International benchmarking of stage at diagnosis for six childhood solid tumours (the BENCHISTA project): a population-based, retrospective cohort study

Laura Botta, Fabio Didonè*, Angela Lopez-Cortes, Adela Cañete Nieto, Emmanuel Desandes, Lisa L Hjalgrim, Zsuzsanna Jakab, Charles A Stiller, Bernward Zeller, Gemma Gatta†, Kathy Pritchard-Jones†, on behalf of the BENCHISTA Project Working Group‡*

Summary

Background International variation in childhood cancer survival might be explained by differences in stage at diagnosis, among other factors. As part of the BENCHISTA project, we aimed to assess geographical variation in tumour stage at diagnosis through the application, by population-based cancer registries working with clinicians, of the international consensus Toronto Childhood Cancer Stage Guidelines.

Methods This population-based, retrospective cohort study involved 67 cancer registries from 23 European countries, Australia, Brazil, Japan, and Canada. Participating cancer registries applied the Toronto Guidelines to stage all incident cases of six childhood solid tumours—neuroblastoma, medulloblastoma, and Wilms tumour (age 0–14 years) and Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma (age ≤19 years)—diagnosed between Jan 1, 2014, and Dec 31, 2017. Eligible cancer registries were those able to assign stage according to the Toronto Guidelines; information on the staging investigations conducted was collected where available. European countries were grouped by geographical area and non-European countries were considered individually. We used χ^2 tests to compare stage distribution across these geographical areas and multivariable logistic models to estimate odds ratios (ORs) for metastatic stage at diagnosis, using central Europe (Austria, Belgium, France, Germany, the Netherlands, and Switzerland) as the comparison. Sensitivity analyses were conducted to overcome potential bias from non-random missing stage information for some geographical areas and cancer types.

Findings Data from 10 937 patients with cancer (6031 [55·1%] male and 4906 [44·9%] female) were analysed. Tumour staging was complete for 93·1% (10 180 of 10 937) of patients, ranging from 88·7% (1347 of 1518 patients) with medulloblastoma to 96·5% (1083 of 1122 patients) with Ewing sarcoma. Stage distribution differed statistically by geographical area for neuroblastoma, Wilms tumour, osteosarcoma, and rhabdomyosarcoma, but not for Ewing sarcoma or medulloblastoma. After excluding patients with missing stage information and, for the sarcomas, patients aged 18–19 years, the proportions of patients with metastases detected at diagnosis were 50·3% with neuroblastoma (1435 of 2852 patients; including 1159 [40·6%] stage M and 276 [9·7%] stage MS), 35·1% with medulloblastoma (473 of 1347 patients; stages M1–M4), 32·6% with Ewing sarcoma (335 of 1028 patients), 29·0% with rhabdomyosarcoma (368 of 1267 patients), 25·5% with osteosarcoma (345 of 1353 patients), and 18·2% with Wilms tumour (384 of 2114 patients). After adjusting by age group, significant differences in the proportions of patients with metastases detected at diagnosis were found between geographical areas for neuroblastoma, Wilms tumour, osteosarcoma, and rhabdomyosarcoma.

Interpretation Assessed at a population level, the stage at diagnosis shows significant variation between geographical areas for several childhood tumours. This finding highlights the need for earlier diagnosis and standardisation of investigations for distant metastases. To enable ongoing comparisons, further cooperation efforts are required between cancer registries and clinicians regarding the sustainable and standardised use of the Toronto Guidelines at diagnosis.

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*Joint first authors

†Joint last authors

‡Members listed in the appendix (pp 25–27)

Evaluative Epidemiology Unit, Department of Epidemiology and Data Science, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (L Botta MSc, F Didonè MSc, G Gatta MD); **Developmental Biology and Cancer Research & Teaching Department, UCL Great Ormond Street Institute of Child Health, University College London, London, UK** (A Lopez-Cortes MSc, Prof K Pritchard-Jones PhD); **Hospital UiP La Fe, Paediatric Oncology and Hematology Unit, Valencia, Spain** (A Cañete Nieto PhD); **National Registry of Childhood Cancers, CRESS, UMRS 1153, INSERM, Paris-Cité University/National Registry of Childhood Solid Tumors, CHRU Nancy, Vandœuvre-lès-Nancy, France** (E Desandes MD); **Department of Paediatrics and Adolescent Medicine, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark** (L L Hjalgrim PhD); **National Childhood Cancer Registry, Hungarian Pediatric Oncology Network, Department of Pediatrics, Semmelweis University, Budapest, Hungary** (Z Jakab MD); **National Disease Registration Service, Transformation Directorate, NHS England, London, UK** (C A Stiller MSc); **Division of Paediatrics and Adolescent Medicine, Oslo University Hospital, Oslo, Norway** (B Zeller MD)

Introduction

Survival from childhood cancer varies internationally, whether assessed at a population level or within clinical research studies.[1–9] One hypothesis to explain this variation is that tumours are diagnosed at a later stage in some geographical areas than others. The extent of tumour spread at diagnosis (tumour stage) is one of the most important prognostic factors determining overall survival and event-free survival. Tumour stage is also a determinant of the intensity of treatment required by the patient, and therefore their risk of late sequelae.

Most population-based cancer registries hold incomplete data on tumour stage for childhood cancers. Staging

Correspondence to:
Prof Kathy Pritchard-Jones, Developmental Biology and Cancer Research & Teaching Department, UCL Great Ormond Street Institute of Child Health, University College London, London WC1N 1EH, UK
k.pritchard-jones@ucl.ac.uk

See Online for appendix

Research in context

Evidence before this study

Overall survival from childhood cancer varies at a population level both within Europe and globally. Differences in tumour stage distribution at diagnosis, among other factors, could contribute to explaining this variation. The Toronto Childhood Cancer Stage Guidelines were developed through international consensus in 2014 to standardise the recording of tumour stage by cancer registries and thereby facilitate comparisons. We searched MEDLINE from Jan 1, 2016, to July 3, 2024, with no language restrictions, using the search terms "cancer", "child", and "Toronto staging guidelines". We prioritised evidence from population-based studies. The Australian Children's Cancer Registry and four registries in sub-Saharan Africa have applied the Toronto Guidelines at a regional or national population level. A pilot study within the European Joint Action on Rare Cancers tested the feasibility of applying the Toronto Guidelines to cases of neuroblastoma and Wilms tumour in 25 population-based cancer registries, with a further study testing application of the guidelines to patients with brain tumours in Italy. To our knowledge, no international benchmarking studies of Toronto Guideline stage at diagnosis have been done.

