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

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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 73 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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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

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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. 73 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, 73 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.

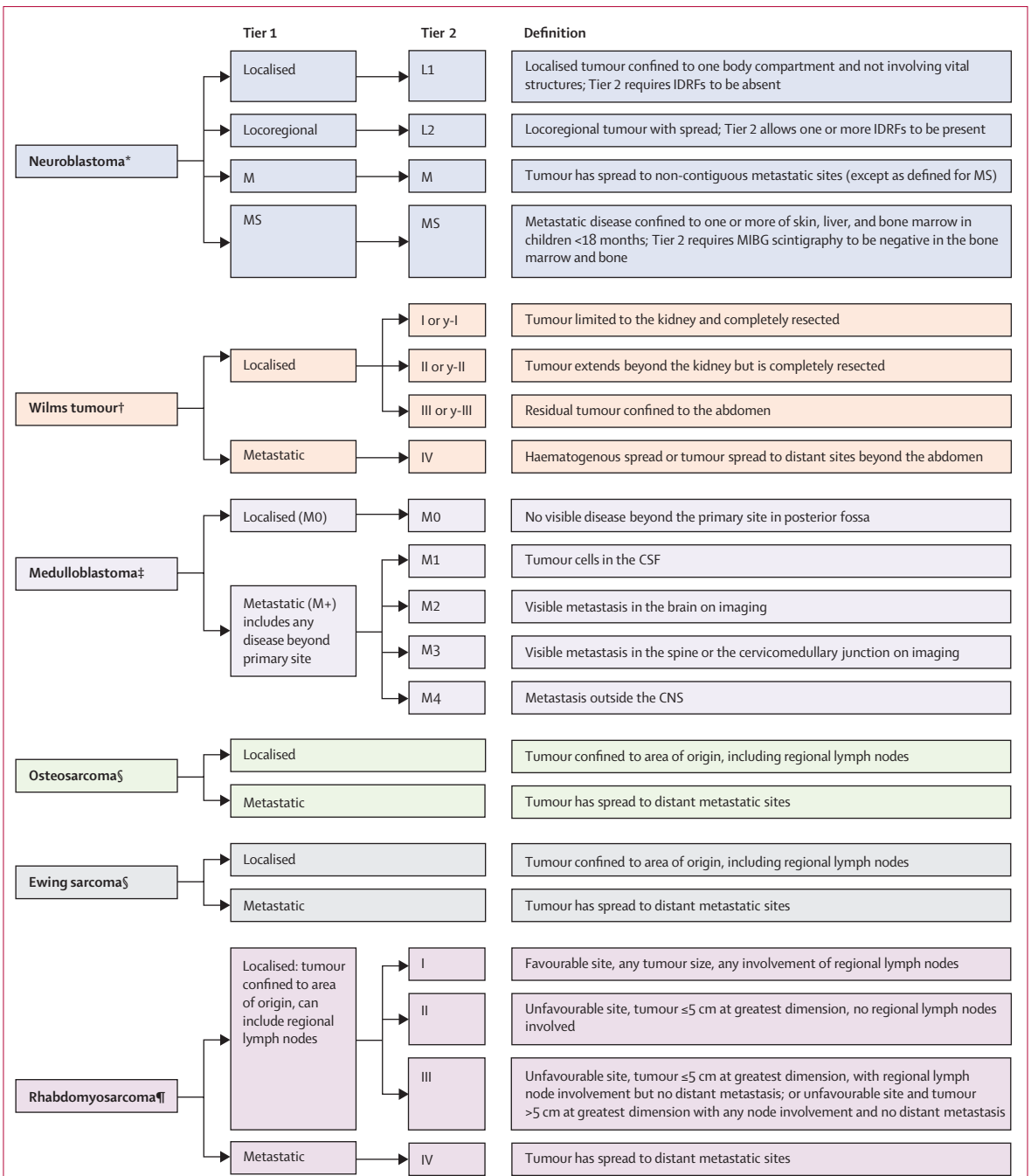

Figure 1: **Summary of the Toronto Childhood Cancer Stage Guidelines**

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

73 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

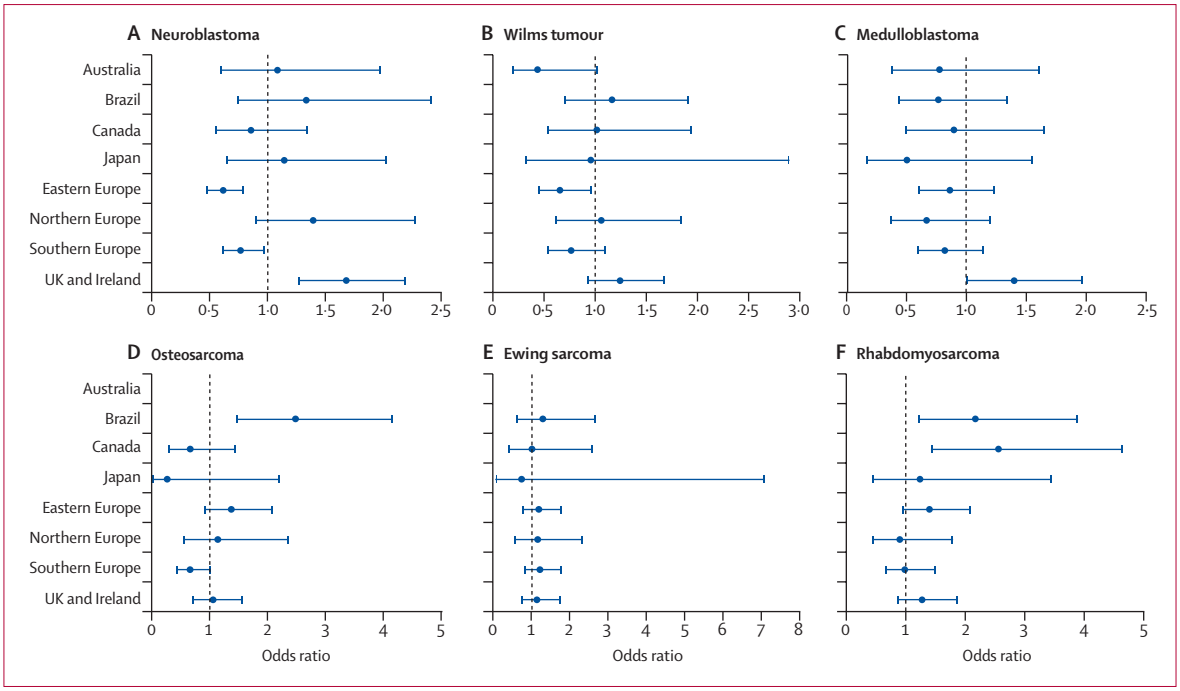

Figure 2: **Age-adjusted odds ratios for being diagnosed at a metastatic stage in each geographical area compared with central Europe**
Data are OR and 95% CI (appendix p 18). ORs are derived from logistic regression models adjusted for age group. The scale of the x-axis varies between panels. Data from 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 73 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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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Botta L, Didonè F, Lopez-Cortes A, et al. International benchmarking of stage at diagnosis for six childhood solid tumours (the BENCHISTA project): a population-based, retrospective cohort study. *Lancet Child Adolesc Health* 2025; **9:** 89–99.

