of published literature to examine whether there is evidence for a seasonal pattern in births, indicating exposure to perinatal risk factors with seasonal variation, among children and adults with CNS tumors

- explore the abovementioned research hypothesis about birth seasonality of childhood CNS tumors in original data coming from the network of population-based cancer registries in SEE countries

D. We pooled data from several sources to provide the most comprehensive to-date overview of the clinical epidemiology of GC, a very rare malignancy, with the distinct feature of a widespread and rapid CNS infiltration, which is traditionally associated with very poor prognosis. Specifically, we aimed to:
   - estimate for the first time the incidence and survival rates of this rare malignancy in data coming from the SEER network of population-based cancer registries in the US covering the period 1973-2014
   - extract individual-level data from all case reports and case series that have to date been published on this tumor subtype and explore the diagnostic hallmarks of GC including the clinical picture, the neuroimaging features, and the histopathological alterations that characterize this tumor
   - use the abovementioned individual-level dataset to provide an overview of the prognostic factors of GC, and systematically explore associations of different treatment approaches with PFS and OS
   - explore whether childhood GC differs from GC in adults, in accordance with other glial tumors, and provide an overview of the clinical picture and prognostic features of GC in children and adolescents (0-18 years)
   - explore whether IDH mutations in patients with GC are associated with the occurrence of seizures at the time of diagnosis of GC, as has been reported for other gliomas.

MATERIALS AND METHODS

A. Meta-analytical approaches in descriptive epidemiology of primary central nervous system tumors: pooling data across cancer registries to delineate the incidence, mortality, and survival patterns of CNS tumors in childhood, adolescence and young adulthood

Studies #1-2: Incidence, mortality and survival patterns of CNS tumors among adolescents and young adults (15-39 years) in Southern-Eastern Europe and the US

Participating registries

For these studies we expanded an already established collaboration on childhood malignancies [201-203] of 14 cancer registries operating in 12 SEE countries (Belarus, Croatia, Cyprus, Malta, Montenegro, Greater Poland, Portugal Central, Portugal North, Romania-Cluj, Romania-Iasi, Serbia Central, Slovenia, Turkey-Izmir, Ukraine). Following approval of pre-defined protocols, the 14 registries provided data on incident primary CNS tumors diagnosed among AYAs (15-39 years) with variable registration periods extending from 1990 to 2014. The definition of the AYAs age spectrum was based on the guidelines by the National Cancer Institute [204]. For comparability reasons, data CNS tumor cases among AYAs were additionally extracted from the SEER database, which covers 18 registries in the US [205,206]. Although SEER provided data for a period ranging from 1973 to 2012, only cases diagnosed in the most recent 1990-2012 period were included in the analyses, as to enable meaningful comparisons with the SEE registries.

Diagnostic classification and behavior

CNS tumors were defined according to the International Classification of Disease- 10th Edition (ICD-10) [207]. The following codes were included: C70.0 -C72.9 and C75.1-C75.3 for tumors of malignant behavior, D32.0-D33.9 and D35.2-D35.4 for benign tumors, as well as D42.0-D43.9 and D44.3-D44.5 for tumors of borderline/unknown behavior. CNS tumors with non-malignant behavior, as defined by the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) (coding 0, 1 or 2) [208], were not systematically recorded in 8 SEE registries (Croatia, Cyprus, Greater Poland, Romania-Iasi, Serbia Central, Slovenia, Ukraine, Turkey-Izmir). SEER started systematic registration

of non-malignant CNS tumors in 2004. Therefore, only malignant CNS tumors (ICD-O-3 behavior code 3) were considered for the analyses. Incidence data for non-malignant CNS tumors are presented for comparability reasons.

For classification purposes, we used the Barr *et al.*[209] diagnostic classification system for tumors in AYAs. Specifically, based on morphology and topography, CNS tumors were classified to: "astrocytoma", "other glioma", "ependymoma", "medulloblastoma and other PNETs", "other specified intracranial and intraspinal neoplasms" and "unspecified intracranial and intraspinal neoplasms". Given the significant survival discrepancies, "astrocytomas" were also examined in the sub-categories "low-grade astrocytic tumors", "glioblastoma and anaplastic astrocytoma", and "astrocytoma not otherwise specified, NOS"), whereas "medulloblastoma and other PNETs" into "medulloblastoma" and "supratentorial PNETs", also in accordance with the Barr *et al.* [209] diagnostic classification.

Other variables

In addition to ICD-O-3 coded data on morphology and behavior, the SEE registries provided demographic information (age, sex), date of diagnosis, topography of the tumor (ICD-10 coded), method of diagnosis (coded according to European Network for Cancer Registries recommendations [210]) and place of residence. Similar variables were extracted from the SEER database. All registries covered the 15-39-year age spectrum, apart from Belarus, which restricted registration to individuals aged 19 years or less. The underlying population figures for the respective registration years stratified by age, sex and calendar year were made available by the participating registries. We classified place of residence at diagnosis as urban, semi-urban and rural depending on the recommendations by the national statistical services of each country. To facilitate a comparison with the SEER data, semi-urban and urban categories were merged and the variable was considered as dichotomous.

Follow-up and mortality data

Follow-up data for each registry included vital status for the longest follow-up period available and date at last contact. We assessed survival as an endpoint based on the date of diagnosis. Due to the inadequacy of follow-up data for the period before 2007, Serbia Central was excluded from all survival analyses. Similarly, cases diagnosed by death certificate only or lost to follow-up were excluded from the survival analysis. Data on mortality from CNS tumors at regional or national level were provided by the respective national statistical services. Cause of death for CNS tumors was

coded according to ICD-10 and included the codes C70.0-C72.9 and C75.1-C75.3. Official mortality data were not available for the two Romanian registries and Turkey-Izmir, which were excluded from the mortality analysis. The US mortality data for the total AYAs population, provided by the National Center for Health Statistics, were downloaded from the SEER website [46].

Statistical analysis

Based on the number of incident cases in five age groups (15-19, 20-24, 25-29, 30-34, 35-39 years), annual crude (CIR) and age-adjusted incidence rates (AIR) for malignant and non-malignant CNS tumors (excluding pilocytic astrocytoma) were calculated for each cancer registry (and are expressed as cases per million individuals per year). The World (Segi) population was used for the age-adjusted calculations [211]. Furthermore, CIRs and AIRs for malignant only CNS tumors by diagnostic categories were calculated for each individual registry and for the overall SEE region and SEER. Similarly, based on number of deaths by age group (15-19, 20-24, 25-29, 30-34, 35-39 years) we calculated crude and age-adjusted mortality rates for malignant CNS tumors for each registry. Comparisons of incidence and mortality rates between the SEE region and SEER were implemented by calculating 95% confidence intervals (CI) using the z-test, whereas the internal variability across the SEE registries was evaluated using one-way ANOVA. We estimated annual percent changes (APC) of incidence and mortality rates with Poisson regression analysis and evaluated the presence of potential breaks in temporal trends with Joinpoint regression analysis.

Kaplan–Meier curves were derived to calculate cumulative survival of malignant CNS tumors for the 6-month, 1–. 2-, 3-, 5- and 10-year periods since diagnosis stratified 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 OS of malignant CNS tumors in the SEE region, survival rates were calculated for the registration period 2001-2009, which was common among the majority of the largest SEE registries; time trends were evaluated based on survival rates in three 3-year periods (2001-2003; 2004-2006; 2007-2009). The log-rank test was used for statistical evaluation of differences in survival rates.

Lastly, we designed Cox proportional-hazard models for OS including age group, sex, diagnostic period (in 5-year intervals), diagnostic group, and registry. Alternative to the registry variable, place of residence was introduced in the model. All analyses were repeated by geographical region (SEE, SEER) and thereafter sub-analyses were performed by age group (15-19, 20-39 years) and by diagnostic category. Furthermore, in sensitivity analyses we restricted cases to either those diagnosed within the last 10 registration years for each registry and or those diagnosed after 2000.

Statistical analysis was performed with the SAS software (V9.4, SAS Institute Inc) and Joinpoint Regression Program (V4.1.1, National Cancer Institute).

Study #3: Incidence and survival patterns of childhood pilocytic astrocytomas in Southern-Eastern Europe and the US

Participating registries

For this study, we leveraged data from the same informal SEE network of 12 countries including 14 childhood cancer registries (Belarus, Bulgaria, Croatia, Cyprus, Greece, Malta, Central Portugal, North Portugal, Romania-Cluj, Northeast Romania, Serbia, Slovenia, Ukraine, Turkey-Izmir) [202,212]. Individual registries, provided primary data on incident childhood (0-14 years) CNS tumors diagnosed during variable registration periods expanding from 1983 to 2014. Additionally, following signing of a Research Data Agreement, data on childhood CNS tumors were extracted from the SEER database, covering 18 cancer registries across US during 1973-2012 [205,206].

Registration of pilocytic astrocytomas and variables used in the study

All CNS tumors were codified by morphology and behavior using ICD-O-3 [208] and were classified according to ICCC-3 [20]. Cases of pilocytic astrocytoma were determined by their ICD-O-3 morphology code 9421 and data for all childhood (0-14 years) were extracted. According to ICD-O-3, established in 2001, pilocytic astrocytomas are classified as tumors of uncertain behavior, whereas precedent classifications considered them as malignant [19]. Serbia and Cyprus, collecting solely malignant tumors, were excluded from analyses, whereas Ukraine starting registration in 2001 confirmed the non-systematic collection of pilocytic astrocytomas and was, thus, excluded from incidence analysis. Yet, Ukrainian data were retained in survival analysis given that they randomly recorded a sub-sample of pilocytic astrocytomas. Bulgaria, despite pertaining to malignant tumors, confirmed that it maintained systematic collection of pilocytic astrocytomas after the classification change. In SEER, pilocytic astrocytomas were systematically collected as malignant tumors until 2001 and despite the official start of registration of non-malignant tumors in 2004, an informal ongoing registration of pilocytic astrocytomas was preserved during 2001-2004.

We coded topography according to ICD-10 [207] and classified pilocytic astrocytomas to the following CNS locations: supratentorial site (C71.0-C71.5, C75.1-C75.3), cerebellum (C71.6), optic

nerve (C72.3), brainstem (C71.7), spinal cord (C72.0), overlapping locations (C71.8) and unspecified topography (C71.9). SEE registries, except for Croatia, further provided information on place of residence, classified as urban, semi-urban, rural. The classification was different for each country and was based on the respective guidelines of the national statistical services for each country, which have already taken into account the special needs of each country's population [213]. For comparability with SEER classification, we dichotomized the variable to rural and urban place of residence merging the urban and semi-urban categories.

Follow-up data

Survival, as an endpoint, was assessed on the basis of date of diagnosis, date and status at last contact or lost to follow-up date. As all-cause mortality is negligible in children 0-14 years and thus the observed survival closely reflects the disease outcome. Cases diagnoses by death certificate only and cases lost to follow-up cases were excluded from the survival analysis.

Statistical analysis

We calculated CIRs by age group (0-4, 5-9, 10-14 years) and AIRs per million children. We estimated APCs of incidence rates with Poisson regression analysis. Incidence rates and time trends were also estimated for all participating SEE registries combined during the periods 1990-2012 and 2000-2012 [214], when the majority of registries were active. For SEER the estimations pertained to the periods 1973-2012, 1990-2012, 2000-2012. We applied joinpoint regression to unveil potential breaks in trends. Trends of astrocytomas NOS (ICD-O-3 coding: 9400) were also examined to explore potential classification improvements over time.

Consequently, we performed Kaplan-Meier analyses for the overall sample, as well as stratified by age group, sex, topography, geographical region and diagnostic period and we estimated cumulative survival rates for the 6-month, 1-, 2-, 3-, 5- and 10-year periods since diagnosis. Cox proportional-hazard models were designed that included age, sex, diagnostic period and topography in a core model and subsequently, geographical region and place of residence interchangeably. We combined SEE and SEER data in the main analysis, as to increase statistical power, but due to the profound differences in survival between the two regions, we also performed stratified analyses. In sensitivity analyses, we stratified by geographical region, excluded the Ukrainian data, and restricted the analyses to cases diagnosed after 1990 and after 2000. SAS software (V9.4, SAS Institute Inc), Joinpoint Regression Program (V4.1.1, National Cancer Institute) and STATA (V13.0, StataCorp) were used for statistical analyses.

B. Meta-analytical approaches in analytical epidemiology of primary central nervous system tumors: original data analyses and meta-analyses to explore perinatal and early-life risk factors

Study #4: Risk factors for childhood central nervous system tumors in a nationwide Greek case-control study

Study design

Data for this analysis come from a nationwide multi-center case-control study. During the study period (2010-2016), a total of 466 children (0-14 years) of Greek origin with malignant or non-malignant CNS tumors, as defined by ICCC-3 [20], were registered in the NARECHEM-ST; a nationwide registry of childhood malignancies in Greece. Details on the registration methods of NARECHEM-ST have been previously described [202] and are also available online (http://narechem.gr/node/24). We contacted the guardians of these children and obtained an informed consent for participation in our case-control study for 203 CNS tumor cases (participation rate 43.6%). CNS tumor cases included in the case-control study did not differ from the nationwide population of childhood CNS tumors in terms of age, sex, and tumor topography, but the included sample underrepresented tumors of non-malignant behavior and overrepresented embryonal tumors over astrocytomas and tumors of unspecified histology. Summary data of basic demographic and tumor-specific characteristics of the registry population are further available online (http://narechem.gr/node/9). The primary reasons for non-participation in the case-control study were retrospective registration and loss to follow-up, refusal to participate, and fatal malignancies leading to death within a month after diagnosis.

CNS tumors were classified to the 6 diagnostic subgroups of ICCC-3 [20] based on their morphology, behavior, and topography ICD-O-3codes [208]. Controls were children (0-14 years) hospitalized for acute appendicitis (ICD-10 K35 codes) in the pediatric surgical departments of the collaborating hospital within a period of 12 months after the time point of CNS tumor diagnoses in the respective cases and were free of cancer and any major chronic comorbidities. We selected two controls matched for age (±6 months), sex, and participating center, for every case. The refusal rate among controls was minimal (~4%), and in case of refusal the next eligible controls were identified from the records of the department. The protocol has been approved by the Ethics Committee of the Athens University Medical School.

Study variables

Upon agreement by the treating physician, the guardians of all eligible study participants were informed of the study objectives and were interviewed in person or through telephone by a trained interviewer. A structured questionnaire was used, which was designed in the context of the MOBI-KIDS study, an international case-control study of CNS tumors aiming to explore the role of non-ionizing radiation in brain tumorigenesis [39]. The questionnaire covered a series of putative risk factors including sociodemographic, childhood environment and lifestyle variables, perinatal characteristics, family and own medical history. Specifically, we collected data on maternal education, birth weight, gestational age at birth, maternal and paternal age at birth, delivery mode, history of infertility (defined as visit to fertility specialist before conception), history of infection during the first two weeks of life as recalled by the guardian and after examination of the medical records, birth order, sibship size, age at enrollment to kindergarten, maternal alcohol consumption and smoking in the perinatal period (3 months before pregnancy to 3 months after pregnancy), history of living in a farm, pet animals in house, history of allergic disease as recalled by the guardian and as determined by scanning of medical records (atopic dermatitis, allergic rhinitis, asthma, food allergy, known allergy to environmental or pharmaceutical antigens), hypertension in pregnancy, and gestational diabetes. Delivery mode was categorized as spontaneous vaginal delivery, instrument-assisted vaginal delivery, and caesarean section. Size for gestational age was defined as small, appropriate, and large for gestational age, based on the 10^{th} and 90^{th} percentile of the national growth curves. For 18% and 13% of the cases and controls, respectively, we had no available information on gestational week at birth, but rather on gestational month at birth or a raw classification of gestational age, as pre-term, full-term, or post-term. To classify these cases and controls according to size for gestational age, we considered as gestational week at birth, the median gestational week that the respective gestational month or gestational age crude category corresponded to.

Statistical analysis

The frequencies or distributions of the study variables were compared between the cases and controls with a Chi-square test. We next designed a series of multivariable logistic regression models for each of the potential risk factors that were associated with CNS tumors at a p-value ≤0.10 in the unadjusted analyses. Although size for gestational age did not reach a p ≤0.10 in the unadjusted analysis, as both birth weight and gestational age showed such associations, we also designed a logistic regression model for this variable. All models were adjusted for the matching factors (age, sex), maternal education (index of socioeconomic status), and a number of confounding variables determined by conceptual directed acyclic graphs. Specifically, we included in the models only

confounders and no mediators or instruments for the examined associations [215]. We repeated the multivariable analyses for the two most numerous CNS tumor subtypes; astrocytomas (ICCC-3 diagnostic subgroup IIIb) and embryonal tumors (ICCC-3 diagnostic subgroup IIIc). All analyses were based on conditional logistic regression models. We analyzed data with the SAS statistical software (SAS v9.4; SAS Institute, Cary, North Carolina, USA).

Study #5: Birth weight and other anthropometrics at birth in associations with central nervous system tumors: a systematic review and meta-analysis of published studies

Study selection

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [216] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [217] and was based on a pre-defined protocol. Medline/PubMed and Scopus databases were searched up to May 18th, 2016, for publications relevant to the research question; appropriate search terms were combined in a search algorithm (available in **Appendix I**). No language or publication year restrictions were applied. We further manually screened the references of eligible articles and relevant reviews ("snowball") and searched Google Scholar, OpenGrey and ProQuest as sources of grey literature.

We considered as eligible all case-control and cohort studies examining the association of anthropometric measurements at birth with the risk of a primary CNS tumor. The following anthropometric measures were examined: birth weight, birth length, head circumference, size for gestational age, weight-for-length, proportion for optimal birth weight (POBW), proportion for optimal birth length (POBL), proportion for optimal birth weight-for-length (POBWL), ponderal index and fetal growth. We included studies examining both childhood and adult CNS tumors, but we analyzed them separately. Childhood CNS tumors were examined as diagnostic categories of the ICCC-3 [20]. For adult tumors, we examined glioma, meningioma and other non-glial tumors. Excluded were studies referring to populations with genetic syndromes predisposing to CNS tumors, like NF1, NF2, and Li-Fraumeni syndrome and case-control studies, in which individuals with cancer served as controls.

We further contacted authors of studies not quantifying the association of interest but providing indications in their manuscripts that the necessary data were available, so that they provide appropriate analyses or subject-level data. We contacted authors of eligible studies for clarifications.

Eligible studies were evaluated for overlap, based on geographic location, data sources, diagnostic period, age range, and number of cases. In case of overlapping populations, the smallest study was excluded. Study selection was performed by reviewers working in pairs, blindly to each other; disagreements were resolved by consensus.

Data extraction and quality assessment

We extracted in a pre-defined spreadsheet publication details (year, first author, title, journal), information on study characteristics (study design, mean age, age range, sex distribution, sample-size, cohort features/ascertainment of cases and controls), type and assessment of birth anthropometrics, ascertainment of outcome and statistical analysis results. In case of missing data, we searched for previous publications from the same study or we contacted the corresponding authors. Studies were evaluated on quality with the Newcastle-Ottawa Scale [218]. For comparability questions, age was set *a priori* as the most important factor, whereas for cohort studies follow-up was considered adequate at 4 years, with a completeness percentage of >80%. Authors in pairs, independently extracted data and assessed studies on quality. Consensus was reached for disagreements.

Statistical analysis

Among various anthropometric measures, meta-analyses were possible for birth weight and size for gestational age. For birth weight, two approaches were followed: (i) dichotomous analyses for >4,000 g vs. ≤4,000 g and <2,500 g vs. ≥2,500 g (studies not exceeding these cut-off points by more than 500 g were also included); and (ii) an incremental-per 500 g- analysis. To maximize synthesized evidence, we also implemented an alternative categorical approach of the highest and lowest vs. intermediate birth weight categories (preferring, if available, the >4,000 g and <2,500 g vs. 2,500-4,000 g). Effect sizes were adjusted to the desired birth weight categories using the Hamling *et al.* method [219]. Crude ORs from 2x2 tables were estimated for studies not directly providing estimates. Effect estimates corresponding to the highest-adjusted analysis were preferred. For incremental analysis, effect estimates for at least three birth weight categories, were included after estimating the log-linear trend using the generalized least-squares approach [220]. Regarding size for gestational age, estimates for large-for-gestational-age and small-for-gestational-age vs. appropriate-for-gestational-age infants were synthesized.

We used random-effect models to pool the effect estimates separately for the risk of childhood and adult CNS tumors. We evaluated heterogeneity with the Cochran Q statistic and by estimating I^2.

Because of the low sensitivity of the Cochran *Q* test, statistical significance level was set at p<0.10 [221]. For childhood CNS tumors, analyses were conducted for all tumors combined, for the ICCC-3 diagnostic categories and, if available, for additional histological subtypes. If a study presented separate analyses for subtypes of a specific diagnostic category (e.g. low-grade and high-grade astrocytoma), the individual estimates were initially pooled via fixed-effects meta-analysis and the derived estimates were included in the meta-analysis [222]. We further performed subgroup and sensitivity analyses by study design, adjustment level, quality score, birth weight assessment, age group and study population. Regarding adult CNS tumors, only incremental analyses for total CNS tumors and the glioma subtype were feasible.

Where possible, we conducted a dose-response meta-analysis by level of birth weight category. The average "dose" for each birth weight category was calculated as the arithmetic mean of the two category ends, whereas the Berlin *et al.* method was implemented for the open-ended upper categories [223]. A restricted cubic spline model using generalized least square regression with pre-defined knots at 25th, 50th and 75th percentiles, was initially applied for individual studies and study-specific estimates were thereafter pooled using the restricted maximum likelihood method in a random-effects meta-analysis [220].

For meta-analyses including more than 10 effect estimates, we evaluated the possibility of publication bias, by assessing small-study effects the Egger's test [224] and by designing funnel plots. The significance level for publication bias was set at p<0.10. This threshold has been suggested for Egger's tests, because of the usually small number of studies included in meta-analyses, thus diminishing the statistical power of the test [224]. Meta-regression analysis was also performed to assess the potentially modifying effect of age at diagnosis, sex and publication year on the associations of interest. The STATA Software (v13.0) was used for analyses.

Studies #6-7: Seasonality at birth in associations with incidence of childhood central nervous system tumors: a systematic review and a pooled analysis from cancer registries in Southern-Eastern Europe

Study selection for the systematic review

To address this research question, we first performed a systematic review based on a pre-defined protocol, which was in accordance with the PRISMA and the MOOSE guidelines [216,217]. Scopus and Medline/ PubMed were searched up to June 25th, 2017 combining relevant key-terms (search

strategy available in **Appendix I**). The references of eligible articles and relevant reviews were additionally manually screened ("snowball"). No language or publication year restrictions were applied.

We considered as eligible all case-control and cohort studies, as well as cancer registration studies using for comparisons population-based birth month or season rates in order to assess the statistical association between month or season of birth period and risk of subsequent primary CNS tumors. Studies considering either childhood/adolescence (0-14 or 18 years) or adult (19+ years) occurrence of CNS tumors were eligible, but were separately analyzed. Studies referring to populations with genetic syndromes predisposing to CNS tumors, including NF1, NF2, and Li-Fraumeni syndrome, case reports, case series, *in vitro* and animal studies were excluded. Eligible studies were evaluated for potential overlap, based on geographic location, data sources, diagnostic period, age range and number of cases. Pairs of reviewers, blinded to each other, completed the study selection; disagreements were resolved by team consensus.

Data extraction and quality assessment

Extracted data included publication details (year, first author, title, journal), information on study characteristics (study design and geographical area, mean age/age range, proportion of males, sample-size, ascertainment of cases and comparison groups), type and assessment of exposure, control for potential confounding factors, ascertainment of outcome and statistical analysis variables (methodology, results). Authors of original studies were also contacted for missing data.

Studies were *a priori* distinguished by age (childhood vs. adulthood) and were thereafter evaluated on quality with Newcastle-Ottawa Scale [218]. For cohort studies, follow-up was considered adequate at a minimum of 1 year, with a completeness rate >80%. For the evaluation of the cancer registration studies with population frequencies of births per month/season for comparisons, the cohort subscale was used, after slight modifications to abide with the study objectives: three questions referring to the presence of the outcome at the start of the study and to the length and completeness of follow-up were excluded. Again, pairs of reviewers conducted independently data abstraction and quality assessment and thereafter consensus was reached for disagreements.

Pooled analyses in the cancer registries of the Southern-Eastern European countries

Data from the systematic review were not possible to be pooled in meta-analyses due to the vast heterogeneity between studies. Thus, we further aimed to analyze data from a total of 6,369 incident cases of childhood (0-14 years) CNS tumors recorded by the 16 collaborating cancer registries of the

informal SEE network operating in 14 countries (Belarus, Bulgaria, Croatia, Cyprus, Greece, Hungary, Malta, Poland, Portugal, Romania, Serbia, Slovenia, Turkey, Ukraine). Registration periods spanned from 1983 to 2015, Details on registration process and data coding by registry have been described elsewhere [202,225].

Common spikes in the birth days (1st or 15th or 30th of June or 1st of January) were noticed in the raw data of some registries, probably reflecting imputed values in case of missingness of the day of birth; hence, the respective days were excluded from all remaining months of each year in the data provided by the specific registries. Eventually, 355 cases (5.6%) were excluded resulting in a total of 6,014 cases included in current analyses.

Analyses by birth month: Cuzick-Edward's and Walter Elwood tests

Live-birth date data were available for nine countries (Belarus, Croatia, Cyprus, Greece, Hungary, Poland, Portugal, Slovenia, Ukraine) which contributed 83% of childhood CNS tumor cases (4,987 case). The Cuzick and Edward's test was initially used to explore the role of birth month on CNS tumor occurrence in the pooled dataset [226]. The hypothesis was additionally tested using the Walter Elwood test both in the registry-individual and the overall pooled dataset [227]; the latter test is considered a more pertinent analytic method, as it takes into account the number of CNS tumor cases per time unit over the number of available live-births during the same time period in the catchment area of the registry where the respective cases were recorded.

Subgroup analyses were performed by sex and age group (0-4, 5-14 years) for all CNS tumors, as well as by principal histological subtype, notably astrocytomas (N=1,812; 30.1%) and embryonal tumors (N=1,716; 28.5%). Sub-analyses for the remaining less common histological subtypes (N=1,359; 22.6%) and CNS tumors of unknown histology (N=1,127; 18.8%) were not feasible. Overall analyses and sub-analyses were run using both statistical tests for comparison reasons.

Seasonal analyses: registry-specific Poisson regression and meta-analyses

The distribution patterns of CNS tumor cases by season within each year of birth were examined, since the distributions by birth month and registry yielded small numbers. Specifically, incident CNS tumor cases and live-birth data for each participating registry were grouped by season (winter: December, January, February; spring: March, April, May; summer: June, July, August; and autumn: September, October, November). Registry-specific seasonal crude incidence data were used to calculate registry-specific seasonal incidence rate ratios (IRR) through Poisson regression models and were, thereafter, meta-analyzed using random effects meta-analysis [228]. Sub-analyses by sex,

age group (0-4, 5-14 years) and principal histological subtype of CNS tumors (astrocytomas, embryonal tumors) were also performed. Sensitivity meta-analyses excluding registries with higher rates of death certificate only or lower rates of morphologically verified diagnoses were additionally performed.

Statistical significance was set at $p<0.05$. All analyses were conducted using SAS version 9.4 (Carry, NC.) and STATA version 14.1 (College Station TSC).

C. Applying meta-analyses to address questions of clinical epidemiology: the case of the rare central nervous system tumor gliomatosis cerebri

Study #8: Delineating the epidemiology of gliomatosis cerebri: incidence and survival patterns in a population-based cancer registration study

Source of data and study population

To explore the descriptive epidemiology of GC, we extracted data from the publicly available SEER database [46]. For the aims of this study, we extracted available data for all GC cases registered in the SEER database during the entire registration period (1973-2012). GC cases were identified by their ICD-O-3 morphology code [208]. Particularly, cases with an ICD-O-3 morphology code "9381", corresponding to GC, were included in the analysis.

Study variables and follow-up data

Demographic variables that were examined included age, sex, race and urbanization of the place of residence at diagnosis, as a measure of socioeconomic status. Age was classified as follows: 0-14 years (children), 15-39 years (AYAs), 40-64 years (middle-aged adults) and ≥65 years (elderly). As GC in children has been reported to have superior prognosis, compared to adults [149], sensitivity analyses excluding children were conducted. Race was binarily classified to Whites and non-Whites. We dichotomized place of residence to rural and urban based on US definitions.

Available clinical variables included: primary tumor location, method of diagnosis, receipt of radiation therapy and performance of surgery. Primary tumor location was codified according to the ICD-O-3 topography codes and was classified to tumors localized in the cerebral hemispheres (C71.1-C71.4), tumors in deeper structures, infratentorial or overlapping locations (C71.0, C71.5-C71.8) and tumors of unspecified CNS location (C71.9) [208]. Based on the International Agency for Research in Cancer guidelines, method of GC diagnosis was classified to microscopical diagnosis (histology, cytology or unspecified), clinical/radiological diagnosis, and diagnosis via death certificate only [208]. Receipt of radiation therapy or performance of any surgical procedure (including both local tumor excision or gross total resection) at diagnosis were extracted as yes/no variables.

Patients lost to follow-up and death certificate only cases were excluded from the survival analysis. We assessed OS in the longest available follow-up date for each case. Follow-up information was available until December 31st, 2012.

Statistical Analysis

We calculated annual AIRs of GC for the entire registration period (1973-2012). AIRs are expressed as number of GC cases per million per year. AIRs were calculated for the entire population and for subgroups by sex, age group, 10-year time periods and method of diagnosis. Comparisons of AIRs were implemented by calculating the standard error and subsequently *z*-scores, as previously described for incidence rates [229]. To evaluate temporal trends in incidence APCs were calculated via Poisson regression analysis and potential breaks were sought via Joinpoint regression analysis. As we found an increasing trend in incidence only for the first 30 years of registration, we also calculated AIRs for the restricted 2003-2012 period to disentangle the effect of registration improvements or efficiency of GC diagnosis on incidence.

OS was assessed via Kaplan–Meier curves for the entire sample and for subgroups by age group (0-14, 15-39, 40-64, ≥65 years), sex, time period of diagnosis (1973-2002, 2003-2012), primary tumor location, method of diagnosis (clinical/radiological, histological) and received treatment. The log-rank test was used for comparisons. For the evaluation of the prognostic significance of demographic and clinical variables, we applied Cox regression analyses. Univariable analyses were conducted and variables associated with survival at a level of $p<0.20$ were included in a multivariable model. The analysis was repeated after excluding cases aged <15 years at diagnosis. SAS software (V9.4, SAS Institute Inc) and STATA (V13.0, Stata Corp) were used for statistical analysis.

Studies #9-10: Clinical, neuroimaging, histopathological features, prognostic factors, and survival of gliomatosis cerebri: a systematic review based on synthesis of published individual patient data

Search strategy and study selection

To evaluate the detailed clinical, diagnostic, and prognostic features of GC, we then extracted individual-level data from all the cases of GC ever described in biomedical literature and performed a meta-analysis. We followed a pre-defined protocol (publicly available in PROSPERO; registration

number: CRD42016050474) and performed the systematic review according to the PRISMA [216] and the MOOSE [217] guidelines. Specifically, two independent reviewers searched Medline/PubMed and Scopus up to June 30th, 2017, using the terms gliomatosis AND cerebri. No language or publication year restrictions were applied. The reference lists of eligible studies and relevant reviews were additionally hand-searched ("snowball" procedure). At the end of the search, eligible studies were evaluated for potentially overlapping populations. We considered as eligible, case reports, case series, cohort and cross-sectional studies, as well as clinical trials of any type, presenting data on at least one patient with histologically diagnosed GC. *In vitro* and animal studies were excluded, as were studies of non-histologically confirmed GC cases.

Data extraction

Data of eligible studies at individual patient level from the descriptions provided in the publication were extracted in a pre-defined spreadsheet. Variables of interest were: age at diagnosis, sex, treatment center, clinical signs and symptoms before diagnosis, presence of a known genetic disease that predisposes to CNS tumors, time from first symptom to diagnosis, method of diagnosis, details on neuroimaging findings at diagnosis (MRI, MR spectroscopy, CT, PET, or other), diseases included in the differential diagnosis, type of GC (I or II), topography of the tumor (bilateral/unilateral and supratentorial/infratentorial involvement, CNS regions invaded, and number of CNS regions affected), cerebrospinal fluid puncture findings, electroencephalogram findings, histological characteristics (grade, histopathology), and molecular aberrations. Details on tumor topography were extracted either from the text or from the respective images provided in the article. If information on GC type was not directly available, we considered as type II those cases with clear radiological evidence of a well-defined focal lesion with contrast enhancement [126]. The number of CNS regions involved was determined as follows: the frontal, temporal, parietal, and occipital lobes as well as the basal ganglia including thalamus of both sides were regarded as separate regions each; the brainstem/cerebellum and spinal cord were also considered as separate regions [135].

Further, we extracted follow-up data (response to treatment, progression status, survival status, time to progression, time to death). Response to treatment was examined as radiological and clinical. For the evaluation of radiological response, we followed the criteria by McDonald *et al*. [230] harmonized for GC by Glas *et al.* [135], where possible. Particularly, a partial response required a 50% reduction of contrast-enhancing lesions or a reduction of T2 hyperintensities by at least 25%. Complete response required complete regression of all T1 and T2 lesions; due to restricted numbers of GC tumors with complete response, these categories were merged for the purposes of the current study. Disease progression was defined as >25% increase of contrast-enhancing or T2 hyperintense lesions, whereas all other situations were considered as a stable disease. If detailed data were not available,

the definitions used in the individual studies were used to classify response, stable disease or progressive disease. Regarding the clinical response to treatment, demonstration of improvement of the symptomatology at diagnosis (remission or decrease in the severity of the symptoms) was considered a response; stable disease was defined as no change in clinical picture following treatment and progressive disease, as deterioration of the symptomatology (new symptoms or increased severity of already experienced symptoms).

Authors of case series with missing data at an individual patient level were contacted; in case of no reply, cumulative information for the aforementioned variables was extracted and was used instead. Particularly, we extracted HRs along with their 95% Confidence Intervals for prognostic factors of PFS and OS. If the HRs were not directly presented they were calculated from Kaplan-Meier curves [231]. Pairs of independent abstractors performed the abstraction of data, which were subsequently re-evaluated and harmonized by a single investigator in case of disagreement.

Statistical analysis

Categorical variables were presented as observed counts, whereas percentages and continuous variables were presented as mean or median values with the corresponding standard error or range, depending on the distribution of the variable. These summary statistics from individual data patients were then combined with descriptive data from studies presenting only summary data. Therefore, the numbers per variable are different depending on data availability in the included studies. Chi-square, Fisher's exact test, Mann-Whitney *U*, and *t* -test, and one-way analysis of variance (ANOVA) were used to identify differences among subgroups.

Factor analysis was performed across 21 symptoms that were extracted to identify clustering of symptoms among patients with GC. The factorability of the data was evaluated using a Kaiser–Meyer–Olkin value. Weighted least squares estimation with mean and variance adjustment was used for factor extraction as the recommended extraction method for binary data and oblique rotation was performed to allow for correlations between symptoms [232]. We determined the number of factors based on Eigenvalues >1 and the screeplot and we considered only factors with loadings >0.3 [233,234]. Structure coefficients (correlations) >0.30 were required for a symptom to be grouped under a symptom cluster and clinical plausibility was taken into account for the final grouping [233]. To identify predictors of GC progression at diagnosis, we examined in ordinal logistic regression analysis the variables impacting on the number of CNS regions affected by the neoplasm. Variables showing an association at a *p*-value <0.20 in the univariable analysis, were additionally included in a multivariable model.

GC patients, not diagnosed post mortem and with available follow-up information were included in the primary survival analyses of individual patient-data. The effect of potential prognostic factors on PFS and OS was initially examined in univariable Cox regression. Next, where possible, we combined in meta-analysis the HRs derived from individual-patient data analysis with the summary statistics from published studies. Heterogeneity in meta-analyses was evaluated with the I2 and the Cochran Q statistic. We used fixed-effects models for the meta-analyses if no heterogeneity was present, and random-effects models in case of heterogeneity (I2 ≥50% or Cochran Q-derived p <0.10).

Subsequently, we undertook multivariable analyses after selecting a core set of variables to be included in the models. The selection was based on literature reports for prognostic factors, findings of the univariable analysis, availability (missing values <30%) and collinearity of the candidate variables. Thus, the core Cox proportional hazards model included age, sex, histology, grade, GC type, and number of CNS regions affected. Imputation of missing values was used for sex, histology, grade, GC type and CNS regions affected taking into account age, survival time, survival status, PFS, progression status, as well as the remaining imputed variables. Logistic regression analysis was used for imputations of the binary variables sex, histology and GC type, whereas multinomial and ordinal regression analyses were undertaken for grade and CNS regions affected, respectively. Twenty iterations were performed. Following multiple imputations, the additional variables were additively and alternatively introduced in the model.

To examine the effect of first-line treatment on OS and PFS, the 3 variables (chemotherapy, radiotherapy, surgery) were concurrently included in the aforementioned model; a new variable entailing the combination of treatments was alternatively introduced in the model. In sensitivity analyses, we excluded all patients who did not receive any treatment to enable comparisons between the groups. Finally, in a multinomial logistic regression model, we explored potential predictors of radiological response to treatment. Statistical significance level for all analyses was set at a two-sided *p*-value <0.05. All analyses were performed using SAS (v9.4, SAS Institute Inc), IBM SPSS (v23.0, Armonk, NY: IBM Corp) and STATA (v13.0, StataCorp) softwares.

Study #11: Clinical features of gliomatosis cerebri among children and adolescents

To explore whether GC presented with different feature in children, compared to adults, in accordance with other CNS tumors, we then restricted our analyses to 182 GC patients aged ≤18 years at diagnosis from the same combined dataset. We first compared clinical and tumor characteristics at baseline, between patients aged ≤18 and >18 years at diagnosis, as to examine

whether pediatric GC entails unique features. Chi-square, Fisher's exact test and Mann-Whitney *U* test were used to identify differences between patients aged ≤18 and >18 years at diagnosis. Specifically, chi-square test was used for all comparisons of categorical variables, unless one of the compared categories included ≤5 observations; on that occasion, Fisher's exact test was preferred. For the only continuous variable (time from symptoms to diagnosis), a Mann-Whitney *U* test was used because it was not normally distributed. Subsequently, for the survival analysis, we included only GC patients who had available follow-up information and were not post mortem diagnosed (N=141).

The effect of potential prognostic factors on OS was initially examined in multivariable Cox proportional hazard models. A core set of variables, determined by literature reports for prognostic factors,12 findings of the univariable analysis, data availability (missing values <30%) and collinearity of the candidate variables, was included in the multivariable models. These variables were age, sex, histology, grade, GC type (I or II), and number of CNS regions affected. Multiple imputation was performed for missing values in sex, histology, grade, GC type and affected CNS regions by considering age, survival time, and the remaining imputed variables. Logistic regression analysis was used for imputations of the binary variables sex, histology and GC type, whereas multinomial and ordinal regression analyses were undertaken for grade and CNS regions affected, respectively. Twenty iterations were performed. Following multiple imputations, the additional potentially prognostic risk factors were additively and alternatively introduced in the model.

To examine the effect of first-line treatment on OS, three variables (chemotherapy, radiotherapy, surgery) were concurrently included in the aforementioned model. Furthermore, a new variable entailing the combination of treatments was alternatively introduced in the model. For this analysis, only treatment combinations administered to >10 patients with GC were considered and we excluded all patients who did not receive any treatment to enable comparisons between the groups; chemotherapy alone was used as the reference category in this analysis. Statistical significance level for all analyses was set at a two-sided *p*-value <0.05. All analyses were performed by SAS (v9.4, SAS Institute Inc) and STATA (v13.0, StataCorp).

Study #12: IDH mutations as predictors of seizure occurrence in gliomatosis cerebri and other gliomas

Finally, we aimed to explore in the individual-level dataset coming from the aforementioned individual-level data meta-analysis, if IDH1 mutations, a common molecular alteration in gliomas that has been associated with improved survival, is also associated with the occurrence of seizures. We first compared the distributions of the clinical, imaging, and molecular characteristics between patients who presented or not seizures at or before the time of diagnosis. Chi-square, Fisher's exact test and Mann-Whitney *U* test were used to identify differences, as appropriately. We then oved into a multivariable logistic regression model of seizure occurrence at baseline all variables showing significant or suggestive associations ($p<0.10$) in the univariable analysis. These included age, sex, tumor expansion to the frontal or temporal lobes, and presence of IDH1 mutations. The multivariable analysis was restricted to 40 patients with available data on all these variables and on occurrence of seizures at baseline.

Then, we systematically reviewed Medline/PubMed to identify any cross-sectional study of patients with any type of gliomas, which explored the associations between IDH1 mutations and occurrence of seizures at the time of diagnosis (pre-operatively). Relevant data were extracted and the Odds Ratios reported by the studies were meta-analysed with random-effects meta-analyses. Statistical significance level for all analyses was set at a two-sided *p*-value <0.05. All analyses were performed by SAS (v9.4, SAS Institute Inc) and STATA (v13.0, StataCorp).

RESULTS

A. Meta-analytical approaches in descriptive epidemiology of primary central nervous system tumors: pooling data across cancer registries to delineate the incidence, mortality, and survival patterns of CNS tumors in childhood, adolescence and young adulthood

Studies #1-2: Incidence, mortality and survival patterns of central nervous system tumors among adolescents and young adults (15-39 years) in Southern-Eastern Europe and the US

Quality indicators of the registries

A total of 11,438 malignant CNS tumor cases diagnosed among individuals aged 15-39 years were recorded in the 14 SEE registries operating during variable time periods ranging from 1990 to 2014 and another 13,573 incident cases were extracted from the SEER database (1990-2012) amounting to a grand total of 25,011 cases available for the analyses. As shown in **Table 5**, half of the SEE registries had nationwide coverage with the remaining registries covering between 5% (Turkey-Izmir) to 76% (Serbia Central) of the respective national population in the age range 15-39-years; respectively, SEER data cover 28% of the US population. death certificate only diagnoses corresponded to <3% of the total cases in all the registries, except for the 2 Romanian registries (~12%) and Cyprus (6%); notably though, 4 of the registries (Greater Poland, the 2 Portuguese registries, Slovenia) had no death certificate only diagnoses owing to the lack of access to these data. The proportion of morphologically verified diagnoses was >70% in all the registries except the Croatian (57.2%), whereas in the Portuguese and Slovenian registries this percentage, equaled or exceeded that of SEER (92.3%). Regarding the proportion of cases of unspecified morphology, a wide variation was observed among the SEE registries (ranging from 9.9% in Turkey-Izmir to >40% in Croatia and Serbia Central), reaching a cumulative 30% (mainly driven by the 34.6% in Ukraine which contributes half of the overall SEE cases), which is considerably higher than the 2.5% cases of unspecified morphology registered in SEER. The very low mortality-to-incidence ratio noted in Cyprus (0.1) and Montenegro (0.0) should be interpreted in the context of the very low number of incident cases and deaths. Serbia Central had a very low mortality-to-incidence ratio (0.34) in comparison to the other registries, where it ranged from 0.49 (Croatia) to 0.63 (Greater Poland).

Table 5. Registration of malignant central nervous system (CNS) tumors among adolescents and young adults (15-39 years) in 14 Southern and Eastern European cancer registries and Surveillance, Epidemiology, and End Results Program (SEER), US: Characteristics and quality indicators.

Registry (registration period)	N cases	Population covered (millions)[a]	% national population coverage	% DCOs	% MVs	% unspecified morphology[b]	M/I	% lost to follow-up	mean follow-up (months±SD)	End of follow-up
Belarus (1990-2014)[c]	239	18.0	100	0.8	84.5	19.2	0.56	3.5	124 ± 71	03/2016
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	03/2016
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
Poland- Greater Poland (1999-2014)	627	20.9	10	0.0	79.9	16.7	0.63	5.8	84 ± 52	12/2015
Portugal Central (1999-2009)	233	8.8	23	0.0	91.9	16.3	0.56	0.0	139 ± 39	05/2016
Portugal North (1999-2010)	385	14.3	32	0.0	93.5	17.4	0.55	0.0	115 ± 43	12/2015
Romania- Cluj (2008-2012)	90	5.4	13	12.2	72.2	32.2	n/a[d]	0.0	55 ± 15	12/2014
Romania- Iasi (2008-2011)	136	5.4	18	12.5	81.6	26.5	n/a[d]	0.0	28 ± 19	12/2012
Serbia Central (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	06/2016
Turkey- Izmir (1993-2014)	891	33.1	5	1.2	85.1	10.0	n/a[d]	0.1	69 ± 65	02/2016
Ukraine (2000-2012)	6475	223.1	100	1.8	71.4	34.6	0.58	3.7	63 ± 48	12/2015
SEER, US (1990-2012)	13573	520.9	28	0.6	92.3	2.5	0.38	4.3	84 ± 69	12/2012

As presented in [235].

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

[b] Unspecified morphology category includes cases in the sixth diagnostic category ("Unspecified intracranial and intraspinal neoplasms") of the classification of cancer in adolescents and young adults.

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

[d] The two Romanian registries and Turkey-Izmir did not avail mortality data.

[e] Serbia has been excluded from the survival analysis due to non-availability of the follow-up data for cases diagnosed before 2007.

Abbreviations: DCO, death certificate only; MV, microscopically verified; M/I, mortality to incidence rate; SD: standard deviation; n/a: not available.

Incidence rates

The AIR of malignant CNS tumors among AYAs was variable in the SEE registries (**Table 6**); yet, the overall AIR for the entire SEE over the various study periods spanning from 1990 to 2014 (28.1 per million individuals) was higher ($p<0.001$) compared to that of SEER spanning from 1990-2012 (24.7 per million individuals). Among SEE registries, the AIR ranged from a low 14.2 (Romania-Cluj), 17.8 (Cyprus) and 18.9 (Malta) to the high 27.8 (Ukraine), 28.9 (Greater Poland), 30.8 (Croatia) and the rather outlier figure of 44.1 per million individuals in Serbia Central. ANOVA yielded statistically significant internal variability within the SEE registries ($F=13.79$, $p<0.001$). As expected, incidence rates increased by age group and males outnumbered females (male-to-female ratio: 1.2 in SEE overall, 1.3 in SEER). Of note, however, is the high CIR in the 15-19-year age group in Serbia Central, Croatia and Greater Poland as well as in the 35-39-year age group in Serbia Central, Croatia and Ukraine when compared to those in SEER.

On the contrary, the rates for non-malignant CNS tumors (not including pilocytic astrocytomas) were considerably lower in the 7 SEE registries that systematically recorded them (range 7.7 to 31.7 per million AYAs), as compared to SEER (55.2 cases per million), with a clear female preponderance (male-to-female ratio 0.4 to 0.8 in SEE registries and 0.5 in SEER). Similar to malignant tumors, the incidence increased with age. Regarding pilocytic astrocytomas the incidence rates among 10 SEE registries varied considerably. Without considering the small Romanian registries and Montenegro, the AIR for the ages 15-39 years ranged from 1.4 cases per million in Greater Poland to 2.9 and 3 cases per million in Portugal North and Slovenia, respectively. In contrast to the other tumor subtypes, the incidence of pilocytic astrocytoma decreased with age, whereas no consistent preponderance by sex was identified.

Table 6. Number of incident cases, crude and age-adjusted incidence rates (CIR, AIR) and male-to-female (M:F) ratios of malignant and non-malignant central nervous system tumors per million adolescents and young adults (15-39 years) in 14 Southern and Eastern European cancer registries and Surveillance, Epidemiology, and End Results Program (SEER), US.

	Malignant tumors								Non-malignant tumors[a]							
	N	CIR (by age group years)					M:F	AIR	N	CIR (by age group years)					M:F	AIR
Registries (registration period)	Cases	15-19	20-24	25-29	30-34	35-39			Cases	15-19	20-24	25-29	30-34	35-39		
Belarus (1990-2014)[b]	239	13.3	-	-	-	-	1.2	-	42	2.3	-	-	-	-	0.7	-
Croatia (2001-2013)	608	21.2	21.2	39.0	41.0	46.2	1.2	30.8	-	-	-	-	-	-	-	-
Cyprus (1998-2013)	85	12.7	12.3	23.1	19.8	23.7	1.9	17.8	-	-	-	-	-	-	-	-
Malta (1995-2014)	56	10.7	13.7	19.3	34.6	22.0	2.0	18.9	43	3.6	10.3	12.3	21.9	29.4	0.8	14.1
Montenegro (2013)	6	22.7	23.4	0.0	89.9	0.0	0.9	25.1	6	0.0	0.0	65.5	22.5	47.8	0.4	25.6
Poland- Greater Poland (1999-2014)	627	23.7	23.1	29.4	37.2	38.3	1.2	29.3	-	-	-	-	-	-		
Portugal Central (1999-2009)	233	13.7	18.8	27.7	27.8	40.8	1.2	24.5	100	5.9	7.0	12.5	12.3	17.5	0.4	10.5
Portugal North (1999-2010)	385	15.7	20.9	25.0	29.4	40.7	1.5	25.1	335	5.6	18.4	28.3	28.7	32.3	0.6	21.4
Romania-Cluj (2008-2012)	90	2.3	9.1	15.4	24.8	26.5	1.3	14.2	47	1.2	7.3	9.1	9.9	13.7	0.5	7.7
Romania-Iasi (2008-2011)	136	17.6	18.4	19.2	32.2	38.1	0.8	23.8	-	-	-	-	-	-	-	-
Serbia Central (1999-2013)	1216	36.2	35.1	45.8	53.1	58.1	1.2	44.3	-	-	-	-	-	-	-	-
Slovenia (1990-2013)	391	12.8	14.5	19.1	28.1	35.2	1.6	20.6	-	-	-	-	-	-	-	-
Turkey- Izmir (1993-2014)[c]	891	17.4	18.4	23.0	35.1	42.0	1.3	25.7	948[c]	17.3	27.1	41.0	49.5	65.4	0.4	37.6
Ukraine (2000-2012)	6475	19.1	18.6	26.4	36.9	45.7	1.2	27.8	-	-	-	-	-	-	-	-
SEER, US (1990-2012)[d]	13573	15.4	19.4	26.4	31.5	36.7	1.3	24.7	15626[d]	30.1	38.3	55.7	74.5	95.4	0.5	55.2

As presented in [235].

[a] Pilocytic astrocytomas have not been included in the non-malignant central nervous system tumors category.

[b] Data from Belarus available only for the age group 15-19 years.

[c] Data for non-malignant central nervous system tumors for Turkey-Izmir available only for the period 2000-2014.

[d] Data for non-malignant central nervous system tumors for SEER available only for the period 2004-2012.

Temporal trends

Incidence time trends are shown in **Table 7**. Despite the variable time periods of data availability, a statistically significant decrease of malignant CNS tumors incidence was noted during a 13-year period in Croatia (APC: -4%; 2001-2013). By contrast, increasing trends were documented in Greater Poland (APC: +2.7%; 1999-2014), Portugal North (APC: +3.5%; 1999-2010), Turkey-Izmir (APC: +2.1%; 1993-2014) and Ukraine (APC: +0.7%; 2000-2012). In SEER, a marginally decreasing tendency was identified, which could be interpreted as no change from zero (APC: -0.3%; 1990-2012). Regarding non-malignant tumors and pilocytic astrocytomas, statistically significant annual trends were found in Belarus, Turkey-Izmir and SEER. The joinpoint regression analysis, where possible, did not reveal any break of significant changes in the trends observed in SEE registries or SEER.

Table 7. Annual percent changes (APC) and 95% confidence intervals (95% CI) for malignant and non-malignant central nervous system tumors among adolescents and young adults (15-39 years) in the 14 participating Southern and Eastern European cancer registries and Surveillance, Epidemiology, and End Results Program (SEER), US, as estimated by Poisson regression analysis.

Registries (registration period)	Malignant tumors	Non-malignant tumors[a]
Belarus (1990-2014)[b]	0.1 (-1.7; 2.0)	13.3 (7.6; 19.2)
Croatia (2001-2013)	-2.5 (-4.6; -0.4)	-
Cyprus (1998-2013)	-3.9 (-8.2; 0.6)	-
Malta (1995-2014)	1.2 (-3.3; 6.0)	2.2 (-3.0; 7.7)
Montenegro (2013)[c]	-	-
Poland- Greater Poland (1999-2014)	2.7 (0.9; 4.4)	-
Portugal Central (1999-2009)	2.4 (-1.7; 6.7)	3.4 (-2.8; 10.0)
Portugal North (1999-2010)	3.5 (0.5; 6.5)	0.6 (-2.5; 3.8)
Romania-Cluj (2008-2012)	6.2 (-8.2; 22.9)	2.7 (-16.1; 25.7)
Romania-Iasi (2008-2011)	-7.9 (-21.1; 7.6)	-
Serbia Central (1999-2013)	-0.4 (-1.7; 0.9)	-
Slovenia (1990-2013)	0.3 (-1.1; 1.8)	-
Turkey- Izmir (1993-2014)	2.1 (1.0; 3.1)	6.1 (4.5; 7.7)[d]
Ukraine (2000-2012)	0.7 (0.0; 1.3)	-
SEER, US (1990-2012)	-0.3 (-0.6; -0.1)	2.6 (2.0; 3.3)[e]

As presented in [235].

[a] Pilocytic astrocytomas have not been included in the non-malignant central nervous system tumors category.

[b] Data from Belarus available only for the age group 15-19 years.

[c] APC was not estimated for Montenegro, as well as for pilocytic astrocytomas for the Romanian registries due to lack of data.

[d] APC for non-malignant central nervous system tumors for Turkey-Izmir refers to the period 2000-2014.

[e] APC for non-malignant central nervous system tumors for SEER refers to the period 2004-2012.

Distribution by demographic characteristics and diagnostic subtypes

The distribution of malignant CNS tumor cases by the study variables is presented in **Table 8**. Overall, both the age and sex distribution were rather similar among the SEE and SEER registries with males exceeding females. An increasing frequency of cases with the advancement of age was observed with no clear differences between the compared age groups in SEE and SEER. Regarding the diagnostic subtypes, the strikingly different percentages of "unspecified intracranial and intraspinal neoplasms" between SEE and SEER overall (30% vs. 2.5%, respectively), as well as among the individual SEE registries (range 10% to 40%) hinders formal comparisons; yet, a high proportion of the malignant CNS tumors in the 15-39 age range were astrocytomas (SEER: 44.8%, SEE: 48.7%) with glioblastomas and anaplastic astrocytomas being the prevailing subgroups (almost half of astrocytomas). The most pronounced difference across the remaining specified subgroups was evident in the "other glioma" category (SEE:11.8%, SEER: 31.6%). A strong negative correlation between the percentage of "other gliomas" and the "unspecified category" across the individual SEE registries and SEER (r=-0.67, p=0.007) was also noticeable. Ependymomas and embryonal tumors (medulloblastomas and other PNETs) comprised <10% of the cases across all SEE registries and SEER.

Figure 9 depicts the CIRs by diagnostic group of malignant CNS tumors, age group and sex in the 14 SEE registries overall compared to SEER. As a rule, similar patterns between the SEE registries and SEER were observed; particularly, for astrocytoma and other glioma an increase by age group among both males and females was shown, with the male preponderance widening by increasing age. As already mentioned, the incidence for "other gliomas" was overall lower in SEE. Ependymomas seemed to present a rather stable rate by age group without between-sex differences in both geographical regions, whereas the CIRs for medulloblastoma and other PNETs decreased with increasing age; although the male-specific incidence was higher in this diagnostic category compared to females, the discrepancy was diminished by increasing age. The rates for the last two diagnostic categories in SEER were extremely low and similar for both sexes and across all age groups in contrast to the SEE registries, where the rates, especially for the "unspecified neoplasms" were increasing with advancing age.

Table 8. Distribution (%) of demographic characteristics and diagnostic subtypes of malignant central nervous system tumors among adolescents and young adults (15-39 years) in 14 Southern and Eastern European cancer registries and Surveillance, Epidemiology, and End Results Program (SEER), US.

Variable	Belarus[a] (N=239)	Croatia (N=608)	Cyprus (N=85)	Greater Poland (N=627)	Malta (N=56)	Monte negro (N=6)	Portugal Central (N=233)	Portugal North (N=385)	Romania-Cluj (N=90)	Romania-Iasi (N=136)	Serbia Central (N=1216)	Slovenia (N=391)	Turkey-Izmir (N=891)	Ukraine (N=6475)	SEE overall (N=11438)	SEER, US (N=13573)
Sex																
Male	56.1	56.6	63.5	55.2	67.9	50.0	54.5	59.5	54.4	46.3	53.9	61.1	56.6	54.6	55.3	57.3
Female	43.9	43.4	36.5	44.8	32.1	50.0	45.5	40.5	45.6	53.7	46.1	38.9	43.4	45.4	44.7	42.7
Age group (years)																
15-19	100.0	12.0	14.1	15.3	10.7	16.7	9.0	10.1	2.2	12.5	14.7	10.2	12.5	13.0	14.7	11.5
20-24	0.0	12.8	14.1	16.4	14.3	16.7	13.7	14.8	11.1	15.4	15.4	12.5	14.2	13.7	13.7	14.5
25-29	0.0	20.1	25.9	21.1	19.7	0.0	21.9	19.2	18.9	14.7	20.7	17.4	17.8	18.7	18.7	20.2
30-34	0.0	25.8	21.2	24.4	33.9	66.6	22.3	23.4	33.3	26.5	23.7	26.4	26.4	24.5	24.2	24.6
35-39	0.0	29.3	24.7	22.8	21.4	0.0	33.1	32.5	34.5	30.9	25.5	33.5	29.1	30.1	28.7	29.2
Diagnostic group[b]																
Astrocytomas																
Specified low-grade astrocytic tumors	10.5	0.2	3.5	18.2	1.8	0.0	6.0	10.4	5.6	5.1	1.1	3.1	4.5	5.2	5.3	6.2
Glioblastoma and anaplastic astocytoma	18.8	23.8	14.1	17.1	23.2	50.0	15.9	19.0	24.4	28.7	21.4	39.6	20.9	24.7	23.6	27.7
Astrocytoma, NOS	15.1	11.8	31.8	9.4	26.8	16.7	19.8	14.3	8.9	12.5	20.4	9.0	14.7	16.6	15.9	14.8
Other glioma	9.6	14.6	16.5	16.3	16.1	0.0	26.2	25.4	11.1	11.7	8.7	22.5	30.2	7.1	11.8	31.6
Ependymoma	8.4	4.8	10.6	7.3	1.8	16.7	6.0	6.5	7.8	2.9	1.1	5.9	9.2	3.0	4.1	7.3
Medulloblastoma and other PNETs																
Medulloblastoma	9.2	2.8	2.3	3.7	5.3	0.0	0.0	3.4	6.7	3.7	1.3	4.1	5.6	2.5	2.9	4.4
Supratentorial PNETs	6.7	2.0	1.2	1.6	0.0	0.0	6.4	1.5	2.2	1.5	1.3	2.8	1.5	1.3	1.7	3.0

Other specified intracranial and intraspinal neoplasms	2.5	8.1	4.7	4.4	1.8	0.0	3.4	2.1	1.1	7.4	4.4	2.0	3.4	5.1	4.7	2.5
Unspecified intracranial and intraspinal neoplasms	19.2	31.9	15.3	22.0	23.2	16.7	16.3	17.4	32.2	26.5	40.3	11.0	10.0	34.6	30.0	2.5

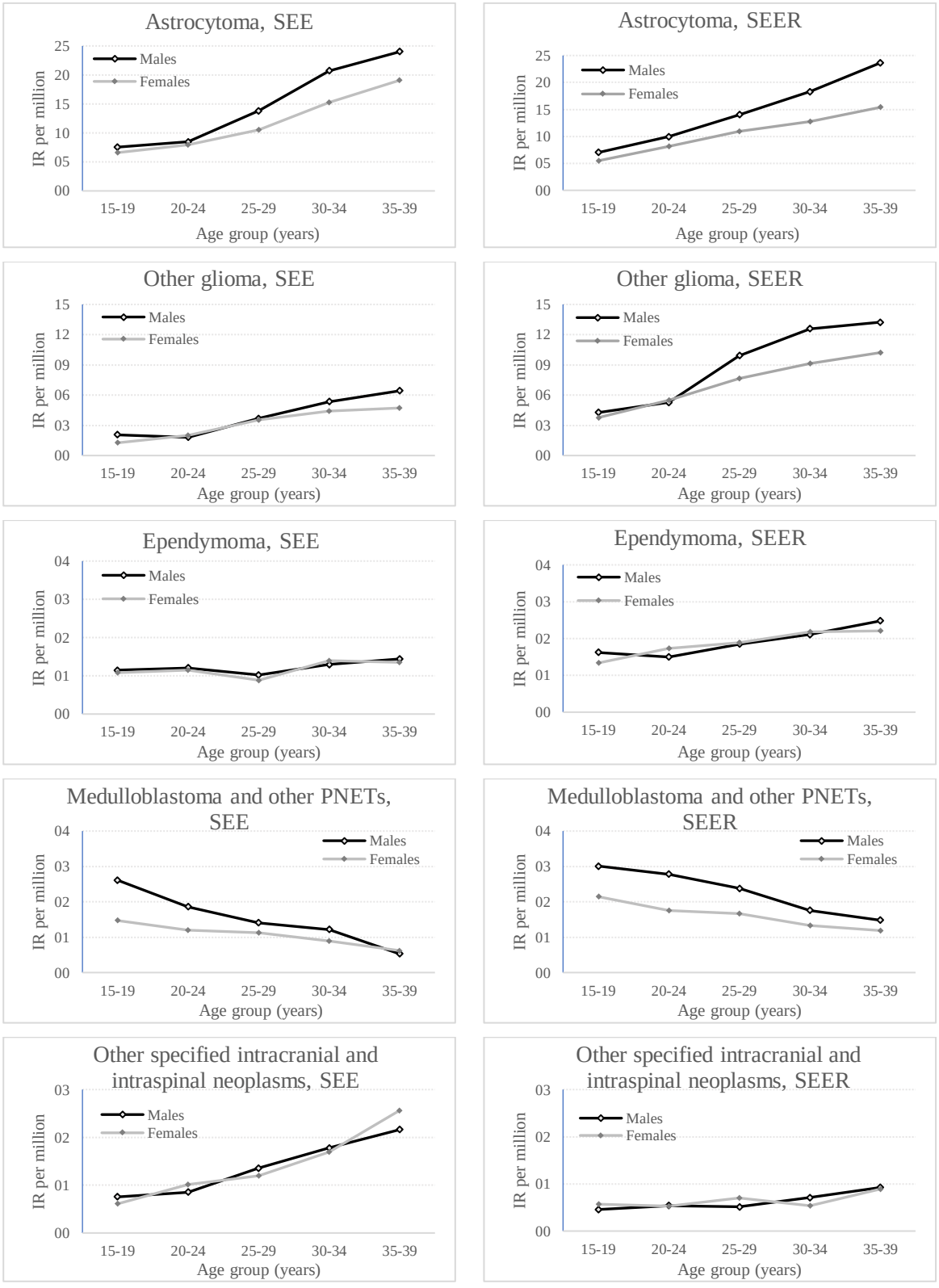
As presented in [235].

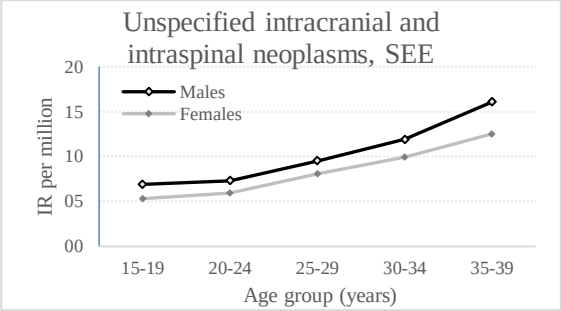
[a] Data for Belarus available only for the age group 15-19 years.

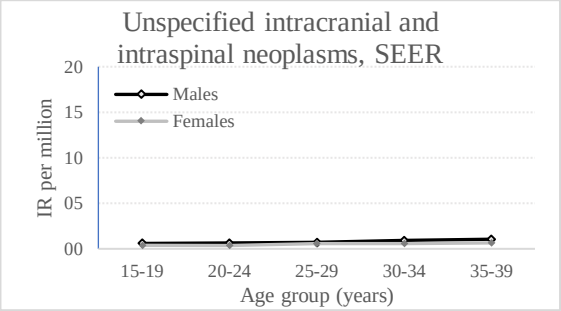
[b] Classification by diagnostic groups according to the classification of cancer in adolescents and young adults proposed by Barr *et al.* [209].

Abbreviations: NOS, not otherwise specified; PNET, primitive neuroectodermal tumors.

Figure 9. Crude incidence rates (IR) per million adolescents and young adults (15-39 years) for malignant central nervous system tumors by age group, sex and diagnostic group in 14 Southern and Eastern European (SEE) cancer registries (left panel) and Surveillance, Epidemiology, and End Results Program (SEER), US (right panel).







As presented in [235].
Abbreviations: PNET, primitive neuroectodermal tumors.

Mortality rates

Table 9 presents the crude and age-adjusted mortality rates of malignant CNS tumors among AYAs and also the respective incidence rates to put mortality rates in context. Specifically, age-adjusted mortality rates ranged from 12.2 (Slovenia) to 18.5 (Greater Poland) deaths per million in the SEE countries, besides Cyprus and Montenegro, where the rates may not be reliable on account of small numbers; overall, the respective rate derived from SEER, US 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-to-female ratio: 1.4-2.0 in SEE countries and 1.5 in the US). Declining mortality trends were generally noted in SEE registries reaching statistical significance in Serbia (1999-2013; APC, -2.4%) and Slovenia (1990-2015; APC, -2.4%) without any significant breaks in trends. An annual decrease in mortality of 1.6% was also evident in the US which was however restricted to the period 1990-2007, followed by a stable rate thereafter (2007-2012).

Table 9. Crude and age-adjusted and mortality rates (CMR, AMR) of malignant central nervous system tumors per million adolescents and young adults (15-39 years), male to female (M:F) ratios and annual percent change (APC; 95% Confidence Intervals, CI) in Southern and Eastern European cancer registries and Surveillance, Epidemiology, and End Results Program (SEER), US.

Registries	Time period	N Deaths	CMR (by age group, years)					AMR (15-39 years)		
			15-19	20-24	25-29	30-34	35-39	Rate	M:F	APC (95% CI)
Belarus[a]	2002-2014	66	7.4	-	-	-	-	-	1	-0.2 (-6.6; 6.7)[a]
Croatia	1995-2013	460	10.2	8.5	12.0	18.8	31.4	15.1	1.4	-0.1 (-1.8; 1.5)
Cyprus	2004-2014	7	0.0	2.7	0.0	4.4	3.2	1.8	2.5	-2.1 (-22.8; 24.2)
Malta	1995-2014	40	7.2	12.0	7.0	25.5	20.2	13.3	2	-0.4 (-5.6; 5.1)
Montenegro[b]	2013	0	0.0	0.0	0.0	0.0	0.0	0.0	-	-

Poland- Greater Poland	1999-2014	404	11.6	10.6	18.5	25.0	33.2	18.5	1.5	-0.9 (-3.0; 1.2)
Portugal Central	1999-2009	105	5.2	7.0	10.9	14.9	19.6	11.9	1.4	0.3 (-5.6; 6.6)
Portugal North	1999-2010	176	9.3	8.1	8.4	15.0	19.5	12.3	1.5	-0.9 (-5.1; 3.5)
Romania-Cluj[c]		-	-	-	-	-	-	-	-	-
Romania-Iasi[c]		-	-	-	-	-	-	-	-	-
Serbia Central	1999-2013	451	8.3	9.4	14.7	22.5	29.4	15.6	1.6	-2.4 (-4.5; -0.3)
Slovenia	1990-2015	255	7.2	8.6	8.3	16.4	25.5	12.2	1.8	-2.4 (-4.0; -0.7)
Turkey- Izmir[c]		-	-	-	-	-	-	-	-	-
Ukraine	2005-2012	2339	9.7	9.8	13.5	24.3	29.8	16.2	1.4	-1.3 (-3.0; 0.5)
SEER, US[d]	1990-2013	25158	5.4	5.7	8.3	12.7	18.4	9.4	1.5	-1.6 (-1.8; -1.4)

As presented in [236].

[a] Belarus availed data only for the age group 15-19 years.

[b] Owing to non-availability of data, no APC has been estimated for Montenegro. Mortality analyses were also not meaningful for Montenegro due to no CNS tumor deaths in the availing period.

[c] Turkey-Izmir and the two Romanian registries were excluded from mortality analysis owing to non-availability of data.

[d] Incidence analysis has been based on the cases registered in the population covered by SEER, whereas the mortality analysis is based on the total US population.

Survival by age, sex, geographical region and diagnostic subtypes

After excluding death certificate only diagnoses, lost to follow-up cases 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 survival analyses. As shown in **Table 10**, the overall 5-year survival of malignant CNS tumors among AYAs was 46% in SEE registries; this unfavorable figure is statistically significantly lower compared to the 67% of SEER (p<0.001). 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 (SEE 5-year survival: 76% vs. SEER:92%), followed by other specified intracranial and intraspinal neoplasms (SEE 5-year survival: 71% vs. SEER: 84%), other glioma (SEE 5-year survival: 63% vs. SEER: 80%) and low-grade astrocytoma (SEE 5-year survival: 59% vs. SEER: 76%). Glioblastoma and anaplastic astrocytoma was by far the tumor with the worst prognosis (SEE 5-year survival: 28% vs. SEER: 37%). Worth noting is the vast disparity between SEE registries and SEER regarding survival in the category of unspecified neoplasms (SEE 5-year survival: 36% vs. SEER: 72%), 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). The 5-year survival ranged between 52% and 65%, but was below 50% in Ukraine (38%) and Slovenia (49%). In cross-country comparisons during the most recent and rather common (last 5 or 10 years) registration periods, improvements in survival noted in the majority of countries led to diminished differences across the largest registries with the exception of a persistent low survival rate in Ukraine influencing the overall SEE performance.

Table 10. Kaplan-Meier-derived overall survival (95% Confidence Intervals, CI) of adolescent and young adults (15-39 years) with malignant central nervous system tumors at 6 months, 1, 2, 3, 5 and 10 years after diagnosis by diagnostic group[a] in 13 Southern and Eastern European (SEE) cancer registries[b] and Surveillance, Epidemiology, and End Results Program (SEER), US.

Diagnostic group	6-month % (95% CI)	1-year % (95% CI)	2-year % (95% CI)	3-year % (95% CI)	5-year % (95% CI)	10-year % (95% CI)
Specified low-grade astrocytic tumors						
SEE	96 (94-98)	91 (88-93)	84 (81-87)	77 (73-80)	59 (54-63)	42 (37-47)
SEER, US	98 (96-98)	96 (94-97)	89 (87-91)	84 (81-86)	76 (72-79)	60 (56-64)
Glioblastoma and anaplastic astrocytoma						
SEE	82 (80-83)	67 (65-69)	48 (46-51)	39 (37-41)	28 (26-30)	16 (15-18)
SEER, US	91 (90-92)	80 (78-81)	59 (57-60)	48 (46-49)	37 (35-39)	27 (25-29)
Astrocytoma, NOS						
SEE	86 (84-88)	81 (78-82)	72 (70-74)	66 (63-68)	55 (52-57)	38 (35-41)
SEER, US	97 (96-98)	94 (93-95)	88 (87-90)	82 (80-84)	72 (69-74)	57 (54-60)
Other glioma						
SEE	94 (92-95)	89 (87-90)	81 (79-83)	75 (72-77)	63 (60-66)	44 (40-48)
SEER, US	98 (98-99)	96 (95-97)	91 (90-92)	87 (86-88)	80 (79-81)	65 (63-67)
Ependymoma						
SEE	93 (90-95)	90 (86-92)	85 (81-88)	80 (76-84)	76 (71-80)	69 (64-74)
SEER, US	99 (98-99)	98 (97-99)	96 (94-97)	95 (93-96)	92 (90-94)	90 (87-92)
Medulloblastoma						
SEE	94 (91-97)	89 (84-92)	79 (73-83)	72 (66-77)	57 (50-63)	43 (36-50)
SEER, US	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)
SEER, US	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)
SEER, US	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)
SEER, US	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)
SEER, US	96 (95-96)	91 (90-91)	81 (81-82)	75 (75-76)	67 (66-68)	56 (54-57)

As presented in [236].

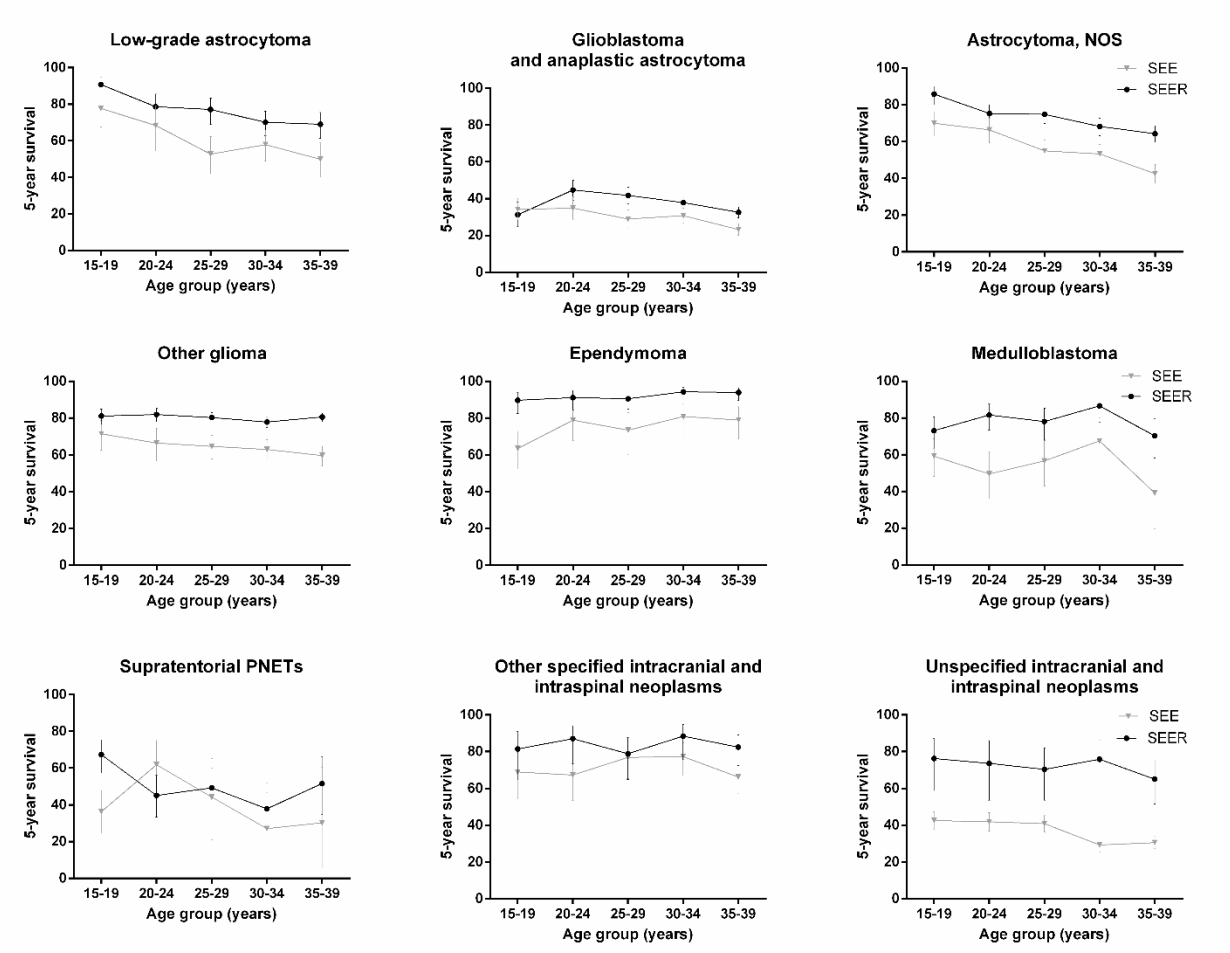
[a] Classification by diagnostic groups according to the classification of cancer in adolescents and young adults proposed by Barr *et al.* [209]

[b] Serbia has been excluded from the survival analysis due to lack of follow-up data for cases diagnosed before 2007. Belarus has been excluded from the overall survival analysis, as the childhood registry availed data only for cases aged 15-19 years.

Abbreviations: NOS, not otherwise specified; PNET, primitive neuroectodermal tumors.

Figure 10 depicts the age-specific 5-year survival rates of the malignant CNS tumors by histological subtype in SEE and SEER. Increasing age was associated with worse outcome in both SEE registries and SEER (p<0.001) for astrocytic tumors (low-grade astrocytoma, glioblastoma and anaplastic astrocytoma, astrocytoma NOS) and other gliomas, and among cases with unspecified neoplasms only in the SEE registries. On the contrary, a trend for higher survival by increasing age group was noted among patients with ependymoma in the SEE registries (p=0.04). Survival differences by sex were also evident. Particularly, female sex was associated with higher survival from astrocytoma NOS and other glioma both in the SEE registries (p=0.003 and 0.03, respectively) and SEER (p<0.001 for both subtypes), but also from low-grade astrocytoma (p<0.001), glioblastoma and anaplastic astrocytoma (p<0.001) and unspecified neoplasms (p=0.01) in SEER, as well as other specified neoplasms in SEE (p=0.008).

Figure 10. Age-specific 5-year overall survival of adolescent and young adults (15-39 years) with malignant central nervous system tumors in 13 Southern and Eastern European (SEE) cancer registries and Surveillance, Epidemiology, and End Results Program (SEER), US by diagnostic group.

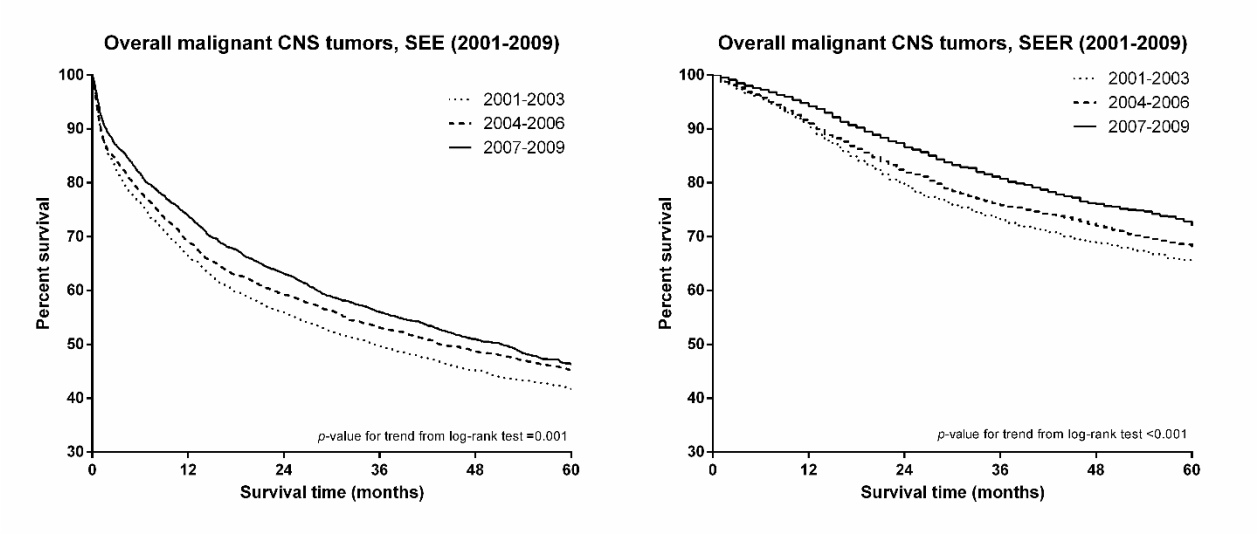


As presented in [236]. Diagnostic classification has been conducted in accordance with Barr *et al.*[209] The error bars correspond to the 95% Confidence Intervals. Serbia Central has been excluded from survival analyses due to non-availability of follow-up data for cases diagnosed before 2007. Belarus has only been included in the 15-19 years' age group analysis.

Temporal trends in survival

Figure 11 depicts Kaplan-Meier derived 5-year survival curves for the periods 2001-2003, 2004-2006 and 2007-2009 in the 9 SEE registries, which contributed data for this period and SEER, US. Improving trends (p<0.001) in survival were recorded in both regions with 5-year survival rates increasing (SEE: 41% to 46%; SEER: 65% to 72%). Low number of cases did not allow further comparisons by diagnostic subtype, as to evaluate whether these improvements pertained to specific histological subtypes.

Figure 11. Kaplan-Meier derived 5-year survival curves for malignant central nervous system (CNS) tumors diagnosed among adolescents and young adults (15-39 years) in 9 Southern-Eastern European (SEE) registries and Surveillance, Epidemiology, and End Results Program (SEER), US during the period 2001-2009 by 3-year time intervals.



As presented in [236].
Registries availing data for the entire 2001-2009 time-period include: Croatia, Cyprus, Malta, Poland-Greater Poland, Portugal Central, Portugal North, Slovenia, Turkey- Izmir, and Ukraine.

Cox regression analysis: prognostic factors

The unadjusted Kaplan-Meir-derived trends were replicated in the multivariable Cox models (**Table 11**), notably diagnosis at older age groups (compared to 15-19 years) and male sex were inversely associated with outcome. All other diagnostic subtypes were associated with worse survival compared to ependymoma, whereas glioblastoma and anaplastic astrocytoma patients and patients diagnosed with supratentorial PNETs were at highest risk of death (7-fold and 5-

fold, respectively, compared to ependymoma). Compared to SEER, significantly increased risk of death was noted for malignant CNS tumors in most SEE registries. Interestingly, CNS tumor patients residing at diagnosis in rural areas, were at a 36% increased risk of death, compared to individuals residing in urban or semi-urban areas.

In stratified by age group (15-19 and 20-39 years) analyses (**Table 11**, right columns) males seemed to have worse outcomes only in the older age group, whereas disparities in survival by histological subtype were generally narrower in the 15-19-years'age group. Particularly, as opposed to older individuals, patients aged 15-19 years with low-grade astrocytoma, astrocytoma NOS, other glioma and other specified intracranial and intraspinal neoplasms were not at increased risk of death, compared to ependymoma.

Similar were the findings when SEE data were analyzed separately from those of SEER. The effect estimates for age groups, histological subtypes and rural residency at diagnosis were identical between the two geographical regions albeit the effect estimate for male sex, was higher in SEER (HR: 1.26, 95% CI: 1.19-1.34 vs. 1.08, 95% CI: 1.02-1.13 in SEE). The analyses by registry, where meaningful, showed similar results for age, histological diagnosis and rural residencies across the registries, whereas the aggravating male effect was statistically significant only in some of the large registries (Croatia, Portugal North, Slovenia and Ukraine), but the effect size was towards the same direction in all of them (data not shown). Restricting the analyses to the last 10 registration years for each registry, as well as to all cases diagnosed after 2000 did not materially change the findings (data not shown).

To identify potential histology-specific determinants of the outcome, the Cox analysis was repeated by histological subtype. Interestingly, male sex was an independent negative predictor of outcome for all astrocytic tumors (low-grade astrocytoma, glioblastoma and anaplastic astrocytoma and astrocytoma NOS), other glioma and other specified intracranial and intraspinal neoplasms, but had no impact for ependymoma, embryonal tumors (medulloblastoma, supratentorial PNETs) and unspecified neoplasms. The negative impact of increasing age was clearly evident for low-grade astrocytoma, astrocytoma NOS and unspecified neoplasms, although more prominent in the former (HR for ages 35-39, compared to 15-19 years: 3.16, 95% CI: 2.24-4.46). In glioblastoma and anaplastic astrocytoma patients, although no trend effect was evident, subjects in the oldest group (35-39 years) were also at increased risk of death (HR: 1.21, 95% CI: 1.08-1.37). Similarly, compared to the 15-19 years, diagnosis of supratentorial PNETs at 30-34 years was also associated with a higher risk of death. Conversely, increasing age seemed to have a positive effect on ependymoma outcome; ependymoma patients diagnosed at 30-34 and 34-39 years of age were at almost half the risk of death, compared to 15-19-year individuals (HR: 0.51, 95% CI: 0.33-0.78 and HR: 0.58, 95% CI: 0.39-0.89).

Table 11. Cox proportional-hazard modeling-derived hazard ratios (HR) for death and 95% confidence intervals (CI) among adolescents and young adults (15-39 years) with malignant central nervous system tumors in 13 Southern and Eastern European registries[a] and Surveillance, Epidemiology, and End Results Program (SEER), US, by study variables.

	All AYAs-15-39 years (N=22,856)					***Adolescents 15-19 years (N= 2,999)***					***Young adults 20-39 years (N= 20,086)***				
Variable	**% Deaths**	**HR**	**95% CI**		***p*-value**	**% Deaths**	**HR**	**95% CI**		***p*-value**	**% Deaths**	**HR**	**95% CI**		***p*-value**
Age group (years)															
15-19	35.6	*Reference*										n/a			
20-24	39.1	1.15	1.06	1.25	0.001						39.1	*Reference*			
25-29	43.1	1.29	1.19	1.39	<0.001						43.1	1.12	1.04	1.20	0.002
30-34	45.2	1.40	1.30	1.50	<0.001						45.2	1.22	1.14	1.31	<0.001
35-39	51.3	1.57	1.46	1.69	<0.001						51.3	1.38	1.29	1.47	<0.001
Sex															
Male	46.9	1.15	1.10	1.20	<0.001	37.5	0.94	0.83	1.06	0.31	48.4	1.17	1.12	1.22	<0.001
Female	41.5	*Reference*				36.2	*Reference*				42.4	*Reference*			
Diagnostic period															
5 year-increment		0.92	0.90	0.94	<0.001		0.92	0.86	0.97	0.005		0.92	0.90	0.94	<0.001
Diagnostic group[b]															
Astrocytomas															
Specified low-grade astrocytic tumors	36.5	2.66	2.25	3.14	<0.001	19.2	0.75	0.50	1.13	0.17	39.4	3.26	2.72	3.92	<0.001
Glioblastoma and anaplastic astocytoma	63.0	6.61	5.72	7.64	<0.001	61.5	3.72	2.77	4.99	<0.001	63.2	7.51	6.37	8.84	<0.001
Astrocytoma, NOS	42.2	3.00	2.59	3.49	<0.001	23.0	0.92	0.66	1.29	0.65	44.9	3.62	3.06	4.29	<0.001
Other glioma	31.5	2.38	2.05	2.76	<0.001	22.7	1.11	0.80	1.53	0.54	32.3	2.74	2.31	3.24	<0.001
Ependymoma	14.0	*Reference*				21.3	*Reference*				12.8	*Reference*			
Medulloblastoma and other PNETs															
Medulloblastoma	31.6	2.49	2.07	3.00	<0.001	34.5	1.61	1.14	2.29	0.008	31.6	2.68	2.17	3.31	<0.001
Supratentorial PNETs	48.0	5.13	4.27	6.18	<0.001	43.9	2.29	1.62	3.23	<0.001	51.2	6.29	5.08	7.79	<0.001
Other specified intracranial and intraspinal neoplasms	25.2	1.65	1.38	2.02	<0.001	29.0	1.24	0.79	1.94	0.35	24.7	1.79	1.44	2.23	<0.001

Unspecified intracranial and intraspinal neoplasms	60.3	5.46	4.70	6.34	<0.001	54.6	2.73	2.01	3.71	<0.001	61.8	6.39	5.40	7.58	<0.001
Registry															
Belarus[c]		n/a				52.2	1.84	1.49	2.27	<0.001		n/a			
Croatia	41.9	1.03	0.90	1.18	0.68	35.7	0.98	0.65	1.49	0.94	42.7	1.03	0.89	1.19	0.70
Cyprus	52.0	2.14	1.56	2.94	<0.001	63.6	2.89	1.36	6.10	0.006	50.0	2.03	1.43	2.88	<0.001
Malta	58.2	1.45	1.02	2.06	0.04	66.7	2.33	0.86	6.27	0.09	57.1	1.33	0.92	1.94	0.13
Montenegro	16.7	0.53	0.08	3.77	0.53		n/a				20.0	0.67	0.09	4.77	0.69
Poland- Greater Poland	37.2	1.07	0.94	1.23	0.32	30.2	1.02	0.69	1.49	0.93	38.5	1.07	0.92	1.23	0.38
Portugal Central	56.5	1.30	1.09	1.55	0.003	52.4	1.72	0.94	3.16	0.08	58.9	1.26	1.05	1.51	0.01
Portugal North	55.9	1.56	1.36	1.80	<0.001	55.3	1.91	1.23	2.98	0.004	56.0	1.51	1.30	1.75	<0.001
Romania- Cluj	31.7	0.90	0.61	1.34	0.60		n/a				32.5	0.93	0.63	1.38	0.72
Romania- Iasi	15.7	0.76	0.48	1.22	0.26	18.8	0.85	0.27	2.66	0.78	15.2	0.73	0.44	1.22	0.23
Slovenia	65.2	1.49	1.31	1.69	<0.001	50.0	1.68	1.07	2.64	0.02	67.0	1.49	1.31	1.70	<0.001
Turkey- Izmir	37.4	1.29	1.15	1.45	<0.001	29.1	1.22	0.85	1.76	0.28	38.6	1.31	1.16	1.48	<0.001
Ukraine	62.5	2.34	2.23	2.46	<0.001	53.5	2.19	1.88	2.56	<0.001	63.9	2.35	2.23	2.48	<0.001
SEER	35.7	*Reference*				25.3	*Reference*				37.1	*Reference*			
Alternatively introduced to the "registry" variable															
Place of residence[c]															
Rural	56.1	1.36	1.30	1.43	<0.001	50.3	1.45	1.26	1.67	<0.001	57.2	1.35	1.28	1.43	<0.001
Urban/Semi-urban	42.8	*Reference*				34.4	*Reference*				44.1	*Reference*			

As presented in [236].

[a] Serbia has been excluded from survival analyses due to non-availability of follow-up data for cases diagnosed before 2007.