Added value of this study

This study shows that international collaboration between cancer registries to apply Toronto Guidelines for comparable benchmarking at a population level is feasible. 67 cancer registries from 23 European and four non-European countries documented tumour stage at diagnosis in 93·1% of 10 937 patients with six childhood solid tumours diagnosed between Jan 1, 2014 and Dec 31, 2017. Quality assurance included obtaining data on staging investigations used at an individual-patient level. We found international variation in tumour stage at diagnosis, most demonstrably for neuroblastoma, and highlight variation in the use of some staging investigations that could lead to less sensitive detection of metastatic disease in some countries or regions.

Implications of all the available evidence

High-quality, comparable documentation of childhood cancer tumour stage at diagnosis is essential to further understanding of observed survival differences between populations and geographical regions. Wider application of the Toronto Guidelines by cancer registries across multiple years and to the full range of applicable childhood cancers is necessary for health systems to establish baseline evidence and monitor improvement efforts (eg, in early diagnosis). Increased and sustainable use of the guidelines will require close collaboration with clinicians and specific support to enable cancer registry staff to use them as part of routine national cancer intelligence and to make these data available for regular international benchmarking to assess trends.

systems used for adult cancers are not easily applicable to paediatric tumours, and access to the necessary clinical data sources to assign tumour stage is variable and can be difficult. In 2014, an international working group developed consensus staging guidelines for paediatric cancers, known as the Toronto Childhood Cancer Stage Guidelines (or Toronto Guidelines), which include a two-tier system depending on the resources available.[10,11] Cancer registries have successfully applied these staging guidelines at a national level in Australia (Tier 2) and Rwanda (Tier 1), for several tumour types in pilot studies in Europe (Tier 2), and to three regional registries in sub-Saharan Africa (Tier 1).[12–17]

For the **EUROCARE project** see https://www.iss.it/en/eurocare-il-progetto

The International Benchmarking of Childhood Cancer Survival by Stage (BENCHISTA) project was conceived as a collaboration between cancer registries, working closely with clinical experts, to apply the Toronto Guidelines to six childhood solid tumour types, chosen to represent those for which geographical differences in overall survival have been observed.[1,4–6] The broad aim of the BENCHISTA project is to improve understanding of the reasons for variation in childhood cancer survival between countries by comparing internationally standardised data on stage at diagnosis, non-stage prognostic factors, treatment modalities, and relapse.

For more on the **BENCHISTA project** see https://www.ucl.ac.uk/child-health/research/developmental-biology-and-cancer/benchista-project

Here we aimed to assess the first hypothesis of the BENCHISTA project: that there is variation in tumour stage at diagnosis between geographical areas. In addition, we report information used by cancer registries to assign stage at diagnosis, including data sources and types of investigation used for staging.

Methods

Study design and participants

The BENCHISTA project is a retrospective, population-based multinational cohort study. The full study protocol[18] was published at the outset of the project, and the project group's experiences of standardisation, accuracy, and harmonisation parameters are described in detail and publicly shared elsewhere.[19] We invited all European cancer registries participating in the European Cancer Registry-based study on the survival and care of patients with cancer (the EUROCARE project) to take part in the BENCHISTA project.[4] Additional cancer registries were invited on the basis of their ability to apply Toronto Guidelines. Ultimately, 67 cancer registries from 23 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and the UK), Australia, Brazil, Canada, and Japan participated in the project. Participating cancer registries are listed in the appendix (pp 25–27) and on the BENCHISTA project website. Cancer registries committed to provide pseudonymised, patient-level data on all incident cases of six paediatric solid tumours, diagnosed over at least three consecutive calendar years

	Total patients	Neuroblastoma	Wilms tumour	Medulloblastoma	Osteosarcoma	Ewing sarcoma	Rhabdomyosarcoma
Central Europe	3739 (34·2%)	1083 (36·0%)	797 (35·5%)	578 (38·1%)	607 (37·8%)	314 (28·0%)	360 (25·0%)
Austria	166	41	28	17	31	21	28
Belgium	206	52	45	24	36	24	25
France	1428	391	232	203	208	192	202
Germany	1307	453	383	235	236	0	0
Netherlands	460	94	82	75	69	64	76
Switzerland	172	52	27	24	27	13	29
Northern Europe	461 (4·2%)	102 (3·4%)	102 (4·5%)	62 (4·1%)	55 (3·4%)	59 (5·3%)	81 (5·6%)
Denmark	109	26	18	13	12	16	24
Norway	88	18	21	9	9	12	19
Sweden	264	58	63	40	34	31	38
Eastern Europe	1547 (14·1%)	491 (16·3%)	297 (13·2%)	204 (13·4%)	172 (10·7%)	177 (15·8%)	206 (14·3%)
Bulgaria	137	42	27	15	6	26	21
Czech Republic	228	55	39	42	27	26	39
Estonia	32	9	9	4	3	3	4
Hungary	211	64	41	27	28	26	25
Poland	694	260	141	84	68	65	76
Romania	245	61	40	32	40	31	41
Southern Europe	2041 (18·7%)	589 (19·6%)	343 (15·3%)	254 (16·7%)	301 (18·7%)	290 (25·8%)	264 (18·3%)
Greece	168	54	43	25	15	15	16
Italy*	840	240	124	100	145	121	110
Malta	6	1	3	2	0	0	0
Portugal	215	59	38	28	30	32	28
Slovenia	39	8	4	3	7	9	8
Spain	773	227	131	96	104	113	102
UK and Ireland	1846 (16·9%)	416 (13·8%)	425 (18·9%)	238 (15·7%)	265 (16·5%)	180 (16·0%)	322 (22·4%)
England	1488	335	338	186	214	150	265
Ireland	139	34	33	24	27	6	15
Northern Ireland	47	10	17	5	2	6	7
Scotland	96	23	20	13	15	11	14
Wales	76	14	17	10	7	7	21
Non-European	1303 (11·9%)	324 (10·8%)	281 (12·5%)	182 (12·0%)	207 (12·9%)	102 (9·1%)	207 (14·4%)
Australia†	295	76	66	44	37	25	47
Brazil‡	493	65	126	69	106	48	79
Canada§	360	115	63	50	50	24	58
Japan¶	155	68	26	19	14	5	23
Total	10 937	3005	2245	1518	1607	1122	1440

Data are number of patients or n (%). The coverage of a population-based cancer registry refers to the population and geographical area it encompasses. Countries with partial national coverage are indicated with footnotes. *Registries cover Milan, Basilicata, Bergamo, Campania, Catania Messina Enna, Emilia-Romagna, Insubria, Liguria, Mantua and Cremona, Marche, Palermo, Ragusa, Sassari, Siracusa, Tuscany, Trapani, Umbria, Veneto, Brianza, Friuli-Venezia Giulia, Piedmont, Apulia, Trento, Genoa, and Nuoro. †Registries cover Victoria, Queensland, and the Northern Territory. ‡Registries cover Aracaju, Belém, Belo Horizonte, Campinas, Curitiba, the Federal District, Barretos, Fortaleza, Jau, João Pessoa, Mato Grosso, and Recife. §Registry covers Ontario (Pediatric Oncology Group of Ontario). ¶Registries cover 62% of patients in Tokyo and Osaka. See appendix (pp 7–14) for further information on quality indicators for all countries.

