Global survival trends for brain tumours, by histology: analysis of individual records for 67,776 children diagnosed in 61 countries during 2000-2014 (CONCORD-3)

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All authors declare no conflicts of interest.

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Abstract

Introduction

Tumours of the central nervous system are among the leading causes of cancer-related death in children. Population-based cancer survival reflects the overall effectiveness of a health care system in managing cancer. Inequity in access to care world-wide may result in survival disparities.

Methods

We considered children (0-14 years) diagnosed with a brain tumour during 2000-2014, regardless of tumour behaviour. Data underwent a rigorous, three-phase quality control as part of CONCORD-3. We implemented a revised version of the International Classification of Childhood Cancer (3rd edition) to control for under-registration of non-malignant astrocytic tumours. We estimated net survival using the unbiased non-parametric Pohar Perme estimator.

Results

The study included 67,776 children. We estimated survival for 12 histology groups, each based on relevant ICD-O-3 codes. Age-standardised five-year net survival for low-grade astrocytoma ranged between 84% and 100% world-wide during 2000-2014. In most countries, five-year survival was 90% or more during 2000-2004, 2005-2009 and 2010-2014. Global variation in survival for medulloblastoma was much wider, with age-standardised five-year net survival between 47% and 86% for children diagnosed during 2010-2014.

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Conclusions

To the best of our knowledge, this study provides the largest account to date of global trends in population-based survival for brain tumours in children, by histology. We devised an enhanced version of ICCC-3 to account for differences in cancer registration practices world-wide. Our findings may have public health implications, because low-grade glioma is one of the six index childhood cancers included by WHO in the Global Initiative for Childhood Cancer.

Keywords

childhood cancer, brain tumour, survival, international comparisons, cancer registries

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Key points

A global study of trends in population-based survival from brain tumours in children

Wide variation in survival suggests inequalities in access to care

Survival estimates provide a baseline for evaluating the WHO Global Initiative for Childhood Cancer

Importance of the study

We conducted novel, up-to-date analyses of brain tumour survival in children, using CONCORD-3 data. The geographical coverage of CONCORD-3 was broader than any previous international comparison of cancer survival. A standardised protocol for data collection ensured that information was collected based on the same set of patient-related and tumour-related variables. For the first time in an international comparison of survival, we implemented a revised version of ICCC-3 to account for international differences in registration practice for low-grade tumours. We presented what are, to our knowledge, the first global survival estimates for low-grade tumours in children. Although low-grade glioma is one of the six index childhood cancers included by WHO in the Global Initiative for Childhood Cancer, global survival estimates for this histology group are not available. Our findings may be used as a benchmark to monitor improvements in survival from childhood brain tumours at a global level.

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Introduction

Tumours of the central nervous system (CNS) rank second after leukaemia as a cause of cancer-related death in children.[1] CNS tumours may originate in the brain, the meninges or the spinal cord, but the brain is by far the most common site. In children, age-standardised (world) incidence rates in 2018 ranged from an estimated 0.5 per 100,000 person-years in Africa to 2.3 in Europe and the Americas.[2] Health care disparities, however, may lead to substantial under-diagnosis or under-registration. Up to 57% of childhood cancer diagnoses may be missed in Western Africa, compared with 3% in North America and Western Europe.[3]

Health care facilities are unevenly distributed world-wide.[4-6] In some countries, for instance, radiotherapy facilities are simply not available. Unmet need for treatment due to sub-optimal access to the healthcare system translates to many years of life lost and extended periods of disability.[7] Given that only 10% of children live in high-income countries, the social burden of childhood cancer in low-income and middle-income countries is disproportionately great in countries that are generally least well equipped to deal with that burden.[8, 9]

Population-based survival is a key metric to evaluate the performance of the health care system in a given country in managing cancer.[10-12] In 2015, the CONCORD programme began global surveillance of trends in cancer survival with data for patients diagnosed during the 15-year period 1995-2009.[13] The third cycle of the programme (CONCORD-3), covering 71 countries, included individual data for more than 37 million patients diagnosed during 2000-2014 with one of 18 common cancer types, including childhood brain tumours.[14] Global differences in age-

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standardised five-year net survival for all childhood brain tumours combined were very wide, ranging between 29% in Brazil and 89% in Sweden.

Brain tumours represent a disparate group of subtypes, with more than 50 histological entities.[15] Histology is an important determinant of outcome, so international comparisons in brain tumour survival can be more meaningful for health care planning if they account for histology. Survival estimates that take account of histology enable better interpretation of international differences in survival for all brain tumours combined, since these differences are confounded by the heterogeneity of clinical behaviour and global variation in the distribution of histological types.[16]

The third edition of the International Classification of Childhood Cancer (ICCC-3) has become established as the standard tool for categorising childhood tumours by histology.[17] ICCC-3 is a scheme with three progressively more granular tiers. However, the third tier does not contain distinct entities for astrocytoma, so it is not possible to analyse low-grade and high-grade astrocytic tumours separately using data classified with ICCC-3, and alternative approaches are seldom used.[18] The third edition of the International Classification of Diseases for Oncology defines as non-malignant (ICD-O-3 behaviour code 0 or 1) most of the low-grade brain tumours, including pilocytic astrocytoma,[19] which alone comprises 70% of all childhood astrocytic tumours.[16, 20]

This has important implications for international comparisons of brain tumour survival. Non-malignant tumours are not consistently recorded world-wide, due to differences in health regulations and cancer registration practice. Registration of non-malignant brain tumours is important because not only tumour behaviour, but

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the anatomical site also has an effect on diagnosis, treatment choices and outcome. The World Health Organisation (WHO) grade of the tumour must therefore be incorporated in survival analyses for astrocytic tumours in children, because international comparisons of survival based on data coded to ICCC-3 are otherwise uninterpretable, owing to the very different proportions of low-grade and high-grade astrocytic tumours in cancer registry data.

