Global trends in survival from brain tumours in adolescents and young adults: a systematic review.

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Abstract

Background Brain tumours represent an important cause of cancer-related death in adolescents and young adults. Most are diagnosed in low-income and middle-income countries. We aimed to conduct the first systematic review of time trends and geographical variation in survival in this age group. **Methods** We included observational studies describing population-based survival from astrocytic tumours in patients aged 15-39 years. We queried six electronic databases from database inception to 30 September 2018. This review is registered with PROSPERO, number CRD42018111981. **Results** Among 5,245 retrieved records, 20 studies fulfilled the inclusion criteria. Only one study was partly conducted in middle-income countries. Five-year survival from astrocytoma (broad morphology group) varied between 48% and 71% (1973-2004), without clear trends or geographic differences. Adolescents with astrocytoma had better outcomes than young adults, but survival values were similar when non-malignant tumours were excluded. During 2002-2007, five-year survival for WHO grade I-II tumours was in the range 75-93% in England, Germany, and the US, but lower in South-Eastern Europe (59%). Five-year survival for anaplastic astrocytoma varied between 40% and 55% (2002-2007). Five-year survival from glioblastoma was in the range 15-23% (1991-2009). **Conclusions** Survival from astrocytic tumours remained somewhat steady over time, with little change between 1973 and 2009. Survival disparities were difficult to examine, because nearly all the studies were conducted in affluent countries. Studies often adopted the International Classification of Childhood Cancer, which, however, did not allow to accurately describe variation in survival. Larger studies are warranted, including under-represented populations and providing more recent survival estimates. **Keywords** Population-based survival, brain tumours, adolescents, young adults, time trends.

Introduction

Primary tumours of the central nervous system (CNS) are rare. In adolescents and young adults (15-39 years), the estimated world-standardised incidence rate in 2018 was 15 new cases per million in 2018, ranging from 29 in Western Europe to 4.4 in Eastern Africa.(1) Although uncommon, in 20-39 year-olds, CNS tumours ranked only second among the leading causes of cancer-related deaths in countries with very high human development index.(2) Adolescents and young adults are patients with distinct needs, and services provided for children and older adults may not be adequate.(3)

In adolescents and young adults (15-39 years), almost 80% of CNS tumours are diagnosed in low-income and middle-income countries.(1) Where the burden of CNS tumours is highest, however, patients may encounter obstacles in being diagnosed and treated for their disease. For instance, access to radiotherapy is extremely unequal worldwide. Density of radiotherapy machines varies between 4.9 or more per million population in Western Europe, North America, Australia and Japan, and 0.4 per million in the rest of the world.(4) The divide between the number of diagnoses and the availability of treatment

facilities will inevitably translate to missed opportunities of care (and cure), years of life lost, and financial hardship in families where patients are the breadwinners.

Mortality is a key indicator in epidemiological surveillance, but it does not provide information on the course of the disease following a cancer diagnosis. By contrast, population-based survival incorporates the follow-up component, and reflects the overall effectiveness of a healthcare system in managing that cancer.(5, 6)

The CNS comprises brain, spinal cord and meninges. Brain tumours are, by far, the most important group. In the third cycle of the CONCORD programme (CONCORD-3), broad disparities in survival emerged among more than 650,000 adults who were diagnosed with a primary brain tumour in 58 countries world-wide during 2000-2014. Age-standardised five-year net survival for all brain tumour subtypes and all ages combined (15-99 years) ranged between 15% in Thailand and 42% in Croatia.

Brain tumour morphology is the most important predictor of clinical outcome. In patients aged 15-44 years, the European average five-year relative survival during 2000-2007 was 14% for glioblastoma, but 56% for lower-grade astrocytic tumours.(7)

For adolescents and young adults diagnosed with a given brain tumour subtype, it is currently not known how survival varies around the world, and whether it has improved over time.