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Toronto Childhood Cancer Stage Guidelines – Stage definition by tumour type

The following information has been adopted and summarised for each tumour type included in the BENCHISTA project (1–4).

<table>
<tr><th colspan="4">NEUROBLASTOMA</th></tr>
<tr><td colspan="4">Neuroblastoma was defined according to the ICCC-3rd ed.: 4a—Neuroblastoma and Ganglioneuroblastoma; ICD-O codes for morphology are 9490 and 9500, and codes for topography are C00.0-C69.9, C73.9-C76.8, and C80-9.
Cases aged up to <15 years old.
The International Neuroblastoma Risk Group Staging System should be used for both Tiers (5).
The stage has to be defined at the time of diagnosis before any surgical resection. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour, provided it is before any systemic therapy is started.
Tier 1 criteria are simplified proxies of Tier 2 that do not require assessment of image-defined risk factors for use in settings where cross-sectional imaging is not available.</td></tr>
<tr><td colspan="4">Information required for staging</td></tr>
<tr><td colspan="2">Tier 1</td><td colspan="2">Tier 2</td></tr>
<tr><td colspan="2">Age
Distant metastatic disease
Site of metastases
Locoregional spread</td><td colspan="2">Age
Distant metastatic disease
Site of metastases
Number of image-defined risk factors
MIBG for bone/bone marrow</td></tr>
<tr><td colspan="4">Staging criteria</td></tr>
<tr><td colspan="2">Tier 1</td><td colspan="2">Tier 2</td></tr>
<tr><td>Localised</td><td>Localised tumour not involving vital structures and confined to one body compartment</td><td>Stage L1</td><td>Localised tumour that does not involve any vital structures as defined by the list of IDRFs (i.e. there are no IDRFs) and the tumour must be confined within one body compartment, neck, chest, abdomen, or pelvis.
An intraspinal tumour extension that does not fulfil the criteria for an IDRF is consistent with stage L1</td></tr>
<tr><td>Locoregional</td><td>Locoregional tumour with spread</td><td>Stage L2</td><td>Locoregional tumour with one or more IDRFs.
The tumour may be ipsilaterally contiguous within body compartments (i.e., a left-sided abdominal tumour with left-sided lung, bone or pleura involvement should be considered stage L2). However, a clearly left-sided abdominal tumour with right-sided lung, bone or pleura (or vice versa) involvement is defined as metastatic disease</td></tr>
<tr><td>Metastatic</td><td>Distant metastatic disease (except stage MS)</td><td>Stage M</td><td>Distant metastatic disease (i.e., not contiguous with the primary tumour) except as defined for stage MS.
Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumour with enlarged lower mediastinal nodes or a pelvic tumour with inguinal lymph node involvement is considered locoregional disease.
Ascites and/or pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumour</td></tr>
<tr><td>MS</td><td>Metastatic disease confined to skin, liver, and/or bone marrow in a patient less than 18 months (547 days).</td><td>Stage MS</td><td>Metastatic disease confined to skin, liver, and/or bone marrow, in a patient less than 18 months (547 days).
MIBG scintigraphy must be negative in bone and bone marrow</td></tr>
</table>

WILMS TUMOUR
Wilms tumour was defined according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes: nephroblastoma 6a1: ICD-O morphology codes are 8959, 8960, and topography code is C649. Cases aged up to <15 years old. The stage is based on the surgery specimen, whatever its timing, whereas the overall stage (localised, metastatic, bilateral) Is based on imaging at diagnosis. Two major protocols exist: the Children's Oncology Group/National Wilms Tumour Study Group (COG) protocol, where the staging system is based on the surgical specimen (nephrectomy) assessed prior to any chemotherapy, which is only given after surgery, and the International Society of Paediatric Oncology (SIOP) protocol, where the stage is based on the findings at surgery after the patient has received neoadjuvant chemotherapy. Both groups recognise the presence of metastatic (stage IV) disease at diagnosis, based on imaging findings.

Information required for staging			
Tier 1		**Tier 2**	
Distant metastatic disease		Treatment protocol Distant metastatic disease Involvement of abdominal lymph nodes Biopsy (including fine needle aspiration) prior to resection (COG protocol) Biopsy (excluding fine needle aspiration) prior to resection (SIOP protocol) Complete excision of tumour Tumour confined to the kidney	
Staging criteria – COG Protocol			
Tier 1		**Tier 2**	
Localised	Tumour confined to area of origin including abdominal lymph nodes	Stage I	Tumour is limited to the kidney and completely excised: - Renal capsule intact, not penetrated by tumour - No tumour invasion of veins or lymphatics of renal sinus - No prior biopsy - Negative margins
		Stage II	Tumour extends beyond kidney but completely resected: - Tumour penetrates renal capsule - Tumour in lymphatics or veins of renal sinus - Tumour in renal vein with margin not involved - No nodal or haematogenous metastases - Negative margins
		Stage III	Residual tumour or nonhaematogenous metastases confined to abdomen: -Involved abdominal nodes -Peritoneal contamination or tumour implant -Tumour spillage of any degree occurring before or during surgery -Gross residual tumour in abdomen -Biopsy of tumour (including fine-needle aspiration) prior to removal of kidney -Resection margins involved by tumour
Metastatic	Distant metastases present at diagnosis	Stage IV	Haematogenous metastases or spread beyond abdomen at diagnosis
Staging criteria – SIOP Protocol			
Localised	Tumour confined to area of origin including abdominal lymph nodes	Stage y-I	Tumour limited to kidney and completely resected: - Renal capsule may be infiltrated by tumour, but tumour does not reach the outer surface - Tumour may protrude or bulge into the pelvic system or ureter, but does not infiltrate - Vessels of renal sinus not involved
		Stage y-II	Tumour extends beyond kidney but completely resected: - Tumour penetrates renal capsule into perirenal far - Tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside renal parenchyma but is completely resected - Tumour infiltrates adjacent organs or vena cava but is completely resected
		Stage y-III	Incomplete excision of the tumour (gross or microscopic extension beyond the resection margins): -Involved abdominal lymph nodes, including necrotic tumour or chemotherapy-induced changes -Tumour rupture before or intraoperatively -Tumour has penetrated the peritoneal surface -Tumour thrombi present at resection margins -Surgical biopsy prior to resection (Does not include needle biopsy)
Metastatic	Distant metastases present at diagnosis	Stage IV	Haematogenous metastases or spread beyond abdomen at diagnosis

