Title: Childhood cancer staging in a population-based registry: feasibility and validity of the Toronto Childhood Cancer Stage Guidelines

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Abbreviations: ACCR – Australian Childhood Cancer Registry; ICCC-3 – International Classification of Childhood Cancers, 3rd edition; TNM – tumour-node-metastasis; UICC – Union for International Cancer Control; ALL acute lymphoblastic leukaemia; AML acute myeloid leukaemia; HL Hodgkin lymphoma; NHL non-Hodgkin lymphoma; CI confidence interval.

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Abstract

Background: Stage at diagnosis is a critical variable for assessing global efforts to increase awareness of childhood cancer and improve outcomes. However, consistent information on childhood cancer stage is lacking from population cancer registries worldwide. The Toronto Childhood Cancer Stage Guidelines, compiled through a consensus process involving an international panel, were designed to provide a standard framework for population registries to collect information on stage at diagnosis for childhood cancers. We aimed to assess the feasibility of implementing the Toronto Guidelines within a population cancer registry.

Methods: A sample of 1,412 children (0-14 years old) diagnosed during the period 2006-2010 with one of 16 childhood malignancies was drawn from the Australian Childhood Cancer Registry. Data items were extracted from hospital records and stage was assigned using computer algorithms derived from the Toronto Guidelines. In addition, expert reviewers independently assigned stage to a random subsample of 160 cases (10 per malignancy type).

Findings: Stage could be assigned for 93% (n=1,318) of the 1,412 cases overall, ranging from 84% (48 of 57 cases) for non-rhabdomyosarcoma soft tissue sarcoma to 100% for hepatoblastoma (n=46). In contrast, stage at diagnosis was recorded by the treating physician for 39% (n=555) of the 1,412 cases. The computer algorithm assigned the same stage as did one or more independent expert reviewers in 155 (97%) of the 160 cases assessed.

Interpretation: We conclude that, using data routinely available in medical records, the Toronto Childhood Cancer Stage Guidelines provide a highly functional framework that is feasible for use by population cancer registries to stage the majority of childhood cancer patients at diagnosis. Stage data has the potential to inform interventions targeting improved diagnosis and survival.

Funding: This project was funded by Cancer Australia through an initiative to strengthen national data capacity for reporting cancer stage at diagnosis.

Research in context

Evidence before this study

Uniform, agreed rules for staging childhood cancers within population registries have been lacking. No peer-reviewed papers, irrespective of year of publication, could be found on PubMed wherein the UICC-endorsed Toronto Childhood Cancer Stage Guidelines had been applied within a population cancer registry, using the search terms ("childhood" OR "paediatric" OR "pediatric") AND "cancer registry" AND ("stage" OR "staging") AND "Toronto". We confirmed this result by checking the Web of Science for relevant papers that cited the original article by Gupta et. al. (2016) (12) and again none were found.

Added value of this study

This is the first study internationally to implement and assess the Toronto Childhood Cancer Stage Guidelines. Stage was successfully attributed to 93% of cases using the detailed Tier 2 classifications and to 94% of cases using the more basic Tier 1 classifications, designed for low and middle income countries where resources devoted to cancer registration are generally limited.

Implications of all the available evidence

The Toronto Childhood Cancer Stage Guidelines are the only international consensus staging framework for childhood malignancies. Our findings demonstrate the feasibility of implementing the Toronto Guidelines for assigning stage at diagnosis of childhood cancer within a population cancer registry in a high income country. Implementation of the Toronto Guidelines has the potential to achieve internationally consistent childhood cancer staging information, which is essential for population surveillance and comparisons of cancer outcomes.

Introduction

Cancer stage describes the extent of disease and is usually established at the time of diagnosis. It is a powerful indicator of prognosis (1-4) and is the basis of treatment planning.(5-8) Data on cancer stage are recommended for inclusion in population cancer registry collections(9) for the evaluation of initiatives targeting improved diagnosis of cancer at a population level and because this information is essential for meaningful population surveillance and cross-country comparisons of cancer outcomes.(10)

Childhood cancer is a leading cause of mortality within the 0-14 age group for high income countries. It is fundamentally different to adult cancer in its biology, clinical classification, and treatment. The tumour-node-metastasis (TNM) system(11) used for staging many adult malignancies is inadequate for staging most cancers that occur in childhood. For several types of childhood cancers, there is no universally accepted staging system and multiple systems are in clinical use.