As age increases from childhood to early adulthood, the morphology distribution shifts progressively from a predominance of low-grade gliomas (e.g. pilocytic astrocytoma) to a higher proportion of more aggressive tumours. The use of the International Classification of Childhood Cancer (ICCC) has been often extended to adolescents and young adults,(8, 9) but in the light of the differences in the morphology distribution, it is unclear whether alternative strategies, such as Birch's classification, should be adopted.(10)

We aimed to address these questions by systematically synthesising the scientific evidence pertaining to population-based survival from brain tumours in adolescents and young adults.

Methods

This systematic review focussed on prospective, observational studies presenting survival from brain tumours in adolescents and young adults.

We queried six electronic databases (Dissertation and Theses Global, Embase, Medline, Open Grey, Scopus and Web of Science) from database inception to 30 September 2018. Search strategies were specific to each database, and included terms referring to four domains: disease, statistical method, study design, and outcome. A professional librarian at the London School of Hygiene and Tropical Medicine reviewed the search strategies (Appendix, page 2).

There is no consensus on the definition of “young adults”, and in most studies the upper age boundary varied between 24 and 39 years. We adopted a comprehensive approach by including patients aged 15-39 years. However, studies including individuals who overlapped this age range were still eligible.

We extracted data from published reports. Eligible studies had to include survival estimates from primary data collected in population-based cancer registries. For a given country or region, hospital-based estimates were retained only if no population-based estimates were available.

Studies were eligible if they included estimates derived from a time-to-event analysis and survival probabilities up to at least five years. More specifically, survival probabilities had to be estimated as observed survival, relative survival or net survival.⁽¹¹⁾ These outcome measures do not require knowledge of the cause of death.

We did not put restrictions relating to language or publication status. However, because morphology classifications changed substantially after 1995, we did not include earlier reports.

If a study did not clearly meet the eligibility criteria, we decided on inclusion or exclusion through discussion.

We were interested in both non-malignant and malignant brain tumours. We focussed on astrocytic tumours, because data for rarer subtypes were too scanty to allow robust comparisons.

Since morphological groupings differed between studies, we combined similar definitions (e.g. anaplastic astrocytoma and astrocytoma World Health Organisation (WHO) grade III) under a common descriptor (Appendix, page 4) but, where possible, without combining morphologies with different clinical behaviour (i.e. WHO grade). Definitions sharing the same code in the International Classification of Diseases for Oncology (ICD-O) Third Edition were merged. Then we conducted a sensitivity analysis by re-grouping morphologies according to the Birch classification, to explore whether less granular categories were equally informative. The Birch system subdivides astrocytic tumours into three categories: low-grade tumours, glioblastoma plus anaplastic astrocytoma, and astrocytoma NOS.(10)

From each eligible study, we abstracted five-year survival probabilities by morphology. When studies provided survival estimates for more than one calendar period or considered more than one age group (e.g. patients aged 15-19 years and 20-24 years), each estimate was considered separately. Where available, we collected specifications on the reference classification used for morphology definitions, data quality indicators (e.g. proportion of microscopically verified tumours, patients lost to follow-up and poorly specified/unspecified morphologies), and completeness of ascertainment.

Calendar periods differed between studies, and their length also varied. Therefore, we have presented the results labelled with the middle year of the calendar period.

The systematic review is registered with [PROSPERO, number CRD42018111981](#).

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for submission for publication.

Results

The database search yielded 5,245 records. We screened these records for eligibility from the title and the abstract. We then assessed the full text of the remaining 330 publications for eligibility. This process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1).(12) Twenty studies were included in the systematic review.

The calendar period for incident cases ranged from 1968 to 2014. Twelve studies (60%) were conducted in one or more European countries, four in the US, two in Asia (South Korea and Japan), one comprised patients from the US and Germany, and one international study was carried out in Europe, but including also Cyprus and Turkey, and the US. Only one study included any data from middle-income countries (Table 1).(13)

Young adults were defined as individuals up to the age of 24 years in six studies, up to age 39 in six studies, and up to age 44 in three studies. Three studies adopted alternative age definitions of the upper boundary (29, 40, or 49 years). The eligible studies collectively provided 75 survival estimates: 14 for adolescents only (15-19 years), 23 for young adults (20 years or more) only, and 38 estimates for adolescents and young adults combined (Table 1).