[b] Classification by diagnostic groups according to the classification of cancer in adolescents and young adults proposed by Barr *et al.,* [209].

[c] Belarus has been included in the analysis of only the 15-19 years' age group.

[d] After excluding cases with unknown place of residence: *N*=21,291 in total dataset analysis; *N*=2,810 in the 15-19-years age group analysis; *N*= 18,713 in 20-39-years age group analysis.

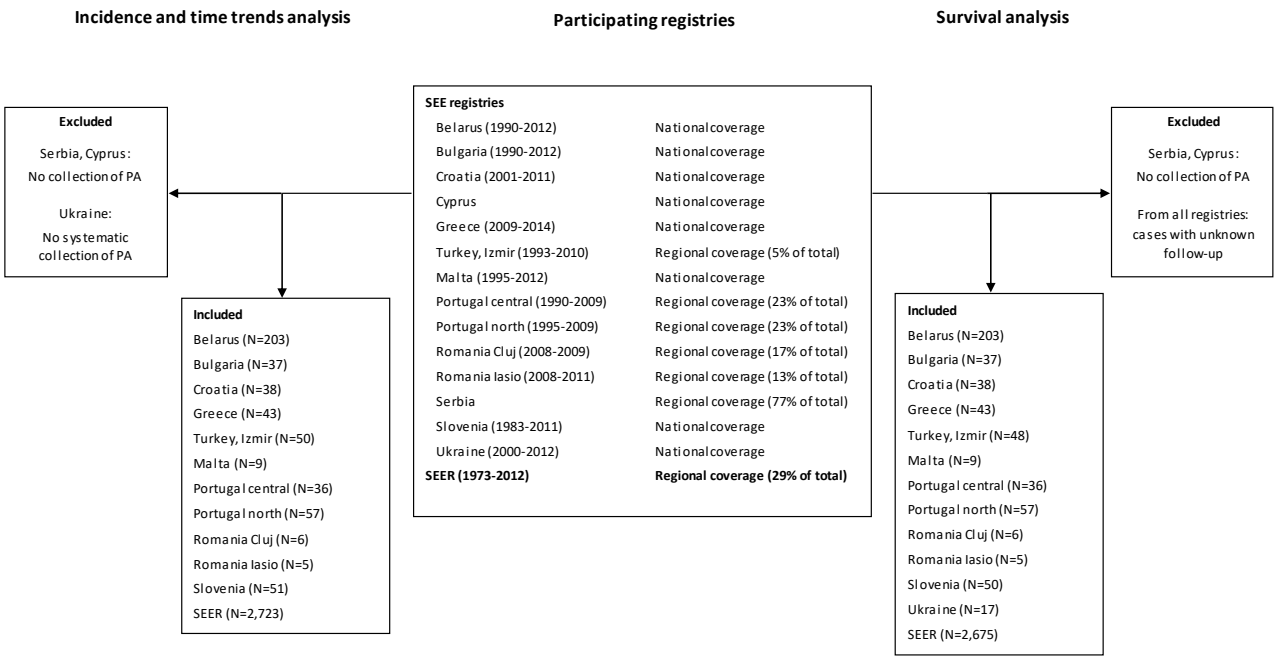
Abbreviations: NOS, not otherwise specified; PNET, primitive neuroectodermal tumors.

Study #3: Incidence and survival patterns of childhood pilocytic astrocytomas in Southern-Eastern Europe and the US

Descriptive registry characteristics

SEE registries amounted 552 cases of pilocytic astrocytoma (1983-2014), whereas 2,723 pilocytic astrocytoma cases were derived from the SEER database (1973-2012). Out of the 12 SEE registries, 7 have nationwide coverage, whereas SEER covers 29% of childhood US population. No death certificate only cases were identified in SEE and only 1 in SEER and morphologically verified (MVs) cases comprised 97% of the total in both areas. pilocytic astrocytoma represented 41.5% of astrocytomas in SEE and 55.0% in SEER, accounting for 19.0% and 25.2% of all childhood CNS tumors, respectively. By contrast, astrocytomas NOS cases represented 22.6% of astrocytomas among SEE, with significant cross-registry disparities and 29.7% in SEER. The vast majority of cases (98%) were followed-up and therefore included in the survival analysis; mean follow-up duration was 8.8 years. Details on the registries included in each analysis are presented in **Figure 12**.

Figure 12. Flow diagram of the inclusion of participating registries in the analyses



As presented in [201].
Abbreviations: SEE, Southern and Eastern European; SEER, Surveillance, Epidemiology, and End Results.

Incidence rates and time trends

The combined AIR of pilocytic astrocytoma (**Table 12**) in SEE in 1990-2012 was 4.2/10^6 children increasing to 5.1/10^6 during the most recent 2000-2012 period. In SEER, pilocytic astrocytoma incidence was 7.1/10^6 during the entire 1973-2012 registration period and twice as high (8.4/10^6) compared to SEE during 1990-2012. Statistically significant increasing trends were recorded in both areas (annually, SEE: +4.1%, 1990-2012; SEER: +4.6%, 1973-2012); yet, the Joinpoint analysis revealed time-points when the rapid increase in incidence was smoothed. In particular, in SEER the 11.1% annual increase until 1995 was followed by a smaller increase of 1.3%, whereas in SEE registries a break in 1997 was noted, when the pronounced until then, annual rise of 17.8% was substituted by a non-significant 1.1% increasing pattern. Examination of the temporal trends in pilocytic astrocytoma as compared to those of astrocytoma NOS revealed mirror temporal patterns in SEER (PA: +4.6%, astrocytomas NOS: -4.3%). On the other hand, the pilocytic astrocytoma increase in SEER was accompanied by a rather stable incidence of astrocytomas NOS.

Demographic and clinical characteristics

PA cases were evenly distributed by age group and sex (male-to-female ratio: 1.02; **Table 13**); compared to SEE, however, age at diagnosis was lower in SEER (6.8 vs. 7.7 years, $p<0.001$). Regarding tumor topography, pilocytic astrocytoma were most commonly (36.5%) located in cerebellum, followed by supratentorial locations (21.8%). Brainstem pilocytic astrocytoma represented 10.9%, whereas tumors of the optic nerve and the spinal cord accounted for <10% of cases. Brain pilocytic astrocytoma of overlapping locations were more common in SEE. A differential topography pattern, however, emerged for infants (**Figure 13**); particularly, a lower proportion of cerebellar (7.4%) and brainstem (5.5%) tumors was observed, as opposed to the preponderance of supratentorial (31.5%) and optic nerve tumors (20.4%); brain pilocytic astrocytoma of unspecified topography were also more common in infants (30.2%). No sex differences in tumor topography were noted ($p=0.82$).

Table 12. Age-adjusted incidence rates (AIR) and crude age-specific incidence rates (CIR) per million children, as well as annual percent change (APC) and 95% Confidence Intervals (CI) for childhood (0-14 years) pilocytic astrocytomas overall and by age in 11 participating Southern and Eastern European (SEE)[a] registries and the Surveillance, Epidemiology, and End Results (SEER), US.

Registry	N	Pilocytic astrocytomas[b] (0-14 years)			Pilocytic astrocytomas[b] (0-4 years)			Pilocytic astrocytomas[b] (5-9 years)			Pilocytic astrocytomas[b] (10-14 years)		
		AIR	APC (95% CIs)	p-value	CIR	APC (95% CIs)	p-value	CIR	APC (95% CIs)	p-value	CIR	APC (95% CIs)	p-value
Belarus (1990-2012)	203	4.9	+5.0 (2.8, 7.2)	<0.001	4.5	+5.5 (1.3, 9.3)	<0.001	5.2	+4.2 (0.6, 8.0)	0.02	4.9	+5.7 (2.0, 9.5)	0.002
Bulgaria (1990-2012)	37	1.3	+17.4 (10.7, 24.6)	<0.001	1.0	+16.1 (3.0, 30.8)	0.01	1.8	+18.8 (8.7, 29.9)	<0.001	1.0	+16.6 (4.9, 29.6)	0.004
Croatia (2001-2011)	38	5.1	+2.6 (-7.4, 13.7)	0.63	6.7	+0.3 (-13.7, 16.7)	0.97	3.2	+12.8 (-10.4, 41.8)	0.31	5.1	+3.3 (-12.3, 21.7)	0.70
Greece (2009-2014)	43	4.6	+1.6 (-14.8, 21.0)	0.86	6.7	+5.6 (-17.5, 35.2)	0.67	4.7	-1.3 (-26.5, 32.7)	0.93	1.9	-5.1 (-40.6, 51.8)	0.83
Turkey, Izmir (1993-2010)	50	3.6	+9.2 (3.1, 15.6)	<0.001	2.8	+3.6 (-7.2-15.8)	0.53	4.4	+11.3 (1.4, 22.3)	0.025	3.6	+11.1 (0.8, 22.5)	0.03
Malta[d] (1995-2012)	9	8.2	--	--	13.8	--	--	4.9	--	--	4.5	--	--
Portugal central (1990-2009)	36	4.8	+0.4 (-5.1, 6.2)	0.88	5.0	+0.6 (-7.8, 9.8)	0.89	3.9	-3.5 (-13.4, 7.5)	0.5	3.9	+3.7 (-6.3, 14.7)	0.48
Portugal north (1995-2009)	57	6.7	-0.2 (-6.0, 6.0)	0.96	5.2	-2.6 (-13.3, 9.3)	0.65	7.1	+4.6 (-5.6, 15.9)	0.4	7.1	+2.6 (-11.8, 7.5)	0.60
Romania Cluz[d] (2008-2009)	6	4.3	--	--	2.4	--	--	4.5	--	--	6.6	--	--
Romania,Iasio[d] (2008-2011)	5	2.9	--	--	3.6	--	--	0.0	--	--	5.2	--	--
Slovenia (1983-2011)	51	4.7	+3.6 (0.3, 7.1)	0.03	1.9	+2.2 (-5.7, 10.6)	0.60	6.5	+6.3 (1.0, 11.9)	0.02	5.7	+1.7 (-3.4, 7.2)	0.52
SEE[d](1990-2012)	515	4.2	+4.1 (2.7, 5.5)	<0.001	4.1	+3.9 (1.4, 6.5)	0.002	4.2	+4.5 (2.1, 6.9)	<0.001	3.8	+3.9 (1.5, 6.3)	0.001
SEE[d] (2000-2012)	355	5.1	+1.1 (-1.7, 4.0)	0.43	5.2	+1.5 (-3.6, 6.9)	0.57	5.3	+1.3 (-3.4, 6.3)	0.59	4.6	+0.6 (-4.1, 5.6)	0.81
SEER (1973-2012)	2723	7.1	+4.6 (4.2, 5.1)	<0.001	7.5	+4.7 (4.0, 5.5)	<0.001	7.3	+4.5 (3.7, 5.3)	<0.001	6.4	+4.7 (3.9, 5.5)	<0.001
SEER (1990-2012)	2554	8.4	+2.1 (1.4, 2.8)	<0.001	8.8	+2.6 (1.5, 3.8)	<0.001	8.6	+2.1 (1.0, 3.3)	<0.001	7.7	+1.4 (0.2, 2.6)	0.02
SEER (2000-2012)	2039	9.1	+0.6 (-0.6, 1.8)	0.32	9.8	-0.8 (-2.6, 1.3)	0.49	9.2	+1.2 (-0.8, 3.2)	0.24	8.0	+1.3 (-0.8, 3.5)	0.21

As presented in [201].

[a]Ukraine was not included in incidence and time trends analysis due to not systematic registration of pilocytic astrocytomas. Serbia and Cyprus were not included in this analysis as they did not avail data on pilocytic astrocytomas

[b] International classification of diseases in Oncology (ICD-O-3) coding: 9421

[c] ICD-O-3 coding: 9400 (Astrocytomas, not otherwise specified; NOS)

[d]APC was not calculated for Malta and the 2 Romanian registries, due to the small number of cases and limited available study periods.

Table 13. Distribution of demographic characteristics, histological subtype and topography of childhood (0-14 years) pilocytic astrocytomas in the 12 participating registries in Southern and Eastern Europe (SEE)[a] and the Surveillance, Epidemiology, and End Results (SEER), US.

Variables	Total	SEE	SEER	
	N (%)	N (%)	N (%)	p-value
Age at diagnosis				0.009[b]
<1 year	108 (3.3)	12 (2.2)	96 (3.5)	
1-4 years	1016 (31.0)	154 (27.9)	862 (31.7)	
5-9 years	1120 (34.2)	193 (35.0)	927 (34.0)	
10-14 years	1031 (31.5)	193 (35.0)	838 (30.8)	
Sex				0.82[b]
Male	1658 (50.6)	277 (50.2)	1658 (50.6)	
Female	1617 (49.4)	275 (49.8)	1617 (49.4)	
Topography				
Supratentorial	713 (21.8)	113 (20.5)	600 (22.0)	0.42[b]
Frontal lobe	67 (9.4)	9 (8.0)	58 (9.7)	
Temporal lobe	105 (14.7)	15 (13.3)	90 (15.0)	
Parietal lobe	50 (7.0)	13 (11.5)	37 (6.2)	
Occipital lobe	24 (3.4)	4 (3.5)	20 (3.3)	
Ventricle	159 (22.3)	29 (25.7)	130 (21.7)	
Cerebrum	302 (42.4)	42 (37.2)	260 (43.3)	
Pineal gland	6 (0.8)	1 (0.9)	5 (0.8)	
Cerebellum	1196 (36.5)	194 (35.1)	1002 (36.8)	0.46[b]
Brainstem	358 (10.9)	45 (8.2)	313 (11.5)	0.02[b]
Spinal cord	116 (3.5)	12 (2.2)	104 (3.8)	0.06[b]
Optic nerve	185 (5.8)	34 (6.2)	152 (5.6)	0.59[b]
Brain overlapping	141 (4.3)	45 (8.2)	96 (3.5)	<0.001[b]
NOS topography	565 (17.3)	109 (19.8)	456 (16.8)	0.09[b]

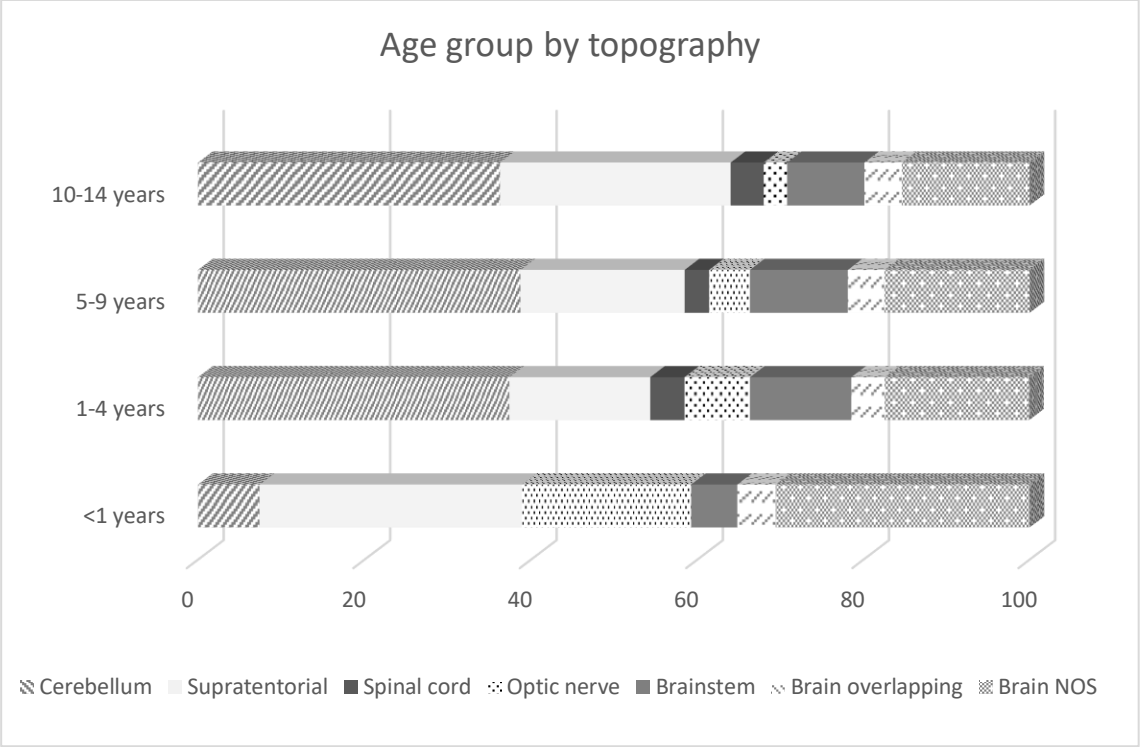
As presented in [201].

[a] Serbia and Cyprus: not included in the analysis due to non-pilocytic astrocytomas data availability

[b] p-value derived from chi-square test

[c] p-value derived from two-tailed t-test.

Figure 13. Distribution of topography of childhood (0-14 years) pilocytic astrocytomas by age group in 12 participating registries of Southern and Eastern Europe (SEE) and the Surveillance, Epidemiology, and End Results (SEER), US.

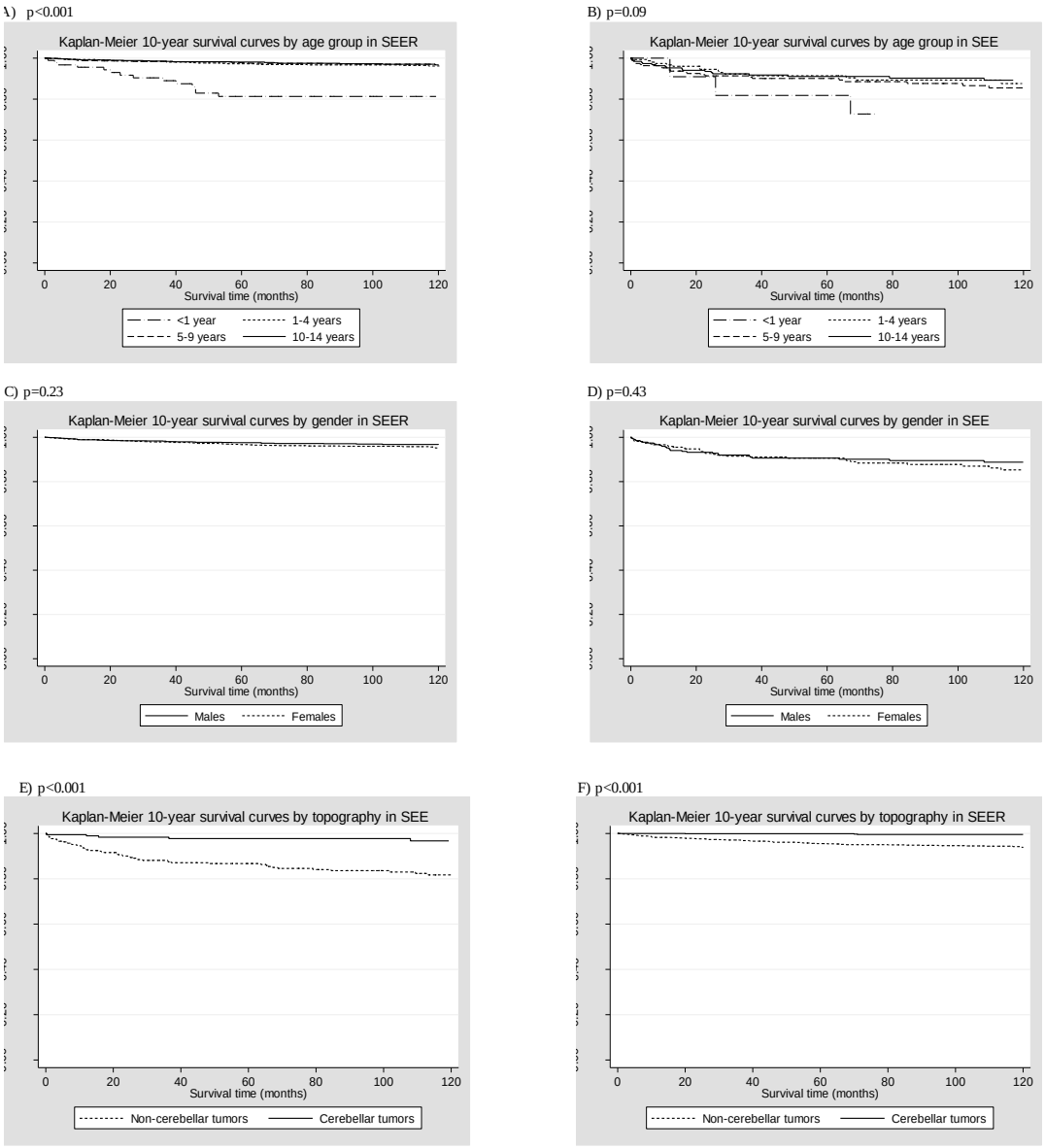


As presented in [201].
Abbreviations: NOS, not otherwise specified.

Survival analysis

Regarding survival, although cumulative 10-year survival approached 95% reflecting the rather curable nature of pilocytic astrocytoma, significant disparities between SEE and SEER were noted with the former presenting poorer outcomes (10-year survival 87% vs. 96%, $p<0.001$). Among SEE registries, only Belarus had a 10-year survival >90%, whereas the highest 5-year survival (95.4%) was recorded in Greece, which, however, availed data only for the most recent registration period (2009-2014). Pilocytic astrocytoma showed significantly lower survival among infants in SEER ($p<0.001$; **Figure 14A**), as well as a marginally lower survival in SEE (p=0.09; **Figure 14B**), whereas no significant difference was found by sex (**Figures 14C-6D**). Tumors in cerebellum had an excellent 10-year survival (99%), which was significantly higher than non-cerebellar pilocytic astrocytoma ($p<0.001$; **Figures 14E-6F**). Improvements over registration periods in survival were present for both SEE and SEER. In SEER the improvement in 5-year survival was limited to a period until 1990, being stably >95% thereafter. Conversely, 5-year survival in SEE registries showed a significant increase from <80% before 1995, to 94% in latest registration years. Improvements were restricted to non-cerebellar tumors.

Figure 14. Kaplan-Meier 10-year survival curves of childhood (0-14 years) pilocytic astrocytomas in 12 registries of Southern and Eastern Europe (SEE) and the Surveillance, Epidemiology, and End Results (SEER), US by (A-B) age group, (C-D) sex. and (E-F) topography.



As presented in [201].

In the multivariable Cox regression analysis (**Table 14**), age at diagnosis<1 year, compared to 10-14 years (HR: 3.96, 95%CI: 2.28-6.90) and female sex (HR: 1.38, 95%CI: 1.01-1.88) were associated with higher risk of death. Any tumor location other than cerebellum, was associated with considerably worse outcome (9- to 12-fold higher risk of death). Children diagnosed in SEE, compared to the US, had a significantly 4-fold higher risk of death. Irrespective of country, however, rural residence was associated with worse outcome. The effects were similar in SEE and SEER. Restricting analyses to cases diagnosed after 1990 or after 2000, did not materially change the results, neither did stratification by SEE/SEER or exclusion of the Ukrainian data.

Table 14. Death Cox proportional-hazard modeling-derived Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) among children (0-14 years) with pilocytic astrocytoma in the 12 participating registries in Southern and Eastern Europe (SEE)[a] and Surveillance, Epidemiology, and End Results (SEER), US by study variables.

Variables [b]	Total dataset (N=3,224)				SEE data (N=549)				SEER data (N=2,675)			
	Deaths (%)	HR	95% CI	p-value	Deaths (%)	HR	95% CI	p-value	Deaths (%)	HR	95% CI	p-value
Age at diagnosis												
<1 year	18.6	3.96	2.28-6.90	<0.001	36.4	2.18	0.73-6.52	0.16	16.5	6.31	3.21-12.40	<0.001
1-4 years	4.9	1.26	0.83-1.91	0.28	9.8	0.98	0.50-1.94	0.95	4.0	1.62	0.94-2.78	0.08
5-9 years	4.9	1.26	0.84-1.89	0.27	14.5	1.52	0.85-2.71	0.16	2.9	1.16	0.65-2.05	0.62
10-14 years	4.1	reference			10.4	reference			2.7	reference		
Sex												
Male	4.5	reference			11.2	reference			3.1	reference		
Female	5.7	1.38	1.01-1.88	0.04	13.2	1.28	0.79-2.09	0.31	4.2	1.42	0.95-2.13	0.09
Diagnostic period (5-year increment)	5.1	0.78	0.67-0.89	<0.001	12.2	0.76	0.61-0.95	0.02	3.6	0.76	0.63-0.91	0.004
Topography												
Cerebellum	0.7	reference			2.6	reference			0.3	reference		
Supratentorial	8.5	12.13	5.78-25.4	<0.001	19.6	8.75	3.31-23.1	<0.001	6.4	18.82	5.78-61.3	<0.001
Brainstem	8.2	12.86	5.88-28.1	<0.001	20.0	11.11	3.71-33.3	<0.001	6.5	21.36	6.34-71.9	<0.001
Spinal cord	7.0	11.42	4.28-30.4	<0.001	16.7	6.82	1.32-35.3	0.02	5.9	20.95	5.23-83.9	<0.001
Optic nerve	6.0	9.37	3.73-23.5	<0.001	17.7	6.17	1.86-20.4	0.004	3.4	11.22	2.63-47.8	0.001
Brain overlapping	6.5	8.70	3.35-22.5	<0.001	9.1	3.31	0.89-12.3	0.07	5.4	15.28	3.65-64.0	<0.001
NOS topography	7.1	9.97	4.64-21.4	<0.001	17.2	7.43	2.75-20.1	<0.001	4.5	13.21	3.91-44.7	<0.001
Geographical region [c]												
SEER	3.6	reference			n/a				n/a			
SEE	12.2	4.07	2.95-5.61	<0.001								
Place of residence [c]												
Urban	4.4	reference			11.6	reference			3.3	reference		
Rural	10.3	2.23	1.53-3.27	<0.001	14.6	1.23	0.71-2.12	0.46	7.4	2.01	1.15-3.51	0.01

As presented in [201].

[a] Serbia and Cyprus were not included in this analysis as they did not avail data on pilocytic astrocytomas

[b] Core model includes age, sex, diagnostic period and topography

[c] Geographic region and place of residence were interchangeably additionally introduced in the core model

B. Meta-analytical approaches in analytical epidemiology of primary central nervous system tumors: original data analyses and meta-analyses to explore perinatal and early-life risk factors

Study #4: Risk factors for childhood central nervous system tumors in a nationwide Greek case-control study

A total of 203 childhood CNS tumor cases and 406 age-, sex-, and center-matched controls were included in this study. The majority of the tumors (74%) were of malignant behavior. Intracranial/intraspinal embryonal tumors (ICCC-3 IIIc) and astrocytomas (ICCC-3 IIIb) were the most common diagnostic subtypes corresponding to 34% and 31% of the total CNS tumors, respectively. Ependymomas (ICCC-3 IIIa), other specified tumors (ICCC-3 IIIe), and other gliomas (ICCC-3 IIId) represented 12%, 10% and 7% of the cases, respectively, whereas tumors of unspecified histology were only 4% of the cases.

Table 15 presents the distribution of the potential risk factors by case-control status. In the crude comparisons, instrument-assisted delivery, maternal alcohol consumption during pregnancy, and history of living in a farm were more common among childhood CNS tumor cases, as compared to controls. On the contrary, increasing maternal age at birth and increasing birth order were inversely associated with CNS tumors. Maternal education, birth weight, gestational age at birth, size for gestational age, paternal age at birth, visit to a fertility specialist before pregnancy, history of infection in the first two weeks of life, sibship size, age at kindergarten enrollment, maternal smoking in the peripartum period, presence of a pet animal in house, history of allergic diseases, and hypertension or gestational diabetes during pregnancy were not associated with CNS tumors.

Table 15. Distributions of cases with childhood central nervous system (CNS) tumors and controls by study variables.

Variables	Cases (N=203)		Controls (N=406)		p-value[a]
	N	%	N	%	
Age (y)					matching
0-4	91	44.8	174	42.9	
5-9	58	28.6	120	29.6	
10-14	54	26.6	112	27.6	
Index child's sex					matching
Male	112	55.2	224	55.2	
Female	91	44.8	182	44.8	
Maternal education					0.15
High school or lower	107	52.7	215	53.0	
Technical school/ University or higher	94	46.3	169	41.7	

Missing	2	1.0	22	5.4	
Birth weight (g)					0.10
<2500	12	5.9	41	10.1	
2500-3999	176	86.7	338	83.3	
≥4000	9	4.4	17	4.2	
Missing	6	3.0	10	2.5	
Gestational age at birth					0.08
Pre-term	17	8.4	51	12.6	
Full-term	184	90.6	332	82.0	
Post-term	2	1.0	4	1.0	
Missing	0	0	18	4.4	
Size for gestational age					0.19
SGA	12	5.9	42	10.3	
AGA	158	77.8	301	74.1	
LGA	27	13.3	58	14.3	
Missing	6	3.0	5	1.2	
Maternal age at birth (years)					0.011
<25	40	19.7	60	14.8	
25-29	63	31.0	110	27.1	
30-34	63	31.0	134	33.0	
35-39	27	13.3	71	17.5	
≥40	4	2.0	19	4.5	
Missing	6	3.0	12	3.0	
Paternal age at birth (years)					0.34
<25	14	6.9	29	7.1	
25-29	34	16.8	55	13.6	
30-34	65	32.0	128	31.5	
35-39	50	24.6	100	24.6	
≥40	31	15.3	75	18.5	
Missing	9	4.4	19	4.7	
Delivery mode					<0.0001
Spontaneous vaginal delivery	104	51.2	194	47.8	
Instrument-assisted vaginal delivery	14	6.9	3	0.7	
Caesarean section	82	40.4	205	50.5	
Missing	3	1.5	4	1.0	
Fertility specialist visit before pregnancy					0.09
Yes	17	8.4	19	4.7	
No	182	89.7	362	89.2	
Missing	4	2.0	25	6.2	
Infection in first two weeks					0.99
Yes	3	1.5	6	1.5	
No	197	97.0	394	97.0	
Missing	3	1.5	6	1.5	
Sibship size					0.26
1	54	26.6	98	24.1	
2	101	49.8	197	48.5	
≥3	48	23.7	111	27.3	
Missing	0	0.0	0	0.0	
Birth order					0.002
1	120	59.1	193	47.5	
2	64	31.5	144	35.5	

≥3	19	9.4	69	17.0	
Missing	0	0.0	0	0.0	
Child's age at kindergarten enrollment (y)					0.34
≤1.5	13	6.4	36	8.9	
>1.5	176	86.7	353	86.9	
Missing	14	6.9	17	4.2	
Alcohol consumption 3 months before, during, or 3 months after pregnancy					0.0002
Yes	50	24.6	46	11.3	
No	150	73.9	320	78.8	
Missing	3	1.5	40	9.9	
Smoking 3 months before, during, or 3 months after pregnancy					0.92
Yes	75	37.0	151	37.2	
No	121	59.6	244	60.1	
Missing	7	3.5	11	2.7	
History of living in a farm					0.0005
Yes	34	16.8	27	6.6	
No	168	82.8	341	84.0	
Missing	1	0.5	38	9.4	
Pet animals in house					0.35
Yes	46	22.7	106	26.1	
No	156	76.9	297	73.2	
Missing	1	0.5	3	0.7	
History of allergic diseases					0.11
Yes	49	24.1	72	17.7	
No	150	73.9	327	80.5	
Missing	4	2.0	7	1.7	
Hypertension in pregnancy					0.50
Yes	7	3.5	10	2.5	
No	195	96.1	391	96.3	
Missing	1	0.5	5	1.2	
Gestational diabetes					0.62
Yes	11	5.4	26	6.4	
No	191	94.1	375	92.4	
Missing	1	0.5	5	1.2	

As presented in [237].
[a] p-values were derived from Chi-square test.
Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

The multivariable analysis (**Table 16**) revealed bidirectional associations for mode of delivery, with instrument-assisted delivery increasing (OR: 7.82, 95%CI: 2.18-28.03) and caesarean delivery marginally decreasing (OR: 0.67, 95%CI: 0.45-0.99) odds for CNS tumors, as compared to spontaneous vaginal delivery. The analysis also showed a higher birth order to be associated with a lower risk for childhood CNS tumors in a dose-response pattern. Alcohol consumption during pregnancy and history of living in a farm were associated with 2-fold and 5-fold increased odds for childhood CNS tumors, respectively.

Table 16. Multivariable associations of study variables with the risk of childhood (0-14 years) central nervous system (CNS) tumors.

Variables[a]	Total CNS tumors (N=203)			Astrocytomas (N=63)			Embryonal tumors (N=70)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Birth weight (500-gr increment)	1.15	0.92-1.44	0.23	1.23	0.70-2.18	0.47	0.96	0.67-1.37	0.81
Gestational age (1-week increment)	1.04	0.91-1.19	0.58	0.93	0.65-1.32	0.66	1.08	0.87-1.34	0.50
Size for gestational age									
SGA	0.52	0.24-1.13	0.10	0.51	0.12-2.26	0.37	0.52	0.14-1.89	0.32
AGA	Ref			Ref			Ref		
LGA	0.78	0.42-1.44	0.43	0.67	0.12-3.61	0.64	0.49	0.18-1.35	0.17
Maternal age at birth (5-yr increment)	0.86	0.70-1.05	0.13	0.81	0.54-1.19	0.28	0.98	0.73-1.32	0.89
Delivery mode									
Spontaneous vaginal delivery	Ref			Ref			Ref		
Instrument-assisted vaginal delivery	7.82	2.18-28.03	0.002	5.40	0.99-30.29	0.05	n/a		
Caesarean section	0.67	0.45-0.99	0.04	0.58	0.26-1.30	0.19	0.62	0.31-1.24	0.17
Birth order									
1	Ref			Ref			Ref		
2	0.60	0.40-0.89	0.01	0.57	0.28-1.18	0.13	1.15	0.58-2.28	0.69
≥3	0.34	0.18-0.63	0.0006	0.39	0.12-1.27	0.11	0.72	0.26-2.01	0.53
Fertility specialist visit before pregnancy	1.68	0.83-3.41	0.15	0.63	0.12-3.42	0.32	1.49	0.50-4.41	0.47
Alcohol consumption 3 months before, during, or 3 months after pregnancy	2.35	1.45-3.81	0.0006	10.49	2.93-37.60	0.0003	1.65	0.73-3.71	0.23
History of living in a farm	4.98	2.40-10.32	<0.0001	5.82	1.43-23.66	0.01	10.88	2.43-48.77	0.002

As presented in [237].

[a] Only variables associated with CNS tumors at a p-value ≤0.10 in the univariable analysis (Table 15) were considered in multivariable analyses. For every variable we constructed separate multivariable conditional logistic regression analysis models adjusting for the matching factors (age, sex), maternal education, and a number of other factors.

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

Although underpowered, the sub-analyses for the two most common histological subtypes of childhood CNS tumors, i.e. astrocytoma (N=63) and embryonal tumors (N=70), provided hints that astrocytoma drove the associations identified for birth order, instrument-assisted delivery, and maternal alcohol consumption in pregnancy, whereas the associations of CNS tumor risk with history of living in a farm and caesarean section seemed to be similar among the two subtypes.

Study #5: Birth weight and other anthropometrics at birth in associations with central nervous system tumors: a systematic review and meta-analysis of published studies

Results of search strategy

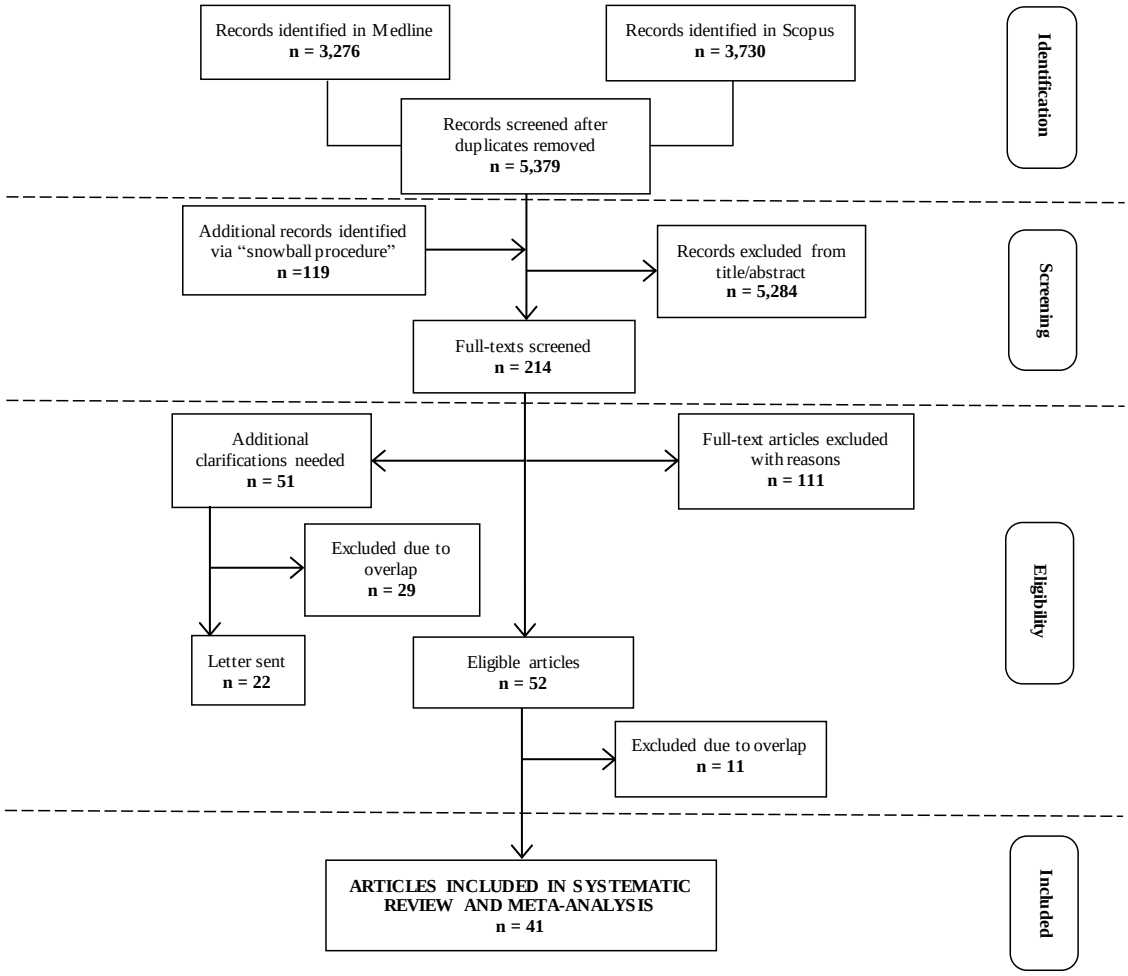
Figure 15 depicts the steps of study selection. The initial search yielded 5,379 articles after duplicates were removed, whereas 119 additional articles were identified through "snowball"; no additional study was found via grey literature search After exclusion of 11 overlapping studies, 41 articles were finally deemed eligible for this review [75,94,105-107,238-273].

Description of studies

Eligible study characteristics are summarized in **Appendix II**. Taken as a whole, the 32 case-control studies [75,94,105,107,239-241,243-247,249,250,252,254-260,263-272] included 46,673 primary CNS tumor cases and 518,771 controls, whereas the 9 cohort studies [106,238,242,248,251,253,261,262,273] studying a cumulative population of 10,444,895 individuals identified 6,494 incident primary CNS tumors. All studies examined CNS tumor incidence, except for the oldest study exploring mortality [254]. Cases of 34 studies were derived from cancer registries or population-based studies [75,94,105-107,238,240-243,247,248,250-259,261-266,268-273], whereas 7 included center-based cases [239,244-246,249,260,267]. Although the majority of studies concerned childhood CNS tumors, 4 studies included exclusively or primarily (>90%) adults [238,239,251,273]; one study covered both age groups (0-38 years), but the vast majority of cases were children and was therefore included only in the childhood analyses [242]. Mean follow-up among the cohort studies ranged between 11.2 and 19.5 years in studies referring to children, whereas adult cohorts were followed for a mean period of 22 to 36.6 years Birth weight and the other perinatal anthropometric

characteristics were derived via birth records [75,107,240,243,247,254,257-259,267,269-271] or were extracted from birth registries [94,105,106,242,248,251,253,259,261,262,264,273] for most included studies, whereas interview with parents was the method of assessment for 17 studies [238,239,241,244-246,249,250,252,255,256,260,263,265,266,268,272]. Notably, 19 articles [105-107,239,240,242,244,246,247,251,255,258,259,262,264,267-269,273] were published after 2007 (45,638 cases) when the search for the previously published meta-analysis ended [108].

Figure 15. Flowchart on the selection of eligible studies.



As presented in [274].

Quality evaluation

The assessment of study quality by study is presented in **Appendix III**. The overall study quality is considered high, as 31 out of 41 studies scored 7 or more points in Newcastle-Ottawa scale. Case-control studies were mainly compromised by the non-reported or non-similar between

cases and controls response rate, as well as by the non-clarification of exclusion of cancer cases in the control group. On the other hand, the inadequacy of follow-up (completeness <80% in 3 out of 6 childhood studies and 2 out of 3 studies on adult population) led to decreased quality in cohort studies.

Meta-analysis: Birth weight and childhood CNS tumors

Table 17 presents the analyses of the association of birth weight with total CNS tumors, diagnostic categories and histological subtypes, whereas **Figure 16** depicts the respective forest plots. High birth weight (>4,000 g vs. ≤4,000 g) was associated with increased overall risk of a CNS tumor (OR: 1.14, 95%CI: 1.08-1.20, 22,330 cases), whereas the linear analysis showed a 3% risk increase by 500 g-increment. This effect was statistically significant and stronger for astrocytoma (4,000 g vs. ≤4,000 g, OR: 1.22, 95%CI: 1.13-1.31, 7,456 cases; $OR_{500\ g\text{-}increment}$: 1.04, 95%CI: 1.02-1.05, 9,573 cases) applying to both low- (2,759 cases) and high-grade (815 cases) tumors; for low-grade astrocytoma though a linear pattern was identified, as low birth weight was also associated with decreased risk. An increased risk by high birth weight also emerged for embryonal CNS tumor in the categorical (4,000 g vs. ≤4,000 g, OR: 1.16, 95% CI: 1.04-1.29, 3,574 cases) and incremental analysis (500 g-increment, OR: 1.02, 95% CI: 1.01-1.04, 4,525 cases). No association between birth weight and childhood ependymoma (1,352-1,977 cases) was documented. Low birth weight (<2,500 g vs. ≥2,500 g) was not associated with either overall risk of CNS tumor or subtypes. Regarding the remaining ICCC-3 diagnostic categories (other gliomas, other specified tumors and unspecified tumors), marginal associations emerged for high birth weight, but the analyses were limited by the paucity of studies. Notably, no heterogeneity was recorded in the majority of analyses, except for the incremental overall analysis of birth weight with CNS tumor (I^2: 57.8%, p-value=0.001). The results of the alternative high and low vs. intermediate birth weight analyses showed practically similar results.

Sensitivity analyses (**Table 18**) on studies examining exclusively children up to 14 years showed likewise results for overall risk of CNS tumor, astrocytoma and embryonal tumor but also revealed an increased risk of ependymoma by high birth weight (4,000 g vs. ≤4,000 g, OR: 1.27, 95% CI: 1.05-1.55; $OR_{500\ g\text{-}increment}$: 1.03, 95% CI: 1.00-1.05). Subgroup analyses by subtypes pertaining to the younger age group (0-5 years) was rather hampered by the low number of study arms (n≤2); yet, the combined CNS tumors analysis on this age group showed the similar results as the overall childhood analysis. Notably, the findings remained robust among studies of high quality, studies adjusting for gestational age estimates, registry/population-based studies, and studies assessing birth weight by secure records/birth registry data. Exclusion of studies restricted to CNS tumors did not alter the findings. There were only a few cohort studies, which did not allow investigations by study design.

The dose-response analysis by birth weight level (**Figure 17**) replicated these findings, showing increased risk for combined CNS tumors, astrocytoma and embryonal tumor in high birth weight values. For the birth weight range below the median 3,250 g knot, the risk was attenuated. The p-values for non-linearity were 0.02 for the combined CNS tumor outcome, 0.03 astrocytoma and 0.06 for embryonal CNS tumor. Non-significant and non-linear trends were found for ependymoma (p-non-linearity: 0.45).

Table 17. Results of meta-analyses for birth weight and risk of childhood central nervous system (CNS) tumors by International Classification of Childhood Cancer- 3rd Edition (ICCC-3) diagnostic categories.

ICCC-3 diagnostic subtypes	>4000 g vs. ≤4000 g[a]				<2500 g vs. ≥2500 g[a]				500 gr-increment			
	N cases	*n*[b]	OR (95% CI)	Heterogeneity (I^2, *p*)	*N cases*	*n*[b]	OR (95% CI)	Heterogeneity (I^2, *p*)	*N cases*	*n*[b]	OR (95% CI)	Heterogeneity (I^2, *p*)
Total CNS tumors	22,330	22	1.14 (1.08-1.20)	0.0%, 0.62	21,531	16	1.03 (0.93-1.13)	8.1%, 0.36	21,778	17	1.03 (1.01-1.04)	57.6%, 0.002
Ependymoma	1,374	8	1.12 (0.94-1.34)	0.0%, 0.46	1,352	7	1.10 (0.76-1.61)	24.6%, 0.24	1,977	8	1.01 (0.98-1.05)	12.4%, 0.33
Astrocytoma	7,456	12	1.22 (1.13-1.31)	0.0%, 0.64	7,231	10	0.98 (0.86-1.11)	0.0%, 0.51	9,573	10	1.04 (1.02-1.05)	32.8%, 0.15
Low-grade	2,759	4	1.15 (1.02-1.29)	0.0%, 0.46	2,759	4	0.75 (0.60-0.95)	0.0%, 0.79	2,759	4	1.02 (0.99-1.05)	46.5%, 0.13
High-grade	815	2	1.60 (1.21-2.11)	0.0%, 0.62	815	2	1.18 (0.78-1.79)	0.0%, 0.59	815	2	1.05 (1.02-1.08)	0.0%, 0.69
Embryonal CNS tumor	3,574	13	1.16 (1.04-1.29)	0.0%, 0.51	3,375	11	1.06 (0.88-1.26)	0.0%, 0.99	4,525	12	1.02 (1.01-1.04)	21.1%, 0.24
Medulloblastoma	676	2	0.91 (0.69-1.21)	0.0%, 0.59	676	2	0.98 (0.62-1.56)	0.0%, 0.51	676	2	1.03 (0.94-1.13)	0.0%, 0.33
PNET	311	1	1.01 (0.44-2.33)	-	311	1	0.88 (0.46-1.68)	-	311	1	1.11 (0.91-1.36)	-
ATRT	44	1	1.71 (0.76-3.86)	-	44	1	2.89 (1.27-.6.60)	-	44	1	1.09 (1.00-1.19)	-
Other gliomas	1,226	4	1.21 (0.93-1.56)	17.1%, 0.31	1,226	4	0.99 (0.59-1.66)	54.6%, 0.09	1,835	5	1.02 (0.99-1.06)	0.0%, 0.80
Other specified tumors	659	2	1.14 (0.90-1.45)	0.0%, 0.32	659	2	0.75 (0.48-1.19)	0.0%, 0.84	1,277	3	1.03 (0.96-1.10)	53.4%, 0.12
Unspecified tumors	372	2	1.19 (0.84-1.67)	0.0%, 0.79	372	2	1.26 (0.68-2.32)	32.6%, 0.22	704	3	1.01 (0.95-1.06)	15.8%, 0.31

As presented in [274].

[a] In the >4,000 vs. ≤4,000 g and the <2,500 vs. ≥2,500 g analyses, were also included study arms treating birth weight as a dichotomous variable in cut-off points ± 500 g from 4,000 or 2,500 g, respectively.

[b] Number of study arms.

Abbreviations: PNET: Primitive neuroectodermal tumor, ATRT: Atypical teratoid-rhabdoid tumor

Table 18. Results of the sensitivity and subgroup meta-analyses examining the association between birth weight and risk of childhood central nervous system (CNS) tumors, ependymomas, astrocytomas and embryonal CNS tumors.

	Total CNS tumors			Ependymoma			Astrocytoma			Embryonal CNS tumor		
Analyses[a]	n[b]	OR (95% CI)	Heterogeneity (I^2, p)	n[b]	OR (95% CI)	Heterogeneity (I^2, p)	n[b]	OR (95% CI)	Heterogeneity (I^2, p)	n[b]	OR (95% CI)	Heterogeneity (I^2, p)
Sensitivity analyses by age group												
0-14 years												
>4,000 vs. ≤4000	16	1.14 (1.09-1.20)	0.0%, 0.89	6	1.27 (1.05-1.55)	0.0%, 0.94	9	1.25 (1.14-1.37)	0.0%, 0.77	10	1.18 (1.05-1.32)	0.0%, 0.52
<2,500 vs. ≥2,500	15	1.04 (0.95-1.14)	0.0%, 0.40	5	0.98 (0.53-1.79)	55.1%, 0.06	7	0.99 (0.82-1.19)	21.5%, 0.27	8	1.14 (0.94-1.38)	0.0%, 0.97
0-5 years												
>4,000 vs. ≤4000	5	1.20 (1.07-1.36)	0.0%, 0.73	-	--	--	2	1.34 (0.93-1.93)	0.0%, 0.69	2	1.15 (0.79-1.67)	0.0%, 0.64
<2,500 vs. ≥2,500	4	1.02 (0.75-1.39)	27.4%, 0.25	-	--	--	1	0.84 (0.34-2.08)	--	1	1.45 (0.76-2.75)	--
Subgroup analyses by level of adjustment												
Unadjusted for gestational age												
>4,000 vs. ≤4000	17	1.14 (1.02-1.27)	11.1%, 0.32	4	0.99 (0.73-1.34)	0.0%, 0.78	8	1.19 (1.07-1.33)	0.0%, 0.54	9	1.17 (0.98-1.39)	12.5%, 0.33
<2,500 vs. ≥2,500	12	1.04 (0.90-1.19)	0.0%, 0.53	3	1.16 (0.68-1.98)	0.0%, 0.93	6	0.98 (0.75-1.29)	27.1%, 0.23	7	0.98 (0.74-1.30)	0.0%, 0.99
Adjusted for gestational age												
>4,000 vs. ≤4000	5	1.14 (1.08-1.21)	0.0%, 0.98	4	1.17 (0.87-1.57)	34.8%, 0.20	4	1.24 (1.12-1.37)	0.0%, 0.47	4	1.15 (0.99-1.33)	0.0%, 0.57
<2,500 vs. ≥2,500	4	1.00 (0.85-1.18)	51.9%, 0.10	4	1.06 (0.55-2.06)	61.5%, 0.05	4	0.98 (0.83-1.15)	0.0%, 0.71	4	1.11 (0.88-1.40)	0.0%, 0.78
Subgroup analyses by study quality												
Studies of higher quality (NOS 7-9)												
>4,000 vs. ≤4000	15	1.15 (1.09-1.21)	0.0%, 0.87	7	1.10 (0.92-1.33)	4.3%, 0.39	11	1.22 (1.13-1.31)	0.0%, 0.55	11	1.16 (1.04-1.30)	0.0%, 0.67
<2,500 vs. ≥2,500	11	1.01 (0.92-1.10)	0.0%, 0.58	6	1.09 (0.71-1.68)	37.1%, 0.16	9	0.96 (0.85-1.10)	0.0%, 0.65	9	1.05 (0.87-1.26)	0.0%, 0.98
Studies of lower quality (NOS<7)												
>4,000 vs. ≤4000	7	1.06 (083-1.34)	35.9%, 0.15	1	1.47 (0.65-3.30)	--	1	1.21 (0.67-2.19)	--	2	0.98 (0.41-2.38)	71.5%, 0.06
<2,500 vs. ≥2,500	5	1.29 (0.88-1.89)	28.7%, 0.23	1	1.15 (0.25-5.30)	--	1	1.96 (0.78-4.90)	--	2	1.18 (0.54-2.57)	0.0%, 0.74
Sensitivity analysis excluding studies focused exclusively on CNS tumors												
Studies examining overall primary CNS tumors												
>4,000 vs. ≤4000	13	1.14 (1.08-1.20)	0.0%, 0.95	6	1.26 (1.02-1.55)	0.0%, 0.95	7	1.24 (1.12-1.37)	0.0%, 0.56	8	1.24 (1.09-1.40)	0.0%, 0.92

<2,500 vs. ≥2,500	11	1.02 (0.90-1.17)	34.2%, 0.13	6	1.04 (0.58-1.85)	49.3%, 01.0	6	1.02 (0.87-1.20)	0.0%, 0.44	7	1.08 (0.88-1.32)	0.0%, 0.96
Subgroup analyses by study design												
Case-control studies												
>4,000 vs. ≤4000	22	1.14 (1.08-1.20)	0.0%, 0.62	7	1.19 (0.98-1.46)	0.0%, 0.51	11	1.26 (1.15-1.37)	0.0%, 0.69	12	1.20 (1.07-1.34)	0.0%, 0.72
<2,500 vs. ≥2,500	16	1.03 (0.93-1.13)	8.1%, 0.36	6	1.06 (0.64-1.75)	36.7%, 0.16	9	0.97 (0.84-1.13)	2.7%, 0.41	10	1.08 (0.89-1.29)	0.0%, 0.99
Cohort studies												
>4,000 vs. ≤4000	1	1.13 (1.03-1.24)	--	1	0.93 (0.65-1.33)	--	1	1.14 (1.00-1.30)	--	1	0.88 (0.64-1.20)	--
<2,500 vs. ≥2,500	1	0.90 (0.75-1.10)	--	1	1.20 (0.66-2.19)	--	1	1.00 (0.75-1.32)	--	1	0.85 (0.45-1.60)	--
Sensitivity analysis by method of cases identification												
Registry-based/ population-based studies												
>4,000 vs. ≤4000	17	1.14 (1.09-1.20)	0.0%, 0.95	8	1.12 (0.94-1.34)	0.0%, 0.46	11	1.21 (1.12-1.31)	0.0%, 0.57	11	1.16 (1.04-1.30)	0.0%, 0.63
<2,500 vs. ≥2,500	14	1.03 (0.92-1.14)	19.5%, 0.24	7	1.10 (0.76-1.61)	24.6%, 0.24	9	0.97 (0.85-1.12)	2.9%, 0.41	9	1.07 (0.89-1.28)	0.0%, 0.98
Subgroup analyses by method of birth weight assessment												
Birth certificates/ delivery notes/ birth registry data												
>4,000 vs. ≤4000	10	1.14 (1.08-1.20)	0.0%, 0.88	6	1.10 (0.90-1.36)	17.5%, 0.30	7	1.22 (1.12-1.33)	9.9%, 0.35	8	1.15 (1.01-1.30)	4.2%, 0.40
<2,500 vs. ≥2,500	8	0.99 (0.89-1.09)	9.4%, 0.36	6	1.0 (0.69-1.77)	48.9%, 0.10	6	0.98 (0.86-1.13)	0.0%, 0.92	7	1.05 (0.86-1.28)	0.0%, 0.92
Interview with parents												
>4,000 vs. ≤4000	12	1.16 (0.97-1.38)	21.6%, 0.23	2	1.26 (0.63-2.55)	0.0%, 0.47	5	1.21 (0.96-1.53)	0.0%, 0.71	5	1.20 (0.93-1.54)	0.0%, 0.43
<2,500 vs. ≥2,500	8	1.18 (0.97-1.43)	0.0%, 0.51	2	1.00 (0.31-2.27)	0.0%, 0.77	4	1.04 (0.55-1.96)	55.7%, 0.07	4	1.08 (0.73-1.62)	0.0%, 0.96

As presented in [274].

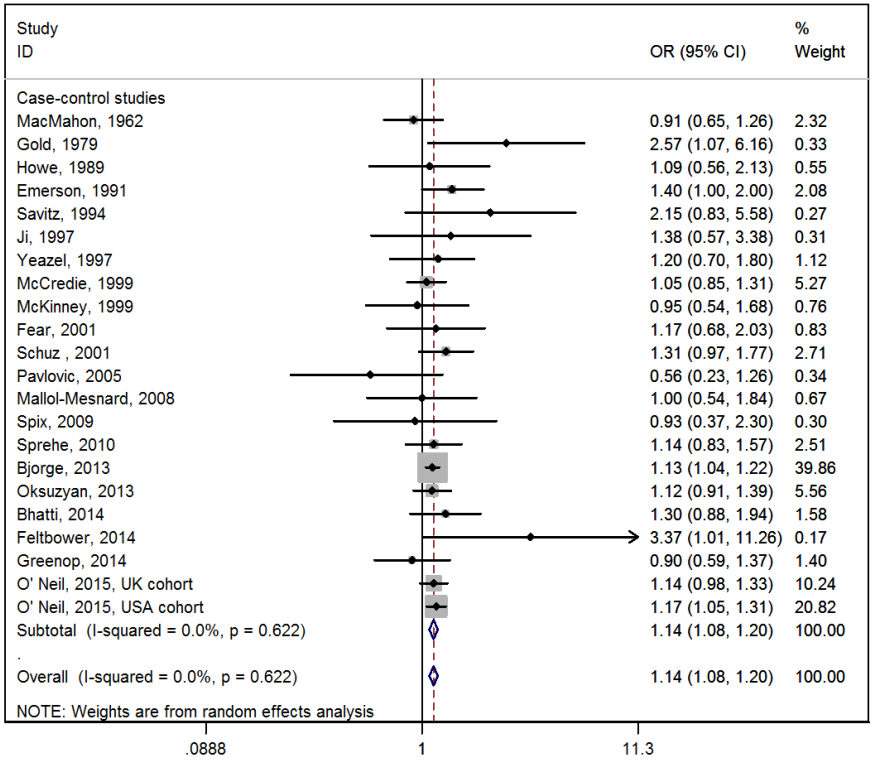
[a] In the >4,000 vs. ≤4,000 g and the <2,500 vs. ≥2,500 g analyses, were also included study arms treating birth weight as a dichotomous variable in cut-off points within +/- 500 g from 4,000 or 2,500 g, respectively.

[b] Number of study arms

Abbreviations: NOS: Newcastle-Ottawa Scale

Figure 16. Associations between high birth weight (>4,000 g vs. ≤4,000 g) and risk of childhood (A) central nervous system (CNS) tumors (overall analysis), (B) ependymomas, (C) astrocytomas, and (D) embryonal CNS tumors.

A



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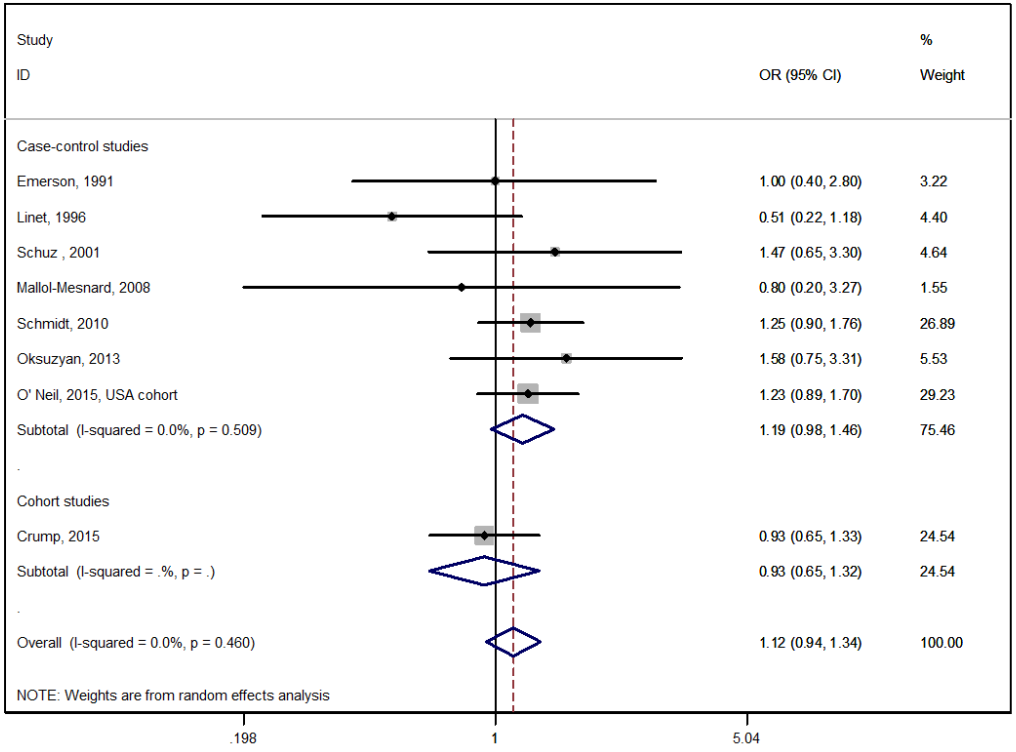

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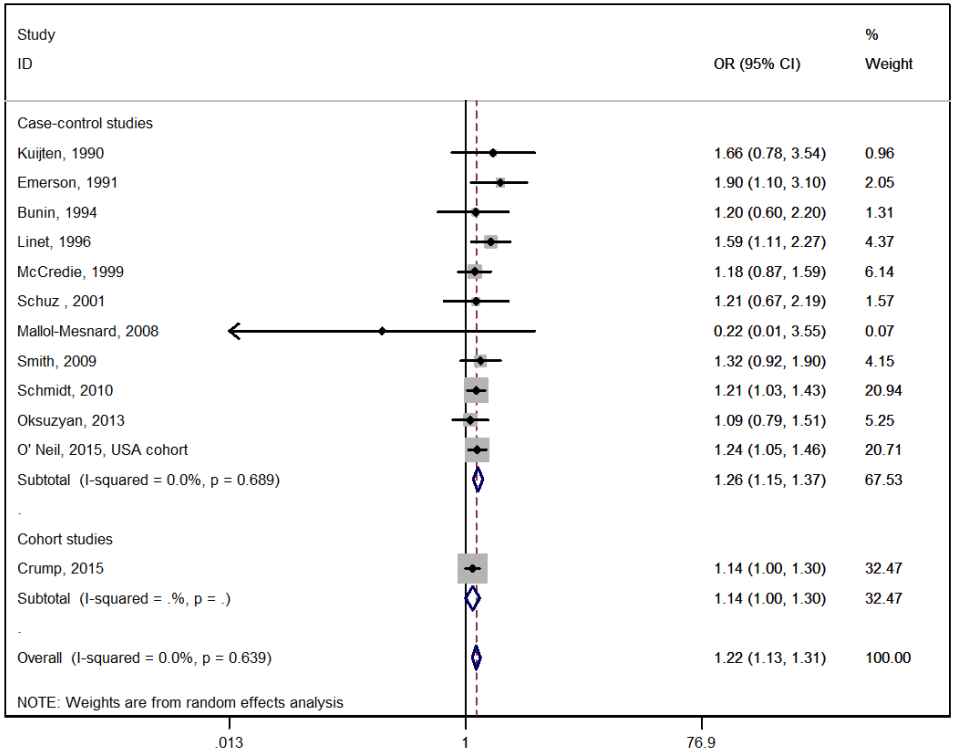
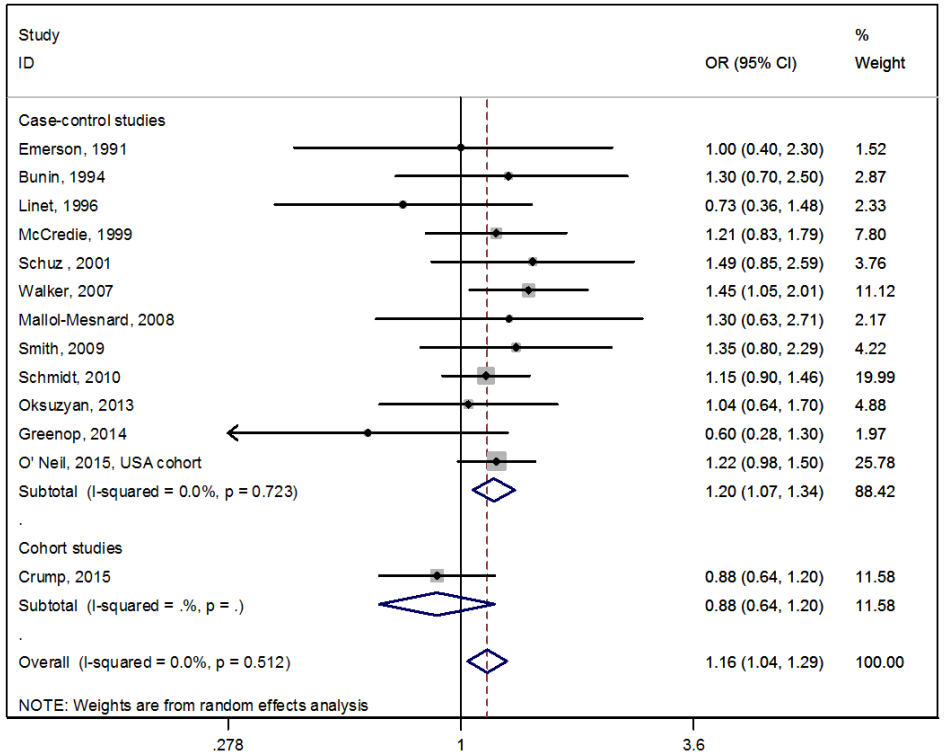
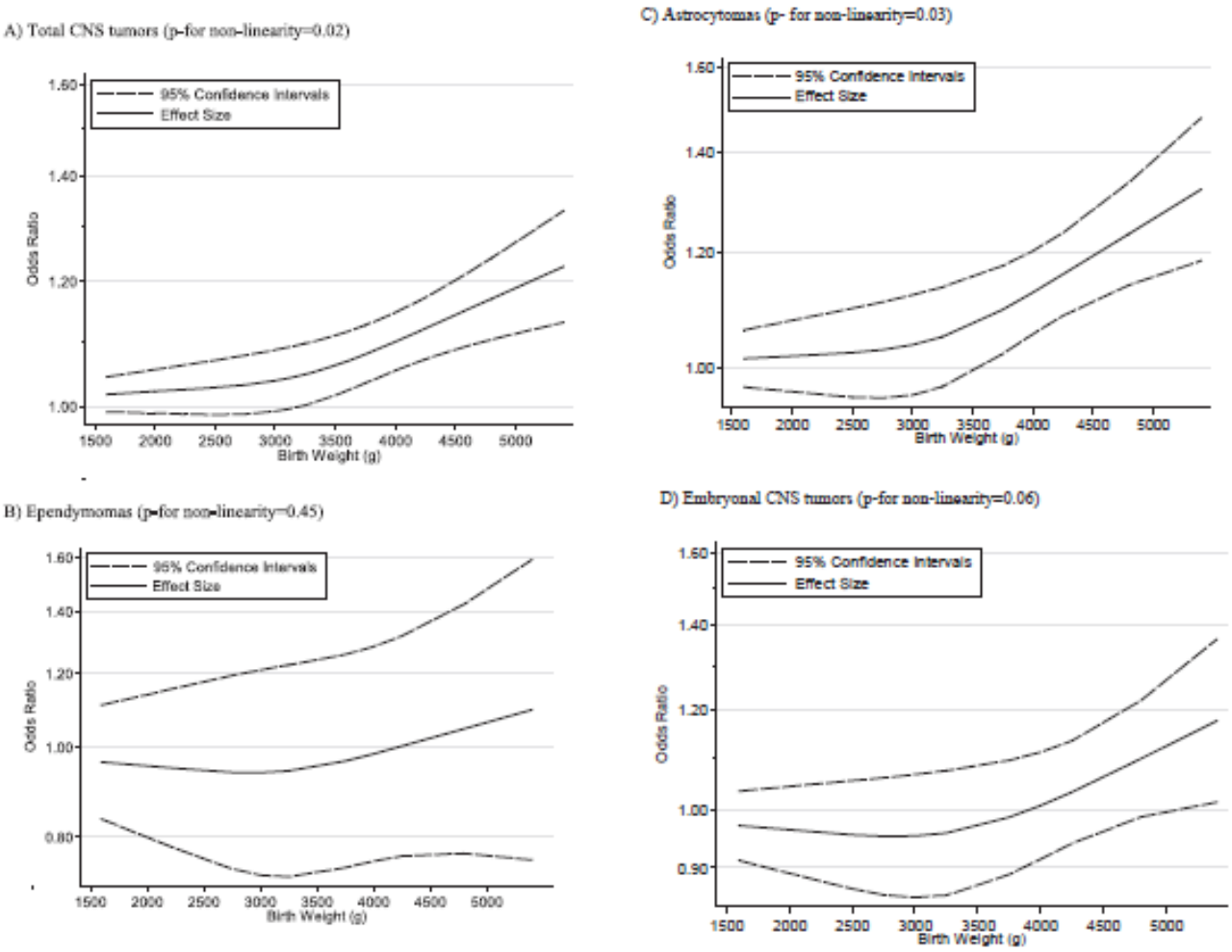


D



As presented in [274].
Effect sizes in the individual studies are indicated by the data markers (shaded boxes around the data markers reflect the statistical weight of the study); 95% Confidence Intervals are indicated by the error bars. The pooled-effect estimate with its 95% CIs is depicted as a diamond. Apart from the overall analysis, the sub-analyses on case–control (upper panels) and cohort (lower panels) studies are presented.

Figure 17. Dose-response relationships of birth weight with the risk of childhood (A) central nervous system (CNS) tumors (overall analysis), (B) ependymomas, (C) astrocytomas, and (D) embryonal CNS tumors.



As presented in [274].
The solid line represents the odds ratio, whereas the dashed lines correspond to the 95% confidence intervals, as derived from cubic spline models.

Publication year, age of cases and sex did not exert modifying results in the main analyses of the combined CNS tumor outcome and astrocytoma, as recorded from meta-regression. Additionally, no significant publication bias was found in the categorical analyses. The Egger's test showed however significant publication bias for the incremental overall analysis of CNS tumor.

Meta-analysis: Other anthropometric measurements and childhood CNS tumors

Table 19 shows the results of the analyses on size for gestational age. The combined CNS tumor analysis showed an increased risk for large for gestational age infants, compared to appropriate for gestational age (OR: 1.12, 95%CI: 1.03-1.22); yet, no increased risk was found for diagnostic categories, where analyses were compromised by the study paucity. Interestingly, SGA infants had a decreased risk for astrocytoma (OR: 0.79, 95% CI: 0.67-0.94; 4 studies), but also an increased risk for ependymoma (OR: 1.89, 95%CI: 1.00-3.58; 2 studies). No heterogeneity was recorded.

Table 19. Results for meta-analysis of size for gestational age and risk of childhood central nervous system (CNS) tumors, ependymomas, astrocytomas and embryonal CNS tumors.

Size for gestational age	*n*[a]	N cases	OR (95% CI)	Heterogeneity *(I^2, p)*
Total CNS tumors				
SGA vs AGA	7	10,339	0.93 (0.84-1.02)	0.0%, 0.87
LGA vs AGA			1.12 (1.03-1.22)	0.0%, 0.76
Ependymoma				
SGA vs AGA	2	623	1.89 (1.00-3.58)	8.2%, 0.30
LGA vs AGA			1.52 (0.95-2.54)	0.0%, 0.81
Astrocytoma				
SGA vs AGA	2	2,794	0.70 (0.51-0.97)	0.0%, 0.58
LGA vs AGA			0.96 (0.75-1.21)	0.0%, 0.97
Embryonal CNS tumor				
SGA vs AGA	3	1,394	1.18 (0.57-2.44)	69.7%, 0.04
LGA vs AGA			1.10 (0.68-1.77)	57.4%, 0.10

As presented in [274].
[a] Number of study arms.
Abbreviations: SGA: small for gestational age, AGA: appropriate for gestational age, LGA: large for gestational age

The paucity of relevant studies and their major overlap [105,106,242,246,248,262,264], precluded a meta-analysis on other perinatal anthropometric characteristics. Bjorge *et al.* [105], in a sample of 5,163 cases reported increased risk of a CNS tumor for children born with high head circumference, whereas Crump *et al.* [242], also found an increased risk by increasing fetal growth (2,809 cases). Among CNS tumor subtypes though, significant associations of increasing birth length, head circumference and fetal growth emerged solely for astrocytoma [242,262,264] and notably in 2 studies restricted to pilocytic astrocytoma [242,262]. The effects for ependymoma, embryonal CNS tumor or non-astrocytic glioma were non-significant in all studies [106,242,246,248,262,264]. Proportions of optimal birth weight, length, and weight-for-length

did not show significant associations with childhood CNS tumor risk in 2 studies [106,246].

Synthesis: Adult CNS tumors

Four studies examined the association of birth weight with risk of an adult CNS tumor [238,239,251,273]. Increasing birth weight (500 g-increment) was not associated with either overall CNS tumor risk (2 studies; OR: 0.99, 95%CI: 0.98-1.00; 1,091 cases) or glioma risk (3 studies; OR: 1.03, 95%CI: 0.98-1.07; 2,052 cases). Interestingly though, 2 studies [251,273] stratifying analyses by sex, reported male-restricted statistically significant associations of high birth weight with glioma.

Studies #6-7: Seasonality at birth in associations with incidence of childhood central nervous system tumors: a systematic review and a pooled analysis from cancer registries in Southern-Eastern Europe

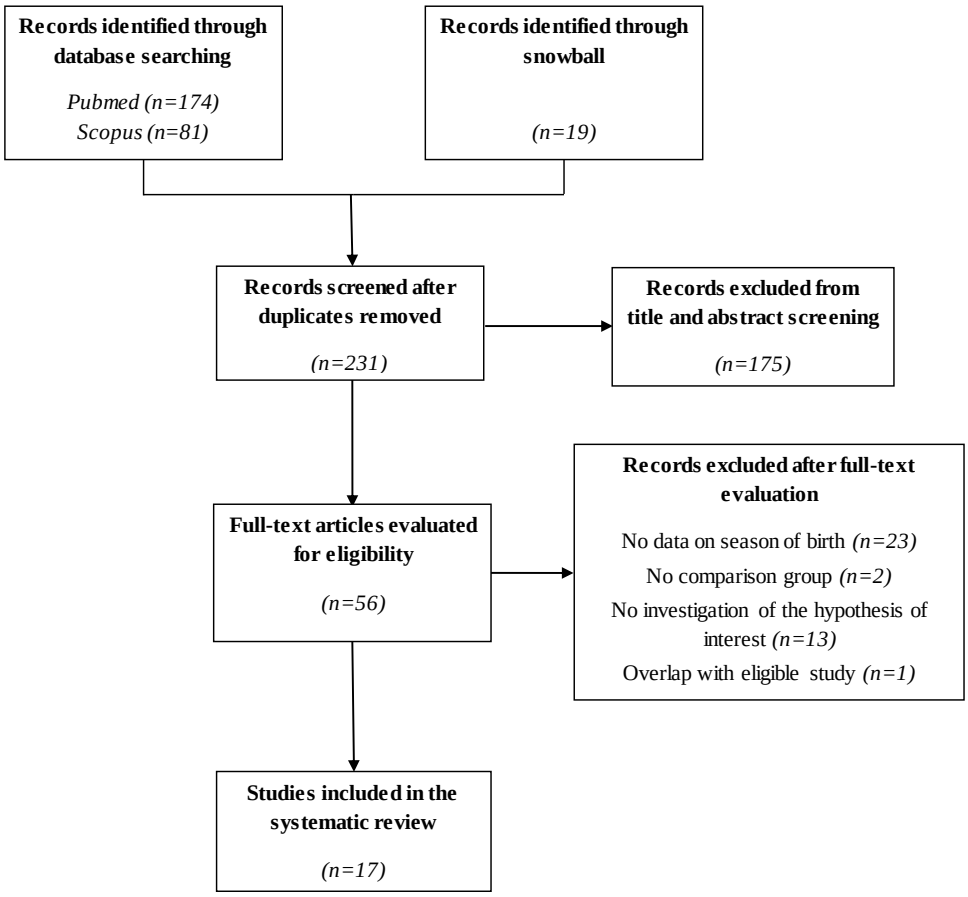
Search strategy

The search strategy of the 2 databases yielded 212 results after duplicates were removed, whereas 19 additional articles were identified via snowball. After screening the full-text of 56 potentially eligible articles, eventually 17 met the preset eligibility criteria [239,248,275-289]; the flowchart of the selection process is graphically presented in **Figure 18**.

The detailed characteristics of the eligible studies are available in **Appendix II**. Out of the 17 eligible articles, 3 were case-control studies of actively collected CNS tumor patients in clinical settings [239,275,277], only 1 was a prospective nationwide cohort [248] and the remaining 13 cancer register-based studies estimated the observed over expected rates using seasonal or monthly distributions of births among the case series vs. those in respective populations; the comparison group in the latter studies was derived from the same age national, county or all cancers registry population [276,278-281,283-290]. All studies were conducted in the Northern hemisphere of the Globe; particularly, 5 in the US [239,275,277,279,280], 4 in Nordic countries [248,285,286,290], 4 in the UK [276,278,284,288], 2 in Germany [281,287] and 2 in Japan [283,289] yielding a grand total of 20,523 CNS tumor cases. Nine studies focused exclusively on children (0 to 5, 14, 15 or 18 years as upper age limit) with CNS tumors [248,276,278,280,283-286,289]; 1 examined all age groups, but analyzed separately childhood (0-18 years) and adult

CNS tumors [279]; 1 focused exclusively on teenagers and young adults (TYAs; 15-24 years at diagnosis) [288]; the remaining 6 examined adult populations with the lower age limit ranging from 15+ to 18, 19 or 20 years [239,275,277,281,287,290]. Seasonality of birth was assessed mainly through structured interviews or medical records in case-control studies and medical records or via registration data in the remaining studies.

Figure 18. Flow chart showing the process for selection of eligible studies.



As presented in [291].

Quality assessment

The detailed assessment of study quality is presented in **Appendix III**. The quality of case-control and cohort studies was satisfactory (no cumulative loss >2 points in Newcastle-Ottawa scale), apart from 2 studies compromised by non-representativeness of the general population [239,275], whereas the quality of the cancer registry-based studies was systematically hampered due to lack of control for potentially confounding factors.

Season of birth and incidence of CNS tumors: Studies in children

Eight out of 10 studies showed some evidence in seasonality of birth patterns with the overall or specific CNS tumor subtypes risk [248,276,279,280,283-285,289]; no measures of the magnitude of the association were, however, presented; whereas an overall lack of consistency regarding the month/season of the maximum occurrence was evident ranging from August to February (**Table 20**).

Table 20. Association of birth seasonality (*: p-value<0.10, **: p-value<0.05, ***: p-value<0.01, ns: non-significant statistical association) with central nervous system (CNS) tumors in children and adolescents: summary presentation of findings in eligible studies.

1st Author, Year, Country, [Ref]	N cases (age)	Overall CNS tumors	Astrocytoma/ Other glioma	Ependymoma	Embryonal tumors	Covariates	Statistics
Makino, 2011, Japan, [33]	115 (0-14 y)	Dec-Feb**	Dec-Feb*	ns (p=0.59)	ns (p=0.56)	none	Chi-square: observed vs. expected
Basta, 2010, UK, [37]	702 (0-14 y)	ns (p=0.52)	Astrocytomas: Oct*, (females**) Other gliomas: ns (p=0.82)	ns (p=0.52)	PNETs: ns (p=0.11)	none	Chi-square; Poisson regression; Harmonic models
Schmidt, 2010, Nordic countries, [23]	2771 (0-14 y)	ns (p=0.31); ns by age group (p=0.10 for 0-4 and p=0.81 for 5-14 years)	Astrocytomas: ns (p=0.19) Other gliomas: ns (p=0.78)	ns (p=0.26)	ns (p=0.67)	none	Walter and Elwood's test
Schmidt, 2009, Denmark, [32]	1640 (0-14 y)	ns (p=0.83)	Astrocytomas: ns (p=0.48) Other gliomas: ns (p=0.19)	Dec-Jan** (5-19 y***, females***)	PNETs: ns (p=0.74)	none	Walter and Elwood's test
Hoffman, 2007, USA, [39]	4522 (0-19 y)	ns (p=0.22)	Pilocytic: ns (p=0.13) Other astrocytomas: ns (p=0.79)	ns (p=0.95)	Medulloblastomas: Oct-Nov** (5-19 y***, females **, residency in non-metropolitan areas***); Other embryonal: ns (p=0.14)	none	Edward's test; Walter and Elwood's test
Halperin, 2004, USA, [28] • Duke University Medical Center	100 (0-19 y)				Medulloblastomas: Sep-Nov**	none	Chi-square: observed vs. expected
• Central Cancer Registry of North Carolina	64 (0-19 y)				Medulloblastomas: Sep-Nov**		
• Los Angeles/San Jose/Monterey, California SEER	44 (0-19 y)				Medulloblastomas: Sep-Nov**		
	683				Medulloblastomas:		

• National SEER	(0-19 y)				ns (p=0.69)		
McNally, 2002, UK, [40]	1045 (0-14 y)	Dec*	All astrocytomas: Nov** Pilocytic: ns (p=0.29) Other astrocytomas: Dec*	Feb*	ns (p=0.63)	none	Edward's test
Feltbower, 2001, UK, [38] • Cumbria	86 (0-14 y)	ns (p=0.48)				none	Walter and Elwood's test; logistic regression
• Northern RHA	474 (0-14 y)	p=0.08, peak month nr					
• Yorkshire RHA	455 (0-14 y)	ns (p=0.84)					
Heuch, 1998, Norway, [29]	459 (0-15 y)	Dec-Feb***; Summer: IRR=1.19 (0.91-1.55); Fall: IRR=1.23 (0.94-1.61); Winter: IRR=1.44 (0.95–2.17), with spring as reference	ns (p=0.19); Summer: IRR= 1.20 (0.78–1.83) Fall: IRR=0.93 (0.59–1.48) Winter: IRR=1.52 (1.19-1.97), with spring as reference		Medulloblastomas: ns (p=0.26); Summer: IRR=0.69 (0.34-1.37) Fall: IRR=1.14 (0.61-2.10) Winter: IRR=1.32 (0.74-2.38), with spring as reference	age, sex	Log-linear Poisson regression
Yamakawa, 1982, Japan, [42]	128 (0-5 y)				Medulloblastomas: Aug-Oct*	none	Chi-square: observed vs. expected

As presented in [291].

Abbreviations: SEER, Surveillance, Epidemiology and End Results program; RHA, Regional Health Authority; PNET, Primitive Neuroectodermal Tumors.

CNS tumors overall: The Norwegian cohort study (N=459), the most recent Japanese (N=115) and a UK study with registry controls (N=1,045) showed peaks in the period December to February [248,283,284], whereas the remaining 5 studies encompassing over 10,000 cases in Nordic countries, UK and US showed no statistically significant effects [276,278,280,285,286].

Astrocytoma: Among the 7 studies presenting separate analyses by histological subtypes, only 3 [276,283,284] comprising 31, 264, and 422 cases, respectively, found a significant peak between October and February; again, the largest studies, including the cohort study, did not confirm these findings [280,285,286].

Ependymoma: Schmidt *et al.* (2009) and McNally *et al.*, reported clustering of ependymomas births in winter months (December to February), which in the former study was evident only among females aged 5-19 years [284,285], as contrasted to the remaining 4 studies showing no significant association [276,280,283,286].

Embryonal tumors: Statistically significant peaks in births during fall months (September to November) were shown for medulloblastomas, in the 2 largest studies from the US [279,280] and August-October in a study among Japanese children aged 0-5 years [289]; even within components of these studies, however, the results were not homogenous; notably, in the study by Halperin *et al.*, the same statistically significant fall peak was evident in 3 different sites but not in the SEER derived component [279], whereas according to Hoffman *et al.,* it was stronger for females aged over 5 years and those residing in metropolitan areas [280]. The 6 remaining studies entailing embryonal tumor analyses [248,283,284], pertaining also the only study on PNETs did not show any seasonal birth variation [276]..

Season of birth and incidence of CNS tumors: Studies in adults

A total of 7 studies (**Table 21**), with individual sample sizes ranging from 101 to 2,174 cases, investigated seasonality of birth among adult cases of CNS tumors [239,275,277,279,281,282,287] and the results are summarized below along with those of the only study (1,882 cases) that examined exclusively AYAs [288].

CNS tumors overall: Only one small (N=101 cases) size study [282] examined seasonality of birth in association with all types of CNS tumors and reported a statistically significant increased occurrence among those born in winter months (December to February), whereas the AYAs study (N=1,882 cases) did not find any pattern in birth seasonality [288].

Glioma: Four out of 7 studies examining gliomas in adults, showed a statistically significant pattern of birth seasonality [277,281,282,288], 3 with peaks in winter months [277,281,290] and the TYAs study presenting peaks in April and October only among males for astrocytomas or in May and November for other gliomas [288]. In 1 study the winter peak was significant only for glioblastoma, but not for anaplastic astrocytoma [281], whereas another study showed that the effect was evident only for high-grade gliomas [282]. Brenner *et al., who* conducted stratified analyses for gliomas [277] reported a seasonality pattern only among left-handed or ambidextrous individuals, and only among those without a history of autoimmune/allergic diseases; it is possible that these analyses were limited by the small sample size though. By contrast, the largest German study (2,174 cases) did not reveal any significant seasonality effect for gliomas [287], neither did 2 of the case-control studies [239,275].

Meningioma: The 2 small studies, encompassing 33 and 187 adult cases, respectively, showed similar winter peaks for meningiomas [277,282].

Embryonal tumors: Lastly, no statistically significant birth seasonality pattern for medulloblastomas emerged in any of the US regional cohorts and SEER, studied by Halperin *et al.* [279]. Conversely, the AYAs study showed a significant peak in March and September births, which was, however, evident only for females [288].

Table 21. Association of birth seasonality (*: p-value<0.10, **: p-value<0.05, ***: p-value<0.01, ns: non-significant statistical association) with central nervous system (CNS) tumors in adults: summary presentation of findings in eligible studies.

1st Author, Year, Country, [Ref]	N cases (age)	Overall CNS tumors	Glioma	Meningioma	Embryonal tumors	Covariates	Statistics
Anic, 2013, USA [30]	889 (>18 y)		ns; Winter: OR=0.96 (0.74-1.24); Spring: OR=0.97 (0.75-1.26); Summer: OR=1.03 (0.80-1.33), with fall as reference			State of residence, age, sex	Unconditional logistic regression
Van Laar, 2013, UK, [41]	1882 (15-24 y)	May, Nov (p=0.16)	Astrocytomas both sex: Jan (p=0.12), males only: Apr**, Oct**; Other gliomas: May**, Nov**		Medulloblastomas: Jan, Jul (p=0.26); females only: Mar**, Sep**	sex	Harmonic curves
Amirian, 2010, USA [36]	489 (>18 y)		ns (p=0.83)			none	Chi-square: observed vs. expected
Staykov, 2009, Germany [31]	2174 (≥15 y)		ns; males: Dec (p=0.54); females: Apr (p=0.11)			sex	Sinusoidal curve, Edwards test, Roger-test
Koch, 2006, Germany [22]	697 (mean age: 40.9 y)		Glioblastoma: Dec-Feb** Anaplastic astrocytoma: spring/summer (ns, nr)			none	Circannual cosinor model
Mainio, 2006, Finland [27]	101 (20-82 y)	Dec-Feb**	Dec-Feb** (except low-grade)	Dec-Feb**		none	Chi-square: observed vs. expected
Brenner, 2004, USA [26]	686 (>18 y)		Feb**; left-handed/ambidextrous***	Jan** (males**)		education, marital status, place of birth, handedness, birth order, history of allergy/autoimmune disease	Unconditional logistic regression

Halperin, 2004, USA [28] • Duke University Medical Center • Central Cancer Registry, North Carolina, USA • Partial California SEER • National SEER	22 (>19 y)				Medulloblastomas: ns (p=0.27)	none	Chi-square: observed vs. expected
	26 (>19 y)				Medulloblastomas: ns (p=0.28)		
	31 (>19 y)				Medulloblastomas: ns (p=0.88)		
	239 (>19 y)				Medulloblastomas: ns (p=0.49)		

As presented in [291].

Abbreviations: SEER, Surveillance, Epidemiology and End Results program.

Distribution of childhood CNS tumor cases in the SEE registries

Table 22 shows the distribution of the 6014 incident CNS tumor cases by age and histology among the 16 participating cancer registries operating during continuous time periods of variable length between 1983 and 2015. The bulk of cases were astrocytomas or embryonal tumors, while there was a slight preponderance of boys ranging from 46.7% to 60.0%. Approximately half of CNS tumors cases were diagnosed during early childhood (<4 years).

Season/month of birth and risk of CNS tumors

The summary seasonal effect estimates for childhood CNS tumors overall, as well as by sex and principal histology are presented in **Table 23**. Children born during the winter season of the year were at a slightly increased risk of developing a CNS tumor overall (IRR: 1.06, 95% CI: 0.99-1.14; **Figure 19**), and of embryonal histology specifically (IRR: 1.13, 95% CI: 1.01-1.27). Intriguingly, the winter peak of embryonal tumors was sizable among boys (IRR: 1.24, 95% CI: 1.05-1.46). The association between winter season of birth and risk of CNS tumors was positive, albeit non-significant among girls (0-14 years). Nevertheless, a clustering of astrocytomas was found among girls born during spring (IRR: 1.23, 95% CI: 1.03-1.46; **Table 23**). Analyses in younger children <5 years (**Table 24**) showed that the winter clustering of CNS tumors among boys was higher in the course of the first five years of life (IRR: 1.33, 95% CI: 1.03-1.71). By contrast, boys under 5 years born during summer seemed to be at a lower risk of developing an embryonal CNS tumor (IRR: 0.73, 95% CI: 0.54-0.99). Despite the larger numbers of cases, results in the age group 5-14 years did not reach statistical significance, apart from a significant winter peak of CNS tumors among girls (IRR: 1.17, 95% CI: 1.00-1.38) probably driven by embryonal tumors (IRR: 1.17, 95% CI: 0.90-1.53), and a clustering of astrocytomas among girls born during spring (IRR: 1.28, 95% CI: 1.04-1.58).