Table 1: **Distribution of patients included by geographical area and tumour type**

between Jan 1, 2014, and Dec 31, 2017, according to the age range of patients they register: those aged 0–19 years for Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma, which are most frequently seen in adolescents; and those aged 0–14 years for neuroblastoma, Wilms tumour, and medulloblastoma, which are most frequently seen in children. Participating countries had full population coverage except for Italy, Poland (as the participating registry is clinical and identifies cases through the national network of designated centres), Australia, Brazil, Canada, and Japan (table 1).

The project was developed with the involvement of parents of children with cancer, and they are represented in the project working group (one individual) and the independent advisory board (two individuals).

Cancer registration uses routine health-care data and is collected without explicit consent in most countries.

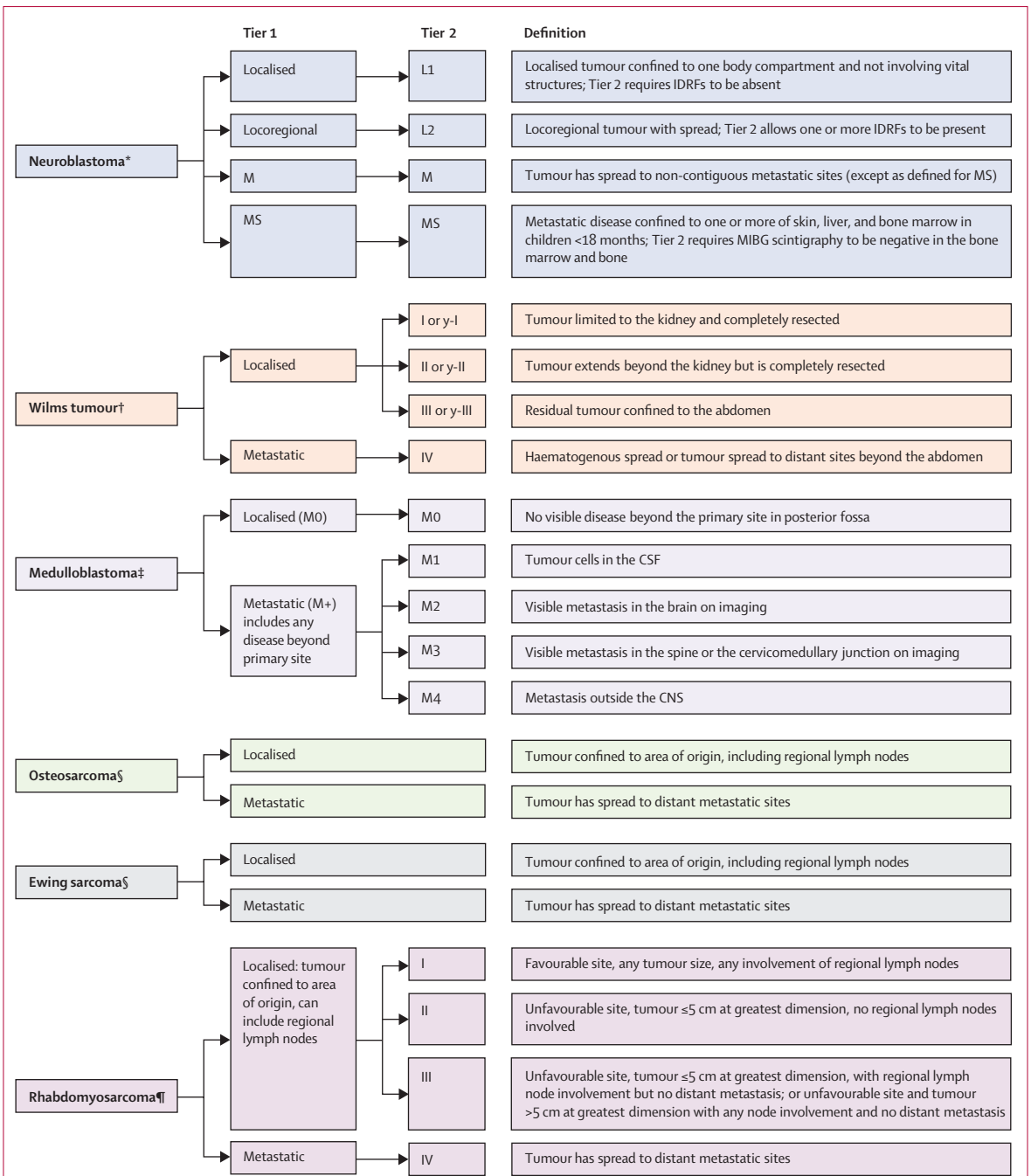

Figure 1: **Summary of the Toronto Childhood Cancer Stage Guidelines**

For the **CanStaging tool** see https://www.canstaging.org/tool?tnm_version=Toronto

For more detailed information, see appendix (pp 3–6), previous related publications,[1–4] and the CanStaging tool. Note that staging investigations to be used for detection of metastases and assessment of the primary site of the tumour are not standardised at an international level. IDRFs=image-defined risk factors. MIBG=*meta*-iodobenzylguanidine. *For neuroblastoma, Tier 2 is identical to the International Neuroblastoma Risk Group Staging System. Tier 1 staging uses the same principles but is simplified for when insufficient imaging information is available or imaging has not been conducted. MS is a distinct subtype of metastatic neuroblastoma confined to very young children and has a distinctive pattern of metastases. †For Wilms tumour, assessment of abdominal tumour stage is made after tumour surgery (usually complete nephrectomy). The prefix y indicates nephrectomy after a period of preoperative chemotherapy; the absence of this prefix indicates the assignment of stage after surgery without any preceding chemotherapy. Assessment of the presence of metastases is done before any chemotherapy, regardless of the timing of surgery to the primary tumour. ‡For medulloblastoma, Tier 2 staging requires results from CSF sampling obtained by lumbar puncture 14 days after surgery as well as cross-sectional imaging of the whole neuraxis. §For osteosarcoma and Ewing sarcoma, metastatic disease is defined as any evidence of tumour beyond the primary involved bone. ¶For rhabdomyosarcoma, Tier 2 staging incorporates TNM (tumour, node, metastasis) staging and requires assessment of tumour size (≤5 cm or >5 cm at the greatest dimension) and classification of anatomical site as favourable or unfavourable (appendix pp 3–6).