To date, studies of survival from childhood brain tumours by histology have not been readily comparable because of differences in study design, especially as to the inclusion or exclusion of non-malignant brain tumours.[16] Nearly all these studies have been conducted in high-income countries. No data are currently available for Africa, Central and South America, or most of Asia.

We set out to conduct a world-wide study of population-based survival from childhood brain tumours, using data collected with a central protocol, checked for quality using standardised rules and analysed with the same robust statistical methods.

Patients and methods

For CONCORD-3, individual tumour registrations for 71,526 children (0-14 years) diagnosed with a brain tumour (ICD-O-3 topography code C71), whether malignant or non-malignant, during 2000-2014 were provided by 261 cancer registries in 61 countries.

Each tumour record was subjected to rigorous quality checks for eligibility and definite or possible errors.[21] Possible errors included implausible combinations of

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age, sex, site and morphology. Each registry was invited to confirm or refute records with possible errors.

We defined 12 histology groups, each comprising a set of relevant ICD-O-3 codes. The methodology and the principles for selecting the ICD-O-3 codes are explained elsewhere.[16] In brief, the histology groups were based on ICCC-3, but we devised more granular categories for astrocytic tumours by incorporating WHO grade, which forms part of the tumour subtype definition. The sixth digit of the ICD-O-3 code defines the grade of differentiation of a tumour (Rule G), as assigned by the pathologist or the tumour registrar. We used the sixth digit of the morphology code to reclassify tumours recorded as "astrocytoma NOS" to more specific astrocytic subtypes (Supplementary Table 1).

Net survival is the cumulative probability that cancer patients survive their cancer up to a given time since diagnosis (e.g. five years), after accounting for competing risks of death (background mortality) and for informative censoring. Net survival can be directly estimated obtained using the unbiased, non-parametric Pohar Perme estimator.[22] Data on background mortality are derived from life tables of all-cause mortality specific for single year of age, sex, single calendar year and race/ethnicity (where information was available) in the general population of each participating country or territory.[23] We used the software package *stns*[24] implemented in STATA (version 16).

Survival was not estimated if fewer than ten patients were available for a given histology group, calendar period and country or region. If 10-49 patients were available, we produced unstandardised estimates of survival for all ages combined. We attempted age standardisation if 50 children or more were available.

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Standardisation was obtained by applying equal weights to the age-specific survival estimates for children aged 0-4, 5-9 and 10-14 years.[25,26] If a single age-specific estimate could not be computed, we pooled the records for two adjacent age groups and attributed the aggregated estimate to both age groups before age standardisation. We did not combine data for consecutive calendar periods.[14]

The cohort approach provides a survival estimate for a group of patients diagnosed in the same year and all followed up for the same amount of time, e.g., for at least five years. We used the cohort approach for patients diagnosed during 2000-2004 and 2005-2009. For children diagnosed during 2010-2014, we adopted the period approach, since five years of follow-up were not available for most patients. This approach combines the most recent follow-up data for cancer patients diagnosed during a specified year and the follow-up data for patients diagnosed up to five years earlier and who were still alive at the start of the specified year of diagnosis. The survival prediction derived from this approach is conditional because it incorporates the survival probabilities matured over the preceding years when most of the individuals were diagnosed. Empirical evidence shows that period estimates provide a good approximation to the cohort estimates when they become available in due course.[27, 28]

We produced five-year survival estimates for tumours in each histology group, by country and calendar period. For selected tumour types, we also examined longer-term survival, up to 10 years from diagnosis.

We flagged survival estimates as less reliable if 15% or more of patients were lost to follow-up or censored within five years. We also considered estimates as less reliable if 15% or more of registrations were based solely on a death certificate or

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autopsy and excluded, because their survival time is unknown. Finally, survival estimates were flagged as less reliable if 15% or more of records were excluded from analysis because they contained one or more incomplete dates. Unreliable estimates were not included in pooled national survival estimates unless they were the only estimates available from that country, in which case the national estimate is flagged.

The CONCORD programme is approved by the UK's statutory Health Research Authority (reference ECC 3-04(i)/2011; last update 2 November 2021), the National Health Service Research Ethics Service (11/LO/0331; 12 January 2022), and the London School of Hygiene & Tropical Medicine Ethics Committee (12171; 21 November 2021).

Results

The proportion of records with incomplete dates was less than 1% in North America, Asia, Europe and Oceania, 2.4% in Central and South America and 10.7% in Africa. Overall, children registered through a death certificate only (DCO) comprised 1.1% of all submissions. DCO proportions for Africa (6.8%) and Central and South America (5.9%) were higher than in other continents (2% or less). The proportion of brain tumours with histological confirmation was generally high, in the range 88-98%. Brain tumours registered with a non-specific histology (ICD-O-3 morphology code 8000-8005) only represented 3.2% of all brain tumour diagnoses in North America, but they accounted for 26.3% in Africa (Supplementary Table 2). Following quality checks, 67,776 records were retained for analysis (94.8% of those eligible for inclusion).

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Of the 67,776 children potentially eligible for survival analyses, we excluded a further 6,559 (9.7%) because the morphology code did not fall within one of the histology groups selected for this study. We also excluded 6,310 (9.3%) records from 57 registries for which survival estimates were deemed less reliable. The analyses included 54,907 tumour records (81.0% of eligible tumour records).

Comments in this section are focussed on reliable, age-standardised survival estimates. When examining time trends, we only discuss countries for which reliable, age-standardised survival estimates were available for 2000-2004, 2005-2009 and 2010-2014. For each continent, countries are listed in alphabetical order.