Among the registries contributed live birth data and included in the seasonal analyses, only the Croatian and Ukrainian ones showed relatively lower rates of morphologically verified cases (73% and 78%, respectively). After the exclusion of the aforementioned registries, the results remained essentially similar with those of the main analyses. Of note, in the sensitivity meta-analyses the winter peak of embryonal CNS tumors in boys became even stronger and remained significant after the Bonferroni correction (IRR: 1.41, 95% CI: 1.15-1.72, p=0.0009), especially among younger <5 years boys (IRR: 1.51, 95% CI: 1.11-2.05, p=0.009). In the seasonal analyses of month of birth, a statistically significant peak of CNS tumors was found among children (p=0.03), and specifically boys (p=0.05) born in February.

Table 22. Total numbers of live-births* and characteristics of the 6014 childhood (0-14 years) CNS tumors registered by the 16 registries operating in 14 Southern-Eastern European countries

Registry, Country	Total live-births, N (available period)	Study period of registration	CNS tumors N	Astrocytomas %	Embryonal tumors %	Other Histology %	Unknown Histology %	Boys %	Age <4 years %
Childhood Cancer Sub-Registry of Belarus, BE	2 040 205 (1997-2016)	1990-2012	726	28.8	36.2	23.7	11.3	57.3	33.8
Bulgarian National Cancer Registry BNCR, BU	--	1990-2012	471	29.5	27.6	11.7	31.2	56.1	31.9
Croatian National Cancer Registry, CR	754,570 (1998-2015)	2001-2013	250	20.0	25.6	20.8	33.6	60.0	36.4
Cyprus Cancer Registry, CY	221,040 (1992-2015)	1998-2015	60	28.3	21.7	36.7	13.3	46.7	45.0
NARECHEM-ST, GR	3,936,462 (1980-2015)	2010-2014	169	23.7	47.9	28.4	0.0	58.0	50.3
Hungarian Childhood Cancer Registry, HU	2,722,271 (1990-2016)	1990-2015	1,074	30.5	35.9	33.4	0.2	55.3	35.9
Malta National Cancer Registry, MT	--	1995-2012	31	41.9	35.5	16.1	6.5	48.4	29.0
Greater Poland Cancer Registry, PL**	1,277,446 (1984-2013)	1999-2014	254	21.3	28.7	21.6	28.4	53.5	40.2
Centre Region of Portugal Cancer Registry, PT**	357,693 (1995-2010)	1995-2009	142	22.5	33.8	28.2	15.5	59.9	40.9
North Region of Portugal Cancer Registry, PT**	518,520 (1995-2010)	1990-2009	185	26.0	28.7	37.7	7.6	61.6	44.3
Romania (Northeast), RO**	--	2008-2009	22	40.9	27.3	22.7	9.1	68.2	40.9
Cluj Regional Romanian Cancer Registry, RO**	--	2008-2011	26	23.1	19.3	38.4	19.2	50.0	46.2
Cancer Registry of Central Serbia, RS	--	1999-2011	300	32.0	17.8	11.5	38.7	49.3	34.7
Cancer Registry of Slovenia, SI	492,040 (1990-2014)	1983-2011	179	32.4	30.7	29.6	7.3	63.7	43.0
Izmir Cancer Registry (Turkey) TR**	--	1993-2010	177	23.7	28.3	44.6	3.4	54.2	33.3
National Cancer Registry of Ukraine, UKR	5,891,354 (2000-2012)	2000-2012	1,948	34.5	21.9	15.3	28.3	54.2	33.3

*Live-births with known date of birth; **Regional registry

Table 23. Meta-analysis-derived seasonal Incidence Rate Ratios (IRR) and 95% Confidence Intervals (95% CIs) for childhood (0-14 years) central nervous system (CNS) tumors registered in 9 countries overall and by principal histological subtype and sex

Study group	Season	Total CNS tumors (N: 4,987)	Astrocytomas (N: 1,507)	Embryonal tumors (N: 1,461)
		IRR (95% CIs)	**IRR (95% CIs)**	**IRR (95% CIs)**
Total	Winter	1.06 (0.99-1.14)	1.03 (0.90-1.17)	1.13 (1.01-1.27)
	Spring	1.04 (0.98-1.11)	1.06 (0.95-1.19)	0.99 (0.88-1.12)
	Summer	0.94 (0.87-1.01)	1.03 (0.92-1.16)	0.90 (0.80-1.02)
	Autumn	0.98 (0.90-1.07)	0.94 (0.78-1.14)	1.00 (0.89-1.13)
Boys	Winter	1.07 (0.98-1.18)	1.08 (0.91-1.28)	1.24 (1.05-1.46)
	Spring	1.09 (0.96-1.23)	0.95 (0.75-1.21)	1.00 (0.84-1.19)
	Summer	0.93 (0.85-1.02)	1.07 (0.90-1.26)	0.89 (0.75-1.06)
	Autumn	0.94 (0.85-1.03)	0.92 (0.77-1.10)	0.96 (0.77-1.19)
Girls	Winter	1.08 (0.98-1.20)	1.10 (0.82-1.46)	1.04 (0.84-1.28)
	Spring	1.03 (0.92-1.14)	1.23 (1.03-1.46)	1.00 (0.81-1.24)
	Summer	0.96 (0.83-1.10)	1.04 (0.86-1.25)	0.94 (0.76-1.16)
	Autumn	0.94 (0.85-1.05)	0.88 (0.66-1.18)	1.08 (0.88-1.33)

In **bold**: statistically significant associations.
*Sex distribution live-birth data was missing for Belarus.

Table 24. Age-specific (0-4 and 5-14 years) meta-analysis-derived seasonal Incidence Rate Ratios (IRR) and 95% Confidence Intervals (95% CIs) for childhood central nervous system (CNS) tumors registered in 9 countries overall and by principal histological subtype and sex.

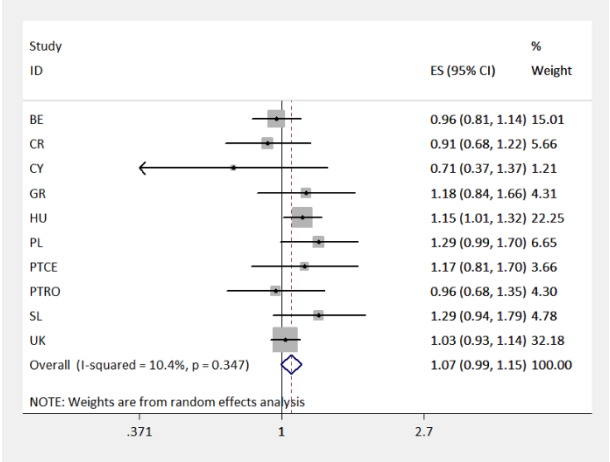
0-4 years				
Study group	**Season**	**Total CNS tumors (N: 1,801) IRR (95% CIs)**	**Astrocytomas (N: 432) IRR (95% CIs)**	**Embryonal tumors (N: 589) IRR (95% CIs)**
Total	Winter	1.11 (1.00-1.23)	1.15 (0.92-1.42)	1.17 (0.97-1.40)
	Spring	1.01 (0.91-1.13)	1.07 (0.86-1.33)	0.97 (0.80-1.18)
	Summer	0.98 (0.88-1.08)	1.12 (0.91-1.39)	0.88 (0.69-1.12)
	Autumn	0.95 (0.85-1.06)	0.91 (0.60-1.40)	1.05 (0.88-1.27)
Boys*	Winter	1.16 (1.00-1.35)	1.17 (0.85-1.61)	1.33 (1.03-1.71)
	Spring	1.07 (0.92-1.25)	1.07 (0.77-1.48)	1.01 (0.77-1.32)
	Summer	0.93 (0.80-1.09)	1.24 (0.92-1.69)	0.73 (0.54-0.99)
	Autumn	0.90 (0.77-1.05)	0.71 (0.49-1.03)	1.11 (0.85-1.44)
Girls*	Winter	1.05 (0.88-1.25)	1.21 (0.86-1.69)	0.91 (0.63-1.29)
	Spring	1.01 (0.85-1.21)	1.17 (0.84-1.65)	1.02 (0.73-1.44)
	Summer	1.06 (0.89-1.25)	1.19 (0.85-1.66)	1.19 (0.87-1.63)
	Autumn	1.06 (0.82-1.38)	0.92 (0.52-1.62)	1.07 (0.78-1.48)
5-14 years				
Study group	**Season**	**Total CNS tumors (N: 3,186) IRR (95% CIs)**	**Astrocytomas (N: 1,075) IRR (95% CIs)**	**Embryonal tumors (N: 872) IRR (95% CIs)**
Total	Winter	1.08 (0.95-1.22)	0.97 (0.84-1.12)	1.13 (0.97-1.31)
	Spring	1.06 (0.97-1.16)	1.06 (0.93-1.22)	1.02 (0.88-1.19)
	Summer	0.93 (0.86-1.01)	1.01 (0.88-1.16)	0.92 (0.79-1.08)
	Autumn	0.98 (0.88-1.09)	1.01 (0.88-1.15)	0.98 (0.84-1.14)
Boys*	Winter	1.04 (0.92-1.16)	1.05 (0.85-1.29)	1.20 (0.97-1.48)
	Spring	1.11 (0.94-1.30)	0.96 (0.74-1.22)	1.04 (0.83-1.29)
	Summer	0.94 (0.83-1.05)	1.03 (0.83-1.28)	1.01 (0.82-1.25)
	Autumn	0.97 (0.86-1.09)	1.08 (0.88-1.33)	0.86 (0.69-1.08)
Girls*	Winter	1.17 (1.00-1.37)	0.95 (0.73-1.23)	1.17 (0.90-1.53)
	Spring	1.04 (0.90-1.21)	1.28 (1.04-1.58)	1.04 (0.79-1.38)
	Summer	0.93 (0.78-1.10)	1.06 (0.85-1.31)	0.84 (0.63-1.12)
	Autumn	0.94 (0.83-1.08)	0.91 (0.70-1.16)	1.10 (0.84-1.44)

In **bold**: statistically significant associations.
*Sex distribution live-birth data was missing for Belarus.

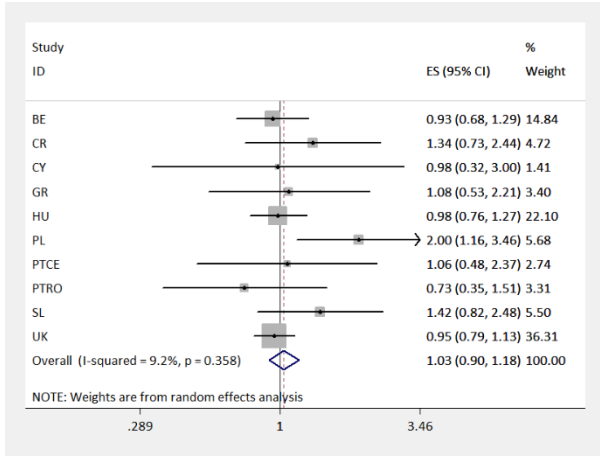
Figure 19. Forest plot depicting the association between winter season of birth and risk of (a) central nervous system (CNS), (b) astrocytomas and (c) embryonal tumors in childhood (0-14 years).

A

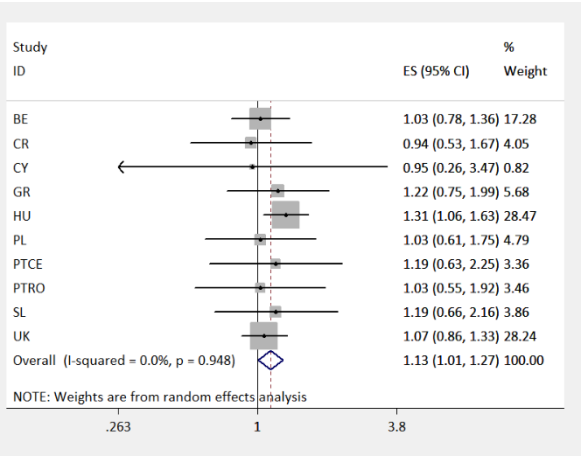
Full sample



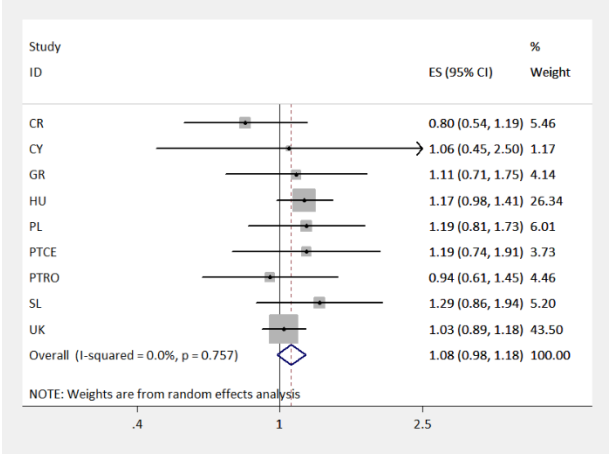
B

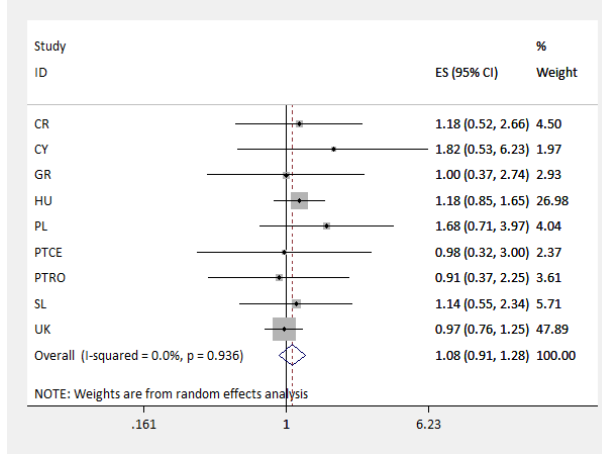


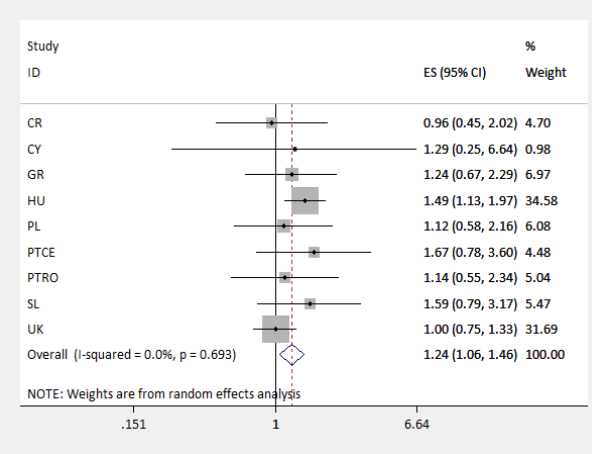
C



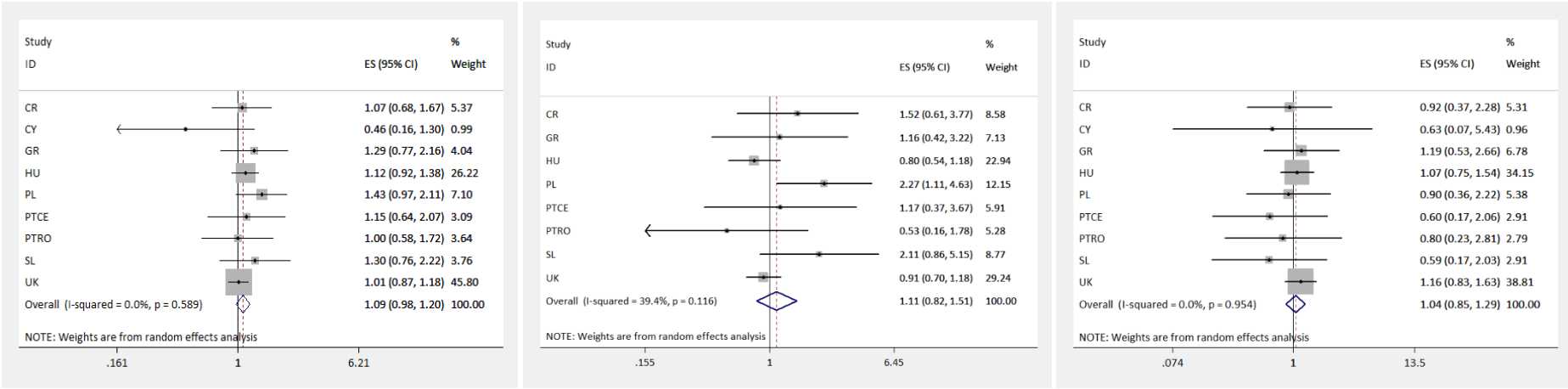
Males







Females


Study
ID
ES (95% CI)
%
Weight
CR 1.07 (0.68, 1.67) 5.37
CY 0.46 (0.16, 1.30) 0.99
GR 1.29 (0.77, 2.16) 4.04
HU 1.12 (0.92, 1.38) 26.22
PL 1.43 (0.97, 2.11) 7.10
PTCE 1.15 (0.64, 2.07) 3.09
PTRO 1.00 (0.58, 1.72) 3.64
SL 1.30 (0.76, 2.22) 3.76
UK 1.01 (0.87, 1.18) 45.80
Overall (I-squared = 0.0%, p = 0.589) 1.09 (0.98, 1.20) 100.00
NOTE: Weights are from random effects analysis
.161
1
6.21
Study
ID
ES (95% CI)
%
Weight
CR 1.52 (0.61, 3.77) 8.58
GR 1.16 (0.42, 3.22) 7.13
HU 0.80 (0.54, 1.18) 22.94
PL 2.27 (1.11, 4.63) 12.15
PTCE 1.17 (0.37, 3.67) 5.91
PTRO 0.53 (0.16, 1.78) 5.28
SL 2.11 (0.86, 5.15) 8.77
UK 0.91 (0.70, 1.18) 29.24
Overall (I-squared = 39.4%, p = 0.116) 1.11 (0.82, 1.51) 100.00
NOTE: Weights are from random effects analysis
.155
1
6.45
Study
ID
ES (95% CI)
%
Weight
CR 0.92 (0.37, 2.28) 5.31
CY 0.63 (0.07, 5.43) 0.96
GR 1.19 (0.53, 2.66) 6.78
HU 1.07 (0.75, 1.54) 34.15
PL 0.90 (0.36, 2.22) 5.38
PTCE 0.60 (0.17, 2.06) 2.91
PTRO 0.80 (0.23, 2.81) 2.79
SL 0.59 (0.17, 2.03) 2.91
UK 1.16 (0.83, 1.63) 38.81
Overall (I-squared = 0.0%, p = 0.954) 1.04 (0.85, 1.29) 100.00
NOTE: Weights are from random effects analysis
.074
1
13.5

C. Applying meta-analyses to address questions of clinical epidemiology: the case of the rare CNS tumor gliomatosis cerebri

Study #8: Delineating the epidemiology of gliomatosis cerebri: incidence and survival patterns in a population-based cancer registration study

Clinical and demographic characteristics

A total of 176 GC cases were recorded in the SEER database during the entire registration period (1973-2012). **Table 25** presents the demographic and clinical characteristics of the registered patients. Mean age at diagnosis was 57.4 years (SD: 22.8). Although age ranged from 1 to 98 years, the majority of the cases were diagnosed in older age groups (31% in 40-64 years and 49% in ≥65 years). Childhood (0-14 years) GC comprised only 9% of the cases. A male preponderance was noted (54%). The majority of the cases were Caucasians (90.3%) lived in urban areas at diagnosis (93%) and were diagnosed in the latter 2 decades of registration (1993-2012; 94%).

61% of the patients had a microscopical confirmation of the diagnosis, whereas diagnosis by clinical/radiological methods was established in 36% of the patients; death certificate only cases corresponded to less than 3%. Regarding primary tumor location, 28% of the GC tumors were restricted in the cerebral lobes, whereas 46% were located in deeper and infratentorial structures or in overlapping brain areas; in one fourth of the cases, primary tumor location was not specified. Among cases with available treatment information, 33% and 25% received radiation therapy or had a surgical resection of the tumor, respectively.

Incidence rates and time trends

The annual AIR of GC in the SEER-covered population during the entire 40-year registration period (1973-2012), was 0.10/million individuals (**Table 26**). The incidence increased considerably by age having a peak after 65 years at 0.43/million (**Figure 20A**). Overall, GC was more common in males, with an overall male-to-female ratio of 1.4. When restricting the registration period to the last 10 years (2003-2012), the overall AIR increased to 0.15 cases/million individuals, whereas the AIR for the elderly individuals (≥65 years) reached 0.61/million.

Table 25. Distribution of the study variables among patients with gliomatosis cerebri in the SEER database (1973-2012).

Variables	Gliomatosis cerebri cases (N=176)	
	N	%
Age at diagnosis (years)		
0-14	15	8.5
15-39	19	10.8
40-64	55	31.3
≥65	87	49.4
Mean ± SD (Range)	57.6 ± 22.8 (1-98)	
Sex		
Male	95	54.0
Female	81	46.0
Race		
Caucasian	159	90.3
Non-Caucasian	17	9.7
Time period of diagnosis		
1973-1982	3	1.7
1983-1992	8	4.6
1993-2002	56	31.8
2003-2012	109	61.9
Place of residence		
Rural	12	6.8
Urban	164	93.2
Basis of diagnosis		
Microscopical confirmation	107	60.8
Non-microscopical diagnosis*	64	36.4
Death certificate only	5	2.8
Primary tumor location		
Cerebral hemispheres	50	28.4
Elsewhere in the CNS, specified	81	46.0
Brain, unspecified	45	25.6
Radiotherapy		
No	111	63.1
Yes	55	31.2
Missing	10	5.7
Surgery		
No	117	66.5
Yes	38	21.6
Missing	21	11.9

As presented in [292].

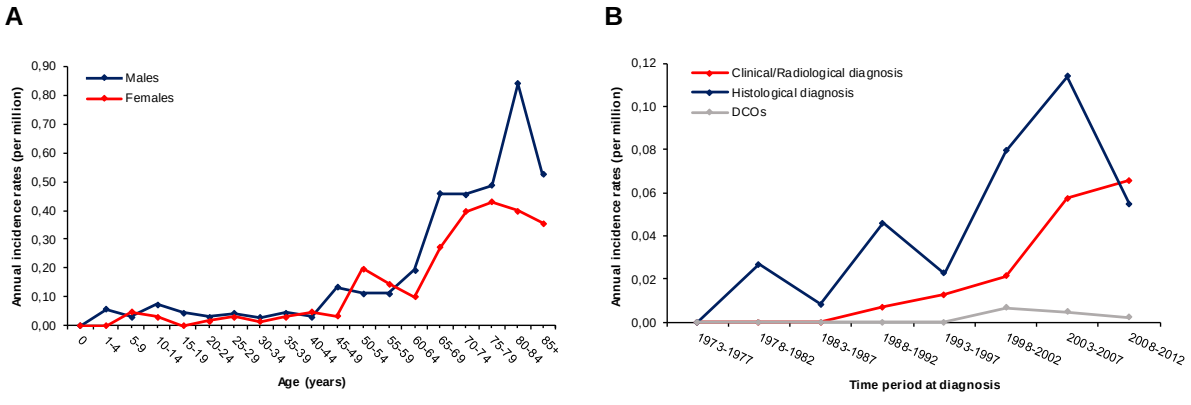
Table 26. Age-adjusted incidence rates (AIR), male-to-female ratios (M:F) and annual percent changes (APC) of gliomatosis cerebri in the Surveillance, Epidemiology, and End Results Program (SEER, 1973-2012).

Age group	AIR[a]	M:F[b]	APC
1973-2012			
0-14 years	0.04	1.9	+5.4 (-0.9; +12.1)
15-39 years	0.03	2.1	**+9.0 (+2.0; +16.5)**
40-64 years	0.10	1.1	**+7.8 (+3.6; +12.3)**
≥65 years	0.43	1.4	**+5.6 (+2.7; +8.5)**
Total	0.10	1.4	**+7.0 (+4.9; +9.2)**
2003-2012			
0-14 years	0.06	1.4	-1.1 (-20.3; +22.7)
15-39 years	0.05	2.4	-7.1 (-22.7; +11.8)
40-64 years	0.15	1.0	-7.6 (-16.9; +2.8)
≥65 years	0.61	1.4	-3.6 (-11.7; +5.2)
Total	0.15	1.3	-4.5 (-10.1; +1.5)

As presented in [292].
Bold indicates statistical significance (p<0.05).
[a] AIRs are presented in cases per million individuals per year.
[b] M:F ratios were calculated by dividing incidence rates for males and females.

A statistically significant temporal increase in GC incidence emerged over the registration period (APC 7%, 95%CI: 4.9-9.2; **Table 26**). The Joinpoint regression analysis revealed that the increase in GC incidence rates was pertained to the period 1973-2002, followed by a plateau in the subsequent last 10 years of registration (2003-2012). **Figure 20B** depicts the temporal changes in GC incidence by method of diagnosis showing an increase in incidence of both histologically and clinically/radiologically diagnosed tumors over the registration period. Of note, the increase was more abrupt for tumors diagnosed via clinical/radiological methods, as the incidence rates increased from 0 until 1987 to 0.07/million in the latest 5-year registration period (2008-2012), overcoming the rate for histological diagnoses (0.05/million).

Figure 20. Gliomatosis cerebri (A) annual incidence rates (per million individuals) by age group and sex and (B) temporal trends by method of diagnosis in the population covered by Surveillance, Epidemiology, and End Results Program (SEER, 1973-2012).



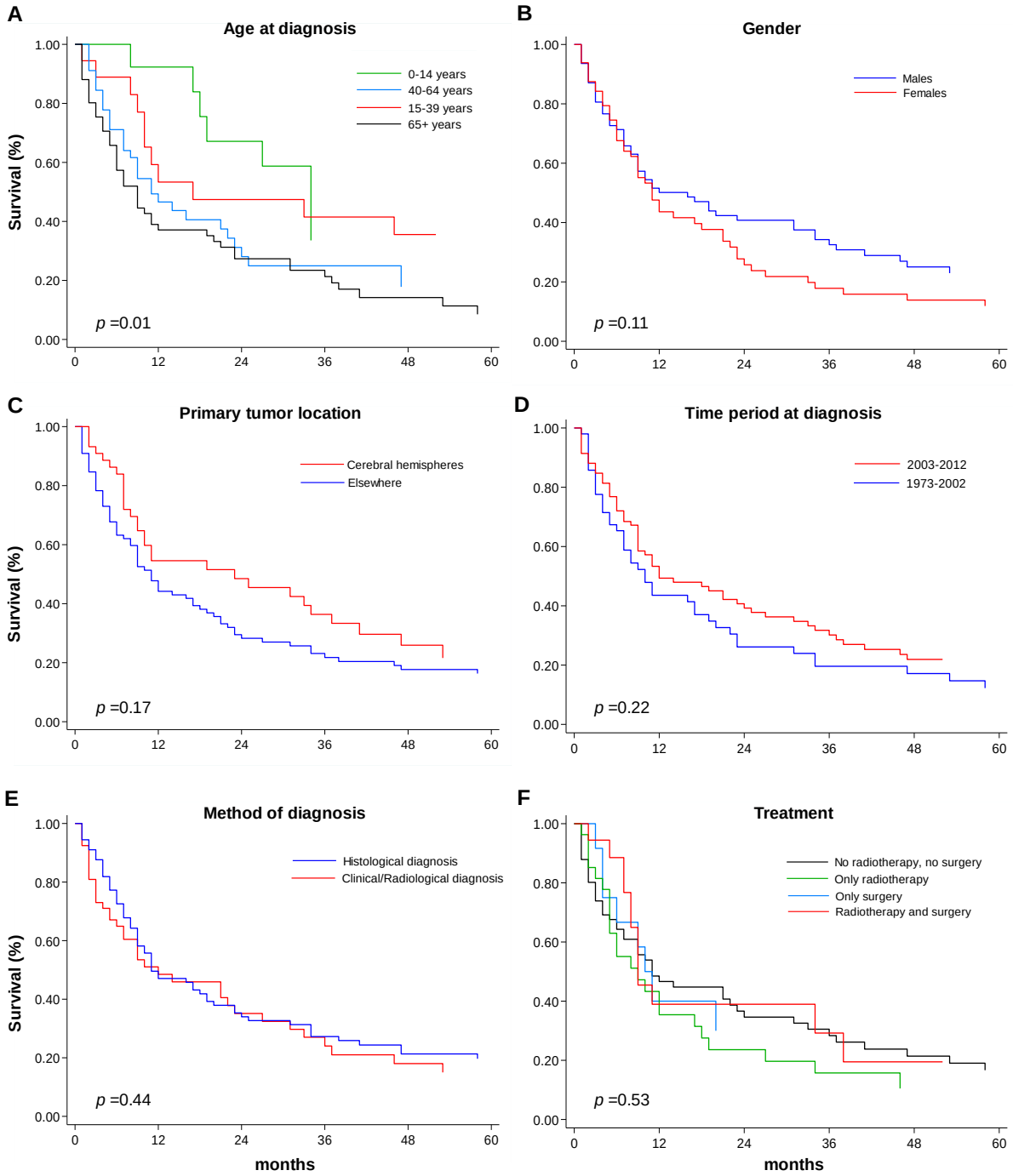
As presented in [292].

Survival

Confirming the poor prognosis of the disease, overall 1-year, 2-year and 5-year survival rates in the SEER dataset were 47% (95%CI: 38-55%), 34% (95%CI: 26-42%) and 18% (95%CI: 11-26%), respectively, with a median OS of 9 months (range: 1-298). **Figure 21** depicts the Kaplan-Meier curves by the study variables. Age was identified as impacting on survival (*p*-log-rank trend test=0.01) with the age groups of children (0-14 years) and AYAs (15-39 years) showing improved outcomes (5-year OS: 33%, 95%CI: 10-59% and 35%, 95%CI: 15-57%, respectively; median survival: 34 and 14.5 months, respectively), compared to middle-aged (40-64 years) and elderly (≥65 years) adults (5-year OS: 18%,95% CI: 7-32%, and 8%, 95%CI: 2-19%, respectively; median survival 9.5 and 6 months, respectively). Furthermore, male sex (5-year OS: 23%, 95%CI: 13-34% vs. 12%, 95%CI: 5-22% among females) and primary tumor location in the cerebral hemispheres (5-year OS: 22%, 95%CI: 10-37% vs. 15%, 95%CI: 8-24% for tumors located in other brain areas), showed a tendency for increased survival rates, but no statistically significant effects emerged (*p*=0.11 and 0.17, respectively). When restricting analyses to2003-2012, 5-year survival increased to 22% (95% CI: 13-32%), from 12% (95% CI: 5-24%) for patients diagnosed in the period 1973-1992, but the difference was not statistically significant (*p*=0.22). Methods of diagnosis (*p*=0.44) and treatment with radiation therapy or surgical excision were not associated with survival (*p*=0.53).

Table 27 presents the results of the univariable and multivariable Cox proportional hazard models in the total sample and in the subsample of patients ≥15 years at diagnosis. The multivariable analysis confirmed increasing age (by 5 year-increment) to be a negative prognostic factor for GC, increasing the risk of death by 8% and 7%, respectively, in the two models. Furthermore, residence in a rural area at diagnosis was an additional risk factor for death., In the restricted dataset that excluded children, a marginally significant association of primary tumor location in the cerebral hemispheres with improved OS outcome was identified (HR: 0.64, 95%CI: 0.41-1.02). Lastly, among patients aged ≥15 years at diagnosis, more recent diagnostic time period was also associated with improved outcome. Race, method of diagnosis, receipt of radiation therapy and surgery did not seem to affect OS.

Figure 21. Kaplan-Meier overall survival curves of patients with gliomatosis cerebri with available follow-up time in the Surveillance, Epidemiology, and End Results Program (SEER) (1973-2012) by (A) age group at diagnosis, (B) sex, (C) primary tumor location, (D) time period at diagnosis, (E) method of diagnosis, and (F) treatment.



As presented in [292].
The *p*-values are derived from the log-rank test.

Table 27. Cox proportional hazard models for the effect of study variables on the survival of patients diagnosed with gliomatosis cerebri in the Surveillance, Epidemiology, and End Results Program (SEER) database (1973-2012).

Variables	***Overall dataset***								***Adolescents and adults (≥15 years)***							
	Univariable analysis N=143				***Multivariable analysis N=107***				***Univariable analysis N=130***				***Multivariable analysis N=99***			
	HR	**95% CI**		***p*-value**	**HR**	**95% CI**		***p*-value**	**HR**	**95% CI**		***p*-value**	**HR**	**95% CI**		***p*-value**
Age (5-year increment)	1.07	1.03	1.12	0.001	1.08	1.03	1.12	<0.001	1.06	1.01	1.12	0.03	1.07	1.01	1.13	0.03
Sex (female vs. male)	1.36	0.92	1.99	0.12	1.25	0.85	1.85	0.27	1.36	0.92	1.99	0.12	1.14	0.75	1.72	0.54
Race (Caucasian vs. other)	1.28	0.66	2.45	0.47					1.43	0.72	2.85	0.31				
Place of residence (rural vs. urban)	2.33	1.07	5.04	0.03	2.40	1.08	5.34	0.03	2.13	0.98	4.64	0.06	2.24	0.99	5.08	0.05
Period of diagnosis (10-year increment)	0.91	0.67	1.24	0.53					0.69	0.48	0.98	0.04	0.66	0.46	0.94	0.02
Primary tumor location (Cerebral hemispheres vs. elsewhere)	0.75	0.50	1.14	0.18	0.78	0.51	1.20	0.26	0.61	0.39	0.95	0.03	0.64	0.41	1.02	0.06
Method of diagnosis (Clinical/radiological vs. histological)	1.15	0.77	1.73	0.49					1.12	0.74	1.70	0.60				
Radiotherapy (Yes vs. no)	1.13	0.76	1.68	0.54					0.97	0.63	1.48	0.89				
Surgery (Yes vs. no)	0.82	0.51	1.32	0.42					0.73	0.44	1.20	0.21				

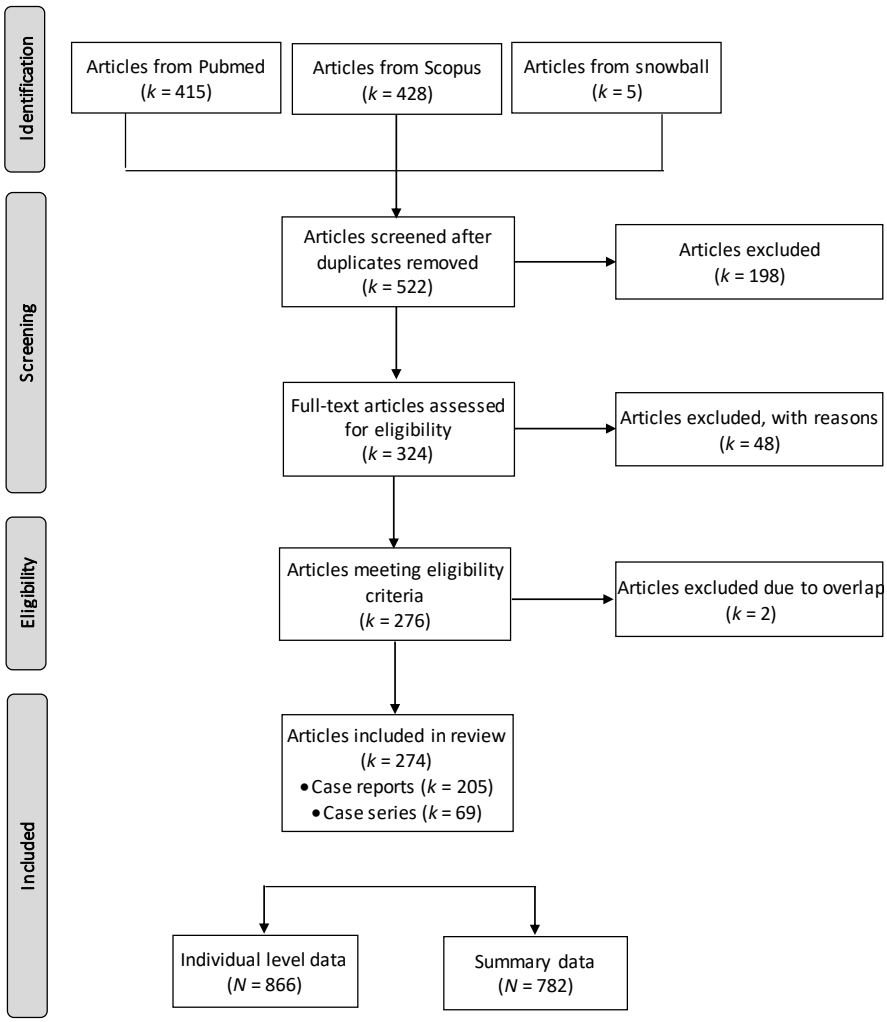
As presented in [292].
Bold indicates statistical significance ($p<0.05$).

Studies #9-10: Clinical, neuroimaging, histopathological features, prognostic factors, and survival of gliomatosis cerebri: a systematic review based on synthesis of published individual patient data

Search strategy results

The successive steps for selection of eligible articles in this systematic review are summarized in **Figure 22**. The search strategy yielded 522 unique records. Of them, 274 articles (205 case reports and 69 case series) met the eligibility criteria and were included. Individual patient data were available and extracted for 866 patients with GC. Additionally, we extracted summary statistics for 782 patients, for whom individual level data were not presented. Two studies were excluded due to overlap on the populations and information provided.

Figure 22. Flowchart on the selection of eligible studies.



As presented in [293].
k refers to number of studies and *N* refers to number of patients.

Characteristics of the patients at diagnosis

Table 28 presents basic demographic, histological and neuroimaging characteristics. Males represented 58.9% of the study subjects. Mean age at diagnosis was 43.6 years and the median time elapsed from symptom onset to diagnosis was 4 months. Presence of a genetic syndrome predisposing to CNS tumors was recorded in only 1.5% of cases with only 3.7% of the tumors emerging as a secondary expansion of an already diagnosed glioma. Diagnosis identified by autopsy after death (7.5%) were substantially more frequent in studies published before 1995 (42.1% vs. 3.6%, $p<0.001$). The majority of tumors (79.1%) were of astrocytic pathology and of grade II (52.1%). Regarding CNS infiltration at diagnosis, 29.9% of the cases already presented infratentorial involvement, 35% expanded bilaterally, and 28.9% affected 6 or more CNS regions. In almost one third of the patients (31.4%), a focal contrast-enhanced mass was also evident in addition to the diffuse component, thus corresponding to GC type II phenotype.

Clinical features and tumor topography

The factor analysis of the presenting symptoms identified 5 clusters of symptoms, as detailed in **Figure 23A**; the Kaiser–Meyer–Olkin value was 0.78, well above the >0.60 threshold commonly used to assess factorability of data[232]. The most common symptom at diagnosis was seizures (49.8%) comprising a symptom group by itself and negatively correlated with all other clusters. Symptoms named under the category of "intracranial hypertension", included headache, nausea/vomiting, papilledema, and visual disturbances and were present in 48.1% of the patients; 47.4% of the patients had focal motor or sensory deficits, cranial nerves paresis, speech disorders or abnormal reflexes, which were grouped together by factor analysis and were named under "focal neurological deficits". Cognitive, behavioural or psychiatric symptoms were present in 41.3% of the GC patients, whereas 21.3% of the patients also presented "cerebellar symptoms".

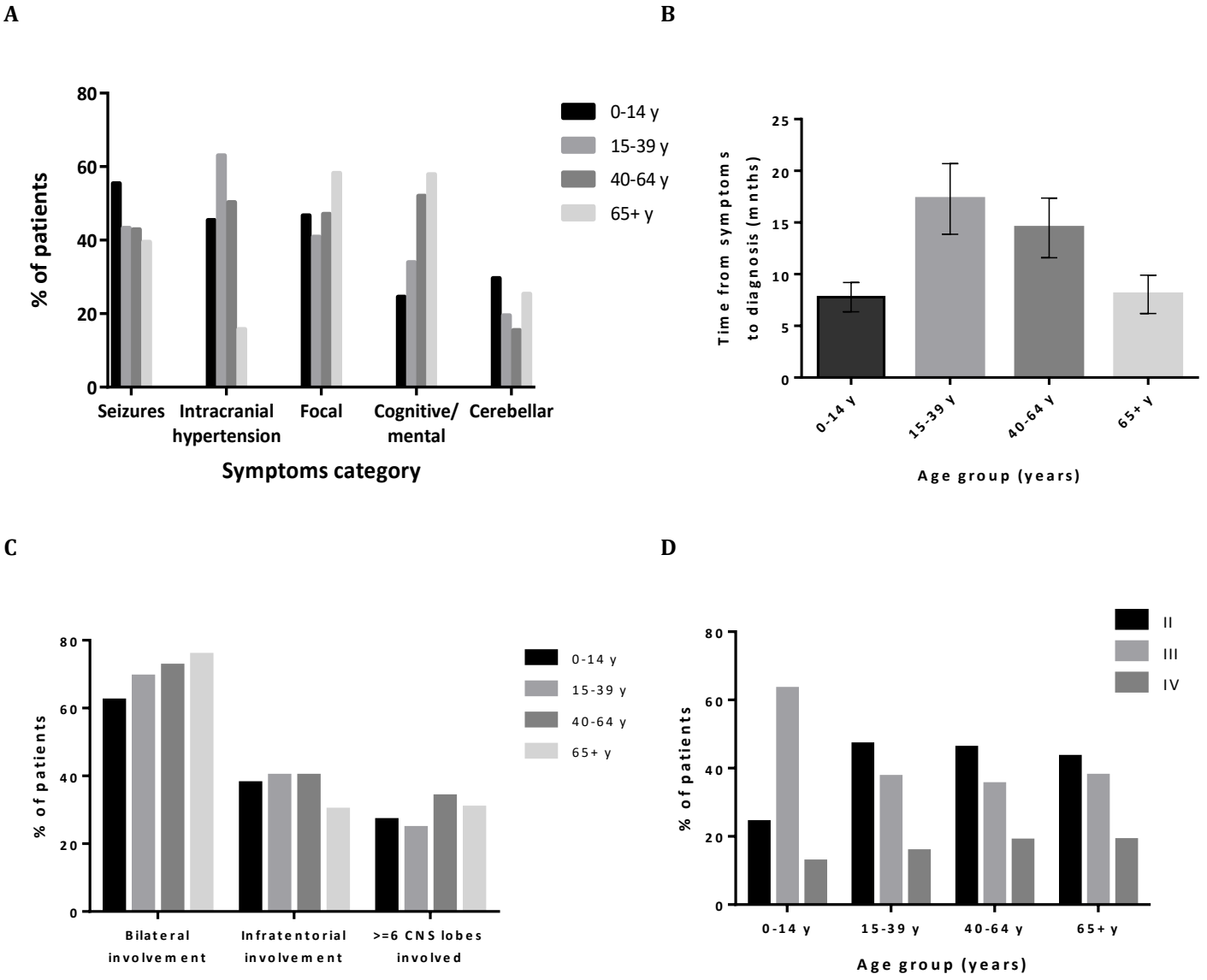
The most common regions affected by GC were the temporal (78.7%), frontal (72.7%), and parietal lobes (60.3%), followed by corpus callosum (49.1%), the diencephalon and basal ganglia (48.4%), and the occipital lobe (33.6%) (**Figure 23B**). The brainstem was affected in 29.3% of the patients, cerebellum in 12.4%, and the spinal cord in 6.7%. **Figure 23C** presents the associations between symptoms and tumor topography. Seizures were associated with infiltration of the frontal and temporal lobes, whereas cognitive/mental symptoms with infiltration of the parietal and occipital lobes, and the corpus callosum. Expansion of the pathology to the corpus callosum was also associated with intracranial hypertension and cerebellar symptoms. Tumor expansion in the diencephalon and the basal ganglia, the brainstem and the spinal cord was associated with focal neurological deficits. Cerebellar symptoms were additionally associated with infiltration of the cerebellum, the brainstem and the spinal cord.

Table 28. Demographic, histological and imaging characteristics of 1,648 patients with gliomatosis cerebri (GC).

Variables	**N (%)**
Sex (N=15,19)	
Male	895 (58.9)
Female	624 (41.1)
Age at diagnosis, years (N=794)	
0-14	141 (17.8)
15-39	225 (28.3)
40-64	307 (38.7)
≥65	121 (15.2)
Mean age, years (N=1,576)	43.6
Time from symptoms to diagnosis, months (N=410)	
Median (IQR)	4 (1-12)
Genetic syndrome (N=793)	
Yes	12 (1.5%)
No	781 (98.5%)
Primary tumor (N=1,111)	
Yes	1070 (96.3)
No	41 (3.7)
Diagnosis with autopsy (N=828)	
Yes	62 (7.5)
No	766 (92.5)
Histology subtype (N=1,091)	
Astrocytoma	863 (79.1)
Oligodendroglioma	127 (11.6)
Oligoastrocytoma	101 (9.3)
Grade (N=1,291)	
II	673 (52.1)
III	480 (37.2)
IV	138 (10.7)
Tumor location (N=690)	
Solely supratentorial	484 (70.1)
Expansion to infratentorial regions	206 (29.9)
Bilateral involvement (N=942)	
Yes	612 (65.0)
No	330 (35.0)
CNS regions involved (N=508)	
<6	361 (71.1)
≥6	147 (28.9)
GC type (N=1,227)	
I	842 (68.6)
II	385 (31.4)

As presented in [293].
The number of GC patients with available data across the variables differ depending on missing information in the respective variables, due to not being reported in the published articles.

Figure 23. Impact of age on tumor characteristics. Associations of age at diagnosis with (A) presenting symptoms, (B) time elapsed from symptoms to diagnosis*, (C) tumor imaging progression, and (D) tumor grade.

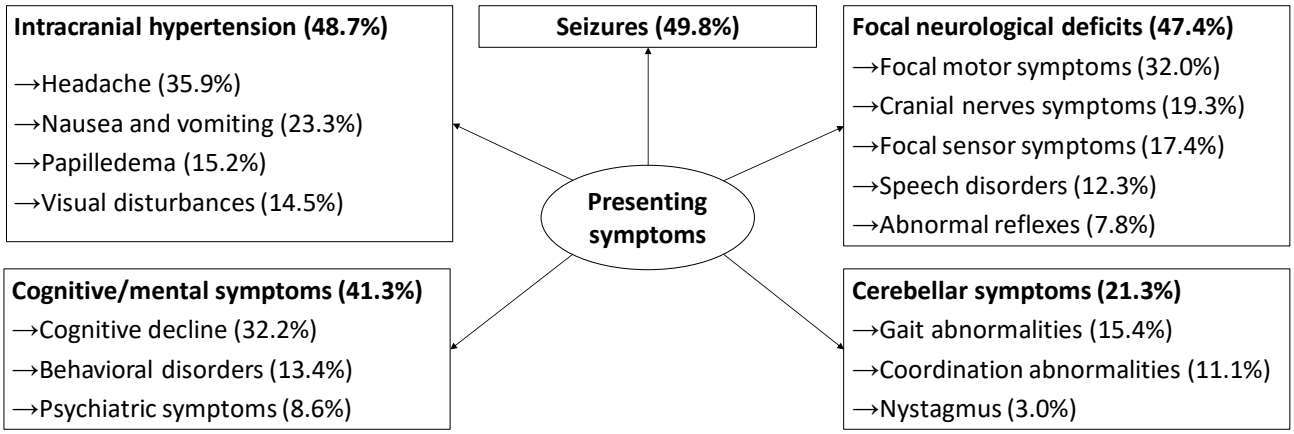


As presented in [293].

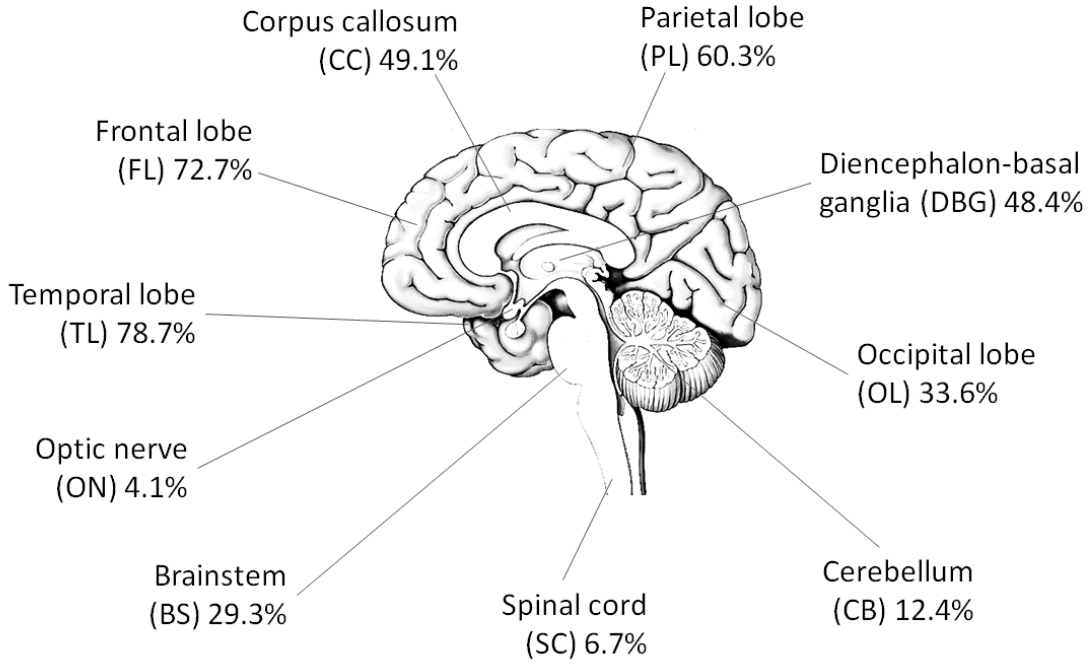
Presence of seizures decreased, whereas presence of cognitive/mental symptoms increased with increasing age (**Figure 24A**); as expected, intracranial hypertension symptoms were considerably lower in the older age group (65+ years). Time from symptoms to diagnosis was lowest in the younger and older age categories (0-14 and 65+ years) (**Figure 24B**). The older age group at diagnosis was also associated with higher prevalence of bilaterally expanded tumors (**Figure 24C),** whereas low-grade tumors were less common in the younger age group (0-14 years) (**Figure 24D**).

Figure 24. Clinical features and topography of gliomatosis cerebri. (A) Frequency of presenting signs and symptoms, and grouping based on factor analysis. (B) Central nervous system region involved in patients with gliomatosis cerebri. (C) Associations of symptom categories with topography.

A



B



C

Symptoms	FL	TL	PL	OL	CC	DBG	ON	CB	BS	SC
Seizures	•	•								
ICH symptoms					•		•			•
Focal neurological deficits						•			•	•
Cognitive/mental symptoms			•	•	•					
Cerebellar symptoms					•			•	•	•

As presented in [293].
Figure 24B: Categorization of symptoms derived from factor analysis.
Figure 24C: The dots correspond to statistically significant associations derived from chi-square test.

Neuroimaging findings and diagnostic workup

Evaluation of the neuroimaging reports showed that MRI provided the most consistent findings, with diffuse hyperintensities in T2 or FLAIR sequences being evident in the entireness (100%) of the 1237 GC cases with available MRI images (**Table 29**). Evaluation of the tumors post-contrast enhancement in the T1 sequence showed areas of focal enhancement in 35.7% of the patients. There were no reports from the perfusion and the diffusion MRI sequences. MR spectroscopy was also found to provide consistent findings across patients with GC. Specifically, the most common findings included increased choline, creatinine, and myoinositol, and decreased NAA levels in the areas affected by the tumor for >85% of the patients, whereas in >90%the tumors also presented increased choline-to-creatinine and choline-to-NAA and decreased NAA-to-creatinine ratios. On the contrary, CT and PET were rather non-informative providing inconsistent findings across the patients. CT scanning, available in N=199) showed a hypodense lesion in 58.5% of the GC tumors, but also an isodense and hyperdense lesion in 19.7% and 6.4% of the cases, respectively, whereas no CT lesion could be found in 15.4% of the tumors. Finally, among 35 patients with available PET imaging, 45.7% showed hypermetabolic, 42.9% hypometabolic tumor activity and 11.4% no lesion.

Table 29. Imaging findings of gliomatosis cerebri tumors at diagnosis.

Neuroimaging method	Findings	%
MRI (N=1237)	Diffuse hyperintensities	100
	Contrast enhancement	35.7
MR Spectroscopy (N=84)	Increased choline	95.1
	Increased creatinine	88
	Decreased NAA	97.6
	Increased choline: creatinine ratio	93.7
	Increased choline: NAA ratio	97.6
	Decreased NAA: creatinine ratio	97.9
	Increased myoinositol	88.9
CT (N=199)	Hypodense lesion	58.5
	Isodense lesion	19.7
	Hyperdense lesion	6.4
	No lesion	15.4
PET (N=35)	Hypometabolic lesion	45.7
	Hypermetabolic lesion	42.9
	No lesion	11.4

As presented in [293].
Abbreviations: MRI, magnetic resonance imaging; MR, magnetic resonance; CT, computed tomography; PET, positron emission tomography; NAA, N-acetylaspartate.

For 86 patients, there were available data on cerebrospinal fluid examination. Of them, 18.6% showed pleiocytosis, whereas cytology was positive for malignant cells in only 3 patients (3.5%). High protein and low glucose levels were found in 13 (15.1%) and 4 patients (4.7%), respectively. Among 62 patients with available electroencephalogram, abnormal findings were found in 50 (80.7%), but they were not consistent across patients. Based on reports from the original studies, GC most commonly mimicked infectious encephalitis or meningitis, autoimmune demyelinating diseases and cerebrovascular events.

Histopathological features and molecular aberrations

Low-grade astrocytoma (38.2%) and anaplastic astrocytoma (33.5%) comprised the most common histopathological diagnoses of GC. In 15.3% of the GC tumors, the histopathological features were in line with glioblastoma. Oligodendroglioma, anaplastic oligodendroglioma, oligoastrocytoma and anaplastic oligoastrocytoma corresponded each to 3-4% of the total number of cases. More than two thirds of the cases across all histological subtypes corresponded to GC type I, except for glioblastoma; 73% of all glioblastomas had a neuroimaging picture of GC type II. O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation (41%) and IDH1 mutations (36.5%) were the most common molecular aberrations. **Table 30** presents the molecular aberrations of the tumors according to grade and histology. IDH1 mutations were more common in tumors of lower grade. Furthermore, IDH1 mutations, MGMT promoter methylation and codeletion of the 1p and 19q chromosomes were significantly more common among oligodendroglial and oligoastrocytic tumors, when compared to astrocytomas.

Table 30. Molecular characteristics of gliomatosis cerebri tumors by grade and histology.

Genetic alteration N (%)	Grade				Histology		
	II	III	IV	p-value	Astrocytic	Oligodendroglial involvement	p-value
IDH1 mutations	52/120 (43.3)	28/87 (32.2)	5/26 (19.2)	0.04[a]	29/127 (22.8)	28/48 (58.3)	<0.0001
TP53 mutations	5/41 (12.2)	2/53 (3.8)	4/24 (16.7)	0.18[a]	8/90 (8.9)	1/10 (10.0)	0.99[a]
PTEN mutations	1/17 (5.9)	1/20 (5.0)	1/16 (6.3)	0.99[a]	3/30 (10.0)	0/5 (0.0)	0.62[a]
EGFR amplification	0/20 (0.0)	1/22 (4.6)	2/16 (12.5)	0.27[a]	3/49 (6.1)	0/9 (0.0)	0.60[a]
MGMT promoter methylation	9/24 (37.5)	15/41 (36.6)	10/17 (58.8)	0.26	24/70 (34.3)	10/13 (76.9)	0.006[a]
1p19q deletion	6/36 (16.7)	4/44 (9.1)	0/20 (0.0)	0.12[a]	5/105 (4.8)	8/10 (80.0)	<0.0001[a]

As presented in [293].

[a] *p*-values derived from Fisher's exact test.

Abbreviations: EGFR, epidermal growth factor receptor; IDH1, isocitrate dehydrogenase 1; MGMT, O6-mMethylguanine DNA methyltransferase; PTEN, Phosphatase and tensin homolog; TP53, tumor protein p53.

Determinants of tumor expansion

Lastly, we examined determinants of tumor expansion at diagnosis in an ordinal regression model (**Table 31**). A younger age at diagnosis (0-14 years), cognitive/mental symptoms, cerebellar symptoms, increasing duration of the period between symptom onset and diagnosis, increasing grade and presence of an oligodendroglial component were associated with increasing number of infiltrated CNS regions. Molecular aberrations of the tumor were not found to be associated with number of affected CNS regions, but the number of patients with available molecular characteristics were low. In the multivariable analysis (N=134), only the duration between symptom onset and diagnosis remained statistically significant (OR per month: 1.024, 95% CI: 1.010-1.038).

Table 31. Determinants of central nervous system invasion in gliomatosis cerebri. Univariable and multivariable ordinal regression analysis with number of CNS regions affected as dependent variable.

		Univariable		Multivariable
Variables	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
Age at diagnosis, years	437		134	
0-14		**1.74 (1.12-2.69)**		0.98 (0.43-2.22)
15-39		Ref		Ref
40-64		1.50 (0.98-2.30)		1.46 (0.69-3.12)
≥65		1.44 (0.82-2.53)		1.21 (0.43-3.36)
Sex	437			
Male		Ref		
Female		1.11 (0.80-1.55)		
Clinical presentation	361			
Seizures		1.01 (0.70-1.46)		
Focal deficit		1.26 (0.88-1.82)		
Cognitive/ mental symptoms		**1.74 (1.20-2.52)**		1.00 (0.53-1.89)
ICH symptoms		1.15 (0.80-1.66)		
Cerebellar symptoms		**2.12 (1.38-3.26)**		1.62 (0.82-3.21)
Time from symptoms to diagnosis	249		134	
Months (increment)		**1.014 (1.004-1.025)**		**1.024 (1.010-1.038)**
Histology subtype	338		134	
Astrocytoma		Ref		Ref
Oligodendroglial involvement		**1.88 (1.11-3.20)**		1.28 (0.54-3.06)
Grade	314		134	
II		Ref		Ref
III		**1.69 (1.11-2.57)**		1.54 (0.79-2.99)
IV		**2.21 (1.19-4.12)**		2.25 (0.89-5.70)
Molecular characteristics				
IDH1 mutations	51	0.39 (0.09-1.65)		
TP53 mutations	62	1.31 (0.37-4.59)		
PTEN mutations	25	7.93 (0.51-124.09)		
MGMT promoter methylation	37	0.31 (0.08-1.22)		
1p/19q codeletion	67	2.25 (0.56-9.10)		

As presented in [294]. *Abbreviations:* EGFR, epidermal growth factor receptor; IDH1, isocitrate dehydrogenase 1; MGMT, O6-methylguanine DNA methyltransferase; PTEN, Phosphatase and tensin homolog; TP53, tumor protein p53.

Survival analysis

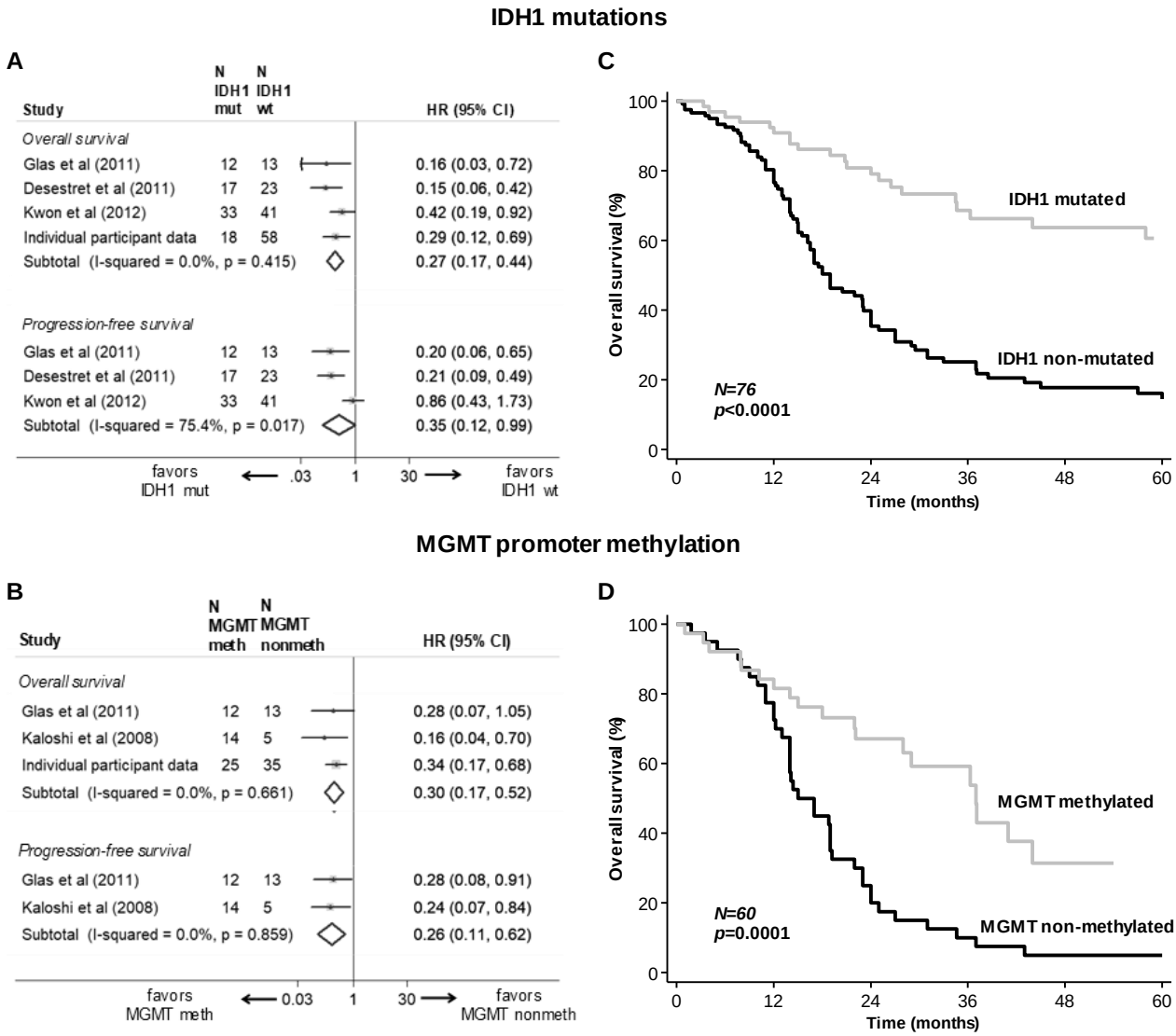
Individual level data could be extracted on 866 patients (IPD) out of whom 523 were not *postmortem* autopsy diagnoses and had follow-up information; summary data were available for another 782 patients. These patients were included in the survival analyses. Hazard Ratios reported or calculated for the later dataset were meta-analyzed along with the effect estimates of the IPD dataset, depending on data availability. Kaplan-Meier survival curves showed a 61% (95%CI: 56-65%) 1-year, 18% (95%CI: 14-22%), 5-year and 10% (95%CI: 6-14%) 10-year OS and 53% (95%CI: 45-60%), 13% (95%CI: 5-25%), and 4% (95%CI: 0-17%) PFS rates, respectively. The median OS and PFS times were 13 (IQR: 6-24) and 10 (IQR: 4-20) months, respectively.

Prognostic factors

The results of the IPD analysis were in line with results from the other studies and also confirmed by the meta-analysis with results from studies offering only summary statistics. Of note, IDH1 mutation and methylation of the MGMT promoter were associated with decreased risk of death (HR: 0.27, 95%CI: 0.17-0.44 and HR: 0.30, 95%CI: 0.17-0.52, respectively) and progression (HR: 0.35, 95%CI: 0.23-0.99 and HR: 0.26, 95%CI: 0.11-0.62, respectively) (**Figure 25).**

Results of the multivariable analysis are shown in **Table 32**. Age at diagnosis ≥65 years was strongly associated with worse OS (HR: 2.32, 95%CI: 1.62-3.31), and marginally with PFS (HR: 1.68, 95%CI: 0.96-2.96). Sex and histology were not associated with OS or PFS, whereas the effect of grade was only associated with PFS (HR for grade III vs. II: 1.57, 95%CI: 1.02-2.40 and HR for grade IV vs. III: 1.74, 95%CI: 0.98-3.10). A type II GC was associated with worse OS (HR: 1.49, 95%CI: 1.12-1.98) and PFS (HR: 1.56, 95%CI: 1.04-2.34), whereas invasion of increasing number of CNS regions was associated with worse OS (HR per 1 more region: 1.09, 95%CI: 1.01-1.18). Among clinical symptoms, an increased risk of death was noted for patients presenting focal neurological deficits (HR: 1.41, 95%CI: 1.07-1.86) and cerebellar symptoms were associated with worse PFS (HR: 2.20, 95%CI: 1.42-3.39); in contrast, seizures were associated with prolonged OS (HR: 0.77, 95%CI: 0.60-1.00) and PFS (HR: 0.68, 95%CI: 0.47-0.95). Increasing number of symptoms (counting seizures, focal neurological deficits, intracranial hypertension symptoms, cerebellar symptoms, and cognitive/mental symptoms) was also an independent predictor of worse OS (HR: 1.21, 95%CI: 1.05-1.40). Data were limited (N=75 for OS and N=40 for PFS) regarding the strong association of Karnofsky performance scale score (<70) with poor outcome (HR_{OS}: 3.58, 95%CI: 1.73-7.39 and HR_{PFS}: 4.48, 95%CI: 1.39-14.4, respectively). As expected, response to treatment (HR: 0.16, 95%CI: 0.08-0.30) or stable disease (HR: 0.33, 95%CI: 0.19-0.59) compared to progressive disease were strongly associated with increased OS. MRI contrast enhancement was also a negative predictor for OS and PFS, whereas bilateral symmetric involvements of the two hemispheres was negatively associated with OS (HR: 1.42, 95%CI: 1.03-1.96). Among histopathological and molecular characteristics, increased tumor proliferation, as defined by a Ki67 positivity in >5% of the tumor cells was associated with lower OS (HR: 2.32, 95%CI: 1.11-4.86). Finally, the multivariable analysis confirmed IDH1 mutation (HR: 0.16, 95%CI: 0.05-0.49) and MGMT promoter methylation (HR: 0.23, 95%CI: 0.09-0.59) as positive prognostic factors.

Figure 25. Impact of isocitrate dehydrogenase 1 (IDH1) mutations and methylation of the O^6-methylguanine DNA methyltransferase (MGMT) promoter on prognosis of patients with gliomatosis cerebri. Meta-analysis of the crude effects of (A) IDH1 mutation and (B) methylation of the MGMT promoter on overall and progression-free survival, and (C, D) Kaplan-Meier curves for overall survival.



As presented in [294].

Table 32. Multivariable Cox regression analysis for overall and progression-free survival.

Variable	Category	Overall survival			Progression-free survival		
		N	HR (95%CI)	p-value	N	HR (95%CI)	p-value
Core model [a]		523			224		
Age, years	0-14		1.28 (0.95-1.73)	0.10		1.01 (0.65-1.56)	0.98
	15-39		ref			ref	
	40-64		1.13 (0.86-1.49)	0.39		0.98 (0.65-1.50)	0.94
	65+		**2.32 (1.62-3.31)**	**<0.001**		1.68 (0.96-2.96)	0.07
Sex	female vs. male		1.06 (0.85-1.33)	0.59		1.08 (0.76-1.52)	0.68
Histology	astrocytoma vs. other		1.43 (0.94-2.17)	0.09		1.28 (0.74-2.20)	0.37
Grade	II		ref			ref	
	III		1.17 (0.91-1.51)	0.22		**1.57 (1.02-2.40)**	**0.04**
	IV		1.21 (0.83-1.77)	0.32		1.74 (0.98-3.10)	0.06
GC type	II vs. I		**1.49 (1.12-1.98)**	**0.007**		**1.56 (1.04-2.34)**	**0.03**
CNS regions affected	1 lobe more		**1.09 (1.01-1.18)**	**0.04**		1.02 (0.93-1.12)	0.67
Additional variables alternatively introduced							
Clinical factors							
Time from symptoms to diagnosis	1 month more	234	0.99 (0.98-1.00)	0.12	143	0.99 (0.98-1.01)	0.51
Seizures	yes vs. no	382	0.77 (0.60-1.00)	0.05	202	0.68 (0.47-0.95)	0.02
Focal deficit	yes vs. no	357	1.41 (1.07-1.86)	0.02	202	1.40 (0.98-2.00)	0.06
Cognitive/ mental symptoms	yes vs. no	382	1.26 (0.95-1.67)	0.11	202	1.27 (0.88-1.84)	0.21
ICH symptoms	yes vs. no	383	1.23 (0.94-1.60)	0.14	202	0.76 (0.54-1.09)	0.13
Cerebellar symptoms	yes vs. no	358	1.38 (0.98-1.95)	0.06	203	2.20 (1.42-3.39)	<0.001
Number of symptoms	1 category more	357	1.21 (1.05-1.40)	0.009	202	1.10 (0.91-1.33)	0.32
Karnofsky score	<70 vs. ≥70	75	3.58 (1.73-7.39)	0.001	40	4.48 (1.39-14.4)	0.01
Response to treatment	Response	153	0.16 (0.08-0.30)	<0.001		-	-
	Stable disease		0.33 (0.19-0.59)	<0.001		-	-
	Progressive disease		ref			-	-
Imaging factors							
Contrast enhancement in MRI	yes vs. no	391	1.48 (1.12-1.96)	0.006	196	1.74 (1.18-2.55)	0.005
Infratentorial involvement	yes vs. no	263	1.19 (0.85-1.68)	0.31	154	1.33 (0.85-2.06)	0.21
Bilateral involvement	yes vs. no	306	1.19 (0.87-1.63)	0.96	174	1.32 (0.83-2.09)	0.24
Symmetric invasion	yes vs. no	285	1.42 (1.03-1.96)	0.03	154	1.15 (0.73-1.81)	0.54
Molecular characteristics							
Ki67 (%)	≥5 vs. <5	93	2.32 (1.11-4.86)	0.02	53	2.70 (0.75-9.70)	0.13
IDH1 mutation	yes vs. no	76	0.16 (0.05-0.49)	0.001	4	-	-
TP53 mutations	yes vs. no	71	0.98 (0.34-2.86)	0.97	5	-	-
PTEN mutations	yes vs. no	34	0.92 (0.06-14.8)	0.95	0	-	-
EGFR amplification	yes vs. no	27	4.52 (0.39-51.9)	0.22	2	-	-
MGMT promoter methylation	yes vs. no	60	0.23 (0.09-0.59)	0.002	4	-	-
1p /19q deletion	yes vs. no	91	0.44 (0.14-1.37)	0.16	2	-	-

As presented in [294].

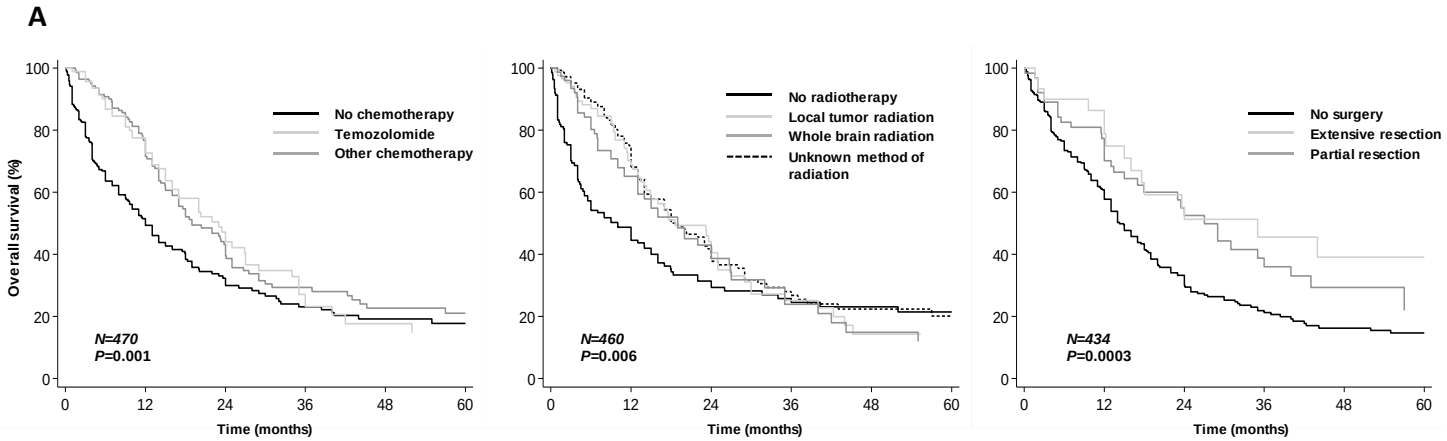
The analysis was conducted after multiple imputation for the variables included in the core model.

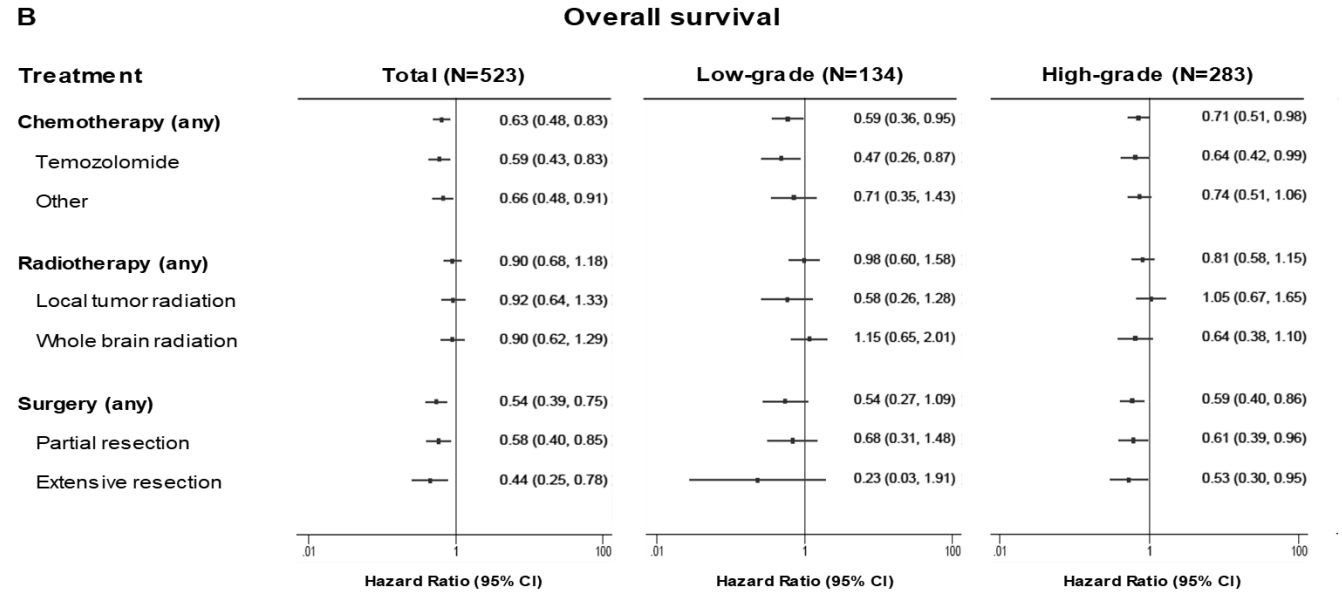
Impact of treatment on outcome

The univariable analysis showed a positive association of chemotherapy, radiotherapy, and surgical resection with OS. **Figure 26A** depicts the Kaplan-Meier survival curves for the different treatment modalities and clearly demonstrated that chemotherapy, radiotherapy, and surgical resection of the GC tumor were associated with prolonged survival. However, no significant differences across the different chemotherapy modalities (protocols including temozolomide or not), radiation approaches (focal tumor or whole brain radiation), and extent of resection (partial or extensive/subtotal) were noted. The multivariable analyses, presented in **Figures 26B and 26C**, adjusted for sex, age, histology, grade, GC type and CNS regions affected showed that chemotherapy and surgical resection were indeed associated with higher OS and PFS, whereas no independent positive association with radiotherapy was identified; only whole brain radiation was associated with PFS. No considerable differences between low-grade and high-grade GC tumors were noted with regard to the impact of treatment on OS and PFS, with the exception of focal tumor radiation which was found to be positively associated only for low-grade tumors.

We subsequently examined the effect of combined treatment modalities on survival (**Table 33**). When compared to patients who received no treatment at all, all combinations of therapy were associated with prolonged OS and PFS. Afterwards we excluded patients who received no treatment to avoid confounding by treatment indication, as patients who received no treatment might have been more likely to have more progressive and advanced tumors. Setting chemotherapy alone as the reference group, no other treatment combination showed a statistically significant improved outcome; on the contrary, radiation alone and radiation plus chemotherapy were associated with worse OS, whereas surgery alone was associated with lower PFS.

Figure 26. Impact of treatment on overall and progression-free survival in patients with gliomatosis cerebri (GC). (A) Kaplan-Meier curves for overall survival by type of chemotherapy, radiotherapy and surgery. (B, C) Effect of specific treatments on overall and progression-free survival, as derived from multivariable Cox regression analyses adjusted for age, sex, histology, grade, GC type, and number of central nervous system (CNS) lobes affected.





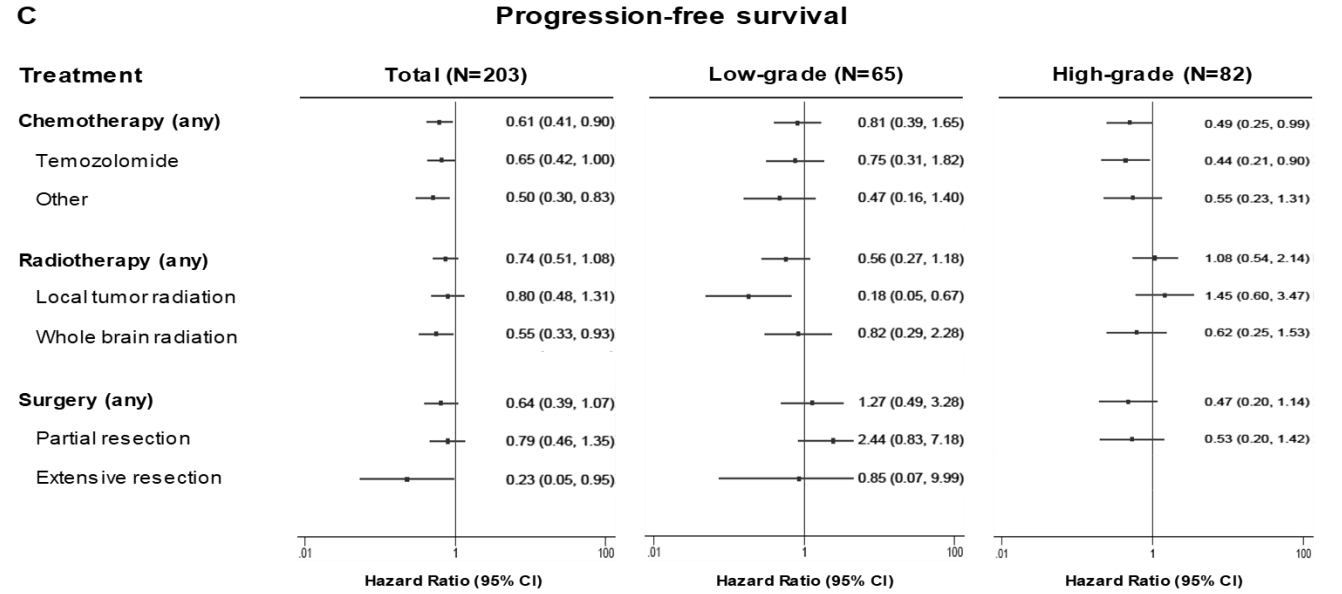


Table 33. Multivariable Cox regression analysis for the effects of treatment combinations on overall and progression-free survival among patients with gliomatosis cerebri.

First line treatment		Overall survival			Progression-free survival		
	N	HR (95%CI)	p-value		N	HR (95%CI)	p-value
No treatment	78	ref			28	ref	
Chemotherapy alone	35	0.33 (0.19-0.58)	<0.001		27	0.29 (0.15-0.58)	0.001
Radiotherapy alone	95	0.68 (0.48-0.98)	0.04		48	0.44 (0.24-0.79)	0.007
Surgery alone	14	0.51 (0.24-1.09)	0.07		8	1.12 (0.44-2.88)	0.81
Chemotherapy + Radiotherapy	116	0.54 (0.39-0.77)	0.001		60	0.42 (0.24-0.74)	0.005
Surgery + Chemotherapy	8	0.39 (0.15-1.01)	0.06		2	0.19 (0.02-1.51)	0.16
Surgery + Radiotherapy	21	0.33 (0.16-0.67)	0.002		8	0.15 (0.04-0.67)	0.01
Surgery + Chemotherapy + Radiotherapy	50	0.26 (0.16-0.43)	<0.001		22	0.20 (0.09-0.44)	<0.001
Exclusion of patients who received no treatment							
Chemotherapy alone	35	ref			27	ref	
Radiotherapy alone	95	2.28 (1.28-4.05)	0.005		48	1.56 (0.81-3.00)	0.19
Surgery alone	14	1.50 (0.62-3.63)	0.37		8	4.11 (1.52-11.14)	0.005
Chemotherapy + Radiotherapy	116	1.74 (1.01-3.01)	0.047		60	1.62 (0.89-2.96)	0.11
Surgery + Chemotherapy	8	1.28 (0.45-3.60)	0.64		2	0.73 (0.09-5.96)	0.77
Surgery + Radiotherapy	21	1.06 (0.46-2.45)	0.90		8	0.49 (0.11-2.21)	0.36
Surgery + Chemotherapy + Radiotherapy	50	0.79 (0.42-1.48)	0.46		22	0.69 (0.31-1.51)	0.35

As presented in [294].
Results adjusted for age, sex, histology, grade, GC type, and number of CNS lobes affected.

Finally, we explored predictors of radiological response to treatment. Astrocytic pathology was associated with better response to treatment in both stable (OR: 0.17, 95%CI: 0.04-0.81) and progressive disease (OR: 0. 21, 95%CI: 0.05-0.81). On the contrary, presence of cerebellar symptoms, higher number of presenting symptoms, and invasion of more CNS regions were associated with higher risk of stable disease vs response.

Study #11: Clinical features of gliomatosis cerebri among children and adolescents

Table 34 presents the main tumor characteristics for included patients and comparisons between GC patients aged ≤18 and >18 years. As compared to adult GC, pediatric GC was more commonly associated with a genetic syndrome predisposing to CNS tumors, was less likely to be an astrocytic tumor, and was more commonly a higher grade tumor. Furthermore, pediatric GC tumors were less likely to expand bilaterally to both hemispheres and were more likely to be type I GC tumors. As

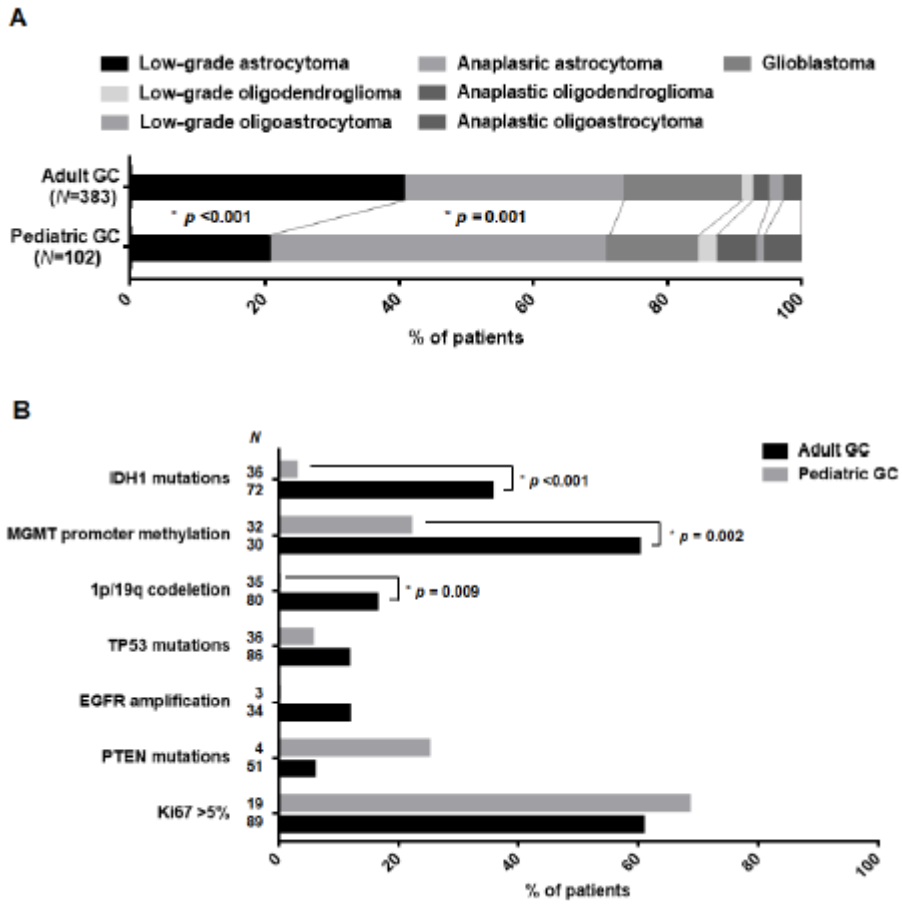
depicted in **Figure 27**, the most common histologic subtype of pediatric GC was anaplastic astrocytoma, as opposed to low-grade astrocytoma in adult patients. Lastly, MGMT promoter methylation, IDH1 mutations, and codeletion of 1p/19q were less common molecular aberrations in pediatric GC, as compared to adult GC.

Table 34. Demographic, histological and imaging characteristics of children and adult patients with gliomatosis cerebri (GC).

Variables	Pediatric GC (0-18 years)	Adult GC (>18 years)	p-value
Sex			0.13[a]
Male	114 (62.6)	330 (56.3)	
Female	68 (37.4)	256 (43.7)	
Time from symptoms to diagnosis, months			0.69[b]
Median (IQR)	5 (1.3-9)	5 (1.5-13)	
Genetic syndrome			<0.001[c]
Yes	9 (5.2)	3 (0.6)	
No	164 (94.8)	470 (99.4)	
Primary tumor			0.99[c]
Yes	139 (97.2)	440 (97.1)	
No	4 (2.8)	13 (2.9)	
Diagnosis with autopsy			0.34[a]
Yes	11 (6.0)	50 (8.2)	
No	171 (94.0)	562 (91.8)	
Histology subtype			0.008[a]
Astrocytoma	101 (82.8)	404 (90.0)	
Oligodendroglioma	11 (9.0)	20 (4.4)	
Oligoastrocytoma	10 (8.2)	25 (5.6)	
Grade			<0.001[a]
II	29 (25.4)	203 (46.8)	
III	67 (58.8)	156 (35.9)	
IV	18 (15.8)	75 (17.3)	
Tumor location			0.87[a]
Solely supratentorial	79 (61.2)	195 (62.1)	
Expansion to infratentorial regions	50 (38.8)	119 (37.9)	
Bilateral involvement			0.003[a]
Yes	79 (59.8)	260 (73.7)	
No	53 (40.2)	93 (26.3)	
CNS regions involved			0.19[a]
<6	119 (74.8)	226 (69.1)	
≥6	40 (25.2)	101 (30.9)	
GC type			0.04[a]
I	108 (73.0)	276 (63.6)	
II	40 (27.0)	158 (36.4)	

As presented in [295].
The results are presented as N (%), except otherwise stated. Two-sided p-values are presented throughout.
[a] Chi-square test.
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.
Abbreviations: CNS, central nervous system; IQR, interquartile range.

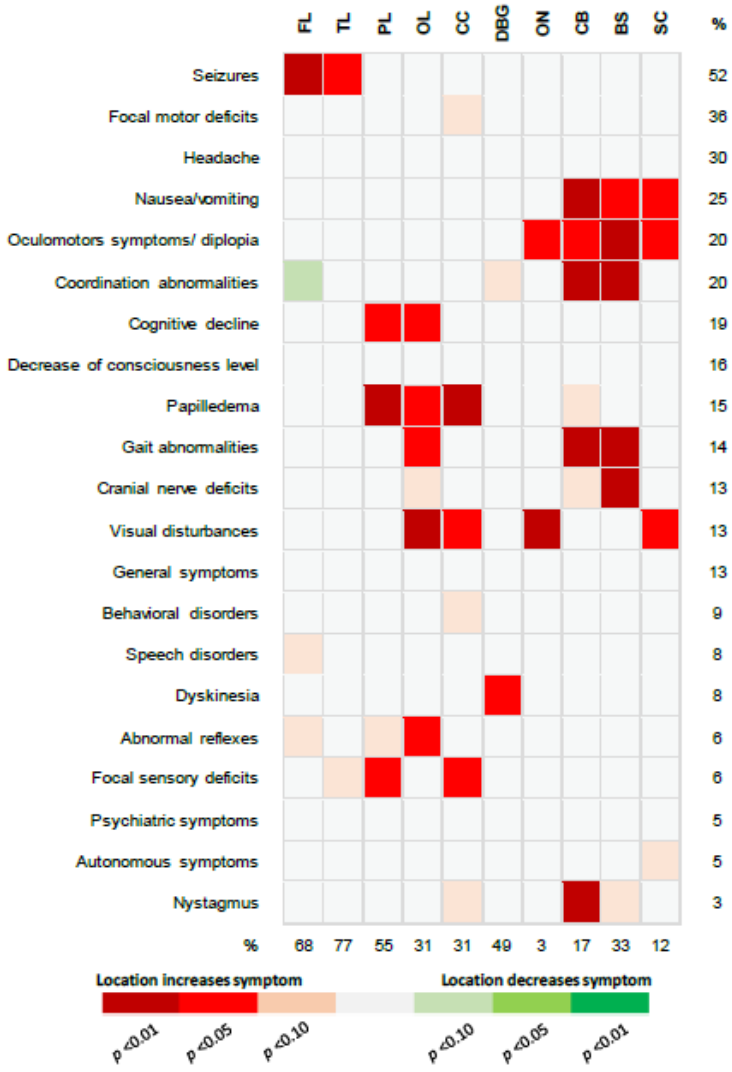
Figure 27. Differences in the (A) histological subtype, and (B) molecular aberrations between patients with pediatric and adult gliomatosis cerebri (GC).



