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The histology of brain tumors for 67 331 children and 671 085 adults diagnosed in 60 countries during 2000-2014: a global, population-based study (CONCORD-3)

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Abstract

Background. Global variations in survival for brain tumors are very wide when all histological types are considered together. Appraisal of international differences should be informed by the distribution of histology, but little is known beyond Europe and North America.

Methods. The source for the analysis was the CONCORD database, a program of global surveillance of cancer survival trends, which includes the tumor records of individual patients from more than 300 population-based cancer registries. We considered all patients aged 0-99 years who were diagnosed with a primary brain tumor during 2000-2014, whether malignant or nonmalignant. We presented the histology distribution of these tumors, for patients diagnosed during 2000-2004, 2005-2009, and 2010-2014.

Results. Records were submitted from 60 countries on 5 continents, 67 331 for children and 671 085 for adults. After exclusion of irrelevant morphology codes, the final study population comprised 60 783 children and 602 112 adults. Only 59 of 60 countries covered in CONCORD-3 were included because none of the Mexican records were eligible. We defined 12 histology groups for children, and 11 for adults. In children (0-14 years), the proportion of low-grade astrocytomas ranged between 6% and 50%. Medulloblastoma was the most common subtype in countries where low-grade astrocytoma was less commonly reported. In adults (15-99 years), the proportion of glioblastomas varied between 9% and 69%. International comparisons were made difficult by wide differences in the

proportion of tumors with unspecified histology, which accounted for up to 52% of diagnoses in children and up to 65% in adults.

Conclusions. To our knowledge, this is the first account of the global histology distribution of brain tumors, in children and adults. Our findings provide insights into the practices and the quality of cancer registration worldwide.

Key Points

- A study on the histology distribution of brain tumors spanning 59 countries in 5 continents.
- Wide international variation suggesting disparities in registration practices and data quality.
- Robust evidence for actions aimed to improve data quality and to harmonize data collection worldwide.

Importance of the Study

To our knowledge, this is the first study of the histology distribution of brain tumors worldwide. We analyzed individual records for nearly 700 000 patients diagnosed with a primary brain tumor in 59 countries, during 2000-2014. Many countries were included for the first time in international comparisons. Data were collected using the same protocol to ensure robustly comparable information. We considered children and adults separately, using distinct histology groupings. The global variation in the histology distribution was remarkable. We provided evidence that such variation may be mainly due to international differences in cancer registration practices but also to wide disparities in the quality of data. This study population will be used for further global comparisons of brain tumor survival by histology. Our study should prompt cancer registries to improve data quality and to cooperate internationally for the harmonization of data collection.

Central nervous system (CNS) tumors encompass more than 50 histological subtypes, with distinct genetic hallmarks, clinical behavior, and survival.[1]

CNS tumors represent an important cause of cancer-related death in children, adolescents, and young adults.[2,3] Given that most of the patients live in low- and middle-income countries, the social burden of brain tumors is disproportionately great in countries that are generally least well equipped to deal with that burden.[2,4,5]

In order to make a robust international comparison of the frequency of the various histological types of brain tumor, it is first necessary to define suitable histology groupings. The standard framework for presenting data on tumors in children is the International Classification of Childhood Cancer, third edition (ICCC-3[6]), based on the International Classification of Diseases for Oncology, third edition (ICD-O-3). A separate framework for adolescents and young adults was devised by Barr et al.[7] Further schemes for grouping brain tumors by their histology include those used in Cancer Incidence in Five Continents (CI5), the Central Brain Tumor Registry of the United States (CBTRUS), and the European Information Network on Rare Cancers (RARECARENet).[8–10] Such strategies are not specific to children or adults, however, and the level of granularity varies.

The distribution of brain tumors by histology has only been described as part of analyses of incidence or survival by histology in a given country, region, or territory,[11] but differences in study design do not allow valid comparisons. Large international population-based studies, such as the Automated Childhood Cancer Information System (ACCIS) and the European Cancer Registry-based study on survival and care of cancer patients (EUROCARE), used standardized data collection, but they only include European countries.[12–14] African, Central and South American, and Asian countries are substantially under-represented in brain tumor studies by histology.[11]

The CONCORD program established global surveillance of trends in cancer survival in 2015.[15] The third cycle, in 2018 (CONCORD-3), included individual data for more than 37 million patients from 71 countries, diagnosed with 1 of the 18 common tumors during 2000-2014. CONCORD-3 highlighted the wide global disparities in survival from all brain tumors combined.