Eight of the 20 studies had a regional population coverage, four were based on national registries, seven were international studies drawing data from both regional and national registries, and in one study the information was not available (Table 1).

The completeness of ascertainment was only specified in four of the 20 studies.(14-17) Twelve (60%) of the 20 studies provided details on data quality indicators: two studies only specified the criteria for exclusions (e.g. diagnoses based on death certificate only or autopsy), and ten reported at least the proportion of microscopically verified tumours (Table 1).

The proportion of microscopically verified tumours referred specifically to brain tumours in four studies, (7, 13, 18, 19) while in five the parameter was for all tumours combined.(15, 20-23) In the two international comparisons, the proportion of microscopically verified tumours varied between 57% and 96% (South-Eastern European (SEE) consortium, plus US), and between 61% and 95% in the EURO CARE-5 study, covering adolescents and young adults diagnosed during 1999-2007 in 27 European countries.(7, 13) One study comprised exclusively patients with microscopically verified tumours (Appendix, page 5) . (24)

Five studies did not clarify the reference classification. In the remaining 15 studies, the second or third editions of the International Classification of Diseases for Oncology (ICD-O) were the reference classification (Table 1).(9, 25)

Ten of the 20 eligible studies grouped all astrocytic morphologies under the broad definition “astrocytoma”, but two of these studies did not clarify the behaviour of eligible tumours (only malignant, or both malignant and non-malignant) (Appendix, page 5).(26, 27) Ten studies considered either subgroups (i.e. low-grade astrocytoma or high-grade astrocytoma) or single morphologies (e.g. diffuse astrocytoma, glioblastoma).

In 13 studies (65%), the outcome measure was observed survival (i.e. all-cause survival), while in seven studies it was relative survival (Table 1).

For astrocytoma as a broad morphology group, survival estimates referred mostly to patients aged 15-24 years. No studies were available from low-income or middle-income countries. Nearly all estimates of five-year survival fell within the range 48-71% during 1973-2004, with little variation in survival between countries or over time, and largely overlapping confidence intervals.(14, 16, 17, 20, 21, 23, 24, 26, 28, 29) In the only US study, however, five-year survival was higher than in Europe: 73% versus 65% around 1988, and 81% versus 64% around 2000.(15) In the EURO CARE-5 study for diagnoses during 2000-2007, five-year survival from astrocytoma was 51% in adolescents (15-19 years), similar (48%) in patients up to age 34, but lower (39%) in the 35-39 age group (Figure 2).(23)

Among the studies using the broad definition “astrocytoma”, we identified four possible combinations of age (adolescents (15-19 years), or adolescents and young adults combined (15-44 years)), and tumour behaviour (all behaviours or malignant only). Five-year survival from non-malignant and malignant astrocytomas combined was slightly higher in adolescents (15-19 years, 60-81%) than in the broader age group (15-44 years, 48-68%), except in Eastern Europe and France, where values were lower (52%).(28, 29) Conversely, five-year survival for malignant astrocytomas in adolescents was very similar to the values observed in adolescents and young adults combined (Figure 3).

Five-year survival from low-grade astrocytoma (WHO grade I and II combined), was 87% or more for patients aged 16-29 years, in England, Germany, and the US (2002-2005). In the same countries, survival was lower (75%) when individuals up to age 39 (49 years in one study) were also included.(13, 27, 30) In the SEE consortium, five-year survival for patients diagnosed in 2005 was much lower (59%, 15-39 year-olds) (Figure 4).(13)

Five-year survival from high-grade astrocytoma (WHO grade III and IV combined) was 18% in England, in 1997,(27) while it varied between 27% and 39% in Germany, United States and the SEE consortium, during 2002-2005 (Figure 4).(13, 30)