As presented in [295].
P-values are two-sided and are derived from chi-square tests.

Temporal (75%), frontal (69%), and parietal lobes (55%) were the most common CNS regions affected in pediatric GC tumors, followed by diencephalon and basal ganglia (49%), brainstem (33%), occipital lobe (31%), and corpus callosum (31%) (**Figure 28**). A total of 39% of the tumors expanded to infratentorial CNS regions, whereas 60% affected bilaterally both cerebral hemispheres. Regarding clinical presentation of GC, seizures were the most common symptom, occuring in 52% of the patients, followed by focal motor deficits (36%), and headache (30%) (**Figure 28**). Seizures were associated with tumor expansion to the frontal and temporal lobe, whereas expansion to infratentorial CNS regions (cerebellum, brainstem) was associated with nausea/vomitting, oculomortor disorders and diplopia, coordination abnormalities, gait disturbances, cranial nerve deficits, and nystagmus. Cognitive decline was associated with infiltration of the parietal and occipital lobes, whereas tumor expansion to the parietal and occipital lobes, as well as to the corpus callosum was associated with papilledema (**Figure 28**).

Figure 28. Frequencies of presenting symptoms and associations with neuroanatomic expansions of the tumor among patients with pediatric gliomatosis cerebri (GC, 0-18 years).



As presented in [295].
P-values are two-sided and are derived from Chi-square tests.
Abbreviations: FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; CC, corpus callosum; DBG, diencephalon-basal ganglia; ON, optic nerve; CB, cerebellum; BS, brainstem; SC, spinal cord.

Among the study variables (**Table 35**), age at diagnosis >4 years was associated with higher risk of death, as compared to age 0-4 years at diagnosis ($HR_{5\text{-}9}$: 2.38 [1.39-6.40]; $HR_{10\text{-}14}$: 1.97 [0.94-4.16]; $HR_{15\text{-}19}$: 2.43 [1.07-5.54]). Furthermore, an increasing number of affected CNS regions (HR: 1.14, 95%CI: 1.00-1.29) and symptoms of coordination abnormalities (HR: 2.04, 95%CI: 1.05-3.94) and cognitive decline (HR: 2.07, 95% CI: 1.03-4.18) were associated with worse OS. On the contrary, IDH1 mutations were associated with prolonged OS (HR: 0.03, 95%CI: 0.001-0.85).

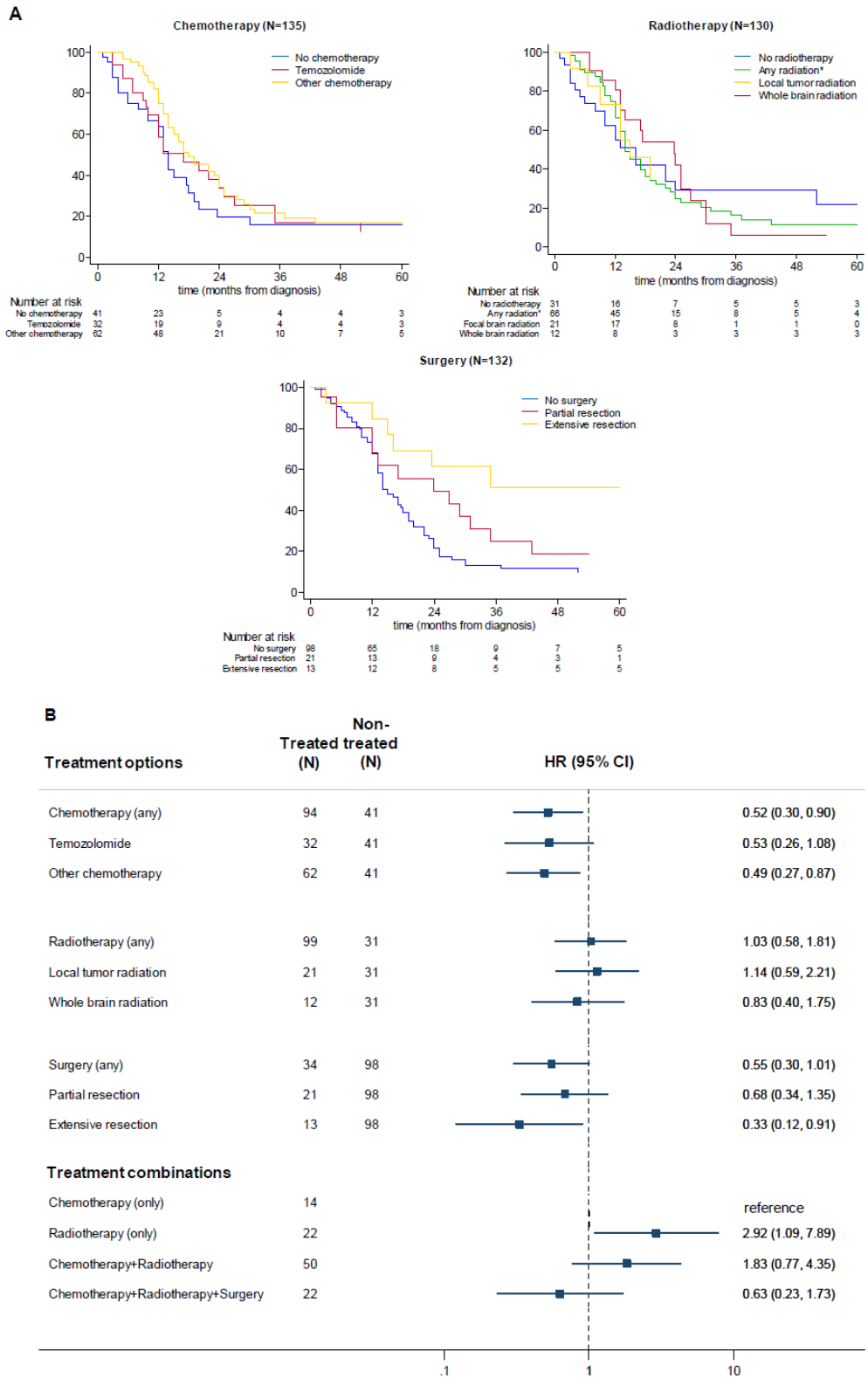
Table 35. Multivariable Cox regression analysis for overall survival.

Variable	Category		Overall survival	
		N	HR (95% CI)	p-value
Core model [a]		141		
Age, years	0-4		ref	
	5-9		**2.98 (1.39-6.40)**	**0.005**
	10-14		1.97 (0.94-4.16)	0.07
	15-18		**2.43 (1.07-5.54)**	**0.04**
Sex	female vs. male		1.32 (0.87-2.02)	0.19
Histology	astrocytoma vs. other		1.32 (0.63-2.76)	0.46
Grade	II		ref	
	III		1.30 (0.78-2.14)	0.31
	IV		1.54 (0.68-3.48)	0.30
GC type	II vs. I		1.11 (0.68-1.81)	0.68
CNS regions affected	1 region more		**1.14 (1.00-1.29)**	**0.048**
Additional variables alternatively introduced [b]				
Clinical factors				
Time from symptoms to diagnosis	1 month more	60	0.95 (0.90-1.01)	0.07
Seizures	yes vs. no	101	0.74 (0.44-1.23)	0.24
Focal motor deficit	yes vs. no	101	1.12 (0.63-2.00)	0.70
Headache	yes vs. no	101	1.59 (0.85-2.96)	0.15
Nausea/vomiting	yes vs. no	101	1.34 (0.67-2.68)	0.41
Oculomotor symptoms/diplopia	yes vs. no	101	1.39 (0.70-2.77)	0.35
Coordination abnormalities	yes vs. no	101	**2.04 (1.05-3.94)**	**0.03**
Cognitive decline	yes vs. no	101	**2.07 (1.03-4.18)**	**0.04**
Decrease of consciousness level	yes vs. no	101	1.46 (0.61-3.46)	0.39
Imaging factors				
Contrast enhancement in MRI	yes vs. no	113	1.11 (0.65-1.89)	0.70
Infratentorial involvement	yes vs. no	91	1.00 (0.55-1.82)	0.99
Bilateral involvement	yes vs. no	94	1.19 (0.65-2.18)	0.58
Symmetric invasion	yes vs. no	91	1.27 (0.67-2.41)	0.47
Molecular characteristics				
IDH1 mutation	yes vs. no	34	**0.03 (0.001-0.85)**	**0.04**
TP53 mutations	yes vs. no	32	0.25 (0.03-2.44)	0.23
MGMT promoter methylation	yes vs. no	31	0.61 (0.16-2.31)	0.47

As presented in [295].
The analysis was conducted after multiple imputation for the variables included in the core model.
[a] Two-sided p-values derived from multivariable Cox regression analysis.
[b] The additionally introduced variables were included in the core model interchangeably and were not subject to multiple imputation.
Abbreviations: CNS, central nervous system; GC, gliomatosis cerebri; HR, hazard ratio; IDH1, Isocitrate dehydrogenase 1; MGMT, O6-methylguanine-DNA-methyltransferase; MRI, magnetic resonance imaging; TP53, Tumor protein 53.

For the different treatment modalities (**Figure 29**), chemotherapy was associated with lower risk of death (HR: 0.50, 95%CI: 0.32-0.90) with the effect size being similar for temozolomide and other chemotherapy regimens. Extended surgical resection was also an independent predictor of prolonged survival (HR: 0.33, 95%CI: 0.12-0.91). On the contrary, radiotherapy (either restricted to the tumor or whole brain radiation) was not associated with OS. When however, restricting analyses to patients who received any treatment, no treatment combinations were identified as superior to chemotherapy alone for prolonging OS of pediatric GC. Importantly, patients receiving solely radiotherapy had worse prognosis, as compared to patients receiving only chemotherapy.

Figure 29. Association of received treatment with overall survival. (A) Unadjusted Kaplan-Meier curves, (B) multivariable effects of different treatment regimens and different treatment combinations (lowest panel) on risk of death.



As presented in [295].

* Any radiation indicates administration of radiotherapy, but of unknown focus (local tumor or whole brain).

Study #12: IDH mutations as predictors of seizure occurrence in gliomatosis cerebri and other gliomas

Association between IDH mutations and seizure occurrence in the gliomatosis cerebri cohort

Table 36 illustrates the distribution of demographic, clinical, and molecular characteristics of GC among patients with GC who presented with or without seizures at diagnosis. Expansion of the tumor in the frontal and temporal lobe was associated with a higher possibility of seizure occurrence before diagnosis. Older age and male sex also showed suggestive associations (p=0.05 and 0.06, respectively) with higher seizure occurrence. On the contrary, IDH mutations were more likely reported in patients with GC presenting with seizures at baseline (44% vs. 9%).

Table 36. Demographic, histological and imaging characteristics of patients with gliomatosis cerebri (GC) stratified by presence of seizures at the time of diagnosis.

Variables	N	Seizures	No seizures	p-value
Age, mean (SD)	541	40.2 ± 21.2	36.7 ± 21.7	0.06
Sex, % males	541	61.9	53.5	0.051
Time from symptoms to diagnosis, months	363	5 [1-15]	4 [2-11]	0.64
Histology	324			0.68
Low-grade astrocytoma		35.1	39.2	
Low-grade oligodendroglioma		7.4	4.0	
Low-grade oligoastrocytoma		2.0	1.7	
Anaplastic astrocytoma		32.4	34.1	
Oligodendroglioma		3.4	5.7	
Oligoastrocytoma		4.7	4.0	
Glioblastoma		14.9	11.3	
Tumor location				0.87
Frontal lobe	423	80.7	63.6	**0.0001**
Temporal lobe	421	83.0	74.1	**0.03**
Parietal lobe	425	62.8	60.3	0.60
Occipital lobe	420	33.5	39.8	0.19
Deep locations	418	55.1	52.9	0.66
Brainstem	419	27.8	38.5	0.02
Cerebellum	418	14.5	16.7	0.54
≥6 CNS regions involved	409	32.8	30.2	0.58
GC type II (N=582)	438	31.1	27.0	0.36
Molecular alterations				
IDH mutations	40	44.4	9.1	**0.02**
TP53 mutations	24	25.0	25.0	0.99
MGMT promoter methylation	22	50.0	50.0	0.99
1p/19q codeletion	34	25.0	33.3	0.35

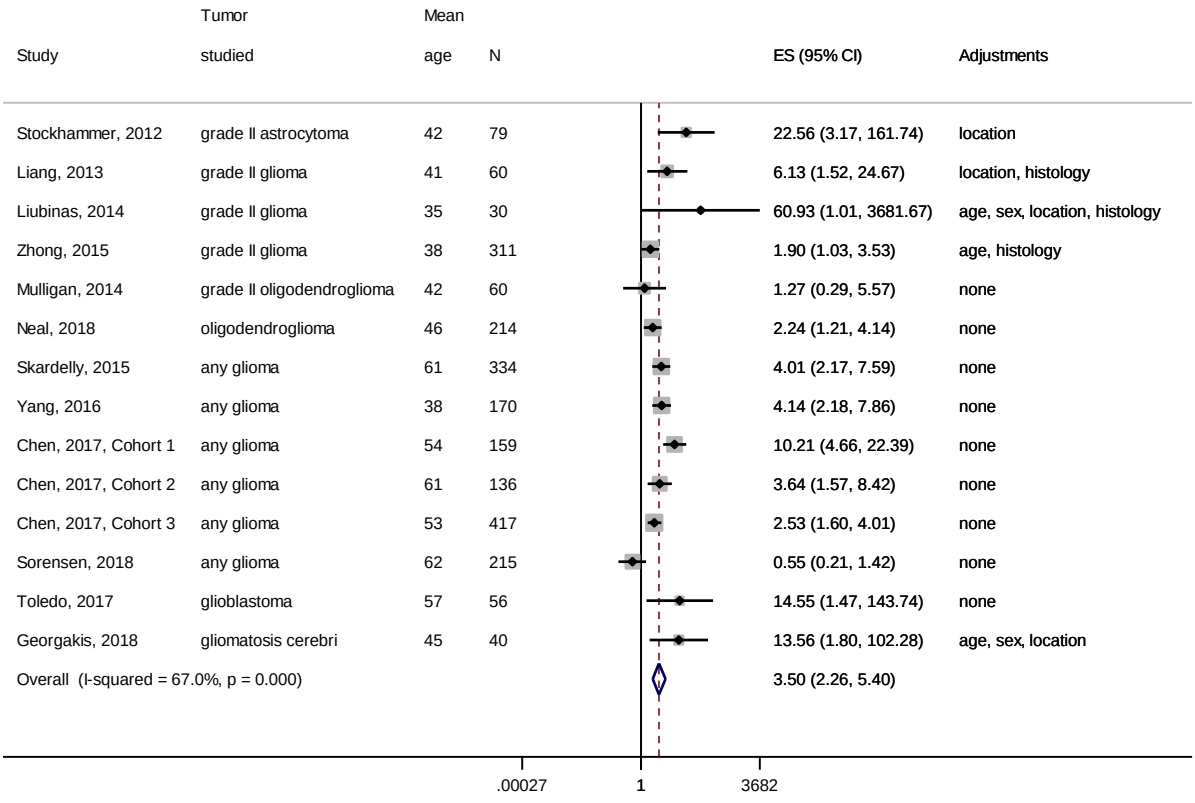
In multivariable analyses restricted to a sub-sample of 40 GC patients with available data on age, sex, tumor location, and IDH mutations, presence of the latter was associated with 13-fold higher odds of seizure occurrence at the time of diagnosis of the tumor (**Table 37**).

Table 37. Multivariable logistic regression analysis for the risk of seizures at the time of diagnosis.

Variables (N=40)	OR	95% CI	p-value
Age (1 year more)	0.96	0.93-1.00	0.06
Sex (male vs. female)	0.98	0.16-6.03	0.98
Frontal/temporal lobe infiltration	2.72	0.21-35.95	0.76
IDH mutations	13.56	1.80-102.3	0.01

We then meta-analyzed our results with those from another 11 studies identified through systematic review, which explored the associations between IDH mutations and occurrence of pre-operative seizures in patients with glioma of any type. IDH mutations were associated with 3.5-higher pooled odds of seizures, as compared to lack of the mutations (**Figure 30**).

Figure 30. Meta-analysis of our study along with other studies on the association of IDH1 mutations and the risk of pre-operative seizures among patients with any glioma.



DISCUSSION

A. Meta-analytical approaches in descriptive epidemiology of primary central nervous system tumors: pooling data across cancer registries to delineate the incidence, mortality, and survival patterns of CNS tumors in childhood, adolescence and young adulthood

In this first set of studies we pooled data from population-based cancer registries in the area of Southern-Eastern Europe and the US (SEER data) to address research questions related to the incidence and survival of primary CNS tumors in the specific age groups of children (0-14 years) and AYAs (15-39 years). In the first study, we found significantly higher incidence rates of malignant CNS tumors among AYAs in SEE, as compared to SEER for the period 1990-2014. Furthermore, we confirmed that astrocytoma was the most common diagnosed CNS tumor subtype, and noted a male preponderance and a linearly increasing incidence trend by age. Of note were the increasing temporal trends in 4 SEE registries established since 1999 (Greater Poland, Portugal North, Turkey-Izmir, Ukraine), as contrasted to a rather stable rate in SEER. In the second study, we explored prognosis of malignant CNS tumors in AYAs and found higher mortality and lower survival rates in SEE as compared to the US for all age groups and tumor subtypes. Yet, we showed declining mortality and increasing survival rates in the majority of the SEE registries (1990-2014). Glioblastoma and anaplastic astrocytoma were the tumor subtypes with the worst prognosis, whereas increasing age, male gender, and rural residence at diagnosis were associated with shortened survival. Finally, in the third study, we explored the incidence and survival patterns of childhood pilocytic astrocytomas in a large sample size of 3,275 incident cases in SEE and SEER. We found a higher incidence of pilocytic astrocytomas in SEER, as compared to the SEE registries and increasing trends over the study period (1990-2012) which seemed to stabilize though in the years. More than one third of pilocytic astrocytomas were located in cerebellum, followed by supratentorial locations, except for infants, among whom supratentorial and optic nerve tumors prevailed. Overall 10-year survival reached a high 95%, increasing over registration period, whereas age <1 year at diagnosis, female gender, non-cerebellar location, and rural place of residence were associated with worse outcome from this, otherwise non-malignant, tumor.

The AYAs age group has been suggested to cover the spectrum of 15-39 years [204]; yet, there is a limited number of published studies, exclusively examining the epidemiology of malignant CNS tumors in this age group, possibly because of the lack of consensus among scientists and the recognition that a single definition may not be applicable in all circumstances [296]. The overall AIR for malignant CNS tumors among AYAs as estimated from SEER during the most recent period in

this study (24.7 per million; 1990-2012) is slightly higher than in a previous report (22.6 per million) spanning 1975-1998 [50] albeit lower than the one reported for the overall USA region (33 cases per million) during 2008-2012 [297]. Our overall SEE estimation (28.1 per million in the period 1990-2014) is comparable to those estimated by the EUROCARE project for the period 1995-2002 (27 cases per million) among individuals aged 20-39 years [298].

Comparisons with data from other developed regions are difficult because of the different definitions previously used for AYAs, the use of different classification systems for CNS tumors (e.g. inclusion or exclusion of non-malignant tumors) and reports from confined areas without nationwide coverage. For example, in an England-wide study (1979-1997), incidence rates of 15.6 and 17.6 per million individuals were noted for the age groups 15-19 and 20-24 years, respectively, which are in line with those reported from SEE registries with stable data, after excluding the outlier values noted overall in Serbia Central [299]. The overall AIR for malignant-only CNS tumors from the multiple sites of Italian registries was of similar order of magnitude (18 cases per million) in the period 2003-2008, although in the age range of 13-23 years, which is different from the one that we have analyzed [300]. In a study from Shanghai, China, the combined incidence of malignant and non-malignant CNS tumors around the same period 2003-2005 was estimated to 33 per million males and 43 per million females aged 15-49 years [301].

Highest rates are generally recorded in developed countries of Europe, North America and Australia with variations attributed overall to availability of modern neuroimaging technology, provision of health care services as well as completeness and quality of cancer registration [60]. Within SEE, a considerably higher AIR was noted in Serbia Central (44.3 per million), evident across all age subgroups, including also childhood (0-14 years) [202] and the adjacent country of Croatia (30.8 per million), which has been previously attributed to be possibly associated with the war of the 1990s [302], over and beyond concerns on the quality of the registration (extremely low value of morphologically verified cases in the Croatian registry and high proportion of unspecified cases in Serbia Central).

When comparing the rates of non-malignant CNS tumors, the considerably lower rates across SEE registries in comparison to SEER indicate incomplete registration in the SEE countries. This is further supported by the increasing temporal trends that point to improved registration policies by longer registration periods. Indeed, non-malignant tumors are more likely to slip registration, as these tumors are commonly managed outside oncology departments that might comprise the primary network of the registry. Similarly, pilocytic astrocytomas could slip registration due to their good prognosis or they could be wrongly categorized in astrocytoma NOS, glioma NOS, or unspecified CNS tumors categories.

Astrocytoma comprised by far the most common diagnostic subtype across SEE registries and SEER, corresponding to almost half of the AYAs malignant CNS tumors; this is in accordance with

previous literature [297,299,303], but higher compared to the proportion of astrocytomas among malignant CNS tumors in childhood [202]. Otherwise, the most striking discrepancy between SEE and SEER concerned "other gliomas" (11.6% vs. 31.6%, respectively) and "unspecified intracranial and intraspinal neoplasms" (31.1% vs. 2.5%, respectively). Within SEE registries, significant differences were also documented for these two subtypes; a relatively strong negative correlation between the two proportions across the registries could actually indicate misclassification and coding of other glioma cases as unspecified, possibly on account of lack of use of advanced diagnostic pathologic methods or the registration policies in some SEE countries. Further exploring this possibility, the correlation between the proportion of non-morphologically verified other glioma cases and the overall relative frequency of other gliomas was not significant (r=0.07, p=0.83); this could however, indicate that the proportion of other glioma non-morphologically verified cases that are misclassified as unspecified tumors is the same across registries. Conversely, the overall proportion of non-morphologically verified malignant CNS tumors, as an indicator of availability of pathologic diagnostic methods, was strongly correlated with other glioma incidence and relative frequency (r=0.48, p=0.07).

The distribution of CNS tumors in all age groups follows an overall increasing pattern (evident also after 24 years among AYAs) and reaching a peak of 185 cases per million individuals over 65 years of age [60,297,298,304,305]. Interesting variations by subtype were identified, which were similar in both SEE registries and SEER. Notably, the incidence of glial tumors linearly increased in both geographical regions, independently of gender, with the exception of ependymoma, where the rates were rather stable. Conversely, embryonal CNS tumors, but also pilocytic astrocytomas, as expected [306,307], were less frequently diagnosed with the progression of age.

The gender distribution of malignant CNS tumors was similar across the SEE registries and the SEER data with a male preponderance of approximately 1.3, which is a consistent finding across all age groups. Indeed, in the large European RARECARE project with data from 76 registries, the male-to-female ratios ranged between 1.3 and 1.5 across histological subtypes (13), in agreement with data from the USA [308], Australia [309], the Netherlands [310], Italy [300], but also Central and Southern America [304]. This gender difference was mostly profound for astrocytomas and other gliomas with a tendency to increase by increasing age, but also for embryonal tumors with a narrowing trend by increasing age group. On the contrary, in accordance with the literature [311], non-malignant CNS tumors showed a female preponderance in both SEE registries and SEER.

Bidirectional temporal trends in incidence were recorded in the SEE registries compared to SEER. With the exception of Croatia, where a sizeable declining trend was noted during the last 13 years, significant increases were evident in 3 SEE registries operating since 1999 (Greater Poland, Portugal North, Ukraine), and in Turkey-Izmir in the period 1993-2014. On the contrary, a very small, annual decrease of 0.3% was documented in SEER over the period 1990-2012, indicating a

rather stable temporal trend; in this context, a stable temporal trend is also noted, when exploring the total 1973-2012 SEER registration period (data not shown). Along the same lines, data from the UK show increasing trends of 1.4% annually over a 19-year period (1979-2007) for the 15-24-year age group [299], whereas nationwide data from the Netherlands demonstrate an overall increase of overall adult gliomas in the period 1989-2010, which is mainly attributed to an increase in glioblastoma [305]. Similarly, the China experience shows a significant increase over a 32-year period, especially for females, possibly reflecting improvements in registration of female patients [301]. On the contrary, the Australian database covering AYAs aged 15-39 years over a more recent period (1982-2005) demonstrated a significant decreasing trend (APC, -1.3%) for males, but stable trends for females [309]. A report spanning 1989-2009 of cancer in AYAs (15-29 years) in the Netherlands also showed a decrease for astrocytomas for males and females (APC, - 4%), whereas a significant increase for other CNS tumors was observed for females [310]. In accordance with our findings for SEER, the CBTRUS report, entailing more databases, shows an annual decreasing trend in overall CNS tumors among AYAs for the period 1995-2012 [308] also evident among adults in the overall US region for the period 2000-2010 [312]. The increasing temporal trends for more distant time periods have been attributed to the diagnostic advances in neuroimaging technology [313]; it is rather unlikely, however, to also explain the observed increase in SEE registries, as they primarily avail data for periods after 2000, notably when MRI was widely available. Conversely, the increases could reflect improvements in registration policies leading to better classification of diseases and completeness of the recording of the tumors. It is not easy, however, to ecologically correlate the observed time trends to environmental exposures leading to CNS tumorigenesis in the SEE region.

Regarding survival, as expected, our findings from the 18 SEER, US data analyses approximate the recently reported by CBTRUS [297], which include the whole US population; likewise, the population-based analyses conducted in the context of the EUROCARE project in the overall European region (2000-2007), showed a rather intermediate outcome rate (5-year survival, 57%) for AYAs with malignant CNS tumors between those we calculated for SEE or SEER [314]. Of note, there are wide variations within the European region; indeed, the survival patterns derived from German data (2002-2006) for the age groups 15-29, 30-39 and 40-49 years, were similar to those of SEER for low-grade astrocytoma, glioblastoma and anaplastic astrocytoma, astrocytoma NOS and other glioma [315]. 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 is not feasible as it also included non-malignant CNS tumors [316]. In accordance with previous studies for childhood CNS tumors [201,212] and other childhood and adult cancers [317-319], rural residence was also associated with worse prognosis, thus indicating the important role of socioeconomic status and healthcare delivery in outcome indicating room for further improvements at a population level.

Besides the definite role of socioeconomic differences in the observed prognosis disparities between SEE and the US, other parameters should also be taken into account. Particularly, access to the healthcare system, the availability of specified neuro-oncological centers in the US, the improved neurosurgical outcomes in the US, the vast difference in the proportion of patients included in clinical trials, which impact on survival, and differences in treatment-related factors including type of adjuvant therapy, aggressiveness of relapse treatment and supportive care could partly explain the discrepancies [320,321]. Furthermore, the availability of temozolomide and the possible delay in being incorporated in the clinical practice in the SEE countries could also play a role in the observed disparities, especially for high-grade gliomas [322]. However, completeness of registration is an additional important factor; in particular, if less aggressive tumors are more likely to slip registration in SEE due to their management in non-oncology departments, then a phenomenally lower survival might emerge. Lastly, the variable ethnic distribution in the US population could impact on the higher survival and lower mortality rates, compared to SEE, that were observed in the study.

Still, outcome differences for malignant CNS tumors were also evident when comparing across the SEE registries. Particularly, Croatia, Greater Poland, Romania-Cluj and Izmir reported 5-year survival rates higher than 60%, which are 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 OS rate in Ukraine (38%) that contributed more than half of the SEE cases. In addition to the economic disadvantage of country (the only participating one classified to the lower middle income countries[323]), this low rate should be interpreted in the context of incidence, mortality and registration issues. Particularly, the overall mortality rate in Ukraine does not seem to be higher compared to the other SEE countries. Concurrently the increasing incidence over the registration period along with the high proportion of histologically unspecified cases possibly indicate incomplete registration in the first active years of this nationwide registry. Given that cases most easily slipping registration are the ones with the best prognosis that could also be treated outside collaborating oncology departments, this could phenomenally lead to a recording of cases with averagely worse prognosis.

Despite these disparities, survival gains in SEER, as previously reported [297,324] and the SEE region over the period 2001-2009 should be noted, also evident in declining mortality trends in the majority of the SEE registries and reaching 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,[314] Australia,[309] the UK,[325] and Brazil,[326] indicating 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 effect of socioeconomic variables, however, non-modifiable demographic factors seem to independently impact on outcomes and shape the international variation of rates. In line with literature [297,314], increasing age among AYAs diagnosed with malignant CNS tumors is a negative prognostic factor. This finding has been confirmed in our finding for both SEE regions and SEER and the impact was furthermore quantified by tumor subtype allowing the identification of specific patterns by disease subtype. Specifically, increasing age was more detrimental for all astrocytic tumors, other glioma and supratentorial PNETs, as opposed to an inverse positive effect for ependymoma.

Survival differences by gender have been also previously described along with an overall higher incidence of specific subtypes of CNS tumors in males [297,327]. Our study also showed that male gender was independently associated with worse prognosis, especially among older individuals and those diagnosed with astrocytoma, other glioma and other unspecified neoplasms. By contrast, in our previous studies with SEE data focusing in children, no gender difference in survival had been identified for malignant CNS tumors [212]; even better prognosis for males was noted for the non-malignant childhood pilocytic astrocytoma [201]. Several mechanisms have been implicated as contributing to the overall male vulnerability to CNS carcinogenesis [328]. Interestingly, gender disparities in CNS tumors incidence and survival are also evident across different molecular subtypes of the same histological diagnosis [329]. This finding highlights the need for a more comprehensive and subtype-specific focus as to better clarify the underlying mechanisms of gender differences in CNS tumorigenesis.

The overall prognosis of AYAs with malignant CNS tumors (5-years survival, 46%) in the SEE region does not actually differs from the one we recently reported for children (5-year survival, 47%) residing in the SEE [212]; this non-existence of survival gap between the two age groups is in line with the recent EUROCARE report from Europe [314] and the CBTRUS report from the US [297]. Valid comparisons between children and AYAs, however, should take into account the differential epidemiology of the CNS tumors. As the proposed classifications for children [20] and AYAs [330] are almost identical, when examining the differences across the diagnostic subcategories, a higher 5-year survival of ependymal (76% vs 51%) and embryonal tumors (52% vs. 41%) was evident among AYAs compared to children, as opposed to a lower for astrocytomas (41% vs 61%) and other specified intracranial and intraspinal neoplasms (36% vs. 58%). The worse outcome of children with embryonal tumors and ependymomas, has been reported in the past and could be attributed to the aggressiveness of these tumors in infants and young children [331,332]. On the other hand, the decreasing survival rates observed for astrocytomas by increasing age could at least partially be explained by the increasing incidence of high-grade astrocytic tumors as age advances. Therefore, despite the reported worse cancer outcome among AYAs compared to children, these specific findings as well as the weight of the different histological types in shaping the OS figures

should be taken into account to show whether survival among children largely differs compared to that among AYAs regarding CNS tumors [316].

With regards to childhood pilocytic astrocytoma, there is a paucity of published data in Europe on its incidence. Yet, studies from England (AIR: $7.5/10^6$; 1995-2003) and Switzerland ($8.3/10^6$; 1980-1994) show higher rates approaching those of the US [333,334]. In the current study the overall lower incidence in SEE ($4.2/10^6$ in 1990-2012; $5.1/10^6$ after 2000) compared to SEER ($8.4/10^6$ in 1990-2012; $9.1/10^6$ after 2000) could be attributed to underreporting and registration gaps; specifically, as pilocytic astrocytoma comprise a treatable tumor, usually managed outside oncology departments, they could have slipped registration in SEE registries, which have been initiated most recently and may not avail an extensive network for complete registration. Furthermore, the recent ICD-O-3 change in behavior could have led to modification of registration policies adopted with variable delays. The younger-by 1 year- age at diagnosis in SEER may also indicate earlier tumor identification, possibly on account of better healthcare delivery system; in this context, some pilocytic astrocytoma in SEE, despite their development during the conventional childhood period could have been diagnosed after 14 years leading to a phenomenal decrease of childhood incidence.

Increasing temporal trends, yet attenuated after 2000, were recorded in both SEE and SEER. Regarding SEER, the increasing trend was opposite to the decrease of astrocytomas NOS, indicating improvements in diagnostic classification of CNS tumors over time [335]. The rates of astrocytomas NOS in SEE registries remained, however, stable, possibly implying welcome improvements in registration processes [335-337]. Besides registry improvements, advances in neuroimaging modalities, especially the wide use of MRI, could be responsible for these trends. Indeed, the trends are in accordance with an overall temporal increase in childhood CNS tumor incidence in developed countries [338], and contrasted to the stable trends in countries of lower socioeconomic status [339,340]; the diagnostic improvements have been suggested as the main contributors to these observations [313]. If this stipulation were genuine for PA, disease diagnosis at an earlier time due to use of imaging methods would have been expected to result in a more pronounced increase among younger children; such a trend has not been noted, though, in this study. It has lastly been suggested that the increase in childhood astrocytomas could be rather real due to exogenous environmental factors, not yet identified [337,341].

Prognosis of pilocytic astrocytoma reached a high 94.5% 10-year survival, which significantly increased from 79% to 94% since 1990 in SEE, whereas in SEER remained stable over 95% thereafter. The cerebellar pilocytic astrocytoma have a diachronic excellent prognosis and survival gains pertain exclusively to outcome improvements of non-cerebellar tumors. In fact, it is now well-established that gross-total resection of pilocytic astrocytoma is a major predictor of outcome [342], with the greater amount of resection leading to higher possibility of cure [343]. The diagnostic advancements and the improved access to healthcare delivery, leading to earlier

diagnosis and, thus, surgery with higher probabilities of total resection, along with management improvements through development of pediatric neurosurgery and establishment of specified childhood CNS tumors centers have contributed to survival gains. The considerable improvement in SEE is also in accordance with the overall rather declining trends of malignant CNS tumors mortality and improved survival over time, which was recently reported for the same area [212]. Significant outcome disparities between the less affluent SEE countries and the US were found; similar disparities, impacting on prognosis of childhood CNS tumors between European regions, as well as between UK and the US have been described [320,344,345]. Apart from the availability of specified pediatric neuro-oncological centers in the US, differences in treatment-related factors including type of adjuvant therapy, aggressiveness of relapse treatment and supportive care could partly explain the discrepancy. Completeness of registration should be also taken into account, however, in assessing the SEER vs. SEE survival discrepancies. In particular, if less aggressive tumors are more likely not to be registered in SEE due to their management in non-oncology departments, then a falsely worse prognosis might emerge.

Intriguingly, rural residence, considered as proxy of healthcare access [212,346], was associated with a 2-fold increased risk of death in our study. Previous studies have shown similar worse outcomes for other childhood and adult tumors [317,319]; rural residence would be expected to either prolong the time needed for diagnosis or impact on the treatment received by the patient. Given the non-malignant nature of pilocytic astrocytoma and the fact that in most cases treatment is limited to surgery, the former seems more possible in this occasion. To further evaluate this notion, we examined the age at diagnosis of residents of rural and urban areas; indeed, urban residence was associated with a lower age at diagnosis in both SEE (7.5 vs. 8.4 years) and SEER (6.7 vs. 7.3 years) implying possibly diagnosis at an earlier and possibly more favorable stage. The finding was more pronounced in SEER, as contrasted to SEE; possibly the difference in rural definition between countries, as well as the between-country differences in the healthcare systems could explain this discrepancy.

Data regarding tumor location, derived mainly from single-center case series, as well as our data confirm that childhood pilocytic astrocytoma are most frequently (37%) located in cerebellum apart from infants in whom supratentorial and optic nerve tumors prevail [12-15]. The excellent prognosis of cerebellar pilocytic astrocytoma (10-year survival exceeding 99%) compared to any other CNS location [347,348], has been traditionally attributed to both the feasible gross-total resection,[348] as well as the greater plasticity of cerebellum [349] in childhood leading to fewer neurological deficits.[350,351] It should be also taken into account, however, that cerebellar pilocytic astrocytoma have been reported to be also characterized by differential genetic origins compared to supratentorial tumors [352].

Regardless of socioeconomic, geographical and tumor-specific characteristics, however, non-modifiable individual factors, notably age and gender, impact also on survival. The poorer outcome of infants with low-grade gliomas is poorly understood; there might be an interaction between age and non-surgical treatment, which is more frequently preferred in this age group given the adversities of performing neurological surgeries [353,354]. Likewise, radiation, the presumably most effective treatment for unresectable PA, may be substituted in infants and young children by chemotherapy given concerns for its neurocognitive and neuroendocrine toxicities [355]. On the other hand, the differential topographic pattern of infant PA, including lower prevalence of cerebellar-located tumors, could impact on survival; the optic nerve pilocytic astrocytoma preponderance in this age is possibly attributed to NF1-related tumors [356,357], anyway linked to worse prognosis [358], especially in children <1 year [359]. Notably though, the effect of age remained unchanged after adjustment for topography. Recent findings, however, indicate that infant low-grade gliomas might comprise a more aggressive disease, compared to pilocytic astrocytoma in older children, as they are characterized by a different genetic composition, including mutations of components of the MAPK pathway, which has been identified as of paramount importance in pediatric low-grade gliomas [360]; particularly, Ho *et al.* showed that the BRAF-V600E mutation is more common in infants and is associated with worse prognosis, independently of topography and histology [361].

Statistically significant, but of low magnitude, gender differences in childhood pilocytic astrocytoma outcome were shown for the first time in this study, of similar direction in both SEE registries and SEER. No difference in topography or age at diagnosis by gender that could explain this differential was evident. Previous molecular analyses for prognostic factors have either not evaluated or not reported, possibly due to lack of statistical power, gender differences. Therefore, future research is needed to confirm this finding and stipulate on potential differential pathogenetic features by gender.

Limitations

These studies had specific limitations, mainly related to the variable quality of registration. First, the proportion of morphologically verified cases among malignant CNS tumors in AYAs was considerably lower in the majority of SEE registries compared to SEER. This might explain the high proportion of unspecified neoplasms in the SEE registries (10-40%) compared to SEER (2.5%), which hinders the interpretation of the findings by histological subtypes. Given the extremely low survival rates of this diagnostic category in SEE (5-year survival: 36%, higher only than the glioblastoma/anaplastic astrocytoma category), were they rightly 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 US. It is worth-noting, however, that intense efforts have been undertaken by international bodies, such as the European Network of Cancer Registries, the European Commission and the International Agency of Cancer Registration aiming at improving quality of cancer registration and enhancing the low percentages of morphologically verified diagnoses reported for CNS tumors e.g. in Georgia (38% for all ages) [362], Central and Southern American national registries (65% for AYAs) [304], Norway (67% for AYAs) [58], and Austria (81% for AYAs) [363]. Histological diagnosis of CNS tumors is increasingly required, as new molecular, personalized treatments are becoming available and novel improved techniques and expertise allow biopsy of tumors which are located in traditionally non-approachable regions, like the brainstem [364].

Second, the difficulties associated with the neuropathological diagnosis of CNS tumors should be considered. Under the non-availability 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 the tumors could be very challenging [365]. 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. Regarding pilocytic astrocytomas for example, the high proportion of cases in the astrocytoma NOS category, approaching 30% of all astrocytomas in SEER and SEE registries, may underestimate incidence and impact on time trends and survival findings. The much higher incidence of pilocytic astrocytoma in SEER, compared to SEE, as well as the variations between SEE registries indicate potential underreporting of this non-malignant tumor in SEE. This could have led to selection bias, as less aggressive tumors would be more likely to slip registration (as they are usually treated at non-oncology departments, which may not be encompassed in the registration networks) and possibly underestimation of the survival rates in SEE. Changes in classification of pilocytic astrocytoma over time could have influenced registration process and consequently the reported findings.

Third, the cross-registry variation regarding the time period examined poses difficulties for direct comparisons between registries, as well as between the SEE region and SEER. The highly variable time periods examined across the SEE registries did not also allow for the evaluation of an average time trend for the incidence of CNS tumors in the SEE region. Fourth, the non-availability and the non-public access to primary data from the European region, which would probably comprise a closer to SEE reference population, as compared to SEER, is considered a drawback of our study. In this context, the heterogeneity of the healthcare system reality, the medical approaches, and the genetic composition of the populations, between SEE and the US should be taken into account. Fifth, regarding the survival analysis, the fact that only vital status was available not allowing the estimation of relative survival rates and the non-availability of more detailed individual clinical data are among the inherent limitations; regarding 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, no treatment-related data or data on molecular markers with prognostic value were available in this dataset.

B. Meta-analytical approaches in analytical epidemiology of primary central nervous system tumors: original data analyses and meta-analyses to explore perinatal and early-life risk factors

In the second set of studies, we explored perinatal and early-life risk factors of primary CNS tumors, by leveraging data from the Greek nationwide case-control study of the NARECHEM-ST, from the collaborating cancer registries from the area of Southern Eastern Europe, and from the published literature in systematic reviews and meta-analyses. In the case-control study, a number of perinatal and early-life risk factors were associated with the risk of childhood CNS tumors. Of specific interest is the positive association with instrument-assisted vaginal delivery as contrasted to the inverse association with cesarean delivery. Moreover, maternal consumption of alcohol during pregnancy and history of living in a farm were associated with increased risk of childhood CNS tumors, whereas higher birth order was associated with decreased risk of childhood CNS tumors. In a meta-analysis of 41 studies including more than 50,000 cases of CNS tumors, we further demonstrated high birth weight (>4,000 g) and large for gestational age size at birth to be associated with an increased risk of primary CNS tumors among children. High birth weight was specifically associated with astrocytoma and embryonal CNS tumor and remained robust in a number of sensitivity analyses. The associations followed a non-linear pattern with null effects below the normal birth weight range. Next, in a systematic review of 17 studies (all in the Northern hemisphere), we examined whether seasonal variations at birth could be associated with the incidence of CNS tumors. The published studies provided some evidence for a potential clustering of births among children and adults with CNS tumors in winter months, but the results were based on studies suffering lack of power, were not consistent across studies for specific histological subtypes, and did not allow pooling in meta-analysis. To further address this question, we then pooled data from 6,000 incident cases of primary CNS tumors registered in 16 population-based cancer registries and explored variations in birth seasonality, as compared to the total amount of live births in the underlying region during the same time periods. We found a clustering of births among boys with embryonal CNS tumors born in winter months, mostly marked in the course of the first five years of life. By contrast, boys under five years born during summer were at a lower risk of developing an embryonal CNS tumor.

Our analysis in the Greek case-control study showed that instrument-assisted delivery is associated with increased risk of childhood CNS tumors. An older case-control study had also reported that delivery assisted by forceps is associated with a 2.6-fold increased risk of childhood CNS tumors [366], but a more recent study examining the association with vacuum extraction found no significant association [367]. Instrument-assisted delivery with the use of either forceps or vacuum extraction is associated with higher risk of brain injury [368,369]. Interestingly, it has been

suggested in adults that traumatic brain injury might increase the risk for subsequent glioma [370,371], but this has not been confirmed in larger populations [372]. While this finding is of interest, potential sources of bias related to the case-control study design such as selective recall bias should not be excluded. The inverse association between caesarean section and risk of CNS tumors, in contrast to other childhood malignancies [373,374], might indicate a gradient by mode of delivery regarding the possibility of brain trauma, but requires cautious interpretation, as we did not avail data to differentiate between emergency and elective caesarean section.

We found a dose-response association between higher birth order and risk of childhood CNS tumors. Previous case-control studies have reported similar results for overall childhood CNS tumors [94,107,243,375,376] and particularly for astrocytomas [375], and embryonal tumors [376], but this is not consistent in the literature [79,242,246,258,286,367]. Our analysis by tumor subtypes was underpowered but showed that the effect might be specific to astrocytomas. Birth order is traditionally used in epidemiologic studies as a surrogate marker of frequency and timing of exposure to infections in early life [81,286]. Specifically, later-born children are considered to be exposed to a larger burden of infections at an earlier age, as compared to their older siblings [81,286]. Hence, earlier exposure to infections possibly associates with an earlier maturation of the immune system that might act protectively against tumorigenesis [377]. However, other mechanisms including different hormonal exposure of later conceived fetuses [378] and microchimerism [379] might also be involved in the observed association.

History of living in a farm was associated with a 5-fold increase in the risk of CNS tumors, which was consistent for both astrocytomas and embryonal tumors. This finding might be related to exposure to pesticides early in life. A meta-analysis has shown that paternal exposure to pesticides either during pregnancy or early in life after birth is associated with increased risk of childhood CNS tumors [47]. Individual studies have further shown that residential use of pesticides is particularly associated with astrocytomas [380] and embryonal tumors [381], which might also relate to the genetically determined capacity of the child to metabolize toxic pesticide substances [382,383]. Pesticides are designed to act in the nervous system and some of them have been shown to be carcinogenic in animal models [28,384]. Alternative explanations could include a lower risk of allergies, socioeconomic disparities, and exposure to animals, but none of these factors were associated with CNS tumors in our analysis.

Alcohol consumption was further associated with increased risk of CNS tumors. While this finding is in accordance with studies in other childhood neoplasms, including leukemia [385] and neuroblastoma [386], it contradicts the results from a combined analysis of two population-based French studies that showed no evidence of an association [72]. Alcohol consumption might simply be an indicator of other lifestyle choices during pregnancy which could explain the increase in the risk of CNS tumors and possibly also the differences between the two studies.

Previous studies and meta-analyses have explored whether birth anthropometric measures impact on the risk of other cancers. In particular, high birth weight has been found to increase risk for childhood and adolescence/young adulthood tumors, like acute leukemia [387], neuroblastoma [388], bone tumor [389] and testicular cancer [390], but also for adulthood tumors, including colorectal [391] and breast cancer [392]. Interestingly, U-shape associations with both high and low birth weight have been described for acute myeloid leukemia, neuroblastoma, testicular and colorectal cancer [387,388,390,391].

Regarding CNS tumors, a previous meta-analysis (2008), including 8 studies, had also shown an increased risk of childhood astrocytoma and medulloblastoma by high birth weight [108]. However, the current study has been conducted on a much larger sample-size (e.g. 7,456 vs. 1,819 cases in the astrocytoma analysis), allowing confirmation of the robustness of the findings across different study designs and methodologies, examination of the risk of bias via meta-regression and publication bias analyses, as well as evaluation of the birth weight effect throughout its entire range. Additionally, we meta-analyzed, for the first time, other birth anthropometrics documenting also an increased risk for a CNS tumor among large for gestational age children; along with the sensitivity analysis on studies adjusting for gestational age, this result disentangles the effect of birth weight from the potentially confounding role of gestational age. We lastly attempted to explore associations of birth weight with adult CNS tumors; the published data were scarce but the findings did not seem to support an association.

Birth anthropometric measures represent complex proxies of fetal growth. Risk factors for infant macrosomia include maternal and paternal high birth weight, previous macrosomic birth, ethnicity, multiparity, maternal obesity and nutritional status, gestational diabetes and hypertension, non-smoking and high maternal age, indicating both genetic and environmental determinants [393]. Therefore, only assumptions could be made regarding the underlying biological links with CNS tumorigenesis. Infant macrosomia might be associated with the number, size or proliferative potential of CNS cells; indeed, birth weight seems to be positively associated with the proliferative potential of neurosphere progenitor cells and their differentiation rates to astrocytes and neurons in newborn rats [394]. These undifferentiated cells are susceptible to oncogenic mutations and therefore an increased birth weight could indicate either a general genetic predisposition to CNS tumorigenesis or environmental exposures concurrently leading to accelerated fetal growth and facilitating an increase in CNS tumor risk. Growth factor pathways have been implied as the link mediating the observed associations [105,242]. Of note, umbilical cord plasma levels of insulin-like growth factor (IGF)-1 and IGF-2 that inhibit apoptosis and promote tumorigenesis, have been linearly associated with birth weight and birth length [395]. Except for its crucial role in brain development [396], the IGF-system is also involved in gliomagenesis; particularly, glioma cell lines express more IGF-1 receptors than normal astrocytes [397], serum levels and genetic polymorphisms of IGF-1 have been associated with the adult glioma risk [398] and IGF-1 receptor

blockade may inhibit glioblastoma growth [399]. These findings are in line with the stronger associations found for astrocytoma, but relevant data on the role of IGF-1on childhood astrocytic tumor are missing. Similarly, IGF-1and IGF-2 have been implied in the growth of PNET [400], medulloblastoma [400] and ependymoma [401]. The role of the IGF-system in carcinogenesis is further supported by the lower risk of cancer described in series of patients with congenital IGF-1 deficiency [402]. Besides growth-related factors other tentative mechanisms meriting research include the adipokines pathway [403] and the in utero exposure to estrogens [404], as well as tentative genetic and epigenetic determinants [405].

The lack of associations for adult tumors could be attributed to the longer interval between birth and the outcome making the association subject to confounders. Nevertheless, the potential male-specific association of high birth weight with glioma risk identified in 2 studies merits further consideration [251,273], as a stronger association of high BMI with adult glioma for males has also been described [406].

During the last decades, temporal increases in mean birth weight of children in Western countries had been recorded [407], with a reverse of this trend after 1990 [408]. Challenging is therefore to explore whether temporal trends in birth weight have contributed to the overall increase in childhood CNS tumor incidence consistently being reported before 2000 in developed countries [409]. Additionally, the approximately 10% of infants currently born macrosomic [84] may reflect a large proportion of the population exposed to increased risk for a fatal malignancy. Given the continuous global increase in obesity rates [410] and the positive association of maternal overweight/obesity at pregnancy with increased risk of high birth weight [393], this proportion might further increase in the future.

The association of season of birth with the diagnosis of pediatric cancer has been previously investigated [276,411,412] in an attempt to shed light in the complex etiology of childhood carcinogenesis. Certain researchers have suggested a seasonal variation for some types of cancer, such as leukemia, non-Hodgkin lymphoma, neuroblastoma and CNS tumors [276,288,412], whereas other studies have not confirmed similar associations [411]. Consistently with our findings, a recent systematic review of the literature (N=7 studies) [291] showed a potential peak of births among children and adults with CNS tumors in fall and winter months; however, the results were in general based on studies suffering lack of power, which did not report the size of effect, neither were the findings confined to specific histological subtypes. The potentially seasonal clustering of births in fall among children later diagnosed with embryonal tumors has also been reported in previous US studies for medulloblastoma, the most common pediatric embryonal tumor [279,280].

A wide range of candidate factors could explain the observed higher incidence of CNS tumors, and specifically embryonal tumors, among boys born in winter months. One of them is exposure to pesticides, herbicides or fungicides; their highly variant use throughout the year could potentially

explain seasonal patterns encountered in agricultural areas. Pesticides have been found to be carcinogenic in animal models, whereas epidemiologic studies show that childhood or perinatal parental exposure to pesticides is associated with increased risk of CNS tumorigenesis [47,413]. Parents could carry pesticide compounds in their shoes and clothes after work and expose their children in the house [414]. The placental permeability to pesticides [415], the comparatively larger and more permeable to lipophilic compounds infant skin surface [416,417], and the immature until 6 months of age blood-brain barrier make it feasible for environmental compounds to reach the brain [418].

As serum vitamin D levels depend on sunlight, a respective seasonal pattern has been well established [419]. Lower levels of serum vitamin D have been associated with increased risk for several malignancies [420]. Studies in rats demonstrate that newborns of vitamin D depleted mothers have more mitotic and fewer apoptotic cells in the brain [421,422], which could be associated with a vulnerability to carcinogenicity. Nevertheless, the only to-date study examining the association of maternal vitamin D levels with risk of childhood CNS tumors found a dependent on birth weight association [240].

Immune system maturity of the index child might be another alternative. Atopic diseases, including asthma [423], atopic dermatitis [424], food allergy [425] and allergy to a variety of environmental antigens [426], as well as autoimmune disorders [427,428] have been linked with variability in the season of birth. Exposure to allergens and infectious agents in early life, which follows a seasonal pattern, might promote immune system development, thus determining the risk of immune-mediated disorders [429], which have also been associated with decreased risk of childhood and adult CNS tumors [430-432].

Exposure to infections in early life is highly variable by season and proxies of early-life infections, like earlier and longer daycare attendance or higher birth order, are associated with a decreased risk of childhood CNS tumors [74,79]. Conversely, a later exposure to infections, extending up to the first 6 years of life has been linked with higher risk of glioma and meningioma [80]. This inconsistency could indicate two distinct mechanisms of disease; on the one hand, exposure to infections early in life (before 3 years of age) might be related to immunity development, which is associated with a decreased risk of CNS tumors, whereas, infections later in childhood might be implicated in an infectious origin of the disease. The hypothesis of the viral origin of CNS tumors has been examined especially in the case of human herpesviruses, but their direct impact on neoplasia has not yet been proven [433]. More recent evidence suggests that birth seasonality might be related to patterns of epigenetic modifications, as it was associated with specific DNA methylation patterns in adults [434]. Epigenetic alterations seem to also play a role in brain tumorigenesis, [435], necessitating a further investigation of this concept.

Other factors that may mediate or confound the observed associations include birth weight,

handedness, and diet. Birth weight has been reported to vary by season of birth [436,437]. Meta-analysis results from our group show that birth weight >4,000 g is associated with increased risk of childhood CNS tumors, specifically astrocytomas and embryonal tumors [438], which might indicate a confounding role on the effect of birth seasonality. Right-handedness has been associated with an increased risk of adult glioma [439]; likewise, birth seasonal patterns have shown a higher likelihood of being right-handed if born between March and July [440]. In this context, it has been shown that being right-handed and born in spring-winter months is associated with the higher likelihood of developing gliomas [277]. Lastly, maternal nutrition could follow seasonal variability in accordance with crop cycles or use of preservatives. For example, dietary intake of N-Nitroso compounds, used as cured meat preservatives by mothers during pregnancy, has been associated with increased risk of CNS tumors in the offspring [441], whereas yellow-orange, cruciferous vegetables, fresh fish and grains have been found to be associated with decreased risk [442].

Limitations

Specific limitations of this set of studies should be noted. First, regarding the case-control study, despite the nationwide coverage, our analyses were primarily based on an inherently rather small sample size and were thus underpowered to detect significant signals for several risk factors. This did not allow any meaningful analyses by CNS tumor subtypes. Furthermore, there were small differences in tumor characteristics between cases included in the case-control study and those recorded in the nationwide registry during the same time period. The underrepresentation of non-malignant tumors (mainly pilocytic astrocytomas) relates to the relatively short hospitalization of these patients leading to difficulties in recruitment after discharge, whereas tumors of unspecified histology were mainly identified retrospectively during extensive search of alternative sources for completion of registration and were thus not possible to be recruited in the case-control study. Although these differences might introduce selection bias in our case-control study, we believe that the differences are relatively small to affect the results of our association analyses. No biological data were available to more precisely define some of the variables of interest, such as exposure to infections based on serological measurements and genetic variants that may predispose to increased toxicity following exposure to pesticides. Finally, we could not differentiate between emergency and elective cesarean section that have been shown to differentially influence the risk for childhood malignancies.

Second, classification changes and diagnostic improvements over time may have introduced heterogeneity in the meta-analyses for birth weight and other anthropometric measurements. Yet, publication year in the meta-regression analysis did not seem to affect the findings. Studies assessing birth weight through parental interview are definitely subject to recall bias. The findings

were replicated, however, among studies extracting birth weight information from secure records or birth registry databases. The use of different birth weight categories by individual studies could have contributed to between-study heterogeneity. For this reason, we implemented dichotomous, categorical and incremental approaches for birth weight while re-calculating suitable estimates; despite the potential methodological deviations in the re-calculations, the methodology used has been validated [219,220]. Despite the lack of heterogeneity and publication bias in the dichotomous and categorical analyses, the incremental analyses on overall childhood CNS tumor and astrocytoma were characterized by significant heterogeneity and publication bias, respectively. Given, additionally, the evident non-linearity of the examined associations, a cautious interpretation of the incremental analyses is necessary. It was not possible to conduct gender sub-analyses in order to evaluate previous reports for male-specific associations of birth anthropometrics with cancer; moreover, no meta-analysis could be performed for other growth indices, notably birth length, head circumference and fetal growth measurements. Lastly, the analyses for an adult CNS tumor, were based on relatively few studies, thus precluding the extraction of meaningful results.

Third, the results from the systematic review on birth seasonality should be cautiously interpreted, in view of limitations inherent to the study design and data availability of eligible studies including variable criteria for selection of the comparison groups, statistical analysis methods and low sample size for subtype analyses. Indeed, CNS tumors comprise a highly heterogeneous group of malignancies, in terms of etiology, hence analyses by subtype, but also by grade, are considered essential. The lack of confirmation of the findings of the Danish [32] and the Norwegian [29] study in the subsequent Nordic countries study [23] poses several concerns; likewise the inconsistency of the medulloblastoma findings among children in different parts of the US in contrast to the nonsignificant ones derived from SEER [28], raise intriguing considerations about whether a genuine association may exist or whether the variable exposures in the diverse settings comprising SEER may offset a genuine association observed in a specific State. Moreover, control for confounding was rather an exception in the eligible studies, whereas the higher CNS tumor risk among individuals born in late fall or winter was not consistently found across studies by tumor subtype. Lastly, the fact that a meta-analysis was not feasible precludes the possibility of cumulative interpretation of the findings. The highly heterogeneous results across studies, however, could either indicate that different factors are implemented in the association of season of birth with CNS tumors in each dataset or could point to the heterogeneity of the methodological approaches, e.g. in statistical analysis, implemented by each study. We attempted to separately examine studies investigating seasonality among children and adults, as the epidemiology of the tumors in these age groups is grossly different. Given the proximity of birth as an event to the occurrence of CNS tumors, we hypothesized that if an effect of birth seasonality was actually evident, it would be more profound among children; in adults, a seasonally variant underlying

perinatal exposure would have a less strong effect on the risk of tumorigenesis in the CNS. Nevertheless, no specific pattern was identified.

Lastly, the analysis for birth seasonality in the SEE cancer registries is also subject to limitations. These might include the variable study periods of data registration across the SEE registries. The lengthy study period (1983-2015) may have also impacted on the results of our study given that seasonal exposures may have changed over the 30-year study period. Moreover, individual registries may have different recording processes, though international standards were generally followed, and the between-study heterogeneity was non-significant in any meta-analyses. Clinical data, including information on cytogenetics, stage, grade and other histological subtypes of CNS tumors apart from astrocytomas and embryonal tumors, were also missing in traditional cancer registries. Although the quality of registration was generally high in most registries as indicated by the large proportion of morphologically verified and small proportion of death certificate only diagnoses following the criteria of the ICCC-3 [20], certain registries still suffered small proportion of morphologically verified (Croatia: 73%, Malta: 78%, Romania Northeast: 58% and Ukraine: 78%) or large proportion of death certificate only diagnoses (Bulgaria: 11.6% and Romania Northeast: 23.0%) diagnoses. Nevertheless, only two of these registries (Croatia and Ukraine) participated in the seasonal meta-analyses and hardly changed the results of the main analyses; by contrast, the exclusion of Croatian and Ukrainian registries showed an even stronger association between the winter birth season and embryonal CNS tumor incidence in boys, with no evidence of type I error. Furthermore, our analyses may have been hampered by the number of missing live birth data in five countries, although these countries contributed only 17% of CNS incident cases.

C. Applying meta-analyses to address questions of clinical epidemiology: the case of the rare CNS tumor gliomatosis cerebri

In this final set of studies, we applied meta-analytical approaches to provide for the first time a comprehensive overview of the epidemiology, the clinical features, and the prognostic factors for GC, a rare fatal CNS glial tumor with distinct extensively infiltrating growth pattern. First, in a population-based study on the publicly available SEER data we estimated the overall annual incidence of GC to 1 case per 10 million individuals. We found a male preponderance and an increasing incidence among the elderly. Increasing trends in incidence during precedent decades stabilized in the most recent registration years and we noted a tendency for clinical/radiological methods of diagnosis to substitute the gold-standard histological diagnosis. We confirmed the poor prognosis of GC over time, with a 5-year survival rate of 18% and a median survival of 9 months. Increasing age and rural residence at diagnosis were identified as negative prognostic factors, whereas primary tumor location restricted in the cerebral hemispheres was marginally associated with improved outcome. Second, by leveraging individual-level data from all cases of GC that have ever been described in biomedical literature in case reports and case series, we built a dataset of 1,648 cases, the largest ever for this rare malignancy. Exploiting this dataset, we identified five distinct symptom clusters (seizures, intracranial hypertension, focal deficits, cognitive/mental symptoms, cerebellar symptoms), representing different clinical presentations primarily depending on infiltrated CNS regions. We found no consistent pattern in terms of histology and molecular aberrations with the majority of cases sharing common features with other gliomas. Despite the diagnostic challenges, MRI and MR spectroscopy, as opposed to CT and PET, provided highly consistent findings in the vast majority of GC patients that may guide diagnostic workup. Time elapsed from symptoms to diagnosis was the only independent determinant of CNS tumor expansion at diagnosis. Regarding outcome predictors, older age at diagnosis, high-grade pathology, widespread CNS invasion, symmetric bilateral brain involvement, GC type II, MRI contrast enhancement, focal neurological deficits, cerebellar symptoms, higher symptom burden, functional impairment at diagnosis, and a high proliferation index were all associated with shortened PFS and OS times. On the contrary, seizures at diagnosis, IDH1 mutation and methylation of the MGMT promoter were associated with prolonged OS and PFS. Chemotherapy and surgical resection of the tumor, when feasible, were independently associated with improved outcomes, whereas radiation either as monotherapy or combined with chemotherapy was not superior to chemotherapy alone. Trying to explain the paradoxical association between seizures at diagnosis and improved survival, we were able to show that presence of IDH1 mutations increased the occurrence of seizures in patients with GC, in accordance with the findings in other gliomas, as illustrated in a meta-analysis of all studies. Finally, pooling individual-level data from 182 children

(0-18 years) with GC, we found distinct histopathological and neuroimaging patterns, as compared to adult GC, we identified prognostic factors for OS, and we found significant associations between received treatment and disease outcome. Pediatric, as compared to adult, GC was more likely to be of higher WHO grade, and less likely to carry molecular aberrations related to prolonged survival (IDH1 mutations, MGMT promoter methylation, 1p/19q codeletion). Among children, age >4 years at diagnosis, extended CNS infiltration, coordination abnormalities, and cognitive decline were predictors of worse outcome, whereas IDH1 mutations were also associated with prolonged OS. Similarly to adults, chemotherapy and, when feasible, extended surgical resection were associated with improved outcome, whereas radiotherapy, was not found to be superior to chemotherapy or exert any additional benefit on top of it.

To our knowledge, our study in the SEER data is the first calculating the incidence of GC in in the general population and confirms the rarity of the tumor. For the recent 2008-2012 period, we estimated an incidence rate of 0.15 cases per million individuals. Given that the respective annual incidence rates of malignant glioma and malignant CNS tumors in the USA were 6.13 and 7.23 cases per 100,000 individuals, respectively in that period [308], it can be deducted that GC represents only ~1/400 of all glial tumors and ~1/500 of all malignant CNS tumors. The male preponderance and the increase in incidence among the elderly follow the overall glioma patterns [298,308].

An increase was noted in the incidence of GC over the study period, especially among the preceding decades. This is in line with previous reports showing increases for all CNS tumors before 2000 followed by stable rates thereafter [201,298,313,335,443,444]. The introduction of MRI has been suggested as the main contributor to this observation [313]. Given the aggressiveness of CG, it could be assumed that many patients were undiagnosed in the era of restricted MRI availability. Furthermore, the establishment of GC as a distinct tumor entity, the subsequent increasing awareness of the clinicians, and potential registration gaps in the preceding years could contribute to the increase. The trends were stabilized in the last decade, but a continuous increase of the radiologically diagnosed GC was noted. More modern technologies, like the MR spectroscopy, may allow the radiological diagnosis of GC, and could underlie this increase [127,151,445].

The overall GC outcome in the SEER dataset was poor, with 1-year and 5-year OS rates lower than 50% and 20%, respectively. Furthermore, median survival was 9 months, considerably lower than several single center or multicenter case series that have been published, reporting median rates of 20 months or higher [132-137,139-141,144,446,447]. This may be expected, given that case series are inherently prone to several forms of bias. Particularly, selection bias is an important issue in tertiary center studies; it is more likely that these studies include patients at earlier stages of disease with indications of treatment. Furthermore, an underrepresentation of elderly patients in these studies, who have a much worse prognosis, could underlie the discrepancies. Even among the large retrospective study by Tallibert *et al.*, including 291 GC patients that had been published until

2006 in the literature, median OS was 14.5 months, indicating selection bias in the published studies [142].

In our study, increasing age was the strongest risk factor for worse OS, which is in line with published literature [133,142,447]. Children with GC are known to have better outcome [150] and many studies exclude them from the overall analysis. Although male gender showed a tendency for improved outcome, this was attenuated after adjustment for the remaining confounding factors. According to Tallibert *et al.*, the better outcome among men should be attributed to the higher proportion of oligodendroglial GC tumors that generally show longer survival rates [142]. As expected, tumors restricted to cerebral hemispheres had marginally better outcome, in comparison to tumors with deep structure or infratentorial expansion. On the other hand, radiotherapy and surgical excision of the tumor did not seem to impact on the outcome in this population-based study, as opposed to previous reports [133]. Nevertheless, the difficulties associated with collection of these variables by registration methods, the non-availability of other details regarding the treatment (i.e. inclusion or not of chemotherapy and type of radiation) as well as the lack of adjustment for other important clinical confounders should be accounted when interpreting these results. Lastly, the worse outcome associated with rural residence emphasizes the importance of health care access and has been also reported for other CNS tumor entities [201,448].

In the meta-analysis of individual-level data on GC, the vast majority of the GC tumors were astrocytomas followed by oligodendrogliomas or oligoastrocytomas and one out of two of low-grade behavior. In line with other gliomas, IDH1 mutations and MGMT promoter methylation were the most common molecular aberrations GC [449-451]. These aberrations in addition to the co-deletion of the 1p and 19q chromosomes were associated with an oligodendroglial tumor component, as has been previously described for low-grade diffuse gliomas [449]. In agreement are also our results with recent studies on DNA methylation and copy number profiling data reporting that the majority of the tumors could be classified under other molecularly defined subgroups of non-GC diffuse gliomas in both children [131] and adults [132].

Gliomatosis cerebri might comprise a diagnostic challenge for the clinician. No particular pattern of clinical features was highly consistent. Although seizures were the most commonly reported symptom, they were found in only half of the patients. The majority of the patients presented with more than one symptom out of the five identified clusters dependent on the affected CNS regions. The time elapsed from symptoms to diagnosis was minimal among children; independently of presenting symptoms, the lengthiest time was associated with a more widespread invasion of the CNS, thus highlighting the importance of a timely diagnosis and management of this fatal malignancy.

Furthermore, individual studies included in this systematic review commonly reported mistaking with other diseases, mainly viral encephalitis, inflammatory demyelinating diseases and

cerebrovascular pathology. Several characteristics might be helpful for the clinician in case GC is suspected, such as the MRI findings always showing hyperintensities in the T2 or the FLAIR sequences that might be associated with contrast enhancement in T1. Unfortunately, no data were available on the presentation of GC in the diffusion and perfusion-weighted imaging. MR spectroscopy might facilitate the differential diagnosis before proceeding to biopsy, particularly, increased choline, creatinine and myoinositol levels, as opposed to decreased NAA observed in almost 90% of the GC patients [127,151,445]. On the contrary, other diagnostic procedures, such as CT did not consistently provide specific findings neither did PET in the limited number of cases available. Lastly, CSF examination was normal in most of the cases and EEG showed inconsistent and non-specific abnormalities.

Taillibert *et al.* in 2006 had made the first effort to examine the characteristics of 296 GC patients [142] as contrasted to the 1,648 included in the current systematic review springing from intensive search of two databases and the snowball process without restrictions on publication date or language; to maximize information, a rigorous contact with authors was carried out. A comprehensive analysis was also employed comprising individual and cumulative data of patients. This large dataset allowed examination of a number of associations between disease characteristics, including demographics, clinical patterns, neuroimaging features, histopathological characteristics and molecular aberrations using alternative methods of analyses.

Small case series had previously reported presence of IDH1 mutation and MGMT promoter methylation as favorable prognostic factors for patients with GC [135,137,173] but our study demonstrated that their prognostic significance was independent of other tumor characteristics. Both molecular alterations have been well-established favorable prognostic factors for gliomas in general [452,453], Regarding other molecular characteristics previously examined in patients with GC [135,173], and other gliomas [454], there have been some indications that 1p/19q codeletion and amplification of the EGFR gene might be favorable and unfavorable prognostic factors, respectively. These results were not, however, confirmed in our multivariable analysis, possibly due to inadequate power. Similarly, rather underpowered were the analyses showing that presence of an oligodendroglial component might be independently associated with improved outcome. A higher grade was associated with higher risk of progression and a high proliferation index (Ki67>5%) was further identified as an independent poor outcome predictor.

Regarding neuroimaging indicators, a type II GC, which is considered to indicate focal progression of type I GC, characterized by a solid tumor component in addition to the diffusion component [125,144] as well as contrast enhancement in MRI most usually noted in type II GC, were predictors of poor outcome. A more widespread expansion of the tumor, including a higher number of CNS regions affected and a bilateral symmetric involvement were associated with worse OS [135], but did not seem to affect PFS. A low Karnofsky performance scale, an increasing burden of symptoms,

and presence of focal neurological deficits at diagnosis were found to be independent unfavorable predictors of outcome, indicating the importance of clinical parameters. On the contrary, seizures at baseline were associated with prolonged OS and PFS, which has been previously attributed to either a more favorable molecular profile of epileptogenic tumors or an anti-tumor effect of anti-epileptic drugs [455]. Lastly, in line with the SEER data, patients ≥65 years at GC diagnosis showed significantly shorter OS [129].

The current study confirms the very poor prognosis of patients with GC. Indeed, the median PFS was only 10 months and the OS of 13 months after diagnosis; the latter is considerably lower than the ≥20 months reported by several case series [132-137,139-141,144], but higher than the 9 months figure of the SEER dataset [129]. This may be expected, given that case series conducted in tertiary centers are prone to selection bias, due to inclusion of patients with specific treatment indications and exclusion of elderly patients with worse prognosis.

Regarding treatment, radiation either as a monotherapy or combined with chemotherapy was associated with worse outcome, compared to chemotherapy alone. Nevertheless, local tumor radiation showed an independent beneficial effect restricted to low-grade GC. The beneficial role of chemotherapy is in accordance with individual studies showing prolonged survival with regimens including temozolomide [135,136,140,456], albeit in our study, temozolomide did not seem to confer better outcomes that other chemotherapy regimens. Importantly, in the current analysis surgical resection of the tumor, either partial or subtotal, was associated with prolonged OS in the small number of included patients in accordance with a Chinese case series [457].

In accordance with studies in adults [135,137,173,458,459], IDH1 were associated with better prognosis in pediatric GC, indicating that despite the lethal nature of the disease, there are molecular subgroups of patients that may have favorable clinical outcomes. However, IDH1 mutations, but also other molecular aberrations known to be associated with improved outcomes among gliomas, including MGMT promoter methylation and 1p/19q codeletion [135,173,452-454], were less common among children with GC, as compared to adult patients. IDH1 and IDH2 mutations are known to be very rare among children with high-grade gliomas, as opposed to older patients [460,461], but similarly to other gliomas [235], paradoxicaly pediatric GC tumors are associated with prolonged survival [458].

Besides IDH1 mutations, other clinical and neuroimaging markers that could be of help in the clinical prognostication of children with GC were identifed as independent prognostic factors for OS. Those included age >4 years at diagnosis, higher number of CNS infiltrated regions, and the symptoms of cognitive decline and coordination abnormalities. These symptoms, might also indicate more extensive CNS infiltrations, and have also been associated with worse outcome in adult GC [458], but also other pediatric gliomas [462]. However, an age at diagnosis of 0-4 years is considered an unfavorable prognostic factors for other pediatric CNS tumors [201,212,344,345].

This disparity might relate with a more favorable molecular profile of GC among neonates and young children or with higher brain plasticity, thus increasing the possibility for recovery [463] following the aggressive treatment that the tumor requires.

We further found chemotherapy and surgical resection to be significantly associated with improved outcome, which was contrasted to the lack of any significant effect for radiotherapy. While our retrospectively collected data cannot exclude indication bias, this finding is also consistent with the results from adult GC [458]. Chemotherapy has been previously shown to be effective in patients with GC, but as opposed to previous studies [135,136,140,456]. we did not find any evidence that temozolomide is superior to other regimens. Last but not least, the current analysis showed prolonged OS in the small group of patients (12%), in whom it was possible to perform extensive subtotal resection of the tumor.

Limitations

The limitations of the first study based on the SEER cancer registry are mainly related to the registration-based nature of the study. First, the lack of data on pathological diagnosis (histology and grade), as well as on important clinical variables, like functional performance at diagnosis, duration of symptoms before diagnosis, detailed tumor location and radiological factors, precluded adequate adjustment for confounding in the survival analysis. Given the rapid increase in incidence, it is furthermore possible that several cases diagnosed in the preceding decades could have slipped registration, either due to missed diagnosis or due to flaws related to registration procedures. Lastly, during the extended 40-year time period, the medical practice regarding proper diagnosis and management of GC has changed, which could have affected the results of our study.

Regarding the meta-analysis of case reports and case series, the limitations are related to the comprising studies. First, the included studies were usually conducted within specialized centers which might be a source of selection bias. Indeed, the age distribution of the SEER data was considerably different from the meta-analysis dataset: mean age was 57.6 years in SEER as opposed to 43.6 years in the our pooled dataset, and SEER had a much higher proportion of elderly (≥65 years) patients (49% vs. 15%) [129]. Second, some of the studies were published several years ago, and thus the definitions of histological subtypes might not comply with the current WHO classification, as specifically demonstrated for tumors with 1p/19q deletion that would by definition today be regarded as oligodendrogliomas. Third, the aim of individual case series might be different than the presentation of collective characteristics of the disease with variable impact on the results. For example, although astrocytomas are by far the most common GC histological subtype [144,446], some of the included case series reported a preponderance of oligodendrogliomas [139], or even oligoastrocytomas [464].

Fourth, despite the extensive literature search and data extraction, some of the subgroups analyzed were small due to the fact that not all characteristics could be extracted from the available literature. Fifth, the individual studies did not provide data on serial MRI assessments that would enable the investigation of the role of the growth velocity of the tumor in the associations between time-to-diagnosis and extension of the tumor in the CNS. Sixth, we should note the heterogeneity across included studies in terms of patient characteristics, experience of the center in management of patients with GC, and treatment selection. Seventh, some patients, especially in older publications were diagnosed only by autopsy, thus precluding their inclusion in meaningful analyses regarding the clinical presentation and neuroimaging findings. Lastly, the current approach did not allow us to explore characteristics of treatment options in more detail, including different dosages, different number of cycles and serial administration at different time points against co-administration of different modalities. The rather broad and heterogeneous treatment categories that were examined here might thus preclude meaningful conclusions for clinical practice. As selection for treatment was not based on a formal randomization process, there is a high possibility that our retrospectively collected data are inherently biased by indication.

CONCLUSIONS AND FUTURE RESEARCH DIRECTION

The conclusions of this thesis can be summarized as follows:

- The first attempt to use sizeable sets of registration data on malignant CNS tumors among the distinct population of AYAs (15-39 years) in the region of SEE shows higher rates compared to the US, but similar to those reported for other European regions. Temporal increases in specific SEE registries, as opposed to a rather stable rate in the US could probably be explained by registration improvements. Age and gender distribution by histology are similar in SEE as in the US and other geographical regions. The striking preponderance of cases of unspecified histology within SEE registries points to the need for optimization of CNS cancer registration in the area, as to facilitate comparability with the internationally published data at the histological subtypes level and for the evaluation of new treatments provided.

- Further analyses of this pooled dataset showed considerable outcome discrepancies for malignant CNS tumors in AYAs between SEE registries and the US, indicating international inequalities in healthcare delivery systems. Nevertheless, the declining mortality rates and the increasing survival patterns in both geographical regions during the examined time periods probably reflect the diagnostic and therapeutic advancements of the last decades in the management of this fatal malignancy. As opposed to other cancer types, we found no significant differences regarding prognosis between AYAs and children (0-14 years). Nonmodifiable factors, including age and gender independently impact on outcome, pointing to the need for potentially targeted treatment modalities by age group and gender. The optimization of cancer registration policies and the further recording of clinical and molecular data will allow to explore the identified discrepancies by disease subtype at a population level.

- Pooling a set of data from the same registries in SEE to explore the epidemiology of childhood PA we found significant outcome disparities compared to the US for this otherwise non-malignant childhood tumor, on account mainly of healthcare delivery patterns. The worse survival rates among infants indicates the need for innovative treatment modalities tailored for the youngest patients, whereas the identification of female gender as a potential adverse predictor of outcome merits further research. It is anticipated that registration improvements, especially in the less affluent SEE area will allow to unveil whether the lower PA incidence is genuine, as well as to deeply evaluate the increasing incidence. Similarly, expanding registration processes to include molecular and cytogenetic markers will provide further room for an in-depth evaluation of their prognostic significance.

- Our findings from the Greek case-control study support that instrument-assisted delivery, possibly indicating a delivery-related brain trauma might be associated with higher risk of childhood CNS tumors with potential clinical and public health implications. Furthermore, maternal alcohol consumption during pregnancy and history of living in farm were associated with higher risk, as opposed to higher birth order that was associated with decreased risk, thus highlighting that early-life exposures including toxic agents and infections might play a role in brain tumorigenesis during childhood. These results should be interpreted with caution, due to power issues and require replication and further investigation in large cohort studies and meta-analyses.

- Pooling data in a meta-analysis of published literature, we found high birth weight and large size for gestational age to be associated with increased risk of childhood CNS tumor and notably, with astrocytoma and embryonal tumors. Elucidation of the plausible underlying mechanisms, mainly of the growth factors biological pathways implicated in tumorigenesis may provide further insight into the CNS tumors pathogenesis. Future studies should assess whether modifiable factors leading to infant macrosomia, especially gestational diabetes, might impact on CNS tumorigenesis, whereas additional data derived from cohort studies would be welcome, given the vast preponderance of case-control studies.

- Clustering of births of children or adults with CNS tumors indicating perinatal determinants of the disease cannot be excluded on the basis of to-date published studies. Heterogeneity issues, inadequate control for confounding and lack of reported effect estimates precluded meta-analysis of the mostly underpowered individual studies by specific tumor subtype. Furthermore, birth seasonality, only comprises a broad proxy of several perinatal exposures, which could represent a different underlying exposure by study setting. Yet, this first attempt to summarize current findings seems to be indispensable in showing the type of studies, data and analyses that have to be employed in order to yield actual effect estimates and also points to potential underlying factors that could orient researchers to generate and further explore specific etiologic hypotheses.

- To address the remaining questions raised above, based on >6000 incident cases, we identified age-, gender- and principal histology-specific birth seasonal variations of childhood CNS tumors. These differentials are biologically plausible potentially explained by perinatal determinants of the disease including epigenetic modifications and early-life environmental exposures.

- Our study using population-based registry data from SEER, US over a 40-year time period confirmed the rarity of GC and quantified for the first time its incidence in the population. A male

preponderance and an increasing incidence among the elderly are identified, which are in line with the overall features of gliomas. Despite the fact that GC in not any more recognized as a distinct entity, its special features and its very poor prognosis indicate the need for differential management approaches. The prognosis in our study was considerably lower, compared to center-based case series highlighting the importance of population-based samples in exploration of prognostic factors in future research. Extension of registration to more detailed histological and molecular tumor characteristics could provide the necessary information for identification of markers with prognostic significance.

- In a large systematic review synthesizing published individual patient data regarding features of GC we found no evidence supporting a distinct entity in terms of histopathological and molecular characteristics. Yet, our findings emphasize the importance of MRI and MR spectroscopy in the diagnostic evaluation of patients with suspected GC towards a timely diagnosis associated with a more restricted CNS infiltration. Future large clinical cancer registration and multicenter collaborations offering better quality data might provide additional information about this fatal malignancy.

- Exploiting data from this individual patient-data meta-analysis, we further present the profile of outcome predictors for GC. We identified clinical, neuroimaging, histological and molecular factors to be independently associated with prognosis in patients with GC, which however do not shape a specific prognostic pattern that differentiates this rare tumor from previously described outcome predictors in other gliomas. Among them, IDH1 mutation and MGMT promoter methylation are favorable prognostic factors, whereas neuroimaging markers of focal progression and extensive CNS infiltration are associated with worse outcome. Despite reservations on confounding by indication, chemotherapy and, when feasible, surgical resection of the tumor are associated with prolonged survival, whereas there is no evidence for a beneficial effect of radiotherapy, either alone or on top of chemotherapy. Future multicenter trials are expected to also include patients with GC as to determine the most appropriate management of this fatal malignancy.

- Further exploring difference between pediatric and adult GC, we detected histopathological differences between the two age groups, identified clinical, neuroimaging, and molecular prognostic factors for children diagnosed with GC, and found chemotherapy, and, when feasible, extensive surgical resection, as opposed to radiotherapy, to be associated with prolonged OS. Our results may be informative for alerting clinicians regarding the clinical presentation of the disease, aid in clinical prognostication and identification of high-risk patients with pediatric GC, and guide the design of future clinical trials. Patients with GC should be included in future

multicenter glioma trials, as to determine the most appropriate management for this rare but fatal CNS tumor.

- Finally, attempting to explain why epileptic seizures at the time of diagnosis of GC are associated with prolonged overall and PFS, we showed that IDH1 mutation, a favorable outcome predictor, is associated with a higher occurrence of seizure. This finding is in accordance with other gliomas, as determined in a systematic review and meta-analysis of the literature.

By exploiting national, European, and international population-based cancer registry data, in-house resources, data from published case-control and cohort studies, as well as individual-level data from case reports and case series, with this thesis we were able to address research questions related to all aspects of the epidemiology of primary CNS tumors. We provided the overview of the incidence and survival of malignant CNS tumors in the age group 15-39 years in Southern Eastern Europe and comparisons with the US, explored the epidemiology of pilocytic astrocytoma, the most common primary CNS tumor in childhood, evaluated the role of a series of perinatal and early-life risk factors in the etiology of childhood and adult primary CNS tumors, and finally documented the diagnostic and prognostic features of gliomatosis cerebri, an extremely rare fatal primary CNS tumors with to-date unknown etiology and features. Taken together, this thesis highlights the importance of leveraging available data in order to pool sizeable datasets and answer questions of descriptive, analytical, and clinical epidemiology in the field of primary CNS tumors.

APPENDICES

Appendix I: Search algorithms for meta-analyses

Study #5

(astrocytoma OR xanthoastrocytoma OR glioblastoma OR gliosarcoma OR "gliomatosis cerebri" OR oligodendroglioma OR oligoastrocytoma OR subependymoma OR ependymoma OR astroblastoma OR glioma OR gangliocytoma OR ganglioglioma OR neurocytoma OR liponeurocytomas OR paraganglioma OR pineocytoma OR pineoblastoma OR medulloblastoma OR medulloepithelioma OR neuroblastoma OR ependymoblastoma OR ganglioneuroblastoma OR schwannoma OR neurinoma OR neurofibroma OR perineurioma OR meningioma OR craniopharyngioma OR pituicitoma OR ((astrocytic OR oligodendroglial OR ependymal OR "choroid plexus" OR neuroepithelial OR neuronal OR "neuronal-glial" OR glioneuronal OR pineal OR neuroectodermal OR "teratoid/rhabdoid" OR "teratoid-rhabdoid" OR meningeal OR meningothelial OR pituitary OR craniopharyngeal) AND (cancer OR cancers OR malignant OR malignancy OR malignancies OR tumor OR tumour OR tumours OR tumors OR neoplasm OR neoplasms OR neoplasia OR carcinoma)) OR ((cancer OR cancers OR malignant OR malignancy OR malignancies OR tumor OR tumour OR tumours OR tumors OR neoplasm OR neoplasms OR neoplasia OR carcinoma OR teratoma OR melanoma OR melanocytoma OR melanocytosis OR plasmacytoma OR lymphoma OR germinoma OR choriocarcinoma OR oncocytoma OR lipoma OR angiolipoma OR hibernoma OR liposarcoma OR fibrosarcoma OR histiocytoma OR leiomyoma OR leiomyosarcoma OR rhabdomyoma OR rhabdomyosarcoma OR chondroma OR chondrosarcoma OR osteoma OR osteosarcoma OR osteochondroma OR haemangioma OR hemangioma OR haemangioendothelioma OR hemangioendothelioma OR haemangiopericytoma OR hemangiopericytoma OR angiosarcoma OR sarcoma OR kaposi) AND (brain OR CNS OR "central nervous" OR cerebral OR intracerebral OR intracranial OR cerebrum OR intraspinal OR spinal))) AND (((velocity OR increase OR growth) AND (fetal OR intrauterine)) OR (birth AND head AND circumference) OR ("gestational age" AND (large OR small OR appropriate)) OR AGA OR LGA OR SGA OR (birth AND (length OR weight)) OR “weight for length” OR (ponderal AND index) OR IUGR OR anthropometric OR somatometric OR “proportion of optimal birth weight” OR birthweight)

Study #6

((birth OR labour OR labor) AND (season OR seasonal OR seasonality OR winter OR autumn OR fall OR summer OR spring)) AND (astrocytoma OR xanthoastrocytoma OR glioblastoma OR gliosarcoma OR "gliomatosis cerebri" OR oligodendroglioma OR oligoastrocytoma OR subependymoma OR

ependymoma OR astroblastoma OR glioma OR gangliocytoma OR ganglioglioma OR neurocytoma OR liponeurocytomas OR paraganglioma OR pineocytoma OR pineoblastoma OR medulloblastoma OR medulloepithelioma OR neuroblastoma OR ependymoblastoma OR ganglioneuroblastoma OR schwannoma OR neurinoma OR neurofibroma OR perineurioma OR meningioma OR craniopharyngioma OR pituicytoma OR ((astrocytic OR oligodendroglial OR ependymal OR "choroid plexus" OR neuroepithelial OR neuronal OR "neuronal-glial" OR glioneuronal OR pineal OR neuroectodermal OR "teratoid/rhabdoid" OR "teratoid-rhabdoid" OR meningeal OR meningothelial OR pituitary OR craniopharyngeal) AND (cancer OR cancers OR malignant OR malignancy OR malignancies OR tumor OR tumour OR tumours OR tumors OR neoplasm OR neoplasms OR neoplasia OR carcinoma)) OR ((cancer OR cancers OR malignant OR malignancy OR malignancies OR tumor OR tumour OR tumours OR tumors OR neoplasm OR neoplasms OR neoplasia OR carcinoma OR teratoma OR melanoma OR melanocytoma OR melanocytosis OR plasmacytoma OR lymphoma OR germinoma OR choriocarcinoma OR oncocytoma OR lipoma OR angiolipoma OR hibernoma OR liposarcoma OR fibrosarcoma OR histiocytoma OR leiomyoma OR leiomyosarcoma OR rhabdomyoma OR rhabdomyosarcoma OR chondroma OR chondrosarcoma OR osteoma OR osteosarcoma OR osteochondroma OR haemangioma OR hemangioma OR haemangioendothelioma OR hemangioendothelioma OR haemangiopericytoma OR hemangiopericytoma OR angiosarcoma OR sarcoma OR kaposi) AND (brain OR CNS OR "central nervous" OR cerebral OR intracerebral OR intracranial OR cerebrum OR intraspinal OR spinal)))

Study #12

(seizure OR seizures OR epilepsy OR epileptic OR convulsion OR convulsions) AND (glioma OR gliomas OR gliomatosis OR ((brain OR glial OR cerebral OR "central nervous system" OR CNS) AND (tumor OR tumour OR tumors OR tumours OR malignancy OR malignancies OR cancer))) AND (IDH1 OR IDH2 OR IDH OR "Isocitrate dehydrogenase")

Appendix II: Characteristics of studies included in the meta-analyses.

Study #5

A: Characteristics of eligible case-control studies.