Knowledge of the histology distribution in cohorts of cancer patients used for population-based survival analyses is key to interpreting the worldwide disparities in survival for all brain tumor subtypes combined. Limited access to care is likely to be the main reason for the global inequalities in survival, but international differences could also arise by confounding if the distribution of histological subtypes varies worldwide and there are international differences in survival between the histological subtypes. For health care systems aiming to track cancer outcomes, clinically relevant

survival data by histology are crucial. Only estimates that are based on accurate registration of brain tumors can safely be used by public health officials for cancer control planning at the national and international levels. Robust survival estimates may also be used by clinicians and epidemiologists to monitor adherence to clinical guidelines.

Using the CONCORD-3 database, we aimed to assess international differences in reporting of the histology of brain tumors and the main indicators of data quality in cancer registration, in children and adults. This study aims to help appraise the validity of future global comparisons of survival from brain tumors using CONCORD-3 data.

Patients and Methods

Records were obtained from data supplied by 286 of the 322 population-based cancer registries participating in CONCORD-3. Data were collected using the same protocol and centrally validated for protocol adherence and consistency through a rigorous 3-phase data quality control procedure (details published elsewhere).[15,16] In brief, registrations based on a death certificate or autopsy, age out of range and those with invalid date sequences were excluded. Possible errors included implausible combinations of age, sex, site, and morphology. Each registry was invited to confirm or correct records with possible errors.

The study population comprised children (0-14 years) and adults (15-99 years), diagnosed during 2000-2014 with a tumor originating in the brain (ICD-O-3 topography code C71), and for whom a morphology code was available. We included both primary, malignant tumors (ICD-O-3 behavior code 3) and nonmalignant tumors, whether benign or of uncertain behavior (code 0 or 1, respectively).

We used ICD-O-3 to select the morphology codes and the World Health Organisation (WHO) Classification of Central Nervous System Tumors (fourth edition) for the definition of pathology.[1,17]

Morphology codes in ICD-O-3 such as 9400/3 with the attribute "not otherwise specified" (NOS) can be used in cancer registration. Rule G of ICD-O-3 allows the use of a sixth digit in the morphology code to define the histological grading or degree of differentiation.[17] We used this rule to re-classify tumors coded to "astrocytoma NOS" (ICD-O-3 code 9400/3) to one of the more specific astrocytic subtypes. We did not recode "astrocytoma NOS" with an undetermined grade (grade 9); these were analyzed separately. The sixth digit of the morphology code is assigned by the pathologist or the registrar, while the WHO grade is part of the tumor subtype definition.

The London School of Hygiene and Tropical Medicine's Ethics Committee approved the project.

Results

CONCORD-3 included 67 331 children and 671 085 adults diagnosed with a primary brain tumor in 60 countries during 2000-2014 (Supplementary Tables 1 and 2).

We defined distinct histology groupings for children and adults. For children, we mainly followed ICCC-3,[6] but we made three changes: (1) we introduced a third, more granular tier for astrocytic tumors; (2) three of the four ICCC-3 subgroups of embryonal tumors (atypical teratoid/rhabdoid tumor, medulloepithelioma, and primitive neuroectodermal tumor) were grouped together, and (3) oligoastrocytoma was included in the "oligodendroglial tumor" histology group. For adults, there are no bespoke classification systems, so we based our definitions on advice from expert pathologists. The 12 histology groupings adopted for children, and the 11 groupings adopted for adults are set out in Supplementary Tables 3 and 4, respectively.

We excluded from analysis 6548 children (9.7% of eligible tumor records) and 68 973 adults (10.3%) because the morphology code was (1) not consistent with the WHO classification; (2) consistent with the WHO classification but relevant only for the meninges or the pituitary gland, or (3) missing (Supplementary Tables 5 and 6).

The final study population comprised 60 783 children (90.3% of eligible submissions) and 602 112 adults (89.7%). The study covered only 59 of the 60 countries included in CONCORD-3: Mexico was excluded because none of the records had a valid morphology code. Supplementary Tables 1 and 2 present detailed trends for 2000-2004, 2005-2009, and 2010-2014, by country and histology group.

We focus our comments mainly on the histology distribution for 2005-2009 when proportions were more robust than for 2000-2004 and 2010-2014 because more registries contributed data for the central period. The comments are broadly applicable to earlier and later periods.

Children (0-14 Years)—2005-2009

The proportion of brain tumors classified as low-grade astrocytoma (WHO grade I or II) varied from less than 10% to more than 30%. The proportion was below 10% in African countries, in Brazil, Costa Rica, Ecuador, China, Korea, Thailand, the Russian Federation, and New Zealand; in the range 10%-19% in Argentina, Colombia, Japan, Jordan, Taiwan, Poland, and Australia, and in the range 20%-29% in Chile, Canada, Israel, Singapore, Turkey, Croatia, Denmark, France, Germany, Italy, Norway, Portugal, Spain, and Sweden. These tumors accounted for more than 30% of brain tumors in Puerto Rico, the United States, Belarus, Czech Republic, Finland, Ireland, the Netherlands, Slovakia, Switzerland, and the United Kingdom (Supplementary Table 1, Figure 1).