To address the lack of consistent information on childhood cancer stage within population cancer registries worldwide, an international expert panel including paediatric oncologists, epidemiologists, cancer registrars and advocacy stakeholders reviewed the major staging systems in clinical use and reached consensus on the most appropriate system for use in population cancer registries for each of 16 types of childhood cancer. These were acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), medulloblastoma, ependymoma, neuroblastoma, retinoblastoma, Wilms tumour, hepatoblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, testicular cancer and ovarian cancer.

The criteria and basis for the consensus recommendations are outlined in detail by Gupta and colleagues(12) and summarised in the Supplementary Table. Recognizing that registries are

limited by the resources available to them, tiered staging systems were endorsed. The Tier 2 systems, intended for use in high income countries, require access to data from medical imaging, cytology and other diagnostic tests. The more basic Tier 1 systems are intended for use in low and middle income countries where resources devoted to cancer registration may be limited and in general were derived by collapsing Tier 2 categories to retain comparability.(12) The final recommendations, published as the Toronto Childhood Cancer Stage Guidelines (referred to hereafter as "the Toronto Guidelines"),(12) represent the only international consensus staging framework for childhood malignancies. They have since been endorsed and published by the Union for International Cancer Control (UICC) TNM Prognostic Factors project.(11)

The stated purpose of the Toronto Guidelines is to facilitate the collection of internationally consistent information on childhood cancer stage by population cancer registries for use in cancer control activities and epidemiological analysis. The recommended staging systems are intended specifically to describe the anatomic extent of disease at diagnosis.(12) Stage is one of many prognostic indicators important for risk assessment and treatment planning. Registries may decide to collect additional prognostic data, such as oncogene amplification, as resources permit, but these items do not form part of the measure of stage.(12)

The assignment of cancer stage is a complex exercise requiring the consistent application of detailed criteria that are malignancy-specific and involve a combination of numerous individual data elements. Our aim was to assess the feasibility of implementing the Toronto Guidelines to stage childhood cancer within a population cancer registry using data from medical records.

Methods

The Australian Childhood Cancer Registry

The study was conducted within the Australian Childhood Cancer Registry (ACCR), established in 1983 as a complete database of all cancers diagnosed in children aged under 15 years in Australia.(13) With ethics and legislative approvals, all eight Australian jurisdictional population cancer registries provide information to the ACCR on all incident childhood cancer cases registered nationally each year. Detailed clinical and treatment information is collected from patients' medical records during site visits to the major paediatric oncology treatment centres by the ACCR Clinical Data Manager. National incident cases were available to 31 December 2010 at the time of the study.

Study sample

Eligibility criteria were: Australian residency; aged under 15 years; and diagnosed between 2006 and 2010 with one of the 16 malignancies in the Toronto Guidelines. This project was a national initiative and the sample was selected to ensure inclusion of cases from each of the six Australian states. At the time of data collection, there were eight specialist paediatric oncology centres in Australia, located within five of the six states. The study sample was drawn from eligible cases treated within six of these centres (one centre in each of the five states state plus an additional centre located in the most populous state) and from the major teaching hospital in the remaining state. The two paediatric oncology centres that were not included in the study do not differ in any substantial way from the six that were included. The study sample included all eligible cases, except in hospitals where the number of eligible cases of any single malignancy was more than 30 (as occurred for ALL, AML, NHL and neuroblastoma - the four most common childhood malignancies in Australia). In those instances, to ensure a manageable sample size, a random sample of 30 cases for that hospital/malignancy combination was selected. Randomisation was achieved by assigning all

relevant records a randomly generated number between zero and one, sorting by that number, and then selecting the first 30 records.

Documentation of recommended staging systems

To facilitate consistent application of the recommended systems, both in this study and by other cancer registries, we prepared a staging manual (available at https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf) that lists detailed staging criteria for each of the recommended Tier 1 and Tier 2 staging systems, based on published literature (also refer to the Supplementary Table, and Table 3 in Gupta et. al.(12)). In addition, the manual includes a full list of site and morphology codes (using ICCC-3) for each of the 16 malignancy types.

Data collection

The project was approved by University of Queensland Behavioural and Social Sciences Ethical Review Committee and by another 15 human research ethics committees associated with jurisdictional health departments and hospitals (see Declarations).