Study (Author, year)	Place (study period)	N cases	N controls	Ascertainment of cases	Ascertainment of controls	Matching variables	Age range (years)	Males (% of cases)	Exposure variables	Exposure assessment	Outcome studied	Adjustment factors
O' Neil *et al*., 2015 USA study arm	California (1988-1997), Minnesota (1988-2004), New York (1985-2001), Texas (1990-1998), Washington (1980-2004), USA	3,561	53,716	Population-based cancer registries	Randomly selected from birth records; frequency matched (all but in California)	Birth year, sex (California, Texas)	0-14	55.5	Birth weight	Birth records data	All CNS tumors, ependymomas, astrocytomas, embryonal tumors, other gliomas, other specified and intracranial tumors, other unspecified intracranial tumors	State, year of delivery, gestational age, maternal age, plurality, birth order, maternal race/ ethnicity, sex
O' Neil *et al*., 2015 UK study arm	England and Wales, UK (1980-2007)	5,702	8,106	National Registry of Childhood Tumors	Selected from birth records; individually matched	District of registration, sub-district of registration, birth period, sex	0-14	54.1	Birth weight	Birth registration data	All CNS tumors, ependymomas, astrocytomas, embryonal tumors, other gliomas, other specified and intracranial tumors, other unspecified intracranial tumors	None

Bhatti *et al*., 2014	Washington, USA (1991-2010)	247	247	Cancer Surveillance System of Western Washington and the Washington State Cancer Registry	Selected from birth records; individually matched	Birth year, race, sex	0-14	49.0	Birth weight, size for gestational age	Birth records data	All CNS tumors	None
Feltbower *et al*., 2014	Leeds and Manchester, England, UK (2007-2010)	49	78	UK Principal Treatment Centers of Leeds and Manchester	Leeds: randomly selected from general practice lists; frequency matched Manchester:friend controls; individually matched	Age,sex	0-24	46.8	Birth weight	Parental face-to-face interview	All CNS tumors	Age, sex, deprivation status
Greenop *et al*., 2014	Australia (2005-2010)	319	1,079	Pediatric oncology departments of Australia	Randomly selected via national digit dialing; frequency matched	Age, state of residence, sex	0-14	58.6	Birth weight,size for gestational age, POBW	Mailed questionnaires/ telephone interview with parents	All CNS tumors, astrocytomas (low-grade), embryonal tumors	Age, state of residence, sex, maternal age, birth year group, ethnicity, maternal pre-pregnancy, folate supplementation
Bjorge *et al*., 2013	Denmark, Finland, Norway, Sweden (1967-2010)	17,698	172,422	National Cancer Registries of Nordic countries	Selected from the birth registries; individually matched	Birth country, birth year, sex	0-14	54.3	Birth weight, birth length, head circumference, size for gestational age,	Birth registration data	All CNS tumors	Gestational age, maternal age, parity

									ponderal index			
Anic *et al*, 2013	Nashvile, Birmingham, Tampa, Atlanta, Louisville, USA (2004-2012)	889	903	Only glioma cases; neurosurgery and neuro-oncology clinics	Non-blood related associates and residents from the same communities identified in white page listings; frequency matched	State of residence, age, sex	>18	59.0	Birth weight	Structured interviewer-administered questionnaires	All CNS tumors	Age, state of residence, race, education, sex
Oksuzyan *et al*, 2013	California, USA (1988-2008)	3,308	3,308	California Cancer Registry	Randomly selected from the California Birth Registry ; individually matched	Date of birth,sex	0-15	53.5	Birth weight, size for gestational age	Birth registration data	All CNS tumors, ependymomas,astrocytomas, embryonal tumors (medulloblastomas, PNETs), other gliomas	Race, gestational age, birth order, maternal age, father's education, source of payment for delivery
Heck *et al*, 2013	California, USA (1988-2007)	44	208,178	CNS tumor cases derived from records of the California Cancer Registry	Controls were randomly selected from California birth rolls and frequency matched to cases	Birth year	0-5	56.8	Birth weight, size for gestational age	Birth certificates data	Embryonal tumors (ATRT)	Maternal age, maternal race/ethnicity, birth year, method of payment for prenatal care.
MacLean *et al*, 2010	California, USA (1988-2006)	3,733	14,923	California Cancer Registry	Selected from the California birth certificate database; individually matched	Date of birth, sex	0-14	55.0	Birth weight, size for gestational age	Birth certificates data	All CNS tumors, ependymomas, astrocytomas (low-grade and high-grade), embryonal tumors (medulloblastomas,PNETs)	Date of birth, race/ethnicity, maternal age, maternal education, birth order, sex

Sprehe *et al*, 2010	Texas, USA (1995-2003)	438	13,331	Texas Cancer Registry	Selected from the residual Texas birth files; frequency matched	Birth year	0-4	50.9	Birth weight, size for gestational age	Birth certificates data	All CNS tumors	Ethnicity, maternal age, congenital malformation, birth year, gestational age, sex
Schmidt *et al*, 2010	Denmark, Finland, Sweden, Norway (1985-2006)	3443	16,169	National Cancer Registries of Nordic countries	Randomly selected from National Population Registries; individually matched	Date of birth, sex, country	0-14	53.9	Birth weight, head circumference, size for gestational age	Birth registration data	All CNS tumors, ependymomas, astrocytomas, embryonal tumors, other gliomas, other specified and intracranial tumors, other unspecified intracranial tumors	Country, age, gestational age, sex
Smith *et al*, 2009	England and Wales, UK (1991-1996)	702	6,337	Proactive notification systems setup in all treating hospitals	Randomly selected from population registries; individually matched	Sex, month and year of birth, area of residence at diagnosis	0-14	49.0	Birth weight	Birth registration data	Astrocytomas, embryonal tumors	Study region, age, sex
Spix *et al*, 2009	Germany (1993-2003)	88	204	German Childhood Cancer Registry	Selected from the records of the corresponding register's office (population-based); individually matched	Sex, age, year of diagnosis	0-4	50.0	Birth weight, Size for gestational age	Parental face-to-face interview	All CNS tumors	Age, year of diagnosis, sex

Mallol-Mesnard *et al*, 2008	France (2003-2004)	209	1,681	French pediatric oncology hospital departments	Randomly selected from the French population; frequency matched	Age, number of children living in the household, sex	0-14	59.8	Birth weight	Parental telephone interviews	All CNS tumors, ependymomas, astrocytomas, embryonal tumors, other gliomas	Age, sex
Schuz *et al*, 2007	Germany (1992-1994)	389	2,024	German Childhood Cancer Registry	Selected from complete files of local resident registration offices; individually matched	Date of birth, community, sex,	0-14	58.1	Birth weight, size for gestational age	Mailed self-administered questionnaires	All CNS tumors	Age, degree of urbanization, socioeconomic status, sex
Walker *et al*, 2007	Texas, USA (1990-1998)	766	3,487	Texas Cancer Registry	Randomly selected among Texas birth records; frequency matched	Birth date, sex	0-14	53.1	Birth weight	Birth records data	Embryonal tumors	None
Pavlovic *et al*, 2005	Belgrade, Serbia (1998-2000)	60	60	Consecutive admission to a neurosurgery department	Selected amongst the outpatients of the Community Health Care Centers for Children and Adolescents; individually matched	Age, sex	0-19	50.0	Birth weight	Parental face-to-face interview	All CNS tumors	None
Von Behren and Reynolds, 2003	California, USA (1988–1997)	746	1,491	California Cancer Registry	Selected from the same birth certificate file as cases; individual matched	Date of birth, sex	0-4	56.0	Birth weight	Birth certificates data	All CNS tumors, astrocytomas, embryonal tumors	Age, gestational age, race, paternal place of birth, birth date, sex

Fear *et al*, 2001	Oxford, Cambridge, Reading, UK (1956-1992)	83	166	National Childhood Tumor Registry; available obstetric notes at specific hospitals	Selected from delivery registers at the study hospitals; individually matched	Hospital of birth, month and year of birth, sex,	0-14	49.4	Birth weight	Delivery records data	All CNS tumors	None
Schuz *et al*, 2001	Germany (1988-1994)	466	2,458	German Childhood Cancer Registry; diagnosed at the state of Lower Saxony (1st study) or at the Former Federal Republic of Germany (2nd study)	Selected from complete files of local offices for registration of residents; 1st study: frequency matched; 2nd study: individually matched	1st study: None 2nd study: sex, date of birth within 1 year, community	0-14	56.2	Birth weight	Mailed questionnaires/ telephone interview with parents	All CNS tumors, ependymomas, astrocytomas, embryonal tumors	Age groups of 1 year, and year of birth, degree of urbanization and socioeconomic status, sex,
McKinney *et al*, 1999	Scotland, UK (1991-1994)	75	133	Scottish Cancer Registry; UK National Register of Childhood Cancer	Randomly selected from children registered for primary; individually matched	Health board area of residence, age, sex	0-14	NR	Birth weight	Obstetric/ delivery/ neonatal records data	All CNS tumors	Age, health board area of residence, sex
McCredie *et al*, 1999	Sydney (Australia), Winnipeg (Canada), Valencia (Spain), Los Angeles, San Francisco and Seattle (USA), Milan (Italy), Paris (France), Israel (1976-1994)	1218	2,223	Population-based cancer registries in the areas covered by the participating centers	Electoral rolls (Sydney); telephone directory (Winnipeg); census and telephone books (Paris); national population register (Israel); regional health service (Milan); municipal census (Valencia); random	Age, sex	0-19	53.4	Birth weight	Structured parental face-to-face interviews	All CNS tumors,astrocytomas, embryonal tumors	Centre, age, mother's year of schooling, sex

					digit dialing (USA); individually matched in Israel, Valencia, Los Angeles, Winnipeg, Milan, Sydney; frequency matching in Seattle, Paris, San Francisco							
Yeazel *et al*, 1997	Unites States, Canada, Australia (1982-1989)	315	816	Epidemiologic database of the Children's Cancer Group; multi-institutional study	Selected from general population via random digit dialing	None	NR (child hood)	NR	Birth weight	Parental questionnaires administered by nurses	All CNS tumors	Maternal age, birth order, gestational age, sex
Ji *et al*, 1997	Shangai, China (1981-1991)	107	107	Population-based Shanghai Cancer Registry	Selected from the general population of urban Shanghai individually matched	Birth year, sex	0-14	49.0	Birth weight	Parental face-to-face interview	All CNS tumors	None
Linet, 1996	Sweden (1973-1989)	570	2,850	National Swedish Cancer Registry	Randomly selected from the Medical Birth and Cause of Death Registries; individually matched	Birth year, birth month, sex,	0-17	49.1	Birth weight	Birth registration data	Ependymomas astrocytomas (low-grade and high-grade), embryonal tumors	birth year, birth month, sex
Bunin *et al*, 1994	USA, Canada (1986-1989)	Astrocytomas: 155 PNETs: 166	Controls for astrocytoma: 155 Controls for	Astrocytic glioma or PNET; Children's Cancer Group; multi-institutional study	Selected by random digit dialing; individually matched	Race, birth year, telephone area code and prefix	0-5	For astrocytoma cases: 52 For PNET	Birth weight	Structured parental telephone interview	Astrocytomas, embryonal tumors	Income level

			PNET:166					cases: 60				
Savitz *et al*, 1994	Denver, Colorado, USA (1976-1983)	47	212	1970 Denver Standard Metropolitan Statistical Area	Selected through random digit dialing; frequency matched	Location, age, sex	0-14	NR	Birth weight	Structured maternal face-to-face and telephone interviews	All CNS tumors	Age, wire code
Kuijten *et al*, 1990	Pennsylvania, New Jersey Delaware, USA (1980-1986)	162	162	Hospital tumor registries	Controls were selected by random digit dialing individually matched	age, race, telephone exchange	0-14	56	Birth weight	Maternal telephone interview with mothers	Astrocytomas	None
Howe *et al*, 1989	Toronto & York, Canada (1977-1983)	74	138	Diagnosed in hospitals covering the metropolitan Toronto area and the regional municipality of York	Telephone interview with potential fathers randomly selected from population lists of Ontario; individually matched	Date of birth, area of residence, sex,	0-21	66,2	Birth weight	Parental face-to-face interview	All CNS tumors	Age
Emerson *et al*, 1991	Western Washington, USA (1974-1986)	157	785	CNS tumor cases derived from the Cancer Surveillance System	Controls were randomly selected by computerized birth files of Washington state and were individually matched to cases (1 case: 5 controls)	Year of birth, county of birth	0-10	56,1	Birth weight	Birth certificates data	All CNS tumors, ependymomas, astrocytomas, embryonal tumors	Birth year, county of birth

Gold *et al*, 1979	Baltimore, USA (1965-1975)	84	73	hospital diagnostic listings, death certificates, hospital tumor registries, pathology, radiotherapy clinical oncology records in the Baltimore, MD, Standard Metropolitan Statistical Area	Selected from birth certificates at the Maryland State Health Department; individually matched	sex, date of birth, race	0-19	47,6	Birth weight	Parental face-to-face interviews	All CNS tumors	Date of birth, race, sex
MacMahon *et al*, 1962	New England and Middle Atlantic States, USA (1947-1958)	603	583	Death certificates by the National Office of Vital Statistics	Selected from the next birth certificate in file; individually matched	Date of birth, town/county of birth hospital of birth	0-10	NR	Birth weight	Birth certificates data	All CNS tumors	None

NR: Not reported

Abbreviations:

CNS: Central nervous system, ICCC-3: International Classification of Childhood Cancer-3rd Edition, PNET: Primitive neuroectodermal tumor, ATRT: Atypical terratoid rhabdoid tumor, POBW: Proportion of optimal birth weigth

B: Characteristics of eligible cohort studies.

Study (Author, year)	Place (study period)	N Population	N cases	Population	Mean follow-up duration	Age range at diagnosis (years)	Males (% of cases)	Exposure variables	Exposure assessment	Outcome studied	Adjustment factors
Tettamanti *et al*, 2016	Sweden (1988-2010)	2,032,727	758	Children born in Sweden in 1973-1995; recorded in the Swedish Birth Registry	22 years	15 – 37	51.1	Birth weight, birth length, , head circumference, size for gestational age	Birth registration data	All CNS tumors, gliomas	sex, maternal and paternal age, maternal birthplace, birth cohort parental socioeconomic index at birth, subject birth weight by gestational age, head circumference, birth length
Crump *et al*., 2015	Sweden (1973-2010)	3,571,574	2,809	Swedish Birth Registry	19.5 years	0-38	51.4	Birth weight, birth length, fetal growth	Birth registration data	All CNS tumors, ependymomas, astrocytomas (low-grade and high-grade), embryonal tumors (medulloblastomas)	Birth year, sex, birth weight, parental country of birth, maternal education, family history of brain tumor in a parent or sibling
Kitahara *et al*., 2014	Copenhagen, Denmark (1968-2010)	244,407	608	Copenhagen School Health Records Registry	36.6 years (median)	>18	58.4	Birth weight	Copenhagen School Health Records Registry (reported by parents)	All CNS tumors	Sex

Samuelsen *et al*, 2009	Norway (1967-2002)	1,649,370	870	Live-born children in the Norwegian Medical Birth Registry	NR	0-5	NR	Birth weight	Birth registration data	All CNS tumors	Gestational age, sex
Milne *et al*, 2008	Australia (1980-2005)	576,633	183	Western Australian Data Linkage System	NR	0-14	51.0	POWFL, POBW, POBL	Delivery records and birth registration data	All tumors, ependymomas, astrocytomas, embryonal tumors, other gliomas, other specified and intracranial neoplasms	None
Ahlgren *et al*, 2007	Copenhagen, Denmark (1968-2003)	217,329	333	Children born in 1930-1975 who attended school in Copenhagen municipality; linked to the Danish Civil Registration System	32.1 years	>6	51.0	Birth weight	Copenhagen School Health Records Registry (reported by parents)	All CNS tumors	Age, calendar period
Samuelsen *et al*, 2006	Norway (1978-2002)	1,010,366	453	Live-born singleton births recorded in the Norwegian Medical Birth Registry in 1978-1998; linked to the National Population Registry	12.3 years	0-15	NR	Head circumference	Birth registration data	All tumors, ependymomas,medulloblastomas,pilocytic astrocytomas,low- and high-grade gliomas, mixed gliomas or oligodendrogliomas, diffuse astrocytomas, unbiopsed CNS tumors, miscellaneous CNS tumors	Birth weight, gestational age, sex
Lee *et al*, 2004	Singapore (1992-1999)	229,248	21	Chinese children born in 1992-1998; registered in the Singapore National Registry of Births and Death	NR	0-5	51.8	Birth weight	Birth registration data	All CNS tumors, astrocytomas	Gestational age, maternal age, birth order, sex

Heuch *et al*, 1998	Norway (1967-1993)	1,489,297	459	Children born in Norway in 1967-1992; recorded in the National Medical Birth Registry	11.6 years	0-15	56.6	Birth weight, birth length	Birth registration data	Astrocytomas, embryonal tumors	Age, sex

NR: Not reported
Abbreviations:
CNS: Central nervous system, POWFL:Proportion for optimal weight-for-length, POBW: proportion for optimal birth weight, POBL: proportion for optimal birth length.

Study #6: Characteristics of eligible studies.

1st Author, Year	Region (study period)	Study Design*	N cases/N controls	Age range (years)	Gender (males %), cases/ controls	Ascertainment of cases	Ascertainment of controls/comparison group	Matching/ Adjusting variables	Season of birth assessment
Anic, 2013	USA: Nashville, Tampa, Birmingham, Atlanta, Louisville (2004-2012)	case-control study	889/903	>18	59.0/57.0	Primary gliomas in neurosurgery and neuro-oncology departments	Frequency matched, cancer-free friends and non-blood related associates of cases or same community residents	State of residence, age, gender	interview
Van Laar, 2013	UK: England (1996-2005)	cancer registration study	1882 astrocytomas, 629; other gliomas, 195; ependymomas, 99; medulloblastomas, 111; other, 702	15-24	NR	National TYA cancer registry	Month-specific national birth rates	sex	registry
Makino, 2011	Japan: Kumamoto Prefecture (1989-2003)	cancer registration study	115 astrocytomas, 31; other gliomas, 18; embryonal tumors, 16; germinomas, 20	0-14	NR	Primary intracranial tumors, 30 hospitals, Kumamoto Prefecture	Month- and season-specific birth rates, Kumamoto Prefecture	none	medical records
Amirian, 2010	USA: Texas, Houston (2001-2006)	case-control study	489/540	>18	55.2/49.3	Histologically confirmed gliomas identified by hospital physicians	Frequency matched, cancer-free controls, random-digit dialing	age, sex	interview
Basta, 2010	UK: N. England (1968-2005)	cancer registration study	702 ependymomas, 72; astrocytomas, 264; PNETs, 124; other gliomas, 68	0-14	55.0	Northern Region Young Persons' Malignant Disease Registry	Month-specific birth rates of all cancer cases recorded in the Registry	none	registry
Schmidt, 2010	Denmark, Norway, Finland,	cancer registration study	2771 ependymomas, 311; astrocytomas, 1128; embryonal tumors,	0-14	53.6	National cancer registries	Month-specific national birth rates	none	registry

	Sweden (1985-2006)		519; other gliomas, 217; other, 596						
Schmidt, 2009	Denmark (1970-2003)	cancer registration study	1640 ependymomas, 162; astrocytomas, 607; PNETs, 270; other gliomas, 76; other, 326	0-19	NR	Danish Cancer Registry	Month-specific national birth rates	none	registry
Staykov, 2009	Germany: Bavaria (2002-2005)	cancer registration study	2174	≥15	58.0	Bavaria registry	Month-specific birth rates, Bavaria	sex	registry
Hoffman, 2007	US, CBTRUS (1995-2001)	cancer registration study	4522 embryonal, 664; pilocytic astrocytomas, 864; other astrocytomas, 552; ependymomas, 279; other 2,163	0-19	53.0	13 population-based databases	Month-specific population birth patterns in each State	none	registry
Koch, 2006	Germany: S-E. Bavaria (1992-2003)	cancer registration study	697 glioblastomas, 501; anaplastic astrocytomas, 196	52.5 ±15.7	58.2	Regensburg Regional Cancer Center	Season-specific national birth rates	none	registry
Mainio, 2006	Finland: Oulu (1990-1992)	cancer registration study	101 low-grade gliomas, 19; high-grade gliomas, 22; meningiomas, 33; other, 27	20-82	38.6	Primary CNS tumors at a neurosurgery clinic	Month-specific national birth patterns	none	NR
Brenner, 2004	USA: Boston, Phoenix, Pittsburg (1994-1998)	case-control study	686/799 gliomas, 489; meningiomas, 197	>18	gliomas, 56.4; meningiomas, 23.0/ controls: 44.4	Histologically confirmed intracranial gliomas/ meningiomas diagnosed in the participating hospitals	Frequency matched controls, hospitalized for non-malignant conditions	hospital, age, sex, race /ethnicity, residence to hospital distance	interview, medical records

Halperin, 2004	USA: North Carolina, (1973-1999)	cancer registration study	1209 medulloblastomas	All	NR	Histologically confirmed cases (registries or St Duke University Medical Center	Month and season-specific national birth rates	none	registry
McNally, 2002	UK: N-W. England (1954-1998)	cancer registration study	1045 astrocytomas, 422; ependymomas, 109; embryonal tumors, 200; other, 314	0-14	53.6	Manchester Children's Tumor Registry	Month-specific birth rates of all childhood cancer cases recorded in the Registry	none	registry
Feltbower, 2001	UK: N. England (1968-1995)	cancer registration study	1015	0-14	NR	3 local cancer registries	Month-specific national birth rates	none	registry
Heuch, 1998	Norway (1967-1992)	cohort study	459/1489297 astrocytomas, 168; embryonal tumors, 78	0-15	56.6	Norwegian Cancer Register	Medical Birth Register (national childhood population)	age, sex	registry
Yamakawa, 1982	Japan: Fukuoka-Ohita (1959-1979)	cancer registration study	128 medulloblastomas	0-5	NR	Histologically confirmed cases diagnosed in N-W District of Kyushu or registered in the Brain Tumor Registry, Japan	Month-specific national birth rates	none	registry

* Type of comparison group in the cancer registration studies is shown in the "Ascertainment" column

Abbreviations: NR, Non-reported; CBTRUS, Central Brain Tumor Registry of the United States; CNS, Central nervous system; PNET, Primitive Neuroectodermal Tumors; SD, Standard deviation; TYA, Teenagers and Young Adults.

Appendix III: Quality assessment of studies included in the meta-analyses.

Study #5

Quality assessment with the Newcastle-Ottawa Scale.

A) Case-control studies	**Selection**				**Comparability**		**Outcome**			
Study	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	On age	On other risk factors	Assessment of Exposure	Same method of ascertainment for cases and controls	Non-response rate	**Total**
O'Neill *et al*, 2015, USA data	1	1	1	0	1	1	1	1	0	**7/9**
O'Neil *et al*, 2015, UK data	1	1	1	1	1	1	1	1	1	**9/9**
Bhatti *et al*, 2014	1	1	1	1	1	1	1	1	0	**8/9**
Feltbowler *et al*, 2014	1	0	1	0	1	1	1	1	0	**6/9**
Bjorge *et al*, 2013	1	1	1	1	1	1	1	1	0	**8/9**
Greenop *et al*, 2014	1	1	1	0	1	1	0	1	0	**6/9**
Anic *et al*, 2013	1	0	1	1	1	1	1	1	0	**7/9**
Oksuzyan *et al*, 2013	1	1	1	1	1	1	1	1	0	**8/9**
Heck *et al*, 2013	1	1	1	1	1	1	1	1	0	**8/9**
MacLean *et al*, 2010	1	1	1	0	1	1	1	1	0	**7/9**
Schmidt *et al*, 2010	1	1	1	1	1	1	1	1	0	**8/9**
Smith *et al*, 2009	1	1	1	1	1	1	1	1	1	**9/9**
Spix *et al*, 2009	1	1	0	0	1	1	1	1	0	**6/9**
Sprehe *et al*, 2010	1	1	1	0	1	1	1	1	0	**7/9**
Mallol-Mesnard *et al*, 2008	1	1	1	1	1	1	1	1	0	**8/9**
Schuz *et al*, 2007	1	1	1	0	1	1	0	1	0	**6/9**
Walker *et al*, 2007	1	1	1	1	1	1	1	1	0	**8/9**
Pavlovic *et al*, 2005	1	1	0	1	1	1	1	0	0	**6/9**
MacMahon and Newill, 1962	0	0	0	0	1	0	1	1	0	**3/9**

Von Behren and Reynolds, 2003	1	1	1	0	1	1	1	1	0	**7/9**
Fear *et al*, 2001	1	1	1	0	1	1	1	1	0	**7/9**
Schuz *et al*, 2001	1	1	1	0	1	1	0	1	0	**6/9**
McKinney *et al*, 1999	1	1	1	0	1	1	1	1	0	**7/9**
McCredie *et al*, 1999	1	1	1	0	1	1	1	1	1	**8/9**
Yeazel *et al*, 1997	1	1	1	0	0	1	0	0	0	**4/9**
Ji *et al*, 1997	1	1	1	0	1	1	1	1	0	**7/9**
Linet *et al*, 1996	1	1	1	1	1	1	1	1	0	**8/9**
Bunin *et al*, 1994	1	1	1	0	1	1	1	1	0	**7/9**
Savitz and Ananth, 1994	1	1	1	0	1	1	1	1	0	**7/9**
Emerson *et al*, 1991	1	1	1	0	1	1	1	1	0	**7/9**
Kuijten *et al*, 1990	1	1	1	0	1	1	1	1	0	**7/9**
Howe *et al*, 1989	1	1	1	0	1	1	1	1	0	**7/9**
Gold *et al*, 1979	0	1	1	1	1	1	1	1	0	**7/9**

B) Cohort studies	**Selection**				**Comparability**		**Outcome**			
Study	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Outcome of Not Present at Start of Study	On age	On other risk factors	Assessment of Outcome	Long Enough Follow Up (4 years)	Adequacy of Follow-Up of Cohorts (80%)	**Total**
Tettamani *et al*, 2016	1	1	1	1	1	1	1	1	1	**9/9**
Crump *et al*., 2015	1	1	1	1	1	1	1	1	1	**9/9**
Kitahara *et al*., 2014	1	1	1	1	1	1	1	1	0	**8/9**
Samuelsen *et al*, 2009	1	1	1	1	1	1	1	1	1	**9/9**
Milne *et al*, 2008	1	1	1	0	0	0	1	1	0	**5/9**
Ahlgren *et al*, 2007	1	1	0	0	1	1	1	1	0	**6/9**
Samuelsen *et al*, 2006	1	1	1	1	1	1	1	1	1	**9/9**
Lee *et al*, 2004	1	1	1	1	0	1	1	1	0	**7/9**
Heuch *et al*, 1998	1	1	1	1	1	1	1	1	0	**8/9**

Study #6

Quality assessment with the Newcastle-Ottawa Scale.

A) Case-control studies	**Selection**				**Comparability**		**Outcome**			
Study	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Age	Other risk factors	Assessment of Exposure	Same method of ascertainment for cases and controls	Non-response rate	**Total**
Anic, 2013	1	0	1	1	1	1	1	1	0	**7/9**
Amirian, 2010	1	0	1	1	1	1	1	1	1	**8/9**
Brenner, 2004	1	1	0	0	1	1	1	1	1	**7/9**
B) Cohort and cancer registration studies	**Selection**				**Comparability**		**Outcome**			
Study	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Outcome of Not Present at Start of Study	On age	On other risk factors	Assessment of Outcome	Long Enough Follow Up	Adequacy of Follow Up of Cohorts	**Total**
Van Laar, 2013	1	1	1	N/A	0	1	1	N/A	N/A	**5/6**
Makino, 2011	1	1	1	N/A	0	0	1	N/A	N/A	**4/6**
Basta, 2010	1	1	1	N/A	0	1	1	N/A	N/A	**5/6**
Schmidt, 2010	1	1	1	N/A	1	0	1	N/A	N/A	**5/6**
Schmidt, 2009	1	1	1	N/A	1	1	1	N/A	N/A	**6/6**
Staykov, 2009	1	1	1	N/A	0	0	1	N/A	N/A	**4/6**
Hoffman, 2007	1	1	1	N/A	1	1	1	N/A	N/A	**6/6**
Koch, 2006	1	1	1	N/A	0	0	1	N/A	N/A	**4/6**
Mainio, 2006	0	1	1	N/A	0	0	1	N/A	N/A	**3/6**
Halperin, 2004	1	1	1	N/A	1	0	1	N/A	N/A	**5/6**
McNally, 2002	1	1	1	N/A	0	0	1	N/A	N/A	**4/6**
Feltbowler, 2001	1	1	1	N/A	0	0	1	N/A	N/A	**4/6**
Heuch, 1998 (cohort)	1	1	1	1	1	1	1	1	0	**8/9**

Yamakawa, 1982	1	1	1	N/A	0	0	1	N/A	N/A	**4/6**

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Original Research

Central nervous system tumours among adolescents and young adults (15–39 years) in Southern and Eastern Europe: Registration improvements reveal higher incidence rates compared to the US

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Abstract ***Aim:*** To present incidence of central nervous system (CNS) tumours among adolescents and young adults (AYAs; 15–39 years) derived from registries of Southern and Eastern Europe (SEE) in comparison to the Surveillance, Epidemiology and End Results (SEER), US and explore changes due to etiological parameters or registration improvement via evaluating time trends.
Methods: Diagnoses of 11,438 incident malignant CNS tumours in AYAs (1990–2014) were retrieved from 14 collaborating SEE cancer registries and 13,573 from the publicly available SEER database (1990–2012). Age-adjusted incidence rates (AIRs) were calculated; Poisson and joinpoint regression analyses were performed for temporal trends.
Results: The overall AIR of malignant CNS tumours among AYAs was higher in SEE (28.1/million) compared to SEER (24.7/million). Astrocytomas comprised almost half of the cases in both regions, albeit the higher proportion of unspecified cases in SEE registries (30% versus 2.5% in SEER). Similar were the age and gender distributions across SEE and SEER with a male-to-female ratio of 1.3 and an overall increase of incidence by age. Increasing temporal trends in incidence were documented in four SEE registries (Greater Poland, Portugal North, Turkey-Izmir and Ukraine) versus an annual decrease in Croatia (−2.5%) and a rather stable rate in SEER (−0.3%).
Conclusion: This first report on descriptive epidemiology of AYAs malignant CNS tumours in the SEE area shows higher incidence rates as compared to the United States of America and variable temporal trends that may be linked to registration improvements. Hence, it emphasises the need for optimisation of cancer registration processes, as to enable the in-depth evaluation of the observed patterns by disease subtype.

1. Introduction

Central nervous system (CNS) tumours comprise a heterogeneous group of malignancies of variable behaviour and histology arising from the cerebral parenchyma or the surrounding structures. Across the whole age spectrum, the global annual incidence rate of brain tumours (malignant and non-malignant) is 10.8 cases per 100,000 individuals, according to a recent meta-analysis [1], whereas the GLOBOCAN project using nationwide data from 184 countries estimated the annual incidence of malignant-only CNS tumours to be 3.4 per 100,000 individuals [2]. Increasing temporal trends have been reported especially in the previous decades, which have been explained by the diagnostic advances in neuroimaging technology and improvements in disease classification [3]. Although CNS tumours are traditionally considered a fatal malignancy and are included among the top 10 causes of death due to cancer worldwide, their prognosis has considerably improved over the last decades possibly because of the prompt detection, the optimisation of treatment protocols including the introduction of temozolomide and the advances in neurosurgical procedures [4–6].

CNS tumours are more common among males [1,2] and their age distribution markedly increases with age reaching its peak incidence in individuals >65 years [2], although variations are noted dependent on the histological subtype under study [7]. CNS tumours constitute the second most common cancer in childhood (0–14 years) and the third most common malignancy in the special age group of adolescents and young adults (AYAs; 15–39

years) [4,8,9]. Cancer in AYAs is considered to be a distinct entity from a biological and an epidemiologic perspective, when compared to children and older individuals [10,11]. Malignant CNS tumours are more common in AYAs than in children, but their incidence is lower in comparison to older ages [12]. In addition, the histology of malignant CNS tumours in AYAs differs from other age groups, whereas their incidence also varies by age subgroup, gender and geographical setting, according to the relatively limited descriptive epidemiological data available for this specific population [8].

Reports on the epidemiology of CNS tumours in AYAs are rather scarce compared between the younger and older age groups. Therefore, the objective of our study was to estimate, for the first time, incidence rates and describe gender and age distribution patterns by histology of CNS tumours in the area of Southern and Eastern Europe (SEE), which is rather under-represented in published literature. To facilitate international comparisons, identify registration gaps in the SEE registries and explore potentially original differences in the epidemiology of the CNS tumours across regions of differential socioeconomic status and healthcare access, we used as benchmark the publicly available US data from the Surveillance, Epidemiology and End Results (SEER) database [13]. As to explore potential changes in incidence patterns across the registration periods either due to external environmental etiologic factors or due to alterations in registration practices indicating improvements, we also aimed to evaluate temporal trends of incidence.

2. Methods

2.1. Participating cancer registries

Expanding an already established collaboration on childhood malignancies [14–16] and following approval of a pre-defined common protocol, 14 cancer registries operating in 12 SEE countries (Belarus, Croatia, Cyprus, Malta, Montenegro, Greater Poland, Portugal Central, Portugal North, Romania-Cluj, Romania-Iasi, Serbia Central, Slovenia, Turkey-Izmir and Ukraine) provided data on incident primary CNS tumours diagnosed among AYAs (15–39 years) with variable registration periods extending from 1990 to 2014. The definition of the AYAs age spectrum has been based on the guidelines by the National Cancer Institute [11]. For comparability reasons, data on AYAs CNS tumour cases were additionally extracted from the SEER database covering 18 registries in the US [13,17].

2.2. Diagnostic classification and behaviour

CNS tumours were defined according to the International Classification of Disease – 10th Edition (ICD-10) [18]; more specifically, the following codes were included: C70.0–C72.9 and C75.1–C75.3 for tumours of malignant behaviour, D32.0–D33.9 and D35.2–D35.4 for benign tumours, as well as D42.0–D43.9 and D44.3–D44.5 for tumours of borderline/unknown behaviour. CNS tumours with non-malignant behaviour, as defined by the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) [19] (coding 0, 1 or 2), are not systematically recorded in seven SEE registries (Croatia, Cyprus, Greater Poland, Romania-Iasi, Serbia Central, Slovenia and Ukraine), whereas Turkey-Izmir started systematic registration in 2000 and SEER in 2004. In this context, given the change in the ICD-O-3 behaviour coding of pilocytic astrocytoma (morphology code 9421) to tumour of uncertain behaviour in 2001 (behaviour code 1), this tumour was also not recorded for all registries; particularly, Croatia, Cyprus, Serbia Central and Ukraine did not systematically register cases of pilocytic astrocytoma. Therefore, only malignant CNS tumours, namely those with behaviour code 3 according ICD-O-3, were available in all registries and were thereafter considered in analyses. Data for non-malignant CNS tumours and pilocytic astrocytomas are presented for comparability reasons.

Based on the ICD-O-3 morphology and topography codes, malignant tumours were classified by diagnostic group in the following diagnostic categories according to the suggested classification by Barr *et al.* [20] for cancer in AYAs: astrocytoma (subdivided to specified low-grade astrocytic tumours, glioblastoma and anaplastic astrocytoma, astrocytoma not otherwise specified, NOS), other glioma, ependymoma, medulloblastoma and other primitive neuroectodermal tumours (PNET; subdivided to medulloblastoma and supratentorial PNET), other specified intracranial and intraspinal neoplasms and unspecified intracranial and intraspinal neoplasms.

2.3. Other variables

In addition to ICD-O-3 coded data on morphology and behaviour, the SEE registries provided demographic information (age and gender), date of diagnosis, topography of the tumour (ICD-10 coded), basis of diagnosis, coded according to the European Network for Cancer Registries recommendations [21] and place of residence. Similar variables were extracted from the SEER database for the US data. All registries covered the 15- to 39-year age spectrum, apart from the Belarus collaborating registry, which restricts registration to individuals aged up to 19 years. Moreover, the underlying population figures for the respective registration years stratified by age group, gender and calendar year were made available by the participating registries; respectively, population data were online available for the SEER database.

2.4. Statistical analysis

Based on the number of incident cases in five age groups (15–19, 20–24, 25–29, 30–34 and 35–39 years), crude (CIRs) and annual age-adjusted incidence rates (AIRs) for malignant CNS tumours, non-malignant CNS tumours (excluding pilocytic astrocytoma) and pilocytic astrocytoma were calculated for each cancer registry (and are expressed as cases per million individuals per year). The world (Segi) population was used for the age-adjusted calculations [22]. Furthermore, CIRs and AIRs for malignant-only CNS tumours by diagnostic categories were calculated for each individual registry and for the overall SEE region and SEER. Comparisons of incidence rates between the SEE region and SEER were implemented by calculating standard errors and 95% confidence intervals using the z-test, whereas the internal variability across the SEE registries was evaluated using one-way analysis of variance (ANOVA). Annual percent changes (APCs) of incidence rates were estimated using Poisson regression analysis, whereas the presence of potential breaks in temporal trends was evaluated with joinpoint regression analysis. Statistical analysis was performed with the SAS software (version 9.4, SAS Institute Inc) and Joinpoint Regression Program (version 4.1.1, National Cancer Institute).

3. Results

3.1. Quality indicators of the registries

A total of 11,438 malignant CNS tumour cases diagnosed among individuals aged 15–39 years were recorded in the 14 SEE registries operating during variable time periods ranging from 1990 to 2014, and another 13,573 incident cases were extracted from the SEER database (1990–2012) amounting to a grand total of 25,011 cases available for the analyses. As shown in Table 1, half of the SEE registries had nationwide coverage with the remaining registries covering between 5% (Turkey-Izmir) to 76% (Serbia Central) of the respective national population in the age range 15–39 years; respectively, SEER data cover 28% of the US population. Death certificate only (DCO) diagnoses corresponded to <3% of the total cases in all the registries, except for the two Romanian registries (~12%) and Cyprus (6%); notably though, four of the registries (Greater Poland, the two Portuguese registries, Slovenia) had no DCO diagnoses owing to the lack of access to these data. The proportion of morphologically verified (MV) diagnoses was >70% in all the registries except the Croatian (57.2%), whereas in the Portuguese and Slovenian registries this percentage equalled or exceeded that of SEER (92.3%). Regarding the proportion of cases of unspecified morphology, a wide variation was observed among the SEE registries (ranging from 9.9% in Turkey-Izmir to >40% in Croatia and Serbia Central), reaching a cumulative 30% (mainly driven by the 34.6% in Ukraine which contributes half of the overall SEE cases), which is considerably higher than the 2.5% cases of unspecified morphology registered in SEER.

3.2. Incidence rates

The AIR of malignant CNS tumours among AYAs was variable in the SEE registries (Table 2); yet, the overall AIR for the entire SEE over the various study periods spanning from 1990 to 2014 (28.1 per million

Table 1
Characteristics and quality indicators regarding the registration of cases of malignant (ICD-O-3, behaviour code 3) central nervous system tumours among adolescents and young adults (15–39 years) in the 14 participating Southern and Eastern European cancer registries and SEER, US.

Registries (registration period)	N cases	% National population coverage	DCOs %	MVs %	% Unspecified morphology[a]
Belarus (1990–2014)[b]	239	100	0.8	84.5	19.2
Croatia (2001–2013)	608	100	0.7	57.2	31.9
Cyprus (1998–2013)	85	100	5.8	80.5	15.3
Malta (1995–2014)	56	100	1.8	71.4	23.2
Montenegro (2013)	6	100	0.0	83.3	16.7
Poland-Greater Poland (1999–2014)	627	10	0.0	79.9	22.0
Portugal Central (1999–2009)	233	23	0.0	91.9	16.3
Portugal North (1999–2010)	385	32	0.0	93.5	17.4
Romania-Cluj (2008–2012)	90	13	12.2	72.2	32.2
Romania-Iasi (2008–2011)	136	18	12.5	81.6	26.5
Serbia Central (1999–2013)	1216	76	2.9	78.5	40.3
Slovenia (1990–2013)	391	100	0.0	96.4	11.0
Turkey-Izmir (1993–2014)	891	5	1.2	85.1	10.0
Ukraine (2000–2012)	6475	100	1.8	71.4	34.6
SEER, US (1990–2012)	13,573	28	0.6	92.3	2.5

DCO, death certificate only; MV, morphologically verified.
[a] Unspecified morphology category includes cases in the sixth diagnostic category ('unspecified intracranial and intraspinal neoplasms') of classification of cancer in adolescents and young adults proposed by Barr *et al.* [20].
[b] Data from Belarus, available only for the age group 15–19 years.

Table 2
Number of incident cases, crude and age-adjusted incidence rates and male-to-female ratios of malignant (ICD-0-3, behaviour code 3), non-malignant central nervous system tumours (ICD-O-3, behaviour code 0) and pilocytic astrocytomas per million adolescents and young adults (15–39 years) in 14 Southern and Eastern European cancer registries and SEER, US.

Registries (registration period)	Malignant tumours								Non-malignant tumours[a]								Pilocytic astrocytomas							
	N cases	CIR (by age group, years)					M:F	AIR	N cases	CIR (by age group, years)					M:F	AIR	N cases	CIR (by age group, years)					M:F	AIR
		15–19	20–24	25–29	30–34	35–39				15–19	20–24	25–29	30–34	35–39				15–19	20–24	25–29	30–34	35–39		
Belarus (1990–2014)[b]	239	13.3	–	–	–	–	1.2	–	42	2.3	–	–	–	–	0.7	–	20	1.1	–	–	–	–	0.8	–
Croatia (2001–2013)	608	21.2	21.2	39.0	41.0	46.2	1.2	30.8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cyprus (1998–2013)	85	12.7	12.3	23.1	19.8	23.7	1.9	17.8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Malta (1995–2014)	56	10.7	13.7	19.3	34.6	22.0	2.0	18.9	43	3.6	10.3	12.3	21.9	29.4	0.8	14.1	5	3.6	1.7	1.8	0.0	1.8	1.3	1.9
Montenegro (2013)	6	22.7	23.4	0.0	89.9	0.0	0.9	25.1	6	0.0	0.0	65.5	22.5	47.8	0.4	25.6	0	0.0	0.0	0.0	0.0	0.0	–	0.0
Poland-Greater Poland (1999–2014)	627	23.7	23.1	29.4	37.2	38.3	1.2	29.3	–	–	–	–	–	–			26	3.0	1.6	0.9	0.5	0.3	1.1	1.4
Portugal Central (1999–2009)	233	13.7	18.8	27.7	27.8	40.8	1.2	24.5	100	5.9	7.0	12.5	12.3	17.5	0.4	10.5	13	3.3	1.8	1.1	1.6	0.0	1.3	1.7
Portugal North (1999–2010)	385	15.7	20.9	25.0	29.4	40.7	1.5	25.1	335	5.6	18.4	28.3	28.7	32.3	0.6	21.4	36	4.8	4.4	2.0	1.6	0.3	1.1	2.9
Romania-Cluj (2008–2012)	90	2.3	9.1	15.4	24.8	26.5	1.3	14.2	47	1.2	7.3	9.1	9.9	13.7	0.5	7.7	2	0.0	0.9	0.0	0.8	0.0	0.6	0.3
Romania-Iasi (2008–2011)	136	17.6	18.4	19.2	32.2	38.1	0.8	23.8	–	–	–	–	–	–	–	–	2	2.1	0.0	0.0	0.0	0.0	–	0.5
Serbia Central (1999–2013)	1216	36.2	35.1	45.8	53.1	58.1	1.2	44.3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Slovenia (1990–2013)	391	12.8	14.5	19.1	28.1	35.2	1.6	20.6	–	–	–	–	–	–	–	–	48	5.1	3.3	2.2	1.4	2.2	1.6	3.0
Turkey-Izmir (1993–2014)[c]	891	17.4	18.4	23.0	35.1	42.0	1.3	25.7	948[c]	17.3	27.1	41.0	49.5	65.4	0.4	37.6	60	2.5	2.0	1.4	1.8	1.3	1.3	1.9
Ukraine (2000–2012)	6475	19.1	18.6	26.4	36.9	45.7	1.2	27.8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SEER, US (1990–2012)[d]	13,573	15.4	19.4	26.4	31.5	36.7	1.3	24.7	15,626[d]	30.1	38.3	55.7	74.5	95.4	0.5	55.2	1298	5.1	2.9	1.8	1.5	1.2	1.0	2.7

CIR, crude incidence rate; M:F, male-to-female ratio; SEER, Surveillance, Epidemiology and End Results.
[a] Pilocytic astrocytomas have not been included in the non-malignant central nervous system tumours category.
[b] Data from Belarus, available only for the age group 15–19 years.
[c] Data for non-malignant central nervous system tumours for Turkey-Izmir available only for the period 2000–2014.
[d] Data for non-malignant central nervous system tumours for SEER available only for the period 2004–2012.

individuals) was higher ($p < 0.001$) compared to that of SEER spanning from 1990 to 2012 (24.7 per million individuals). Among SEE registries, the AIR ranged from a low 14.2 (Romania-Cluj), 17.8 (Cyprus) and 18.9 (Malta) to the high 27.8 (Ukraine), 28.9 (Greater Poland), 30.8 (Croatia) and the rather outlier figure of 44.1 per million individuals in Serbia Central. ANOVA yielded statistically significant internal variability within the SEE registries ($F = 13.79$, $p < 0.001$). As expected, incidence rates increased by age group, and males outnumbered females (male-to-female ratio: 1.2 in SEE overall and 1.3 in SEER). Of note, however, is the high CIR in the 15- to 19-year age group in Serbia Central, Croatia and Greater Poland as well as in the 35- to 39-year age group in Serbia Central, Croatia and Ukraine when compared with those in SEER.

On the contrary, the rates for non-malignant CNS tumours (not including pilocytic astrocytomas) were considerably lower in the seven SEE registries that systematically recorded them (range 7.7–31.7 per million AYAs), as compared to SEER (55.2 cases per million), with a clear female preponderance (male-to-female ratio 0.4 to 0.8 in SEE registries and 0.5 in SEER). Similar to malignant tumours, the incidence increased with age. Regarding pilocytic astrocytomas, the incidence rates among 10 SEE registries varied considerably. Without considering the small Romanian registries and Montenegro, the AIR for the ages 15–39 years ranged from 1.4 cases per million in Greater Poland to 2.9 and 3 cases per million in Portugal North and Slovenia, respectively. In contrast to the other tumour subtypes, the incidence of pilocytic astrocytoma decreased with age, whereas no consistent preponderance by gender was identified.

3.3. Temporal trends

Incidence time trends are shown in Table 3. Despite the variable time periods of data availability, a statistically significant decrease of malignant CNS tumours incidence was noted during a 13-year period in Croatia (APC: −4%; 2001–2013). By contrast, increasing trends were documented in Greater Poland (APC: +2.7%; 1999–2014), Portugal North (APC: +3.5%; 1999–2010), Turkey-Izmir (APC: +2.1%; 1993–2014) and Ukraine (APC: +0.7%; 2000–2012). In SEER, a marginally decreasing tendency was identified, which could be interpreted as no change from zero (APC: −0.3%; 1990–2012). Regarding non-malignant tumours and pilocytic astrocytomas, statistically significant annual trends were found in Belarus, Turkey-Izmir and SEER. The joinpoint regression analysis, where possible, did not reveal any break of significant changes in the trends observed in SEE registries or SEER.

3.4. Distribution by demographic characteristics and diagnostic subtypes

The distribution of malignant CNS tumour cases by the study variables is presented in Table 4. Overall, both the age and gender distributions were rather similar among the SEE and SEER registries with males exceeding females. An increasing frequency of cases with the advancement of age was observed with no clear

Table 3
Annual percent changes (APC) and 95% confidence intervals for malignant (ICD-O-3, behaviour code 3), non-malignant (ICD-O-3, behaviour code 0) central nervous system tumours and pilocytic astrocytomas among adolescents and young adults (15–39 years) in the 14 participating Southern and Eastern European cancer registries and SEER, US, as estimated by Poisson regression analysis.

Registries (registration period)	Malignant tumours	Non-malignant tumours[a]	Pilocytic astrocytomas
Belarus (1990–2014)[b]	0.1 (−1.7; 2.0)	**13.3 (7.6; 19.2)**	**11.4 (3.7; 19.7)**
Croatia (2001–2013)	**−2.5 (−4.6; −0.4)**	–	–
Cyprus (1998–2013)	−3.9 (−8.2; 0.6)	–	–
Malta (1995–2014)	1.2 (−3.3; 6.0)	2.2 (−3.0; 7.7)	−4.5 (−18.1; 11.5)
Montenegro (2013)[c]	–	–	–
Poland-Greater Poland (1999–2014)	**2.7 (0.9; 4.4)**	–	1.1 (−7.1; 9.9)
Portugal Central (1999–2009)	2.4 (−1.7; 6.7)	3.4 (−2.8; 10.0)	−0.1 (−15.9; 18.7)
Portugal North (1999–2010)	**3.5 (0.5; 6.5)**	0.6 (−2.5; 3.8)	2.1 (−7.1; 12.3)
Romania-Cluj (2008–2012)	6.2 (−8.2; 22.9)	2.7 (−16.1; 25.7)	-[c]
Romania-Iasi (2008–2011)	−7.9 (−21.1; 7.6)	–	-[c]
Serbia Central (1999–2013)	−0.4 (−1.7; 0.9)	–	–
Slovenia (1990–2013)	0.3 (−1.1; 1.8)	–	1.4 (−2.7; 5.7)
Turkey-Izmir (1993–2014)	**2.1 (1.0; 3.1)**	**6.1 (4.5; 7.7)**[d]	**6.6 (2.1; 11.2)**
Ukraine (2000–2012)	**0.7 (0.0; 1.3)**	–	–
SEER, US (1990–2012)	**−0.3 (−0.6; −0.1)**	**2.6 (2.0; 3.3)**[e]	**2.0 (1.1; 2.9)**

Bold indicates statistical significance (p-value<0.05).
DCO, death certificate only; MV, morphologically verified; SEER, Surveillance, Epidemiology and End Results.
[a] Pilocytic astrocytomas have not been included in the non-malignant central nervous system tumours category.
[b] Data from Belarus, available only for the age group 15–19 years.
[c] APC was not estimated for Montenegro, as well as for pilocytic astrocytomas for the Romanian registries due to lack of data.
[d] APC for non-malignant central nervous system tumours for Turkey-Izmir refers to the period 2000–2014.
[e] APC for non-malignant central nervous system tumours for SEER refers to the period 2004–2012.

Table 4
Distribution (%) of demographic characteristics and diagnostic subtypes of malignant (ICD-O-3, behaviour code 3) central nervous system tumours among adolescents and young adults (15–39 years) in 14 Southern and Eastern European cancer registries and SEER, US.

Variable	Belarus[a]	Croatia	Cyprus	Greater Poland	Malta	Monten egro	Portugal Central	Portugal North
	(N = 239)	(N = 608)	(N = 85)	(N = 627)	(N = 56)	(N = 6)	(N = 233)	(N = 385)
Gender								
Male	56.1	56.6	63.5	55.2	67.9	50.0	54.5	59.5
Female	43.9	43.4	36.5	44.8	32.1	50.0	45.5	40.5
Age group (years)								
15–19	100.0	12.0	14.1	15.3	10.7	16.7	9.0	10.1
20–24	0.0	12.8	14.1	16.4	14.3	16.7	13.7	14.8
25–29	0.0	20.1	25.9	21.1	19.7	0.0	21.9	19.2
30–34	0.0	25.8	21.2	24.4	33.9	66.6	22.3	23.4
35–39	0.0	29.3	24.7	22.8	21.4	0.0	33.1	32.5
Diagnostic group[b]								
Astrocytomas								
Specified low-grade astrocytic tumours	10.5	0.2	3.5	18.2	1.8	0.0	6.0	10.4
Glioblastoma and anaplastic astrocytoma	18.8	23.8	14.1	17.1	23.2	50.0	15.9	19.0
Astrocytoma, NOS	15.1	11.8	31.8	9.4	26.8	16.7	19.8	14.3
Other glioma	9.6	14.6	16.5	16.3	16.1	0.0	26.2	25.4
Ependymoma	8.4	4.8	10.6	7.3	1.8	16.7	6.0	6.5
Medulloblastoma and other PNETs								
Medulloblastoma	9.2	2.8	2.3	3.7	5.3	0.0	0.0	3.4
Supratentorial PNETs	6.7	2.0	1.2	1.6	0.0	0.0	6.4	1.5
Other specified intracranial and intraspinal neoplasms	2.5	8.1	4.7	4.4	1.8	0.0	3.4	2.1
Unspecified intracranial and intraspinal neoplasms	19.2	31.9	15.3	22.0	23.2	16.7	16.3	17.4

NOS, not otherwise specified;
PNET, primitive neuroectodermal tumours.a
Data for Belarus, available only for the age group 15–19 years.b
Classification by diagnostic groups according to the classification of cancer in adolescents and young adults proposed by Barr *et al.* [20].

differences between the compared age groups in SEE and SEER. Regarding the diagnostic subtypes, the strikingly different percentages of 'unspecified intracranial and intraspinal neoplasms' between SEE and SEER overall (30% versus 2.5%, respectively), as well as among the individual SEE registries (range 10–40%) hinders formal comparisons; yet, a high proportion of the malignant CNS tumours in the 15–39 age range were astrocytomas (SEER: 44.8%, SEE: 48.7%) with glioblastomas and anaplastic astrocytomas being the prevailing subgroups (almost half of astrocytomas). The most pronounced difference across the remaining specified subgroups was evident in the 'other glioma' category (SEE: 11.8%, SEER: 31.6%). A strong negative correlation between the percentage of 'other gliomas' and the 'unspecified category' across the individual SEE registries and SEER ($r = -0.67$, $p = 0.007$) was also noticeable. Ependymomas and embryonal tumours (medulloblastomas and other PNETs) comprised <10% of the cases across all SEE registries and SEER.

Fig. 1 depicts the CIRs by diagnostic group of malignant CNS tumours, age group and gender in the 14 SEE registries overall compared to SEER. As a rule, similar patterns between the SEE registries and SEER were observed; particularly, for astrocytoma and other glioma, an increase by age group among both males and females was shown, with the male preponderance widening by increasing age. As already mentioned, the incidence for 'other gliomas' was overall lower in SEE. Ependymomas seemed to present a rather stable rate by age group without between-gender differences in both geographical regions, whereas the CIRs for medulloblastoma and other PNETs decreased with increasing age; although the male-specific incidence was higher in this diagnostic category compared with females, the discrepancy was diminished by increasing age. The rates for the last two diagnostic categories in SEER were extremely low and similar for both genders and across all age groups in contrast to the SEE registries, where the rates, especially for the 'unspecified neoplasms' were increasing with advancing age.

4. Discussion

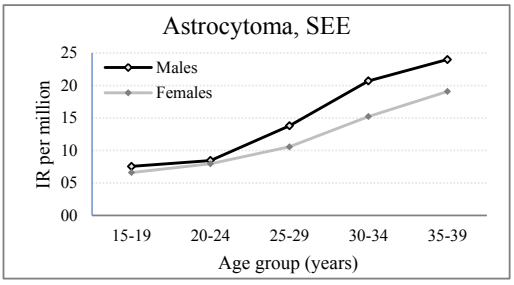
In this study, we have examined the epidemiologic patterns of CNS tumours in the region of SEE among the

Romania-Cluj (N = 90)	Romania-Iasi (N = 136)	Serbia Central (N = 1216)	Slovenia (N = 391)	Turkey-Izmir (N = 891)	Ukraine (N = 6475)	SEE overall (N = 11,438)	SEER, US (N = 13,573)
54.4	46.3	53.9	61.1	56.6	54.6	55.3	57.3
45.6	53.7	46.1	38.9	43.4	45.4	44.7	42.7
2.2	12.5	14.7	10.2	12.5	13.0	14.7	11.5
11.1	15.4	15.4	12.5	14.2	13.7	13.7	14.5
18.9	14.7	20.7	17.4	17.8	18.7	18.7	20.2
33.3	26.5	23.7	26.4	26.4	24.5	24.2	24.6
34.5	30.9	25.5	33.5	29.1	30.1	28.7	29.2
5.6	5.1	1.1	3.1	4.5	5.2	5.3	6.2
24.4	28.7	21.4	39.6	20.9	24.7	23.6	27.7
8.9	12.5	20.4	9.0	14.7	16.6	15.9	14.8
11.1	11.7	8.7	22.5	30.2	7.1	11.8	31.6
7.8	2.9	1.1	5.9	9.2	3.0	4.1	7.3
6.7	3.7	1.3	4.1	5.6	2.5	2.9	4.4
2.2	1.5	1.3	2.8	1.5	1.3	1.7	3.0
1.1	7.4	4.4	2.0	3.4	5.1	4.7	2.5
32.2	26.5	40.3	11.0	10.0	34.6	30.0	2.5

distinct population of AYAs (15–39 years) exploiting population-based data from 14 cancer registries operating in 12 countries for the available time periods spanning from 1990 to 2014; comparisons with the US data from SEER (1990–2012) were also undertaken. A statistically significant higher incidence of malignant CNS tumours compared to SEER was overall noted in SEE, mostly influenced by the high rates in Serbia (44.3 per million), Croatia (30.8) and Ukraine (27.8), the latter comprising >50% of the studied population. Age and gender patterns, as well as the distribution by major diagnostic subtypes were similar between the two regions. Particularly, despite the between-subtype variations, a male preponderance and a linearly increasing incidence trend by age were noted; these features were primarily profound for astrocytoma, which comprised the most commonly diagnosed subtype and other gliomas. Of note are the increasing temporal trends in four SEE registries mostly established since 1999 (Greater Poland, Portugal North, Turkey-Izmir and Ukraine), as contrasted to a decreasing trend in Croatia and a rather stable rate in SEER, but also the high proportion of unspecified cases among SEE registries (>30% in Serbia Central, Ukraine and Croatia) versus a low 2.5% in SEER. Scarce data for non-malignant CNS tumours indicate lower incidence rates in the SEE registries, as compared with SEER, a female preponderance and increasing temporal trends in Belarus, Turkey-Izmir and SEER.

The AYAs age group has been suggested to cover the spectrum of 15–39 years [11]; yet, there is a limited number of published studies, exclusively examining the epidemiology of malignant CNS tumours in this age group, possibly because of the lack of consensus among scientists and the recognition that a single definition may not be applicable in all circumstances [23]. The overall AIR for malignant CNS tumours among AYAs as estimated from SEER during the most recent period in this study (24.7 per million; 1990–2012) is slightly higher than in a previous report (22.6 per million) spanning 1975–1998 [24] albeit lower than the one reported for the overall US region (33 cases per million) during 2008–2012 [8]. Our overall SEE estimation (28.1 per million in the period 1990–2014) is comparable to those estimated by the EUROCARE project for the period 1995–2002 (27 cases per million) among individuals aged 20–39 years [25].

Comparisons with data from other developed regions are difficult because of the different definitions


Astrocytoma, SEE
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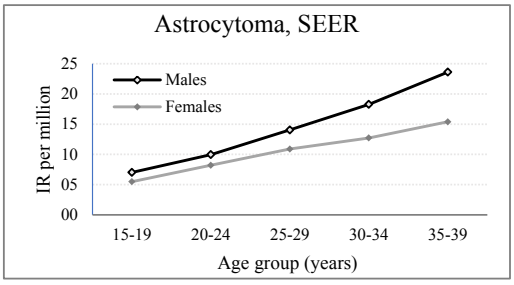
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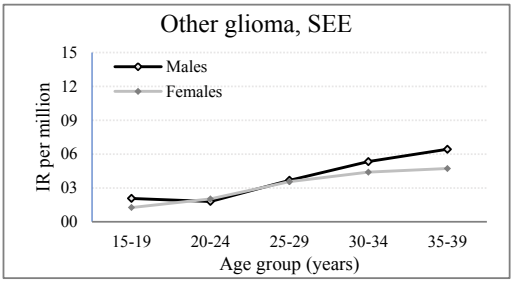
Age group (years)


Other glioma, SEE
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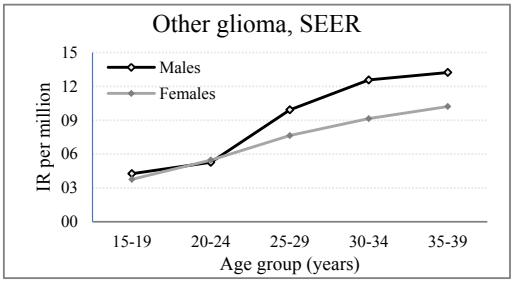
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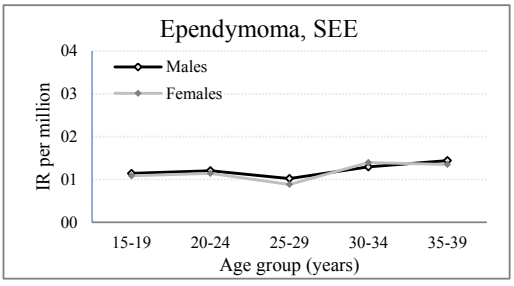
Age group (years)


Ependymoma, SEE
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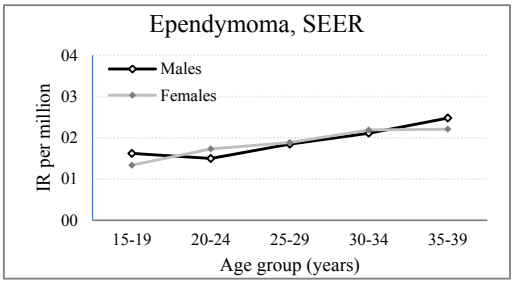
Ependymoma, SEER
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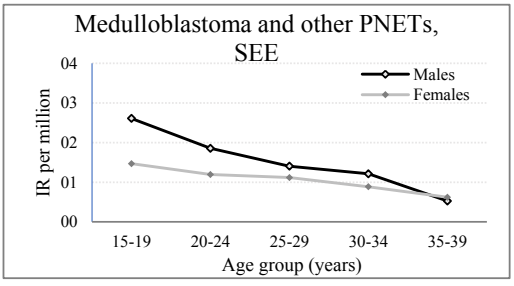
Medulloblastoma and other PNETs, SEE
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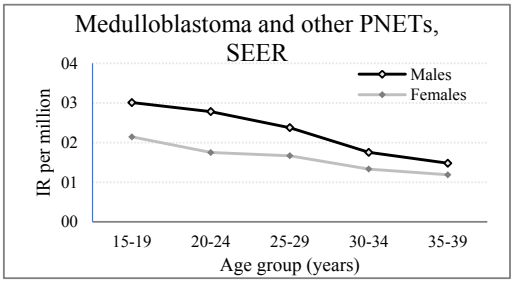
Age group (years)


Medulloblastoma and other PNETs, SEER
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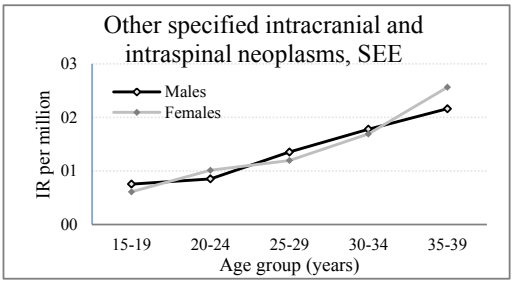
Other specified intracranial and intraspinal neoplasms, SEE
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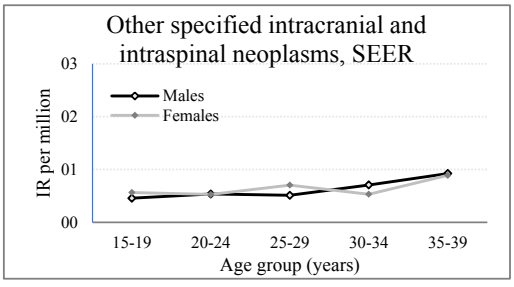
Age group (years)


Other specified intracranial and intraspinal neoplasms, SEER
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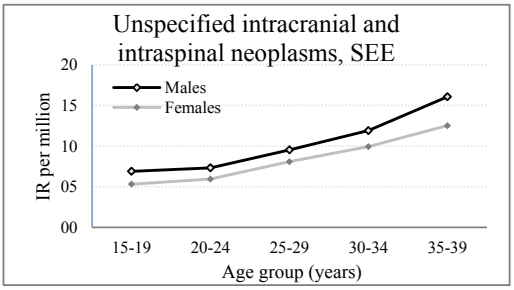
Age group (years)


Unspecified intracranial and intraspinal neoplasms, SEE
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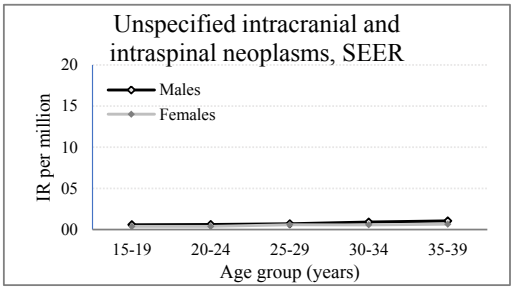
Age group (years)


Unspecified intracranial and intraspinal neoplasms, SEER
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Age group (years)

previously used for AYAs, the use of different classification systems for CNS tumours (e.g. inclusion or exclusion of non-malignant tumours) and reports from confined areas without nationwide coverage. For example, in an England-wide study (1979–1997), incidence rates of 15.6 and 17.6 per million individuals were noted for the age groups 15–19 and 20–24 years, respectively, which are in line with those reported from SEE registries with stable data, after excluding the outlier values noted overall in Serbia Central [26]. The overall AIR for malignant-only CNS tumours from the multiple sites of Italian registries was of similar order of magnitude (18 cases per million) in the period 2003–2008, although in the age range of 13–23 years, which is different from the one that we have analysed [27]. In a study from Shanghai, China, the combined incidence of malignant and non-malignant CNS tumours around the same period 2003–2005 was estimated to 33 per million males and 43 per million females aged 15–49 years [28].

Highest rates are generally recorded in developed countries of Europe, North America and Australia with variations attributed overall to the availability of modern neuroimaging technology, provision of healthcare services as well as completeness and quality of cancer registration [29]. Within SEE, a considerably higher AIR was noted in Serbia Central (44.3 per million), evident across all age subgroups, including also childhood (0–14 years) [15] and the adjacent country of Croatia (30.8 per million), which has been previously attributed to be possibly associated with the war of the 1990s [30], over and beyond concerns on the quality of the registration (extremely low value of MV cases in the Croatian registry and high proportion of unspecified cases in Serbia Central).

When comparing the rates of non-malignant CNS tumours, the considerably lower rates across SEE registries in comparison to SEER indicate incomplete registration in the SEE countries. This is further supported by the increasing temporal trends that point to improved registration policies by longer registration periods. Indeed, non-malignant tumours are more likely to slip registration, as these tumours are commonly managed outside oncology departments that might comprise the primary network of the registry. Similarly, pilocytic astrocytomas could slip registration due to their good prognosis or they could be wrongly categorised in astrocytoma NOS, glioma NOS or unspecified CNS tumour categories.

Astrocytoma comprised by far the most common diagnostic subtype across SEE registries and SEER, corresponding to almost half of the AYAs malignant CNS tumours; this is in accordance with previous literature [8,26,31], but higher compared to the proportion of astrocytomas among malignant CNS tumours in childhood [15]. Otherwise, the most striking discrepancy between SEE and SEER concerned 'other gliomas' (11.6% versus 31.6%, respectively) and 'unspecified intracranial and intraspinal neoplasms' (31.1% versus 2.5%, respectively). Within SEE registries, significant differences were also documented for these two subtypes; a relatively strong negative correlation between the two proportions across the registries could actually indicate misclassification and coding of other glioma cases as unspecified, possibly on account of lack of use of advanced diagnostic pathologic methods or the registration policies in some SEE countries. Further exploring this possibility, the correlation between the proportion of non-MV other glioma cases and the overall relative frequency of other gliomas was not significant ($r = 0.07$, $p = 0.83$); this could however, indicate that the proportion of other glioma non-MV cases that are misclassified as unspecified tumours is the same across registries. Conversely, the overall proportion of non-MV malignant CNS tumours, as an indicator of availability of pathologic diagnostic methods, was strongly correlated with other glioma incidence and relative frequency ($r = 0.48$, $p = 0.07$).

The distribution of CNS tumours in all age groups follows an overall increasing pattern (evident also after 24 years among AYAs) and reaches a peak of 185 cases per million individuals over 65 years of age [8,25,29,32,33]. Interesting variations by subtype were identified, which were similar in both SEE registries and SEER. Notably, the incidence of glial tumours linearly increased in both geographical regions, independently of gender, with the exception of ependymoma, where the rates were rather stable. Conversely, embryonal CNS tumours, but also pilocytic astrocytomas, as expected [34,35], were less frequently diagnosed with the progression of age.

The gender distribution of malignant CNS tumours was similar across the SEE registries and the SEER data with a male preponderance of approximately 1.3, which is a consistent finding across all age groups. Indeed, in the large European RARECARE project with data from 76 registries, the male-to-female ratios ranged between 1.3 and 1.5 across histological subtypes [13], in agreement with data from the United States of America [12], Australia [36], the Netherlands [37], Italy [27], and also Central and Southern America [32]. This gender difference was mostly profound for astrocytomas and other gliomas with a tendency to increase by increasing

Fig. 1. Crude incidence rates per million adolescents and young adults (15–39 years) for malignant (ICD-O-3, behaviour code 3) central nervous system tumours by age group, gender and diagnostic group in 14 Southern and Eastern European cancer registries (left panel) and SEER, US (right panel). Abbreviations: IR, incidence rates; PNET, primitive neuroectodermal tumours; SEE, Southern and Eastern European; SEER, Surveillance, Epidemiology and End Results.

age, but also for embryonal tumours with a narrowing trend by increasing age group. On the contrary, in accordance with the literature [38], non-malignant CNS tumours showed a female preponderance in both SEE registries and SEER.

Bidirectional temporal trends in incidence were recorded in the SEE registries compared to SEER. With the exception of Croatia, where a sizeable declining trend was noted during the last 13 years, significant increases were evident in three SEE registries operating since 1999 (Greater Poland, Portugal North and Ukraine), and in Turkey-Izmir in the period 1993–2014. On the contrary, a very small, annual decrease of 0.3% was documented in SEER over the period 1990–2012, indicating a rather stable temporal trend; in this context, a stable temporal trend is also noted, when exploring the total 1973–2012 SEER registration period (data not shown). Along the same lines, data from the United Kingdom show increasing trends of 1.4% annually over a 19-year period (1979–2007) for the 15- to 24-year age group [26], whereas nationwide data from the Netherlands demonstrate an overall increase of overall adult gliomas in the period 1989–2010, which is mainly attributed to an increase in glioblastoma [33]. Similarly, the China experience shows a significant increase over a 32-year period, especially for females, possibly reflecting improvements in registration of female patients [28]. On the contrary, the Australian database covering AYAs aged 15–39 years over a more recent period (1982–2005) demonstrated a significant decreasing trend (APC, −1.3%) for males, but stable trends for females [36]. A report spanning 1989–2009 of cancer in AYAs (15–29 years) in the Netherlands also showed a decrease for astrocytomas for males and females (APC, −4%), whereas a significant increase for other CNS tumours was observed for females [37]. In accordance with our findings for SEER, the Central Brain Tumor Registry of the United States (CBTRUS) report, entailing more databases, shows an annual decreasing trend in overall CNS tumours among AYAs for the period 1995–2012 [12], also evident among adults in the overall US region for the period 2000–2010 [39]. The increasing temporal trends for more distant time periods have been attributed to the diagnostic advances in neuroimaging technology [3]; it is rather unlikely, however, to also explain the observed increase in SEE registries, as they primarily avail data for periods after 2000, notably when magnetic resonance imaging was widely available. Conversely, the increases could reflect improvements in registration policies leading to better classification of diseases and completeness of the recording of the tumours. It is not easy, however, to ecologically correlate the observed time trends to environmental exposures leading to CNS tumourigenesis in the SEE region.

Our study presents a comprehensive review and cross-country comparisons on incidence patterns, demographics, typology and time trends of malignant CNS tumours in the distinct age group of 15–39 years providing for the first time, population-based estimates from this scarcely represented in literature geographical area. The large sample size of 11,438 primary malignant CNS tumours and the availability of similar size (>13,500 cases) primary data for a comparable time period from the US region, which allowed several subanalyses by histology and demographic factors, should also be noted among the strengths of the study. Finally, half of the SEE registries, contributing 70% of the cases, had nationwide coverage, whereas the proportion of diagnoses directly from death certificates was minimal.

Nevertheless, the findings of the present study should be interpreted taking into account specific limitations, mainly related to the variable quality of registration in SEE. Particularly, the proportion of MV cases, with the exceptions of the two Portuguese and the Slovenian registries, was considerably lower in the majority of SEE registries compared with SEER. This could also explain the high proportion of unspecified neoplasms in the SEE registries (10–40%) compared to SEER (2.5%), which hinders the interpretation of the findings by histological subtypes. It is worth noting, however, that intense efforts have been undertaken by international bodies, such as the European Network of Cancer Registries, the European Commission and the International Agency of Cancer Registration aiming at improving quality of cancer registration and enhancing the low percentages of MV diagnoses reported for CNS tumours, for example in Georgia (38% for all ages) [40], Central and Southern American national registries (65% for AYAs) [32], Norway (67% for AYAs) [41] and Austria (81% for AYAs) [42]. Histological diagnosis of brain tumours is increasingly required because new molecular, personalised treatments are becoming available and novel improved techniques and expertise allow biopsy of tumours which are located in traditionally non-approachable regions, like the brainstem [43]. In addition, the cross-registry variation regarding the time period examined poses difficulties for direct comparisons between registries. We are also aware that data from more affluent European regions would comprise a closer to SEE and more appropriate reference population for comparability. Nevertheless, despite the availability, there was no public access to raw data, and the readily available SEER database was preferred. In this context, the heterogeneity regarding the registration regulations and procedures, the healthcare system reality and the genetic composition of the populations, between SEE and the US is considered a drawback of the study and should be taken into account when interpreting the data. Finally, the highly variable time periods examined across the SEE registries did not allow for the evaluation of an average time trend for the incidence of CNS tumours in the SEE region.

In conclusion, this first attempt to use sizeable sets of registration data on malignant CNS tumours among the

distinct population of AYAs collected in 12 SEE countries during the recent decades shows higher rates compared with those from SEER but similar to those previously reported from studies in other European countries. Similar are also the age and gender distributions. Temporal increases in specific SEE registries, as opposed to a rather stable rate in SEER could probably be explained by registration improvements. The striking preponderance of cases of unspecified histology within SEE registries points to the need for optimisation of CNS cancer registration in the area, as to facilitate comparability with the internationally published data at the histological subtype's level and for the evaluation of new treatments provided.

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None.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

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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

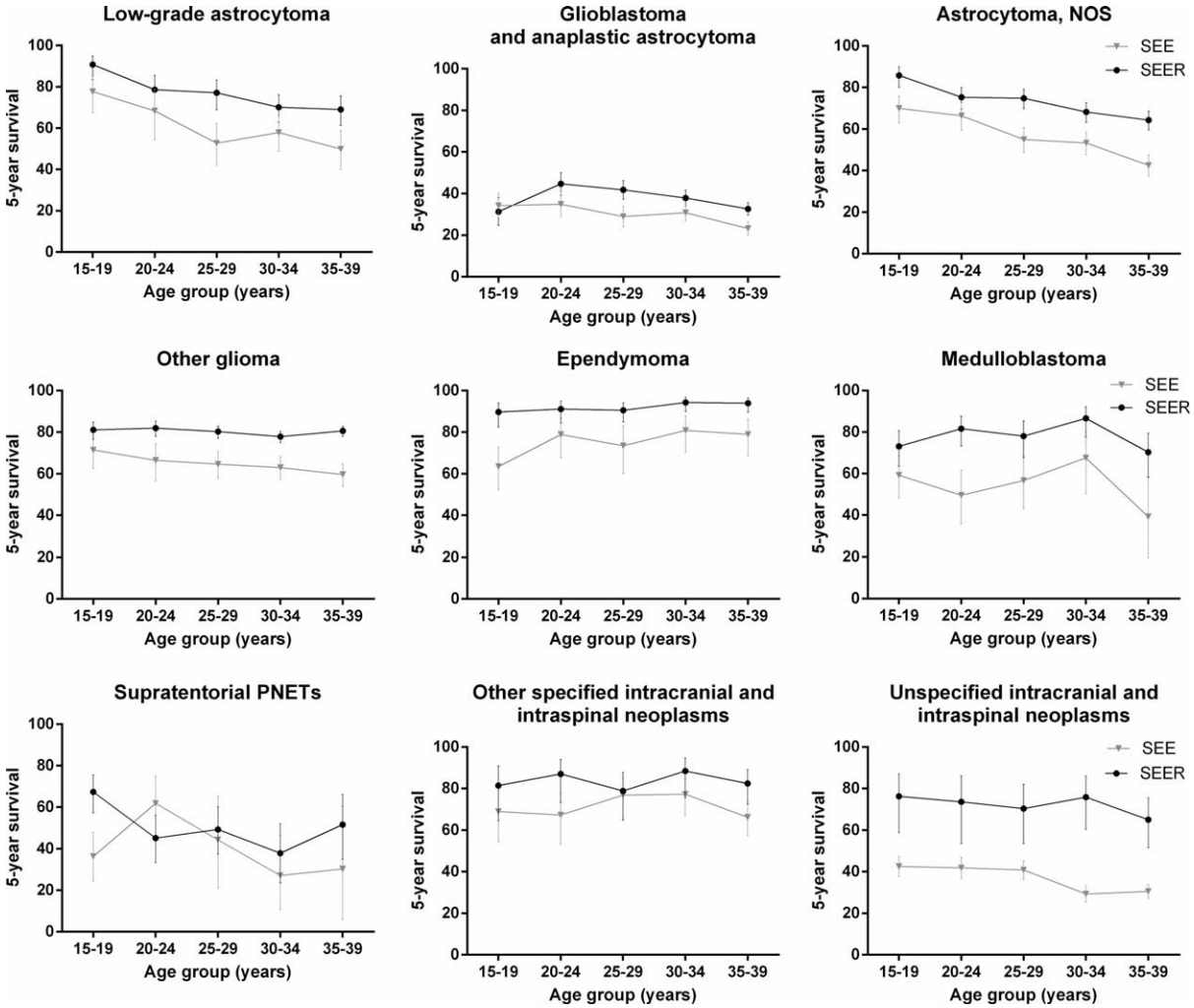

Figure 1. Age-specific 5-year overall survival for adolescents and young adults (15-39 years old) with malignant (*ICD-O-3* behavior code 3) central nervous system tumors in 13 SEE cancer registries and the US SEER program by diagnostic group. The diagnostic classification was performed in accordance 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

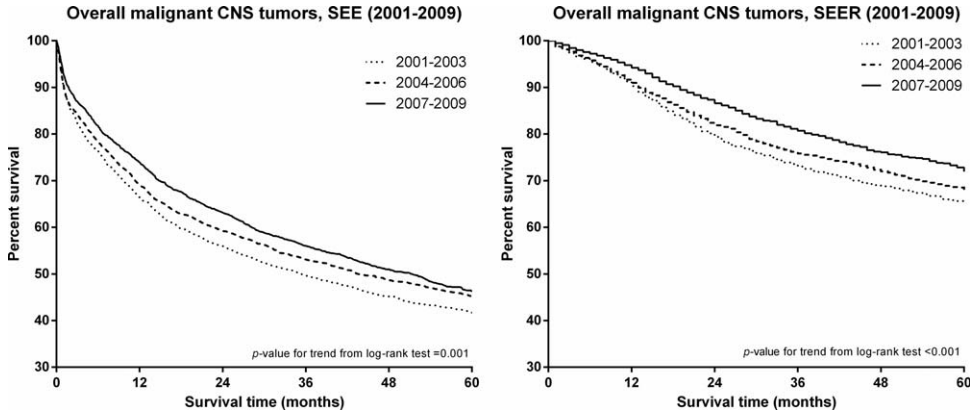

Figure 2. Kaplan-Meier–derived 5-year survival curves for malignant (*ICD-O-3* behavior code 3) CNS tumors diagnosed among adolescents and young adults (15-39 years old) in 9 SEE registries and the US SEER program during 2001-2009 in 3-year intervals. Registries providing data for the entire 2001-2009 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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CLINICAL STUDY

Incidence, time trends and survival patterns of childhood pilocytic astrocytomas in Southern-Eastern Europe and SEER, US

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Abstract Pilocytic astrocytomas (PA) comprise the most common childhood central nervous system (CNS) tumor. Exploiting registry-based data from Southern and Eastern Europe (SEE) and SEER, US, we opted to examine incidence, time trends, survival and tentative outcome disparities of childhood PA by sociodemographic and clinical features. Childhood PA were retrieved from 12 SEE registries (N = 552; 1983–2014) and SEER (N = 2723; 1973–2012). Age-standardized incidence rates (ASR) were estimated and survival was examined via Kaplan–Meier and Cox regression analysis. ASR of childhood PA during 1990–2012 in SEE was 4.2/10^6, doubling in the USA (8.2/10^6). Increasing trends, more prominent during earlier registration years, were recorded in both areas (SEE: +4.1%, USA: +4.6%, annually). Cerebellum comprised

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the most common location, apart from infants in whom supratentorial locations prevailed. Age at diagnosis was 1 year earlier in SEE, whereas 10-year survival was 87% in SEE and 96% in SEER, improving over time. Significant outcome predictors were age <1 year at diagnosis diagnosis (hazard ratio, HR [95% confidence intervals]: 3.96, [2.28–6.90]), female gender (HR: 1.38, [1.01–1.88]), residence in SEE (HR: 4.07, [2.95–5.61]) and rural areas (HR: 2.23, [1.53–3.27]), whereas non-cerebellar locations were associated with a 9- to 12-fold increase in risk of death. The first comprehensive overview of childhood PA epidemiology showed survival gains but also outcome discrepancies by geographical region and urbanization pointing to healthcare inequalities. The worse prognosis of infants and, possibly, females merits further consideration, as it might point to treatment adjustment needs, whereas expansion of systematic registration will allow interpretation of incidence variations.

Keywords Pilocytic astrocytomas · Childhood · CNS tumors · Cancer registries · Survival · Incidence

Introduction

Pilocytic astrocytomas (PA) represent 20% of total central nervous system (CNS) tumors among children (0–14 years) [1], comprising the most common histological subtype in this age group [2, 3]. They are characterized by special histopathological features, and are classified as of borderline behavior tumors due to their considerably good prognosis (International Classification of Diseases for Oncology, third edition; ICD-O-3) [4].

Despite their high incidence, there is a paucity of population-based studies on the epidemiology of childhood PA. The latest annual age-standardized incidence rate (ASR) in the US is 9.3 per million children [2], whereas studies from the UK and Switzerland, report annual ASRs of 7.5 (1995–2003) and 8.3 (1980–1994) per million, respectively [5, 6]. Increasing incidence trends have been reported in the US during the last decades [7, 8], whereas studies in Europe, referring to astrocytomas in general, have also shown overall increasing patterns [9–11].

The excellent prognosis of childhood PA following surgical resection is reflected in a 10-year survival exceeding 90% [2, 5, 12]. Despite their treatable nature, however, disparities in outcome have been recorded even between countries availing high health coverage and quality healthcare [13]. Tumor-specific characteristics, like location, percentage of resection, leptomeningeal dissemination and pathologic features have been reported to influence prognosis [14], whereas less is known on survival disparities by sociodemographic variables.

To this end, we opted to comprehensively explore the epidemiology of childhood PA using population-based data from an informal cancer registries network in Southern and Eastern Europe (SEE 1983–2014) and the Surveillance Epidemiology and End Results Program (SEER 1973–2012), US. Exploiting the largest to-date primary dataset on childhood PA, we sought to assess incidence, and temporal trends, as well as, to describe basic demographic (age, gender) and clinical (topography) characteristics. More importantly, we aimed to unveil potential predictors of disease outcome and seek for cross-country disparities, probably reflecting healthcare system inequalities.

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Methods

Participating registries

The informal SEE network, established in the context of the EUROCOURSE project [11, 15–17], includes 14 childhood cancer registries (Belarus, Bulgaria, Croatia, Cyprus, Greece, Malta, Central Portugal, North Portugal, Romania-Cluj, North-east Romania, Serbia, Slovenia, Ukraine, Turkey-Izmir) operating in 12 countries and coordinated by the Nationwide Registry of Childhood Hematological Malignancies and Brain Tumors (NARECHEM-BT) in Greece [11, 17]. Individual registries, provided primary data on incident CNS tumors diagnosed during variable registration periods expanding from 1983 to 2014.

Additionally, following signing of a Research Data Agreement, data on childhood CNS tumors were extracted from the SEER database, covering 18 cancer registries across US during 1973–2012 [18].

Pilocytic astrocytomas ascertainment

Morphology/behavior

All CNS tumors were codified by morphology and behavior using ICD-O-3 [19] and were classified according to the International Classification for Childhood Cancer, third edition (ICCC-3) [20]; PA cases (morphology code 9421) were thereafter extracted.

According to ICD-O-3, established in 2001, PA are classified as tumors of uncertain behavior, whereas precedent classifications considered them malignant [19]. Serbia and Cyprus, collecting solely malignant tumors, were excluded from analyses, whereas Ukraine starting registration in 2001 confirmed the non-systematic collection of PA and was, thus, excluded from incidence analysis; yet, Ukrainian data were retained in survival analysis given a random recording of PA cases. Bulgaria, despite pertaining to malignant tumors, confirmed that it maintained systematic collection of PA after the classification change. In SEER, PA were systematically collected as malignant tumors until 2001; although registration of non-malignant tumors officially started in 2004, an informal ongoing registration of PA was preserved in SEER during 2001–2004.

Registry definition of PA, might include either morphologically verified cases, or less usually cases clinically defined without available histological examination or cases defined solely by the death certificate. Nevertheless, non-histologically verified cases might definitely be missed in the NOS categories.

Topography

Topography was coded via the International Statistical Classification of Diseases-10th Edition (ICD-10) [21] and was classified to supratentorial site (C71.0–C71.5, C75.1–C75.3), cerebellum (C71.6), optic nerve (C72.3), brainstem (C71.7), spinal cord (C72.0), tumors in overlapping (C71.8) locations and brain PA of unspecified topography (C71.9).

Place of residence

SEE registries, except for Croatia, provided information on place of residence, classified as urban, semi-urban, rural. The classification was different for each country and was based on the respective guidelines of the National Statistical Services, which have already taken into account the special needs of each country's population [22]. For comparability with SEER classification, a dichotomization to rural and urban place of residence (incorporating "urban" and "semi-urban" categories) was applied.

Follow-up data

Survival, as an endpoint, was assessed on the basis of date of diagnosis, date and status at last contact or lost to follow-up date. As all-cause mortality is negligible in children 0–14 years, the observed survival closely reflects the disease outcome. Death certificate only (DCO) and lost to follow-up cases were excluded from survival analysis.

Statistical analysis

Crude incidence rates (CIRs) by age group (0–4, 5–9, 10–14 years) and age-standardized incidence rates (ASR) per million children, using the World (Segi) standard population, were calculated for PA. Annual percent changes (APC) of incidence rates were estimated using Poisson regression analysis. Given the low numbers of PA cases in individual SEE registries and the consequent inadequacy to unveil temporal trends, incidence rates and time trends were also estimated for all participating SEE registries combined during the periods 1990–2012 and 2000–2012 [23], when the majority of registries were active; for SEER estimations pertained to the periods 1973–2012, 1990–2012, 2000–2012. Joinpoint regression analyses were performed to identify potential breaks in trends, whereas trends of astrocytomas NOS (ICD-O-3 coding: 9400) were also examined to explore tentative improvement of classification over time.

Consequently, Kaplan–Meier analysis was conducted for the overall sample, as well as stratified by age group, gender, topography, geographical region and diagnostic period and cumulative survivals for the 6-month, 1–3-, 5- and 10-year periods since diagnosis were calculated. Lastly, Cox proportional-hazard models were designed encompassing age, gender, diagnostic period and topography in a core model and subsequently, geographical region and place of residence interchangeably. SEE and SEER data were combined

in the main analysis, as to increase statistical power, but due to the profound differences in survival between the two regions, stratified analyses were also performed. Cox analysis was repeated stratified by geographical region, excluding Ukranian data, and restricted to cases diagnosed after 1990 and after 2000.

SAS software (V9.4, SAS Institute Inc), Joinpoint Regression Program (V4.1.1, National Cancer Institute) and STATA (V13.0, StataCorp) were used for statistical analyses.

Results

Descriptive registry characteristics

SEE registries amounted 552 PA cases (1983–2014), whereas 2,723 PA cases were derived from the SEER database (1973–2012). Characteristics of the participating registries along with quality indicators [24] are presented in Supplemental Table S1. Out of the 12 SEE registries, seven have nationwide coverage, whereas SEER covers 29% of childhood US population. No DCO cases were identified in SEE and only one in SEER and morphologically verified (MVs) cases comprised 97% of the total in both areas. PA represented 41.5% of astrocytomas in SEE and 55.0% in SEER, accounting for 19.0 and 25.2% of all childhood CNS tumors, respectively. By contrast, astrocytomas NOS cases represented 22.6% of astrocytomas among SEE, with significant cross-registry disparities and 29.7% in SEER. The vast majority of cases (98%) were followed-up and therefore included in the survival analysis; mean follow-up duration was 8.8 years. Details on the registries included in each analysis are presented in Fig. 1.

Incidence rates and time trends

The combined ASR of PA (Table 1) in SEE in 1990–2012 was $4.2/10^6$ children increasing to $5.1/10^6$ during the most recent 2000–2012 period. In SEER, PA incidence was $7.1/10^6$ during the entire 1973–2012 registration period and twice as high ($8.4/10^6$) compared to SEE during 1990–2012. Statistically significant increasing trends were recorded in both areas (annually, SEE: +4.1%, 1990–2012; SEER: +4.6%, 1973–2012); yet, the Joinpoint analysis revealed time-points when the rapid increase in incidence was smoothed. In particular, in SEER the 11.1% annual increase until 1995 was followed by a smaller increase of 1.3%, whereas in SEE registries a break in 1997 was noted, when the pronounced until then, annual rise of 17.8% was substituted by a non-significant 1.1% increasing pattern. Examination of the temporal trends in PA as compared to those of astrocytoma NOS (Supplemental Figure S1) revealed mirror temporal patterns in SEER (PA +4.6%, astrocytomas NOS −4.3%). On the other hand, the PA increase in SEER was accompanied by a rather stable incidence of astrocytomas NOS.