Five-year survival from diffuse astrocytoma was in the range 63-76% in Germany and the US, during 2002-2007.(13, 19, 30) In both the EUROCare-5 consortium (27 European countries combined) and the SEE consortium (Southern and Eastern Europe), average five-year survival was around 55% in 2005 (Figure 4).(7, 13)

The survival probability at five years for South-Korean patients diagnosed with anaplastic astrocytoma in 2002 was 40%.(24) In the US, five-year survival was similar in 2003 (36%), but much higher in 2007 (55%) (Figure 4).(19, 31)

Five-year survival from glioblastoma was in the range 15-23% in England, the EUROCare-5 consortium, the US and South Korea, without improvements in the 20 years between 1991 and 2009 (Figure 4).(7, 18, 19, 24, 32)

Lastly, studies were grouped according to Birch's classification.(10) Such system does not adopt the broad definition "astrocytoma", so studies using this definition were excluded from the analysis. None of the studies focussed solely on adolescents (15-19). Five-year survival from low-grade astrocytic tumours was mostly in the range 71-93%.(13, 19, 27, 30, 33) Five-year survival from high-grade astrocytic tumours mostly varied between 14% and 40%.(7, 13, 18, 19, 24, 27, 30-32). Five-year survival for astrocytoma not otherwise specified was in the range 55-76% (Supplementary Figure).(7, 13, 30)

Discussion

To our knowledge, this is the first systematic review summarising international trends in survival from astrocytic tumours in adolescents and young adults (15-39 years).

Outcomes remained somewhat steady over time, with little change over the 35 years between 1973 and 2009.

Five-year survival for all astrocytic tumours combined was in the range 39-73%. Survival was much lower in studies only including patients with malignant astrocytomas or considering broader age groups.

Five-year survival was in the range 50-75% for diffuse astrocytoma, but it rose to 75% or more when WHO grade I and II tumours were combined. The survival probability at five years was 25% or less for glioblastoma, in the range 35-55% for anaplastic astrocytoma, and mostly between 25% and 40% when the two morphologies were jointly considered. For a given morphology, older patients experienced poorer outcomes.

Nearly all the studies were conducted in high-income countries, noticeably in high-income countries in Europe, and in the US. In these settings, survival was similar. Only one international study included patients diagnosed in middle-income countries (Belarus, Bulgaria, Montenegro, Romania, Serbia, Turkey, Ukraine). In this study (SEE consortium) the average five-year survival for low-grade astrocytic tumours was at least 15% lower than in more affluent countries (England, Germany and the US), but the gap in survival was smaller (around 10%) for high-grade astrocytic tumours, for which little can be done.(13)

Eleven out of 20 studies extended the use of the International Classification of Childhood Cancer (ICCC) to adolescents and young adults. The distribution of astrocytic tumours with different clinical behaviour varies widely with age. Pilocytic astrocytoma, the most common non-malignant astrocytic tumour, accounts for 60% of all astrocytomas in children, compared to 47% in adolescents (15-19 years), and 19% in the 15-39 age group.(19) Pilocytic astrocytoma is associated with a survival probability at five years of around 90%, while survival for higher-grade astrocytomas is 50% or less.(19) Therefore, any grouping strategy combining morphologies with very different outcomes will result in inflated, misleading survival estimates. When we stratified the 11 studies using the information they provided on the eligible tumour behaviours, survival trends in adolescents (15-19 years) became slightly clearer, with lower five-year survival when non-malignant astrocytic tumours were excluded. When broader age groups were considered (upper age limit 24 years or more), however, survival was similar after inclusion or exclusion of patients with non-malignant astrocytic tumours. These tumours are rare in older adults, and their impact on survival estimates for the broad morphology “astrocytoma” is likely to be smaller with increasing age. Yet, in Eastern European adolescents, survival for all-behaviour astrocytomas was in line with the values observed for malignant-only astrocytomas.(28, 29) Such finding suggests under-registration of non-malignant tumours.