MEDULLOBLASTOMA			
Medulloblastoma was defined according to the ICCC-3rd ed. The ICCC-3.1 diagnostic group/subgroup and ICD-O codes for morphology are 3c.1—Medulloblastomas: 9470-9472, 9474, 9480; and ICD-O-3 site codes: C700-C729, C753. Cases aged up to <15 years old. The definition of stage by imaging has to be at the time of diagnosis, prior to surgical resection. The TG follows the staging proposed by L Harisiadis and CH Chang (6). Cerebrospinal fluid (CSF) testing needs to be by lumbar puncture and is usually recommended to be performed on day 14. If any earlier result is negative, it does not need repeating. If an earlier result is positive, it must be repeated at or after day 14 to reduce false positives. This means that cases may need to be followed for some time after the hospital discharge to complete staging.			
Information required for staging			
Tier 1		**Tier 2**	
Distant metastases Tumour cells in the cerebrospinal fluid		Distant metastases Metastatic site from imaging Tumour cells in cerebrospinal fluid	
Staging criteria			
Tier 1		**Tier 2**	
Localised	Localised disease	M0	No visible disease on imaging (MRI brain and spine) beyond primary site of disease and no tumour cells in the cerebrospinal fluid (CSF)
Metastatic	Disease beyond local site (e.g., other lesions in brain or spine OR tumour cells in CSF OR distant metastases)	M1	Tumour cells in the CSF
		M2	Visible metastasis in brain
		M3	Visible metastases in spine OR Visible metastasis in cervicomedullary (junction)
		M4	Metastasis outside of the central nervous system

OSTEOSARCOMA			
Osteosarcoma was defined according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes: 8a – Osteosarcoma: 9180-9187, 9192-9195 and ICD-O-3 site codes: C400-C419, C760-C768, C809. Cases aged up to <20 years old. The definition of stage has to be at the time of diagnosis, prior to any treatment. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started. “Skip lesions”, “skip metastases” or “seeding” in the same bone as the primary tumour are considered localised and not metastatic disease; if in a different bone to the primary tumour, these are considered metastatic.			
Information required for staging			
Tier 1		**Tier 2**	
Distant metastases		Distant metastases	
Staging criteria			
Tier 1		**Tier 2**	
Localised	Tumour confined to the area of origin including regional lymph nodes	Localised	Tumour confined to the area of origin including regional lymph nodes
Metastatic	Distant metastases present	Metastatic	Distant metastases present

EWING SARCOMA			
Ewing sarcoma was defined according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes: 8c1 – Ewing Tumour and Askin Tumour of Bone: 9260 and ICD-O-3 site codes: C400-C419, C760-C768, C809 and 9365 in site codes C400-C419 8c2 – pPNET of Bone: 9364 and ICD-O-3 site codes: C400-C419. Cases aged up to <20 years old. The definition of stage has to be at the time of diagnosis, prior to any treatment. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started. “Skip lesions”, “skip metastases” or “seeding” in the same bone as the primary tumour are considered localised and not metastatic disease; if in a different bone to the primary tumour, these are considered metastatic. According to the updated TG (2), the staging system of Ewing sarcoma is the same as that of osteosarcoma. Therefore, Ewing sarcoma can be combined with osteosarcoma to form a single group of bone sarcomas.			
Staging criteria			
Tier 1		**Tier 2**	
Localised	Tumour confined to the area of origin including regional lymph nodes	Localised	Tumour confined to the area of origin including regional lymph nodes
Metastatic	Distant metastases present	Metastatic	Distant metastases present

RHABDOMYOSARCOMA

Rhabdomyosarcoma was defined according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes ICCC-3 diagnostic group/subgroup and morphology codes: 9a – Rhabdomyosarcomas: 8900-8902, 8910, 8912, 8920 and ICD-O-3 site codes: C000-C809. Cases aged up to <20 years old.
The stage has to be defined at the time of diagnosis, prior to any treatment, according to standard clinical TNM rules, with nodal involvement assessed by imaging and/or lymph node biopsy, if performed prior to chemotherapy. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour, provided it is before any systemic therapy is started. Code 8991 (embryonal sarcoma) is excluded.

Information required for staging

Tier 1	Tier 2
Distant metastases	Distant metastases Regional lymph node involvement Tumour size Tumour site (favourable or unfavourable)

Favourable and unfavourable anatomic sites of disease

Favourable anatomic sites
- Orbit
- Head and neck (excluding parameningeal tumours)
  - Scalp
  - Parotid
  - Oral cavity
  - Larynx
  - Oropharynx
  - Cheek
  - Hypopharynx
  - Thyroid and parathyroid
  - Neck
- Genitourinary sites (excluding bladder and prostate tumours)
- Gallbladder and bile ducts

Unfavourable anatomic sites
- Bladder
- Prostate
- Extremity
- Parameningeal
  - Middle ear
  - Nasal cavity
  - Paranasal sinuses
  - Nasopharynx
  - Infratemporal fossa/pterygopalatine
  - Parapharyngeal area
- Trunk
- Retroperitoneum
- All other sites not noted as favourable

Site of disease (modified TNM classification to assign Tier 2)

T – Tumour size
- T0 = no evidence of primary tumour
- T1 = tumour confined to a single anatomic site
- T1a = tumour ≤ 5cm in greatest dimension
- T1b = tumour > 5cm in greatest dimension
- T2 = extension beyond anatomic site
- T2a = tumour ≤ 5cm in greatest dimension
- T2b = tumour > 5cm in greatest dimension
- Tx = Primary tumour cannot be assessed

N – Regional nodes
- N0 = regional lymph nodes not involved
- N1 = regional lymph nodes involved
- Nx = regional lymph nodes cannot be assessed (especially sites that preclude lymph node evaluation)

M – Metastasis
- M0 = no distant metastasis
- M1 = distant metastasis

Staging criteria

Tier 1		Tier 2	
Localised	Tumour confined to the area of origin including the regional lymph nodes	Stage I	Favourable site and Any T Any N M0
		Stage II	Unfavourable site and T1a, T2a N0 M0
		Stage III	Unfavourable site and T1a, T2a N1 M0 T1b, T2b Any N M0
Metastatic	Distant metastases present	Stage IV	Any site Any T Any N M1

Appendix description

Data quality indicators in Table 1 and Supplementary Table 1 are reported for all the registries/countries together with the number of cases contributed to BENCHISTA.

The indicators reported in these tables are defined by the project protocol (4) and provide an indication of the quality of diagnosis and of possible missing incident cases. Moreover, a further indicator was calculated for the quality of the stage definition in rhabdomyosarcoma.

The proportion of DCO cases (i.e., verified by death certificate only) should be minimal and indicate the access to major sources by registries and how precise the diagnosis is. The % DCO cases are reported for all childhood cancers for each country in the main Table 1 (all are <1% except Brazil (7·4%) and Bulgaria (5·6%). Further breakdown by individual regional registry for Brazil, Italy, Japan and Spain is shown in Supplementary Table 1. The DCO cases are excluded from all analyses.

Microscopically verified (MV) cases (cytologically or histologically verified) are for many tumours ≥90% or very close to this high proportion. The main exceptions are neuroblastoma and Wilms tumour, where the initial diagnosis may be clinical or biochemical, with delayed surgery, and there was a heterogeneous interpretation by cancer registries (CRs) of the required timing of MV. This is also an indication of difficulties in access to the pathological reports for some registries.