High-grade astrocytomas (WHO grade III or IV) comprised less than 10% of all brain tumors in Argentina, Colombia, Costa Rica, Puerto Rico, Canada, the United States, China, Israel, Japan, Korea, Singapore, Turkey, and in 17 of 28 participating European countries. The proportion was in the range 10%-20% in African countries, and in Brazil, Ecuador, Jordan, Taiwan, Thailand, Germany, Poland, the Russian Federation, Australia, and New Zealand (Supplementary Table 1, Figure 1).

Unspecified astrocytomas (ICD-O-3 code 9400/39) accounted for less than 10% of brain tumors in 30 of 59 countries, but the proportion was in the range 10%-19% in African

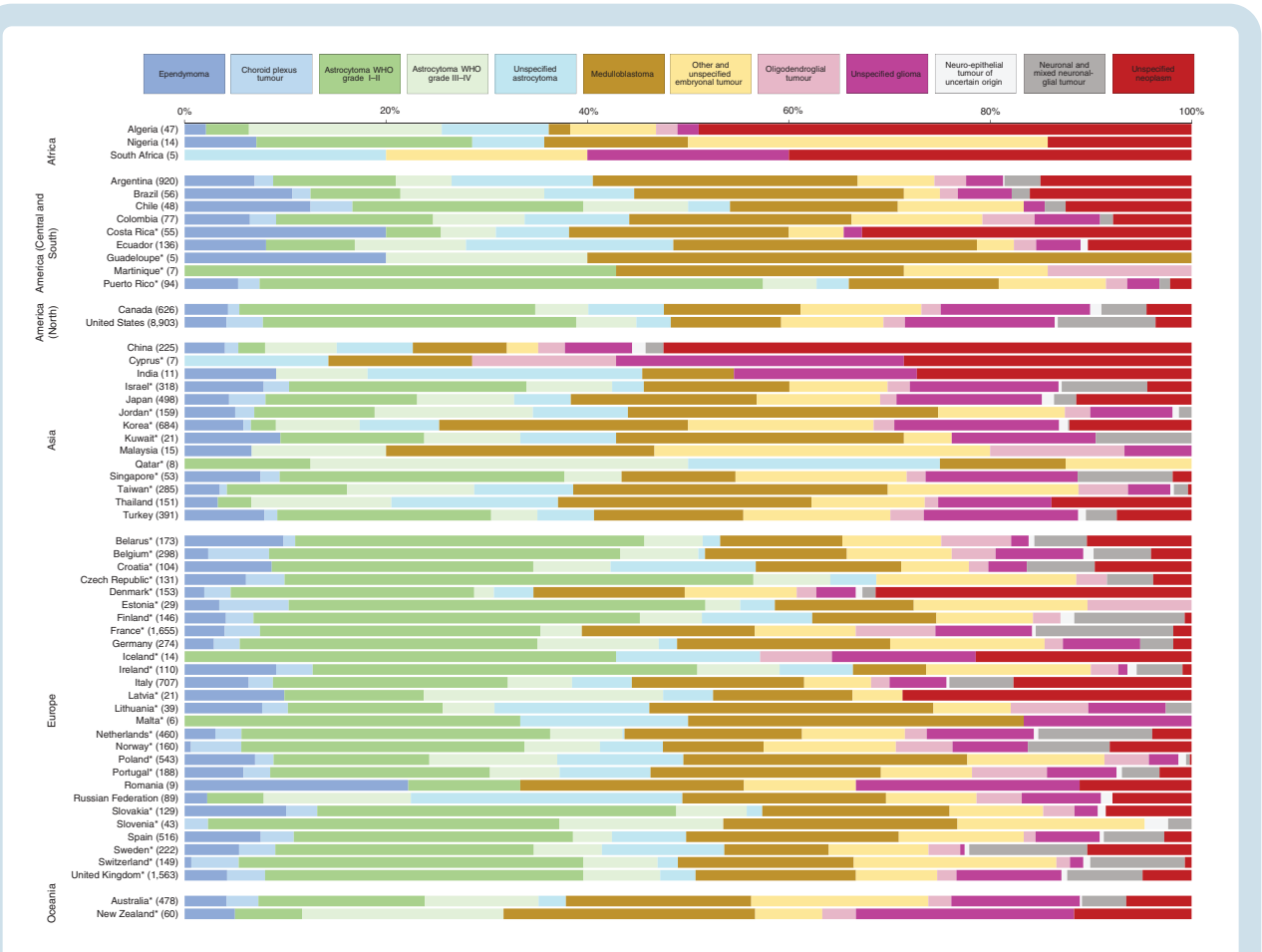

Fig. 1 Histology distribution (%) by country, children (0-14 years), 2005-2009. Numbers in brackets are counts (all brain tumors combined). *Data with 100% coverage of the national population.