The Birch classification aimed to overcome the limitations of the ICCC by recognising that the distributions of morphology of brain tumours differ substantially between children, and adolescents and young adults.(10) We re-grouped the studies based on this classification. Five-year survival from low-grade astrocytic tumours was mostly in the range 70-90% during 1997-2007, and five-year survival from

high-grade astrocytic tumours varied between 15 and 55% during 1991 and 2009. Birch's classification may be more appropriate than ICCC in describing survival from astrocytic tumours in adolescents and young adults. The large variability in survival we highlighted, however, suggest that combining different morphologies will still result in loss of information. This seems particularly relevant to high-grade morphologies, namely glioblastoma and anaplastic astrocytoma. Anaplastic astrocytoma often recurs as glioblastoma, but outcomes at five years are remarkably different (Supplementary Figure).(19)

Birch's classification comprises also the category astrocytoma not otherwise specified (NOS). In most of the studies using such definition, survival estimates were around 70%.(19, 30, 34) These values are in line with those observed for diffuse astrocytoma (WHO grade II). In the ICD-O-3, diffuse astrocytoma is one of the alternative descriptors of astrocytoma not otherwise specified.(35) Conversely, in the WHO classification (4th edition), astrocytoma not otherwise specified is not a separate definition and the corresponding ICD-O-3 code is attributed to diffuse astrocytoma.(36) Given that the definitions "astrocytoma not otherwise specified" and "diffuse astrocytoma" refer to the same entity, we recommend against using the definition "astrocytoma NOS" as a synonym for unspecified astrocytic tumours (Supplementary Figure).

In adolescents and young adults, more than one fourth of astrocytic tumours are glioblastomas.(19) In 2005, a randomised clinical trial showed that two-year survival was 26% in patients treated with radiotherapy plus temozolomide chemotherapy, and only 10% in those receiving radiotherapy.(37) Since, the concomitant treatment has become the standard of care for adults younger than 70 years. We could not explore the benefit of this treatment protocol at population level, because very few survival estimates are available for patients diagnosed after 2005. In this systematic review, five-year survival was in the range 14-23%. In older adults (40 years or more), five-year survival is below 10%. Glioblastoma is defined as primary when it arises as a WHO grade IV lesion, and secondary if it has developed from a lower-grade glioma. Secondary glioblastomas are characterised by mutation of the isocitrate dehydrogenase (IDH) gene. Patients with *IDH*-mutated glioblastomas are younger than those affected by *IDH* wild-type glioblastomas (median age at diagnosis 32 years versus 59 years), and have a more favourable outcome.(38) We chose to report only five-year survival to improve comparability between studies, because it was the most commonly adopted outcome measure. For glioblastoma, however, shorter-term survival estimates may be more informative.

Information on data quality indicators was inadequately reported, and often totally missing (42% of studies). Data quality indicators tell us about cancer registry practices (e.g. sources of data, type of follow-up), and affect the reliability of the data.(39) Most frequently, studies indicated the proportion of microscopically verified tumours. Histologic confirmation of brain tumours may not be possible if the

patient is clinically unfit to surgery or a biopsy, or if tumour location bars a diagnostic procedure. In each of the two large international studies reviewed here, the proportion of microscopically verified tumours varied widely between the participating registries. The average proportion of microscopically verified tumours in these two studies was similar (around 80%), but the SEE consortium also included middle-income countries, where access to care may be sub-optimal.(7, 13) In some of the more affluent European countries, however, the proportion of microscopic verification was also rather low (e.g. 63% in Italy).(7) Proportions which are very high may indicate over-reliance on pathology reports, and, therefore, a restricted number of data sources, leading to incompleteness of case ascertainment. Furthermore, patients with microscopically verified brain tumours may not necessarily represent the whole population, because they were at least able to undergo an invasive diagnostic procedure. If only these patients are included in the study, survival estimates may be higher. The overall completeness of case ascertainment was specified only in four studies, where it was 95% or more. Lower levels may suggest that a cancer registry fails to capture all the data within its catchment area, and this may lead to under-ascertainment of brain tumours.(40)