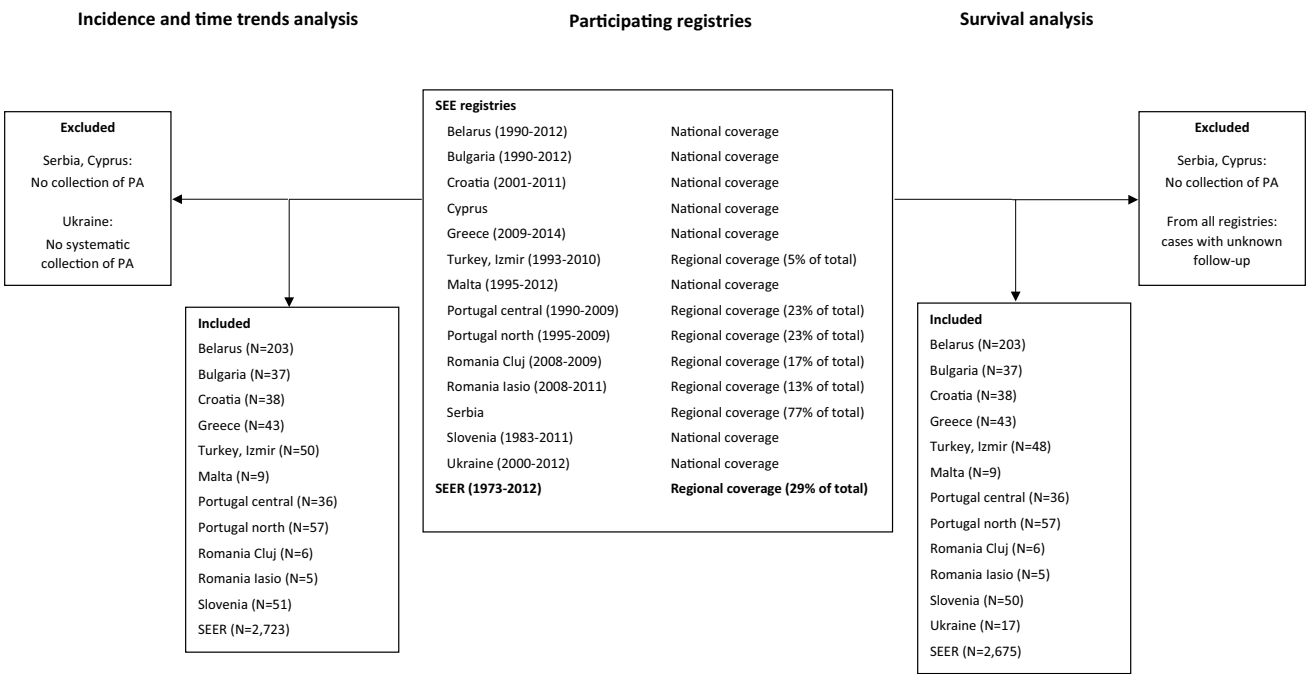

Fig. 1 Flow diagram of the inclusion of participating registries in the analyses

Table 1 Age-standardized incidence rates (ASR) and crude age-specific incidence rates (CIR) per 10^{-6} children, as well as annual percent change (APC) and 95 % confidence intervals (CI) for childhood (0–14 years) pilocytic astrocytomas overall and by age in 11 participating Southern and Eastern European (SEE) registries and the Surveillance, Epidemiology, and End Results (SEER), US

Registry	N	Pilocytic astrocytomas[a] (0–14 years)			Pilocytic astrocytomas[a] (0–4 years)			Pilocytic astrocytomas[a] (5–9 years)			Pilocytic astrocytomas[a] (10–14 years)		
		ASR	APC (95 % CIs)	*p* value	CIR	APC (95 % CIs)	*p* value	CIR	APC (95 % CIs)	*p* value	CIR	APC (95 % CIs)	*p* value
Belarus (1990–2012)	203	4.9	**+5.0 (2.8, 7.2)**	**<0.001**	4.5	**+5.5 (1.3, 9.3)**	**<0.001**	5.2	**+4.2 (0.6, 8.0)**	**0.02**	4.9	**+5.7 (2.0, 9.5)**	**0.002**
Bulgaria (1990–2012)	37	1.3	**+17.4 (10.7, 24.6)**	**<0.001**	1.0	**+16.1 (3.0, 30.8)**	**0.01**	1.8	**+18.8 (8.7, 29.9)**	**<0.001**	1.0	**+16.6 (4.9, 29.6)**	**0.004**
Croatia (2001–2011)	38	5.1	+2.6 (−7.4, 13.7)	0.63	6.7	+0.3 (−13.7, 16.7)	0.97	3.2	+12.8 (−10.4, 41.8)	0.31	5.1	+3.3 (−12.3, 21.7)	0.70
Greece (2009–2014)	43	4.6	+1.6 (−14.8, 21.0)	0.86	6.7	+5.6 (−17.5, 35.2)	0.67	4.7	−1.3 (−26.5, 32.7)	0.93	1.9	−5.1 (−40.6, 51.8)	0.83
Turkey, Izmir (1993–2010)	50	3.6	**+9.2 (3.1, 15.6)**	**<0.001**	2.8	+3.6 (−7.2–15.8)	0.53	4.4	**+11.3 (1.4, 22.3)**	**0.025**	3.6	**+11.1 (0.8, 22.5)**	**0.03**
Malta[b] (1995–2012)	9	8.2	–	–	13.8	–	–	4.9	–	–	4.5	–	–
Portugal central (1990–2009)	36	4.8	+0.4 (−5.1, 6.2)	0.88	5.0	+0.6 (−7.8, 9.8)	0.89	3.9	−3.5 (−13.4, 7.5)	0.5	3.9	+3.7 (−6.3, 14.7)	0.48
Portugal north (1995–2009)	57	6.7	−0.2 (−6.0, 6.0)	0.96	5.2	−2.6 (−13.3, 9.3)	0.65	7.1	+4.6 (−5.6, 15.9)	0.4	7.1	+2.6 (−11.8, 7.5)	0.60
Romania Cluz[b] (2008–2009)	6	4.3	–	–	2.4	–	–	4.5	–	–	6.6	–	–
Romania, Iasi[b] (2008–2011)	5	2.9	–	–	3.6	–	–	0.0	–	–	5.2	–	–
Slovenia (1983–2011)	51	4.7	**+3.6 (0.3, 7.1)**	**0.03**	1.9	+2.2 (−5.7, 10.6)	0.60	6.5	**+6.3 (1.0, 11.9)**	**0.02**	5.7	**+1.7 (−3.4, 7.2)**	**0.52**
SEE (1990–2012)	515	4.2	**+4.1 (2.7, 5.5)**	**<0.001**	4.1	**+3.9 (1.4, 6.5)**	**0.002**	4.2	**+4.5 (2.1, 6.9)**	**<0.001**	3.8	**+3.9 (1.5, 6.3)**	**0.001**
SEE (2000–2012)	355	5.1	+1.1 (−1.7, 4.0)	0.43	5.2	+1.5 (−3.6, 6.9)	0.57	5.3	+1.3 (−3.4, 6.3)	0.59	4.6	+0.6 (−4.1, 5.6)	0.81
SEER (1973–2012)	2723	7.1	**+4.6 (4.2, 5.1)**	**<0.001**	7.5	**+4.7 (4.0, 5.5)**	**<0.001**	7.3	**+4.5 (3.7, 5.3)**	**<0.001**	6.4	**+4.7 (3.9, 5.5)**	**<0.001**
SEER (1990–2012)	2554	8.4	**+2.1 (1.4, 2.8)**	**<0.001**	8.8	**+2.6 (1.5, 3.8)**	**<0.001**	8.6	**+2.1 (1.0, 3.3)**	**<0.001**	7.7	**+1.4 (0.2, 2.6)**	**0.02**
SEER (2000–2012)	2039	9.1	+0.6 (−0.6, 1.8)	0.32	9.8	−0.8 (−2.6, 1.3)	0.49	9.2	+1.2 (−0.8, 3.2)	0.24	8.0	+1.3 (−0.8, 3.5)	0.21

Ukraine was not included in incidence and time trends analysis due to not systematic registration of pilocytic astrocytomas. Serbia and Cyprus were not included in this analysis as they did not avail data on pilocytic astrocytomas

Bold indicates statistical significance (p-value < 0.05)

[a]International classification of diseases in oncology (ICD-O-3) coding: 9421

[b]APC was not calculated for Malta and the 2 Romanian registries, due to the small number of cases and limited available study periods

Demographic and clinical characteristics

PA cases were evenly distributed by age group and gender (male-to-female ratio: 1.02; Table 2); compared to SEE, however, age at diagnosis was lower in SEER (6.8 years vs. 7.7 years, $p<0.001$). Regarding tumor topography, PA were most commonly (36.5%) located in cerebellum, followed by supratentorial locations (21.8%). Brainstem PA represented 10.9%, whereas tumors of the optic nerve and the spinal cord accounted for <10% of cases. Brain PA of overlapping locations were more common in SEE. A differential topography pattern, however, emerged for infants (Fig. 2); particularly, a lower proportion of cerebellar (7.4%) and brainstem (5.5%) tumors was observed, as opposed to the preponderance of supratentorial (31.5%) and optic nerve tumors (20.4%); brain PA of unspecified topography were also more common in infants (30.2%). No gender differences in tumor topography were noted ($p=0.82$).

Survival analysis

Supplemental Table S2 shows the Kaplan–Meier derived survival in SEE and SEER during different time intervals. Although cumulative 10-year survival approached 95% reflecting the rather curable nature of PA, significant disparities between SEE and SEER were noted with the former presenting poorer outcomes (10-year survival 87% vs. 96%, $p<0.001$). Among SEE registries, only Belarus had a 10-year survival >90%, whereas the highest 5-year survival (95.4%) was recorded in Greece, which, however, availed data only for the most recent registration period (2009–2014).

PA presented significantly lower survival among infants in SEER ($p<0.001$; Fig. 3a), as well as a marginally lower survival in SEE ($p=0.09$; Fig. 3b), whereas no significant difference was found by gender (Fig. 3c, d). Tumors located in cerebellum had an excellent 10-year survival (99%), which was significantly higher compared to non-cerebellar PA in both SEE and SEER ($p<0.001$; Fig. 3e, f).

Improvements in PA outcome were evident for both SEE and SEER over registration periods (Supplemental Figure S2). In SEER the improvement in the already high 5-year survival was limited to the period until 1990, being stably >95% thereafter. On the contrary, the increase in 5-year survival in SEE registries showed a significant increase from

Table 2 Distribution of demographic characteristics, histological subtype and topography of childhood (0–14 years) pilocytic astrocytomas in the 12 participating registries in Southern and Eastern Europe (SEE) and the Surveillance, Epidemiology, and End Results (SEER), US

Variables	Total N (%)	SEE N (%)	SEER N (%)	*p* value
Age at diagnosis				0.009[a]
<1 years	108 (3.3)	12 (2.2)	96 (3.5)	
1–4 years	1016 (31.0)	154 (27.9)	862 (31.7)	
5–9 years	1120 (34.2)	193 (35.0)	927 (34.0)	
10–14 years	1031 (31.5)	193 (35.0)	838 (30.8)	
Gender				0.82[a]
Male	1658 (50.6)	277 (50.2)	1658 (50.6)	
Female	1617 (49.4)	275 (49.8)	1617 (49.4)	
Topography				
Supratentorial	713 (21.8)	113 (20.5)	600 (22.0)	0.42[a]
Frontal lobe	67 (9.4)	9 (8.0)	58 (9.7)	
Temporal lobe	105 (14.7)	15 (13.3)	90 (15.0)	
Parietal lobe	50 (7.0)	13 (11.5)	37 (6.2)	
Occipital lobe	24 (3.4)	4 (3.5)	20 (3.3)	
Ventricle	159 (22.3)	29 (25.7)	130 (21.7)	
Cerebrum	302 (42.4)	42 (37.2)	260 (43.3)	
Pineal gland	6 (0.8)	1 (0.9)	5 (0.8)	
Cerebellum	1196 (36.5)	194 (35.1)	1002 (36.8)	0.46[a]
Brainstem	358 (10.9)	45 (8.2)	313 (11.5)	0.02[a]
Spinal cord	116 (3.5)	12 (2.2)	104 (3.8)	0.06[a]
Optic nerve	185 (5.8)	34 (6.2)	152 (5.6)	0.59[a]
Brain overlapping	141 (4.3)	45 (8.2)	96 (3.5)	<0.001[a]
NOS topography	565 (17.3)	109 (19.8)	456 (16.8)	0.09[a]

Serbia and Cyprus: not included in the analysis due to non pilocytic astrocytomas data availability

[a] *p* value derived from Chi square test

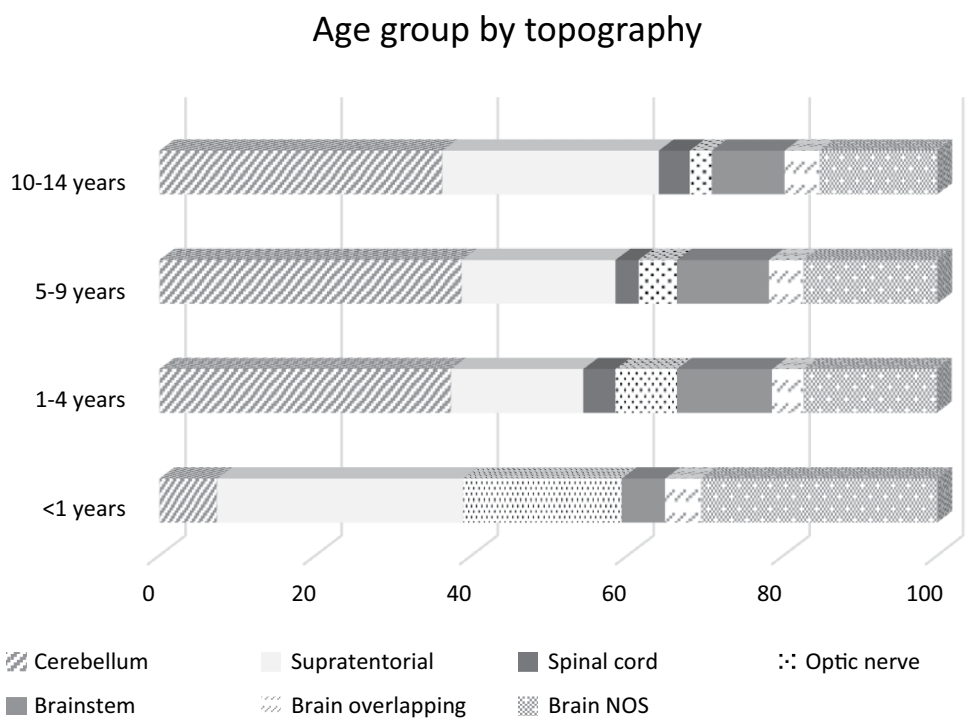

Fig. 2 Distribution of topography of childhood (0–14 years) pilocytic astrocytomas by age group in 12 participating registries of Southern and Eastern Europe (SEE) and the Surveillance, Epidemiology, and End Results (SEER), US

<80% before 1995, to 94% in the latest registration years. Improvements were restricted to non-cerebellar tumors.

The multivariate Cox regression analysis (Table 3) confirmed findings of the crude Kaplan–Meier analysis. Specifically, age at diagnosis <1 year, compared to 10–14 years (HR: 3.96, 95% CI: 2.28–6.90) and female gender (HR: 1.38, 95% CI: 1.01–1.88) were associated with higher risk of death, whereas occurrence of PA in any other location, compared to cerebellum, was associated with considerably worse outcome (9- to 12-fold increased risk of death). After introducing geographical region, children diagnosed in SEE, compared to the US, had a significantly fourfold increased risk of death. Irrespective of country, however, rural residence was sizably associated with worse outcome (HR: 2.23, 95% CI: 1.53–3.27). The effects were similar in both SEE registries and SEER, except for an attenuation of the effect of age at diagnosis <1 year in SEE, possibly because of the low number of cases in this age group, as well as a non-significant effect of rural residency in the SEE registries. Restricting analyses to cases diagnosed after 1990 or after 2000, did not materially change the results, neither did stratification by SEE/SEER or exclusion of the Ukrainian data (data not shown).

Discussion

Epidemiologic features, including incidence, time trends and survival patterns of childhood PA were studied exploiting a dataset of 3,275 incident cases in SEE and SEER, US. A considerably higher incidence of PA was estimated for SEER compared to SEE registries, whereas the increasing trends during precedent decades seemed to stabilize in most recent periods. More than one-third of PA were located in cerebellum, followed by supratentorial locations, except for infants, among whom supratentorial and optic nerve tumors prevailed. Overall 10-year survival reached a high 95%, increasing over registration period, whereas age <1 year at diagnosis, female gender, non-cerebellar location, rural place of residence and residence in SEE countries were associated with worse outcome from this, otherwise non-malignant, tumor.

There is a paucity of published data in Europe on the incidence of childhood PA; yet, studies from England (ASR: $7.5/10^6$; 1995–2003) and Switzerland ($8.3/10^6$; 1980–1994) show higher rates approaching those of the US [5, 6]. In the current study the overall lower incidence in SEE ($4.2/10^6$ in 1990–2012; $5.1/10^6$ after 2000) compared to SEER ($8.4/10^6$ in 1990–2012; $9.1/10^6$ after 2000) could be attributed to underreporting and registration gaps; specifically, as PA comprise a treatable tumor, usually managed outside oncology departments, they could have slipped registration in SEE registries, which have been initiated most recently and may not avail an extensive network for complete registration. Furthermore, the recent behavior change in ICD-O-3 could have led to modification of registration policies adopted with variable delays. The younger-by 1 year- age at diagnosis in SEER may also indicate earlier tumor identification, possibly on account of better healthcare delivery system; in this context, some PA in SEE, despite their development

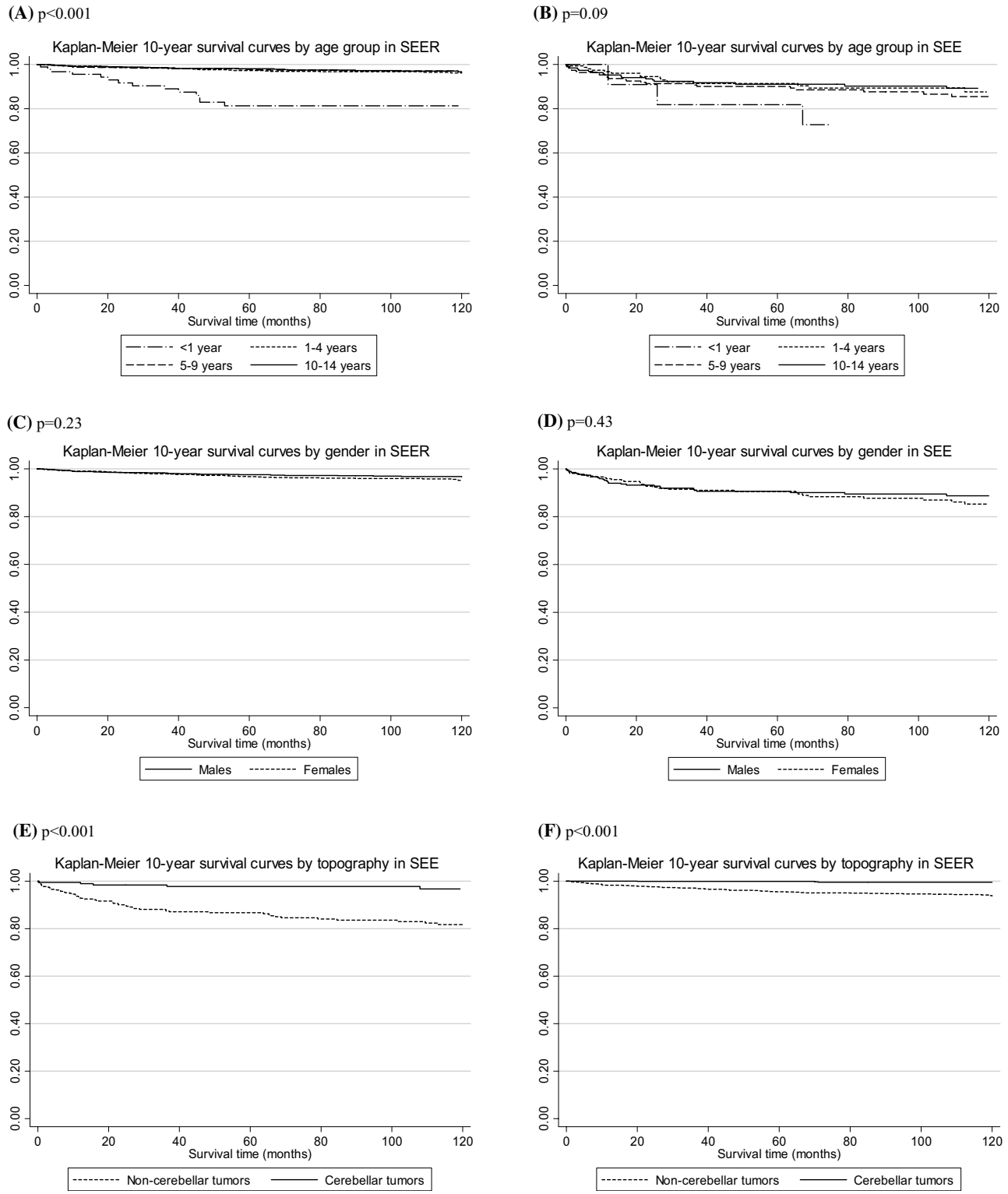

Fig. 3 Kaplan–Meier 10-year survival curves of childhood (0–14 years) pilocytic astrocytomas in 12 registries of Southern and Eastern Europe (SEE) and the Surveillance, Epidemiology, and End Results (SEER), US by (**a, b**) age group, (**c, d**) gender and (**e, f**) topography

during the conventional childhood period could have been diagnosed after 14 years leading to a phenomenal decrease of childhood incidence.

Increasing temporal trends, yet attenuated after 2000, were recorded in both SEE and SEER. Regarding SEER, the increasing trend was opposite to the decrease of

Table 3 Death Cox proportional-hazard modeling-derived hazard ratios (HR) and 95% confidence intervals (95% CI) among children (0–14 years) with pilocytic astrocytoma in the 12 participating registries in Southern and Eastern Europe (SEE) and the Surveillance, Epidemiology, and End Results (SEER), US by study variables

Variables[a]	Total dataset (N = 3224)				SEE data (N = 549)				SEER data (N = 2675)			
	Deaths (%)	HR	95% CI	*p* value	Deaths (%)	HR	95% CI	*p* value	Deaths (%)	HR	95% CI	*p* value
Age at diagnosis												
<1 years	18.6	3.96	2.28–6.90	<0.001	36.4	2.18	0.73–6.52	0.16	16.5	6.31	3.21–12.40	<0.001
1–4 years	4.9	1.26	0.83–1.91	0.28	9.8	0.98	0.50–1.94	0.95	4.0	1.62	0.94–2.78	0.08
5–9 years	4.9	1.26	0.84–1.89	0.27	14.5	1.52	0.85–2.71	0.16	2.9	1.16	0.65–2.05	0.62
10–14 years	4.1	Reference			10.4	Reference			2.7	Reference		
Gender												
Male	4.5	Reference			11.2	Reference			3.1	Reference		
Female	5.7	1.38	1.01–1.88	0.04	13.2	1.28	0.79–2.09	0.31	4.2	1.42	0.95–2.13	0.09
Diagnostic period (5-year increment)	5.1	0.78	0.67–0.89	<0.001	12.2	0.76	0.61–0.95	0.02	3.6	0.76	0.63–0.91	0.004
Topography												
Cerebellum	0.7	Reference			2.6	Reference			0.3	Reference		
Supratentorial	8.5	12.13	5.78–25.45	<0.001	19.6	8.75	3.31–23.14	<0.001	6.4	18.82	5.78–61.31	<0.001
Brainstem	8.2	12.86	5.88–28.14	<0.001	20.0	11.11	3.71–33.30	<0.001	6.5	21.36	6.34–71.93	<0.001
Spinal cord	7.0	11.42	4.28–30.45	<0.001	16.7	6.82	1.32–35.36	0.02	5.9	20.95	5.23–83.97	<0.001
Optic nerve	6.0	9.37	3.73–23.56	<0.001	17.7	6.17	1.86–20.42	0.004	3.4	11.22	2.63–47.81	0.001
Brain overlapping	6.5	8.70	3.35–22.56	<0.001	9.1	3.31	0.89–12.35	0.07	5.4	15.28	3.65–64.00	<0.001
NOS topography	7.1	9.97	4.64–21.41	<0.001	17.2	7.43	2.75–20.09	<0.001	4.5	13.21	3.91–44.70	<0.001
Additionally alternatively introduced variables to the model[b]												
Geographical region												
SEER	3.6	Reference			na				na			
SEE	12.2	4.07	2.95–5.61	<0.001								
Place of residence[c]												
Urban	4.4	Reference			11.6	Reference			3.3	Reference		
Rural	10.3	2.23	1.53–3.27	<0.001	14.6	1.23	0.71–2.12	0.46	7.4	2.01	1.15–3.51	0.01

NOS not otherwise specified

Serbia and Cyprus were not included in this analysis as they did not avail data on pilocytic astrocytomas

[a]Core model includes age, gender, diagnostic period and topography

[b]Geographic region and place of residence were interchangeably additionally introduced in the core model

[c]N = 3144 cases (excluding 38 Croatian cases with non-available data on place of residence, as well, as 42 missing cases) in the total sample, N = 509 for the SEE analysis, N = 2635 for the SEER analysis

astrocytomas NOS, indicating improvements in diagnostic classification of CNS tumors over time [8]. The rates of astrocytomas NOS in SEE registries remained, however, stable, possibly implying welcome improvements in registration processes [8, 25, 26]. Besides registry improvements, advances in neuroimaging modalities, especially the wide use of MRI, could be responsible for these trends. Indeed, the trends are in accordance with an overall temporal increase in childhood CNS tumor incidence in developed countries [9], and contrasted to the stable trends in countries of lower socioeconomic status [27, 28]; the diagnostic improvements have been suggested as the main contributors to these observations [29]. If this stipulation were genuine for PA, disease diagnosis at an earlier time due to use of imaging methods would have been expected to result in a more pronounced increase among younger children; such a trend has not been noted, though, in this study. It has lastly been suggested that the increase in childhood astrocytomas could be rather real due to exogenous environmental factors, not yet identified [26, 30].

Prognosis of PA reached a high 94.5% 10-year survival, which significantly increased from 79 to 94% since 1990 in SEE, whereas in SEER remained stable over 95% thereafter. The cerebellar PA have a diachronic excellent prognosis and survival gains pertain exclusively to outcome improvements of non-cerebellar tumors. In fact, it is now well-established that gross-total resection of PA is a major predictor of outcome [31], with the greater amount of resection leading to higher possibility of cure [32]. The diagnostic advancements and the improved access to healthcare delivery, leading to earlier diagnosis and, thus, surgery with higher probabilities of total resection, along with management improvements through development of pediatric neurosurgery and establishment of specified childhood CNS tumors centers have contributed to survival gains. The considerable improvement in SEE is also in accordance with the overall rather declining trends of malignant CNS tumors mortality and improved survival over time, which was recently reported for the same area [17]. Significant outcome disparities between the less affluent SEE countries and the US were found; similar disparities, impacting on prognosis of childhood CNS tumors between European regions, as well as between UK and the US have been described [10, 13, 33]. Apart from the availability of specified pediatric neuro-oncological centers in the US, differences in treatment-related factors including type of adjuvant therapy, aggressiveness of relapse treatment and supportive care could partly explain the discrepancy. Completeness of registration should be also taken into account, however, in assessing the SEER vs. SEE survival discrepancies. In particular, if less aggressive tumors are more likely not to be registered in SEE due to their management in non-oncology departments, then a falsely worse prognosis might emerge.

Intriguingly, rural residence, considered as proxy of healthcare access [17, 34], was associated with a twofold increased risk of death in our study. Previous studies have shown similar worse outcomes for other childhood and adult tumors [35, 36]; rural residence would be expected to either prolong the time needed for diagnosis or impact on the treatment received by the patient. Given the non-malignant nature of PA and the fact that in most cases treatment is limited to surgery, the former seems more possible in this occasion. To further evaluate this notion, we examined the age at diagnosis of residents of rural and urban areas; indeed, urban residence was associated with a lower age at diagnosis in both SEE (7.5 years vs. 8.4 years) and SEER (6.7 years vs. 7.3 years) implying possibly diagnosis at an earlier and possibly more favorable stage. The finding was more pronounced in SEER, as contrasted to SEE; possibly the difference in rural definition between countries, as well as the between-country differences in the healthcare systems could explain this discrepancy.

Data regarding tumor location, derived mainly from single-center case series, as well as our data confirm that childhood PA are most frequently (37%) located in cerebellum apart from infants in whom supratentorial and optic nerve tumors prevail [37–40]. The excellent prognosis of cerebellar PA (10-year survival exceeding 99%) compared to any other CNS location [14, 41], has been traditionally attributed to both the feasible gross-total resection, [41] as well as the greater plasticity of cerebellum [42] in childhood leading to fewer neurological deficits [43, 44]. It should be also taken into account, however, that cerebellar PA have been reported to be also characterized by differential genetic origins compared to supratentorial tumors [45].

Regardless of socioeconomic, geographical and tumor-specific characteristics, however, non-modifiable individual factors, notably age and gender, impact also on survival. The poorer outcome of infants with low-grade gliomas is poorly understood; there might be an interaction between age and non-surgical treatment, which is more frequently preferred in this age group given the adversities of performing neurological surgeries [46, 47]. Likewise, radiation, the presumably most effective treatment for unresectable PA, may be substituted in infants and young children by chemotherapy given concerns for its neurocognitive and neuroendocrine toxicities [48]. On the other hand, the differential topographic pattern of infant PA, including lower prevalence of cerebellar-located tumors, could impact on survival; the optic nerve PA preponderance in this age is possibly attributed to neurofibromatosis-related tumors [49, 50], anyway linked to worse prognosis [51], especially in children <1 year [52]. Notably though, the effect of age remained unchanged after adjustment for topography. Recent findings, however, indicate that infant low-grade gliomas might comprise a more aggressive disease, compared

to PA in older children, as they are characterized by a different genetic composition, including mutations of components of the MAPK pathway, which has been identified as of paramount importance in pediatric low-grade gliomas [16]; particularly, Ho et al. showed that the BRAF-V600E mutation is more common in infants and is associated with worse prognosis, independently of topography and histology [53].

Statistically significant, but of low magnitude, gender differences in childhood PA outcome were shown for the first time in this study, of similar direction in both SEE registries and SEER. No difference in topography or age at diagnosis by gender that could explain this differential was evident. Previous molecular analyses for prognostic factors have either not evaluated or not reported, possibly due to lack of statistical power, gender differences; therefore, future research is needed to confirm this finding and stipulate on potential differential pathogenetic features by gender.

Our findings should be viewed under limitations mainly related to registration. Despite the lack of DCO cases on account of the non-lethal PA nature, the high proportion of astrocytoma NOS, approaching 30% of all astrocytomas in SEER and SEE registries, may underestimate incidence and impact on time trends and survival findings. The much higher incidence of PA in SEER, compared to SEE, as well as the variations between SEE registries indicate potential underreporting of this non-malignant tumor in SEE; this could have led to selection bias, as less aggressive tumors would be more likely to slip registration (as they are usually treated at non-oncology departments, which may not be encompassed in the registration networks) and possibly underestimation of the survival rates in SEE. Furthermore, changes in classification of PA could have influenced registration process and consequently the reported findings. Other limitations entail the small, by necessity, number of PA in some participating registries, the variable study periods and the different registration policies, especially in SEE. Lastly, no treatment-related data or data on molecular markers with prognostic value were available in this dataset.

In conclusion, this study, exploiting publicly available registration data, comprises the first comprehensive overview on epidemiologic features, including incidence, time trends and survival, of childhood PA. Despite significant survival gains over time in the SEE countries there are still significant disparities compared to the US for this non-malignant childhood tumor, on account mainly of healthcare delivery patterns. The worse survival among infants indicates the need for innovative treatment modalities tailored for the youngest patients, whereas the identification of female gender as a potential adverse predictor of outcome merits further research. It is anticipated that registration improvements, especially in the less affluent SEE area will allow to unveil whether the lower PA incidence is genuine, as well as to deeply evaluate the increasing incidence. Similarly, expanding registration processes to include molecular and cytogenetic markers will provide further room for an in-depth evaluation of their prognostic significance.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Review

Anthropometrics at birth and risk of a primary central nervous system tumour: A systematic review and meta-analysis

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Embryonal CNS tumours;
Childhood;
Meta-analysis

Abstract ***Background:*** The aetiology of primary central nervous system (CNS) tumours remains largely unknown, but their childhood peak points to perinatal parameters as tentative risk factors. In this meta-analysis, we opted to quantitatively synthesise published evidence on the association between birth anthropometrics and risk of primary CNS tumour.
Methods: Eligible studies were identified via systematic literature review; random-effects meta-analyses were conducted for the effect of birth weight and size-for-gestational-age on childhood and adult primary CNS tumours; subgroup, sensitivity, meta-regression and dose–response by birth weight category analyses were also performed.
Results: Forty-one articles, encompassing 53,167 CNS tumour cases, were eligible. Birth weight >4000 g was associated with increased risk of childhood CNS tumour (OR: 1.14, [1.08–1.20]; 22,330 cases). The risk was higher for astrocytoma (OR: 1.22, [1.13–1.31]; 7456 cases) and embryonal tumour (OR: 1.16, [1.04–1.29]; 3574 cases) and non-significant for ependymoma (OR: 1.12, [0.94–1.34]; 1374 cases). Increased odds for a CNS tumour were also noted among large-for-gestational-age children (OR: 1.12, [1.03–1.22]; 10,339 cases), whereas insufficient data for synthesis were identified for other birth anthropometrics. The findings remained robust across subgroup and sensitivity analyses controlling for several sources of bias, whereas no significant heterogeneity or publication bias were documented. The limited available evidence on adults (4 studies) did not reveal significant associations between increasing birth weight (500-g increment) and overall risk CNS tumour (OR: 0.99, [0.98–1.00]; 1091 cases) or glioma (OR: 1.03, [0.98–1.07]; 2052 cases).
Conclusions: This meta-analysis confirms a sizeable association of high birth weight, with childhood CNS tumour risk, particularly astrocytoma and embryonal tumour, which seems to be independent of gestational age. Further research is needed to explore underlying mechanisms, especially modifiable determinants of infant macrosomia, such as gestational diabetes.

1. Introduction

Primary central nervous system (CNS) tumours comprise the most common solid tumour in children and the leading cause of childhood cancer mortality [1]. Despite the breakthrough in the elucidation of their molecular pathogenesis over the last decades [2], their etiologic factors remain largely unknown; only ionising radiation and specific genetic syndromes have been implicated as causes of CNS tumourigenesis [3]. The high incidence of primary CNS tumour in childhood, however, rationally points to prenatal and perinatal factors potentially impacting on the aetiology.

Birth anthropometrics comprise crude but consistent indices of a diversity of underlying factors, including genetics, maternal nutritional status and environmental exposures during pregnancy. Previous studies have indicated a sizeable association between birth weight and specific childhood cancers, mainly acute leukaemia and neuroblastoma [4,5]. Regarding CNS tumours, however, study findings remain controversial; a meta-analysis of 2008 supported an association of high birth weight with childhood astrocytoma and medulloblastoma [6], but it was based on solely 8 publications, which did not allow the evaluation of the potential sources of bias and the potentially confounding role of gestational age on the observed findings; additionally, it did not take into account alternative birth anthropometrics more precisely assessing foetal growth.

Since 2008, a considerable number of large population-based case-control and cohort studies have been published. Therefore, in this study, we opted to systematically review and quantitatively synthesise published literature on the association between perinatal anthropometric characteristics and risk of a primary CNS tumour, aiming to also evaluate the robustness of the findings, disentangle the effect of gestational age from the reported associations and explore the risk of bias from the individual studies.

2. Methods

2.1. Study selection

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines (Supplementary Table 1) [7] and was based on a pre-defined protocol (available as Supplementary Material). Medline and Scopus databases were searched up to May 18th, 2016, for publications relevant to the research question; appropriate search terms were combined in an algorithm (Supplementary Methods). No language or publication year restrictions were applied. The references of eligible articles and relevant reviews were consequently manually screened for additional articles ("snowball"). Additionally, we searched Google Scholar, OpenGrey and ProQuest as sources of grey literature.

Eligible were case-control and cohort studies examining the association of anthropometric measurements at birth, namely birth weight, birth length, head circumference, size for gestational age, weight-for-length, proportion for optimal birth weight (POBW), proportion for optimal birth length (POBL), proportion for optimal birth weight-for-length (POBWL), ponderal index and foetal growth, with the risk of a primary CNS tumour. Studies considering either childhood or adult CNS tumours were eligible but were separately studied. Childhood CNS tumours were examined as diagnostic categories of the International Classification of Childhood Cancer-3rd Edition (ICCC-3); for adult tumours, we aimed to examine glioma, meningioma and other non-glial tumours. Excluded were studies referring to populations with genetic syndromes predisposing to CNS tumour, like neurofibromatosis and Li-Fraumeni syndrome and case-control studies, in which individuals with cancer of other subtype than CNS tumour served as controls.

Authors of studies not quantifying the association of interest but availing necessary information in their published manuscript, were contacted to provide appropriate analyses or subject-level data. Accordingly, authors of eligible studies were contacted for clarifications. All eligible studies were evaluated for overlap, based on geographic location, data sources, diagnostic period, age range and number of cases. In case of overlapping populations, the smaller study was excluded (Supplementary Methods).

Study selection was performed by reviewers working in pairs, blindly to each other; disagreements were resolved by consensus.

2.2. Data extraction and quality assessment

Extracted data comprised publication details (year, first author, title, journal), information on study characteristics (study design, mean age, age range, gender distribution, sample-size, cohort features/ascertainment of cases and controls), type and assessment of birth anthropometrics, ascertainment of outcome and statistical analysis results. Previous publications were sought or authors were contacted for missing data.

Studies were evaluated on quality with the Newcastle-Ottawa Scale [8]. For comparability questions, age was set as the most important factor, whereas for cohort studies follow-up was considered adequate at 4 years, with a completeness percentage >80%.

Authors in pairs, independently conducted data abstraction and quality assessment; consensus was reached for disagreements.

2.3. Statistical analysis

Among various anthropometric measures, meta-analysis was possible for birth weight and size for gestational age. Regarding birth weight, two approaches were followed: particularly, (i) dichotomous analyses for >4000 g versus ≤4000 g and <2500 g versus ≥2500 g (studies not exceeding these cut-off points by more than 500 g were also included) and (ii) an incremental-per 500-g analysis. To maximise synthesised evidence an alternative categorical approach of the highest and lowest versus intermediate birth weight categories (preferring, if available, the >4000 g and <2500 g versus 2500–4000 g) was also implemented. Effect sizes were adjusted to the desired birth weight categories using the Hamling *et al.*[9] method, whereas crude odds ratios (ORs) from 2 × 2 tables were estimated for studies not directly providing estimates. Effect estimates corresponding to the highest-adjusted analysis were preferred. For incremental analysis, effect estimates for at least three birth weight categories, were included after estimating the log-linear trend using the generalised least-squares approach [10]. Regarding size for gestational age, estimates for large-for-gestational-age (LGA) and small-for-gestational-age (SGA) versus appropriate-for-gestational-age (AGA) infants were synthesised.

Random-effect models were used to calculate pooled effect estimates separately for the risk of childhood and adult CNS tumour. Heterogeneity was evaluated through Cochran Q statistic and by estimating I^2; because of the low sensitivity of the Cochran Q test, statistical significance level was set at $p < 0.10$, as has been previously suggested [11]. For childhood CNS tumours, analyses were conducted for all tumours combined, for the ICCC-3 diagnostic categories and, if available, further histological subtypes. If a study presented separate analyses for subtypes of a specific diagnostic category (e.g. low-grade and high-grade astrocytoma), the individual estimates were initially pooled via fixed-effects meta-analysis and the derived estimates were included in the meta-analysis [12]. Subgroup and sensitivity analyses by study design, adjustment level, quality score, birth weight assessment, age group and study population were also conducted. Regarding adult CNS tumours, only incremental analyses for total CNS tumours and the glioma subtype were feasible.

Where possible, a dose–response meta-analysis by level of birth weight category was conducted. The average 'dose' for each birth weight category was calculated as the arithmetic mean of the two category ends, whereas the Berlin *et al.*[13] method was implemented for the open-ended upper categories. A restricted cubic spline model, using generalised least square regression with pre-defined knots at 25th, 50th and 75th percentiles, was initially applied for individual studies and study-specific estimates were thereafter pooled using the restricted maximum likelihood method in a random-effects meta-analysis [10].

For meta-analyses including more than 10 effect estimates, publication bias was statistically evaluated using the Egger's test [14] after funnel plots were designed.

Similarly to heterogeneity, the significance level for publication bias was set at $p < 0.10$; this has been suggested for Egger's tests, because of the usual small number of studies included in meta-analyses, thus diminishing the statistical power of the test [14]. Meta-regression analysis was also conducted to assess the potentially modifying effect of age at diagnosis, gender and publication year on the associations of interest. The STATA Software (v13.0) was used for analyses.

3. Results

3.1. Results of search strategy

Fig. 1 depicts the steps of study selection. The initial search yielded 5379 articles after duplicates were removed, whereas 119 additional articles were identified through 'snowball'; no additional study was found via grey literature search after the exclusion of 11 overlapping studies, 41 articles were finally deemed eligible for this review [15–55]. Details of search strategy and the retrieved articles references are available in Supplementary Methods.

3.2. Description of studies

Eligible study characteristics are summarised in Supplementary Table 4. Taken as a whole, the 32 case-control studies [16–19,21–26,28,29,31,33–38,40–42,45–54] included 46,673 primary CNS tumour cases and 518,771 controls, whereas the 9 cohort studies [15,20,27,30,32,39,43,44,55] studying a cumulative population of 10,444,895 individuals identified 6494 incident primary CNS tumours. All studies examined CNS tumour incidence, except for the oldest study exploring mortality [35]. Cases of 34 studies were derived from cancer registries or population-based studies [15,17–22,26,27,29–41,43–48,50–55], whereas 7 included centre-based cases [16,23–25,28,42,49]. Although the majority of studies concerned childhood CNS tumours, 4 studies included exclusively or primarily (>90%) adults [15,16,30,55]; one study covered both age groups (0–38 years), but the vast majority of cases were children and was therefore included only in the childhood analyses [20]. Mean follow-up among the cohort studies ranged between 11.2 and 19.5 years in studies referring to children, whereas adult cohorts were followed for a mean period of 22–36.6 years birth weight and the other perinatal anthropometric characteristics were derived via birth records [17,21,22,26,34,35,38,40,41,49,51–53] or were extracted from birth registries [18,20,27,30,32,33,39,41,43,44,46,55] for most included studies, whereas interview with parents was the method of assessment for 17 studies [15,16,19,23–25,28,29,31,36,37,42,45,47,48,50,54]. Notably, 19 articles [16–18,20,23,25,26,30,34,36,

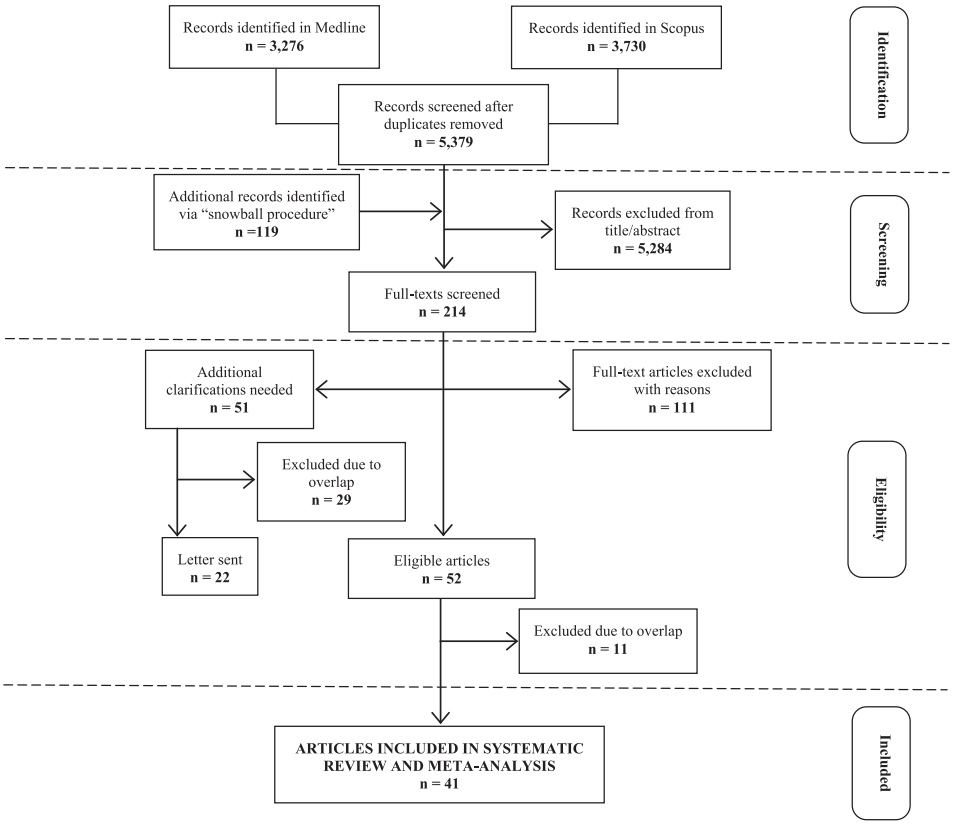


Fig. 1. Flowchart on the selection of eligible studies. Successive steps followed for the identification of eligible studies from the database search to meta-analysis.

39–41,44,46,49–51,55] were published after 2007 (45,638 cases) when the search for the previously published meta-analysis ended [6].

3.3. Quality evaluation

The overall study quality is considered high, as 31 out of 41 studies scored 7 or more points in Newcastle-Ottawa Scale (Supplementary Table 5). Case-control studies were mainly compromised by the non-reported or non-similar between cases and controls response rate, as well as by the non-clarification of exclusion of cancer cases in the control group. On the other hand, the inadequacy of follow-up (completeness <80% in 3 out of 6 childhood studies and 2 out of 3 studies on adult population) led to decreased quality in cohort studies.

3.4. Meta-analysis: childhood CNS tumours

3.4.1. Birth weight

Table 1 presents the analyses of the association of birth weight with total CNS tumours, diagnostic categories and histological subtypes, whereas Fig. 2 and Supplementary Figs. 1–4 depict the respective forest plots. High birth weight (>4000 g vs. ≤4000 g) was associated with increased overall risk of a CNS tumour (OR: 1.14, 95%CI: 1.08–1.20, 22,330 cases), whereas the linear analysis showed a 3% risk increase by 500-g increment. This effect was statistically significant and stronger for astrocytoma (4000 g versus ≤4000 g, OR: 1.22, 95%CI: 1.13–1.31, 7456 cases; $OR_{500\text{-g increment}}$: 1.04, 95%CI: 1.02–1.05, 9573 cases) applying to both low- (2759 cases) and high-grade (815 cases) tumours; for low-grade astrocytoma though a linear pattern was identified, as low birth weight was also associated with decreased risk. An increased risk by high birth weight also emerged for embryonal CNS tumour in the categorical (4000 g versus ≤4000 g, OR: 1.16, 95% CI: 1.04–1.29, 3574 cases) and incremental analysis (500-g increment, OR: 1.02, 95% CI: 1.01–1.04, 4525 cases). No association between birth weight and childhood ependymoma (1352–1977 cases) was documented. Low birth weight (<2500 g versus ≥2500 g) was not associated with either overall risk of CNS tumour or subtypes. Regarding the remaining ICCC-3 diagnostic categories (other gliomas, other specified tumours and unspecified tumours), marginal associations emerged for high birth weight, but the analyses were limited by the paucity of studies. Notably, no heterogeneity was recorded in the majority of analyses, except for the incremental overall analysis of birth weight with CNS tumour (I^2: 57.8%, p-value = 0.001). The results of the

Table 1
Results of meta-analyses for birth weight and risk of a childhood central nervous system (CNS) tumour by International Classification of Childhood Cancer- 3rd Edition (ICCC-3) diagnostic categories.

ICCC-3 diagnostic subtypes	>4000 g vs. ≤4000 g[a]				<2500 g vs. ≥2500 g[a]				500 gr-increment			
	N cases	*n*[b]	OR (95% CI)	Heterogeneity (I^2, *p*)	*N cases*	*n*[b]	OR (95% CI)	Heterogeneity (I^2, *p*)	*N cases*	*n*[b]	OR (95% CI)	Heterogeneity (I^2, *p*)
Total CNS tumours	22,330	22	1.14 (1.08–1.20)	0.0%, 0.62	21,531	16	1.03 (0.93–1.13)	8.1%, 0.36	21,778	17	1.03 (1.01–1.04)	57.6%, 0.002
Ependymoma	1374	8	1.12 (0.94–1.34)	0.0%, 0.46	1352	7	1.10 (0.76–1.61)	24.6%, 0.24	1977	8	1.01 (0.98–1.05)	12.4%, 0.33
Astrocytoma	7456	12	1.22 (1.13–1.31)	0.0%, 0.64	7231	10	0.98 (0.86–1.11)	0.0%, 0.51	9573	10	1.04 (1.02–1.05)	32.8%, 0.15
Low-grade	2759	4	1.15 (1.02–1.29)	0.0%, 0.46	2759	4	0.75 (0.60–0.95)	0.0%, 0.79	2759	4	1.02 (0.99–1.05)	46.5%, 0.13
High-grade	815	2	1.60 (1.21–2.11)	0.0%, 0.62	815	2	1.18 (0.78–1.79)	0.0%, 0.59	815	2	1.05 (1.02–1.08)	0.0%, 0.69
Embryonal CNS tumour	3574	13	1.16 (1.04–1.29)	0.0%, 0.51	3375	11	1.06 (0.88–1.26)	0.0%, 0.99	4525	12	1.02 (1.01–1.04)	21.1%, 0.24
Medulloblastoma	676	2	0.91 (0.69–1.21)	0.0%, 0.59	676	2	0.98 (0.62–1.56)	0.0%, 0.51	676	2	1.03 (0.94–1.13)	0.0%, 0.33
PNET	311	1	1.01 (0.44–2.33)	–	311	1	0.88 (0.46–1.68)	–	311	1	1.11 (0.91–1.36)	–
ATRT	44	1	1.71 (0.76–3.86)	–	44	1	2.89 (1.27-.6.60)	–	44	1	1.09 (1.00–1.19)	–
Other gliomas	1226	4	1.21 (0.93–1.56)	17.1%, 0.31	1226	4	0.99 (0.59–1.66)	54.6%, 0.09	1835	5	1.02 (0.99–1.06)	0.0%, 0.80
Other specified tumours	659	2	1.14 (0.90–1.45)	0.0%, 0.32	659	2	0.75 (0.48–1.19)	0.0%, 0.84	1277	3	1.03 (0.96–1.10)	53.4%, 0.12
Unspecified tumours	372	2	1.19 (0.84–1.67)	0.0%, 0.79	372	2	1.26 (0.68–2.32)	32.6%, 0.22	704	3	1.01 (0.95–1.06)	15.8%, 0.31

Abbreviations: OR, odds ratio; CI, confidence intervals; PNET, Primitive neuroectodermal tumour, ATRT, Atypical teratoid-rhabdoid tumour.
[a] In the >4000 versus ≤4000 g and the <2500 versus ≥2500 g analyses, were also included study arms treating birth weight as a dichotomous variable in cut-off points ± 500 g from 4000 or 2500 g, respectively.
[b] Number of study arms.

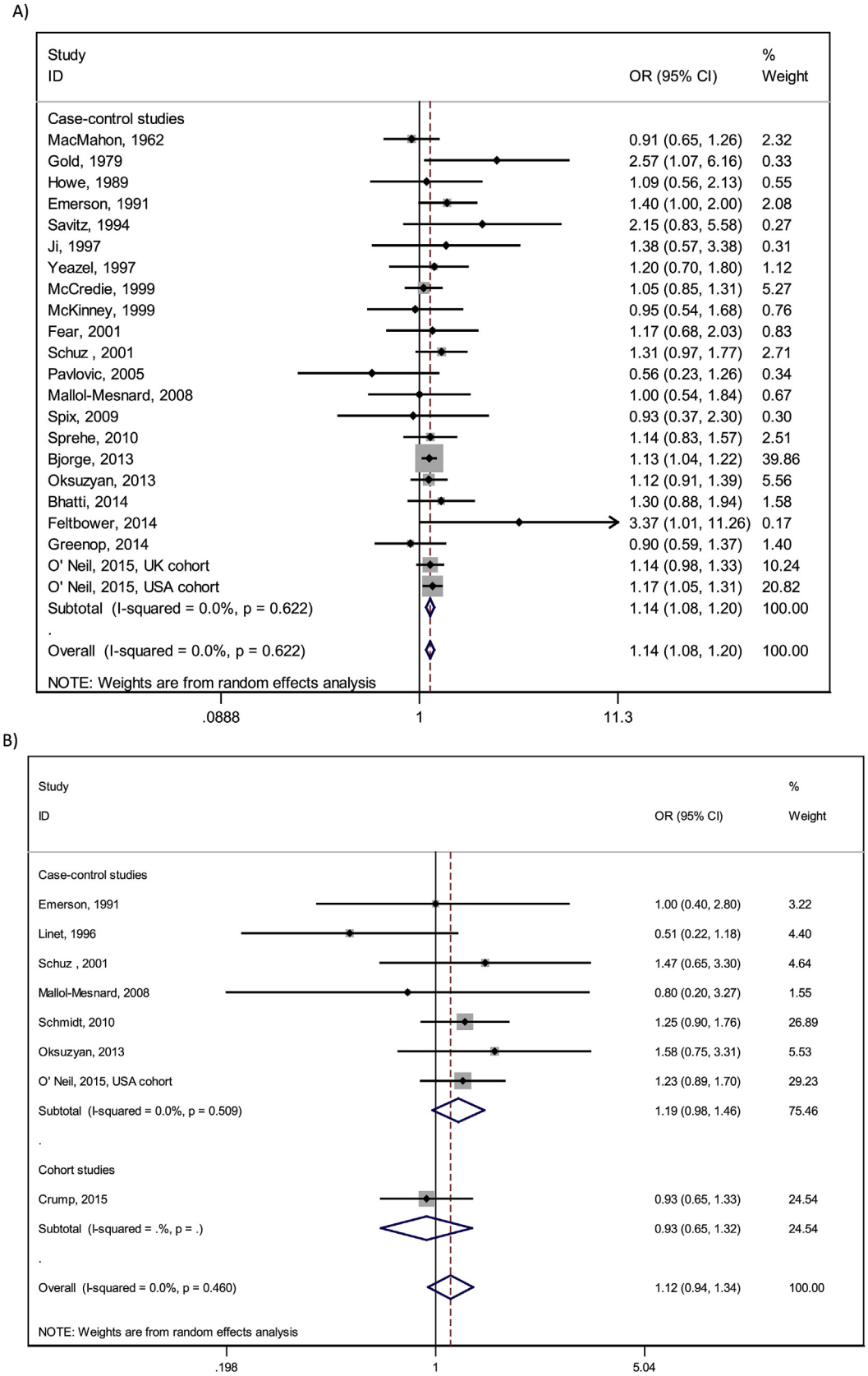
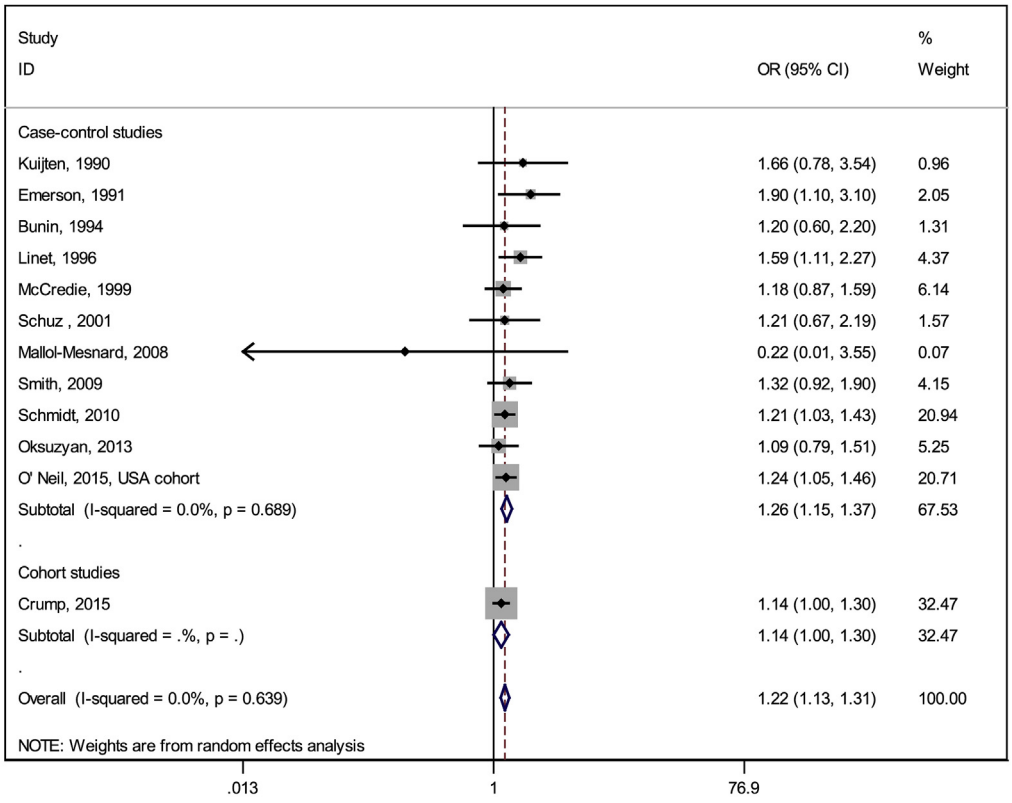


Fig. 2. Associations between high birth weight (>4000 g versus ≤4000 g) and risk of a childhood (A) central nervous system (CNS) tumour (overall analysis), (B) ependymoma, (C) astrocytoma and (D) an embryonal CNS tumour. Effect sizes in the individual studies are indicated by the data markers (shaded boxes around the data markers reflect the statistical weight of the study); 95% confidence intervals are indicated by the error bars. The pooled-effect estimate with its 95% CIs is depicted as a diamond. Apart from the overall analysis, the sub-analyses on case-control (upper panels) and cohort (lower panels) studies are presented.

C)



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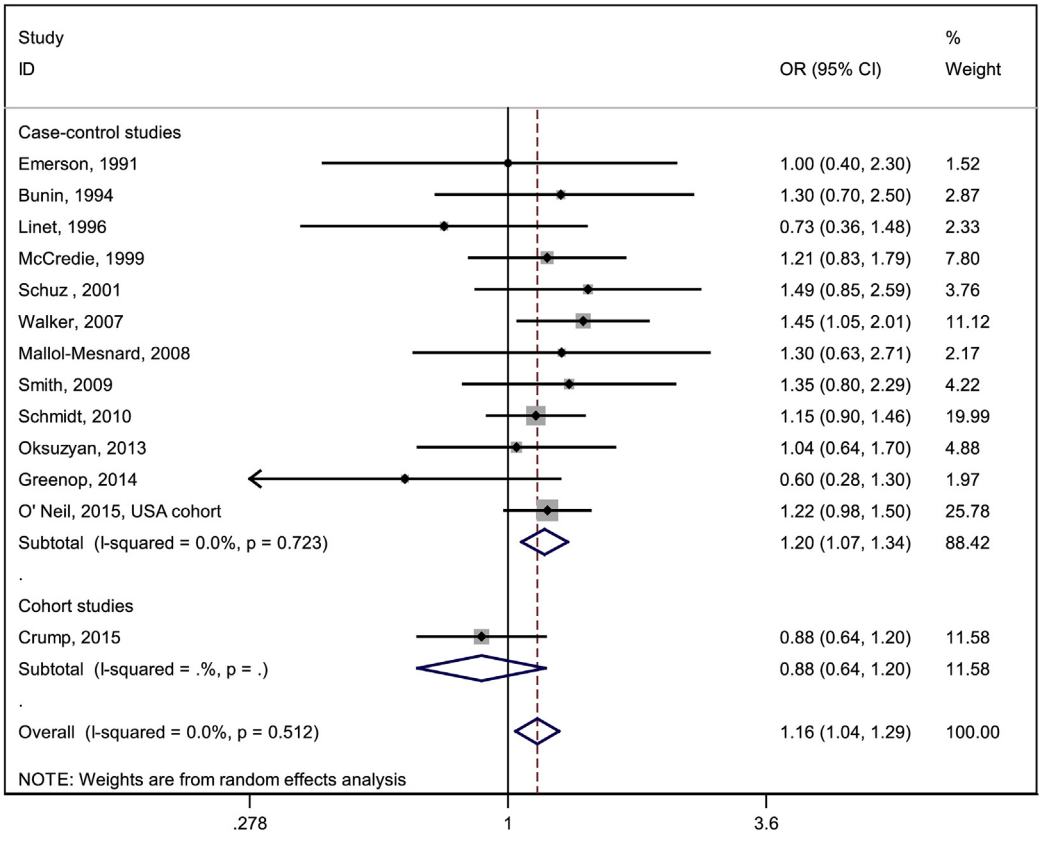

Fig. 2. (*continued*)

alternative high and low versus intermediate birth weight analyses showed practically similar results (Supplementary Table 6).

Sensitivity analyses (Table 2) on studies examining exclusively children up to 14 years showed likewise results for overall risk of CNS tumour, astrocytoma and embryonal tumour but also revealed an increased risk of ependymoma by high birth weight (4000 g versus ≤4000 g, OR: 1.27, 95% CI: 1.05–1.55; $OR_{500\text{-g increment}}$: 1.03, 95% CI: 1.00–1.05). Subgroup analyses by subtypes pertaining to the younger age group (0–5 years) was rather hampered by the low number of study arms ($n \leq 2$); yet, the combined CNS tumours analysis on this age group showed the similar results as the overall childhood analysis. Notably, the findings remained robust among studies of the highest quality, studies with adjusted for gestational age estimates, registry/population-based studies and studies assessing birth weight by secure records/birth registry data. Exclusion of studies restricted to brain tumours did not alter the findings except for a reinforcement of the effect of high birth weight on the risk of ependymoma and embryonal CNS tumour. There were only a few cohort studies, which did not allow investigations by study design.

The dose–response analysis by birth weight level (Fig. 3) replicated these findings, showing increased risk for combined CNS tumours, astrocytoma and embryonal tumour in high birth weight values. For the birth weight range below the median 3250 g knot, the risk was attenuated. The p-values for non-linearity were 0.02 for the combined CNS tumour outcome, 0.03 astrocytoma and 0.06 for embryonal CNS tumour. Non-significant and non-linear trends were found for ependymoma (p-non-linearity: 0.45).

Publication year, age of cases and gender did not exert modifying results in the main analyses of the combined CNS tumour outcome and astrocytoma, as recorded from meta-regression (Supplementary Table 7); Additionally, no significant publication bias was found in the categorical analyses (Supplementary Table 8). The Egger's test showed however significant publication bias for the incremental overall analysis of CNS tumour (funnel plots in Supplementary Fig. 5).

3.4.2. Size for gestational age

Table 3 and online Supplementary Figs. 6–9 show the results of the analyses on size for gestational age. The combined CNS tumour analysis showed an increased risk for LGA infants, compared to AGA (OR: 1.12, 95% CI: 1.03–1.22); yet, no increased risk was found for diagnostic categories, where analyses were compromised by the study paucity. Interestingly, SGA infants had a decreased risk for astrocytoma (OR: 0.79, 95% CI: 0.67–0.94; 4 studies), but also an increased risk for ependymoma (OR: 1.89, 95%CI: 1.00–3.58; 2 studies). No heterogeneity was recorded.

3.4.3. Other anthropometric measurements

The paucity of relevant studies and their major overlap [18,20,25,27,39,44,46], precluded a meta-analysis on other perinatal anthropometric characteristics (Supplementary Table 9). Bjorge *et al.* [18], in a sample of 5163 cases reported increased risk of a CNS tumour for children born with high head circumference, whereas Crump *et al.* [20], also found an increased risk by increasing foetal growth (2809 cases). Among CNS tumour subtypes though, significant associations of increasing birth length, head circumference and foetal growth emerged solely for astrocytoma [20,44,46] and notably in 2 studies restricted to pilocytic astrocytoma [20,44]. The effects for ependymoma, embryonal CNS tumour or non-astrocytic glioma were non-significant in all the studies [20,25,27,39,44,46]. POBW, POBL and POWFL did not show significant associations with childhood CNS tumour risk in 2 studies [25,39].

3.5. Synthesis: adult CNS tumours

Four studies examined the association of birth weight with risk of an adult CNS tumour [15,16,30,55]. Increasing birth weight (500-g increment) was not associated with either overall CNS tumour risk (2 studies; OR: 0.99, 95%CI: 0.98–1.00; 1091 cases) or glioma risk (3 studies; OR: 1.03, 95%CI: 0.98–1.07; 2052 cases). Interestingly though, 2 studies [30,55] stratifying analyses by sex, reported male-restricted statistically significant associations of high birth weight with glioma.

4. Discussion

The present meta-analysis demonstrates an increased risk of a primary CNS tumour among high birth weight (>4000 g) and LGA children. Specifically, the effect of birth weight is mainly evident for astrocytoma and embryonal CNS tumour and remains robust in high-quality and registry-based studies, when assessing birth weight by secure records and after the adjustment for gestational age. In addition, it seems to follow a non-linear pattern with null effects noted below the normal birth weight range. Data were insufficient for in depth examination of other birth anthropometric measurements, as well as, the association with an adult CNS tumour.

Previous studies and meta-analyses have explored whether birth anthropometric measures impact on the risk of other cancers. In particular, high birth weight has been found to increase risk for childhood and adolescence/young adulthood tumours, like acute leukaemia [5], neuroblastoma [4], bone tumour [56] and testicular cancer [57], but also for adulthood tumours, including colorectal [58] and breast cancer [59]. Interestingly, U-shape associations with both high and low birth weight

Table 2
Results of the sensitivity and subgroup meta-analyses examining the association between birth weight and risk of a childhood central nervous system (CNS) tumour, ependymoma, astrocytoma and an embryonal CNS tumour.

Analyses[a]	Total CNS tumours			Ependymoma			Astrocytoma			Embryonal CNS tumour		
	n^b	OR (95% CI)	Heterogeneity (I^2, p)	n^b	OR (95% CI)	Heterogeneity (I^2, p)	n^b	OR (95% CI)	Heterogeneity (I^2, p)	n^b	OR (95% CI)	Heterogeneity (I^2, p)
Sensitivity analyses by age group												
0–14 years												
>4000 versus ≤4000	16	1.14 (1.09–1.20)	0.0%, 0.89	6	1.27 (1.05–1.55)	0.0%, 0.94	9	1.25 (1.14–1.37)	0.0%, 0.77	10	1.18 (1.05–1.32)	0.0%, 0.52
<2500 versus ≥2500	15	1.04 (0.95–1.14)	0.0%, 0.40	5	0.98 (0.53–1.79)	55.1%, 0.06	7	0.99 (0.82–1.19)	21.5%, 0.27	8	1.14 (0.94–1.38)	0.0%, 0.97
0–5 years												
>4000 versus ≤4000	5	1.20 (1.07–1.36)	0.0%, 0.73	–	–	–	2	1.34 (0.93–1.93)	0.0%, 0.69	2	1.15 (0.79–1.67)	0.0%, 0.64
<2500 versus ≥2500	4	1.02 (0.75–1.39)	27.4%, 0.25	–	–	–	1	0.84 (0.34–2.08)	–	1	1.45 (0.76–2.75)	–
Subgroup analyses by level of adjustment												
Unadjusted for gestational age												
>4000 versus ≤4000	17	1.14 (1.02–1.27)	11.1%, 0.32	4	0.99 (0.73–1.34)	0.0%, 0.78	8	1.19 (1.07–1.33)	0.0%, 0.54	9	1.17 (0.98–1.39)	12.5%, 0.33
<2500 versus ≥2500	12	1.04 (0.90–1.19)	0.0%, 0.53	3	1.16 (0.68–1.98)	0.0%, 0.93	6	0.98 (0.75–1.29)	27.1%, 0.23	7	0.98 (0.74–1.30)	0.0%, 0.99
Adjusted for gestational age												
>4000 versus ≤4000	5	1.14 (1.08–1.21)	0.0%, 0.98	4	1.17 (0.87–1.57)	34.8%, 0.20	4	1.24 (1.12–1.37)	0.0%, 0.47	4	1.15 (0.99–1.33)	0.0%, 0.57
<2500 versus ≥2500	4	1.00 (0.85–1.18)	51.9%, 0.10	4	1.06 (0.55–2.06)	61.5%, 0.05	4	0.98 (0.83–1.15)	0.0%, 0.71	4	1.11 (0.88–1.40)	0.0%, 0.78
Subgroup analyses by study quality												
Studies of higher quality (NOS 7–9)												
>4000 versus ≤4000	15	1.15 (1.09–1.21)	0.0%, 0.87	7	1.10 (0.92–1.33)	4.3%, 0.39	11	1.22 (1.13–1.31)	0.0%, 0.55	11	1.16 (1.04–1.30)	0.0%, 0.67
<2500 versus ≥2500	11	1.01 (0.92–1.10)	0.0%, 0.58	6	1.09 (0.71–1.68)	37.1%, 0.16	9	0.96 (0.85–1.10)	0.0%, 0.65	9	1.05 (0.87–1.26)	0.0%, 0.98
Studies of lower quality (NOS<7)												
>4000 versus ≤4000	7	1.06 (083–1.34)	35.9%, 0.15	1	1.47 (0.65–3.30)	–	1	1.21 (0.67–2.19)	–	2	0.98 (0.41–2.38)	71.5%, 0.06
<2500 versus ≥2500	5	1.29 (0.88–1.89)	28.7%, 0.23	1	1.15 (0.25–5.30)	–	1	1.96 (0.78–4.90)	–	2	1.18 (0.54–2.57)	0.0%, 0.74
Sensitivity analysis excluding studies focused exclusively on brain tumours												
Studies examining overall primary CNS tumours												
>4000 versus ≤4000	13	1.14 (1.08–1.20)	0.0%, 0.95	6	1.26 (1.02–1.55)	0.0%, 0.95	7	1.24 (1.12–1.37)	0.0%, 0.56	8	1.24 (1.09–1.40)	0.0%, 0.92
<2500 versus ≥2500	11	1.02 (0.90–1.17)	34.2%, 0.13	6	1.04 (0.58–1.85)	49.3%, 01.0	6	1.02 (0.87–1.20)	0.0%, 0.44	7	1.08 (0.88–1.32)	0.0%, 0.96

(*continued on next page*)

Table 2 (*continued*)

Analyses[a]	Total CNS tumours			Ependymoma			Astrocytoma			Embryonal CNS tumour		
	n^b	OR (95% CI)	Heterogeneity (I^2, p)	n^b	OR (95% CI)	Heterogeneity (I^2, p)	n^b	OR (95% CI)	Heterogeneity (I^2, p)	n^b	OR (95% CI)	Heterogeneity (I^2, p)
Subgroup analyses by study design												
Case-control studies												
>4000 versus ≤4000	22	1.14 (1.08−1.20)	0.0%, 0.62	7	1.19 (0.98−1.46)	0.0%, 0.51	11	1.26 (1.15−1.37)	0.0%, 0.69	12	1.20 (1.07−1.34)	0.0%, 0.72
<2500 versus ≥2500	16	1.03 (0.93−1.13)	8.1%, 0.36	6	1.06 (0.64−1.75)	36.7%, 0.16	9	0.97 (0.84−1.13)	2.7%, 0.41	10	1.08 (0.89−1.29)	0.0%, 0.99
Cohort studies												
>4000 versus ≤4000	1	1.13 (1.03−1.24)	–	1	0.93 (0.65−1.33)	–	1	1.14 (1.00−1.30)	–	1	0.88 (0.64−1.20)	–
<2500 versus ≥2500	1	0.90 (0.75−1.10)	–	1	1.20 (0.66−2.19)	–	1	1.00 (0.75−1.32)	–	1	0.85 (0.45−1.60)	–
Sensitivity analysis by method of cases identification												
Registry-basedlpopulation-based studies												
>4000 versus ≤4000	17	1.14 (1.09−1.20)	0.0%, 0.95	8	1.12 (0.94−1.34)	0.0%, 0.46	11	1.21 (1.12−1.31)	0.0%, 0.57	11	1.16 (1.04−1.30)	0.0%, 0.63
<2500 versus ≥2500	14	1.03 (0.92−1.14)	19.5%, 0.24	7	1.10 (0.76−1.61)	24.6%, 0.24	9	0.97 (0.85−1.12)	2.9%, 0.41	9	1.07 (0.89−1.28)	0.0%, 0.98
Subgroup analyses by method of birth weight assessment												
Birth certificatesldelivery noteslbirth registry data												
>4000 versus ≤4000	10	1.14 (1.08−1.20)	0.0%, 0.88	6	1.10 (0.90−1.36)	17.5%, 0.30	7	1.22 (1.12−1.33)	9.9%, 0.35	8	1.15 (1.01−1.30)	4.2%, 0.40
<2500 versus ≥2500	8	0.99 (0.89−1.09)	9.4%, 0.36	6	1.0 (0.69−1.77)	48.9%, 0.10	6	0.98 (0.86−1.13)	0.0%, 0.92	7	1.05 (0.86−1.28)	0.0%, 0.92
Interview with parents												
>4000 versus ≤4000	12	1.16 (0.97−1.38)	21.6%, 0.23	2	1.26 (0.63−2.55)	0.0%, 0.47	5	1.21 (0.96−1.53)	0.0%, 0.71	5	1.20 (0.93−1.54)	0.0%, 0.43
<2500 versus ≥2500	8	1.18 (0.97−1.43)	0.0%, 0.51	2	1.00 (0.31−2.27)	0.0%, 0.77	4	1.04 (0.55−1.96)	55.7%, 0.07	4	1.08 (0.73−1.62)	0.0%, 0.96

Abbreviations: OR, odds ratio; CI, confidence intervals; NOS, Newcastle-Ottawa Scale.

[a] In the >4000 versus ≤4000 g and the <2500 versus ≥2500-g analyses, were also included study arms treating birth weight as a dichotomous variable in cut-off points within ± 500 g from 4000 or 2500 g, respectively.

[b] Number of study arms.

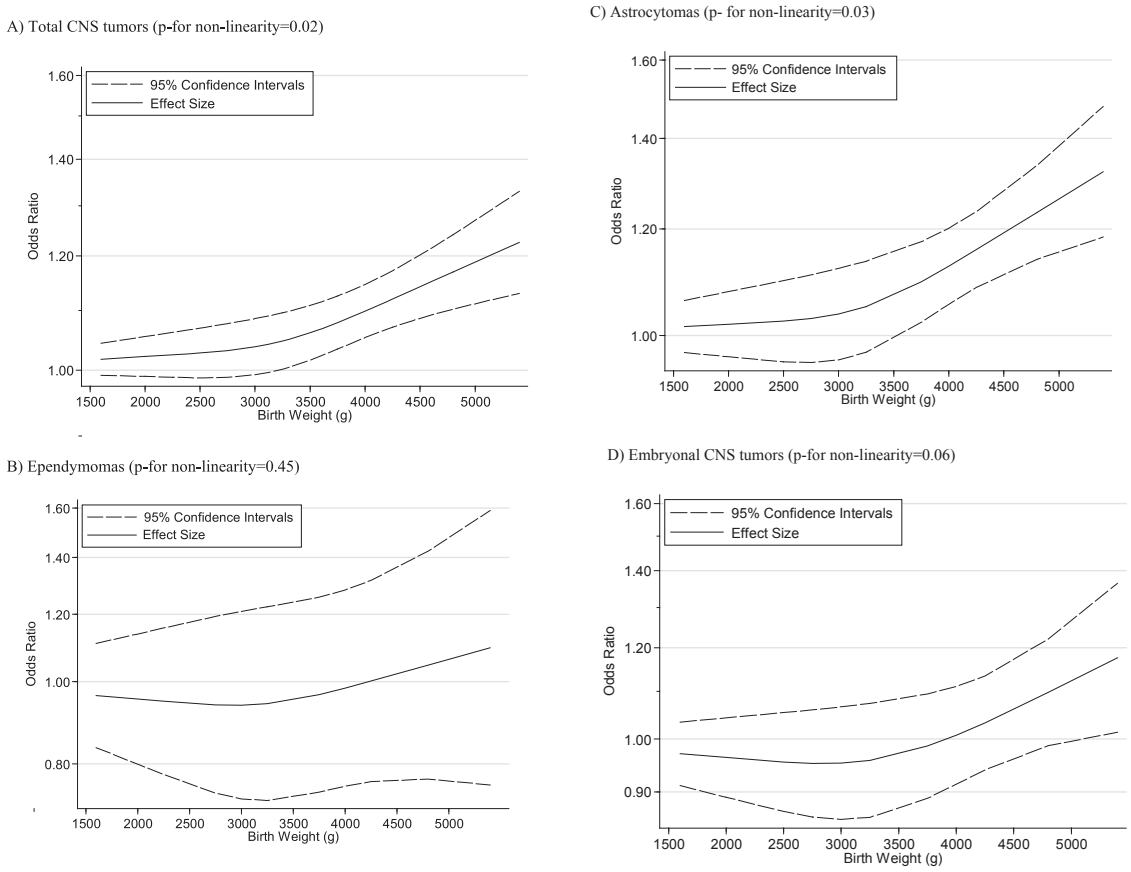

Fig. 3. Dose–response relationships of birth weight with the risk of a childhood (A) central nervous system (CNS) tumour (overall analysis), (B) ependymoma, (C) astrocytoma, and (D) an embryonal CNS tumour. The solid line represents the odds ratio, whereas the dashed lines correspond to the 95% confidence intervals, as derived from cubic spline models.

have been described for acute myeloid leukaemia, neuroblastoma, testicular and colorectal cancer [4,5,57,58].

Regarding CNS tumours, a previous meta-analysis (2008), including 8 studies, had also shown an increased risk of childhood astrocytoma and medulloblastoma by high birth weight [6]. However, the present study has been conducted on a much larger sample-size (e.g. 7456 versus 1819 cases in the astrocytoma analysis), allowing confirmation of the robustness of the findings across different study designs and methodologies, examination of the risk of bias via meta-regression and publication bias analyses, as well as evaluation of the birth weight effect throughout its entire range. Additionally, we meta-analysed for the first time other birth anthropometrics documenting also an increased risk for a CNS tumour among LGA children; along with the sensitivity analysis on studies adjusting for gestational age, this result disentangles the effect of birth weight from the potentially confounding role of gestational age. We finally attempted to explore associations of birth weight with adult CNS tumours; the published data were scarce but the findings did not seem to support an association.

Birth anthropometric measures represent complex proxies of foetal growth. Risk factors for infant macrosomia include maternal and paternal high birth weight, previous macrosomic birth, ethnicity, multiparity, maternal obesity and nutritional status,

Table 3
Results for meta-analysis of size for gestational age and risk of a childhood central nervous system (CNS) tumour, ependymoma, astrocytoma and an embryonal CNS tumour.

Size for gestational age	n^a	N cases	OR (95% CI)	Heterogeneity (I^2, p)
Total CNS tumours				
SGA versus AGA	7	10,339	0.93 (0.84–1.02)	0.0%, 0.87
LGA versus AGA			1.12 (1.03–1.22)	0.0%, 0.76
Ependymoma				
SGA versus AGA	2	623	1.89 (1.00–3.58)	8.2%, 0.30
LGA versus AGA			1.52 (0.95–2.54)	0.0%, 0.81
Astrocytoma				
SGA versus AGA	2	2794	0.70 (0.51–0.97)	0.0%, 0.58
LGA versus AGA			0.96 (0.75–1.21)	0.0%, 0.97
Embryonal CNS tumour				
SGA versus AGA	3	1394	1.18 (0.57–2.44)	69.7%, 0.04
LGA versus AGA			1.10 (0.68–1.77)	57.4%, 0.10

Abbreviations: OR, odds ratio; CI, confidence intervals; SGA, small-for-gestational-age, AGA, appropriate-for-gestational-age; LGA, large-for-gestational-age; CNS, central nervous system.

[a] Number of study arms.

gestational diabetes and hypertension, non-smoking and high maternal age, indicating both genetic and environmental determinants [60]. Therefore, only assumptions could be made regarding the underlying biological links with CNS tumourigenesis. Infant macrosomia might be associated with the number, size or proliferative potential of CNS cells; indeed, birth weight seems to be positively associated with the proliferative potential of neurosphere progenitor cells and their differentiation rates to astrocytes and neurons in newborn rats [61]. These undifferentiated cells are susceptible to oncogenic mutations and therefore an increased birth weight could indicate either a general genetic predisposition to CNS tumourigenesis or environmental exposures concurrently leading to accelerated foetal growth and facilitating an increase in CNS tumour risk. Growth factor pathways have been implied as the link mediating the observed associations [18,20]. Of note, umbilical cord plasma levels of insulin-like growth factor (IGF)-1 and IGF-2 that inhibit apoptosis and promote tumourigenesis, have been linearly associated with birth weight and birth length [62]. Except for its crucial role in brain development [63], the IGF-system is also involved in gliomagenesis; particularly, glioma cell lines express more IGF-1 receptors than normal astrocytes [64], serum levels and genetic polymorphisms of IGF-1 have been associated with the adult glioma risk [65] and IGF-1 receptor blockade may inhibit glioblastoma growth [66]. These findings are in line with the stronger associations found for astrocytoma, but relevant data on the role of IGF-1 on childhood astrocytic tumour are missing. Similarly, IGF-1 and IGF-2 have been implied in the growth of PNET [67], medulloblastoma [67] and ependymoma [68]. The role of the IGF-system in carcinogenesis is further supported by the lower risk of cancer described in series of patients with congenital IGF-1 deficiency [69]. Besides growth-related factors other tentative mechanisms meriting research include the adipokines pathway [70] and the in utero exposure to oestrogens [71], as well as tentative genetic and epigenetic determinants [72].

The lack of associations for adult tumours could be attributed to the longer interval between birth and the outcome making the association subject to confounders. Nevertheless, the potential male-specific association of high birth weight with glioma risk identified in 2 studies merits further consideration [30,55], as a stronger association of high BMI with adult glioma for males has also been described [73].

Our findings should be interpreted in view of limitations related mainly to methodological differences across individual studies. First, classification changes and diagnostic improvements over time may have introduced heterogeneity in sub-analyses by histological subtype; yet, publication year in the meta-regression analysis did not seem to affect the findings. Similarly, some studies examined solely tumours located in the brain instead of overall CNS (brain and spinal cord) tumours; however, as expected, the findings remained unchanged in analyses restricted to the latter group of studies.

Studies assessing birth weight through parental interview are definitely subject to recall bias. The findings were replicated, however, among studies extracting birth weight information from secure records or birth registry databases. The use of different birth weight categories by individual studies could have contributed to between-study heterogeneity. For this reason, we implemented dichotomous, categorical and incremental approaches for birth weight while re-calculating suitable estimates; despite the potential methodological deviations in the re-calculations, the methodology used has been validated [9,10].

Despite the lack of heterogeneity and publication bias in the dichotomous and categorical analyses, the incremental analyses on overall childhood CNS tumour and astrocytoma were characterised by significant heterogeneity and publication bias, respectively. Given, in addition, the evident non-linearity of the examined associations, a cautious interpretation of the incremental analyses is necessary.

It was not possible to conduct gender sub-analyses to evaluate previous reports for male-specific associations of birth anthropometrics with cancer; moreover, no meta-analysis could be performed for other growth indices, notably birth length, head circumference and foetal growth measurements. Finally, the analyses for an adult CNS tumour were based on relatively few studies, thus precluding the extraction of meaningful results.

4.1. Public health perspective and conclusions

During the last decades, temporal increases in mean birth weight of children in Western countries had been recorded [74], with a reverse of this trend after 1990 [75]. Challenging is therefore to explore whether temporal trends in birth weight have contributed to the overall increase in childhood CNS tumour incidence consistently being reported before 2000 in developed countries [76]. In addition, the approximately 10% of infants currently born macrosomic [77] may reflect a large proportion of the population exposed to increased risk of a fatal malignancy. Given the continuous global increase in obesity rates [78] and the positive association of maternal overweight/obesity at pregnancy with increased risk of high birth weight [60], this proportion might further increase in the future. Nevertheless, it should be noted that the preventability of the effect of high birth weight is expected to remain low in clinical practice.

In summary, this meta-analysis showed that high birth weight and large size for gestational age, are associated with increased risk of childhood CNS tumour and notably, with astrocytoma and embryonal tumour. Elucidation of the plausible underlying

mechanisms, mainly of the growth factors biological pathways implicated in tumourigenesis may provide further insight into the CNS tumours pathogenesis. Future studies should assess whether modifiable factors leading to infant macrosomia, especially gestational diabetes, might impact on CNS tumourigenesis, whereas additional data derived from cohort studies would be welcome, given the vast preponderance of case-control studies.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.12.033.

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Perinatal and early life risk factors for childhood brain tumors: Is instrument-assisted delivery associated with higher risk?

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Abbreviations: AGA, appropriate for gestational age; CNS, central nervous system; ICCC-3, International Classification for Childhood Cancer – 3rd Edition; ICD-O-3, International Classification for Diseases in Oncology – 3rd Edition; LGA, large for gestational age; NARECHEM-ST, National Registry for Childhood Hematological Malignancies and Solid Tumors; OR, odds ratio; SGA, small for gestational age

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ABSTRACT

Background: The childhood peak of brain tumors suggests that early-life exposures might have a role in their etiology. Hence, we examined in the Greek National Registry for Childhood Hematological Malignancies and Solid tumors (NARECHEM-ST) whether perinatal and early-life risk factors influence the risk of childhood brain tumors.

Methods: In a nationwide case-control study, we included 203 cases (0–14 years) with a diagnosis of brain tumor in NARECHEM-ST (2010–2016) and 406 age-, sex-, and center-matched hospital controls. Information was collected via interviews with the guardians and we analyzed the variables of interest in multivariable conditional logistic regression models.

Results: Instrument-assisted delivery was associated with higher (OR: 7.82, 95%CI: 2.18–28.03), whereas caesarean delivery with lower (OR: 0.67, 95%CI: 0.45-0.99) risk of childhood brain tumors, as compared to spontaneous vaginal delivery. Maternal alcohol consumption during pregnancy (OR: 2.35, 95%CI: 1.45–3.81) and history of living in a farm (OR: 4.98, 2.40–10.32) increased the odds of childhood brain tumors. Conversely, higher birth order was associated with lower risk (OR for 2nd vs. 1st child: 0.60, 95%CI: 0.40-0.89 and OR for 3rd vs. 1st: 0.34, 95%CI: 0.18-0.63). Birth weight, gestational age, parental age, history of infertility, smoking during pregnancy, allergic diseases, and maternal diseases during pregnancy showed no significant associations.

Conclusions: Perinatal and early-life risk factors, and specifically indicators of brain trauma, exposure to toxic agents and immune system maturation, might be involved in the pathogenesis of childhood brain tumors. Larger studies should aim to replicate our findings and examine associations with tumor subtypes.

1. Introduction

Brain and other central nervous system (CNS) tumors (hereby called brain tumors for simplicity) are the most common solid tumor in childhood (0–14 years) and the leading cause of cancer mortality in this age group [1]. Although several studies have shed light to the molecular pathogenesis of brain tumors in the last years [2–4], uncertainty exists regarding risk factors contributing to their etiology. The only well-established causal risk factors for childhood brain tumors include specific genetic syndromes and exposure to ionizing radiation [5]. However, the peak of the disease in childhood indicates perinatal and early-life risk factors, as potential causes of childhood brain tumors [5–8]. Among them, factors that have been associated with the risk of childhood brain tumors in observational epidemiologic studies include birth weight and infant growth [9], early-life exposure to pesticides [10], surrogates of early-life exposure to infections including sibship size, birth order, history of infections, and age at enrollment to kindergarten [11–13], parental age [14], and allergic conditions [15].

However, in the majority of the abovementioned risk factors the results are rather inconsistent across different studies, possibly because of small sample sizes, as well as heterogeneity in study design, examined populations, and assessment of risk factors. Furthermore, most studies do not specifically examine the associations with specific histological subtypes. In particular, potentially modifiable perinatal and early-life risk factors should be further explored. Here, we analyze for the first time, data from the Greek nationwide case-control study initiated in parallel with the international MOBI-KIDS project [16], aiming at exploring associations of perinatal and early-life exposures with brain tumors among children.

2. Material and methods

2.1. Study design

Data for this analysis come from a nationwide multi-center case-control study. During the study period (2010–2016), a total of 466 children (0–14 years) of Greek origin with CNS tumors, as defined by the 3rd Edition of the International Classification for Childhood Cancer (ICCC-3) [17], were registered in the National Registry for Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST). Tumors of any behavior (malignant or non-malignant) were registered. NARECHEM-ST is a nationwide registry of childhood malignancies in Greece. Details on the registration methods of NARECHEM-ST have been previously described [7] and are also available online (http://narechem.gr/node/24). The guardians of these children were contacted and an informed consent for participation in our case-control study was obtained for 203 brain tumor cases (participation rate 43.6%). Brain tumor cases included in the case-control study did not differ from the nationwide population of childhood brain tumors in terms of age, sex, and tumor topography, but the included sample underrepresented tumors of non-malignant behavior and overrepresented embryonal tumors over astrocytomas and tumors of unspecified histology, as detailed in Supplementary Table 1. Summary data of basic demographic and tumor-specific characteristics of the registry population are further available online (http://narechem.gr/node/9). The primary reasons for non-participation in the case-control study were retrospective registration and loss to follow-up, refusal to participate, and fatal malignancies leading to death within a month after diagnosis. Brain tumors were classified to the 6 diagnostic subgroups of ICCC-3 based on their morphology, behavior, and topography codes of the International Classification for Diseases in Oncology- 3rd Edition (ICD-O-3). Controls were children (0–14 years) hospitalized for acute appendicitis (ICD-10 K35 codes) in the pediatric surgical departments of the collaborating hospital within a period of 12 months after the time point of brain tumor diagnoses in the respective cases and were free of cancer and any major chronic comorbidity. Two controls matched for age (± 6 months), sex, and participating center, were selected for every one of the cases. The refusal rate among controls was minimal (~4%), and in case of refusal the next eligible controls were identified from the records of the department. The study protocol has been approved by the Ethics Committee of the Athens University Medical School.

2.2. Study variables

Upon agreement by the treating physician, the guardians of all eligible study participants were informed of the study objectives and were interviewed in person or through telephone by a trained interviewer. A structured questionnaire was used, which was designed in the context of the MOBI-KIDS study, an international case-control study of brain tumors aiming to explore the role of non-ionizing radiation in brain tumorigenesis [16]. The questionnaire covered a series of putative risk factors including sociodemographic, childhood environment and lifestyle variables, perinatal characteristics, family and own medical history. Specifically, we collected data on maternal education, birth weight, gestational age at birth, maternal and paternal age at birth,

Table 1
Distributions of cases with childhood CNS tumors and controls by study variables.