NOS (not otherwise specified cases) is reported in Table 1 for the general categories of the kidney (ICCC 3rd ed. VI c/ ICCC 3rd ed. VI), brain (ICCC 3rd ed. III f/ICCC 3rd ed. III), soft tissue (ICCC 3rd ed. IX e/ ICCC 3rd ed. IX) and bone (ICCC 3rd ed. VIII e/ ICCC 3rd ed. VIII) tumours, respectively, and presented adjacent to the subcategories of Wilms tumour, medulloblastoma, osteosarcoma, Ewing sarcoma and rhabdomyosarcoma (7). This indicator shows problems of accessing major documents for the definition of diagnosis or short time for diagnosis because facing lethal case (short survival). This indicator represents the percentage of neuroblastoma with unknown primary sites (ICD-O M-9500/3, 9490/3 in C80·9/ ICCC 3rd ed IV a). Except for neuroblastoma, which is very low, the proportions for the other types of tumours were around 7%.

For rhabdomyosarcoma, we developed a quality indicator of stage and site consistency, calculated as the ratio of 'favourable sites' categorized as Stage I plus unfavourable sites categorized as Stage II or Stage III (i.e., correct combinations) and the total of Stage I, II and III. This provides us with a further assessment of staging accuracy, beyond the previous e fictitious cases exercise completed by the CRs before the start of data collection (8). It shows how the definition of favourable and unfavourable sites in rhabdomyosarcoma is complex and often not so clear for CRs, with noticeable variation in the definition of the substage when this tumour is localised.

For Japanese CRs, the overall survival of the included (access to data for TGs) and excluded (no access to data for TGs) cases have been compared showing no difference, suggesting there was no selection bias.

Supplementary Table 1: Quality indicators by country, contributing years, number of total cases and number of cases by tumour type

				Neuroblastoma			Wilms			Medulloblastoma		
Area or Country	**Contributing years**	**Total No. Cases**	**%DCO**	**%NOS**	**No. Cases**	**%MV**	**%NOS kidney**	**No. Cases**	**%MV**	**%NOS brain**	**No. Cases**	**%MV**
Central Europe												
Austria	2015-2017	166	0·1	10·9	41	73	2·6	28	66	10·9	17	100
Belgium	2015-2017	206	0	1·9	52	100	0	45	96	7·5	24	100
France	2014-2016	1,428	0	0·8	391	93	0	232	94	1·8	203	100
Germany	2014-2017	1,307	0	0·2	453	92	0	383	99	1·2	235	96
Netherlands	2014-2017	460	NA	9·4	94	98	0	82	100	7·1	75	100
Switzerland	2015-2017	172	0·3	0	52	96	0	27	100	1·7	24	100
Northern Europe												
Denmark	2014-2017	109	0	13	26	100	7·1	18	100	9	13	100
Norway	2014-2016	88	0·2	0	18	100	0	21	100	5	9	100
Sweden	2014-2017	264	0	0	58	100	0	63	87	5·7	40	100
Eastern Europe												
Bulgaria	2014-2017	137	5·6	0	42	100	6·9	27	93	26·4	15	100
Czechia	2014-2017	228	0	3·6	55	95	0	39	38	0	42	100
Estonia	2014-2017	32	0	0	9	100	0	9	100	11·1	4	100
Hungary	2014-2016	211	0	0	64	91	0	41	98	0	27	100
Poland	2014-2016	694	NA	NA	260	75	NA	141	1	NA	84	71
Romania	2014-2016	245	0	85·2	61	89	100	40	100	54·3	32	100
Southern Europe												
Greece	2014-2016	168	0	0	54	98	100	43	100	64	25	100
Italy*	2014-2017	840	0·1	0	240	98	9·3	124	97	21·1	100	100
Malta	2014-2017	6	1·2	0	1	100	0	3	100	0	2	100
Portugal	2014-2017	215	0·1	0	59	100	0	38	95	3·3	28	100
Slovenia	2015-2017	39	0	0	8	100	0	4	100	18·5	3	100
Spain	2014-2017	773	0·2	1	227	89	13·4	131	90	3·9	96	99
UK and Ireland												
Northern Ireland	2014-2017	47	0·7	0	10	90	0	17	100	20·5	5	100
Ireland	2014-2017	139	0·3	0	34	100	0	33	97	2·6	24	100

England	2014-2017	1,488	0	0	335	98	0·3	338	98	4·7	186	99
Scotland	2014-2016	96	0·2	0	23	100	0	20	100	0·7	13	100
Wales	2014-2017	76	0	0	14	100	10·5	17	100	15·8	10	100
Non-European												
Australia*[a]	2014-2017	295	0·3	0·5	76	93	0	66	97	5·2	44	95
Brazil*	2014-2017	493	7·4	0	65	98	7·3	126	94	22·3	69	99
Canada*[b]	2014-2017	360	0·1	0·4	115	91	0	63	80	0·2	50	98
Japan*[c]	2014-2016	155	0·8	5	68	91	0	26	96	9·5	19	100
Total	2014-2017	10,937	0·7	2·8	3,005	87	7·1	2,245	88	7·4	1,518	94
Desegregated regional distribution												
Brazil												
Aracaju	2014-2016	17	0	0	5	100	0	4	100	0	1	100
Barretos	2014-2017	6	10	0	2	100	0	0	NA	25	2	100
Belem	2014-2017	52	17·1	0	1	0	9·1	18	100	7·7	3	100
Belo Horizonte	2014-2017	65	6·4	0	11	100	5·6	15	100	26·8	11	100
Campinas	2014-2016	16	7·5	0	3	100	0	2	100	17·4	3	100
Curitiba	2014-2017	77	4·6	0	16	100	0	22	100	25	9	100
Distrito Federal	2014-2017	110	3·1	0	12	100	8·3	20	100	16·3	21	100
Fortaleza	2014-2016	32	10·8	0	1	100	0	13	100	42·9	3	100
Jau	2015-2017	2	0	NA	1	100	0	0	NA	0	1	100
Joao Pessoa	2014-2017	23	6·5	0	1	100	0	5	80	30	3	100
Mato grosso	2014-2016	53	10·9	0	7	100	10	16	100	22·2	6	100
Recife	2014-2017	40	4·4	0	5	100	26·7	11	45	37·5	6	83
Italy												
Apulia	2014-2017	103	0	0	33	91	4	19	100	22·8	7	100
Basilicata	2015-2017	5	0	0	1	100	50	0	NA	39·6	1	100
Bergamo	2014-2016	37	0	0	8	100	0	8	88	6·7	5	100
Campania	2015-2017	104	0·1	0	31	100	0	14	93	17·6	14	100
Catania Messina Enna	2014-2017	44	0	0	11	100	10	6	100	21	5	100
Como	2014-2017	13	0	100	4	100	0	2	100	0	2	100