countries, and in Argentina, Colombia, Thailand, Croatia, Finland, Poland, the Russian Federation, and Sweden. The highest levels were seen in Ecuador (20%) and the Russian Federation (27%). Unspecified astrocytoma was ungraded (sixth digit of the ICD-O-3 morphology code) in less than 50% of the cases in Puerto Rico, Israel, Belarus, Belgium, Germany, the Netherlands, Slovakia, and New Zealand; in 50%-99% of the cases in African countries, Ecuador, Canada, the United States, China, Japan, Jordan, Taiwan, Turkey, Czech Republic, Italy, Norway, Poland, Portugal, the Russian Federation, Spain, Switzerland, the United Kingdom, and Australia; 100% ungraded elsewhere. Most cases with known grade were assigned grade 1 or 2 in the United States, Israel, Taiwan, Turkey, France, Germany, the Netherlands, the United Kingdom, and Australia. In Jordan, however, there were slightly more tumors with grade 3-4 than 1-2 (Supplementary Tables 1 and 7, Figure 1).

Medulloblastomas represented less than 10% of brain tumors in African countries, and in China and Ireland. The proportion was in the range 10%-19% in 21 of 59 countries; and in the range 20%-29% in Argentina, Brazil, Korea, Thailand, Poland, and New Zealand; the proportion was 30% in Ecuador, 31% in Jordan in Taiwan (Supplementary Table 1, Figure 1).

Unspecified tumors represented less than 10% of brain tumors in most countries. The proportion was in the range 10%-20% in Argentina, Brazil, Ecuador, Japan, Korea, Thailand, Belarus, Italy, and New Zealand. The proportion was 41% in African countries, 33% in Costa Rica, 52% in China, and 31% in Denmark (Supplementary Table 1, Figure 1).

Adults (15-99 Years)—2005-2009

Diffuse and anaplastic astrocytomas accounted for less than 10% of brain tumors in 26 of 59 countries. The proportion was in the range 10%-19% in Argentina, Brazil, Chile, Ecuador, Puerto Rico, the United States, Cyprus, Israel, Jordan, Qatar, Singapore, Taiwan, Austria, Belgium, Czech Republic, Germany, Latvia, Malta, the Netherlands, Poland, Romania, the Russian Federation, Slovakia, Slovenia, Spain, Switzerland, and New Zealand; the proportion was 21% in Estonia (Supplementary Table 2, Figure 2).

The proportion of brain tumors classified as glioblastoma varied from less than 10% to more than 50%. The proportion was below 10% only in China; in the range 10%-29% in Algeria, Nigeria, Costa Rica, Ecuador, India, Malaysia, Thailand, Malta, and the Russian Federation; in