Data items required for allocation of Tier 1 and Tier 2 stage were extracted from medical records and recorded in a customised spreadsheet by the ACCR Clinical Data Manager during hospital site visits. Data were extracted from diagnostic imaging, cytology, histology and haematology reports; admission and discharge notes; doctors' correspondence and notes and other relevant medical records as required. Items that could not be located were noted. The medical record was carefully reviewed for information on cancer stage at diagnosis as recorded by the treating clinician and when present, the stage and staging system used were noted in the spreadsheet. For each case, the start and finish time of medical record review and data extraction were recorded, and the time taken (minutes) calculated.

The data were categorized and checked for valid ranges and measurement units at the study centre. Apparent errors were referred to the Clinical Data Manager for checking against the original records and correction where necessary.

Development of the staging algorithms

To minimize the potential for human error and variation in the assignment of stage, algorithms for staging were programmed in Stata software. The algorithms are available on request from the authors. Separate Stata programmes were written for each of the 16 malignancy types based on the criteria documented in the staging manual described above. The algorithms and programming logic for each malignancy type were checked, step-by-step, against manual staging performed by the Clinical Data Manager using the same documented staging criteria from which the algorithms were developed. Actual cases as well as hypothetical scenarios involving a wide range of data values were used to thoroughly test each step of the programmes. Refinements were made as required and the process was repeated until there was complete agreement between the stage assigned by the Clinical Data Manager and that assigned using the algorithms.

Assignment of stage

The source data items were entered into the algorithms via the spreadsheet and both Tier 1 and Tier 2 stage were calculated for each case (Figure 1). Stage was recorded as 'undetermined' if the data items required to ascertain stage could not be located in the medical record. In some instances, complete enumeration of all data items was not required, for example, if there was evidence of metastatic disease, it was usually possible to assign stage without requiring data items needed for less advanced stages.

Comparison of stage assigned by computer algorithm and expert reviewers

A random subsample of 160 cases (ten cases for each of the 16 malignancy types) was selected and Tier 2 stage was independently, manually assigned by expert reviewers with appropriate coding or clinical skills, using the data extracted from hospital records and the documented staging criteria. The comparison was restricted to the more complex Tier 2 staging systems, given that Tier 1 can be derived by collapsing Tier 2 categories. The size of the subsample was chosen on practical grounds to balance the time and availability of expert reviewers with the need to include each of the 16 malignancy types. All cases of a malignancy were assigned a randomly generated number between zero and one, sorted by that number, and then the first 10 records were selected. Three expert reviewers each independently staged 10 cases of each of the blood-related cancers (ALL, AML, HL and NHL). Two expert reviewers independently staged 10 cases of each of the 12 solid malignancies. Tier 2 stage assigned by expert reviewers was compared with Tier 2 stage assigned by computer algorithm. At the completion of the comparisons, all cases for which there was a lack of agreement were examined in detail and the algorithms were further refined as necessary.

Analysis

The feasibility of applying the Toronto Guidelines within a population cancer registry setting was assessed using three indicators: (i) the percentage of cases that could be staged; (ii) agreement between stage assigned by the computer algorithms and that assigned by the expert reviewers; and (iii) mean time (minutes) to collect the required data calculated as the average across all cases. Assessment of the second of these indicators (agreement between algorithms and expert reviewers) was somewhat complicated by the fact that the expert reviewers did not always assign the same stage for the same case. Thus, for each malignancy,

we calculated the number of cases for which the algorithm agreed with all, some or none of the expert reviewers. As the staging systems differed from cancer to cancer, results were stratified by malignancy type. Analyses were performed using Stata/SE software v15 for Windows (StataCorp LLC, College Station, Texas)

Role of the funding source

The funder of the study (Cancer Australia) did not have a role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. JFA and DRY had full access to all dataand had final responsibility for the decision to submit for publication.

Results

Study sample

A total of 3,302 children aged under 15 years were diagnosed with cancer in Australia between 2006 and 2010 (Figure 1). Almost three-quarters (n=2,344, 71%) had one of the 16 malignancies included in the Toronto Guidelines, of whom 2,077 children (89%) were treated at a participating hospital. After randomly selecting cases where there were more than 30 children with the same malignancy type in any one hospital, a total of 1,412 children (68% of the 2,077 eligible cases) were included in the study sample.

The most common types of cancers in the study were ALL (n=194, 14%), neuroblastoma (n=166, 12%) and AML (n=151, 11%) (Table 1). Overall median age at diagnosis was four years, varying from a median age of one year for neuroblastoma, retinoblastoma, hepatoblastoma and testicular cancer to 12 years for HL and 12·5 years for osteosarcoma.