For low-grade astrocytomas (WHO grade I and II; 26.6% of all brain tumours included), age-standardised five-year net survival during 2010-2014 was in the range 80-89% in Taiwan, Turkey and Spain; 90-94% in eight of 20 European countries (Belarus, Belgium, France, Greece, Italy, the Netherlands, Slovakia and Switzerland) and in Australia. Survival was highest (95-100%) in Canada, the United States, Israel, Japan, two Eastern European countries (Czech Republic and Poland), Germany, six Northern European countries (Denmark, Finland, Ireland, Norway, Sweden and the United Kingdom) and Portugal. (Supplementary Table 3A, Figure 1).

For children diagnosed with a low-grade astrocytoma during the 15 years between 2000 and 2014, age-standardised five-year net survival remained above 90%, largely unchanged, in North America, Israel, Northern Europe (Finland, Sweden and the United Kingdom), Western Europe (France, the Netherlands, Italy and Switzerland) and Italy. Survival in Spain, 92% during 2000-2004, subsided to values around 85% during 2005-2014. Marked improvements in survival occurred in

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Eastern Europe: survival rose from 78.1% to 92.4% in Belarus and from 86.5% to 95.1% in Poland. Survival in Australia, around 87% during 2000-2009, reached 90.9% during 2010-2014 (Supplementary Table 3A, Figure 2).

Outcomes for high-grade astrocytomas (WHO grade III and IV; 7.4% of all tumours included) were rather poor. Reliable, age-standardised estimates were only available for eight countries. Five-year survival during 2010-2014 was 6.3% in France, 17.1% in the United Kingdom, in the range 20-29% in the United States, South Korea, Taiwan, Italy and Australia; and 31.2% in Poland (Supplementary Table 3A).

Of the five countries for which reliable, age-standardised survival estimates for high-grade astrocytoma were available throughout the study period, four (South Korea, Poland, the United Kingdom and Australia) showed little consistent change in survival during 2000-2014, while five-year survival in the United States declined steadily from 28.9% in 2000-2004 to 23.1% in 2010-2014 (Supplementary Table 3A, Figure 2).

Wide variation in survival was seen for medulloblastoma (15.7% of all brain tumours included), which is the most common embryonal CNS tumour. Age-standardised five-year net survival for children diagnosed between 2010 and 2014 was less than 50% in Belarus and Spain; it ranged between 50% and 59% in Turkey and Greece; between 60% and 69% in Taiwan and seven of 20 European countries (Belgium, France, Italy, the Netherlands, Poland, Switzerland and the United Kingdom). Survival was in the range 70-79% in Canada, the United States, Japan, South Korea, Denmark, Germany and Australia. The highest survival was observed

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in Israel (81.0%), Portugal (80.6%) and Sweden (88.0%) (Supplementary Table 3A, Figure 1).

Fifteen-year trends in age-standardised five-year net survival from medulloblastoma were only available for nine countries. Survival was stable, or fluctuating slightly, in Poland (in the range 55-60%), in France, Italy and Australia (64-72%), and in the United States (70-75%). Survival from medulloblastoma rose from 60.5% to 70.0% in South Korea, from 56.4% to 62.7% in Taiwan, and from 51.8% to 63.3% in the Netherlands, while it fell from 68.8% to 61.5% in the United Kingdom (Supplementary Table 3A, Figure 3).

The subgroup “other and unspecified embryonal tumours” (10.8% of children included in these analyses) consisted almost entirely of atypical/teratoid rhabdoid tumour and embryonal CNS tumour not otherwise specified (NOS) (formerly known as primitive neuroectodermal tumour). Age-standardised five-year net survival (2010-2014) for children diagnosed with one of these tumours ranged between 30% and 39% in Canada and Israel; between 40% and 49% in Japan, Taiwan, Turkey, France, the Netherlands and Australia, and between 50% and 59% in the United States, South Korea, Poland, Sweden and the United Kingdom. Survival was 65.6% in Belgium, 83.5% in Italy and 84.5% in Germany (Supplementary Table 3B).

Trends in age-standardised five-year net survival for the “other and unspecified embryonal tumours” subgroup could be reliably estimated for six countries. In four of them (United States, South Korea, Poland and the United Kingdom), survival remained within the range 48-57% throughout. Survival increased between 2000-2004 and 2010-2014 from 40.7% to 48.6% in France and from 29.9% to 48.2% in Australia (Supplementary Table 3B).

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Data for ependymoma were rather sparse (2,685 records; 4.9% of all brain tumours included in the analyses). Age-standardised five-year net survival for children diagnosed during 2010-2014 was 54.0% in Turkey, 59.7% in South Korea, 79.3% in Poland and in the range 80-90% in the United States, France, Italy and the United Kingdom (Supplementary Table 3A).

Trends in age-standardised five-year net survival for ependymoma could be reliably estimated calculated for three countries (United States, France and the United Kingdom). Survival increased in all three countries, from 65.1-75.8% for children diagnosed in 2000-2004 to 79.1-82.3% in 2005-2009 and 81.3-89.9% in 2010-2014 (Supplementary Table 3A).

Age-standardised five-year net survival estimates for children diagnosed with neuronal and mixed neuronal-glial tumours during 2010-2014 were in the range 89-100% for 10 countries (Canada, United States, Belgium, Finland, France, Italy, the Netherlands, Sweden, the United Kingdom and Australia). For the other, less common histology groups, there were fewer countries with sufficient cases for age-standardised survival to be calculated. Survival of children with choroid plexus tumours during 2010-2014 was at least 90% in the United States, France and the United Kingdom. Five-year survival for oligodendroglial tumours was 51.3% in France, and appreciably higher in the United Kingdom (70.4%), South Korea (73.4%) and the United States (83.0%), during 2010-2014. Age-standardised five-year net survival for children diagnosed with neuroepithelial glial tumours of uncertain origin during 2010-2014 could only be estimated in the United States, where it was 67.1% (Supplementary Table 3A and 3B).