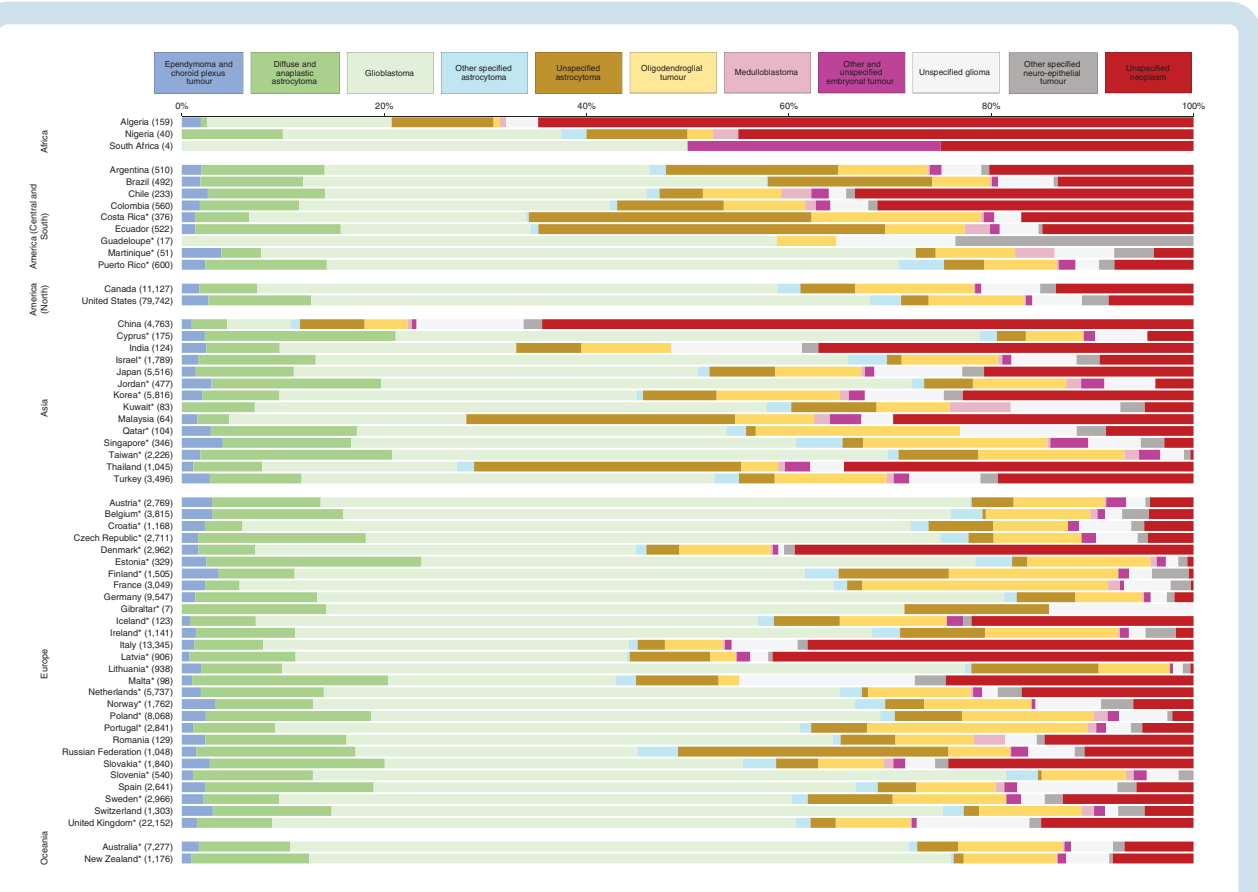

Fig. 2 Histology distribution (%) by country, adults (15-99 years), 2005-2009. Numbers in brackets are counts (all brain tumors combined). *Data with 100% coverage of the national population.

the range 30%-49% in Argentina, Brazil, Chile, Colombia, Japan, Korea, Qatar, Singapore, Taiwan, Turkey, Denmark, Iceland, Italy, Latvia, Romania, Slovakia, and Spain; in the range 50%-70% in Martinique, Puerto Rico, North America, Cyprus, Israel, Jordan, Kuwait, in 21 of 28 participating European countries and in Oceania (Supplementary Table 2, Figure 2).

Unspecified astrocytoma encompassed less than 10% of brain tumors in 43 of 59 countries. The proportion was in the range 10%-19% in Algeria, Argentina, Brazil, Colombia, Finland, and Lithuania, and in the range 20%-29% in Costa Rica, Malaysia, Thailand, and the Russian Federation. The highest level was seen in Ecuador (34%). Unspecified astrocytoma was ungraded (sixth digit of the ICD-O-3 morphology code) in less than 50% of the cases in Puerto Rico, the United States, Cyprus, Israel, Jordan, Qatar, Singapore, Turkey, Belgium, Czech Republic, the Netherlands, Slovakia, Slovenia, Spain, Switzerland, the United Kingdom, and New Zealand; in 50%-99% of the cases in 23 countries; and 100% ungraded in Nigeria, Brazil, Costa Rica, Martinique, Korea, Malaysia, Croatia, Denmark, Estonia, Finland, France, Iceland, Ireland, Latvia, and Sweden. Most cases with known grade were assigned grade 1 in Norway and the Russian Federation, grade 2 or 3 in 30 countries, and grade 4 in Canada (Supplementary Tables 2 and 8, Figure 2).

Brain tumors of unspecified histology accounted for less than 10% of brain tumors in 28 countries. The proportion was in the range 10%-19% in Brazil, Costa Rica, Ecuador, Canada, Turkey, the Netherlands, Romania, the Russian Federation, Sweden, and the United Kingdom; in the range 30%-50% in Nigeria, Chile, Colombia, India, Thailand, Denmark, Italy, and Latvia. The highest levels were seen in Algeria (65%) and China (65%) (Supplementary Table 2, Figure 2).

Basis of Diagnosis—2000-2014

In children, the vast majority of low-grade astrocytomas were histologically verified. The proportion was in the range 90%-94% in Canada and Australia; in the range 95%-99% in the United States, Israel, Japan, Singapore, Turkey, Belgium, Croatia, France, Germany, Italy, the Netherlands, Spain, and the United Kingdom; and 100% in the remaining 38 countries (Supplementary Table 9).

For childhood unspecified neoplasms, a diagnostic confirmation was mostly not available in Central and South America, North America, Asia, Europe, and Oceania (10%-25%), while diagnoses were largely confirmed in Africa (74%) (Supplementary Table 9).