Two-thirds of the studies estimated survival as all-cause survival (i.e. observed survival). The cause of death is not used in international comparisons of cancer survival, because it may be unavailable, or based on unreliable information from the death certificate.(41-43) Observed survival can be readily obtained, but it is biased downwards because it includes death from other causes (i.e. background mortality). Background mortality varies between populations and over time, and it can be derived from life tables.(44) Once competing risks of death are properly accounted for, the estimate will reflect net survival, which is the survival attributable exclusively to cancer. Net survival permits robust international comparisons, and it can now be directly estimated with the non-parametric, unbiased Pohar Perme estimator.(11) Until recently, relative survival has been used as the best approximation of net survival, but this indicator does not allow for informative censoring. Informative censoring arises when the probability of dying from cancer is not independent of the probability of dying from other causes, and this is more frequent in the elderly. We have been obliged to compare studies that used different survival estimators, which may reduce the validity of some comparisons. Nevertheless, given that we considered relatively young patients and nearly all were diagnosed in affluent countries, failing to account for the rather low background mortality is unlikely to lead to substantial bias.

This systematic review presents some limitations. (1) We adopted a wide range of morphology definitions in order to summarise survival variation in as much detail as possible. However, the number of survival estimates in some categories was small, hindering robust comparisons. (2) Many studies (75%) were partly or entirely based on regional data. We assumed that regional survival estimates applied to the whole country, but this assumption may not hold if provision of cancer care is unequally distributed. However, these regions were often also included in national or international studies. Estimates from

studies with different geographical coverage did not differ substantially, so findings from smaller studies were fairly generalisable. (3) We were obliged to present trends using the central year of the calendar period covered by a given study, regardless of its length. Although this strategy improved clarity, when two or more calendar periods overlapped, we could not use differences in length to explore non-linear changes in survival. However, there were no substantial gains in survival for any of the morphologies, so comparisons referring to the central year may be acceptable.

In conclusion, there is a striking gap in knowledge about survival trends in middle-income and low-income countries, where disparities in access to care are reported.(4) Studies with a wider scope, extending to currently under-represented geographical regions, could fill this gap. Moreover, standardised data collection, data quality control, and data analysis using the same statistical methods are required in order to reduce heterogeneity and enable more reliable comparisons. ICCC and Birch’s classification do not allow adequate description of international variation in survival from astrocytic tumours in adolescents and young adults. Revision of these bespoke classifications is warranted, in order to provide sound survival estimates which will ultimately inform cancer control plans.

List Of Abbreviations

CNS	Central nervous system
ICCC	International Classification of Childhood Cancer
ICD-O	International Classification of Diseases for Oncology
IDH	Isocitrate dehydrogenase
NOS	Not otherwise specified
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SEE	South-Eastern European
WHO	World Health Organisation

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Conception and design: FG, CA, MPC; collection and assembly of data: FG; data analysis and interpretation: all authors; manuscript writing: FG wrote the first draft, with input from CA and MPC; final approval of the manuscript: all authors; accountable for all aspects of the work: FG.

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Additional File Details

Supplementary Figure

Five-year survival (%) from specified low-grade astrocytic tumours, glioblastoma and anaplastic astrocytoma, and astrocytoma not otherwise specified (NOS) (Birch’s classification).

Table

Due to technical limitations, table 1 is only available as a download in the supplemental files section.

Figures

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Figure 2

Five-year survival (%) from astrocytoma (broad morphology group). The confidence interval is not displayed when the study did not provide it.

Figure 3

Five-year survival (%) from astrocytoma (broad morphology group), by age group (adolescents, or adolescents and young adults combined) and tumour behaviour (non-malignant plus malignant, or malignant-only). The confidence interval is not displayed when the study did not provide it.

Figure 4

Five-year survival (%) from astrocytoma (low-grade), pilocytic astrocytoma, diffuse astrocytoma, astrocytoma (high-grade), anaplastic astrocytoma, and glioblastoma. The confidence interval is not displayed when the study did not provide it.

Supplementary Files

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