Variables	Cases (N = 203)		Controls (N = 406)		p-value[a]
	N	%	N	%	
Age (y)					matching
0–4	91	44.8	174	42.9	
5–9	58	28.6	120	29.6	
10–14	54	26.6	112	27.6	
Index child's sex					matching
Male	112	55.2	224	55.2	
Female	91	44.8	182	44.8	
Maternal education					0.15
High school or lower	107	52.7	215	53.0	
Technical school/University or higher	94	46.3	169	41.7	
Missing	2	1.0	22	5.4	
Birth weight (g)					0.10
< 2500	12	5.9	41	10.1	
2500–3999	176	86.7	338	83.3	
≥4000	9	4.4	17	4.2	
Missing	6	3.0	10	2.5	
Gestational age at birth					0.08
Pre-term	17	8.4	51	12.6	
Full-term	184	90.6	332	82.0	
Post-term	2	1.0	4	1.0	
Missing	0	0	18	4.4	
Size for gestational age					0.19
SGA	12	5.9	42	10.3	
AGA	158	77.8	301	74.1	
LGA	27	13.3	58	14.3	
Missing	6	3.0	5	1.2	
Maternal age at birth (years)					0.011
< 25	40	19.7	60	14.8	
25–29	63	31.0	110	27.1	
30–34	63	31.0	134	33.0	
35–39	27	13.3	71	17.5	
≥40	4	2.0	19	4.5	
Missing	6	3.0	12	3.0	
Paternal age at birth (years)					0.34
< 25	14	6.9	29	7.1	
25–29	34	16.8	55	13.6	
30–34	65	32.0	128	31.5	
35–39	50	24.6	100	24.6	
≥40	31	15.3	75	18.5	
Missing	9	4.4	19	4.7	
Delivery mode					< 0.0001
Spontaneous vaginal delivery	104	51.2	194	47.8	
Instrument-assisted vaginal delivery	14	6.9	3	0.7	
Caesarean section	82	40.4	205	50.5	
Missing	3	1.5	4	1.0	
Fertility specialist visit before pregnancy					0.09
Yes	17	8.4	19	4.7	
No	182	89.7	362	89.2	
Missing	4	2.0	25	6.2	
Infection in first two weeks					0.99
Yes	3	1.5	6	1.5	
No	197	97.0	394	97.0	
Missing	3	1.5	6	1.5	
Sibship size					0.26
1	54	26.6	98	24.1	
2	101	49.8	197	48.5	
≥3	48	23.7	111	27.3	
Missing	0	0.0	0	0.0	
Birth order					0.002
1	120	59.1	193	47.5	
2	64	31.5	144	35.5	
≥3	19	9.4	69	17.0	
Missing	0	0.0	0	0.0	
Child's age at kindergarten enrollment (y)					0.34
≤1.5	13	6.4	36	8.9	
> 1.5	176	86.7	353	86.9	
Missing	14	6.9	17	4.2	
Alcohol consumption 3 months before, during, or 3 months after pregnancy					0.0002
Yes	50	24.6	46	11.3	
No	150	73.9	320	78.8	
Missing	3	1.5	40	9.9	

(*continued on next page*)

Table 1 (*continued*)

Variables	Cases (N = 203)		Controls (N = 406)		p-value[a]
	N	%	N	%	
Smoking 3 months before, during, or 3 months after pregnancy					0.92
Yes	75	37.0	151	37.2	
No	121	59.6	244	60.1	
Missing	7	3.5	11	2.7	
History of living in a farm					0.0005
Yes	34	16.8	27	6.6	
No	168	82.8	341	84.0	
Missing	1	0.5	38	9.4	
Pet animals in house					0.35
Yes	46	22.7	106	26.1	
No	156	76.9	297	73.2	
Missing	1	0.5	3	0.7	
History of allergic diseases					0.11
Yes	49	24.1	72	17.7	
No	150	73.9	327	80.5	
Missing	4	2.0	7	1.7	
Hypertension in pregnancy					0.50
Yes	7	3.5	10	2.5	
No	195	96.1	391	96.3	
Missing	1	0.5	5	1.2	
Gestational diabetes					0.62
Yes	11	5.4	26	6.4	
No	191	94.1	375	92.4	
Missing	1	0.5	5	1.2	

[a] p-values were derived from Chi-square test.

delivery mode, history of infertility (defined as visit to fertility specialist before conception), history of infection during the first two weeks of life as recalled by the guardian and after examination of the medical records, birth order, sibship size, age at enrollment to kindergarten, maternal alcohol consumption and smoking in the perinatal period (3 months before pregnancy to 3 months after pregnancy), history of living in a farm, pet animals in house, history of allergic disease as recalled by the guardian and as determined by scanning of medical records (atopic dermatitis, allergic rhinitis, asthma, food allergy, known allergy to environmental or pharmaceutical antigens), hypertension in pregnancy, and gestational diabetes. Delivery mode was categorized as spontaneous vaginal delivery, instrument-assisted vaginal delivery, and caesarean section. Size for gestational age was defined as small (SGA), appropriate (AGA), and large for gestational age (LGA), based on the 10^{th} and 90^{th} percentile of the national growth curves. For 18% and 13% of the cases and controls, respectively, we had no available information on gestational week at birth, but rather on gestational month at birth or a raw classification of gestational age, as pre-term, full-term, or post-term. To classify these cases and controls according to size for gestational age, we considered as gestational week at birth, the median gestational week that the respective gestational month or gestational age crude category corresponded to.

2.3. Statistical analysis

The frequencies or distributions of the study variables were compared between the cases and controls with a Chi-square test. We next designed a series of multivariable logistic regression models for each of the potential risk factors that were associated with brain tumors at a p-value ≤ 0.10 in the unadjusted analyses. Although size for gestational age did not reach a $p \leq 0.10$ in the unadjusted analysis, as both birth weight and gestational age showed such associations, we also designed a logistic regression model for this variable. All models were adjusted for the matching factors (age, sex) and maternal education as an index of socioeconomic status, in addition to a number of available confounding variables that were determined by designing conceptual directed acyclic graphs (Supplementary Figure 1). Specifically, we included in the models only confounders and no mediators or instruments for the examined associations [18]. We further repeated the multivariable analyses for the two most numerous brain tumor subtypes, namely astrocytomas (ICCC-3 diagnostic subgroup IIIb) and embryonal tumors (ICCC-3 diagnostic subgroup IIIc). All analyses were based on conditional logistic regression models. Data were analyzed using the SAS statistical software (SAS v9.4; SAS Institute, Cary, North Carolina, USA).

3. Results

A total of 203 childhood brain tumor cases and 406 age-, sex-, and center-matched controls were included in this study. The majority of the tumors (74%) were of malignant behavior. Intracranial/intraspinal embryonal tumors (ICCC-3 IIIc) and astrocytomas (ICCC-3 IIIb) were the most common diagnostic subtypes corresponding to 34% and 31% of the total brain tumors, respectively. Ependymomas (ICCC-3 IIIa), other specified tumors (ICCC-3 IIIe), and other gliomas (ICCC-3 IIId) represented 12%, 10% and 7% of the cases, respectively, whereas tumors of unspecified histology were only 4% of the cases.

Table 1 presents the distribution of the potential risk factors by case-control status. In the crude comparisons, instrument-assisted delivery, maternal alcohol consumption during pregnancy, and history of living in a farm were more common among childhood brain tumor cases, as compared to controls. On the contrary, increasing maternal age at birth and increasing birth order were inversely associated with brain tumors. Maternal education, birth weight, gestational age at birth, size for gestational age, paternal age at birth, visit to a fertility specialist before pregnancy, history of infection in the first two weeks of life, sibship size, age at kindergarten enrollment, maternal smoking in the peripartum period, presence of a pet animal in house, history of allergic diseases, and hypertension or gestational diabetes during pregnancy were not associated with brain tumors.

The multivariable analysis (Table 2) revealed bidirectional associations for mode of delivery, with instrument-assisted delivery being associated with higher (OR: 7.82, 95%CI: 2.18–28.03) and caesarean delivery with marginally lower (OR: 0.67, 95%CI: 0.45-0.99) risk for childhood brain tumors, as compared to spontaneous vaginal delivery.

Table 2
Multivariable associations of study variables with the risk of childhood (0–14 years) brain tumors.

Variables[a]	Total CNS tumors (N = 203)			Astrocytomas (N = 63)			Embryonal tumors (N = 70)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Birth weight (500-gr increment)	1.15	0.92–1.44	0.23	1.23	0.70–2.18	0.47	0.96	0.67–1.37	0.81
Gestational age (1-week increment)	1.04	0.91–1.19	0.58	0.93	0.65–1.32	0.66	1.08	0.87–1.34	0.50
Size for gestational age									
SGA	0.52	0.24–1.13	0.10	0.51	0.12–2.26	0.37	0.52	0.14–1.89	0.32
AGA	Ref			Ref			Ref		
LGA	0.78	0.42–1.44	0.43	0.67	0.12–3.61	0.64	0.49	0.18–1.35	0.17
Maternal age at birth (5-yr increment)	0.86	0.70–1.05	0.13	0.81	0.54–1.19	0.28	0.98	0.73–1.32	0.89
Delivery mode									
Spontaneous vaginal delivery	Ref			Ref			Ref		
Instrument-assisted vaginal delivery	7.82	2.18–28.03	0.002	5.40	0.99–30.29	0.05	n/a		
Caesarean section	0.67	0.45–0.99	0.04	0.58	0.26–1.30	0.19	0.62	0.31–1.24	0.17
Birth order									
1	Ref			Ref			Ref		
2	0.60	0.40–0.89	0.01	0.57	0.28–1.18	0.13	1.15	0.58–2.28	0.69
≥3	0.34	0.18–0.63	0.0006	0.39	0.12–1.27	0.11	0.72	0.26–2.01	0.53
Fertility specialist visit before pregnancy	1.68	0.83–3.41	0.15	0.63	0.12–3.42	0.32	1.49	0.50–4.41	0.47
Alcohol consumption 3 months before, during, or 3 months after pregnancy	2.35	1.45–3.81	0.0006	10.49	2.93–37.60	0.0003	1.65	0.73–3.71	0.23
History of living in a farm	4.98	2.40–10.32	< 0.0001	5.82	1.43–23.66	0.01	10.88	2.43–48.77	0.002

[a] Only variables associated with brain tumors at a p-value ≤ 0.10 in the univariate analysis (Table 1) were considered in multivariable analyses. For every variable we constructed separate multivariable conditional logistic regression analysis models adjusting for the matching factors (age, sex), maternal education, and a number of other factors, as indicated by directed acyclic graphs (Supplementary Figure 1).

The analysis also showed a higher birth order to be associated with a lower risk for childhood brain tumors in a dose-response pattern (OR for 2nd vs. 1st child: 0.60, 95%CI: 0.40-0.89 and OR for 3rd vs. 1st: 0.34, 95%CI: 0.18-0.63). Furthermore, alcohol consumption during pregnancy and history of living in a farm were associated with 2-fold (OR: 2.35, 95%CI: 1.45–3.81) and 5-fold (OR: 4.98, 2.40–10.32) higher odds for childhood brain tumors, respectively.

Although underpowered, the sub-analyses for the two most common histological subtypes of childhood brain tumors, i.e. astrocytoma (N = 63) and embryonal tumors (N = 70), provided hints that astrocytoma drove the associations identified for birth order, instrument-assisted delivery, and maternal alcohol consumption in pregnancy, whereas the associations of brain tumor risk with history of living in a farm and caesarean section seemed to be similar among the two subtypes.

4. Discussion

In this nationwide case-control study a number of perinatal and early-life risk factors were associated with the risk of childhood brain tumors. Of specific interest is the positive association with instrument-assisted vaginal delivery (OR: 7.82, 95%CI: 2.18–28.03) as contrasted to the inverse association with cesarean delivery (OR: 0.67, 95%CI: 0.45-0.99). Moreover, maternal consumption of alcohol during pregnancy (OR: 2.35, 95%CI: 1.45–3.81) and history of living in a farm (OR: 4.98, 2.40–10.32) were associated with higher risk of childhood brain tumors, whereas higher birth order was associated with lower risk of childhood brain tumors (OR for 2 vs. 1: 0.60, 95%CI: 0.40-0.89 and OR for 3 vs. 1: 0.34, 95%CI: 0.18-0.63).

Our analysis showed that instrument-assisted delivery is associated with higher risk of childhood brain tumors. An older case-control study had also reported that delivery assisted by forceps is associated with a 2.6-fold increased risk of childhood brain tumors [19], but a more recent study examining the association with vacuum extraction found no significant association [20]. Instrument-assisted delivery with the use of either forceps or vacuum extraction is associated with higher risk of brain injury [21,22]. Interestingly, it has been suggested in adults that traumatic brain injury might increase the risk for subsequent glioma [23,24], but this has not been confirmed in larger populations [25]. While this finding is of interest, potential sources of bias related to the case-control study design such as selective recall bias should not be excluded. The inverse association between caesarean section and risk of brain tumors, in contrast to other childhood malignancies [26,27], might indicate a gradient by mode of delivery regarding the possibility of brain trauma, but requires cautious interpretation, as we did not avail data to differentiate between emergency and elective caesarean section.

We found a dose-response association between higher birth order and risk of childhood brain tumors. Previous case-control studies have reported similar results for overall childhood brain tumors [11,28–31] and particularly for astrocytomas [28], and embryonal tumors [29], but this is not consistent in the literature [20,32–36]. Our analysis by tumor subtypes was underpowered but showed that the effect might be specific to astrocytomas. Birth order is traditionally used in epidemiologic studies as a surrogate marker of frequency and timing of exposure to infections in early life [36,37]. Specifically, later-born children are considered to be exposed to a larger burden of infections at an earlier age, as compared to their older siblings [36,37]. Hence, earlier exposure to infections possibly associates with an earlier maturation of the immune system that might act protectively against tumorigenesis [38]. However, other mechanisms including different hormonal exposure of later conceived fetuses [39] and microchimerism [40] might also be involved in the observed association.

History of living in a farm was associated with a 5-fold higher risk of brain tumors, which was consistent for both astrocytomas and embryonal tumors. This finding might be related to exposure to pesticides early in life. A meta-analysis has shown that paternal exposure to pesticides either during pregnancy or early in life after birth is associated with increased risk of childhood brain tumors [41]. Individual studies have further shown that residential use of pesticides is particularly associated with astrocytomas [42] and embryonal tumors [43], which might also relate to the genetically determined capacity of the child to metabolize toxic pesticide substances [44,45]. Pesticides are designed to act in the nervous system and some of them have been shown to be carcinogenic in animal models [5,46]. Alternative explanations could include a lower risk of allergies, socioeconomic disparities, and exposure to animals, but none of these factors were associated with brain tumors in our analysis.

Alcohol consumption was further associated with higher risk of brain tumors. While this finding is in accordance with studies in other childhood neoplasms, including leukemia [47] and neuroblastoma [48], it contradicts the results from a combined analysis of two population-based French studies that showed no evidence of an association [49]. Alcohol consumption might simply be an indicator of other lifestyle choices

during pregnancy which could explain the increase in the risk of brain tumors and possibly also the differences between the two studies.

Finally, our results did not support the associations of birth weight and size for gestational age with the risk of childhood brain tumors, which we recently showed in a meta-analysis, possibly because of restricted statistical power in this analysis [9]. This might relate with the very high proportion of caesarean section deliveries in Greece, which leads to infants born on average at an earlier gestational week than expected and consequently with lower but still appropriate for their gestational age birth weights, as compared to other settings [26,50,51]. Due to compliance with the MOBI-KIDS questionnaire, gestational age could not be precisely determined for all participants, thus possibly leading to misclassifications in size for gestational age, which could attenuate a potentially significant effect. Nevertheless, the size of the adjusted for gestational age effect estimate for birth weight in the current case-control study was comparable to the pooled estimate derived in our meta-analysis [9], albeit not reaching statistical significance due to low power issues.

Among the strengths of this study are: the nationwide coverage based on the registration network of NARECHEM-ST in Greece; the wide range of potential perinatal and early-life risk factors for which we collected data following the protocol designed by the multicenter MOBI-KIDS study; and the availability of two sets of age-, sex-, and center-matched controls for each of the brain tumors cases. On the negative side, despite the nationwide coverage, our analyses were primarily based on the inherently rather small size and were thus underpowered to detect significant signals for several risk factors. This did not allow any meaningful analyses by brain tumor subtypes. Furthermore, there were small differences in tumor characteristics between cases included in the case-control study and those recorded in the nationwide registry during the same the period. The underrepresentation of non-malignant tumors (mainly pilocytic astrocytomas) relates to the relatively short hospitalization of these patients leading to difficulties in recruitment after discharge, whereas tumors of unspecified histology were mainly identified retrospectively during extensive search of alternative sources for completion of registration and were thus not possible to be recruited in the case-control study. Although these differences might introduce selection bias in our case-control study, we believe that the differences are relatively small to affect the results of our association analyses. No biological data were available to more precisely define some of the variables of interest, such as exposure to infections based on serological measurements and genetic variants that may predispose to increased toxicity following exposure to pesticides. Finally, we could not differentiate between emergency and elective cesarean section that have been shown to differentially influence the risk for childhood malignancies.

5. Conclusions

In conclusion, our findings show that instrument-assisted delivery, possibly indicating a delivery-related brain trauma might be associated with higher risk of childhood brain tumors with potential clinical and public health implications. Furthermore, maternal alcohol consumption during pregnancy and history of living in farm were associated with higher risk, as opposed to higher birth order that was associated with lower risk, thus highlighting that early-life exposures including toxic agents and infections might play a role in brain tumorigenesis during childhood. These results should be interpreted with caution, due to power issues and require replication and further investigation in large cohort studies and meta-analyses.

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Conflicts of interest

None declared.

Author contributions

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.01.017.

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Review article

Season of birth and primary central nervous system tumors: a systematic review of the literature with critical appraisal of underlying mechanisms

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ABSTRACT

Purpose: Season of birth has been considered a proxy of seasonally varying exposures around perinatal period, potentially implicated in the etiology of several health outcomes, including malignancies.
Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we have systematically reviewed published literature on the association of birth seasonality with risk of central nervous system tumors in children and adults.
Results: Seventeen eligible studies using various methodologies were identified, encompassing 20,523 cases. Eight of 10 studies in children versus four of eight in adults showed some statistically significant associations between birth seasonality and central nervous system tumor or tumor subtype occurrence, pointing to a clustering of births mostly in fall and winter months, albeit no consistent pattern was identified by histologic subtype. A plethora of perinatal factors might underlie or confound the associations, such as variations in birth weight, maternal diet during pregnancy, perinatal vitamin D levels, pesticides, infectious agents, immune system maturity, and epigenetic modifications.
Conclusions: Inherent methodological weaknesses of to-date published individual investigations, including mainly underpowered size to explore the hypothesis by histological subtype, call for more elegant concerted actions using primary data of large datasets taking also into account the interplay between the potential underlying etiologic factors.

Introduction

Primary central nervous system (CNS) tumors are still a highly fatal disease in both children and adults [1]. Despite recent advances in understanding their molecular pathogenesis, their etiology remains largely unknown [2]. Genetic syndromes like neurofibromatosis and Li-Fraumeni syndrome are responsible for only 5% of all primary CNS tumors, whereas exposure to ionizing irradiation is the only well-established environmental etiologic factor [3]. The high frequency of CNS tumors in childhood points to perinatal and neonatal exposures as tentative risk factors; in this context, exposure to pesticides [4], maternal consumption of N-nitroso compounds [5,6], folic acid supplementation during pregnancy [7], fetal growth [8], markers of infection [9–11], and immunologic factors [12] have been investigated [3,13].

Clustering of seasonality patterns at birth of individuals diagnosed later with a CNS tumor could be considered as indirect evidence that external parental factors at conception, during pregnancy or perinatally could affect the disease risk in the offspring. Indeed, winter births have previously been associated with neuropsychiatric disorders, suicide, autoimmune diseases, and several types of childhood and adult cancer [14–21]. Postulated etiologic factors with relevance to seasonal variance include exposure to sunlight affecting the levels of vitamin D_3 in the newborn [22], clustering patterns of infections [22–24], exposure to allergens, pesticides, and other sources of polycyclic aromatic hydrocarbons including soot from home heating fires [25]. Several epidemiologic studies have also investigated birth seasonality patterns of CNS tumors in both children and adults, albeit with rather inconsistent findings. Notably, earlier studies reported a clustering of births of CNS tumor cases in late fall or winter [26–29], not confirmed although by recent investigations showing variable results by histologic subtypes [30–33].

Conflicts of interest: None declared.

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The aim of the present study was to systematically review results of published literature on seasonality of birth and subsequent CNS tumor risk and summarize the reported factors that might underlie this association. Furthermore, we opted to separately examine and compare the results of studies on childhood versus adulthood CNS tumors.

Methods

Study selection

This systematic review was based on a predefined protocol and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Appendix A) [34]. Scopus and MEDLINE/PubMed were searched up to June 25, 2017 combining relevant key terms (search strategy in Appendix B). The references of eligible articles and relevant reviews were additionally manually screened ("snowball"). No language or publication year restrictions were applied.

Eligible were considered case–control and cohort studies, as well as cancer registration studies using for comparisons population-based birth month or season rates to assess the statistical association between month or season of birth period and risk of subsequent primary CNS tumor. Studies considering either childhood/adolescence (0–14 or 18 years) or adult (19+ years) occurrence of CNS tumors were eligible, but were separately examined. Studies referring to populations with genetic syndromes predisposing to CNS tumors, including neurofibromatosis and Li-Fraumeni syndrome, case reports, case series, *in vitro*, and animal studies were excluded. Eligible studies were evaluated for potential overlap, based on geographic location, data sources, diagnostic period, age range, and number of cases. Pairs of reviewers, blinded to each other, completed the study selection; disagreements were resolved by team consensus.

Data extraction and quality assessment

Extracted data included publication details (year, first author, title, journal), information on study characteristics (study design and geographical area, mean age/age range, proportion of males, sample size, ascertainment of cases and comparison groups), type and assessment of exposure, control for potential confounding factors, ascertainment of outcome and statistical analysis variables (methodology and results). Authors of original studies were also contacted for missing data.

Studies were *a priori* distinguished by age (childhood vs. adulthood) and were thereafter evaluated on quality with Newcastle–Ottawa Scale [35]. For cohort studies, follow-up was considered adequate at a minimum of 1 year, with a completeness rate >80%. For the evaluation of the cancer registration studies with population frequencies of births per month/season for comparisons, the cohort subscale was used, after slight modifications to abide with the study objectives; namely, three questions referring to the presence of the outcome at the start of the study and to the length and completeness of follow-up were excluded. Again, pairs of reviewers conducted independently data abstraction and quality assessment; thereafter, consensus was reached for disagreements.

Data synthesis

Because of the highly heterogeneous group of studies in terms of inherent disease characteristics (multiple histologic types, variable frequency of disease by age group), choice of comparison groups, use of adjusting factors, length of overall period, population groups and methods of statistical analysis, an overall meta-analysis using published effect estimates was not feasible. Neither the request of additional data from authors of eligible studies yielded the anticipated figures, as the response rate and the availability of information were not adequate. Thus, only a qualitative synthesis of published data was possible, at present.

Results

The search strategy of the two databases yielded 212 results after duplicates were removed, whereas 19 additional articles were identified via snowball. After screening the full-text of 56 potentially eligible articles, eventually 17 met the preset eligibility criteria [22,23,26–33,36–42]; the flowchart of the selection process is graphically presented in Figure 1.

Characteristics of eligible studies

The study characteristics are summarized in Table 1. Of the 17 eligible articles, three were case–control studies of actively collected CNS tumor patients in clinical settings [26,30,36], only one was a prospective nationwide cohort [29] and the remaining 13 cancer register–based studies estimated the observed over expected rates using seasonal or monthly distributions of births among the case series versus those in respective populations; the comparison group in the latter studies was derived from the same age national, county, or all cancers registry population [22,23,27,28,31–33,37–42]. All studies were conducted in the Northern hemisphere of the Globe; particularly, five in the United States [26,28,30,36,39], four in Nordic countries [23,27,29,32], four in the United Kingdom [37,38,40,41], two in Germany [22,31], and two in Japan [33,42] yielding a grand total of 20,523 CNS tumor cases. Nine studies focused exclusively on children (0–5, 14, 15, or 18 years as upper age limit) with CNS tumors [23,29,32,33,37–40,42]; one examined all age groups, but analyzed separately childhood (0–18 years) and adult CNS tumors [28]; one focused exclusively on teenagers and young adults (TYAs; 15–24 years at diagnosis) [41]; the remaining six examined adult populations with the lower age limit ranging from 15+ to 18, 19, or 20 years [22,26,27,30,31,36]. Seasonality of birth was assessed mainly through structured interviews or medical records in case–control studies and medical records or via registration data in the remaining studies.

Quality assessment

The quality of case–control and cohort studies was satisfactory (no cumulative loss >2 points in NOS), apart from two studies compromised by nonrepresentativeness of the general population [30,36], whereas the quality of the cancer registry–based studies was systematically hampered because of lack of control for potentially confounding factors. The analytical quality score of each study is presented in Appendix C.

Season of birth and incidence of CNS tumors

Studies in children

Eight of 10 studies showed some evidence in seasonality of birth patterns with the overall or specific CNS tumor subtypes risk [28,29,32,33,37,39,40,42]; no measures of the magnitude of the association were, however, presented; whereas an overall lack of consistency regarding the month/season of the maximum occurrence was evident ranging from August to February (Table 2). In particular:

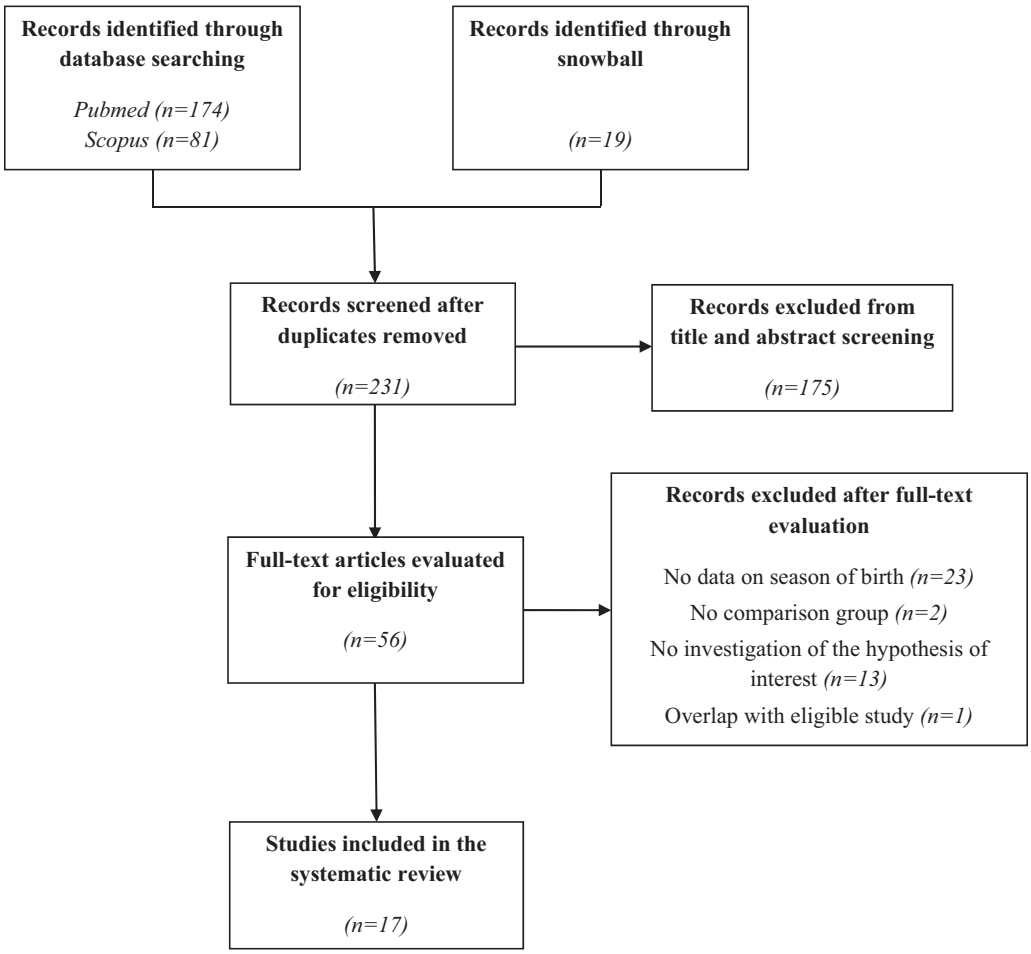

Fig. 1. Flow chart showing the process for selection of eligible studies.

CNS tumors overall. The Norwegian cohort study ($n = 459$), the most recent Japanese ($n = 115$) and a UK study with registry controls ($n = 1045$) showed peaks in the period December to February [29,33,40], whereas the remaining five studies encompassing more than 10,000 cases in Nordic countries, the United Kingdom, and the United States showed no statistically significant effects [23,32,37–39].

Astrocytoma. Among the seven studies presenting separate analyses by histologic subtypes, only three [33,37,40] comprising 31, 264, and 422 cases, respectively, found a significant peak between October and February; again, the largest studies, including the cohort study, did not confirm these findings [23,32,39].

Ependymoma. Schmidt et al. (2009) and McNally et al. reported clustering of ependymomas births in winter months (December to February), which in the former study was evident only among females aged 5–19 years [32,40], as contrasted to the remaining four studies showing no significant association [23,33,37,39].

Embryonal tumors. Statistically significant peaks in births during fall months (September to November) were shown for medulloblastomas, in the two largest studies from the United States [28,39] and August to October in a study among Japanese children aged 0–5 years [42]; even within components of these studies, however, the results were not homogenous; notably, in the study by Halperin et al., the same statistically significant fall peak was evident in three different sites but not in the SEER-derived component [28], whereas according to Hoffman et al., it was stronger for females aged older than 5 years and those residing in metropolitan areas [39]. The six remaining studies entailing embryonal tumor analyses [29,33,40], pertaining also the only study on primitive neuroectodermal tumors did not show any seasonal birth variation [37].

Studies in adults

A total of seven studies (Table 3), with individual sample sizes ranging from 101 to 2174 cases, investigated seasonality of birth among adult cases of CNS tumors [22,26–28,30,31,36] and the results are summarized in the following along with those of the only study (1882 cases) that examined exclusively TYAs [41].

CNS tumors overall. Only one small ($n = 101$ cases) size study [27] examined seasonality of birth in association with all types of CNS tumors and reported a statistically significant increased occurrence among those born in winter months (December to February), whereas the TYAs study ($n = 1882$ cases) did not find any pattern in birth seasonality [41].

Glioma. Four of seven studies examining gliomas in adults showed a statistically significant pattern of birth seasonality [22,26,27,41], three with peaks in winter months [22,26,27] and the TYAs study presenting peaks in April and October only among males for astrocytomas or in May and November for other gliomas [41]. In one study, the winter peak was significant only for glioblastoma,

Table 1
Characteristics of eligible studies

Ref	First author, year	Region (study period)	Study design*	N cases/N controls	Age range (y)	Gender (males %), cases/controls	Ascertainment of cases	Ascertainment of controls/ comparison group	Matching/ adjusting variables	Season of birth assessment
[30]	Anic, 2013	USA: Nashville, Tampa, Birmingham, Atlanta, Louisville (2004–2012)	Case–control study	889/903	>18	59.0/57.0	Primary gliomas in neurosurgery and neuro-oncology departments	Frequency matched, cancer-free friends, and non-blood-related associates of cases or same community residents	State of residence, age, gender	Interview
[41]	Van Laar, 2013	UK: England (1996–2005)	Cancer registration study	1882 astrocytomas, 629; other gliomas, 195; ependymomas, 99; medulloblastomas, 111; other, 702	15–24	NR	National TYA cancer registry	Month-specific national birth rates	Sex	Registry
[33]	Makino, 2011	Japan: Kumamoto Prefecture (1989–2003)	Cancer registration study	115 astrocytomas, 31; other gliomas, 18; embryonal tumors, 16; germinomas, 20	0–14	NR	Primary intracranial tumors, 30 hospitals, Kumamoto Prefecture	Month- and season-specific birth rates, Kumamoto Prefecture	None	Medical records
[36]	Amirian, 2010	USA: Texas, Houston (2001–2006)	Case–control study	489/540	>18	55.2/49.3	Histologically confirmed gliomas identified by hospital physicians	Frequency matched, cancer-free controls, random-digit dialing	Age, sex	Interview
[37]	Basta, 2010	UK: N. England (1968–2005)	Cancer registration study	702 ependymomas, 72; astrocytomas, 264; PNETs, 124; other gliomas, 68	0–14	55.0	Northern Region Young Persons' Malignant Disease Registry	Month-specific birth rates of all cancer cases recorded in the Registry	None	Registry
[23]	Schmidt, 2010	Denmark, Norway, Finland, Sweden (1985–2006)	Cancer registration study	2771 ependymomas, 311; astrocytomas, 1128; embryonal tumors, 519; other gliomas, 217; other, 596	0–14	53.6	National cancer registries	Month-specific national birth rates	None	Registry
[32]	Schmidt, 2009	Denmark (1970–2003)	Cancer registration study	1640 ependymomas, 162; astrocytomas, 607; PNETs, 270; other gliomas, 76; other, 326	0–19	NR	Danish Cancer Registry	Month-specific national birth rates	None	Registry
[31]	Staykov, 2009	Germany: Bavaria (2002–2005)	Cancer registration study	2174	≥15	58.0	Bavaria registry	Month-specific birth rates, Bavaria	Sex	Registry
[39]	Hoffman, 2007	US, CBTRUS (1995–2001)	Cancer registration study	4522 embryonal, 664; pilocytic astrocytomas, 864; other astrocytomas, 552; ependymomas, 279; other 2163	0–19	53.0	13 population-based databases	Month-specific population birth patterns in each State	None	Registry

[22]	Koch, 2006	Germany: S-E. Bavaria (1992–2003)	Cancer registration study	697 glioblastomas, 501; anaplastic astrocytomas, 196	52.5 ± 15.7	58.2	Regensburg Regional Cancer Center	Season-specific national birth rates	None	Registry
[27]	Mainio, 2006	Finland: Oulu (1990–1992)	Cancer registration study	101 low-grade gliomas, 19; high-grade gliomas, 22; meningiomas, 33; other, 27	20–82	38.6	Primary brain tumors at a neurosurgery clinic	Month-specific national birth patterns	None	NR
[26]	Brenner, 2004	USA: Boston, Phoenix, Pittsburg (1994–1998)	Case–control study	686/799 gliomas, 489; meningiomas, 197	>18	Gliomas, 56.4; meningiomas, 23.0/ controls: 44.4	Histologically confirmed intracranial gliomas/ meningiomas diagnosed in the participating hospitals	Frequency-matched controls, hospitalized for nonmalignant conditions	Hospital, age, sex, race/ethnicity, residence to hospital distance	Interview, medical records
[28]	Halperin, 2004	USA: North Carolina, (1973–1999)	Cancer registration study	1209 medulloblastomas	All	NR	Histologically confirmed cases (registries or St Duke University Medical Center)	Month and season-specific national birth rates	None	registry
[40]	McNally, 2002	UK: N-W. England (1954–1998)	Cancer registration study	1045 astrocytomas, 422; ependymomas, 109; embryonal tumors, 200; other, 314	0–14	53.6	Manchester Children's Tumor Registry	Month-specific birth rates of all childhood cancer cases recorded in the Registry	None	Registry
[38]	Feltbower, 2001	UK: N. England (1968–1995)	Cancer registration study	1015	0–14	NR	3 local cancer registries	Month-specific national birth rates	None	Registry
[29]	Heuch, 1998	Norway (1967–1992)	Cohort study	459/1489297 astrocytomas, 168; embryonal tumors, 78	0–15	56.6	Norwegian Cancer Register	Medical Birth Register (national childhood population)	Age, sex	Registry
[42]	Yamakawa, 1982	Japan: Fukuoka-Ohita (1959–1979)	Cancer registration study	128 medulloblastomas	0–5	NR	Histologically confirmed cases diagnosed in N-W District of Kyushu or registered in the Brain Tumor Registry, Japan	Month-specific national birth rates	None	Registry

CBTRUS = Central Brain Tumor Registry of the United States; CNS = central nervous system; NR = nonreported; PNET = primitive neuroectodermal tumors; SD = standard deviation; TYA = teenagers and young adults.
* Type of comparison group in the cancer registration studies is shown in the "Ascertainment" column.

Table 2
Association of birth seasonality (*P value < .10,**P value < .05,***P value < .01, ns = nonsignificant statistical association) with CNS tumors in children and adolescents: summary presentation of findings in eligible studies

First author, year, country, [Ref]	N cases (age)	Overall CNS tumors	Astrocytoma/other glioma	Ependymoma	Embryonal tumors	Covariates	Statistics
Makino, 2011, Japan, [33]	115 (0–14 y)	Dec–Feb**	Dec–Feb*	ns (P = .59)	ns (P = .56)	None	χ^2: observed versus expected
Basta, 2010, UK, [37]	702 (0–14 y)	ns (P = .52)	Astrocytomas: Oct*, (females**) Other gliomas: ns (P = .82)	ns (P = .52)	PNETs: ns (P = .11)	None	χ^2; Poisson regression; Harmonic models
Schmidt, 2010, Nordic countries, [23]	2771 (0–14 y)	ns (P = .31); ns by age group (P = .10 for 0–4 and P = .81 for 5–14 y)	Astrocytomas: ns (P = .19) Other gliomas: ns (P = .78)	ns (P = .26)	ns (P = .67)	None	Walter and Elwood's test
Schmidt, 2009, Denmark, [32]	1640 (0–14 y)	ns (P = .83)	Astrocytomas: ns (P = .48) Other gliomas: ns (P = .19)	Dec–Jan** (5–19 y***, females***)	PNETs: ns (P = .74)	None	Walter and Elwood's test
Hoffman, 2007, USA, [39]	4522 (0–19 y)	ns (P = .22)	Pilocytic: ns (P = .13) Other astrocytomas: ns (P = .79)	ns (P = .95)	Medulloblastomas: Oct–Nov** (5–19 y***, females**, residency in nonmetropolitan areas***) Other embryonal: ns (P = .14)	None	Edward's test; Walter and Elwood's test
Halperin, 2004, USA, [28]	100 (0–19 y)	—	—	—	Medulloblastomas: Sep–Nov**	None	χ^2: observed versus expected
• Duke University Medical Center	64 (0–19 y)	—	—	—	Medulloblastomas: Sep–Nov**		
• Central Cancer Registry of North Carolina	44 (0–19 y)	—	—	—	Medulloblastomas: Sep–Nov**		
• Los Angeles/San Jose/ Monterey, California SEER	683 (0–19 y)	—	—	—	Medulloblastomas: ns (P = .69)		
• National SEER							
McNally, 2002, UK, [40]	1045 (0–14 y)	Dec*	All astrocytomas: Nov** Pilocytic: ns (P = .29) Other astrocytomas: Dec*	Feb*	ns (P = .63)	None	Edward's test
Feltbower, 2001, UK, [38]	86 (0–14 y)	ns (P = .48)	—	—	—	None	Walter and Elwood's test; logistic regression
• Cumbria	474 (0–14 y)	P = .08, peak month nr	—	—	—		
• Northern RHA	455 (0–14 y)	ns (P = .84)	—	—	—		
• Yorkshire RHA							
Heuch, 1998, Norway, [29]	459 (0–15 y)	Dec–Feb***; Summer: IRR = 1.19 (0.91–1.55); Fall: IRR = 1.23 (0.94–1.61); Winter: IRR = 1.44 (0.95–2.17), with spring as reference	ns (P = .19); Summer: IRR = 1.20 (0.78–1.83) Fall: IRR = 0.93 (0.59–1.48) Winter: IRR = 1.52 (1.19–1.97), with spring as reference	—	Medulloblastomas: ns (P = .26); Summer: IRR = 0.69 (0.34–1.37) Fall: IRR = 1.14 (0.61–2.10) Winter: IRR = 1.32 (0.74–2.38), with spring as reference	Age, sex	Log-linear Poisson regression
Yamakawa, 1982, Japan, [42]	128 (0–5 y)	—	—	—	Medulloblastomas: Aug–Oct*	None	χ^2: observed versus expected

CNS = central nervous system; IRR = incidence rate ratio; PNET = primitive neuroectodermal tumors; RHA = regional health authority; SEER = Surveillance, Epidemiology and End Results program.

Table 3
Association of birth seasonality (**P value $< .05$,***P value $< .01$, ns = nonsignificant statistical association) with CNS tumors in adults: summary presentation of findings in eligible studies

First author, year, country, [Ref]	N cases (age)	Overall CNS tumors	Glioma	Meningioma	Embryonal tumors	Covariates	Statistics
Anic, 2013, USA [30]	889 (>18 y)		ns; Winter: OR = 0.96 (0.74−1.24); Spring: OR = 0.97 (0.75−1.26); Summer: OR = 1.03 (0.80−1.33), with fall as reference	—	—	State of residence, age, gender	Unconditional logistic regression
Van Laar, 2013, UK, [41]	1882 (15−24 y)	May, Nov ($P = .16$)	Astrocytomas both genders: Jan ($P = .12$), males only: Apr**, Oct**; Other gliomas: May**, Nov**	—	Medulloblastomas: Jan, Jul ($P = .26$); females only: Mar**, Sep**	Sex	Harmonic curves
Amirian, 2010, USA [36]	489 (>18 y)		ns ($P = .83$)	—	—	None	χ^2: observed versus expected
Staykov, 2009, Germany [31]	2174 (≥15 y)		ns; males: Dec ($P = .54$); females: Apr ($P = .11$)	—	—	Sex	Sinusoidal curve, Edwards test, Roger-test
Koch, 2006, Germany [22]	697 (mean age: 40.9 y)		Glioblastoma: Dec−Feb** Anaplastic astrocytoma: spring/summer (ns, nr)	—	—	None	Circannual cosinor model
Mainio, 2006, Finland [27]	101 (20−82 y)	Dec−Feb**	Dec−Feb** (except low-grade)	Dec−Feb**	—	None	χ^2: observed versus expected
Brenner, 2004, USA [26]	686 (>18 y)		Feb**; left-handed/ambidextrous***	Jan** (males**)	—	Education, marital status, place of birth, handedness, birth order, history of allergy/autoimmune disease	Unconditional logistic regression
Halperin, 2004, USA [28]	22 (>19 y)	—	—	—	Medulloblastomas: ns ($P = .27$)	None	χ^2: observed versus expected
• Duke University Medical Center	26 (>19 y)	—	—	—	Medulloblastomas: ns ($P = .28$)		
• Central Cancer Registry, North Carolina, USA	31 (>19 y)	—	—	—	Medulloblastomas: ns ($P = .88$)		
• Partial California SEER							
• National SEER	239 (>19 y)	—	—	—	Medulloblastomas: ns ($P = .49$)		

CNS = central nervous system; OR = odds ratio; SEER = Surveillance, Epidemiology and End Results program.

but not for anaplastic astrocytoma [22], whereas another study showed that the effect was evident only for high-grade gliomas [27]. Brenner et al., who conducted stratified analyses for gliomas [26], reported a seasonality pattern only among left-handed or ambidextrous individuals, and only among those without a history of autoimmune/allergic diseases; it is possible that these analyses were limited by the small sample size though. By contrast, the largest German study (2174 cases) did not reveal any significant seasonality effect for gliomas [31], neither did two of the case–control studies [30,36].

Meningioma. The two small studies, encompassing 33 and 187 adult cases, respectively, showed similar winter peaks for meningiomas [26,27].

Embryonal tumors. Finally, no statistically significant birth seasonality pattern for medulloblastomas emerged in any of the US regional cohorts and SEER, studied by Halperin et al. [28]. Conversely, the TYAs study showed a significant peak in March and September births, which was, however, evident only for females [41].

Discussion

This first systematic review of published studies conducted in the Northern hemisphere provides some indications for a potential clustering of births among children and adults with CNS tumor types in fall and winter months. It is worth noting that the results were in general based on studies suffering lack of power, which did not report the size of effect, neither were the findings consistent across studies confined to specific histologic subtypes. Even if an association exists, however, birth in fall and winter months is only a proxy of the potential perinatal factors, which could increase the risk for a subsequent CNS tumor development later in life. Indeed, the variation of findings by the study setting or within individual countries in variable periods or different counties points to the very complex interplay between a wide range of environmental and/or genetic factors rather than an isolated factor by its own right.

Potential underlying factors

The wide range of candidate factors conducive to brain carcinogenesis includes exposure to pesticides, herbicides, or fungicides; their highly variant use throughout the year could potentially explain seasonal patterns encountered in agricultural areas. Pesticides have been found to be carcinogenic in animal models, whereas epidemiologic studies show that childhood or perinatal parental exposure to pesticides is associated with increased risk of CNS tumorigenesis [4,43]. Parents could carry pesticide compounds in their shoes and clothes after work and expose their children in the house [44]. The placental permeability to pesticides [45], the comparatively larger and more permeable to lipophilic compounds infant skin surface [46,47], and the immature until 6 months of age blood–brain barrier make it feasible for environmental compounds to reach the brain [48].

As serum vitamin D levels depend on sunlight, a respective seasonal pattern has been well established [49]. Lower levels of serum vitamin D have been associated with increased risk for several malignancies [50]. Studies in rats demonstrate that newborns of vitamin D–depleted mothers have more mitotic and fewer apoptotic cells in the brain [51,52], which could be associated with a vulnerability to carcinogenicity. Nevertheless, the only to-date study examining the association of maternal vitamin D levels with risk of childhood CNS tumors found a dependent on birth weight association [53].

Immune system maturity of the index child might be another alternative. Atopic diseases, including asthma [54], atopic dermatitis [55], food allergy [56], and allergy to a variety of environmental antigens [57], as well as autoimmune disorders [58,59] have been linked with variability in the season of birth. Exposure to allergens and infectious agents in early life, which follows a seasonal pattern, might promote immune system development, thus determining the risk of immune-mediated disorders [60], which have also been associated with decreased risk of childhood and adult CNS tumors [12,61,62].

Exposure to infections in early life is highly variable by season, and proxies of early life infections, like earlier and longer daycare attendance or higher birth order, are associated with a decreased risk of childhood CNS tumors [63,64]. Conversely, a later exposure to infections, extending up to the first 6 years of life has been linked with higher risk of glioma and meningioma [11]. This inconsistency could indicate two distinct mechanisms of disease; on the one hand, exposure to infections early in life (before 3 years of age) might be related to immunity development, which is associated with a decreased risk of CNS tumors, whereas, infections later in childhood might be implicated in an infectious origin of the disease. The hypothesis of the viral origin of CNS tumors has been examined especially in the case of human herpesviruses, but their direct impact on neoplasia has not yet been proven [65].

More recent evidence suggests that birth seasonality might be related to patterns of epigenetic modifications, as it was associated with specific DNA methylation patterns in adults [66]. Epigenetic alterations seem to also play a role in brain tumorigenesis [67], necessitating a further investigation of this concept.

Other factors that may mediate or confound the observed associations include birth weight, handedness, and diet. Birth weight has been reported to vary by season of birth [68,69]. Meta-analysis results from our group show that birth weight >4000 g is associated with increased risk of childhood CNS tumors, specifically astrocytomas and embryonal tumors [70], which might indicate a confounding role on the effect of birth seasonality. Right-handedness has been associated with an increased risk of adult glioma [71]; likewise, birth seasonal patterns have shown a higher likelihood of being right-handed if born between March and July [72]. In this context, it has been shown that being right-handed and born in spring–winter months is associated with the higher likelihood of developing gliomas [26]. Finally, maternal nutrition could follow seasonal variability in accordance with crop cycles or use of preservatives. For example, dietary intake of N-nitroso compounds, used as cured meat preservatives by mothers during pregnancy, has been associated with increased risk of brain tumors in the offspring [73], whereas yellow–orange, cruciferous vegetables, fresh fish, and grains have been found to be associated with decreased risk [74].

Methodologic considerations

Most studies comprising this systematic review yielded statistical significant seasonal patterns, mainly excesses in fall or winter months, in births of CNS tumor cases, which have been examined overall or by tumor subtype. The results should be cautiously interpreted, however, in view of limitations inherent to the study design and data availability of eligible studies including variable criteria for selection of the comparison groups, statistical analysis methods, and low sample size for subtype analyses. Indeed, CNS tumors comprise a highly heterogeneous group of malignancies, in terms of etiology; hence, analyses by subtype, but also by grade, are considered essential.

The lack of confirmation of the findings of the Danish [32] and the Norwegian [29] study in the subsequent Nordic countries study [23] poses several concerns; likewise the inconsistency of the medulloblastoma findings among children in different parts of the United

States in contrast to the nonsignificant ones derived from SEER [28], raise intriguing considerations about whether a genuine association may exist or whether the variable exposures in the diverse settings comprising SEER may offset a genuine association observed in a specific state. Moreover, control for confounding was rather an exception in the eligible studies, whereas the higher CNS tumor risk among individuals born in late fall or winter was not consistently found across studies by tumor subtype. Finally, the fact that a meta-analysis was not feasible precludes the possibility of cumulative interpretation of the findings. The highly heterogeneous results across studies, however, could either indicate that different factors are implemented in the association of season of birth with CNS tumors in each dataset or could point to the heterogeneity of the methodologic approaches, for example, in statistical analysis, implemented by each study.

We attempted to separately examine studies investigating seasonality among children and adults, as the epidemiology of the tumors in these age groups is grossly different. Given the proximity of birth as an event to the occurrence of CNS tumors, we hypothesized that if an effect of birth seasonality was actually evident, it would be more profound among children; in adults, a seasonally variant underlying perinatal exposure would have a less strong effect on the risk of tumorigenesis in the CNS. Nevertheless, no specific pattern was identified.

Recommendations for future research

Subsequent studies aiming to explore the role of birth seasonality on the risk of CNS tumors should take into account the aforementioned limitations of currently available evidence. Particularly, traditional methods to ascertain seasonality peaks, like the Edwards and the Walter and Elwood's test do not provide information regarding the size of the effect, whereas the χ^2 test for comparisons between the observed and the expected per month cases is not additionally informative about the direction of the effect. In this context, using regression analysis methods, like logistic, Poisson or Cox proportional hazard models in population-based studies, comparing the risk for the disease across the four seasons seems a more justified approach; this option could further give the opportunity for adjusting the models for known perinatal confounders that affect the risk for CNS tumors. Finally, even if an effect is actually evident, based on current literature, it seems to be of rather small magnitude, necessitating a large sample size to provide statistically significant effects; for example, for an expected risk ratio of 1.2, given an incidence of primary CNS tumors of around five cases per 100,000 children in the United States [75], a cohort size of more than 500,000 children followed from birth to 14 years would be required to show a statistically significant effect.

Conclusions

In conclusion, clustering of births of children or adults with CNS tumors indicating perinatal determinants of the disease cannot be excluded on the basis of to-date published studies; heterogeneity issues, inadequate control for confounding, and lack of reported effect estimates precluded meta-analysis of the mostly underpowered individual studies by specific tumor subtype. Furthermore, birth seasonality only comprises a broad proxy of several perinatal exposures, which could represent a different underlying exposure by study setting. Yet, this first attempt to summarize current findings seems to be indispensable in showing the type of studies, data, and analyses that have to be used to yield actual effect estimates and also points to potential underlying factors that could orient researchers to generate and further explore specific etiologic hypotheses.

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CLINICAL STUDY

Incidence and survival of gliomatosis cerebri: a population-based cancer registration study

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Abstract

Gliomatosis cerebri (GC) comprises a rare widespread infiltrating growth pattern of diffuse gliomas. We explored the incidence patterns and survival rates of GC in a population-based registration sample from the Surveillance, Epidemiology and End, Results database (1973–2012). GC cases (n = 176) were identified based on their International Classification of Diseases in Oncology (ICD-O-3) morphology code (9381). We calculated age-adjusted incidence rates (AIR) and evaluated temporal trends. Survival was assessed with Kaplan–Meier curves and Cox regression models. The annual AIR of GC was 0.1/million. We noted increasing trends in the preceding registration years (1973–2002; annually, + 7%) and a tendency of clinical/radiological approaches to substitute the gold-standard histological assessment for diagnosis. GC was diagnosed in the entire age spectrum (range 1–98 years), but higher incidence rates (0.43/million) were noted among the elderly (≥ 65 years). A slight male preponderance was identified (male-to-female ratio: 1.4). Median overall survival was 9 months with a 5 year survival rate of 18%. Increasing age, primary tumor location not restricted to the cerebral hemispheres and rural residence at diagnosis were identified as negative prognostic factors, whereas receipt of radiotherapy, surgical treatment, race and method of diagnosis were not associated with outcome. This first comprehensive overview of GC epidemiology exemplifies the rarity of the disease, provides evidence for male preponderance and increased incidence among the elderly and shows lower survival rates compared to the published single center reports. Expansion of registration to histological and molecular characteristics would allow emergence of clinical prognostic factors at the population level.

Keywords Gliomatosis cerebri · Epidemiology · Incidence · Survival · Prognosis · Outcome

Introduction

Gliomatosis cerebri (GC) is a rare diffusely infiltrating brain tumor of poor prognosis with controversial definition, histopathological features and clinical management [1, 2]. Until recently, the 2007 World Health organization (WHO) classification recognized GC as a separate entity, defined as an extensively infiltrative diffuse glioma involving at least three cerebral lobes [3]. Given the lack of evidence for a distinct GC genetic profile [4, 5], the 2016 WHO classification considers GC as a special widespread and invasive growth pattern of the category of diffuse glioma [6]. The majority of GC tumors histologically correspond to II, III, or IV grade astrocytomas [5, 7]. However, patients with GC have poorer prognosis compared to other gliomas of the same grade [8]. The cause for this unique aggressive behavior has not yet been determined. GC commonly affects the hemispheres bilaterally and may extend to deeper gray matter structures

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or infratentorially to the brainstem, the cerebellum, and the spinal cord [1, 2, 9, 10]. Based on neuroradiological findings, GC may be divided to the variants that present diffuse neoplastic growth without a clear solid tumor component (type I GC), and the variants with an obvious mass in addition to the diffuse component (type II GG) [1, 2, 9, 10].

Given its rarity, with less than 1000 cases having been described in the biomedical literature since its first description in 1938 [11], the epidemiology of GC has not yet been explored. There are no population-based studies on the incidence or the gender and age distribution of GC. Furthermore, most studies assessing prognosis of GC are single center-based and thus not representative of the entire disease population. Thus, leveraging the publicly available data of the Surveillance, Epidemiology and End Results (SEER) cancer registry network in the US (1973–2012), we set out to describe for the first time the incidence patterns of GC, the distribution by gender and age in the population, and potential time trends in the disease occurrence. Additionally, we aimed to evaluate the tumor's overall survival and prognostic factors in the population setting, although under the restricted variable availability in registry data.

Methods

Source of data and study population

Data for this study were extracted from the publicly available SEER database [12]. SEER systematically records cancer cases since 1973 via a network of 18 population-based registries in an area covering 28% of the nationwide US population. For the aims of this study, we extracted available data for all GC cases registered in the SEER database during the entire registration period (1973–2012). GC cases were identified by their International Classification for Diseases in Oncology-3rd Edition (ICD-O-3) morphology code [13]. Particularly, cases with an ICD-O-3 morphology code "9381", corresponding to GC, were included in the analysis.

Study variables

Demographic variables that were examined included age, gender, race and urbanization of the place of residence at diagnosis, as a measure of socioeconomic status. Age was classified as follows: 0–14 years (children), 15–39 years (adolescents and young adults), 40–64 years (middle-aged adults) and ≥ 65 years (elderly). As GC in children has been reported to have superior prognosis, compared to adults [14], sensitivity analyses excluding children were conducted. Race was binarily classified to Whites and non-Whites. We dichotomized place of residence to rural and urban based on US definitions.

Available clinical variables included: primary tumor location, method of diagnosis, receipt of radiation therapy and performance of surgery. Primary tumor location was codified according to the ICD-O-3 topography codes and was classified to tumors localized in the cerebral hemispheres (C71.1–C71.4), tumors in deeper structures, infratentorial or overlapping locations (C71.0, C71.5–C71.8) and tumors of unspecified CNS location (C71.9) [13]. Based on the International Agency for Research in Cancer (IARC) guidelines, method of GC diagnosis was classified to microscopical diagnosis (histology, cytology or unspecified), clinical/radiological diagnosis, and diagnosis via death certificates only (DCO) [13]. Receipt of radiation therapy or performance of any surgical procedure (including both local tumor excision or gross total resection) at diagnosis were extracted as yes/no variables.

Follow up data

Patients lost to follow-up and DCO cases were excluded from survival analysis. We assessed overall survival in the longest available follow-up date for each case; follow-up information was available until December 31st, 2012.

Statistical analysis

We calculated annual age-standardized incidence rates (AIR) of GC for the entire registration period (1973–2012). AIRs are expressed as number of GC cases per million per year. AIRs were calculated for the entire population and for subgroups by gender, age group, 10 year time periods and method of diagnosis. Comparisons of AIRs were implemented by calculating the standard error and subsequently z-scores, as previously described for incidence rates [15]. To evaluate temporal trends in incidence, annual percent changes (APC) were calculated via Poisson regression analysis and potential breaks were sought via Joinpoint regression analysis. As we found an increasing trend in incidence only for the first 30 years of registration, we also calculated AIRs for the restricted 2003–2012 period to disentangle the effect of registration improvements or efficiency of GC diagnosis on incidence.

Overall survival was assessed via Kaplan–Meier curves for the entire sample and for subgroups by age group (0–14, 15–39, 40–64, ≥ 65 years), gender, time period of diagnosis (1973–2002, 2003–2012), primary tumor location, method of diagnosis (clinical/radiological, histological) and received treatment. The log-rank test was used for comparisons. For the evaluation of the prognostic significance of demographic and clinical variables, Cox proportional hazard models were utilized. Univariable analyses were conducted and variables associated with survival at a level of $p < 0.20$ were included in a multivariable model. The analysis was repeated after

excluding cases aged < 15 years at diagnosis. SAS software (V9.4, SAS Institute Inc) and STATA (V13.0, Stata Corp) were used for statistical analysis.

Results

Clinical and demographic characteristics

A total of 176 GC cases were recorded in the SEER database during the entire registration period (1973–2012). Table 1 presents the demographic and clinical characteristics of the registered patients. Mean age at diagnosis was 57.4 years (SD: 22.8). Although age ranged from 1 to 98 years, the majority of the cases were diagnosed in older age groups (31% in 40–64 years and 49% in ≥ 65 years). Childhood (0–14 years) GC comprised only 9% of the cases. A male preponderance was noted (54%). The majority of the cases were Caucasians (90.3%) lived in urban areas at diagnosis (93%) and were diagnosed in the latter 2 decades of registration (1993–2012; 94%).

61% of the patients had a microscopical confirmation of the diagnosis, whereas diagnosis by clinical/radiological methods was established in 36% of the patients; DCOs corresponded to less than 3%. Regarding primary tumor location, 28% of the GC tumors were restricted in the cerebral lobes, whereas 46% were located in deeper and infratentorial structures or in overlapping brain areas; in one-fourth of the cases, primary tumor location was not specified. Among cases with available treatment information, 33 and 25% received radiation therapy or had a surgical resection of the tumor, respectively.

Incidence rates and time trends

The annual AIR of GC in the SEER-covered population during the entire 40-year registration period (1973–2012), was 0.10/million individuals (Table 2). The incidence increased considerably by age having a peak after 65 years at 0.43/million (Fig. 1a). Overall, GC was more common in males, with an overall male-to-female ratio of 1.4. When restricting the registration period to the last 10 years (2003–2012), the overall AIR increased to 0.15 cases/million individuals, whereas the AIR for the elderly individuals (≥ 65 years) reached 0.61/million.

A statistically significant temporal increase in GC incidence emerged over the registration period (APC 7%, 95% CI 4.9–9.2; Table 2). The Joinpoint regression analysis revealed that the increase in GC incidence rates was pertained to the period 1973–2002, followed by a plateau in the subsequent last 10 years of registration (2003–2012). Figure 1b depicts the temporal changes in GC incidence by method of diagnosis showing an increase in incidence of both histologically and clinically/radiologically diagnosed tumors over the registration period. Of note, the increase was more abrupt for tumors diagnosed via clinical/radiological methods, as the incidence rates increased from 0 until 1987 to 0.07/million in the latest 5 year registration period (2008–2012), overcoming the rate for histological diagnoses (0.05/million).

Table 1 Distribution of the study variables among patients with gliomatosis cerebri in the SEER database (1973–2012)

Variables	Gliomatosis cerebri cases (n = 176)	
	N	%
Age at diagnosis (years)		
0–14	15	8.5
15–39	19	10.8
40–64	55	31.3
≥ 65	87	49.4
Mean ± SD (range)	57.6 ± 22.8 (1–98)	
Sex		
Male	95	54.0
Female	81	46.0
Race		
Caucasian	159	90.3
Non-Caucasian	17	9.7
Time period of diagnosis		
1973–1982	3	1.7
1983–1992	8	4.6
1993–2002	56	31.8
2003–2012	109	61.9
Place of residence		
Rural	12	6.8
Urban	164	93.2
Basis of diagnosis		
Microscopical confirmation	107	60.8
Non-microscopical diagnosis*	64	36.4
Death certificate only	5	2.8
Primary tumor location		
Cerebral hemispheres	50	28.4
Elsewhere in the CNS, specified	81	46.0
Brain, unspecified	45	25.6
Radiotherapy		
No	111	63.1
Yes	55	31.2
Missing	10	5.7
Surgery		
No	117	66.5
Yes	38	21.6
Missing	21	11.9

*Diagnosis based on clinical/radiological methods

Table 2 Age-adjusted incidence rates (AIR), male-to-female ratios (M:F) and annual percent changes (APC) of gliomatosis cerebri in the SEER database (1973–2012)

Age group	AIR[a]	M:F[b]	APC[c]
1973–2012			
0–14 years	0.04	1.9	+5.4 (−0.9; +12.1)
15–39 years	0.03	2.1	**+9.0 (+2.0; +16.5)**
40–64 years	0.10	1.1	**+7.8 (+3.6; +12.3)**
≥65 years	0.43	1.4	**+5.6 (+2.7; +8.5)**
Total (all ages)	0.10	1.4	**+7.0 (+4.9; +9.2)**
2003–2012			
0–14 years	0.06	1.4	−1.1 (−20.3; +22.7)
15–39 years	0.05	2.4	−7.1 (−22.7; +11.8)
40–64 years	0.15	1.0	−7.6 (−16.9; +2.8)
≥65 years	0.61	1.4	−3.6 (−11.7; +5.2)
Total (all ages)	0.15	1.3	−4.5 (−10.1; +1.5)

[a]AIRs are presented in cases per million individuals per year

[b]M:F ratios were calculated by dividing incidence rates for males and females

[c]Bold indicates statistical significance ($p < 0.05$)

Survival

Confirming the poor prognosis of the disease, overall 1, 2 and 5 year survival rates in the SEER dataset were 47% (95% CI 38–55%), 34% (95% CI 26–42%) and 18% (95% CI 11–26%), respectively, with a median overall survival of 9 months (range 1–298). Figure 2 depicts the Kaplan–Meier curves by the study variables. Age was identified as impacting on survival (p-log-rank trend test = 0.01; Fig. 2a) with the age groups of children (0–14 years) and AYAs (15–39 years) showing improved outcomes (5 year overall survival: 33%, 95% CI 10–59% and 35%, 95% CI 15–57%, respectively; median survival: 34 and 14.5 months, respectively), compared to middle-aged (40–64 years) and elderly (≥65 years) adults (5 year overall survival: 18%, 95% CI 7–32%, and 8%, 95% CI 2–19%, respectively; median survival 9.5 and 6 months, respectively). Furthermore, male gender (5 year overall survival: 23%, 95% CI 13–34% vs. 12%, 95% CI 5–22% among females; Fig. 2b) and primary tumor location in the cerebral hemispheres (5 year overall survival: 22%, 95% CI 10–37% vs. 15%, 95% CI 8–24% for tumors located in other brain areas; Fig. 2c), showed a tendency for increased survival rates, but no statistically significant effects emerged ($p = 0.11$ and 0.17, respectively). When restricting analyses to 2003–2012, 5 year survival increased to 22% (95% CI 13–32%), from 12% (95% CI 5–24%) for patients diagnosed in the period 1973–1992 (Fig. 2d), but the difference was not statistically significant ($p = 0.22$). Methods of diagnosis (Fig. 2e, $p = 0.44$) and treatment with radiation therapy or surgical excision were not associated with survival ($p = 0.53$; Fig. 2f).

Table 3 presents the results of the univariable and multivariable Cox proportional hazard models in the total sample and in the subsample of patients ≥15 years at diagnosis. The multivariable analysis confirmed increasing age (by 5 year-increment) to be a negative prognostic factor for GC, increasing the risk of death by 8 and 7%, respectively, in the two models. Furthermore, residence in a rural area at diagnosis was an additional risk factor for death., In the restricted dataset that excluded children, a marginally significant association of primary tumor location in the cerebral hemispheres with improved overall survival outcome was identified (HR 0.64, 95% CI 0.41–1.02). Lastly, among patients aged ≥15 years at diagnosis, more recent diagnostic time period was also associated with improved outcome. Race, method of diagnosis, receipt of radiation therapy and surgery did not seem to affect overall survival.

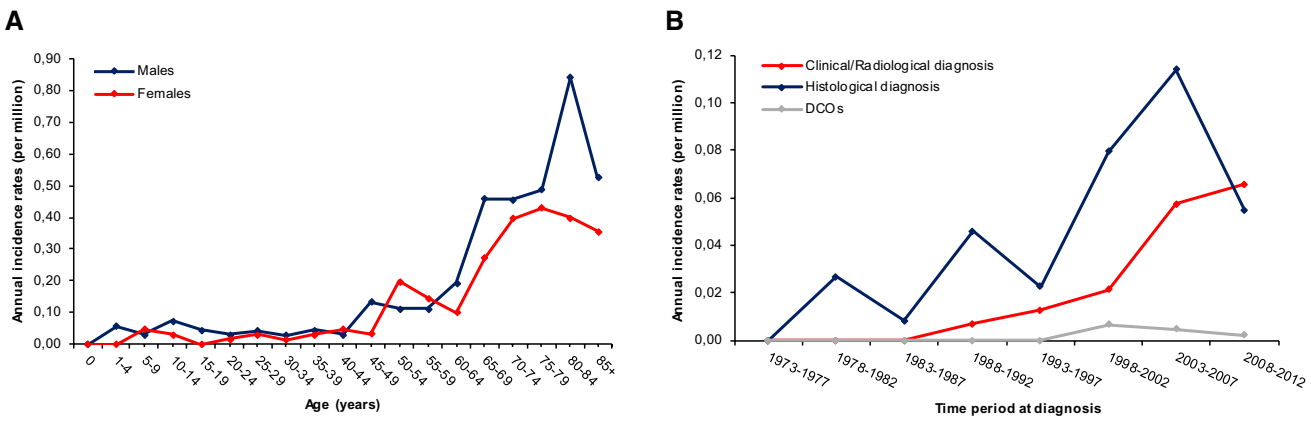

Fig. 1 Gliomatosis cerebri **a** annual incidence rates (per million individuals) by age group and gender and **b** temporal trends by method of diagnosis in the population covered by SEER (1973–2012)

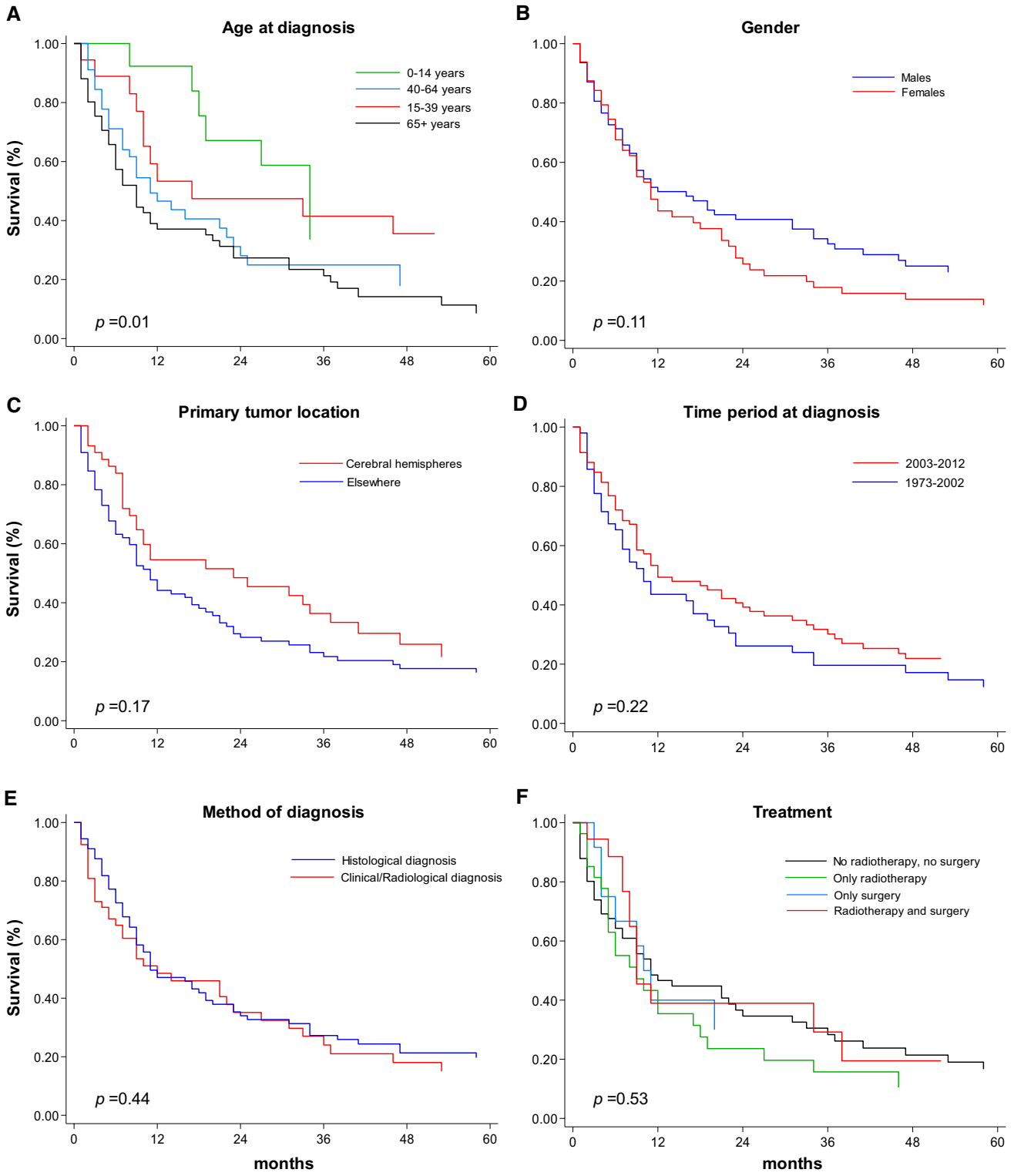

Fig. 2 Kaplan–Meier overall survival curves of patients with gliomatosis cerebri with available follow-up time in the SEER database (1973–2012) by **a** age group at diagnosis, **b** gender, **c** primary tumor location, **d** time period at diagnosis, **e** method of diagnosis, and **f** treatment. The *p* values are derived from the log-rank test

Table 3 Cox proportional hazard models for the effect of study variables on the survival of patients diagnosed with gliomatosis cerebri in the SEER database (1973–2012)

Variables	Overall dataset						Adolescents and adults (≥ 15 years)					
	Univariable analysis N = 143			Multivariable analysis N = 107			Univariable analysis N = 130			Multivariable analysis N = 99		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (5 year increment)	**1.07**	**1.03**	**1.12**	**0.001**	**1.08**	**1.03**	**1.12**	**< 0.001**	**1.06**	**1.01**	**1.12**	**0.03**	**1.07**	**1.01**	**1.13**	**0.03**
Gender (female vs. male)	1.36	0.92	1.99	0.12	1.25	0.85	1.85	0.27	1.36	0.92	1.99	0.12	1.14	0.75	1.72	0.54
Race (Caucasian vs. other)	1.28	0.66	2.45	0.47					1.43	0.72	2.85	0.31				
Place of residence (rural vs. urban)	**2.33**	**1.07**	**5.04**	**0.03**	**2.40**	**1.08**	**5.34**	**0.03**	2.13	0.98	4.64	0.06	2.24	0.99	5.08	0.05
Period of diagnosis (10 year increment)	0.91	0.67	1.24	0.53					**0.69**	**0.48**	**0.98**	**0.04**	**0.66**	**0.46**	**0.94**	**0.02**
Primary tumor location (Cerebral hemispheres vs. elsewhere)	0.75	0.50	1.14	0.18	0.78	0.51	1.20	0.26	**0.61**	**0.39**	**0.95**	**0.03**	0.64	0.41	1.02	0.06
Method of diagnosis (Clinical/radiological vs. histological)	1.15	0.77	1.73	0.49					1.12	0.74	1.70	0.60				
Radiotherapy (yes vs. no)	1.13	0.76	1.68	0.54					0.97	0.63	1.48	0.89				
Surgery (yes vs. no)	0.82	0.51	1.32	0.42					0.73	0.44	1.20	0.21				

Bold indicates statistical significance ($p < 0.05$)

Discussion

In this population-based study on the publicly available SEER data we have explored the epidemiologic features of GC, a rare glial tumor with distinct extensively infiltrating growth pattern. We estimated the overall annual incidence of GC to 1 case per 10 million individuals and we found a male preponderance and an increasing incidence among the elderly. Increasing trends in incidence during precedent decades stabilized in the most recent registration years and we noted a tendency for clinical/radiological methods of diagnosis to substitute the gold-standard histological diagnosis. The prognosis of GC was poor over time, with a 5 year survival rate of 18% and a median survival of 9 months. Increasing age and rural residence at diagnosis were identified as negative prognostic factors, whereas primary tumor location restricted in the cerebral hemispheres was marginally associated with improved outcome.

To our knowledge, this is the first study calculating the incidence of GC in in the general population setting confirming the rarity of the tumor. For the recent 2008–2012 period, we estimated an incidence rate of 0.15 cases per million individuals. Given that the respective annual incidence rates of malignant glioma and malignant CNS tumors in the USA were 6.13 and 7.23 cases per 100,000 individuals, respectively in that period [16], it can be deducted that GC represents only ~ 1/400 of all glial tumors and ~ 1/500 of all malignant CNS tumors. The male preponderance and the increase in incidence among the elderly follow the overall glioma patterns [16, 17].

An increase was noted in the incidence of GC over the study period, especially among the preceding decades. This is in line with previous reports showing increases for all brain tumors before 2000 followed by stable rates thereafter [17–22]. The introduction of magnetic resonance imaging (MRI) has been suggested as the main contributor to this observation [20]. Given the aggressiveness of CG, it could be assumed that many patients were undiagnosed in the era of restricted MRI availability. Furthermore, the establishment of GC as a distinct tumor entity, the subsequent increasing awareness of the clinicians, and potential registration gaps in the preceding years could contribute to the increase. The trends were stabilized in the last decade, but a continuous increase of the radiologically diagnosed GC was noted. More modern technologies, like the MR spectroscopy, may allow the radiological diagnosis of GC, and could underlie this increase [9, 23, 24].

The overall GC outcome in the SEER dataset was poor, with 1 and 5 year overall survival rates lower than 50 and 20%, respectively. Furthermore, median survival was 9 months, considerably lower than several single center

or multicenter case series that have been published, reporting median rates of 20 months or higher [5, 8, 25–34]. This may be expected, given that case series are inherently prone to several forms of bias. Particularly, selection bias is an important issue in tertiary center studies; it is more likely that these studies include patients at earlier stages of disease with indications of treatment. Furthermore, an underrepresentation of elderly patients in these studies, who have a much worse prognosis, could underlie the discrepancies. Even among the large retrospective study by Tallibert et al., including 291 GC patients that had been published until 2006 in the literature, median overall survival was 14.5 months, indicating selection bias in the published studies [7].

In our study, increasing age was the strongest risk factor for worse overall survival, which is in line with published literature [7, 25, 27]. Children with GC are known to have better outcome [35] and many studies exclude them from the overall analysis. Although male gender showed a tendency for improved outcome, this was attenuated after adjustment for the remaining confounding factors. According to Tallibert et al. the better outcome among men should be attributed to the higher proportion of oligodendroglial GC tumors that generally show longer survival rates [7]. As expected, tumors restricted to cerebral hemispheres had marginally better outcome, in comparison to tumors with deep structure or infratentorial expansion. On the other hand, radiotherapy and surgical excision of the tumor did not seem to impact on the outcome in this population-based study, as opposed to previous reports [25]. Nevertheless, the difficulties associated with collection of these variables by registration methods, the non-availability of other details regarding the treatment (i.e. inclusion or not of chemotherapy and type of radiation) as well as the lack of adjustment for other important clinical confounders should be accounted when interpreting these results. Lastly, the worse outcome associated with rural residence emphasizes the importance of health care access and has been also reported for other brain tumor entities [18, 36].

Carroll et al. recently published an article on GC outcome, based on a subsample of the same SEER data that we have used for this study [37]. Nevertheless, that study did not report incidence rates and focused on prognostic parameters. Furthermore, the authors included only cases diagnosed in the period 1999–2010, thus presenting a restricted proportion of the available data and excluded children from the analysis.

Our results should be interpreted under specific limitations, mainly related with the registration-based nature of the study. First, the lack of data on pathological diagnosis (histology and grade), as well as on important clinical variables, like functional performance at diagnosis, duration of symptoms before diagnosis, detailed tumor location and radiological factors, precluded adequate adjustment for confounding in the survival analysis. In the same context, there were no data on received chemotherapy that directly affects survival [7, 29, 33], whereas data on radiotherapy and surgery were rather superficial. Given the rapid increase in incidence, it is furthermore possible that several cases diagnosed in the preceding decades could have slipped registration, either due to missed diagnosis or due to flaws related to registration procedures. Lastly, during the extended 40 year time period, the medical practice regarding proper diagnosis and management of GC has changed, which could have affected the results of our study.

Conclusions

In conclusion, our study confirmed the rarity of GC and quantified for the first time its incidence in the population. A male preponderance and an increasing incidence among the elderly are identified, which are in line with the overall features of gliomas. Despite the fact that GC in not any more recognized as a distinct entity, its special features and its very poor prognosis indicate the need for differential management approaches. The prognosis in our study was considerably lower, compared to center-based case series highlighting the importance of population-based samples in exploration of prognostic factors in future research. Extension of registration to more detailed histological and molecular tumor characteristics could provide the necessary information for identification of markers with prognostic significance.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to declare.

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CLINICAL STUDY

Clinical, neuroimaging and histopathological features of gliomatosis cerebri: a systematic review based on synthesis of published individual patient data

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Abstract

Introduction Gliomatosis cerebri (GC) is a rare fatal widespread infiltrating CNS tumor. As consistent disease features have not been established, the tumor comprises a diagnostic challenge.

Methods We conducted a systematic literature search for published case reports and case series on patients with histologically confirmed GC. Clinical, diagnostic, neuroimaging, histopathological, and molecular data on individual or summary patient level were extracted and analyzed.

Results A total of 274 studies were identified, including 866 patients with individual-level data and 782 patients with summary data (58.9% males, mean age 43.6 years). Seizures (49.8%) were the most common presenting symptom followed by headache (35.9%), cognitive decline (32.2%), and focal motor deficits (32%). Imaging studies showed bilateral hemisphere involvement in 65%, infratentorial infiltration in 29.9% and a focal contrast-enhanced mass (type II GC) in 31.1% of cases. MRI (extensive hyperintensities in T2/FLAIR sequences) and MR spectroscopy (elevated choline, creatinine, and myoinositol levels; decreased NAA levels) showed highly consistent findings across GC patients. Low-grade and anaplastic astrocytoma were the most prevalent diagnostic categories, albeit features of any histology (astrocytic, oligodendroglial, oligoastrocytic) and grade (II–IV) were also reported. Among molecular aberrations, IDH1 mutation and MGMT promoter methylation were the most commonly reported. Increasing time elapsed from symptom onset to diagnosis comprised the only independent determinant of the extent of CNS infiltration.

Conclusion A distinct clinical, neuroimaging, histopathological, or molecular GC phenotype is not supported by current evidence. MRI and MR spectroscopy are important tools for the diagnosis of the tumor before confirmation with biopsy.

Keywords Gliomatosis cerebri · Glioma · Diagnostics · Clinical features · Brain tumor

Introduction

Gliomatosis cerebri (GC) is a brain tumor characterized by a diffuse infiltrating pattern of the central nervous system (CNS) and poor prognosis [1–3]. GC usually affects the CNS

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both hemispheres without affecting the normal architecture of the brain parenchyma and commonly extends to deeper structures, infratentorially or to the spinal cord [1, 2, 4, 5]. GC is a very rare neoplasm with an annual incidence rate of 1.5 cases per 10 million individuals, corresponding to ~ 1 out of 500 malignant CNS tumors, as recently reported in the SEER dataset during the 2003–2012 [6]. Despite its known aggressive behavior, there are many controversies regarding the clinical, histopathological and molecular hallmarks of GC. Until recently GC was considered a separate entity of a diffuse brain tumor affecting at least 3 cerebral lobes [7], but the 2016 WHO classification recognizes GC only as a special widespread and invasive growth pattern of the category of diffuse glioma [8], because of the lack of data supporting a distinct genetic profile [9, 10].

Due to its rarity, the majority of published studies on the tumor are small retrospective case series or case reports, underpowered to examine in depth the clinical features and neuroimaging findings as well as the histopathological and molecular characteristics of GC [1, 3, 11]. Hence, we considered it of interest to conduct a systematic review based on the synthesis of published individual patient data on GC in the biomedical literature. Specifically, we aimed to summarize: (i) the clinical presentation, (ii) the findings of the diagnostic procedures, (iii) the neuroimaging features, as well as patterns and determinants of tumor expansion in the CNS and (iv) the histopathological and molecular characteristics of the tumors.

Methods

The MOOSE [12] and PRISMA [13] guidelines as well as a pre-defined protocol that is publicly available (PROSPERO registration number: CRD42016050474) have been followed in conducting the systematic review. Specifically, two independent reviewers searched Pubmed and Scopus up to June 30th, 2017, using the terms gliomatosis AND cerebri. No language or publication year restrictions were applied. The reference lists of eligible studies and relevant reviews were additionally hand-searched ("snowball" procedure). At the end of the search, eligible studies were evaluated for potentially overlapping populations. We considered as eligible, case reports, case series, cohort and cross-sectional studies, as well as clinical trials of any type, presenting data on at least one patient with histologically diagnosed GC. In vitro and animal studies were excluded, as were studies of non-histologically confirmed GC cases.

Data of eligible studies at individual patient level from the descriptions provided in the publication were extracted (also detailed in Supplementary Table 1) in a pre-defined spreadsheet. Variables of interest were: age at diagnosis, sex, treatment center, clinical signs and symptoms before diagnosis, presence of a known genetic disease that predisposes to brain tumors, time from first symptom to diagnosis, method of diagnosis, details on neuroimaging findings at diagnosis (MRI, MR spectroscopy, CT, PET, or other), diseases included in the differential diagnosis, type of GC (I or II), topography of the tumor (bilateral/unilateral and supratentorial/infratentorial involvement, CNS regions invaded, and number of CNS regions affected), CSF puncture findings, EEG findings, histological characteristics (grade, histopathology), and molecular aberrations. Details on tumor topography were extracted either from the text or from the respective images provided in the article. If information on GC type was not directly available, we considered as type II those cases with clear radiological evidence of a well-defined focal lesion with contrast enhancement [3]. The number of CNS regions involved was determined as follows: the frontal, temporal, parietal, and occipital lobes as well as the basal ganglia including thalamus of both sides were regarded as separate regions each; the brainstem/cerebellum and spinal cord were also considered as separate regions [14]. In case series not presenting data at an individual patient level, the authors were contacted; only cumulative summary data about the aforementioned variables was extracted in case of no reply. Data were extracted by pairs of independent abstractors and were subsequently re-evaluated and harmonized by a single investigator.

Descriptive data analysis presented categorical variables as observed counts, whereas percentages and continuous variables were presented as mean or median values with the corresponding standard error or range, depending on the distribution of the variable. These summary statistics from individual data patients were then combined with descriptive data from studies presenting only summary data. Therefore, the numbers per variable are different depending on data availability in the included studies. Chi Square, Fisher's exact test, Mann–Whitney U, and t test, and one-way ANOVA were used to identify differences among subgroups.

Factor analysis was performed across 21 symptoms that were extracted to identify clustering of symptoms among patients with GC. The factorability of the data was evaluated using a Kaiser–Meyer–Olkin value. Weighted least squares estimation with mean and variance adjustment was used for factor extraction as the recommended extraction method for binary data and oblique rotation was conducted to allow for correlations between symptoms [15]. We determined the number of factors based on Eigenvalues > 1 and the screeplot and we considered only factors with loadings > 0.3 [16, 17]. Structure coefficients (correlations) > 0.30 were required for a symptom to be grouped under a symptom cluster and clinical plausibility was taken into account for the final grouping [16].

To identify predictors of GC progression at diagnosis, we examined in ordinal logistic regression analysis the

variables impacting on the number of CNS regions affected by the neoplasm. Variables showing an association at a p value < 0.20 in the univariable analysis, were additionally included in a multivariable model. Statistical significance level was set at p value < 0.05. All analyses were performed using SAS (v9.4, SAS Institute Inc) and IBM SPSS (v23.0, Armonk, NY: IBM Corp).

Results

Search strategy results

The successive steps for selection of eligible articles in this systematic review are summarized in Supplementary Fig. 1. The search strategy yielded 522 unique records. Of them, 274 articles (205 case reports and 69 case series) met the eligibility criteria and were included. Individual patient data were available and extracted for 866 patients with GC. Additionally, we extracted summary statistics for 782 patients, for whom individual level data were not presented. Two studies were excluded due to overlap on the populations and information provided. A description of the included studies and exclusion of overlapping studies or patients is provided in Supplementary Table 2.

Characteristics of the patients at diagnosis

Table 1 presents basic demographic, histological and neuroimaging characteristics. Males represented 58.9% of the study subjects. Mean age at diagnosis was 43.6 years and the median time elapsed from symptom onset to diagnosis was 4 months. Presence of a genetic syndrome predisposing to CNS tumors was recorded in only 1.5% of cases with only 3.7% of the tumors emerging as a secondary expansion of an already diagnosed glioma. Diagnosis identified by autopsy after death (7.5%) were substantially more frequent in studies published before 1995 (42.1% vs. 3.6%, $p < 0.001$). The majority of tumors (79.1%) were of astrocytic pathology and of grade II (52.1%). Regarding CNS infiltration at diagnosis, 29.9% of the cases already presented infratentorial involvement, 35% expanded bilaterally, and 28.9% affected 6 or more CNS regions. In almost one-third of the patients (31.4%), a focal contrast-enhanced mass was also evident in addition to the diffuse component, thus corresponding to GC type II phenotype.