Emilia Romagna	2014-2017	48	0	0	6	100	0	8	100	36·8	0	NA
Friuli Venezia Giulia	2014-2017	27	0	0	8	100	0	5	100	20	4	100
Genova	2015-2017	10	0	0	5	100	0	0	NA	28·6	1	100
Mantova Cremona	2014-2016	16	0	NA	5	100	100	1	100	52·9	3	100
Marche	2014-2017	29	0·6	0	11	100	0	4	100	2·2	4	100
Milano	2014-2016	51	0	0	17	100	12·5	6	100	18·8	4	100
Monza Brianza	2014-2016	16	0	0	4	100	0	3	100	12·5	2	100
Nord Sardegna	2015-2017	3	0	0	2	100	0	0	NA	0	0	NA
Palermo	2014-2017	27	0·4	0	10	100	0	3	100	10·2	3	100
Piemonte	2014-2017	106	NA	NA	38	97	NA	13	100	NA	11	100
Ragusa Caltanissetta	2014-2017	18	0	0	4	100	16·7	3	100	6·3	3	100
Siracusa	2014-2016	7	0	0	3	100	0	1	100	11·1	1	100
Toscana	2014-2016	57	0	0	11	100	20	10	100	21·2	10	100
Trapani	2014-2016	5	0	0	2	100	0	1	100	60	0	NA
Trento	2014-2017	14	0	0	2	100	0	4	100	3·7	3	100
Umbria	2014-2017	15	0	0	2	100	25	1	0	50	1	100
Varese	2014-2017	14	0	100	4	100	0	2	100	0	1	100
Veneto	2015-2017	87	0	NA	22	100	0	13	92	6·3	17	100
Spain												
Basque country	2014-2017	45	0·4	0	12	100	0	4	100	12·5	4	100
Comunitat Valenciana	2014-2017	101	0	0	21	95	100	15	100	93·8	16	100
Girona	2014-2017	14	0	0	1	100	80	3	100	43·8	4	100
Granada	2014-2017	30	0	0	10	90	0	5	100	0	4	100
Madrid	2015-2017	142	0·5	6·5	31	94	4·3	22	95	3·2	11	100
Murcia	2014-2017	41	0·5	0	11	91	0	9	100	0	5	100
Navarra	2014-2016	11	0	0	4	100	0	2	100	0	1	100
RETI-SEHOP	2015-2017	372	0	0·7	133	85	0	67	82	0	48	98
Tarragona	2014-2017	17	0	0	4	75	0	4	100	3·3	3	100
Japan												
Osaka	2014-2016	81	0·5	0	31	84	0	7	100	21·5	14	93
Tokyo	2014-2017	74	1·1	8	37	97	0	12	100	3·3	12	100

					Osteosarcoma		Ewing sarcoma		Rhabdomyosarcoma			
Area or Country	**Contributing years**	**Total cases**	**%DCO**	**% NOS Bone sarcoma**	**No. Cases**	**%MV**	**No. Cases**	**%MV**	**% NOS Soft Tissue Sarcoma**	**No. Cases**	**%MV**	**% Site and Stage consistency^**
Central Europe												
Austria	2015-2017	166	0·1	10	31	100	21	100	10·3	28	100	0
Belgium	2015-2017	206	0	1·3	36	100	24	100	13·7	25	100	68
France	2014-2016	1,428	0	0·9	208	100	192	100	9·2	202	100	85
Germany	2014-2017	1,307	0	0·2	236	95	0	NA	7·6	0	NA	NA
Netherlands	2014-2017	460	NA	1	69	100	64	100	2·8	76	100	100
Switzerland	2015-2017	172	0·3	2·1	27	100	13	100	7	29	97	67
Northern Europe												
Denmark	2014-2017	109	0	0	12	100	16	100	0	24	100	82
Norway	2014-2016	88	0·2	5·9	9	100	12	100	0	19	100	93
Sweden	2014-2017	264	0	0	34	91	31	100	0	38	100	83
Eastern Europe												
Bulgaria	2014-2017	137	5·6	3·6	6	100	26	100	7·1	21	100	50
Czechia	2014-2017	228	0	0	27	100	26	100	0	39	100	88
Estonia	2014-2017	32	0	0	3	100	3	100	5	4	100	100
Hungary	2014-2016	211	0	1·7	28	100	26	100	8·6	25	100	75
Poland	2014-2016	694	NA	NA	68	96	65	97	NA	76	9	58
Romania	2014-2016	245	0	24·4	40	100	31	100	0	41	98	56
Southern Europe												
Greece	2014-2016	168	0	0	15	100	15	93	5·9	16	100	62
Italy*	2014-2017	840	0·1	12·4	145	99	121	99	9	110	100	85
Malta	2014-2017	6	1·2	0	0	NA	0	NA	0	0	NA	NA
Portugal	2014-2017	215	0·1	4·8	30	93	32	94	8·8	28	100	73
Slovenia	2015-2017	39	0	0	7	100	9	100	10	8	100	83
Spain	2014-2017	773	0·2	12·7	104	100	113	98	9·6	102	99	73
UK and Ireland												
Northern Ireland	2014-2017	47	0·7	0	2	100	6	100	0	7	100	75
Ireland	2014-2017	139	0·3	9·3	27	100	6	100	6·3	15	100	73

England	2014-2017	1488	0	2	214	100	150	99	5·8	265	98	83
Scotland	2014-2016	96	0·2	0	15	100	11	100	10·3	14	100	83
Wales	2014-2017	76	0	14·3	7	100	7	86	7	21	90	85
Non-European												
Australia*[a]	2014-2017	295	0·3	0·8	37	100	25	100	6·7	47	100	83
Brazil*	2014-2017	493	7·4	14·6	106	99	48	96	15	79	99	68
Canada*[b]	2014-2017	360	0·1	1·5	50	98	24	97	6·1	58	98	82
Japan*[c]	2014-2016	155	0·8	6·7	14	100	5	100	6·4	23	100	56
Total	2014-2017	10,937	0·7	6·5	1,607	96	1,122	97	8·1	1,440	90	78
Desegregated regional distribution												
Brazil												
Aracaju	2014-2016	17	0	0	0	NA	4	100	33·3	3	100	100
Barretos	2014-2017	6	10	20	1	100	0	NA	33·3	1	100	100
Belem	2014-2017	52	17·1	0	6	100	13	100	0	11	100	83·3
Belo Horizonte	2014-2017	65	6·4	28·6	7	100	9	100	27·3	12	100	50
Campinas	2014-2016	16	7·5	16·7	0	NA	2	100	25	6	100	0
Curitiba	2014-2017	77	4·6	11·8	11	100	11	100	16·7	8	100	50
Distrito Federal	2014-2017	110	3·1	20·5	12	83	28	96	12·5	17	94	50
Fortaleza	2014-2016	32	10·8	6·7	2	100	8	100	10·5	5	100	66·6
Jau	2015-2017	2	0	NA	0	NA	0	NA	0	0	NA	NA
Joao Pessoa	2014-2017	23	6·5	20	1	100	9	100	0	4	100	50
Mato grosso	2014-2016	53	10·9	6·3	6	100	14	100	22·2	4	100	100
Recife	2014-2017	40	4·4	16·7	2	100	8	100	15·4	8	100	100
Italy												
Apulia	2014-2017	103	0	0	18	100	13	100	8·8	13	100	100
Basilicata	2015-2017	5	0	60	2	100	0	NA	22·2	1	100	100
Bergamo	2014-2016	37	0	0	3	100	8	100	16·7	5	100	60
Campania	2015-2017	104	0·1	2·6	15	100	19	100	11·1	11	100	88·8
Catania Messina Enna	2014-2017	44	0	13·6	7	100	7	100	1·6	8	100	100
Como	2014-2017	13	0	0	1	0	3	100	0	1	100	100