Ethical approval for research use of data in this project was provided by the institutional review boards of the joint data controllers (University College London, London, UK [19963/001] and the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano [INT], Milan, Italy [4622359 – 27/05/2021]) and local ethics committees for countries that required it.[19] Cancer registries transferred a pseudonymised, patient-level data file to the INT according to a project-specific data transfer agreement. All data access, collation, and transfer of the dataset to be included in the project-specific database compiled at the INT was in accordance with country-specific laws and regulations.

Procedures

Using the Toronto Guidelines (figure 1, appendix pp 3–6), cancer registries were required to assign stage at diagnosis at a population level to all their incident cases of six paediatric solid tumours, defined according to the third version of the International Classification of Childhood Cancer (ICCC-3)[20] as neuroblastoma (group IVa), Wilms tumour (group VIa1), medulloblastoma (group IIIc1), osteosarcoma (group VIIIa), Ewing sarcoma of bone (group VIIIc), or rhabdomyosarcoma (group IXa). The ICCC-3 is designed to facilitate the comparison of population-based data.[20] To ensure confidence in the comparability of tumour stage between cancer registries, we provided online training and conducted a quality assurance exercise, as previously described.[19]

Cancer registries were asked to provide Tier 2 staging, which is more detailed, wherever possible; however, Tier 1 staging was acceptable if access to the clinical information required for Tier 2 staging was limited. Follow-up for vital status of at least 3 years was requested. The requested age range for all patients was 0–14 years, with the option to include adolescents aged up to 19 years for the three sarcomas (Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma) if information on patients of this age range was collected by the cancer registry. Data on sex were available for all patients. Race and ethnicity data were not included as they are not routinely collected in a standardised manner by most cancer registries.

Data quality indicators used to assess the completeness and accuracy of population-level data provided by each cancer registry included the proportion of cases ascertained by death certificate only, which was calculated as the number of children who were diagnosed with any cancer only on their death certificate or autopsy divided by the number of all children diagnosed with any cancer in the same time period. Additional quality indicators were the proportion of cases of the six childhood solid tumours that were microscopically verified and the proportion of cases with morphology codes of not otherwise specified (within the overall ICCC-3 category) or with an unspecified topography (for neuroblastoma only; appendix p 7). Owing to the complexity of Tier 2 staging for rhabdomyosarcoma, we calculated a further quality indicator of compatible stages with favourable or unfavourable anatomical sites.

Statistical analysis

To assess differences in stage distribution by tumour type between geographical areas, we used the χ^2 test, excluding cases with missing stage. European countries were grouped into geographical areas as described in previous EUROCARE studies;[4] non-European countries were considered individually (table 1). To maximise the number of participating cancer registries and the accuracy of the geographical comparison, for comparative and descriptive analysis of the sarcomas we included only data from cancer registries that could provide information on all patients younger than 18 years, and excluded those aged 18–19 years.

A multivariable logistic model excluding patients with missing stage was used to estimate the odds (as odds ratio [OR]) of being diagnosed at a metastatic stage in each geographical area by tumour type (excluding the MS subtype for neuroblastoma), in comparison with central Europe as reference category. Central Europe comprises Austria, Belgium, France, Germany, the Netherlands, and Switzerland. A sensitivity analysis was conducted for all included cancers to evaluate change in the ORs when including as covariates only age group, both age group and sex, or only the covariates with significant effect on the likelihood of the model. Age groups were established according to the childhood cancer being investigated (appendix pp 15–16). The likelihood ratio test was also used to identify the effect of geographical area on the probability of being diagnosed at a metastatic stage.

For tumours for which the proportion of cases with missing stage was greater than 20% in at least one geographical area, we conducted sensitivity analyses to establish the effect of the missing stage by predicting three possible scenarios: with all missing stages allocated to M0 (ie, no metastasis) or with random allocations of 70% or 80% to M0. The reported percentages for staging investigation status (conducted or not) excluded the patients with missing status (appendix pp 22–24).

Stata 14 was used for statistical analyses and p values of less than 0·05 were considered significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

67 cancer registries from 23 European countries, Australia, Brazil, Japan, and Canada submitted data from 10 937 patients (6031 [55·1%] male and 4906 [44·9%] female) with the six included childhood solid tumours, diagnosed between Jan 1, 2014 and Dec 31, 2017 (table 1). The German Childhood Cancer Registry could not