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Age-standardised five-year net survival for children diagnosed during 2010-2014 with glioma, otherwise unspecified (ICD-O-3 morphology code 9380/3) varied between 30% and 39% in Japan, France, the Netherlands and Australia; between 40% and 49% in Canada, South Korea, Turkey and the United Kingdom, and in the range 50-61% in the United States, Israel, Belgium and Italy (Supplementary Table 3B).

During 2010-2014, at least 10 children were diagnosed with a brain tumour labelled as unspecified (ICD-O-3 morphology codes 8000-8005) in 22 of 46 countries from which data were available. Variation in age-standardised five-year net survival for these poorly specified neoplasms was remarkable: 35.8% in China, 58.5% in South Korea, 72.3% in Italy, 77.9% in the United Kingdom and in the range 80-89% in the United States, Japan, Turkey, Denmark and Australia (Supplementary Table 3B).

We assessed survival at 10 years for children diagnosed with low-grade astrocytoma or medulloblastoma during 2000-2004 (Supplementary Table 5). For low-grade astrocytoma, age-standardised ten-year survival and five-year survival differed by less than 3% in 12 of the 15 countries for which suitable data were available. The difference was slightly larger (3% or more) in Argentina, Belarus and Australia. For medulloblastoma, the absolute difference between five-year and 10-year net survival was in the range 0-4% in Argentina, the United States, South Korea, Italy, the Netherlands and Australia, but in the range 6-10% in Israel, Taiwan, France, Poland and the United Kingdom.

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Discussion

To our knowledge, this is the largest study on survival from childhood brain tumours to date. Individual records for over 50,000 children were provided to a standard protocol by 261 population-based cancer registries in 61 countries, prepared with the same rigorous quality checks, and analysed with the same, robust statistical methodology.

Age-standardised five-year net survival for low-grade astrocytoma (WHO grade I and II) was 90% or more during the whole period between 2000 and 2014 in most countries. World-wide variation in survival for medulloblastoma was much broader than for low-grade astrocytoma, with age-standardised five-year net survival in the range 47-86% during 2010-2014.

In most previous international comparisons of survival from childhood brain tumours, the broad definition “astrocytoma” has been adopted, in compliance with ICCC-3.[18, 29-32] Such survival estimates cannot be safely compared with those presented here, since we did not merge low-grade and high-grade astrocytic tumours.

More than two-thirds of low-grade brain tumours in children are pilocytic astrocytomas.[20] ICD-O-3 classifies pilocytic astrocytoma as a non-malignant entity (ICD-O-3 behaviour code 1).[19] In the fourth cycle of the cancer-registry based study on survival and care of cancer patients diagnosed in Europe during 1995-1999 (EUROCARE-4), five-year observed survival for astrocytoma (broad group) was rather poor in Eastern Europe, around 64%, irrespective of inclusion of non-malignant tumours, and lower than in other European regions. These findings suggested under-registration of non-malignant brain tumours in Eastern Europe.[30] In

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EUROCARE-5, covering the period 1999-2007, survival from childhood brain tumours was presented by tumour behaviour (malignant or non-malignant), but this design does not account for histology.[33] Alternatively, EUROCARE-5 provided survival estimates for the whole of Europe combined, by single ICD-O-3 morphology code, but this more granular approach cannot be readily implemented in large international comparisons of survival by histology.[34]

Despite international recommendations, non-malignant tumours are still recorded inconsistently, not only in Europe, but world-wide. For instance, health regulations in New South Wales mandate registration of malignant tumours only, while Ecuador started recording non-malignant brain tumours only from 2010. In the CONCORD-3 data for children diagnosed with a brain tumour during 2000-2014, malignant tumours (ICD-O-3 behaviour code 3) accounted for 80% of all tumour records in Australia (but 100% in New South Wales, which comprises 45% of the national population), and the totality of cases in South Korea, Taiwan and New Zealand (data not shown). If these international differences in cancer registration practices are not properly considered, global disparities in survival for all astrocytic tumours may be wrongly interpreted. Survival in countries or regions that only include malignant brain tumours will be systematically lower than in countries where non-malignant tumours are also registered. We conducted a sensitivity analysis. Age-standardised five-year net survival for all astrocytic tumours combined (ICCC-3 category) ranged from 43% to 88% world-wide during 2010-2014 (Supplementary Table 4). By contrast, survival was in the range 84-100% for low-grade tumours and in the range 6-30% for high-grade tumours. The remarkable difference in global disparities in survival when more granular categories are used confirms that international comparisons of survival for astrocytic tumours should take account of

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confounding by tumour grade. Where possible, estimates for low-grade and high-grade tumours should be reported separately.

Even where there is complete registration of non-malignant brain tumours, including pilocytic astrocytoma, variations in registration practice could affect reported survival estimates for low-grade astrocytoma. Pilocytic astrocytoma and the other specific types of WHO grade I astrocytoma all have specific morphology codes in ICD-O-3. Diffuse astrocytoma, however, which is the principal type of WHO grade II astrocytoma, shares the morphology code 9400/3 with astrocytoma NOS. Thus, it is only possible to identify most cases of WHO grade II astrocytoma in datasets from cancer registries that have routinely used and supplied the sixth digit of the morphology code (grade). In CONCORD-3, there were many datasets in which grade was never specified for cases with morphology code 9400/3, including seven where this code accounted for at least 30% of all astrocytomas (Argentina, Brazil, Colombia, Costa Rica, South Korea, Croatia and Latvia), and others where it was very rarely specified.[16] This would lead to a deficit of WHO grade II astrocytoma cases, with a poorer prognosis than WHO grade I, tending to overestimation of survival for low-grade astrocytoma.