Emilia Romagna	2014-2017	48	0	10·5	17	100	10	100	12·5	7	100	100
Friuli Venezia Giulia	2014-2017	27	0	14·3	5	100	3	100	0	2	100	100
Genova	2015-2017	10	0	0	0	NA	2	100	0	2	100	100
Mantova Cremona	2014-2016	16	0	28·6	2	100	4	100	100	1	100	100
Marche	2014-2017	29	0·6	33·3	2	100	4	100	9·1	4	100	33·3
Milano	2014-2016	51	0	5·3	6	100	8	100	10·3	10	100	100
Monza Brianza	2014-2016	16	0	0	2	100	4	100	28·6	1	100	100
Nord Sardegna	2015-2017	3	0	0	1	100	0	NA	0	0	NA	NA
Palermo	2014-2017	27	0·4	12·5	3	100	4	100	0	4	100	50
Piemonte	2014-2017	106	NA	NA	13	100	18	100	NA	13	100	63·6
Ragusa Caltanissetta	2014-2017	18	0	0	1	100	6	100	0	1	100	NA
Siracusa	2014-2016	7	0	50	0	NA	1	100	0	1	100	100
Toscana	2014-2016	57	0	8·3	8	100	10	100	0	8	100	100
Trapani	2014-2016	5	0	0	1	100	1	100	50	0	NA	NA
Trento	2014-2017	14	0	0	2	100	1	100	0	2	100	100
Umbria	2014-2017	15	0	28·6	3	100	5	80	25	3	100	100
Varese	2014-2017	14	0	0	1	100	4	100	0	2	100	100
Veneto	2015-2017	87	0	NA	10	100	14	93	12·9	11	100	100
Spain												
Basque country	2014-2017	45	0·4	33·3	9	100	11	100	9·1	5	100	100
Comunitat Valenciana	2014-2017	101	0	50	14	100	16	100	36·8	19	100	80
Girona	2014-2017	14	0	53·3	3	100	1	100	40	2	100	NA
Granada	2014-2017	30	0	0	5	100	4	100	0	2	100	100
Madrid	2015-2017	142	0·5	3·6	26	96	27	100	4·9	25	96	60
Murcia	2014-2017	41	0·5	15·4	5	100	5	100	0	6	100	100
Navarra	2014-2016	11	0	0	3	67	1	100	0	0	NA	NA
RETI-SEHOP	2015-2017	372	0	0	48	100	35	100	7·6	41	100	68·9
Tarragona	2014-2017	17	0	0	0	NA	4	100	0	2	100	100
Japan												
Osaka	2014-2016	81	0·5	3	13	100	3	100	2·2	13	100	67
Tokyo	2014-2017	74	1·1	9·5	1	100	2	100	9·2	10	100	43

*Countries with partial national coverage. The coverage of a Cancer registry (CR) refers to the population and geographic area it encompasses.
RETI-SEHOP: Spanish Registry of Childhood Tumours.
NA: Not Available.
^ Quality indicator of stage and site consistency described in Appendix description (page 7).
a: CRs of Victoria, Queensland and the Northern Territory. b: CR of Ontario (Pediatric Oncology Group of Ontario). c: 62% of the cases in Tokyo and Osaka.

Supplementary Table 2: Comparison of age distribution by geographical area and tumour type

	Neuroblastoma (0-14 years)					Wilms tumour (0-14 years)					Medulloblastoma (0-14 years)			
Geographical Area	**<18 months**	**18-60 months**	**5-14 years**	**Median age in months at diagnosis**	**Total**	**<1 year**	**1-4 years**	**5-14 years**	**Median age in months at diagnosis**	**Total**	**0-4 years**	**5-14 years**	**Median age in months at diagnosis**	**Total**
Australia	43%	50%	7%	23	76	12%	65%	23%	44	66	27%	73%	107	44
Brazil	28%	49%	23%	33	65	13%	64%	23%	38	126	32%	68%	84	69
Canada	49%	39%	12%	18	115	10%	57%	33%	46	63	32%	68%	84	50
Japan	35%	43%	22%	32	68	16%	69%	15%	32	26	21%	79%	100	19
Central Europe	50%	36%	14%	18	1,083	13%	62%	25%	37	797	32%	68%	83	578
Eastern Europe	51%	37%	12%	17	491	18%	58%	24%	38	297	38%	62%	72	204
Northern Europe	49%	39%	12%	18	102	20%	65%	15%	36	102	35%	65%	79	62
Southern Europe	51%	37%	12%	17	589	18%	53%	29%	43	343	35%	65%	77	254
UK and Ireland	44%	43%	13%	22	416	12%	61%	27%	41	425	37%	63%	79	238
Total	48%	39%	13%	19	3,005	15%	60%	25%	39	2,245	34%	66%	80	1,518
	Pearson chi2(df=16) =35·014; P-value=0·0040					Pearson chi2(df=16) =26·74; P-value=0·044					Pearson chi2(df=8) =6·50; P-value=0·59			
	df=degrees of freedom													

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	Osteosarcoma (<18 years)						Ewing Sarcoma (<18 years)						Rhabdomyosarcoma (<18 years)					
Geographical Area	**0-4 years**	**5-9 years**	**10-14 years**	**15-17 years**	**Median age in months at diagnosis**	**Total**	**0-4 years**	**5-9 years**	**10-14 years**	**15-17 years**	**Median age in months at diagnosis**	**Total**	**<1 year**	**1-9 years**	**10-14 years**	**15-17 years**	**Median age in months at diagnosis**	**Total**
Australia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brazil	2%	11%	45%	42%	170	90	12%	22%	37%	29%	146	41	6%	58%	19%	17%	78	72
Canada	4%	19%	60%	17%	158	48	4%	42%	25%	29%	141	24	5%	71%	17%	7%	75	58
Japan	0%	16%	67%	17%	162	12	40%	20%	20%	20%	105	5	5%	62%	14%	19%	82	21
Central Europe	1%	13%	51%	35%	166	572	9%	18%	44%	29%	155	307	6%	63%	18%	13%	69	354
Eastern Europe	1%	20%	44%	35%	163	160	14%	24%	34%	28%	142	169	10%	59%	18%	13%	71	200
Northern Europe	7%	12%	37%	44%	176	43	12%	21%	53%	14%	145	43	7%	65%	19%	9%	72	57
Southern Europe	0%	20%	45%	35%	162	221	11%	28%	40%	21%	135	208	5%	64%	21%	10%	76	203
UK and Ireland	1%	15%	47%	37%	169	230	7%	26%	37%	30%	147	162	6%	63%	17%	14%	75	298
Total	1%	15%	48%	36%	166	1,376	10%	24%	40%	26%	146	959	6%	63%	18%	13%	73	1,263
	Pearson chi2(df=21) =37·93; P-value=0·013						Pearson chi2(df=21) =32·49; P-value=0·052						Pearson chi2(df=21) =12·69; P-value==0·91					

Note: Sarcomas from Australia, Greece, RETI-SEHOP (Spain), and Denmark cancer registries were removed as they do not routinely collect cases over 15 years old.