	Neuroblastoma (age 0–14 years), Tier 1 stage*						Wilms tumour (age 0–14 years), Tier 2 stage†						Medulloblastoma (age 0–14 years), Tier 2 stage‡						
	L	LR	M	MS	X	Total	I or y-I	II or y-II	III or y-III	IV	X	Total	M0	M1	M2	M3	M4	X	Total
Australia	17 (22%)	10 (13%)	27 (36%)	8 (11%)	14 (18%)	76	20 (30%)	14 (21%)	23 (35%)	6 (9%)	3 (5%)	66	25 (57%)	1 (2%)	1 (2%)	9 (21%)	0	8 (18%)	44
Brazil	12 (18%)	9 (14%)	34 (52%)	7 (11%)	3 (5%)	65	67 (53%)	13 (11%)	8 (6%)	24 (19%)	14 (11%)	126	43 (62%)	4 (6%)	6 (9%)	8 (12%)	1 (1%)	7 (10%)	69
Canada	34 (30%)	22 (19%)	43 (37%)	16 (14%)	0	115	14 (22%)	18 (29%)	18 (29%)	13 (20%)	0	63	33 (66%)	1 (2%)	3 (6%)	12 (24%)	1 (2%)	0	50
Japan	10 (15%)	18 (26%)	30 (44%)	2 (3%)	8 (12%)	68	8 (31%)	5 (19%)	7 (27%)	4 (15%)	2 (8%)	26	14 (74%)	2 (11%)	1 (5%)	1 (5%)	0	1 (5%)	19
Central Europe	195 (18%)	300 (28%)	416 (38%)	88 (8%)	84 (8%)	1083	370 (46%)	135 (17%)	91 (11%)	140 (18%)	61 (8%)	797	344 (60%)	42 (7%)	51 (9%)	97 (17%)	1 (0%)	43 (7%)	578
Eastern Europe	143 (29%)	147 (30%)	154 (31%)	45 (9%)	2 (1%)	491	148 (50%)	56 (19%)	52 (17%)	38 (13%)	3 (1%)	297	118 (58%)	8 (4%)	10 (5%)	40 (19%)	2 (1%)	26 (13%)	204
Northern Europe	20 (20%)	20 (20%)	47 (46%)	15 (14%)	0	102	44 (43%)	19 (19%)	21 (20%)	18 (18%)	0	102	44 (71%)	5 (8%)	3 (5%)	9 (14%)	0	1 (2%)	62
Southern Europe	184 (32%)	130 (22%)	201 (34%)	61 (10%)	13 (2%)	589	128 (37%)	65 (19%)	75 (22%)	48 (14%)	27 (8%)	343	152 (60%)	12 (5%)	13 (5%)	47 (18%)	0	30 (12%)	254
UK and Ireland	78 (19%)	68 (16%)	207 (50%)	34 (8%)	29 (7%)	416	138 (32%)	64 (15%)	109 (26%)	93 (22%)	21 (5%)	425	101 (42%)	17 (7%)	18 (8%)	47 (20%)	0	55 (23%)	238
Total	693 (23·1%)	724 (24·1%)	1159 (38·5%)	276 (9·2%)	153 (5·1%)	3005	937 (41·8%)	389 (17·3%)	404 (18·0%)	384 (17·1%)	131 (5·8%)	2245	874 (57·6%)	92 (6·1%)	106 (7·0%)	270 (17·8%)	5 (0·3%)	171 (11·2%)	1518

Data are n (%) or n. Percentages might not total 100 owing to rounding. For definitions of stages according to the Toronto Guidelines, see figure 1. χ^2 and p values were calculated excluding missing values. *Pearson χ^2=116·17 (df=24); p<0·0001. †Pearson χ^2=116·13 (df=24); p<0·0001. ‡Pearson χ^2=40·6572 (df=32); p=0·14. X=unknown.

Table 2: **Stage distribution by geographical area and tumour type for patients aged 0–14 years with neuroblastoma, Wilms tumour, or medulloblastoma**

provide data on patients with Ewing sarcoma and rhabdomyosarcoma owing to a lack of access to necessary clinical records for staging. For similar reasons, Germany could provide only Tier 1 staging for neuroblastoma, as Tier 2 staging requires knowledge of image-defined risk factors. Data quality indicators by country are shown in the appendix (pp 8–14); all cancer registries met acceptable quality standards.

Tumour stage was documented for 10 180 (93·1%) of 10 937 patients. Tier 1 staging was complete for 10 349 (94·6%) patients and Tier 2 staging was complete for 9744 (89·1%) patients. All subsequent analyses excluded 240 patients aged 18–19 years who had Ewing sarcoma, osteosarcoma, or rhabdomyosarcoma. The completeness of Tier 2 staging varied by tumour type, ranging from 88·7% (1347 of 1518 patients) for medulloblastoma to 96·5% (1083 of all 1122 patients) and 96·7% (1028 of 1063 patients aged <18 years) for Ewing sarcoma (tables 2, 3). For neuroblastoma, stage completeness was 94·9% (2852 of 3005 patients) for Tier 1 and 94·7% (2416 of 2552 patients; excluding Germany) for Tier 2. Owing to the large number of patients with neuroblastoma (n=453) from the German Childhood Cancer Registry, which could not provide Tier 2 staging, all analyses of stage distribution for this cancer were conducted using Tier 1 stage information; for all other cancer types, Tier 2 stage was used.

Significant differences between geographical areas in the overall distribution across all stages were found for neuroblastoma, Wilms tumour, osteosarcoma, and rhabdomyosarcoma, but not for medulloblastoma or Ewing sarcoma (tables 2, 3). Differences occurred not only in the proportion of metastatic cancers but also when considering all other non-metastatic categories for neuroblastoma, Wilms tumour, and rhabdomyosarcoma. For neuroblastoma, the difference in stage distribution by geographical area was also seen when stratifying the analysis by two age groups: <18 months and ≥18 months (appendix p 17).

Excluding those with missing stage information, the proportions of patients with each tumour type presenting with any metastatic disease were 50·3% with neuroblastoma (1435 of 2852 patients; 1159 [40·6%] M and 276 [9·7%] MS), 35·1% with medulloblastoma (473 of 1347 patients; M1–M4); 32·6% with Ewing sarcoma (335 of 1028 patients), 29·0% with rhabdomyosarcoma (368 of 1267 patients), 25·5% with osteosarcoma (345 of 1353 patients), and 18·2% with Wilms tumour (384 of 2114 patients; tables 2, 3). Definitions and information on the categories of all tumours are included in figure 1 and the appendix (pp 3–6).

For the multivariable analysis by tumour type, no differences were observed in the logistic regression models when including only age group or both age group and sex as covariates. Therefore, we present results from the model with only age group as

	Osteosarcoma (age <18 years), Tier 2 stage*				Ewing sarcoma (age <18 years), Tier 2 stage†				Rhabdomyosarcoma (age <18 years), Tier 2 stage‡					
	L	M	X	Total	L	M	X	Total	I	II	III	IV	X	Total
Australia	28 (76%)	8 (22%)	1 (2%)	37	17 (68%)	5 (20%)	3 (12%)	25	12 (26%)	7 (14%)	11 (23%)	12 (26%)	5 (11%)	47
Brazil	42 (47%)	36 (40%)	12 (13%)	90	24 (58%)	13 (32%)	4 (10%)	41	15 (21%)	6 (8%)	14 (20%)	26 (36%)	11 (15%)	72
Canada	38 (79%)	9 (19%)	1 (2%)	48	16 (67%)	7 (29%)	1 (4%)	24	15 (26%)	10 (17%)	8 (14%)	25 (43%)	0	58
Japan	10 (84%)	1 (8%)	1 (8%)	12	4 (80%)	1 (20%)	0	5	3 (14%)	5 (24%)	6 (29%)	6 (29%)	1 (5%)	21
Central Europe	373 (65%)	118 (21%)	81 (14%)	572	211 (69%)	93 (30%)	3 (1%)	307	101 (29%)	44 (12%)	99 (28%)	84 (24%)	26 (7%)	354
Eastern Europe	108 (68%)	52 (32%)	0	160	113 (67%)	56 (33%)	0	169	55 (28%)	16 (8%)	63 (31%)	63 (31%)	3 (2%)	200
Northern Europe	41 (75%)	14 (25%)	0	55	38 (64%)	21 (36%)	0	59	28 (35%)	15 (19%)	18 (22%)	19 (23%)	1 (1%)	81
Southern Europe	215 (79%)	50 (19%)	6 (2%)	271	170 (63%)	89 (33%)	12 (4%)	271	98 (38%)	34 (13%)	52 (20%)	61 (23%)	15 (6%)	260
UK and Ireland	153 (66%)	57 (25%)	20 (9%)	230	100 (62%)	50 (31%)	12 (7%)	162	75 (25%)	24 (8%)	65 (22%)	72 (24%)	62 (21%)	298
Total	1008 (68·3%)	345 (23·4%)	122 (8·3%)	1475	693 (65·2%)	335 (31·5%)	35 (3·3%)	1063	402 (28·9%)	161 (11·6%)	336 (24·2%)	368 (26·4%)	124 (8·9%)	1391