In adults, glioblastomas were mostly histologically verified. The proportion was 79% in Malta; in the range 80%-89%

in Canada, Croatia, Norway, the United Kingdom, and New Zealand; in the range 90%-94% in the United States, Israel, Korea, Kuwait, Austria, Germany, Switzerland, and Australia; in the range 95%-99% in 26 countries; glioblastomas were reported as 100% histologically verified in the remaining 13 countries (Supplementary Table 10).

The proportion of histological verification for unspecified neoplasms, in adults, varied between 4% in Oceania and 65% in Africa (Supplementary Table 10).

Time Trends

The proportion of low-grade astrocytomas in children was fairly stable in all continents during the 15 years between 2000 and 2014. The proportion of unspecified neoplasms rose from 2% to 6% in North America.

In adults, the proportion of glioblastomas during 2000-2014 rose only in Europe (from 46% to 56%) and Oceania (from 57% to 65%). Increasing trends for unspecified neoplasms were observed in Central and South America, while the proportions for both subtypes subsided in Europe and Oceania. In North America, the proportion of unspecified neoplasms rose from 6% to 12%.

Discussion

To our knowledge, this is the first global study of the distribution of brain tumor histology. It spans 60 countries in 5 continents and includes countries, regions, or territories not previously represented in international comparisons. We analyzed individual patient records from 286 population-based cancer registries. Data were collected using the same study protocol and checked using the same data quality procedures to ensure high-quality and robustly comparable information.

There is wide international variation in the distribution of brain tumor subtypes around the world. There were striking international differences in the proportion of low-grade astrocytomas in children (ranging from 6% to 50% in 2005-2009). The proportion of childhood medulloblastomas also varied widely between countries, in several of which it offset the low proportion of low-grade astrocytomas. In adults, the largest international variation was for glioblastomas (from 9% to 69%).

We found wide international disparities in some of the quality indicators, such as the proportion of tumors with an unspecified histology, up to 52% in children and 65% in adults, and the proportion of histologically verified tumors.

Nonmalignant brain tumors should be recorded by all cancer registries because the location of brain tumors is a determinant of the outcome as well as histology. We have provided compelling evidence that remarkable international differences exist in the registration of nonmalignant brain tumors. This was mostly seen for low-grade astrocytomas in children, and for childhood neuronal and mixed neuronal-glial tumors, both of which are mainly nonmalignant subtypes. For instance, Ecuador started recording nonmalignant brain tumors in 2011, while in New South Wales, Australia, only malignant brain tumor subtypes are registered, by law.

ICCC-3 is a well-established standard for conducting studies on childhood tumors, but it does not allow for stratification of astrocytic tumors by WHO grade.[6] Studies on survival from childhood brain tumors published to date have generally adopted ICCC-3, but the interpretation of time trends and international differences is complicated by changes in coding over time and the inconsistent registration of nonmalignant tumors between countries or regions.[11] ICD-O underwent a major change in 2000, coinciding with the release of the third edition. Pilocytic astrocytoma was attributed a behavior code of 3 (malignant) in ICD-O-2 and a behavior code of 1 (borderline) in ICD-O-3.[17,18] In the United States, where registration of nonmalignant tumors has been mandatory since 2004,[19] pilocytic astrocytoma (WHO grade I) alone represented 30% of all childhood gliomas (2007-2011).[20] In countries where nonmalignant tumors are inconsistently recorded, pilocytic astrocytoma has become potentially ineligible for cancer registration since 2000. Failing to record pilocytic astrocytoma, the single most common childhood brain tumor, and any other nonmalignant tumors could potentially lead to underestimation of both incidence and survival for all childhood astrocytic tumors combined, regardless of behavior. If these international differences in cancer registration practices are not properly considered, global disparities in survival for all astrocytic tumors may be wrongly interpreted. Survival in countries or regions that only include malignant brain tumors will be systematically lower than in countries where nonmalignant tumors are also registered. CONCORD-3 showed wide international disparities in survival from childhood brain tumors. For instance, among children diagnosed during 2005-2009, age-standardized 5-year net survival varied from less than 40% in Brazil, 60% in Australia, and close to 80% in Sweden.[15] Those disparities persisted substantially unchanged among children diagnosed during 2010-2014. In our study, during 2005-2009, the proportion of low-grade astrocytoma in Brazil, Australia, and Sweden were 9%, 17%, and 26%, respectively. The use of misleading survival estimates may have huge implications when the public is engaged in research, because it may lead to a distorted perception of cancer burden and risk.

The CONCORD-3 protocol required data to be coded according to ICD-O-3, and both malignant and nonmalignant brain tumors were eligible. In this study, however, pilocytic astrocytoma was still coded as malignant (ICD-O-3 behavior code 3) in 7194 children and 5344 adults. For instance, the proportion of miscoded childhood pilocytic astrocytoma was 70% in Czech Republic and 100% in Canada, the United States, Israel, and Taiwan (data not shown).