In recent years, neuro-pathologists have increasingly classified diagnoses based on molecular characteristics, which has improved the identification of astrocytic tumours with more aggressive behaviour. The relatively broad variation in survival for high-grade astrocytoma suggest that in some countries these strategies may have been implemented earlier than elsewhere. The decrease in survival over time for high-grade astrocytoma in the United States, with concurrent increases in

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survival for unspecified glioma and unspecified tumour, may also reflect improvements in diagnostic accuracy.

Comparisons of survival between countries could be affected by variations in diagnostic practice. There was formerly a marked tendency in France to regard some cases of WHO grade II and grade III astrocytoma as oligodendroglioma,[35] as reflected in the unusually high proportion of childhood brain tumours classed as oligodendroglial tumours in CONCORD-3.[16] Although in France this proportion fell from 7-8% in 2000-2009 to 4.4% in 2010-2014, it was still considerably higher than in most other countries and it seems likely that this would have resulted in underestimation of survival for high-grade astrocytoma. During 2000-2014, the proportion of embryonal tumours that were classed as medulloblastoma was lower in North America and Oceania than in Europe and Asia, and highest in Central and South America. While this could of course be due to real differences in incidence between populations, it seems likely that it was partly due to variation in the frequency with which, for example, atypical/teratoid rhabdoid tumour was identified as such rather than as medulloblastoma. Since atypical teratoid/rhabdoid tumour has a dismal prognosis, this could have led to underestimation of survival for medulloblastoma.

Five-year survival for medulloblastoma during 2010-2014 was in the range 70-80% in several high-income countries. These values are in line with those from recent national studies assessing survival for children diagnosed during 2001-2009 in Germany (72-80%) and the United States (also 72-80%),[16,36-48] but higher than the survival levels seen during the 1990s. This may reflect recent advances in treatment protocols for children with medulloblastoma that revolve around two main pillars:

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reduction of the radiotherapy dose to minimise long-term neurological sequelae, and treatment intensification only for high-risk patients.[49] Other reasons for these survival gains may be the implementation of volumetric radiotherapy, better surgery with removal of larger tumour volumes and fewer complications, and more timely referral for post-surgical treatment.[49,50] However, the wide global inequalities in survival strongly suggest that in some countries, children may still not have access to optimal treatment for medulloblastoma. Most childhood brain tumour subtypes have a favourable outcome, but timely surveillance for relapse and optimal follow-up care are both crucial.[51] The comparisons of five-year and 10-year survival for low-grade astrocytoma and medulloblastoma should be interpreted with caution, because the changes are still small. However, it would seem that net survival tends to plateau after five years in some countries, suggesting low excess mortality among survivors to that point, whereas in other countries, brain tumour survivors may remain at higher long-term risk of death than children in the general population for more than five years.

Up to two-thirds of pilocytic astrocytomas originate in the cerebellum, while the most common supra-tentorial sites are the optic nerve and the optic chiasm. When pilocytic astrocytoma involves the optic pathways, it is also called “optic nerve glioma”.[15] These tumours are often not biopsied, because of the high risk of visual loss, and the diagnosis is made through a combination of imaging and testing of the visual fields. These tumours may thus be incorrectly labelled in the cancer registry with the ICD-O-3 descriptor “glioma not otherwise specified (NOS)” (ICD-O-3 morphology code 9380/3).[34] CONCORD-3 only collected information for tumours originating in the brain. Nevertheless, we cannot exclude that, given the close anatomical proximity, inaccuracies at clinical record level may have led to some optic

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nerve gliomas being wrongly labelled, and submitted, with the ICD-O-3 topography code used for brain (C71), instead of the code for optic pathways (C72.3). We considered that some of the poorly specified gliomas might in fact have been pilocytic astrocytomas of the optic pathways. Five-year survival for unspecified glioma was much lower than for pilocytic astrocytoma, and for 87% of these records, the tumour grade was unspecified (6th digit 9), so we could not confirm the non-malignant behaviour.

In the CONCORD-3 childhood brain tumour dataset, the proportion of tumours of unspecified histology (ICD-O-3 morphology codes 8000-8005) varied widely, ranging from 5.0% in Europe to 21.7% in Africa during 2010-2014.[16] In CONCORD-3, age-standardised five-year net survival for all childhood brain tumours combined was only 29.9% in Brazil, but close to 80% in Denmark, Slovakia and Sweden.[14] After excluding children with tumours of unspecified histology, survival was still poor in Brazil (35%), but only 69% in Denmark, while it remained substantially unchanged in Slovakia and Sweden (data not shown). During 2010-2014, the proportion of tumours of unspecified histology was only 14.6% in Brazil, but 55.1% in Denmark.[16] One may think that patients with tumours of unspecified histology may have been too unwell to undergo biopsy or surgery and, as a result, experience poor outcomes. However, five-year survival during 2010-2014 for Danish children with tumours of unspecified histology was as high as 88.3%. This probably explains the impact of excluding these tumours on survival estimates for all brain tumours combined. Such discrepancies suggest that obstacles to accurate reporting of a brain tumour diagnosis may arise in both the hospital and the cancer registry. If the histology is known for only a subset of brain tumour patients, the interpretation of survival estimates requires great caution, whether for all childhood brain tumours combined

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or for specific tumour sub-types. These survival estimates may not be robustly comparable with estimates from countries where data on histology are more precise. Our findings should enable public health officials to prompt actions aimed at improving the reporting of brain tumours, such as audits at local and national level.