Data are n (%) or n. Percentages might not total 100 owing to rounding. For definitions of stages according to the Toronto Guidelines, see figure 1. For χ^2 and p values, the first set of values quoted for each cancer were calculated excluding missing values and the second set of values were calculated excluding missing values and data from cancer registries in Australia, Denmark, Greece, and Spain (RETI-SEHOP) that did not collect data for patients older than 15 years. *Pearson χ^2=31·39 (df=8), p<0·0001; Pearson χ^2=29·36 (df=7), p<0·0001. †Pearson χ^2=2·72 (df=8), p=0·95; Pearson χ^2=1·18 (df=7), p=0·99. ‡Pearson χ^2=44·54 (df=24), p=0·0070; Pearson χ^2=36·81 (df=21), p=0·018. X=unknown.

Table 3: **Stage distribution by geographical area and tumour type for patients aged <18 years with osteosarcoma, Ewing sarcoma, or rhabdomyosarcoma**

a covariate, because of the known biological effect of age on stage distribution.

Some geographical areas had significant differences in the probability of patients having metastases detected at diagnosis compared with central Europe. For neuroblastoma, patients in the UK and Ireland area had a higher probability of being diagnosed at the metastatic stage (OR 1·67 [95% CI 1·28–2·19]) whereas those in eastern Europe (0·62 [0·48–0·80]) and southern Europe (0·76 [0·60–0·96]) had the lowest probabilities (figure 2, appendix p 18). An additional analysis for neuroblastoma using Tier 2 stage (ie, excluding data from Germany) was conducted and showed similar results for all regions except southern Europe, which no longer had a lower probability than central Europe of patients being diagnosed at a metastatic stage (Tier 1 0·76 [0·60–0·96] and Tier 2 0·91 [0·69–1·19]; appendix p 19). For Wilms tumour, patients from only one geographical area (eastern Europe) had a lower probability than those in central Europe of being diagnosed at a metastatic stage (0·65 [0·44–0·97]). For medulloblastoma, patients in the UK and Ireland had a higher probability of diagnosis with any metastasis (stage M1–M4 combined; 1·45 [1·03–2·04]) than those in central Europe, but the UK and Ireland also reported the highest proportion of patients with medulloblastoma who had missing stage information (23%). The sensitivity analysis, in which the proportion of patients with missing stage who were allocated to M0 or M+ was varied (appendix p 20), showed no difference for the UK and Ireland compared with central Europe as a reference, although all OR point estimates were still greater than 1 except for the scenario in which all missing cases were allocated to M0 (0·94 [0·68–1·29]; p=0·70). For Ewing sarcoma, no significant variation in the proportions of patients with metastasis at diagnosis was observed across geographical areas. For osteosarcoma and rhabdomyosarcoma, only individual countries had significantly different proportions compared with central Europe: Brazil for both osteosarcoma (2·48 [1·49–4·15]) and rhabdomyosarcoma (2·17 [1·21–3·88]) and Canada for rhabdomyosarcoma (2·56 [1·41–4·63]). Only one geographical area (UK and Ireland) had a proportion of patients with missing stage of greater than 20% for two tumour types (medulloblastoma and rhabdomyosarcoma). For the UK and Ireland, in all three scenarios examined in the sensitivity analysis there remained no difference by geographical area (appendix p 20).

Data sources used by cancer registries for staging varied by country according to data availability and access permissions (appendix p 21). Most registries had access to hospital medical records, with pathology reports combined with administrative records being the next most common data sources. Registries in Germany relied on liaison with national tumour-specific clinical registries, and registries in France had a particularly strong relationship with the clinical network of centres that had complete access to hospital clinical records.

63 cancer registries in 24 countries provided patient-level data on the types of staging investigation used, covering around 80% of cases (appendix pp 22–24). For neuroblastoma, notable variation was observed in the use of iodine-based *meta*-iodobenzylguanidine (MIBG) scans—the most sensitive test to identify metastases. For the countries that collected this information, the status (ie, whether conducted or not) of MIBG scans was available for 1786 (78·8%) of 2267 patients. Use of these scans varied from 60·6% (220 of 363) of patients with neuroblastoma in eastern Europe to more than 90% of patients in the other four European areas