Clinical features and tumor topography

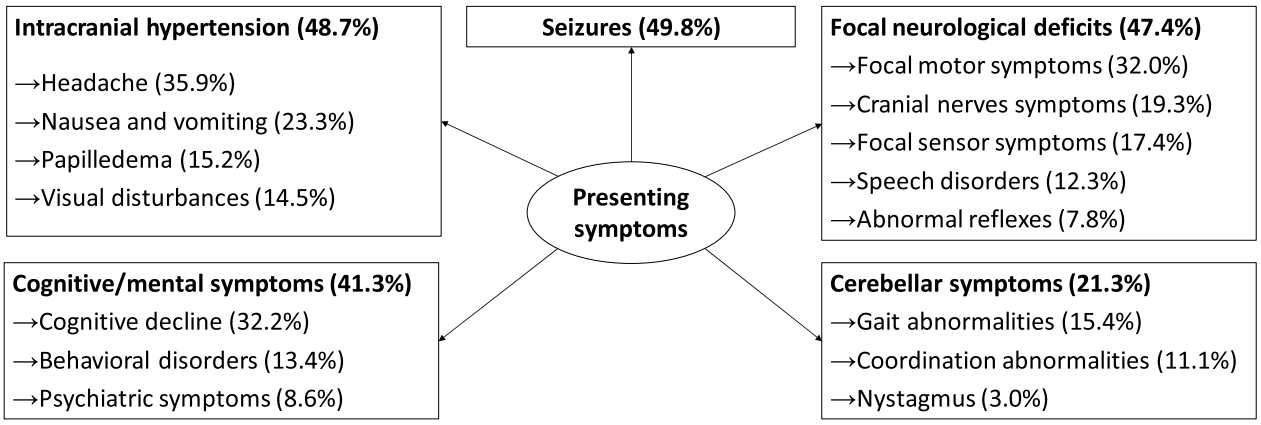
The factor analysis of the presenting symptoms identified 5 clusters of symptoms, as detailed in Fig. 1a, whereas the factor loadings following rotation are presented in Supplementary Table 3; the Kaiser–Meyer–Olkin value was 0.78, well above the > 0.60 threshold commonly used to assess factorability of data [15]. The most common symptom at diagnosis was seizures (49.8%) comprising a symptom group by itself and negatively correlated with all other clusters. Symptoms named under the category of "intracranial hypertension",

Table 1 Demographic, histological and imaging characteristics of 1648 patients with gliomatosis cerebri (GC)

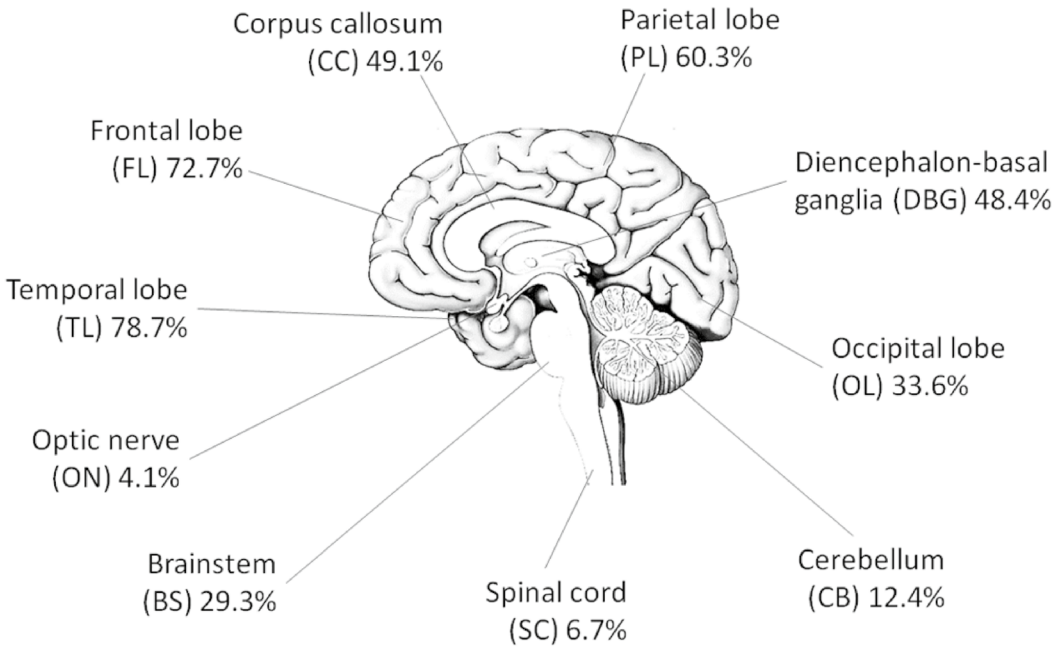
Variables	N (%)
Sex (N = 1519)	
Male	895 (58.9)
Female	624 (41.1)
Age at diagnosis, years (N = 794)	
0–14	141 (17.8)
15–39	225 (28.3)
40–64	307 (38.7)
≥ 65	121 (15.2)
Mean age, years (N = 1576)	43.6
Time from symptoms to diagnosis, months (N = 410)	
Median (IQR)	4 (1–12)
Genetic syndrome (n = 793)	
Yes	12 (1.5%)
No	781 (98.5%)
Primary tumor (N = 1111)	
Yes	1070 (96.3)
No	41 (3.7)
Diagnosis with autopsy (N = 828)	
Yes	62 (7.5)
No	766 (92.5)
Histology subtype (N = 1091)	
Astrocytoma	863 (79.1)
Oligodendroglioma	127 (11.6)
Oligoastrocytoma	101 (9.3)
Grade (N = 1291)	
II	673 (52.1)
III	480 (37.2)
IV	138 (10.7)
Tumor location (n = 690)	
Solely supratentorial	484 (70.1)
Expansion to infratentorial regions	206 (29.9)
Bilateral involvement (n = 942)	
Yes	612 (65.0)
No	330 (35.0)
CNS regions involved (N = 508)	
< 6	361 (71.1)
≥ 6	147 (28.9)
GC type (N = 1227)	
I	842 (68.6)
II	385 (31.4)

The number of GC patients with available data across the variables differ depending on missing information in the respective variables, due to not being reported in the published articles

A



B



C

Symptoms	FL	TL	PL	OL	CC	DBG	ON	CB	BS	SC
Seizures	•	•								
ICH symptoms					•		•			•
Focal neurological deficits						•			•	•
Cognitive/mental symptoms			•	•	•					
Cerebellar symptoms					•			•	•	•

Fig. 1 Clinical features and topography of gliomatosis cerebri. **a** Frequency of presenting signs and symptoms, and grouping based on factor analysis. **b** Central nervous system region involved in patients with gliomatosis cerebri. **c** Associations of symptom categories with topography (the dots correspond to statistically significant associations derived from chi-square test)

included headache, nausea/vomiting, papilledema, and visual disturbances and were present in 48.1% of the patients; 47.4% of the patients had focal motor or sensory deficits, cranial nerves paresis, speech disorders or abnormal reflexes, which were grouped together by factor analysis and were named under "focal neurological deficits". Cognitive,

behavioural or psychiatric symptoms were present in 41.3% of the GC patients, whereas 21.3% of the patients also presented "cerebellar symptoms" (gait or coordination abnormalities and nystagmus).

The most common regions affected by GC were the temporal (78.7%), frontal (72.7%), and parietal lobes (60.3%), followed by corpus callosum (49.1%), the diencephalon and basal ganglia (48.4%), and the occipital lobe (33.6%) (Fig. 1b). The brainstem was affected in 29.3% of the patients, cerebellum in 12.4%, and the spinal cord in 6.7%. Figure 1c presents the associations between symptoms and tumor topography. Seizures were associated with infiltration of the frontal and temporal lobes, whereas cognitive/mental symptoms with infiltration of the parietal and occipital lobes, and the corpus callosum. Expansion of the pathology to the corpus callosum was also associated with intracranial hypertension and cerebellar symptoms. Tumor expansion in the diencephalon and the basal ganglia, the brainstem and the spinal cord was associated with focal neurological deficits. Cerebellar symptoms were additionally associated with infiltration of the cerebellum, the brainstem and the spinal cord.

Presence of seizures decreased, whereas presence of cognitive/mental symptoms increased with increasing age (Supplementary Fig. 2A); as expected, intracranial hypertension symptoms were considerably lower in the older age group (65+ years). Time from symptoms to diagnosis was lowest in the younger and older age categories (0–14 and 65+ years) (Supplementary Fig. 2B). The older age group at diagnosis was also associated with higher prevalence of bilaterally expanded tumors (Supplementary Fig. 2C), whereas low-grade tumors were less common in the younger age group (0–14 years) (Supplementary Fig. 2D).

Neuroimaging findings and diagnostic workup

Evaluation of the neuroimaging reports showed that MRI provided the most consistent findings, with diffuse hyperintensities in T2 or FLAIR sequences being evident in the entireness (100%) of the 1237 GC cases with available MRI images (Table 2). Evaluation of the tumors post-contrast enhancement in the T1 sequence showed areas of focal enhancement in 35.7% of the patients. There were no reports from the perfusion and the diffusion MRI sequences. MR spectroscopy was also found to provide consistent findings across patients with GC. Specifically, the most common findings included increased choline, creatinine, and myo-inositol, and decreased NAA levels in the areas affected by the tumor for > 85% of the patients, whereas in > 90% the tumors also presented increased choline-to-creatinine and choline-to-NAA and decreased NAA-to-creatinine ratios. On the contrary, CT and PET were rather non-informative providing inconsistent findings across the patients. CT scanning, available in N = 199 showed a hypodense lesion in 58.5% of the GC tumors, but also an isodense and hyperdense lesion in 19.7% and 6.4% of the cases, respectively, whereas no CT lesion could be found in 15.4% of the tumors. Finally, among 35 patients with available PET imaging, 45.7% showed hypermetabolic, 42.9% hypometabolic tumor activity and 11.4% no lesion.

Table 2 Imaging findings of gliomatosis cerebri tumors at diagnosis

Neuroimaging method	Findings	%
MRI (N = 1237)	Diffuse hyperintensities	100
	Contrast enhancement	35.7
MR spectroscopy (N = 84)	Increased choline	95.1
	Increased creatinine	88
	Decreased NAA	97.6
	Increased choline:creatinine ratio	93.7
	Increased choline:NAA ratio	97.6
	Decreased NAA:creatinine ratio	97.9
	Increased myoinositol	88.9
CT (N = 199)	Hypodense lesion	58.5
	Isodense lesion	19.7
	Hyperdense lesion	6.4
	No lesion	15.4
PET (N = 35)	Hypometabolic lesion	45.7
	Hypermetabolic lesion	42.9
	No lesion	11.4

NAA N-acetylaspartate

For 86 patients, there were available data on CSF examination. Of them, 18.6% showed pleiocytosis, whereas cytology was positive for malignant cells in only 3 patients (3.5%). High protein and low glucose levels were found in 13 (15.1%) and 4 patients (4.7%), respectively. Among 62 patients with available electroencephalogram, abnormal findings were found in 50 (80.7%), but they were not consistent across patients. Based on reports from the original studies, GC most commonly mimicked infectious encephalitis or meningitis, autoimmune demyelinating diseases and cerebrovascular events (Supplementary Table 4).

Histopathological features and molecular aberrations

Low-grade astrocytoma (38.2%) and anaplastic astrocytoma (33.5%) comprised the most common histopathological diagnoses of GC. In 15.3% of the GC tumors, the histopathological features were in line with glioblastoma. Oligodendroglioma, anaplastic oligodendroglioma, oligoastrocytoma and anaplastic oligoastrocytoma corresponded each to 3–4% of the total number of cases. More than two-thirds of the cases across all histological subtypes corresponded to GC type I, except for glioblastoma; 73% of all glioblastomas

had a neuroimaging picture of GC type II. MGMT promoter methylation (41%) and IDH1 mutations (36.5%) were the most common molecular aberrations.

Table 3 presents the molecular aberrations of the tumors according to grade and histology. IDH1 mutations were more common in tumors of lower grade. Furthermore, IDH1 mutations, MGMT promoter methylation and codeletion of the 1p and 19q chromosomes were significantly more common among oligodendroglial and oligoastrocytic tumors, when compared to astrocytomas.

Determinants of tumor expansion

Lastly, we examined determinants of tumor expansion at diagnosis in an ordinal regression model (Table 4). A younger age at diagnosis (0–14 years), cognitive/mental symptoms, cerebellar symptoms, increasing duration of the period between symptom onset and diagnosis, increasing grade and presence of an oligodendroglial component were associated with increasing number of infiltrated CNS regions. Molecular aberrations of the tumor were not found to be associated with number of affected CNS regions, but the number of patients with available molecular characteristics were low. In the multivariable analysis (N = 134), only the duration between symptom onset and diagnosis remained statistically significant (OR per month: 1.024, 95% CI 1.010–1.038).

Discussion

Individual level data of published GC cases have been incorporated and analyzed in the single dataset of this comprehensive overview of the clinical, neuroimaging, histopathological, and molecular characteristics of the disease. Five distinct clusters of symptoms (seizures, intracranial hypertension, focal deficits, cognitive/mental symptoms, cerebellar symptoms) depending on infiltrated CNS regions have been identified. No consistent pattern in terms of histology and molecular aberrations was found with the majority of cases sharing common features with other gliomas. Despite the diagnostic challenges, MRI and MR spectroscopy, as opposed to CT and PET, provide highly consistent findings in the vast majority of GC patients that may guide diagnostic workup. Time elapsed from symptoms to diagnosis was the only independent determinant of CNS tumor expansion at diagnosis.

The vast majority of the GC tumors were astrocytomas followed by oligodendrogliomas or oligoastrocytomas and one out of two of low-grade behavior. In line with other gliomas, IDH1 mutations and MGMT promoter methylation were the most common molecular aberrations GC [18–20]. These aberrations in addition to the co-deletion of the 1p and 19q chromosomes were associated with an oligodendroglial tumor component, as has been previously described for low-grade diffuse gliomas [18]. In agreement are also our results with recent studies on DNA methylation and copy number profiling data reporting that the majority of the tumors could be classified under other molecularly defined subgroups of non-GC diffuse gliomas in both children [9] and adults [10].

Gliomatosis cerebri might comprise a diagnostic challenge for the clinician. No particular pattern of clinical features was highly consistent. Although seizures were the most commonly reported symptom, they were found in only half of the patients. The majority of the patients presented with more than one symptoms out of five identified clusters dependent on the affected CNS regions. The time elapsed from symptoms to diagnosis was minimal among children; independently of presenting symptoms, the lengthiest time was associated with a more widespread invasion of the CNS, thus highlighting the importance of a timely diagnosis and management of this fatal malignancy.

Table 3 Molecular characteristics of gliomatosis cerebri tumors by grade and histology

Genetic alteration N (%)	Grade			p-value	Histology		*p*-value
	II	III	IV		Astrocytic	Oligodendroglial involvement	
IDH1 mutations	52/120 (43.3)	28/87 (32.2)	5/26 (19.2)	**0.04**[a]	29/127 (22.8)	28/48 (58.3)	**< 0.0001**
TP53 mutations	5/41 (12.2)	2/53 (3.8)	4/24 (16.7)	0.18[a]	8/90 (8.9)	1/10 (10.0)	0.99[a]
PTEN mutations	1/17 (5.9)	1/20 (5.0)	1/16 (6.3)	0.99[a]	3/30 (10.0)	0/5 (0.0)	0.62[a]
EGFR amplification	0/20 (0.0)	1/22 (4.6)	2/16 (12.5)	0.27[a]	3/49 (6.1)	0/9 (0.0)	0.60[a]
MGMT promoter methylation	9/24 (37.5)	15/41 (36.6)	10/17 (58.8)	0.26	24/70 (34.3)	10/13 (76.9)	**0.006**[a]
1p19q deletion	6/36 (16.7)	4/44 (9.1)	0/20 (0.0)	0.12[a]	5/105 (4.8)	8/10 (80.0)	**< 0.0001**[a]

Bold indicates statistically significant results ($p < 0.05$)

EGFR epidermal growth factor receptor, *IDH1* isocitrate dehydrogenase 1, *MGMT* O6-methylguanine DNA methyltransferase, *PTEN* phosphatase and tensin homolog, *TP53* tumor protein p53

[a]*p*-values derived from Fisher's exact test

Table 4 Determinants of central nervous system invasion in gliomatosis cerebri

Variables	Univariable		Multivariable	
	N	OR (95% CI)	N	OR (95% CI)
Age at diagnosis, years	437		134	
0–14		**1.74 (1.12–2.69)**		0.98 (0.43–2.22)
15–39		Ref		Ref
40–64		1.50 (0.98–2.30)		1.46 (0.69–3.12)
≥ 65		1.44 (0.82–2.53)		1.21 (0.43–3.36)
Sex	437			
Male		Ref		
Female		1.11 (0.80–1.55)		
Clinical presentation	361			
Seizures		1.01 (0.70–1.46)		
Focal deficit		1.26 (0.88–1.82)		
Cognitive/mental symptoms		**1.74 (1.20–2.52)**		1.00 (0.53–1.89)
ICH symptoms		1.15 (0.80–1.66)		
Cerebellar symptoms		**2.12 (1.38–3.26)**		1.62 (0.82–3.21)
Time from symptoms to diagnosis	249		134	
Months (increment)		**1.014 (1.004–1.025)**		**1.024 (1.010–1.038)**
Histology subtype	338		134	
Astrocytoma		Ref		Ref
Oligodendroglial involvement		**1.88 (1.11–3.20)**		1.28 (0.54–3.06)
Grade	314		134	
II		Ref		Ref
III		**1.69 (1.11–2.57)**		1.54 (0.79–2.99)
IV		**2.21 (1.19–4.12)**		2.25 (0.89–5.70)
Molecular characteristics				
IDH1 mutations	51	0.39 (0.09–1.65)		
TP53 mutations	62	1.31 (0.37–4.59)		
PTEN mutations	25	7.93 (0.51–124.09)		
EGFR amplification	10	Ref		
MGMT promoter methylation	37	0.31 (0.08–1.22)		
1p/19q codeletion	67	2.25 (0.56–9.10)		

Bold indicates statistically significant results ($p < 0.05$)

Univariable and multivariable ordinal regression analysis with number of CNS regions affected as dependent variable

EGFR epidermal growth factor receptor, *IDH1* isocitrate dehydrogenase 1, *MGMT* O6-methylguanine DNA methyltransferase, *PTEN* phosphatase and tensin homolog, *TP53* tumor protein p53

Furthermore, individual studies included in this systematic review commonly reported mistaking with other diseases, mainly viral encephalitis, inflammatory demyelinating diseases and cerebrovascular pathology. Several characteristics might be helpful for the clinician in case GC is suspected, such as the MRI findings always showing hyperintensities in the T2 or the FLAIR sequences that might be associated with contrast enhancement in T1. Unfortunately, no data were available on the presentation of GC in the diffusion and perfusion-weighted imaging. MR spectroscopy might facilitate the differential diagnosis before proceeding to biopsy, particularly, increased choline, creatinine and myoinositol levels, as opposed to decreased NAA observed in almost 90% of the GC patients [4, 21, 22]. On the contrary, other diagnostic procedures, such as CT did not consistently provide specific findings neither did PET in the limited number of cases available. Lastly, CSF examination was normal in most of the cases and EEG showed inconsistent and non-specific abnormalities.

Besides inherent difficulties in diagnosing GC, other factors related to socioeconomic status of the patients and health care delivery might be related with an early diagnosis and might significantly impact on outcome [6, 23].

Taillibert et al. in 2006 had made the first effort to examine the characteristics of 296 GC patients [24] as contrasted to the 1648 included in the current systematic review

springing from intensive search of two databases and the snowball process without restrictions on publication date or language; to maximize information, a rigorous contact with authors was carried out. A comprehensive analysis was also employed comprising individual and cumulative data of patients. This large dataset allowed examination of a number of associations between disease characteristics, including demographics, clinical patterns, neuroimaging features, histopathological characteristics and molecular aberrations using alternative methods of analyses.

On the negative side, a systematic review can only be as good as its comprising studies. First, data derived only from case reports and case series were usually conducted within specialized centers which might be a source of selection bias. Indeed, the age distribution of the SEER data, which we recently analyzed, was considerably different from the current dataset, as the mean age of the patients was 57.6 years, as opposed to 43.6 years in the current dataset, and it had a much higher proportion of elderly (≥ 65 years) patients (49% vs. 15% in the current dataset) [6]. These age differences, when compared to the population-based setting, might be related to the selective exclusion of frail elderly patients with GC in case series, which raises concerns of selection bias, and necessitates a cautious interpretation of the findings.

Second, some of the studies were published several years ago, and thus the definitions of histological subtypes might not comply with the current WHO classification, as specifically demonstrated for tumors with 1p/19q deletion that would by definition today be regarded as oligodendrogliomas. Third, the aim of individual case series might be different than the presentation of collective characteristics of the disease with variable impact on the results. For example, although astrocytomas are by far the most common GC histological subtype [25, 26], some of the included case series reported a preponderance of oligodendrogliomas [27], or even oligoastrocytomas [28]. Fourth, several analyses were performed by necessity only in subgroups of patients, because of missing data for the specific variables in the respective publications. Fifth, the individual studies did not avail data on serial MRI assessments that would enable the investigation of the role of the growth velocity of the tumor in the associations between time-to-diagnosis and extension of the tumor in the CNS. Finally, some patients, especially in older publications were diagnosed only by autopsy, thus precluding their inclusion in meaningful analyses regarding the clinical presentation and neuroimaging findings.

In conclusion, this large systematic review synthesizing published individual patient data regarding features of GC argues against a distinct entity in terms of histopathological and molecular characteristics but emphasizes the importance of MRI and MR spectroscopy in the diagnostic evaluation of patients with suspected GC towards a timely diagnosis associated with a more restricted CNS infiltration. Future large clinical cancer registration and multicenter collaborations offering better quality data might provide additional information about this fatal malignancy.

Compliance with ethical standards

Conflict of interest No author has anything to declare.

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Prognostic Factors and Survival of Gliomatosis Cerebri: A Systematic Review and Meta-Analysis

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■ BACKGROUND: **Gliomatosis cerebri (GC) is a fatal diffusely infiltrating glioma. Because of its rarity, only scarce evidence is available regarding outcome predictors and the proper management of GC.**

■ METHODS: **Reported studies of patients with histologically confirmed GC were systematically reviewed and individual patient-level data (n = 523) extracted. Multivariable Cox proportional hazard models were fit for overall survival (OS) and progression-free survival (PFS).**

■ RESULTS: **The median OS and PFS were 13 and 10 months, with 5-year rates of 18% and 13%, respectively. Age ≥65 years at diagnosis (hazard ratio for OS [HR_{OS}], 2.32; 95% confidence interval [CI], 1.62–3.31), high-grade tumor (HR_{PFS} for grade III, 1.57; 95% CI, 1.02–2.40; HR_{PFS} for grade IV, 1.74; 95% CI, [0.98–3.10), GC type II (HR_{OS}, 1.49; 95% CI, 1.12–1.98; HR_{PFS}, 1.56; 95% CI, 1.04–2.34), more central nervous system (CNS) regions involved (HR_{OS}, 1.09; 95% CI, 1.01–1.18), focal neurological deficits (HR_{OS}, 1.41; 95% CI, 1.07–1.86), cerebellar symptoms (HR_{PFS}, 2.20; 95% CI, 1.42–3.39), more symptoms at presentation (HR_{OS}, 1.21; 95% CI, 1.05–1.40), Karnofsky performance scale score <70 (HR_{OS}, 3.58; 95% CI, 1.73–7.39; HR_{PFS}, 4.48; 95% CI, 1.39–14.4), magnetic resonance imaging contrast enhancement (HR_{OS}, 1.48; 95% CI, 1.12–1.96; HR_{PFS}, 1.74; 95% CI, 1.18–2.55), symmetric bilateral CNS invasion (HR_{OS}, 1.42; 95% CI, 1.03–1.96), and high proliferation index (Ki-67 >5%; HR_{OS}, 2.32; 95% CI, 1.11–4.86) were independent predictors of poor outcomes. In contrast, seizure occurrence (HR_{OS}, 0.77; 95% CI, 0.60–1.00; HR_{PFS}, 0.68; 95% CI, 0.47–0.95), isocitrate dehydrogenase 1 mutation (HR_{OS}, 0.16; 95% CI, 0.05–0.49), and O6-methylguanine-DNA-methyltransferase promoter methylation (HR_{OS}, 0.23; 95% CI, 0.09–0.59) were associated with prolonged survival. Chemotherapy and surgical resection were associated with improved outcomes, but radiotherapy, whether monotherapy or combined with chemotherapy, was not superior to chemotherapy alone.**

■ CONCLUSIONS: **In the largest study to date on GC, we have identified clinical, imaging, and molecular outcome predictors that are similar to other gliomas and highlight the beneficial effect of chemotherapy and surgical resection, when feasible, on outcomes.**

INTRODUCTION

Gliomatosis cerebri (GC) is a rare diffuse glial tumor of controversial definition and treatment.[1] The 2007 World Health Organization classification recognized GC as a

Key words
- Brain tumor
- Gliomatosis cerebri
- IDH1 mutation
- MGMT promoter methylation
- Prognosis

Abbreviations and Acronyms
CI: Confidence interval
CNS: Central nervous system
GC: Gliomatosis cerebri
HR: Hazard ratio
IDH1: Isocitrate dehydrogenase 1
IPD: Individual patient data
MGMT: O6-Methylguanine-DNA-methyltransferase
OS: Overall survival
PFS: Progression-free survival
SEER: Surveillance, Epidemiology, and End Results

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separate entity, defined as an extensively infiltrative diffuse glioma involving ≥3 cerebral lobes but not affecting the normal histopathological architecture of the brain parenchyma.[2] Because no distinct genetic profile of GC has been identified,[3] the most recent 2016 World Health Organization classification included GC as only a special widespread and invasive growth pattern of diffuse glioma.[4] The histopathologic features of GC can correspond to grade II to IV astrocytomas, oligodendrogliomas, or mixed tumors; however, the prognosis is poorer compared with that of other gliomas of the same grade.[3,5] Using the neuroradiological findings, GC can be divided into variants that present with diffuse neoplastic growth without a clear solid tumor component (type I GC) and variants with an obvious mass, in addition to the diffuse component (type II GG).[1,6-8]

The tumor diffusely infiltrates into the central nervous system (CNS), can affect any region, and has been characterized by a very poor prognosis. Clinical studies have reported 5-year survival rates of 25%–30%, with a median survival of ~20 months.[3,5,9-17] However, the most recent U.S. Surveillance, Epidemiology, and End Results (SEER) data analysis for the period 1973–2012 showed even worse outcomes. In particular, 50% 1-year and 20% 5-year survival rates were found, with a median survival of only 9 months.[18] Although the tumor was first described in 1938, the cause for its uniquely aggressive behavior remains to be explored.[19] Owing to its rarity, data on the prognostic factors and management have been based on small case series with restricted patient numbers.[3,5,9-17] In particular, no consensus has been reached on the standard of care for GC, because patients with GC have traditionally been excluded from glioma trials.[1]

Therefore, we systematically reviewed the reports of patients with histologically confirmed GC and extracted individual patient data (IPD) to assess and quantify the effect of independent prognostic factors and different treatment options and combinations on overall survival (OS) and progression-free survival (PFS).

METHODS

The present systematic review was conducted in accordance with the MOOSE (meta-analyses of observational studies in epidemiology) guidelines[20] and a predefined protocol (publicly available in PROSPERO: CRD42016050474).

Study Selection

Two independent reviewers searched PubMed and Scopus to July 31, 2017, using a combination of the terms "gliomatosis" AND "cerebri." No language or publication year restrictions were applied. The reference lists of the eligible studies and relevant reviews were also manually searched ("snowball" procedure), and eligible studies were evaluated for overlapping data. We considered case reports, case series, cohort and cross-sectional studies and clinical trials of any type that had presented data on ≥1 patient with histologically diagnosed GC to be eligible. In vitro and animal studies and studies of nonhistologically confirmed GC cases were excluded.

Data Abstraction

Data from the eligible studies on an individual patient level were extracted to a predefined spreadsheet using the related descriptions in the reported studies (**Supplemental Table 1**). The variables of interest included clinical and diagnostic data, as previously described,[21] and follow-up data, including response to treatment, progression status, survival status, time to progression, and time to death.

The response to treatment was examined radiologically and clinically. For the evaluation of the radiological response, we used the criteria by Macdonald et al.,[22] harmonized for GC by Glas et al.,[11] where possible. In particular, a partial response required a 50% reduction of contrast-enhancing lesions or a reduction of T2-weighted hyperintensities by ≥25%. A complete response required complete regression of all T1-weighted and T2-weighted lesions. Because of the restricted numbers of GC tumors with a complete response, these categories were merged for the purposes of the present study. Disease progression was defined as >25% increase of contrast-enhancing or T2-weighted hyperintense lesions; all other findings were considered to indicate stable disease. If detailed data were not available, the definitions used in the individual studies were used to classify the response, whether stable or progressive disease. Regarding the clinical response to treatment, demonstration of improvement of the symptoms at diagnosis (remission or a decrease in the symptom severity) was considered a response. Stable disease was defined as no change in the clinical findings after treatment. Progressive disease was defined as deterioration of the symptoms (new symptoms or increased severity of already present symptoms).

The investigators of case series with missing data at an individual patient level were contacted. In the case of no reply, cumulative information for the evaluated variables was extracted and was used instead. We extracted the hazard ratios (HRs) and 95% confidence intervals (CIs) for the prognostic factors for PFS and OS. If the HRs were not directly presented, they were calculated from the Kaplan-Meier curves.[23] Pairs of independent abstractors performed the abstraction of data, which were subsequently re-evaluated and harmonized by a single investigator in the case of disagreement.

Statistical Analysis

Patients with GC that had not been diagnosed at autopsy with follow-up information available were included in the primary analyses of IPD. The effect of potential prognostic factors on PFS and OS was initially examined using univariable Cox regression analysis. Next, where possible, we combined the HRs derived from the IPD analysis with the summary statistics from the reported studies in a meta-analysis. Heterogeneity in the meta-analyses was evaluated using the I^2 and Cochran Q statistic. We used fixed effects models for the meta-analyses if no heterogeneity were present and random effects models in the case of heterogeneity (I^2 ≥50% or Cochran Q-derived $P < 0.10$).

Subsequently, multivariable analyses were performed after selecting a core set of variables to be included in the models. The selection was determined from reported data for prognostic factors, the univariable analysis findings, availability (missing values, <30%), and collinearity of the candidate variables. Thus, the core Cox proportional hazards model included age, sex, histological type, tumor grade, GC type, and number of CNS regions affected. Imputation of missing values was used for sex, histological type, tumor grade, GC type, and CNS regions affected, with consideration

Table 1. Demographic, Histological, and Imaging Characteristics of 523 Patients with Gliomatosis Cerebri

Variable	Patients (*n*, %)
Sex	
Male	285 (57.2)
Female	213 (42.8)
Missing	35 (6.6)
Mean age ± SD at diagnosis (years)	37.6 ± 21.7
Age group (years)	
0–14	115 (22.0)
15–39	152 (29.1)
40–64	191 (36.5)
≥65	65 (12.4)
Missing	0 (0.0)
Histological subtype	
Astrocytoma	358 (87.3)
Oligodendroglioma	25 (6.1)
Oligoastrocytoma	27 (6.6)
Missing	114 (21.4)
Grade	
II	164 (41.8)
III	166 (42.4)
IV	62 (15.8)
Missing	132 (24.8)
CNS regions involved	
Median (IQR)	4 (3–6)
<6	267 (72.8)
≥6	100 (27.2)
Missing	156 (29.8)
GC type	
I	268 (67.2)
II	131 (32.8)
Missing	124 (23.3)
Interval from symptom onset to diagnosis (months)	
Median (IQR)	4 (1–11)
Missing	289 (54.2)
Tumor location	
Solely supratentorial	166 (63.1)
Expansion to infratentorial regions	97 (36.9)
Missing	261 (49.0)
Bilateral involvement	
Yes	210 (68.6)
No	96 (31.4)
Missing	218 (40.9)
Symmetrical involvement	
Yes	246 (67.0)
No	121 (33.0)
Missing	156 (29.8)

SD, standard deviation; CNS, central nervous system; IQR, interquartile range; GC, gliomatosis cerebri.

of age, survival time, survival status, PFS, progression status, and the remaining imputed variables. Logistic regression analysis was used for imputations of the binary variables of sex, histological type, and GC type. In contrast, multinomial and ordinal regression analyses were performed for grade and CNS regions affected, respectively. Twenty iterations were performed. After the multiple imputations, the additional variables were additively and alternatively introduced into the model.

To examine the effect of first-line treatment on OS and PFS, the 3 variables (i.e., chemotherapy, radiotherapy, surgery) were concurrently included in the model. In addition, a new variable entailing the combination of treatments was alternatively introduced into the model. In the sensitivity analyses, we excluded all patients who had not received any treatment to enable comparisons among the groups. Finally, in a multinomial logistic regression model, we explored the potential predictors of a radiological response to treatment.

The statistical significance level for all analyses was set at $P < 0.05$. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA), and STATA, version 13.0 (StataCorp, College Station, Texas, USA) software programs.

RESULTS

The process of study selection has been previously described.[21] In brief, 274 eligible reports were identified from the literature search, with each describing ≥1 patient with GC (**Supplemental Table 2**). Individual level data could be extracted for 866 patients (IPD). Of these 866 patients, GC had not been diagnosed at autopsy for 523 who also had follow-up information available. Summary data were available for another 782 patients. HRs reported or calculated for the later data set were included in the meta-analysis, along with the effect estimates of the IPD data set, depending on data availability.

The descriptive data for the 523 GC patients in the IPD data set are listed in **Table 1**. Males constituted 57.2% of the cases, and the mean age at diagnosis was 37.6 ± 21.7 years. The vast majority of the tumors had astrocytic pathologic features (87.3%), 41.8% were grade II, and 42.4% were grade III. Regarding tumor expansion, 27.2% of the tumors affected ≥6 CNS regions, 32.8% were GC type II, 36.9% had expanded to infratentorial locations, 31.4% involved both hemispheres, and 33% had symmetrical involvement of the 2 hemispheres.

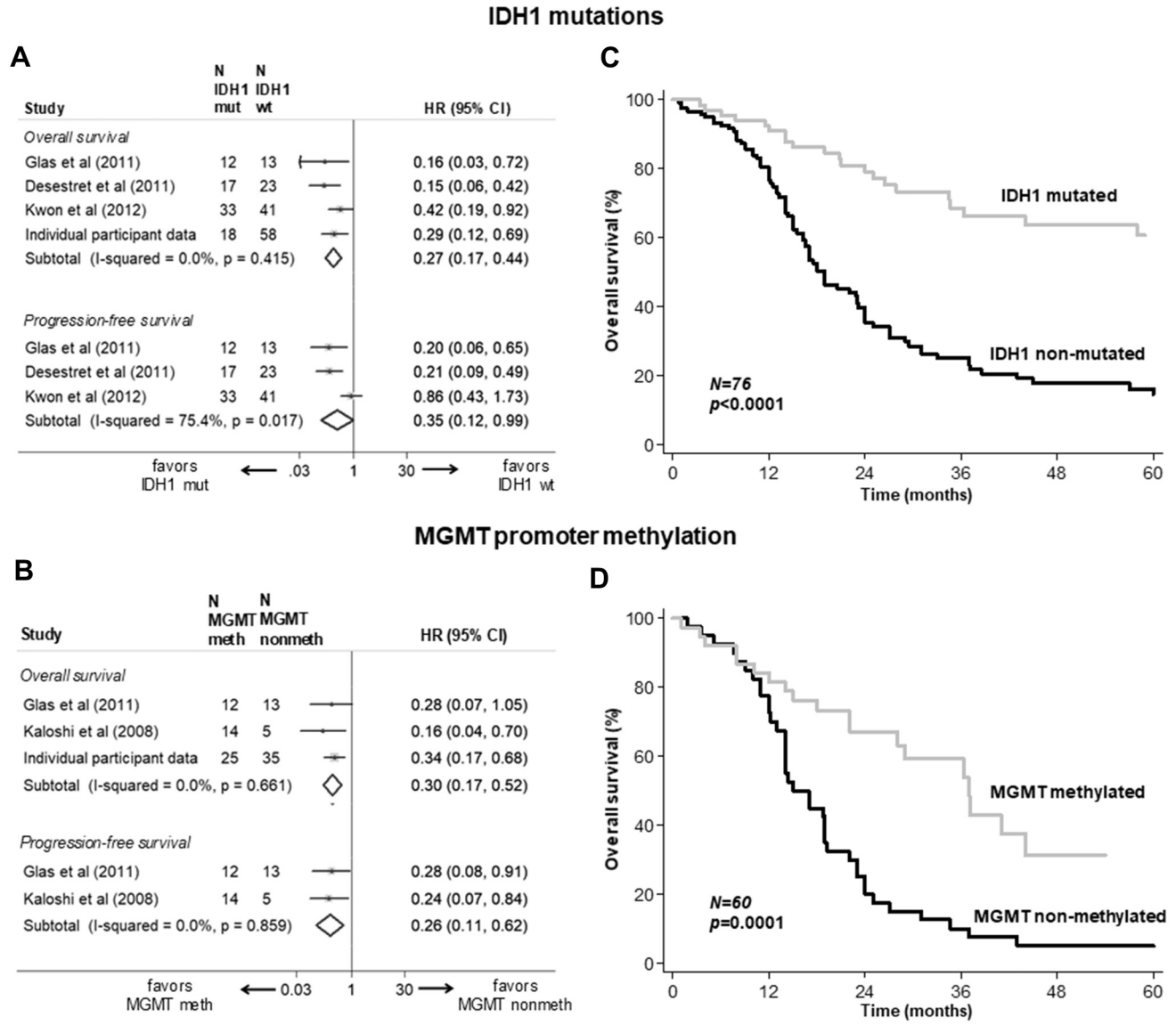

Figure 1. Effect of isocitrate dehydrogenase 1 (IDH1) mutation and methylation of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter on prognosis of patients with gliomatosis cerebri. Meta-analysis of the crude effects of (**A**) IDH1 mutation and (**B**) methylation of the MGMT promoter on overall and progression-free survival and (**C, D**) Kaplan-Meier curves for overall survival. CI, confidence interval; HR, hazard ratio; mut, mutated; wt, wild type.

The Kaplan-Meier survival curves showed 1-year, 5-year, and 10-year OS rates of 61% (95% CI, 56%–65%), 18% (95% CI, 14%–22%), and 10% (95% CI, 6%–14%). The corresponding PFS rates were 53% (95% CI, 45%–60%), 13% (95% CI, 5%–25%), and 4% (95% CI, 0%–17%). The median OS and PFS were 13 months (interquartile range, 6–24) and 10 months (interquartile range, 4–20), respectively.

Prognostic Factors

The results of the univariable analysis of the IPD for OS and PFS are presented in Supplemental Table 2. The results of the meta-analysis of the univariable IPD analysis of studies presenting only summary statistics are shown in Supplemental Figures 1 and 2. The results of the IPD analysis were in line with the results from the other studies and were also confirmed by the meta-analysis results. Isocitrate dehydrogenase 1 (IDH1) mutation and methylation of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter were associated with a decreased risk of death (HR, 0.27; 95% CI, 0.17–0.44; HR, 0.30; 95% CI, 0.17–0.52, respectively) and progression (HR, 0.35; 95% CI, 0.23–0.99; HR, 0.26; 95% CI, 0.11–0.62, respectively; Figure 1).

The results of the multivariable analysis are listed in Table 2. Age at diagnosis of ≥65 years was strongly associated with

Table 2. Multivariable Cox Regression Analysis for Overall and Progression-Free Survival

	OS			PFS		
Variable	**Patients (*n*)**	**HR (95% CI)**	***P* Value**	**Patients (*n*)**	**HR (95% CI)**	***P* Value**
Core model*	523			224		
Age (years)						
0–14		1.28 (0.95–1.73)	0.10		1.01 (0.65–1.56)	0.98
15–39		Reference			Reference	
40–64		1.13 (0.86–1.49)	0.39		0.98 (0.65–1.50)	0.94
≥65		2.32 (1.62–3.31)	<0.001†		1.68 (0.96–2.96)	0.07
Sex (female vs. male)		1.06 (0.85–1.33)	0.59		1.08 (0.76–1.52)	0.68
Histological type (astrocytoma vs. other)		1.43 (0.94–2.17)	0.09		1.28 (0.74–2.20)	0.37
Grade						
II		Reference			Reference	
III		1.17 (0.91–1.51)	0.22		1.57 (1.02–2.40)	0.04†
IV		1.21 (0.83–1.77)	0.32		1.74 (0.98–3.10)	0.06
GC type (II vs. I)		1.49 (1.12–1.98)	0.007†		1.56 (1.04–2.34)	0.03†
CNS regions affected (1 lobe more)		1.09 (1.01–1.18)	0.04†		1.02 (0.93–1.12)	0.67
Additional variables alternatively introduced						
Clinical factors						
Time from symptoms to diagnosis (1 month more)	234	0.99 (0.98–1.00)	0.12	143	0.99 (0.98–1.01)	0.51
Seizures (yes vs. no)	382	0.77 (0.60–1.00)	0.05†	202	0.68 (0.47–0.95)	0.02†
Focal deficit (yes vs. no)	357	1.41 (1.07–1.86)	0.02†	202	1.40 (0.98–2.00)	0.06
Cognitive/mental symptoms (yes vs. no)	382	1.26 (0.95–1.67)	0.11	202	1.27 (0.88–1.84)	0.21
ICH symptoms (yes vs. no)	383	1.23 (0.94–1.60)	0.14	202	0.76 (0.54–1.09)	0.13
Cerebellar symptoms (yes vs. no)	358	1.38 (0.98–1.95)	0.06	203	2.20 (1.42–3.39)	<0.001†
Number of symptoms (1 category more)	357	1.21 (1.05–1.40)	0.009†	202	1.10 (0.91–1.33)	0.32
KPS score (<70 vs. ≥70)	75	3.58 (1.73–7.39)	0.001†	40	4.48 (1.39–14.4)	0.01†
Response to treatment						
Response	153	0.16 (0.08–0.30)	<0.001†		NA	NA
Stable disease		0.33 (0.19–0.59)	<0.001†		NA	NA
Progressive disease		Reference			NA	NA
Imaging factors						
Contrast enhancement on MRI (yes vs. no)	391	1.48 (1.12–1.96)	0.006†	196	1.74 (1.18–2.55)	0.005†
Infratentorial involvement (yes vs. no)	263	1.19 (0.85–1.68)	0.31	154	1.33 (0.85–2.06)	0.21
Bilateral involvement (yes vs. no)	306	1.19 (0.87–1.63)	0.96	174	1.32 (0.83–2.09)	0.24
Symmetric invasion (yes vs. no)	285	1.42 (1.03–1.96)	0.03†	154	1.15 (0.73–1.81)	0.54
Molecular characteristics						
Ki-67 (≥5% vs. <5%)	93	2.32 (1.11–4.86)	0.02†	53	2.70 (0.75–9.70)	0.13
IDH1 mutation (yes vs. no)	76	0.16 (0.05–0.49)	0.001†	4	NA	NA
TP53 mutations (yes vs. no)	71	0.98 (0.34–2.86)	0.97	5	NA	NA
PTEN mutations (yes vs. no)	34	0.92 (0.06–14.8)	0.95	0	NA	NA

Continues

Table 2. Continued

	OS			PFS		
Variable	**Patients (*n*)**	**HR (95% CI)**	***P* Value**	**Patients (*n*)**	**HR (95% CI)**	***P* Value**
EGFR amplification (yes vs. no)	27	4.52 (0.39–51.9)	0.22	2	NA	NA
MGMT promoter methylation (yes vs. no)	60	0.23 (0.09–0.59)	0.002†	4	NA	NA
1p/19q Deletion (yes vs. no)	91	0.44 (0.14–1.37)	0.16	2	NA	NA

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; GC, gliomatosis cerebri; CNS, central nervous system; ICH, intracerebral hemorrhage; KPS, Karnofsky performance scale; NA, not applicable; MRI, magnetic resonance imaging; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine-DNA-methyltransferase.
*The analysis was conducted after multiple imputations for the variables included in the core model.
†Statistically significant.

worse OS (HR, 2.32; 95% CI, 1.62–3.31) and marginally with PFS (HR, 1.68; 95% CI, 0.96–2.96). Sex and histological type were not associated with OS or PFS. However, the effect of grade was only associated with PFS (HR for grade III vs. II, 1.57; 95% CI, 1.02–2.40; HR for grade IV vs. III, 1.74; 95% CI, 0.98–3.10). A type II GC was associated with worse OS (HR, 1.49; 95% CI, 1.12–1.98) and PFS (HR, 1.56; 95% CI, 1.04–2.34). Invasion of an increasing number of CNS regions was also associated with worse OS (HR per 1 more region, 1.09; 95% CI, 1.01–1.18). Among the clinical symptoms, an increased risk of death was found for patients presenting with focal neurological deficits (HR, 1.41; 95% CI, 1.07–1.86), and the presence of cerebellar symptoms was associated with worse PFS (HR, 2.20; 95% CI, 1.42–3.39). In contrast, the presence of seizures was associated with prolonged OS (HR, 0.77; 95% CI, 0.60–1.00) and PFS (HR, 0.68; 95% CI, 0.47–0.95). An increasing number of symptoms (including seizures, focal neurological deficits, intracranial hypertension symptoms, cerebellar symptoms, and cognitive/mental symptoms) was also an independent predictor of worse OS (HR, 1.21; 95% CI, 1.05–1.40). Data were limited ($n = 75$ for OS and $n = 40$ for PFS) regarding a strong association of a Karnofsky performance scale score <70 with poor outcomes (HR_{OS}, 3.58; 95% CI, 1.73–7.39; HR_{PFS}, 4.48; 95% CI, 1.39–14.4, respectively). As expected, a treatment response (HR, 0.16; 95% CI, 0.08–0.30) or stable disease (HR, 0.33; 95% CI, 0.19–0.59) compared with progressive disease was strongly associated with increased OS. Contrast enhancement on magnetic resonance imaging (MRI) studies was also a negative predictor for OS and PFS, and bilateral symmetric involvement of the 2 hemispheres was negatively associated with OS (HR, 1.42; 95% CI, 1.03–1.96). Among the histopathological and molecular characteristics, increased tumor proliferation, defined by Ki-67 positivity in >5% of the tumor cells, was associated with worse OS (HR, 2.32; 95% CI, 1.11–4.86). Finally, multivariable analysis confirmed IDH1 mutation (HR, 0.16; 95% CI, 0.05–0.49) and MGMT promoter methylation (HR, 0.23; 95% CI, 0.09–0.59) as positive prognostic factors.

Effect of Treatment on Outcome

The univariable analysis showed a positive association for chemotherapy, radiotherapy, and surgical resection with OS (**Supplemental Table 3**). The Kaplan-Meier survival curves for the different treatment modalities are shown in **Figure 2A** and clearly demonstrate that chemotherapy, radiotherapy, and surgical resection of the GC tumor were associated with prolonged survival. However, no statistically significant differences were found across the different chemotherapy regimens (protocols with and without temozolomide), radiotherapy approaches (focal tumor or whole brain radiotherapy), and extent of resection (partial or extensive/subtotal). The multivariable analyses (**Figure 2B, C**), adjusted for sex, age, histological type, tumor grade, GC type, and CNS regions affected showed that chemotherapy and surgical resection were associated with greater OS and PFS. In contrast, no independent positive association with radiotherapy was identified. Only whole brain radiotherapy was associated with PFS. No considerable differences between low- and high-grade GC tumors were noted regarding the effect of treatment on OS and PFS, with the exception of focal tumor radiotherapy, which was positively associated only for low-grade tumors.

We subsequently examined the effect of combined treatment modalities on survival (**Table 3**). Compared with patients who had received no treatment at all, all combinations of therapy were associated with prolonged OS and PFS. Next, we excluded those patients who had received no treatment to avoid confounding by treatment indication, because those patients who had not received treatment might have been more likely to have more progressive and advanced tumors. Setting chemotherapy alone as the reference group, no other treatment combination showed statistically significant improved outcomes. In contrast, radiotherapy alone and radiotherapy plus chemotherapy were associated with worse OS and surgery alone was associated with lower PFS.

Finally, we explored the predictors of a radiological response to treatment (**Supplemental Table 4**). Astrocytic pathological type

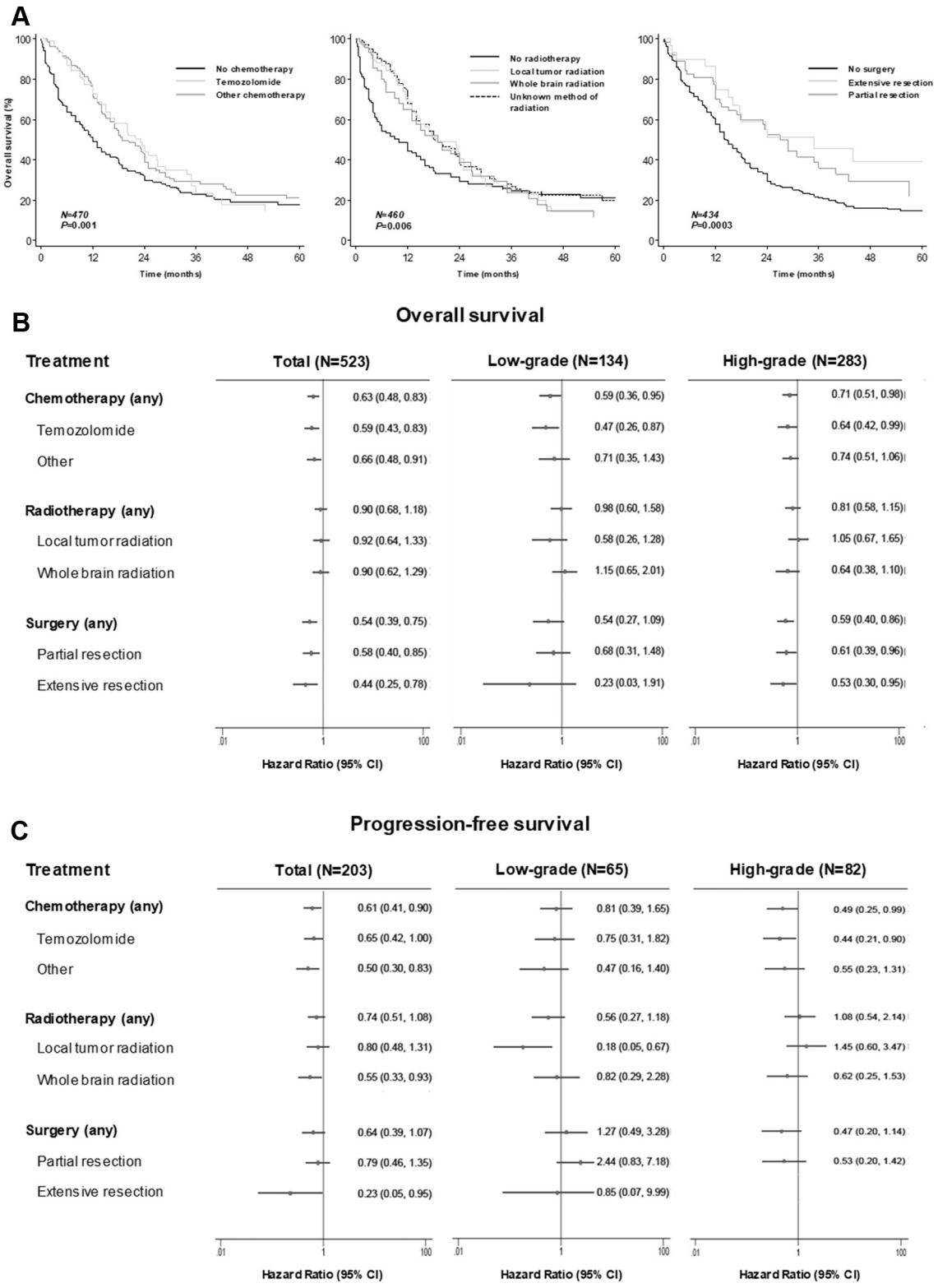

Figure 2. Effect of treatment on overall and progression-free survival for patients with gliomatosis cerebri. (**A**) Kaplan-Meier curves for overall survival stratified by type of chemotherapy, radiotherapy, and surgery. (**B, C**) Effect of specific treatments on overall and progression-free survival derived from multivariable Cox regression analyses adjusted for age, sex, histological type, tumor grade, GC type, and number of central nervous system lobes affected. CI, confidence interval.

Table 3. Multivariable Cox Regression Analysis for Effects of Treatment Combinations on Overall and Progression-Free Survival*

	OS			PFS		
Variable	**Patients (*n*)**	**HR (95% CI)**	***P* Value**	**Patients (*n*)**	**HR (95% CI)**	***P* Value**
First-line treatment						
No treatment	78	Reference		28	Reference	
Chemotherapy alone	35	0.33 (0.19—0.58)	<0.001†	27	0.29 (0.15—0.58)	0.001†
RT alone	95	0.68 (0.48—0.98)	0.04†	48	0.44 (0.24—0.79)	0.007†
Surgery alone	14	0.51 (0.24—1.09)	0.07	8	1.12 (0.44—2.88)	0.81
Chemotherapy, RT	116	0.54 (0.39—0.77)	0.001†	60	0.42 (0.24—0.74)	0.005†
Surgery, chemotherapy	8	0.39 (0.15—1.01)	0.06†	2	0.19 (0.02—1.51)	0.16
Surgery, RT	21	0.33 (0.16—0.67)	0.002†	8	0.15 (0.04—0.67)	0.01†
Surgery, chemotherapy, RT	50	0.26 (0.16—0.43)	<0.001†	22	0.20 (0.09—0.44)	<0.001†
Exclusion of no-treatment group						
Chemotherapy alone	35	Reference		27	Reference	
RT alone	95	2.28 (1.28—4.05)	0.005†	48	1.56 (0.81—3.00)	0.19
Surgery alone	14	1.50 (0.62—3.63)	0.37	8	4.11 (1.52—11.14)	0.005†
Chemotherapy, RT	116	1.74 (1.01—3.01)	0.047†	60	1.62 (0.89—2.96)	0.11
Surgery, chemotherapy	8	1.28 (0.45—3.60)	0.64	2	0.73 (0.09—5.96)	0.77
Surgery, RT	21	1.06 (0.46—2.45)	0.90	8	0.49 (0.11—2.21)	0.36
Surgery, chemotherapy, RT	50	0.79 (0.42—1.48)	0.46	22	0.69 (0.31—1.51)	0.35

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; RT, radiotherapy.
*Results adjusted for age, sex, histological type, grade, gliomatosis cerebri type, and number of central nervous system lobes affected.
†Statistically significant.

was associated with a better response to treatment in both stable (OR, 0.17; 95% CI, 0.04—0.81) and progressive disease (OR, 0.21; 95% CI, 0.05—0.81). In contrast, the presence of cerebellar symptoms, greater number of presenting symptoms, and invasion of more CNS regions were associated with a greater risk of stable disease instead of a treatment response.

DISCUSSION

In the present comprehensive systematic review and IPD meta-analyses, we examined the predictors of outcome and the effect of different treatment modalities on GC prognosis. Older age at diagnosis, high-grade pathological disease, widespread CNS invasion, symmetric bilateral brain involvement, GC type II, MRI contrast enhancement, focal neurological deficits, cerebellar symptoms, greater symptom burden, functional impairment at diagnosis, and a high proliferation index were all negative predictors of a good outcome. In contrast, the presence of seizures at diagnosis, IDH1 mutation, and methylation of the MGMT promoter was associated with prolonged OS and PFS. Chemotherapy and surgical tumor resection, when feasible, were independently associated with improved outcomes. However, radiotherapy, either as monotherapy or combined with chemotherapy, was not superior to chemotherapy alone.

Small case series had previously reported the presence of IDH1 mutation and MGMT promoter methylation as favorable prognostic factors for patients with GC[11,13,24]; however, our study has demonstrated that their prognostic significance is independent of other tumor characteristics. Both molecular alterations have been well-established favorable prognostic factors for gliomas in general.[25,26] Regarding other molecular characteristics previously examined in patients with GC[11,24] and other gliomas,[27] some indications have been found that 1p/19q codeletion and amplification of the *EGFR* gene might be favorable and unfavorable prognostic factors, respectively. These results were not, however, confirmed in our multivariable analysis, possibly owing to inadequate power. Similarly, the analyses showing that presence of an oligodendroglial component might be independently associated with improved outcomes were rather underpowered. A higher grade was associated with a greater risk of progression, and a high proliferation index (Ki-67 >5%) was further identified as an independent predictor of poor outcomes.

Regarding the neuroimaging indicators, a type II GC, considered to indicate focal progression of type I GC (characterized by a solid tumor component and diffuse component),[1,14] and contrast enhancement on MRI (most often noted with type II GC), were predictors of poor outcomes. More widespread tumor expansion, including a greater number of CNS regions affected and bilateral

symmetrical involvement, were associated with worse OS[11] but did not seem to affect PFS. A low Karnofsky performance scale score, an increasing burden of symptoms, and the presence of focal neurological deficits at diagnosis were independent unfavorable predictors of outcome, indicating the importance of the clinical parameters. In contrast, the presence of seizures at baseline was associated with prolonged OS and PFS, although previously attributed to either a more favorable molecular profile of epileptogenic tumors or an antitumor effect of antiepileptic drugs.[28] Finally, in line with the SEER data, patients aged ≥65 years at GC diagnosis had significantly shorter OS.[18]

The results from the present study have confirmed the very poor prognosis of patients with GC. The median PFS and OS was only 10 months and 13 months after diagnosis. The latter was considerably shorter than the ≥20 months reported by several case series[3,9-17] but longer than the 9 months reported in the SEER data set.[18] This can be expected, given that case series conducted in tertiary centers are prone to selection bias, owing to the inclusion of patients with specific treatment indications and the exclusion of elderly patients with a worse prognosis.

Regarding treatment, radiotherapy, either as monotherapy or combined with chemotherapy, was associated with worse outcomes compared with chemotherapy alone. Nevertheless, local tumor radiotherapy showed an independent beneficial effect that was restricted to low-grade GC. The beneficial role of chemotherapy we found is in accordance with individual studies showing prolonged survival with regimens that included temozolomide.[11,12,16,29] Albeit in our study, temozolomide did not seem to confer better outcomes than those with other chemotherapy regimens. In the present analysis, surgical tumor resection, either partial or subtotal, was associated with prolonged OS for the small number of included patients, in accordance with the data from a Chinese case series.[30]

The present study had several methodologic strengths. First, we exploited the maximum available data reported on GC by performing a comprehensive systematic review of the reported studies, intensively extracting data at an individual level, and using multiple imputations to account for missing data in the multivariate analyses. Second, this approach allowed our study to include the largest sample size of patients with GC to date. Third, in addition to the earlier small case series reported and the population-based analysis of the U.S. SEER data we recently reported, the present individual level meta-analysis approach enabled us to evaluate a number of prognostic factors previously reported for other gliomas, in addition to the rare GC entity. Finally, it was possible to explore how different treatment modalities are associated with the disease outcomes, which could guide clinical practice and the design of future clinical trials, including patients with GC.

Our study also had limitations, including the heterogeneity across the included studies in terms of patient characteristics, experience of the center in the treatment of patients with GC, and treatment selection. Furthermore, the sources of data collection for many case reports and case series were usually tertiary specialized centers, which could have introduced a selection bias. Also, despite the extensive literature search and data extraction, some of the subgroups analyzed were small because the results for all the characteristics could not be extracted from the available data. Finally, but not least, the present approach did not allow us to explore the characteristics of treatment options in more detail, including different dosages, different number of cycles, and serial administration at different points compared with coadministration of different modalities. Thus, the rather broad and heterogeneous treatment categories we examined might have precluded meaningful conclusions for clinical practice.

CONCLUSIONS

In the present IPD meta-analysis, we have reported the profile of outcome predictors for GC. We identified clinical, neuroimaging, histological, and molecular factors that were independently associated with the prognosis for patients with GC. However, these did not result in a specific prognostic pattern that differentiates this rare tumor from previously described outcome predictors for other gliomas. Of these, IDH1 mutation and MGMT promoter methylation are favorable prognostic factors, but neuroimaging markers of focal progression and extensive CNS infiltrations have been associated with worse outcomes. Despite reservations on confounding by indication, chemotherapy and, when feasible, surgical resection of the tumor have been associated with prolonged survival, with no evidence found for a beneficial effect of radiotherapy, either alone or combined with chemotherapy. Future multicenter trials should also include patients with GC to determine the most appropriate management of this fatal malignancy.

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Original Article

Gliomatosis Cerebri Among Children and Adolescents: An Individual-Patient Data Meta-analysis of 182 Patients

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Abstract

Background: Gliomatosis cerebri is a rare but fatal widespread infiltrating central nervous system tumor. We aimed to describe diagnostic and prognostic features of gliomatosis cerebri among children and adolescents. **Methods:** We conducted a systematic literature review for published case reports and case series on patients with histologically confirmed gliomatosis cerebri and extracted data on an individual patient level for those aged 0-18 years. Multivariable Cox proportional hazard models were fit for overall survival. **Results:** Following screening of 274 published studies, 182 gliomatosis cerebri patients (63% males) aged 0-18 years with individual-level data available were identified. The most common presenting symptoms were seizures (52%), focal motor deficits (36%), and headache (30%). Imaging showed bilateral hemisphere involvement in 60%, infratentorial infiltration in 39%, and a focal contrast-enhanced mass (type II gliomatosis cerebri) in 27% of cases. Anaplastic astrocytoma was the most common histologic subtype of pediatric gliomatosis cerebri, whereas MGMT promoter methylation, IDH1 mutations, and codeletion of 1p/19q were less common molecular aberrations, as compared to adult gliomatosis cerebri. In the multivariable analyses, age at diagnosis >4 years, extended central nervous system infiltration, coordination abnormalities, and cognitive decline were predictors of worse outcome. Conversely, IDH1 mutations were associated with prolonged overall survival. Chemotherapy and extended surgical resection were associated with improved outcome, whereas radiotherapy was not associated with overall survival and was inferior to chemotherapy alone. **Conclusion:** Gliomatosis cerebri among children and adolescents presents distinct histopathologic and molecular features compared to adults. However, similar associations of chemotherapy, and, when feasible, extended surgical resection, with favorable outcomes were noted among the 2 age groups.

Keywords

gliomatosis cerebri, glioma, children, pediatric, survival, brain tumor.

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Gliomatosis cerebri is a diffuse infiltrating central nervous system tumor with extremely poor prognosis.[1-3] Gliomatosis cerebri usually affects both brain hemispheres without affecting the normal architecture of the brain parenchyma and commonly extends to deeper structures, infratentorially or to the spinal cord.[1,2,4,5] Gliomatosis cerebri is a very rare neoplasm with an annual incidence rate of 1.5 cases per 10 million individuals, corresponding to $\sim$1 of 500 malignant central nervous system tumors, as recently reported in the Surveillance, Epidemiology, and End Results (SEER) registry data.[6] Although until recently considered a separate entity,[7] the 2016 World Health Organization (WHO) classification recognizes gliomatosis cerebri only as a special widespread and invasive growth pattern of the category of diffuse glioma,[8] because of the lack of data supporting a distinct genetic profile.[9,10] However, the etiology

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of the highly aggressive progression of tumors with a gliomatosis cerebri pattern remains to be explored.

Recently, we gathered available evidence for gliomatosis cerebri by performing a systematic review and an individual-patient data meta-analysis on 866 gliomatosis cerebri patients that have been described in biomedical literature.[11,12] Using this approach, it was possible for the first time to study to such an extent the diagnostic features of the disease, its prognostic factors, and the impact of treatment on outcome. Given the well-established differences in the molecular basis and in the epidemiology of brain tumors in children, as compared to the brain tumors later in life,[13,14] in this study, we aimed to elaborate data from the abovementioned data set[11,12] to describe the diagnostic and prognostic features of gliomatosis cerebri among pediatric patients and explore whether they differ from adult gliomatosis cerebri tumors.

Methods

Data for this study come from an individual-patient data meta-analysis of 866 patients with gliomatosis cerebri that have been described in biomedical literature. The methodologic details of the search strategy and data extraction followed by that systematic review and meta-analysis have been previously described.[11,12] Briefly, following the MOOSE[15] and PRISMA[16] guidelines (publicly available predefined protocol in PROSPERO [registration number: CRD42016050474]), we identified all previous studies (case reports, case series, cohorts, cross-sectional studies, clinical trials) presenting data on at least 1 patient with histologically diagnosed gliomatosis cerebri. Afterwards, we extracted demographic, clinical, neuroimaging, and other diagnostic, histologic, molecular, treatment-related, and follow-up data at an individual patient level. For the purpose of the current study, we restricted our analysis to 182 gliomatosis cerebri patients aged $\leq$18 years at diagnosis.

Gliomatosis cerebri was considered a primary tumor when there was no history of previous central nervous system malignancy, whereas secondary gliomatosis cerebri was a tumor developed after a diagnosis of another glioma. Gliomatosis cerebri was defined as type I, when only a diffuse gliomatosis cerebri pattern was identified in neuroimaging, and as type II, when there was clear radiologic evidence of a well-defined focal lesion with contrast enhancement.[3] The number of central nervous system regions involved was determined as follows: the frontal, temporal, parietal, and occipital lobes as well as the basal ganglia including thalamus in both sides were each regarded as separate regions; the brainstem/cerebellum and spinal cord were also considered as separate regions.[17] Survival time was calculated as the period from diagnosis to death. Only first-line treatment was examined.

We first compared clinical and tumor characteristics at baseline, between patients aged $\leq$18 and >18 years at diagnosis, so as to examine whether pediatric gliomatosis cerebri entails unique features. Chi-square, Fisher exact test, and Mann-Whitney *U* test were used to identify differences between patients aged $\leq$18 and >18 years at diagnosis. Specifically, chi-square test was used for all comparisons of categorical variables, unless one of the compared categories included $\leq$5 observations; on that occasion, Fisher exact test was preferred. For the only continuous variable (time from symptoms to diagnosis), a Mann-Whitney *U* test was used because it was not normally distributed. Subsequently, for the survival analysis, we included only gliomatosis cerebri patients who had available follow-up information and were not post mortem diagnosed (N = 141).

The effect of potential prognostic factors on overall survival was initially examined in multivariable Cox proportional hazard models. A core set of variables, determined by literature reports for prognostic factors,[12] findings of the univariable analysis, data availability (missing values <30%) and collinearity of the candidate variables, was included in the multivariable models. These variables were age, sex, histology, grade, gliomatosis cerebri type (I or II), and number of central nervous system regions affected. Multiple imputation was performed for missing values in sex, histology, grade, gliomatosis cerebri type, and affected central nervous system regions by considering age, survival time, and the remaining imputed variables. Logistic regression analysis was used for imputations of the binary variables sex, histology, and gliomatosis cerebri type, whereas multinomial and ordinal regression analyses were undertaken for grade and central nervous system regions affected, respectively. Twenty iterations were performed. Following multiple imputations, the additional potentially prognostic risk factors (clinical, imaging, and molecular characteristics, as detailed in Table 2) were additively and alternatively introduced in the model.

To examine the effect of first-line treatment on overall survival, 3 variables (chemotherapy, radiotherapy, surgery) were concurrently included in the aforementioned model. Furthermore, a new variable entailing the combination of treatments was alternatively introduced in the model. For this analysis, only treatment combinations administered to >10 patients with gliomatosis cerebri were considered and we excluded all patients who did not receive any treatment to enable comparisons between the groups; chemotherapy alone was used as the reference category in this analysis.

Statistical significance level for all analyses was set at a 2-sided *P* value <.05. All analyses were performed by SAS (v9.4, SAS Institute Inc) and Stata (v13.0, StataCorp).

Results

Table 1 presents the main tumor characteristics for included patients and comparisons between gliomatosis cerebri patients aged $\leq$18 and >18 years. As compared to adult gliomatosis cerebri, pediatric gliomatosis cerebri was more commonly associated with a genetic syndrome predisposing to central nervous system tumors, was less likely to be an astrocytic tumor, and was more commonly a higher-grade tumor. Furthermore, pediatric gliomatosis cerebri tumors were less likely to expand bilaterally to both hemispheres and were more likely to be type I gliomatosis cerebri tumors. As depicted in Figure 1, the most common histologic subtype of pediatric gliomatosis cerebri was anaplastic astrocytoma, as opposed to low-grade astrocytoma in adult patients. Lastly, MGMT promoter methylation, IDH1 mutations, and codeletion of 1p/19q were less common molecular aberrations in pediatric gliomatosis cerebri, as compared to adult gliomatosis cerebri.

Temporal (75%), frontal (69%), and parietal lobes (55%) were the most common central nervous system regions affected in pediatric gliomatosis cerebri tumors, followed by diencephalon and basal ganglia (49%), brainstem (33%), occipital lobe (31%), and corpus callosum (31%) (Figure 2). A total of 39% of the tumors expanded to infratentorial central nervous system

Table 1. Demographic, Histologic, and Imaging Characteristics of Children and Adult Patients With Gliomatosis Cerebri.[a]

Variables	Pediatric GC (0-18 y)	Adult GC (>18 y)	*P* value
Sex			.13[b]
Male	114 (62.6)	330 (56.3)	
Female	68 (37.4)	256 (43.7)	
Time from symptoms to diagnosis, mo			.69[c]
Median (IQR)	5 (1.3-9)	5 (1.5-13)	
Genetic syndrome			<.001[d]
Yes	9 (5.2)	3 (0.6)	
No	164 (94.8)	470 (99.4)	
Primary tumor			.99[d]
Yes	139 (97.2)	440 (97.1)	
No	4 (2.8)	13 (2.9)	
Diagnosis with autopsy			.34[b]
Yes	11 (6.0)	50 (8.2)	
No	171 (94.0)	562 (91.8)	
Histology subtype			.008[b]
Astrocytoma	101 (82.8)	404 (90.0)	
Oligodendroglioma	11 (9.0)	20 (4.4)	
Oligoastrocytoma	10 (8.2)	25 (5.6)	
Grade			<.001[b]
II	29 (25.4)	203 (46.8)	
III	67 (58.8)	156 (35.9)	
IV	18 (15.8)	75 (17.3)	
Tumor location			.87[b]
Solely supratentorial	79 (61.2)	195 (62.1)	
Expansion to infratentorial regions	50 (38.8)	119 (37.9)	
Bilateral involvement			.003[b]
Yes	79 (59.8)	260 (73.7)	
No	53 (40.2)	93 (26.3)	
CNS regions involved			.19[b]
<6	119 (74.8)	226 (69.1)	
≥6	40 (25.2)	101 (30.9)	
GC type			.04[b]
I	108 (73.0)	276 (63.6)	
II	40 (27.0)	158 (36.4)	

Abbreviations: CNS, central nervous system; GC, gliomatosis cerebri; IQR, interquartile range.
[a]The results are presented as n (%), unless otherwise stated. Two-sided *P* values are presented throughout.
[b]Chi-square test.
[c]Mann-Whitney *U* test.
[d]Fisher exact test.

regions, whereas 60% affected bilaterally both cerebral hemispheres. Regarding clinical presentation of gliomatosis cerebri, seizures were the most common symptom, occurring in 52% of the patients, followed by focal motor deficits (36%) and headache (30%) (Figure 2). Seizures were associated with tumor expansion to the frontal and temporal lobe, whereas expansion to infratentorial central nervous system regions (cerebellum, brainstem) was associated with nausea/vomiting, oculomotor disorders and diplopia, coordination abnormalities, gait disturbances, cranial nerve deficits, and nystagmus. Cognitive decline was associated with infiltration of the parietal and occipital lobes, whereas tumor expansion to the parietal and

Table 2. Multivariable Cox Regression Analysis for Overall Survival.[a]

			Overall survival	
Variable	Category	n	HR (95% CI)	*P*[b] value
Core model[b]		141		
Age, y	0-4		ref	
	5-9		2.98 (1.39-6.40)	.005
	10-14		1.97 (0.94-4.16)	.07
	15-18		2.43 (1.07-5.54)	.04
Sex	Female vs male		1.32 (0.87-2.02)	.19
Histology	Astrocytoma vs other		1.32 (0.63-2.76)	.46
Grade	II		ref	
	III		1.30 (0.78-2.14)	.31
	IV		1.54 (0.68-3.48)	.30
GC type	II vs I		1.11 (0.68 -1.81)	.68
CNS regions affected	1 region more		1.14 (1.00 -1.29)	.048
Additional variables alternatively introduced[c]				
Clinical factors				
Time from symptoms to diagnosis	1 mo more	60	0.95 (0.90 -1.01)	.07
Seizures	Yes vs no	101	0.74 (0.44 -1.23)	.24
Focal motor deficit	Yes vs no	101	1.12 (0.63-2.00)	.70
Headache	Yes vs no	101	1.59 (0.85-2.96)	.15
Nausea/vomiting	Yes vs no	101	1.34 (0.67-2.68)	.41
Oculomotor symptoms/ diplopia	Yes vs no	101	1.39 (0.70-2.77)	.35
Coordination abnormalities	Yes vs no	101	2.04 (1.05-3.94)	.03
Cognitive decline	Yes vs no	101	2.07 (1.03-4.18)	.04
Decrease of consciousness level	Yes vs no	101	1.46 (0.61-3.46)	.39
Imaging factors				
Contrast enhancement in MRI	Yes vs no	113	1.11 (0.65 -1.89)	.70
Infratentorial involvement	Yes vs no	91	1.00 (0.55 -1.82)	.99
Bilateral involvement	Yes vs no	94	1.19 (0.65-2.18)	.58
Symmetric invasion	Yes vs no	91	1.27 (0.67-2.41)	.47
Molecular characteristics				
IDH1 mutation	Yes vs no	34	0.03 (0.001-0.85)	.04
TP53 mutations	Yes vs no	32	0.25 (0.03-2.44)	.23
MGMT promoter methylation	Yes vs no	31	0.61 (0.16-2.31)	.47

Abbreviations: CNS, central nervous system; GC, gliomatosis cerebri; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; MGMT, O_6-methylguanine-DNA-methyltransferase; MRI, magnetic resonance imaging; TP53, tumor protein 53.
[a]The analysis was conducted after multiple imputation for the variables included in the core model.
[b]Two-sided *P* values derived from multivariable Cox regression analysis.
[c]The additionally introduced variables were included in the core model interchangeably and were not subject to multiple imputation.

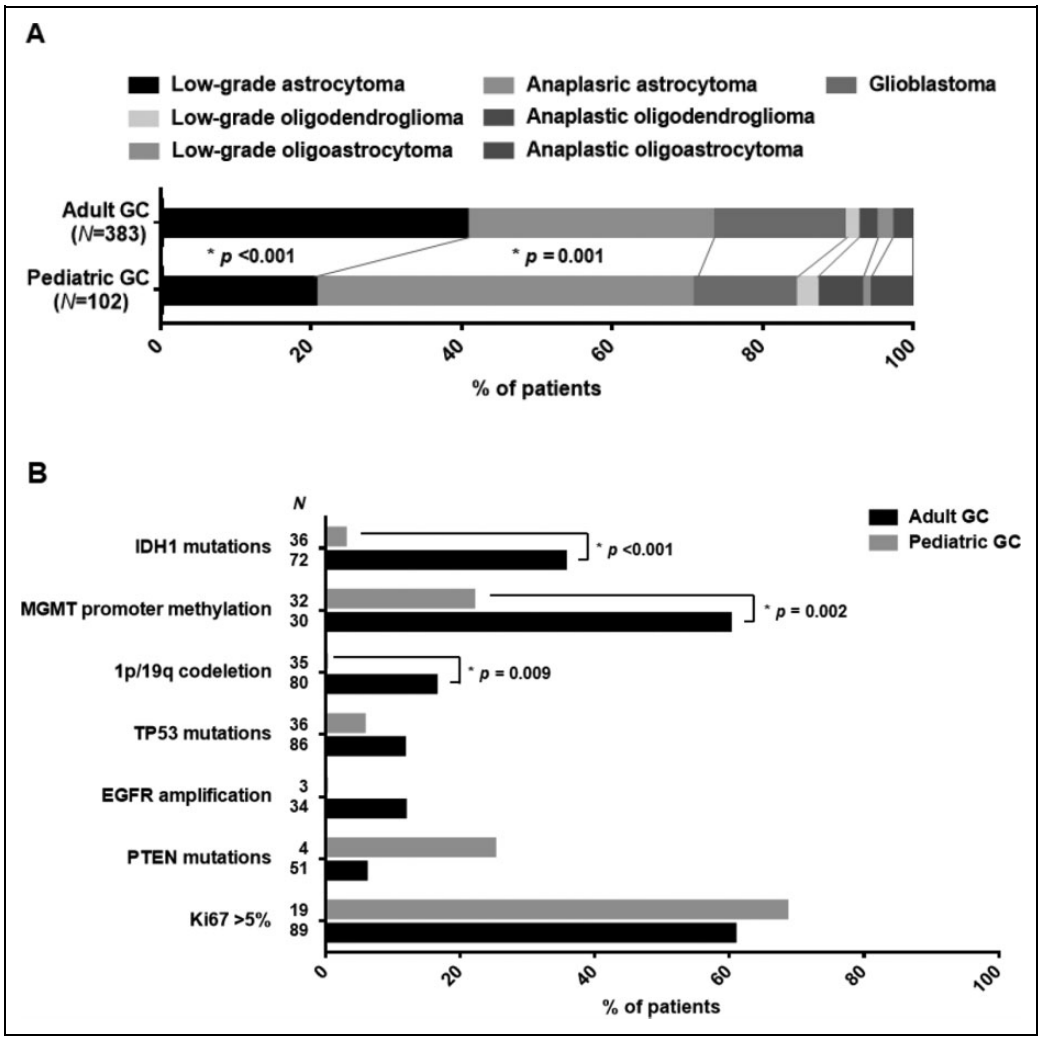

Figure 1. Differences in the (A) histologic subtype and (B) molecular aberrations between patients with pediatric and adult gliomatosis cerebri (GC).
P values are 2-sided and are derived from chi-square tests.

occipital lobes, as well as to the corpus callosum, was associated with papilledema (Figure 2).

Among the study variables (Table 2), age at diagnosis >4 years was associated with higher risk of death, as compared to age 0-4 years at diagnosis ($HR_{5\text{-}9}$: 2.38 [1.39-6.40]; $HR_{10\text{-}14}$: 1.97 [0.94-4.16]; $HR_{15\text{-}19}$: 2.43 [1.07-5.54]). Furthermore, an increasing number of affected central nervous system regions (HR: 1.14, 95% CI: 1.00-1.29) and symptoms of coordination abnormalities (HR: 2.04, 95% CI: 1.05-3.94) and cognitive decline (HR: 2.07, 95% CI: 1.03-4.18) were associated with worse overall survival. On the contrary, IDH1 mutations were associated with prolonged overall survival (HR: 0.03, 95% CI: 0.001-0.85).

For the different treatment modalities (Figure 3), chemotherapy was associated with reduced risk of death (HR: 0.50, 95% CI: 0.32-0.90), with the effect size being similar for temozolomide and other chemotherapy regimens. Extended surgical resection was also an independent predictor of prolonged survival (HR: 0.33, 95% CI: 0.12-0.91). On the contrary, radiotherapy (either restricted to the tumor or whole brain radiation) was not associated with overall survival. When, however, restricting analyses to patients who received any treatment (bottom panel of Figure 3B), no treatment combinations were identified as superior to chemotherapy alone for prolonging the overall survival of patients with pediatric gliomatosis cerebri. Importantly, patients receiving solely radiotherapy had worse prognosis, as compared to patients receiving only chemotherapy.

Discussion

Pooling individual-level data from 182 children (0-18 years) with gliomatosis cerebri, we found distinct histopathologic and neuroimaging patterns, as compared to adult gliomatosis cerebri, we identified prognostic factors for overall survival, and we found significant associations between received treatment and

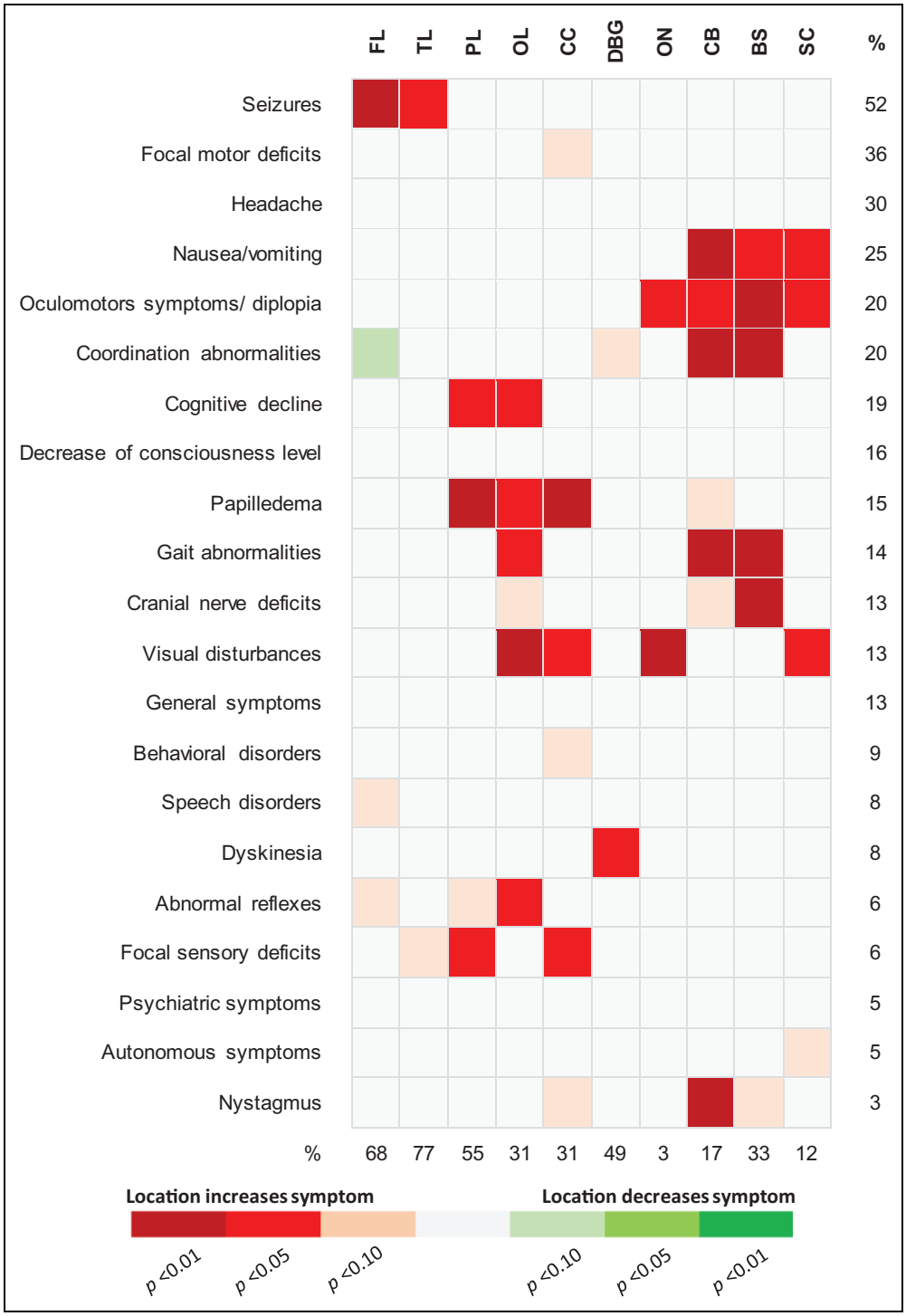

Figure 2. Frequencies of presenting symptoms and associations with neuroanatomic expansions of the tumor among patients with pediatric gliomatosis cerebri (0-18 years).
P values are 2-sided and are derived from chi-square tests.
Abbreviations: BS, brainstem; CB, cerebellum; CC, corpus callosum; DBG, diencephalon-basal ganglia; FL, frontal lobe; OL, occipital lobe; ON, optic nerve; PL, parietal lobe; SC, spinal cord; TL, temporal lobe.

disease outcome. Pediatric, as compared to adult, gliomatosis cerebri was more likely to be of higher WHO grade, and less likely to carry molecular aberrations related to prolonged survival (IDH1 mutations, MGMT promoter methylation, 1p/19q codeletion). Tumors restricted to the supratentorial regions were more likely to present with seizures, cognitive decline, and papilledema, whereas tumors further extending infratentorially most commonly presented with nausea or vomiting,

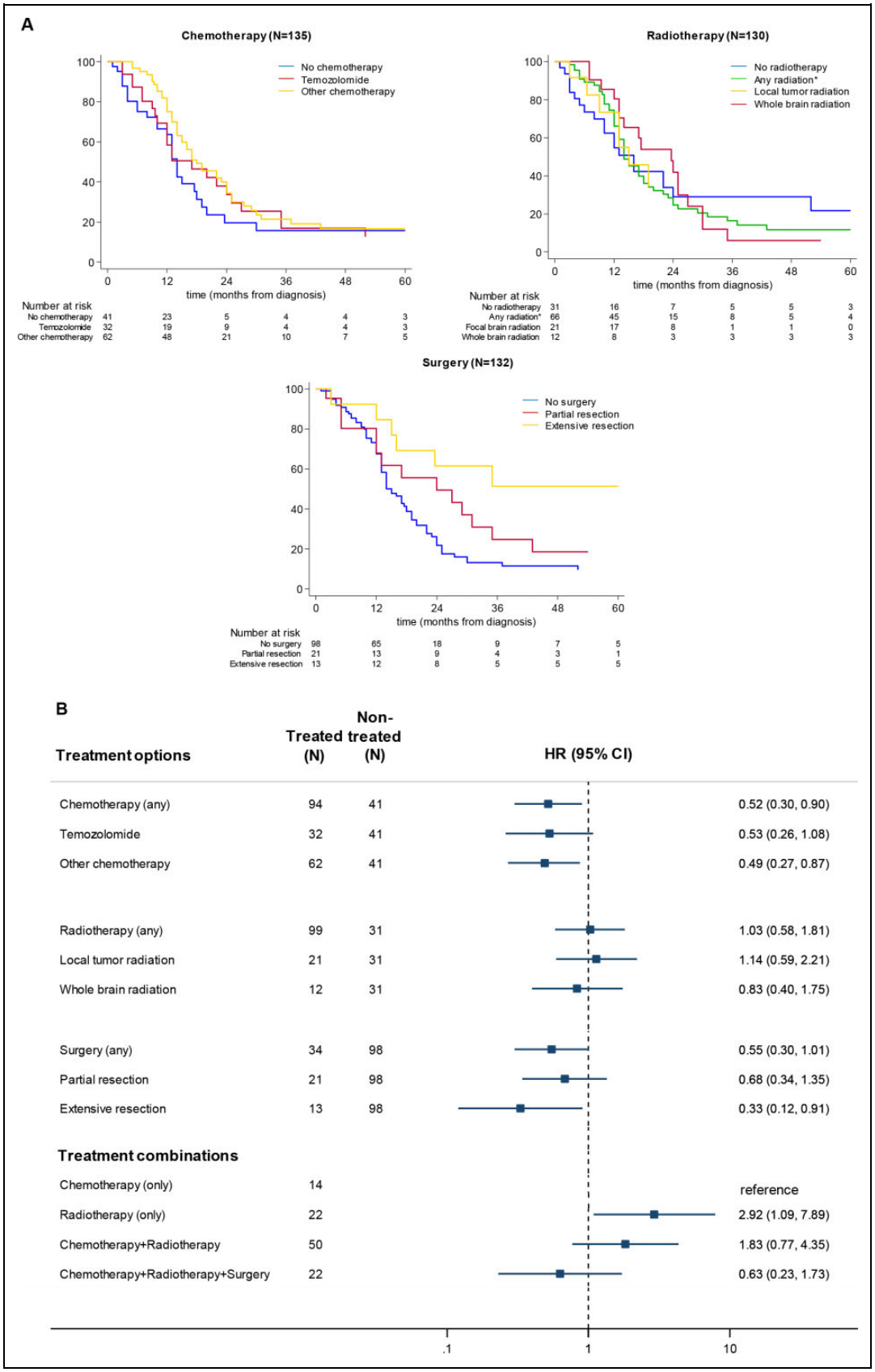

Figure 3. Association of received treatment with overall survival. (A) Unadjusted Kaplan-Meier curves; (B) multivariable effects of different treatment regimens and different treatment combinations (lowest panel) on risk of death.
*Any radiation indicates administration of radiotherapy, but of unknown focus (local tumor or whole brain).

diplopia, and coordination abnormalities. Age >4 years at diagnosis, extended central nervous system infiltration, coordination abnormalities, and cognitive decline were predictors of worse outcome, whereas IDH1 mutations were associated with prolonged overall survival. Chemotherapy and, when feasible, extended surgical resection were associated with improved outcome, whereas radiotherapy was not found to be superior to chemotherapy or exert any additional benefit on top of it.

In accordance with studies in adults,[12,17-20] IDH1 was associated with better prognosis in pediatric gliomatosis cerebri, indicating that despite the lethal nature of the disease, there are molecular subgroups of patients that may have favorable clinical outcomes. However, IDH1 mutations, but also other molecular aberrations known to be associated with improved outcomes among gliomas, including MGMT promoter methylation and 1p/19q codeletion,[17,19,21-23] were less common among children with gliomatosis cerebri, as compared to adult patients. IDH1 and IDH2 mutations are known to be very rare among children with high-grade gliomas, as opposed to older patients,[14,24] but similarly to other gliomas,[25] paradoxically pediatric gliomatosis cerebri tumors are associated with prolonged survival.[12]

Besides IDH1 mutations, other clinical and neuroimaging markers that could be of help in the clinical prognostication of children with gliomatosis cerebri were identified as independent prognostic factors for overall survival. Those included age >4 years at diagnosis, higher number of central nervous system infiltrated regions, and the symptoms of cognitive decline and coordination abnormalities. These symptoms, might also indicate more extensive central nervous system infiltrations, and have also been associated with worse outcome in adult gliomatosis cerebri,[12] but also other pediatric gliomas.[26] However, an age at diagnosis of 0-4 years is considered an unfavorable prognostic factors for other pediatric brain tumors.[27-30] This disparity might relate with a more favorable molecular profile of gliomatosis cerebri among neonates and young children or with higher brain plasticity, thus increasing the possibility for recovery[31] following the aggressive treatment that the tumor requires.

We further found chemotherapy and surgical resection to be significantly associated with improved outcome, which was contrasted to the lack of any significant effect for radiotherapy. Although our retrospectively collected data cannot exclude indication bias, this finding is also consistent with the results from adult gliomatosis cerebri.[12] Chemotherapy has been previously shown to be effective in patients with gliomatosis cerebri, but as opposed to previous studies,[17,32-34] we did not find any evidence that temozolomide is superior to other regimens. Last but not least, the current analysis showed prolonged overall survival in the small group of patients (12%), in whom it was possible to perform extensive subtotal resection of the tumor.

This study has several methodologic strengths. First of all, by performing a systematic review and intensively extracting published data on an individual-level basis, it was possible to create the largest to date data set of patients with pediatric gliomatosis cerebri, a very rare disease entity. Second, we used multiple imputations to account for missing data in multivariate analyses, thus maximizing statistical power and the informativeness of our study. Third, our approach enabled us to examine factors with clinical significance in the prognostication of the patients and also examine how different treatment modalities associate with the disease outcome, thus possibly informing clinical practice.

We should also note the study limitations. Specifically, it was not possible in this report to explore in more detail how specific treatment characteristics, including dosages, number of cycles, and serial administration of multiple treatment combinations, might influence gliomatosis cerebri survival. Furthermore, as selection for treatment was not based on a formal randomization process, there is a high possibility that our retrospectively collected data are biased by indication. Finally, the sources of data collection for many case reports and case series were usually tertiary specialized centers, which might introduce selection bias in the study.

In conclusion, in this individual patient-data meta-analysis of pediatric gliomatosis cerebri, we detected histopathologic differences between the pediatric and the adult type of the disease, we identified clinical, neuroimaging, and molecular prognostic factors for children diagnosed with gliomatosis cerebri, and we found chemotherapy, and, when feasible, extensive surgical resection, as opposed to radiotherapy, to be associated with prolonged overall survival. Our results may be informative for alerting clinicians regarding the clinical presentation of the disease, aid in clinical prognostication and identification of high-risk patients with pediatric gliomatosis cerebri, and guide the design of future clinical trials. Patients with gliomatosis cerebri should be included in future multicenter glioma trials, so as to determine the most appropriate management for this rare but fatal brain tumor.

Author Contributions

MG, GT, and EP designed the study. MKG performed the systematic review and the statistical analysis. MG, GT, AP, and EP interpreted the results. MG and EP drafted the manuscript. MG, GT, AP, and EP critically revised the manuscript for intellectual content. MG, GT, AP, and EP approved the final version.

Declaration of Conflicting Interests

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Ethical Approval

Data presented in this manuscript were derived from previously published peer-reviewed articles, identified during a systematic review. Thus, no ethical approval was required.

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