Glioblastomas comprised 80% of astrocytic tumors in the 40-99 years age group in North America, Europe, and Oceania during 2000-2014, but only 60% or less in Central and South America (data not shown). Glioblastoma incidence was considerably higher in non-Hispanic Whites than in other ethnicities in the United States during 2000-2014, suggesting that risk alleles are more common in populations of predominantly European ancestry.[9,21] Alternatively, a higher proportion of cases in a given population could reflect an older population, because the

incidence of glioblastoma increases with age. In countries where glioblastomas were more frequently reported in 2010-2014 than in 2000-2004 and 2005-2009, we found a concurrent decline in the proportion of unspecified astrocytomas (eg, Croatia, Poland, Portugal, and the United Kingdom) or the proportion of diffuse and anaplastic astrocytomas (eg, Belgium, France, the Netherlands, and Korea). These findings may suggest improved quality in cancer registration but also a refinement in the pathology workup of astrocytic tumors enabling identification of clinically aggressive subtypes.

We combined diffuse astrocytoma and anaplastic astrocytoma in adults into a single group. Sub-optimal reproducibility of the pathological diagnosis of glioma has been clearly established, with an estimated 20%-30% of gliomas re-classified at the independent review.[22,23] Mutations in the isocitrate dehydrogenase (*IDH*) gene 1 or 2 were recognized to be a genetic hallmark of glioblastoma in 2008.[24] These mutations were later found to characterize 70%-80% of WHO grade II and III gliomas.[25] Tumors harboring an *IDH* mutation have a more favorable outcome.[26,27] Grade II or III gliomas with the same genetic profile have a similar clinical behavior, regardless of the pathological grading.[23]

The definition "astrocytoma NOS" was used in previous studies for ill-defined astrocytic tumors which could not be assigned a more precise descriptor (eg, glioblastoma).[13,14] "Astrocytoma NOS," however, is a standalone definition in ICD-O-3, rather than a category for astrocytic tumors that could not be otherwise specified, and it shares the same morphology code with "diffuse astrocytoma" (WHO grade II).[1,17] In 2005-2009, the proportion of brain tumors that were coded as astrocytoma NOS varied widely between countries, suggesting different practices and interpretations among cancer registries. The quality of cancer registration, however, seemed to improve during 2000-2014, because the use of "astrocytoma NOS" fell substantially in several countries (eg, from 41% to 23% in Ecuador or from 29% to 5% in Thailand). We supposed that the recording of grade (rule G in ICD-O) was accurate. For a given record, if the grade (sixth digit of histology) was coded in the range 1-4, the use of the definition "astrocytoma NOS" was assumed to be a random error at coding level; if the grade was not available (coded to 9), we assumed that the tumor could not be defined more precisely. Such a strategy should control for randomly misclassified astrocytic tumors.

We included both histologically confirmed and histologically unconfirmed brain tumors, in line with previous studies.[9,13,14] The diagnosis of a brain tumor may pose challenges due to anatomical constraints for safely performing biopsy or surgery, or the poor clinical condition of the patient. These hurdles may be more relevant for adults, who are frequently diagnosed at an advanced age. Brain tumors often show pathognomonic appearances at neuroimaging, potentially making a firm clinical diagnosis plausible.[28,29] Nevertheless, the differential diagnosis between a solitary metastasis and a high-grade glioma may be challenging in clinical practice if advanced imaging techniques are not available.[30] International coding guidelines currently restrict the use of a specific morphology code in the absence of histological verification to certain clinical situations (eg, neoplasms located in the brain stem). In all other cases, the morphology code for a tumor of unspecified morphology (ie, 8000-8005) should be preferred if the diagnosis cannot be histologically proven. However, with the refinement of neuroimaging, these guidelines may need to be updated.[31]

In these data, the proportion of histological verification for specified tumor subtypes was around 100% in children, while in adults it was slightly lower, but still in the range 90-100%. The higher proportion of histological confirmation in children than in adults may point to increased diagnostic intensity in children or to the existence of specialist pediatric cancer registries. Very high proportions of histological confirmation, however, may also suggest over-reliance on pathology records for cancer registration, or under-ascertainment of brain tumors.[32] The selective recording of only histologically verified brain tumors may ultimately bias survival estimates upward, because patients receiving a biopsy or surgery are more likely to present in better clinical condition and because the availability of these procedures may reflect better access to treatment in general.