We excluded data from cancer registries that were considered less reliable, based on the criteria previously outlined. In a sensitivity analysis, we re-estimated survival by histology after inclusion of data from flagged cancer registries. Overall age-standardised survival estimates were slightly higher. This is not surprising, because one of the reasons for flagging was the high proportion (15% or more) of the patients lost to follow up or censored before five years. The absolute increase, however, was unremarkable, with differences varying between 1.5% in the United States and 4.4% in Spain (data not shown). These findings suggest that the exclusion of less reliable records (9.3% of eligible submissions) did not explain the large differences in survival by country worldwide.

The Lancet Oncology Commission on Sustainable Care for Children with Cancer recently presented evidence for the implementation of cost-effective interventions to reduce the long-term clinical and economic burden of childhood cancer.[52] The evidence included modelled estimates of survival for children diagnosed during 2015-2019, by histology, for over 200 countries and territories. Survival was modelled from CONCORD-3 estimates for 2000-2014. The Commission adopted ICCC-3 to classify childhood tumours, so it could not present any data for low-grade astrocytoma. This was also a major limitation of the Global Burden of Disease study, which cannot account for histology because it is based on topography descriptors from the International Classification of Diseases (ICD).[7,9] We

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have presented, for the first time to our knowledge, survival estimates for low-grade astrocytoma at a global level.

In the CONCORD-3 data for the US, where registration of non-malignant tumours is statutory,[53] astrocytomas accounted for 63.7% of all low-grade gliomas during 2000-2014. Low-grade glioma is one of the six index cancers included in the WHO Global Initiative for Childhood Cancer, which aims to improve five-year net survival for these six childhood cancer types, world-wide, by 2030.[54] The classifier "low-grade glioma" is very ill-defined, and it overlooks the complex histologic makeup of childhood brain tumours. ICCC-3 adopts more granular categories, but it does not consider tumour behaviour. We overcame the limitations of ICCC-3 using a classification that preserves the ICCC-3 framework but incorporates tumour grade. Ultimately, our findings may form the basis for a revision of ICCC-3.

Our study has some limitations. The date of the first course of each major treatment modality was an optional variable in the CONCORD-3 data specification, and data on whether a patient underwent radiotherapy for a brain tumour was only provided available by a few countries. In this context, granular treatment data may be used to assess adherence to treatment guidelines or abandonment of treatment. Data quality was sub-optimal in some countries due to the low precision of histology data,[16] or to the high proportion of patients whose duration of survival was not known. We decided to present, and flag, survival estimates based on these less reliable data as well, if they were the only data available for a given country or territory. We believe that countries should not be excluded from a study for reasons of lower or more questionable data quality, because their inclusion in large international comparisons is crucial to promote change.

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Robust histology data can only become available if a common, statutory framework for data collection is in place. World-wide co-operation between international associations of pathologists and cancer registries will be essential to identify and remove obstacles to the accurate reporting of brain tumour diagnoses, and to promote transition to a more informative and up-to-date neuropathology lexicon. Moreover, the quality of cancer registration can only improve if specific funding to train tumour registrars and to strengthen health information systems in cancer registries is made available. High-quality data, and data from more low-income and middle-income countries, will enable robust global comparisons of survival. These will prove instrumental in monitoring progress toward the global targets for better control of childhood cancer set by the World Health Organisation.

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Figure legends

Figure 1. Age-standardised five-year net survival (%) with 95% confidence interval, by country: children (0-14 years) diagnosed with low-grade astrocytoma or medulloblastoma during 2010-2014. * Countries with 100% coverage of the national population. § Survival estimates not age-standardised. Continents are identified by different colours. In each panel, countries are ranked from highest to lowest, based on survival during 2010-2014.

Figure 2. 15-year trends in age-standardised five-year net survival (%) for children (0-14 years) with WHO grade I and II astrocytoma, by calendar period of diagnosis, continent (or continental region) and country. Countries are only included if age-standardised survival estimates were available for patients diagnosed during 2000-2004, 2005-2009 and 2010-2014. Continents (or continental regions) are identified by different colours. In each panel, countries are ranked from highest to lowest, based on survival during 2000-2004. X-axis: period of diagnosis; Y-axis: age-standardised five-year net survival (%). Standard International Organization for Standardization abbreviations for country names: Australia=AUS; BLR=Belarus; Canada=CAN; Finland=FIN; France=FRA; Israel=ISR; Italy=ITA; Netherlands=NLD; Poland=POL; Spain=ESP; Sweden=SWE; Switzerland=CHE; UK=GBR; USA=USA.

Figure 3. 15-year trends in age-standardised five-year net survival (%) for children (0-14 years) with medulloblastoma, by calendar period of diagnosis, continent (or continental region) and country. Countries are only included if age-standardised