NA: Not available.

Supplementary Table 3: Percentage frequency distribution of stages by geographical area for Neuroblastoma for patients aged less than 18 months and patients aged 18 months or older, together with a chi-square test to assess whether there is a difference in distributions between geographical areas.

	Neuroblastoma (Tier 1)										
	<18 months						≥18 months				
Geographical Area	**L**	**LR**	**M+**	**MS**	**X**	**Total**	**L**	**LR**	**M+**	**X**	**Total**
Australia	33·3	15·1	12·1	24·4	15·1	100	14·0	11·6	53·5	20·9	100
Brazil	16·7	22·2	11·1	38·9	11·1	100	19·2	10·6	68·1	2·1	100
Canada	35·7	23·2	12·5	28·6	0·0	100	23·7	15·3	61·0	0·0	100
Japan	25·0	37·5	20·8	8·3	8·3	100	9·1	20·5	56·8	13·6	100
Central Europe	22·7	31·8	17·9	16·4	11·2	100	13·4	23·6	58·6	4·4	100
Eastern Europe	37·6	30·4	13·6	18·0	0·4	100	20·3	29·5	49·8	0·4	100
Northern Europe	28·0	22·0	20·0	30·0	0·0	100	11·5	17·3	71·2	0·0	100
Southern Europe	40·4	22·8	13·9	20·2	2·6	100	21·6	21·3	55·4	1·7	100
UK and Ireland	23·8	20·4	29·3	18·8	7·7	100	14·9	13·2	65·5	6·4	100
Total	30·0	27·2	17·4	19·0	6·3	100	16·6	21·2	58·3	3·9	100
	Pearson chi2*(24) =75·099; P-value <0·0001						Pearson chi2*(16) =42·045; P-value <0·0001				
	*Calculated excluding missing values L=Localised, LR=Locoregional, M=Distant metastatic disease, MS=Metastatic disease confined to skin, liver, and/or bone marrow in a patient less than 18 months, X=Unknown.										

Supplementary Table 4: Age-adjusted odds ratio (OR) of being diagnosed at a metastatic stage in each geographical area vs Central Europe (reference category)

	Neuroblastoma* Tier 1			Wilms tumour			Medulloblastoma			Osteosarcoma <18 years			Ewing sarcoma <18 years			Rhabdomyosarcoma <18 years		
Geographical Area	**OR**	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**	
Australia	1·08	0·60	1·96	0·43	0·18	1·03	0·80	0·39	1·67									
Brazil	1·34	0·74	2·40	1·16	0·71	1·91	0·79	0·45	1·40	2·48	1·49	4·15	1·31	0·63	2·70	2·17	1·21	3·88
Canada	0·86	0·55	1·35	1·01	0·53	1·94	0·93	0·50	1·71	0·67	0·31	1·46	1·02	0·40	2·59	2·56	1·41	4·63
Japan	1·15	0·65	2·03	0·95	0·31	2·90	0·52	0·17	1·61	0·28	0·04	2·22	0·75	0·08	7·12	1·24	0·44	3·44
Eastern Europe	0·62	0·48	0·80	0·65	0·44	0·97	0·89	0·62	1·28	1·38	0·91	2·10	1·20	0·80	1·81	1·40	0·93	2·07
Northern Europe	1·41	0·87	2·26	1·06	0·61	1·84	0·69	0·38	1·24	1·15	0·56	2·35	1·17	0·59	2·34	0·90	0·45	1·78
Southern Europe	0·76	0·60	0·96	0·76	0·53	1·10	0·85	0·61	1·18	0·69	0·45	1·06	1·24	0·84	1·84	0·99	0·64	1·51
UK and Ireland	1·67	1·28	2·19	1·24	0·92	1·68	1·45	1·03	2·04	1·07	0·72	1·58	1·15	0·75	1·75	1·28	0·87	1·87

*Localised vs Metastatic (MS stage excluded).

Supplementary Table 5: Age-adjusted o dds ratio (OR) of being diagnosed at a metastatic stage in each geographical area vs Central Europe (reference category) – analysis for neuroblastoma (Tier 2)

	Neuroblastoma*§ Tier 2		
Area or Country	**OR**	**95%CI**	
Australia	1·24	0·68	2·27
Brazil	1·66	0·91	3·06
Canada	0·99	0·63	1·59
Japan	1·34	0·75	2·39
Eastern Europe	0·72	0·54	0·95
Northern Europe	1·62	0·99	2·64
Southern Europe	0·91	0·69	1·19
UK and Ireland	2·02	1·49	2·75

*Localised vs Metastatic (MS stage excluded).

§ Germany was excluded from the Central European area for this analysis.

Supplementary Table 6: Sensitivity analysis for multivariable models for the UK and Ireland for Medulloblastoma and Rhabdomyosarcoma

Type of tumour	Parameter	OR	p-value	95%CI	
Medulloblastoma	All stage missing=M0	0·94	0·70	0·68	1·29
	Assuming 80% stage missing= M0 and 20%=Metastatic	1·15	0·40	0·84	1·57
	Assuming 70% stage missing= M0 and 30%=Metastatic	1·25	0·16	0·91	1·71
Rhabdomyosarcoma	All stage missing=Non metastatic	0·94	0·74	0·65	1·36
	Assuming 80% stage missing=Non metastatic and 20%=Metastatic	1·19	0·36	0·83	1·70
	Assuming 70% stage missing=Non metastatic and 30%=Metastatic	1·31	0·14	0·92	1·88

Note: Central Europe (reference category).