In this study, the proportion of tumors of unspecified histology (ICD-O-3 codes 8000-8005) was generally low, but some countries had high proportions, particularly in adults. Interestingly, in countries where the proportion of unspecified tumors was 30% or more, the quality of data was consistently poor across all participating sub-national registries (data not shown). In some countries (eg, Algeria, China), the proportion of tumors of unspecified histology was higher than the proportion of glioblastoma. These findings suggest that barriers to the accurate reporting of a brain tumor may intervene at all stages, including formulation and clinical recording of the diagnosis, data transmission, and data extraction for the cancer registry. If the accuracy of neuropathology reports is called into question, it is important to measure the effect on patient outcomes, which may be poorer if treatment is not appropriate for the specific histology. Furthermore, survival estimates for specific tumor subtypes are likely to be biased if the histology is fully known for only a subset of records, those estimates may not be robustly generalizable to the entire population of a given country or territory. The broad global variation in the proportion of tumors of unspecified histology calls for caution when interpreting the histology distribution itself, but also in interpreting the survival inequalities for individual brain tumor subtypes or for all brain tumors combined. Overall, we found a decline in the proportions of neoplasms of unspecified histology over the 15-year period 2000-2014, but increasing trends were observed in North America for both children and adults, although both the values and the changes were small. Surprisingly, in several countries, most or even 100% of brain tumors with an unspecified histology were reported as histologically confirmed. One would expect that histologically confirmed tumors could be assigned a specific morphology code. This suggests that the basis of diagnosis may be miscoded, so its use as an indicator of data quality requires caution. We did not exclude countries where the quality of brain tumor reporting was poor, because putting these countries in the context of a large international comparison is crucial to prompt action to improve cancer registration.

Our study provided insights into the data quality indicators that are relevant to reporting of brain tumors worldwide, namely the proportion of tumors of unspecified histology and the proportion of histological verification by brain tumor subtype. However, given the scale of the study, we could not explore other important quality measures, for instance whether multiple data sources were used to capture or validate a brain tumor diagnosis. Ascertainment of nonmalignant brain tumors is likely to be incomplete in several countries. While this finding may suggest poor access to care, it is more likely to reflect disparities in local health regulations, which we could not take into account. Other important indicators of data quality are the proportion of brain tumors registered only from a death certificate or detected at autopsy, or the proportion of patients lost to follow-up in countries using active follow-up, or, alternatively, the proportion of patients censored alive before 5 years from diagnosis where passive follow-up is in place. These indicators, however, are only relevant to the estimation of survival and will be analyzed in the future.

In CONCORD-3, we only collected data for tumors of the brain (ICD-O topography code C71). Diagnoses for histological subtypes in other parts of the CNS, such as germ cell tumors of the pineal gland or optic nerve gliomas, were excluded because they were likely to be misclassified or to represent a minority of the true population of patients for that subtype. For instance, germ cell tumors and optic nerve gliomas accounted for 4% and 6% of all childhood CNS tumors, respectively, in England, during 2001-2010.[33] These tumors are uncommon, but they should ideally be included in future iterations of CONCORD.

In this study, the definition of the histology groupings, and the selection of the relevant ICD-O-3 morphology codes, was based on the WHO Classification of Central Nervous System Tumors, fourth edition (2007).[1] In 2016, however, a revision of the WHO classification revolutionized the taxonomy of CNS tumors by defining tumor entities genetically, and prioritizing the molecular profile over the traditional WHO grading system.[34] ICD-O-3 was updated accordingly. From 2018, the CBTRUS started collecting population-based data from 48 statewide cancer registries using the 2016 WHO categories.[9] It may take a long time for other cancer registries worldwide to follow suit and for data to be used in survival analyses. However, in some countries, molecular assays may simply be unavailable. Notwithstanding these obstacles, international and continental associations of cancer registries should promote transition to the new neuropathology lexicon for data collection, paving the way for modern, informative international comparisons in brain tumor survival by histology.

In conclusion, this study population will be used for further global comparisons of brain tumor survival by histology. International disparities in survival can only be interpreted if a detailed analysis of the histology distribution in each cancer population is available. The quality of data is sub-optimal in several countries. Data from countries with low proportions of ill-defined tumors (ie, of unspecified histology or labeled as NOS) and in which the histology distribution is fairly reproducible over time, may be used to improve the comparability of survival estimates for all brain tumors combined. Standardization by histology, using proportionally weights based on a reliable histology distribution, is one possible approach.

In practice, hurdles to the collection of robust histology data can only be overcome if International Associations of Cancer Registries (IACR) and pathologists (IAP) can cooperate to promote harmonization of data collection. The Global Initiative for Cancer Registry Development (GICR),[35] led by the International Agency for Research on Cancer and the Union for International Cancer Control (UICC), aims to help countries improve the quality of their population-based cancer data by training registry staff and strengthening local health information systems. Other strategies, relevant to both long-standing and more recent cancer registries, include audits at the local and national level on the quality of pathological diagnosis, as well as the quality and completeness of cancer registration. Ultimately, these initiatives would enable clinicians, policy-makers, and other stakeholders to use population-based data on the incidence and survival from brain tumors for public health purposes with greater confidence.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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