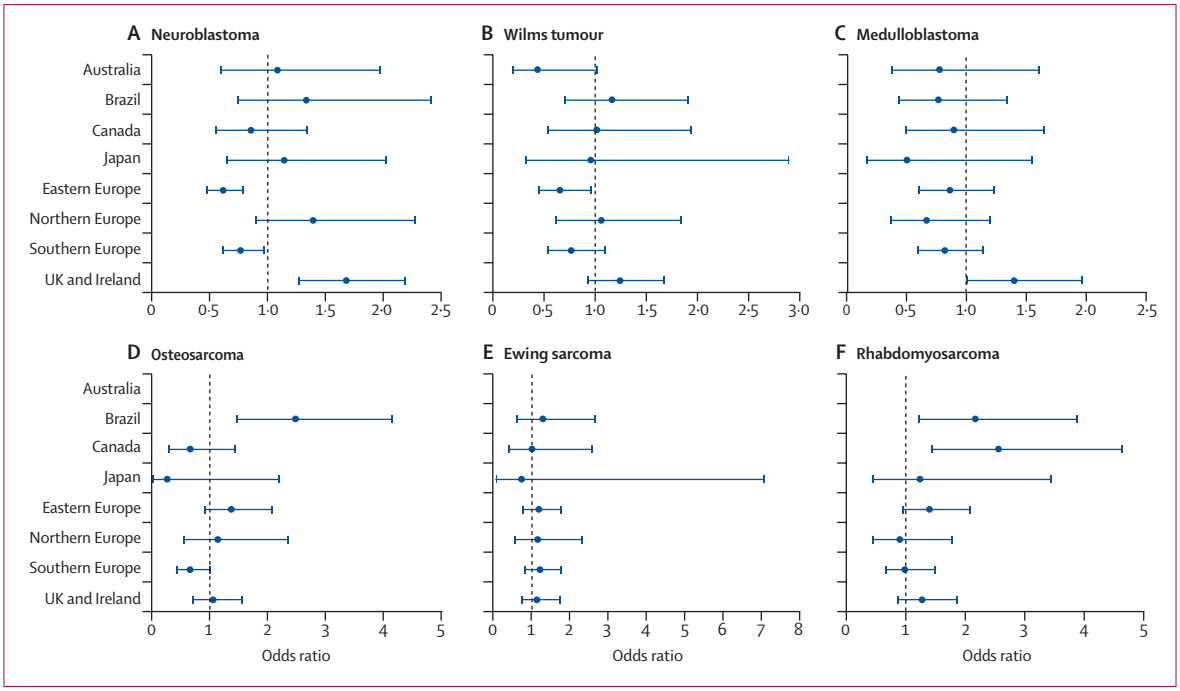

Figure 2: **Age-adjusted odds ratios for being diagnosed at a metastatic stage in each geographical area compared with central Europe**
Data are OR and 95% CI (appendix p 18). ORs are derived from logistic regression models adjusted for age group. The scale of the x-axis varies between panels. Data from patients aged 0–14 years were considered for neuroblastoma, Wilms tumour, and medulloblastoma and from patients younger than 18 years for osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma. Data from cancer registries in Australia, Denmark, Greece, and Spain (RETI-SEHOP) were not used in the analysis of sarcomas because these registries do not routinely collect data for patients older than 15 years. For neuroblastoma, the MS stage category was excluded. Data from cancer registries in the following countries were excluded because the percentage of patients with missing stage information for the respective types of cancer was greater than 30%: Austria and Wales for Wilms tumour, Estonia for medulloblastoma, Austria and Germany for osteosarcoma, Wales for Ewing sarcoma, and Austria for rhabdomyosarcoma. OR=odds ratio.

(excluding unknown values; appendix p 22). For Wilms tumour, CT scans of the chest were used to document lung metastases in 1161 (82·9%) of 1400 patients for whom test information was available, with the lowest proportion being in eastern Europe (149 [50·0%] of 297 patients). Among the key investigations for staging medulloblastoma, CSF cytology was less likely to be conducted (in 795 [88·8%] of 895 patients for whom test information was available) than whole neuraxis MRI (in 928 [95·7%] of 970 patients for whom test information was available). In patients with the three sarcomas, regional variation was observed in the use of PET scans, with central and northern Europe having the highest proportions (497 [59·4%] of 836 patients) and eastern Europe having the lowest (106 [19·1%] of 555 patients).

Discussion

The BENCHISTA project has shown the feasibility of documenting tumour stage at diagnosis at a population level using the international consensus Toronto Childhood Cancer Stage Guidelines and their utility for international comparisons of late diagnosis. Nearly 11 000 cases of six childhood solid tumours diagnosed between Jan 1, 2014 and Dec 31, 2017 were documented by 67 cancer registries representing 23 European and four non-European countries.

The proportion of patients for whom tumour staging was complete was high and was similar to the 95% achieved in the European pilot study of neuroblastoma and Wilms tumour,[13] in which 25 registries participated (23 of which also contributed data to BENCHISTA), and to the 94% achieved by a study of all childhood cancers using the Australian Children's Cancer Registry.[16,21]

Staging completeness was lowest for medulloblastoma, as many cancer registries reported difficulties in accessing the results of CSF analysis, which is generally conducted separately from tumour excision surgery.[15] Nearly all cancer registries were able to assign stage at the higher Tier 2 level, an important exception being Germany for neuroblastoma, owing to a lack of access to clinical information on imaging-defined risk factors. We therefore used Tier 1 stage for this tumour type only.

We found significant variations in overall stage distribution between geographical areas for neuroblastoma, Wilms tumour, osteosarcoma, and rhabdomyosarcoma, but not for medulloblastoma or Ewing sarcoma. This finding is in keeping with previous reports for neuroblastoma[7] and Wilms tumour[9,22] that show a more advanced stage distribution at diagnosis in the UK than in France and Germany. No population-level stage comparison data are available for the other tumour types.

Using central Europe (Austria, Belgium, France, Germany, the Netherlands, and Switzerland) as the reference geographical area, we found a significantly higher probability of metastases at diagnosis for neuroblastoma and medulloblastoma in the UK and Ireland, for osteosarcoma and rhabdomyosarcoma in Brazil, and for rhabdomyosarcoma in Canada. By contrast, eastern Europe showed the lowest probability of metastases at diagnosis for neuroblastoma and Wilms tumour and southern Europe for neuroblastoma. The lower proportion of patients with neuroblastoma and Wilms tumour with metastases at diagnosis in eastern Europe could be explained by the less frequent use of MIBG scanning (for neuroblastoma) and CT thorax scanning (for Wilms tumour) in these countries, whereas in southern Europe, 91% of patients with neuroblastoma had an MIBG scan, confirming the accuracy of their more favourable stage distribution at diagnosis. However, the lower likelihood of metastatic disease at diagnosis for patients with neuroblastoma in southern Europe based on Tier 1 staging lost significance when including only countries with Tier 2 staging, possibly due to the reduced power as a result of excluding cases from Germany, which were in the comparator group. For medulloblastoma, we conducted a sensitivity analysis for the UK and Ireland owing to concern expressed by the English cancer registry that they do not routinely receive CSF analysis results when they are negative, potentially biasing staged cases towards being metastatic. This analysis supported caution in interpreting this result. The higher proportion of patients with metastases on diagnosis with osteosarcoma and rhabdomyosarcoma observed in Brazil should be reliable, as most patients were staged by CT thorax and bone scans whereas few had the more sensitive PET scan. Information on the staging investigations used was not available for Canada.