Supplementary Table 7: Distribution of sources used for staging by country by tumour type

All six tumours combined							
Country	**Pathology report and administrative files**	**Hospital clinical records (including pathology report)**	**Clinical study group only**	**Including all files***	**Others**	**Missing**	**Total**
Australia	17%	54%	0%	0%	22%	7%	295
Austria	2%	1%	0%	38%	42%	17%	166
Belgium	29%	33%	0%	33%	3%	2%	206
Brazil	44%	47%	0%	2%	3%	4%	493
Bulgaria	99%	0%	0%	0%	1%	0%	137
Canada	0%	0%	0%	0%	0%	100%	360
Czechia	99%	0%	0%	1%	0%	0%	228
Denmark	0%	97%	0%	3%	0%	1%	109
England	0%	85%	0%	0%	6%	9%	1,488
Estonia	0%	100%	0%	0%	0%	0%	32
France	0%	100%	0%	0%	0%	0%	1,428
Germany	0%	2%	98%	0%	0%	0%	1,307
Greece	5%	95%	0%	0%	0%	0%	168
Hungary	0%	0%	0%	100%	0%	0%	211
Ireland	0%	100%	0%	0%	0%	0%	139
Italy	70%	7%	0%	14%	9%	0%	840
Japan	0%	0%	0%	0%	0%	100%	155
Malta	100%	0%	0%	0%	0%	0%	6
Netherlands	100%	0%	0%	0%	0%	0%	460
Northern Ireland	6%	92%	0%	0%	2%	0%	47
Norway	65%	0%	0%	35%	0%	0%	88
Poland	29%	0%	16%	49%	4%	2%	694
Portugal	0%	100%	0%	0%	0%	0%	215
Romania	96%	0%	0%	0%	4%	0%	245
Scotland	87%	6%	0%	0%	7%	0%	96
Slovenia	100%	0%	0%	0%	0%	0%	39
Spain	21%	33%	0%	27%	7%	12%	773
Sweden	43%	5%	0%	0%	52%	0%	264
Switzerland	85%	2%	0%	8%	5%	0%	172
Wales	66%	1%	0%	1%	13%	19%	76
Total	26%	38%	13%	10%	5%	8%	10,937

*Hospital clinical records, pathological reports, administrative files and clinical study group documentation.

Supplementary Table 8: Imaging performed before any treatment by geographical area* and by tumour type

	Neuroblastoma							
	Thorax X-ray and abdominal ultrasound				MIBG scan			Total
Area or Country	**Both done**	**At least one done**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	
Brazil	32%	28%	12%	28%	49%	23%	28%	65
Japan	25%	18%	0%	57%	40%	3%	57%	68
Central Europe	36%	51%	12%	1%	93%	7%	0%	536
Eastern Europe	59%	18%	1%	22%	45%	29%	26%	491
Northern Europe	57%	25%	18%	0%	98%	2%	0%	102
Southern Europe	55%	32%	4%	9%	78%	7%	15%	589
UK and Ireland	29%	30%	0%	41%	49%	2%	49%	416
Total	45%	32%	5%	18%	68%	11%	21%	2,267

	Wilms tumour							
	Thorax: X-ray and CT scan				CT Thorax			Total
Area or Country	**CT Thorax performed**	**Chest x-ray performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	
Brazil	71%	6%	2%	21%	71%	6%	23%	126
Japan	NA	46%	0%	54%	0%	0%	100%	26
Central Europe	89%	3%	7%	1%	89%	9%	2%	332
Eastern Europe	50%	47%	3%	0%	50%	50%	0%	297
Northern Europe	78%	22%	0%	0%	78%	6%	16%	102
Southern Europe	75%	11%	3%	11%	74%	13%	13%	343
UK and Ireland	69%	3%	1%	27%	69%	0%	31%	425
Total	70%	15%	3%	12%	70%	15%	15%	1,651

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	Medulloblastoma						
	Cerebrospinal fluid (CSF) cytology			Gadolinium-enhanced MRI of the whole neuraxis			Total
Area or Country	**Performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	
Brazil	62%	15%	23%	65%	10%	25%	69
Japan	0%	0%	100%	0%	0%	100%	19
Central Europe	86%	9%	5%	93%	3%	4%	268
Eastern Europe	72%	14%	14%	85%	5%	10%	204
Northern Europe	95%	5%	0%	100%	0%	0%	62
Southern Europe	79%	9%	12%	82%	7%	11%	254
UK and Ireland	48%	4%	48%	81%	0%	19%	238
Total	71%	9%	20%	83%	4%	13%	1,114

	Osteosarcoma										
	Thorax: x-ray and CT				Positron emission tomography (PET) scans			Bone scan			Total
Area or Country	**CT Thorax performed**	**Chest x-ray performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	
Brazil	63%	1%	5%	31%	3%	33%	64%	49%	14%	37%	106
Japan	NA	86%	0%	14%	0%	0%	100%	43%	36%	21%	14
Central Europe	83%	1%	8%	8%	39%	53%	8%	71%	21%	8%	302
Eastern Europe	96%	1%	0%	3%	12%	75%	13%	88%	8%	4%	172
Northern Europe	95%	5%	0%	0%	49%	51%	0%	65%	35%	0%	55
Southern Europe	76%	4%	2%	18%	32%	41%	27%	48%	26%	26%	301
UK and Ireland	56%	2%	0%	42%	5%	18%	77%	42%	2%	56%	265
Total	75%	3%	3%	19%	23%	43%	34%	59%	16%	25%	1,215

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	Ewing sarcoma										
	Thorax: x-ray and CT				Positron emission tomography (PET) scans			Bone scan			Total
Area or Country	**CT Thorax performed**	**Chest x-ray performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	
Brazil	58%	2%	25%	15%	33%	33%	34%	54%	15%	31%	48
Japan	NA	60%	0%	40%	0%	0%	100%	60%	0%	40%	5
Central Europe	91%	2%	4%	3%	77%	20%	3%	53%	44%	3%	250
Eastern Europe	89%	3%	1%	7%	29%	50%	21%	63%	26%	11%	177
Northern Europe	91%	5%	2%	2%	76%	22%	2%	58%	39%	3%	59
Southern Europe	74%	6%	4%	16%	40%	31%	29%	55%	20%	25%	289
UK and Ireland	51%	2%	1%	46%	9%	12%	79%	43%	2%	55%	181
Total	77%	4%	3%	16%	43%	28%	29%	54%	25%	21%	1,009

	Rhabdomyosarcoma										
	Thorax: x-ray and CT				Positron emission tomography (PET) scans			Bone scan			Total
Area or Country	**CT Thorax performed**	**Chest x-ray performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	**Performed**	**Not performed**	**Unknown**	
Brazil	64%	4%	13%	19%	9%	53%	38%	53%	25%	22%	79
Japan	NA	52%	0%	48%	0%	0%	100%	22%	30%	48%	23
Central Europe	81%	3%	12%	4%	66%	29%	5%	34%	61%	5%	284
Eastern Europe	60%	7%	10%	23%	16%	63%	21%	32%	43%	25%	206
Northern Europe	81%	15%	4%	0%	60%	38%	2%	48%	49%	3%	81
Southern Europe	76%	6%	1%	17%	44%	33%	23%	48%	27%	25%	264
UK and Ireland	61%	3%	2%	34%	19%	18%	63%	34%	6%	60%	322
Total	69%	6%	6%	19%	36%	34%	30%	38%	33%	29%	1,259

*Note: Australia, Canada, Germany and The Netherlands cases are not included in these tables as these CRs could not provide information on staging investigations. All the other cases are included regardless of age group.

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