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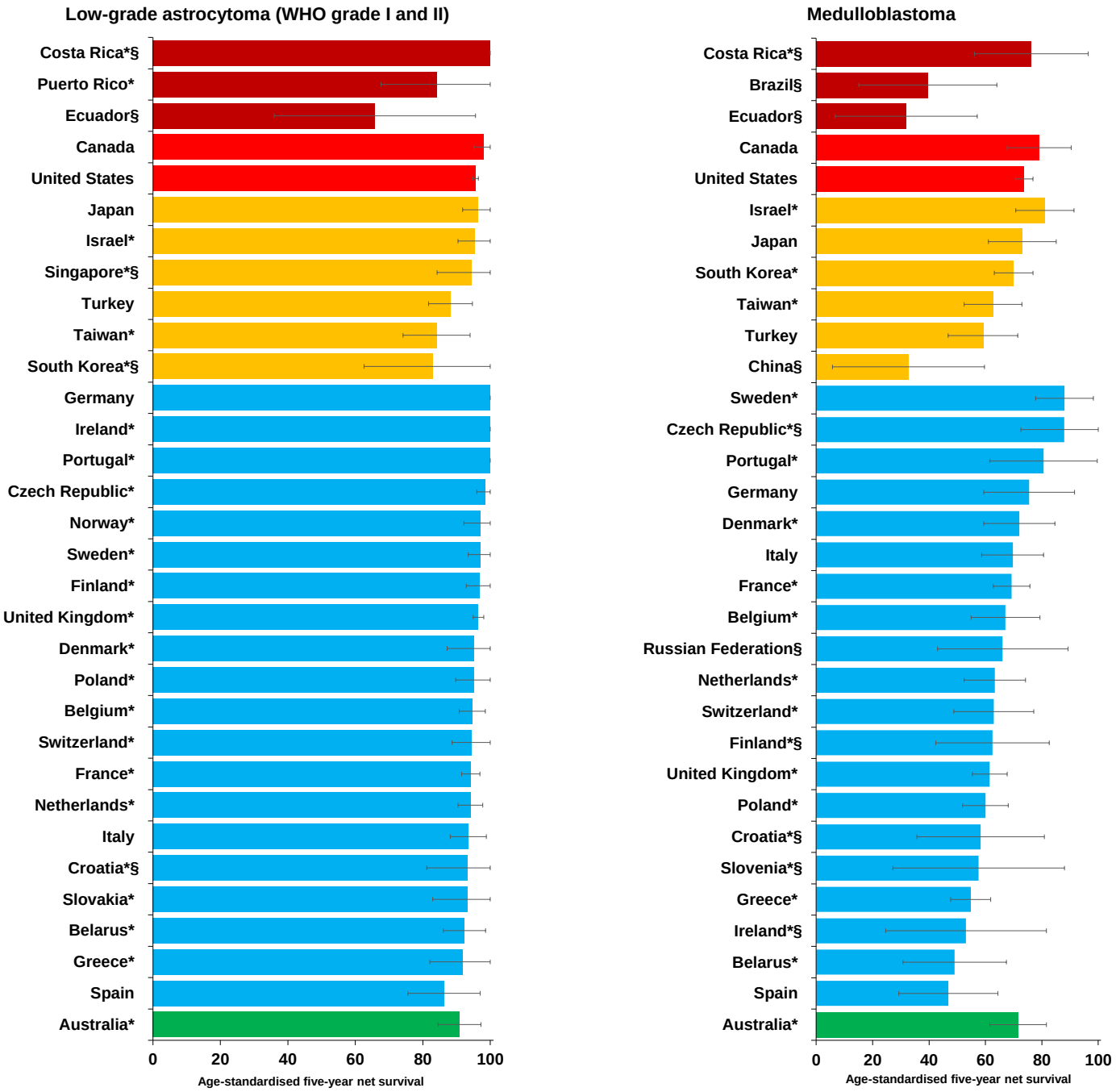
Figure 1. Age-standardised five-year net survival (%) with 95% confidence interval, by country: children (0-14 years) diagnosed with low-grade astrocytoma or medulloblastor 2010-2014.



* Countries with 100% coverage of the national population. § Survival estimates not age-standardised. Continents are identified by different colours. In each panel, countries are ranked from highest to lowest, based on survival during 2010-2014.

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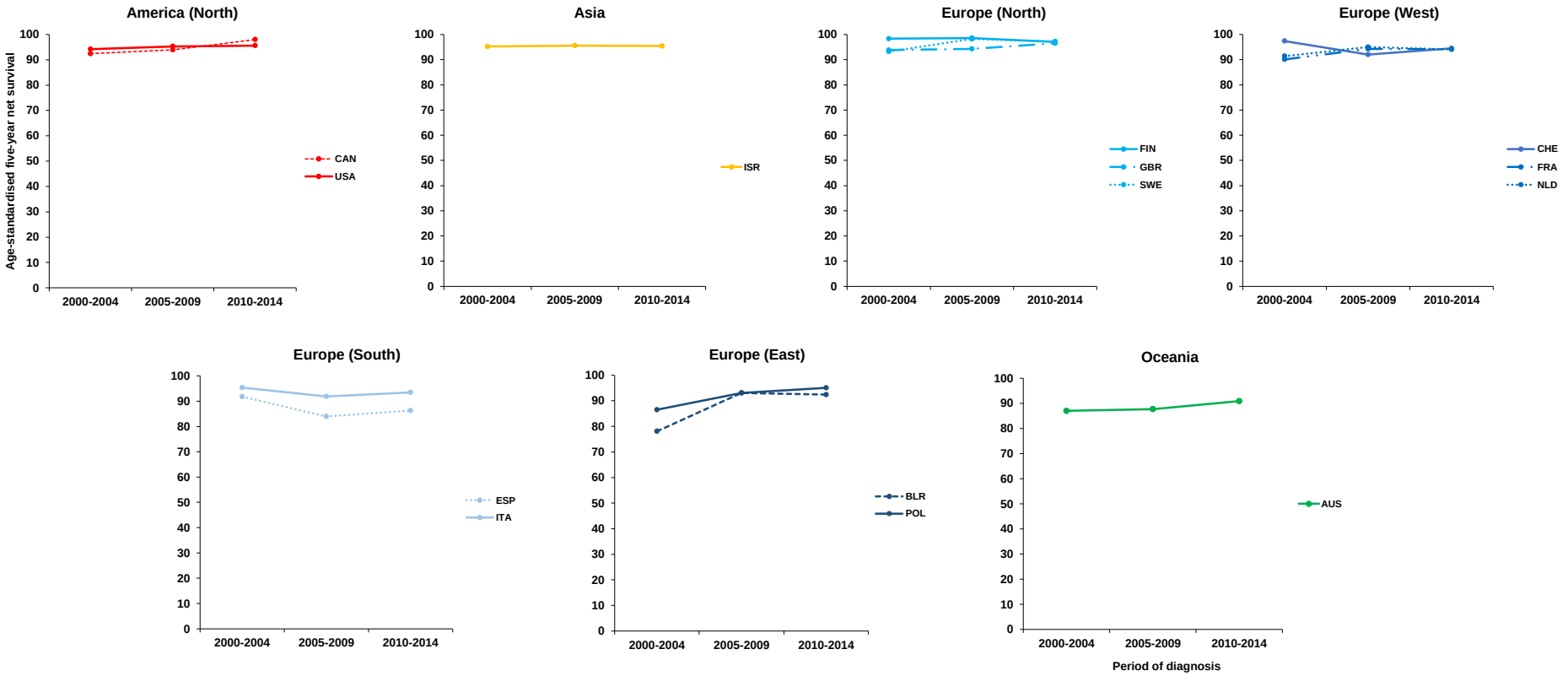