For all six tumour types in our study, the overall proportions of patients with metastases detected at diagnosis—documented at a population level and mainly in Europe—are similar to those reported by the Australian Children's Cancer Registry for patients aged 0–14 years and diagnosed between 2006 and 2014 (57·0% with neuroblastoma [50·7% M and 6·3% MS], 17·4% with Wilms tumour, 31·4% with medulloblastoma, 26·3% with osteosarcoma, 33·0% with Ewing sarcoma, and 22·6% with rhabdomyosarcoma).[16] However, some low-income and middle-income countries have applied the Toronto Guidelines to their data and found much higher proportions. For Wilms tumour, Parkin and colleagues[14] reported that, at a city or regional population level, 50·4% of patients are diagnosed at the metastatic stage in Abidjan, Côte d'Ivoire; Harare, Zimbabwe; and Kyadondo county, Uganda combined. Furthermore, the Rwanda National Cancer Registry reported that the proportions of patients with metastases detected at diagnosis were 31·7% for Wilms tumour, 56·7% for osteosarcoma, and 31·8% for rhabdomyosarcoma.[17] Data collected across seven institutions in sub-Saharan Africa, participating in clinical studies with the Franco-African Pediatric Oncology Group, used the Toronto Guidelines to assign Tier 1 stage for 89% of all patients with relevant solid tumours (excluding CNS tumours), with proportions with metastases (excluding patients who were unstaged) of 62% for neuroblastoma, 36% for Wilms tumour, 52% for bone tumours, and 41% for rhabdomyosarcoma.[23] These marked differences from our results and those from Australia are expected, given the challenges of late diagnosis of childhood cancer in many low-income and middle-income countries. We note that all but two countries in our study—Brazil and Bulgaria—are categorised as high-income countries according to the World Bank.

Our study had some limitations due to practical constraints. First, the cohort had relatively small numbers of patients in some analytical groups after stratification by cancer type, stage category, and geographical area. These small numbers reflect the study period, encompassing only 3 to 4 years of incidence data from each participating registry. This short study period was necessary because, for most cancer registries, retrospective application of the Toronto Guidelines was feasible only for patients diagnosed relatively recently owing to both resource (ie, registration officer time) and data access constraints. Additionally, data for patients aged 18–19 years were not consistently gathered during the study period, which limited the sample size and age range available for analysis. Second, the Toronto Guidelines do not specify how metastases should be investigated. As such, there is likely to be some variation in the use of staging investigations of different sensitivities for tumour detection and in their clinical interpretation in each country or geographical area, according to their usual clinical practice. We aimed to understand this potential for stage migration by collecting patient-level information on the staging investigations used and to mitigate potential variation in the documentation of tumour stage by providing training with clinical experts and a project-specific helpdesk. Stage migration will be further investigated in relation to survival in the tumour-specific analyses envisioned in the second phase of this project. Our quality-assurance processes showed almost complete concordance in determining metastatic stage for Wilms tumour and bone sarcomas, with some discrepancies noted in differentiating between localised disease subcategories for neuroblastoma, medulloblastoma, and rhabdomyosarcoma. Third, data access permissions limited the number of patients, the level of clinical detail, or both that could be contributed by some cancer registries. Most of these issues were due to variable interpretations of the General Data Protection Regulation in Europe, ethical committee rules, and privacy rules outside Europe.

The strengths of our study include its origin as a large-scale collaboration between cancer registries,

all of which were involved in defining the project's protocol, solving data access challenges, and resolving ambiguities in applying the Toronto Guidelines—together with expert clinical support—to achieve a very high level of stage completeness. By studying six solid tumours with unambiguous histological codes for identification and through cancer registries providing patient-level data on all incident cases in their population within the same 3–4-year calendar period, we ensured an unbiased and comparable representation of each population and tested the application of the Toronto Guidelines in a real-world setting. Furthermore, we received positive feedback from cancer registries stating that participation in the BENCHISTA project had improved their data collection capabilities to apply the Toronto Guidelines to data from subsequent patients, enabling them to contribute to sustainable comparisons and trend analysis of stage distribution and survival by stage in the future.

In conclusion, the BENCHISTA project has provided, to our knowledge, the first multinational, population-level, comparative measurement of tumour stage distribution for childhood cancer using the international consensus Toronto Guidelines. Although variation in disease natural history between populations is a possibility, the principal modifiable factors that could account for the significant geographical variation in the probability of being diagnosed with more advanced stage disease for some tumour types are delayed presentation and variation in the availability or use of some staging procedures. This finding highlights the need, even in high-income countries, for health systems to focus on earlier diagnosis and the best use of initial staging procedures to accurately assess the extent of disease, in order to propose optimal treatment options and potentially improve survival. Such efforts are already underway in some countries, including the UK.[24] Furthermore, variation in the use of the most sensitive staging investigations, as in some eastern European countries, could mean that distant metastases are missed in some patients.

Our experience in the BENCHISTA project enables us to make recommendations for future benchmarking studies that aim to understand the factors underlying variation in survival between countries. These recommendations include acknowledging the importance of strong links between cancer registry staff and clinicians trained in paediatric oncology, to facilitate more complete and accurate collection and interpretation of tumour staging information, as well as co-developing the data collection protocol with all involved parties, to ensure a common understanding of the use of patient-level data that complies with the varying interpretation of the General Data Protection Regulation between countries or even at regional levels within the same country. Ultimately, the BENCHISTA project has laid the groundwork for cancer registries to make the best use of routinely collected clinical and health-care data, including linkage to clinical registries, to capture more of the variables that could contribute to understanding international variation in overall survival. Further in-depth analyses related to survival by stage and tumour-specific data collected on non-stage prognostic factors and treatment variables are planned for the next phase of the project, as well as wider inclusion of cancer registries in low-income and middle-income countries.

Contributors

KP-J, GG, and LB conceptualised the project. All authors contributed to study design. LB, FD, GG, AL-C, CAS, ZJ, and ED developed the methods. LB and AL-C searched the literature. KP-J, GG, LB, AL-C, FD, ACN, and LLH produced training resources. All authors contributed to the investigation, data collection and pseudonymisation. LB, FD, and GG curated the data in the central database. LB and FD analysed the data and all authors interpreted the data. LB, FD, and AL-C were responsible for data presentation. KP-J, GG, LB, AL-C, and FD wrote the original draft of the manuscript, which was reviewed by all authors. KP-J, GG, LB, AL-C, FD, ACN, LLH, ZJ, CAS, and BZ were responsible for project administration. KP-J and GG acquired funding and supervised the project. LB, FD, and GG directly accessed and verified the underlying data. All authors had full access to the outputs of all analyses and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data availability

The datasets used for this project are merged, managed, and stored by the data controller at the INT, Milan, Italy. The original contributions presented in the study are included in the Article and its appendix. Further inquiries should be directed to KP-J.

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