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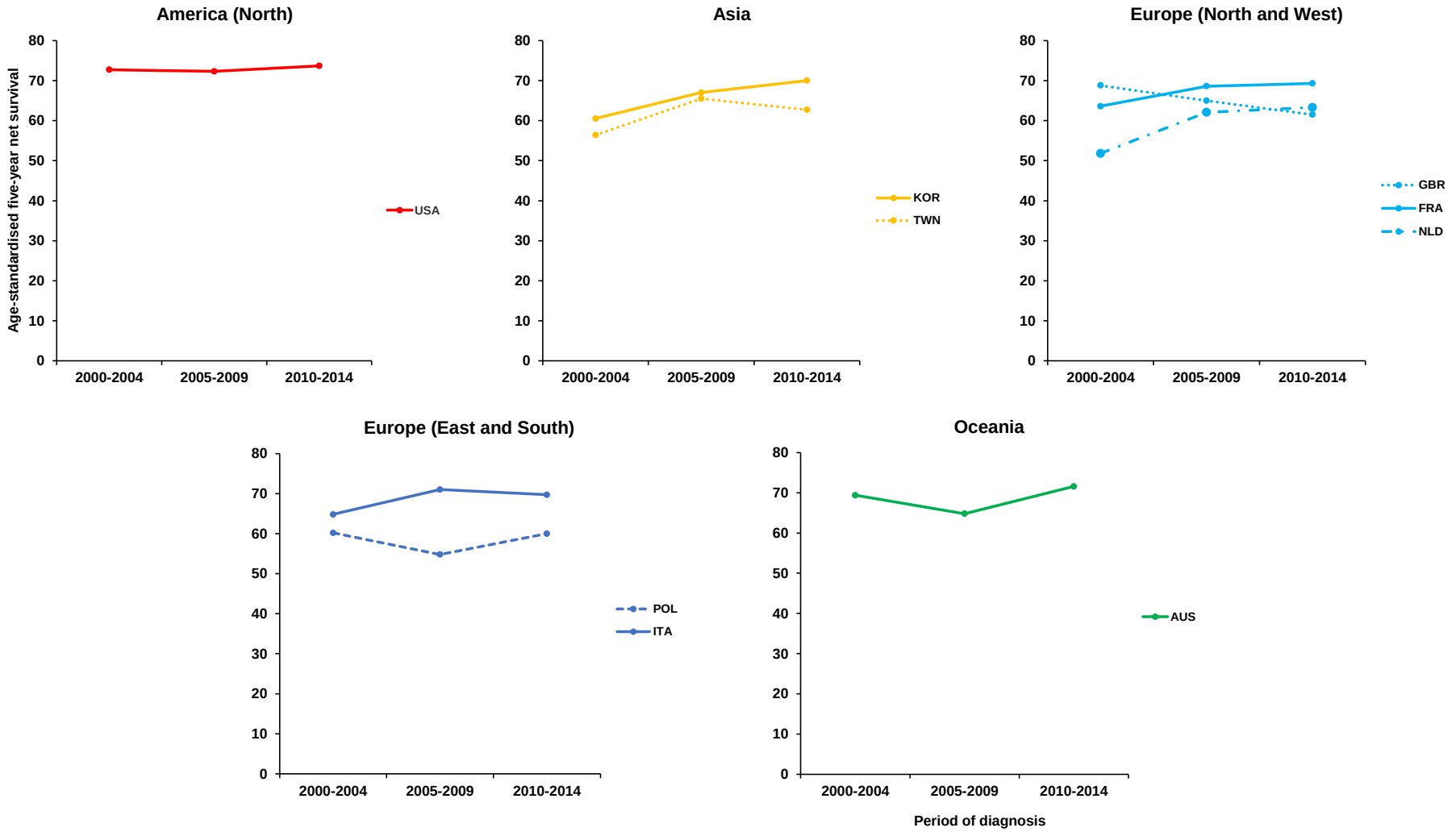

Countries are only included if age-standardised survival estimates were available for patients diagnosed during 2000-2004, 2005-2009 and 2010-2014. Continents (or continental regions) are identified by different colours. In each panel, countries are ranked from highest to lowest, based on survival during 2000-2004. X-axis: period of diagnosis; Y-axis: age-standardised five-year net survival (%). Standard International Organization for Standardization abbreviations for country names: Australia=AUS; France=FRA; Italy=ITA; Netherlands=NLD; South Korea: KOR; Poland: POL; Taiwan: TWN; UK=GBR; USA=USA.

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