Proportion of cases for whom stage could be assigned

A total of 93% (1,318 of 1,412 cases) had sufficient information in the medical record to enable stage to be assigned according to the detailed Tier 2 criteria and an additional 11 cases (for a total of 1,329 of 1,412 (94%)) according to the more basic Tier 1 criteria (Table 2). For Tier 1, the percentage of children for whom stage could be assigned varied from 87% for AML (131 of 151 cases) to 100% for hepatoblastoma (n=46). For Tier 2, stage could be assigned for 84% of cases of non-rhabdomyosarcoma soft tissue sarcoma (48 of 57 cases) up to 100% for hepatoblastoma (n=46). The largest difference between Tier 1 and Tier 2 was for children with rhabdomyosarcoma, for whom 97% could be staged under the Tier 1 criteria compared with 88% for Tier 2 (89 and 82 of 92 cases, respectively). Information on cancer stage recorded by the treating clinician could be located for 555 (39%) of the 1,412 patients. Of the 94 cases for whom Tier 2 stage was unable to be assigned, the most common reason (n=48, 51%) was that one or more of the required data items could not be located in the medical records at the treating hospital. In a further 29 cases (31%), some of the patients' medical records were held at another hospital and it was outside the study scope to track these down. For the remaining 17 cases (19%) the information in the medical record was not sufficiently clear to allow stage to be assigned.

Overall, about a quarter (341 of 1,318 cases, 26%) of children in the sample with sufficient information to allocate Tier 2 stage had advanced/metastatic disease at diagnosis. The distribution was similar when only solid tumours were considered, with 211 of 784 cases (27%) having advanced/metastatic disease. The percentage presenting with advanced/metastatic disease varied significantly between malignancy types, ranging from less than 5% (<5 of 107 cases combined) of children with germ cell tumours (ovarian or testicular cancer) or retinoblastoma to 55% (87 of 159 cases) of children with neuroblastoma.

Agreement of staging algorithm with expert reviewers

There was very good agreement between Tier 2 stage assigned by the computer algorithm and Tier 2 stage assigned by the expert reviewers for most malignancy types (Table 3). In particular, stage assigned by the algorithm matched stage assigned by all of the expert reviewers in 132 (83%) of the 160 cases assessed. In a further 23 cases (14%) in which expert reviewers assigned different stages to the same case, the algorithm agreed with at least one expert reviewer. Complete agreement between the algorithm and the expert reviewers was lowest for rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, being achieved in only about half of the ten cases assessed for each of these two malignancies. However, there was also considerable variation between the two expert reviewers for these malignancies. Overall, there was agreement with at least one expert reviewer in 9 out of 10 cases of each of these two cancers. In five of the 160 cases (3%), the algorithm did not agree with any of the expert reviewers although it should be noted that these cases were spread across five different types of cancer.

Time taken to collect staging information

Medical record review and data extraction took an average of 18 minutes per case. The average time varied between malignancy types in line with the number and complexity of data items required for allocation of stage (Table 4). Retinoblastoma cases took the least amount of time for medical record review and data extraction (11 minutes each on average) compared to a mean of 22 minutes per case for rhabdomyosarcoma.

Discussion

Here we describe the first implementation and evaluation of the Toronto Childhood Cancer Stage Guidelines, the only international framework for the collection of childhood cancer stage by population registries, recently endorsed by the UICC. By applying detailed staging

criteria and algorithms developed from the Toronto Guidelines to data extracted from routine medical records, childhood cancer stage could be assigned for the vast majority of cases of the 16 malignancy types in the Guidelines. Together, these cancers comprise approximately three-quarters of all childhood cancers diagnosed in Australia and other Western countries. The high level of agreement overall demonstrated here between stage assigned by computer algorithms and stage assigned by independent expert reviewers indicates that these staging rules are robust and likely to result in reproducible and accurate results. Staging of rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma was associated with a somewhat lower level of agreement than the other malignancy types and the staging criteria for these cancers may require further clarification and improvement if this is repeated in other populations. Finally, the feasibility of applying the Toronto Guidelines in practice depends not only the availability of the required information but also on the labour cost associated with locating and recording the data for each patient. We were able to demonstrate that, with appropriate access to the required medical records, these data could be collected in a timely manner. Given the very low incidence of childhood cancer (estimated worldwide at 141 per million person-years(14)), the additional time required to collect stage information for children on a population basis, above and beyond the time already spent in registry activities, is likely to be manageable for most established population cancer registries. Thus, our results indicate that the Toronto Guidelines(12) are likely to provide a feasible and practical framework for population cancer registries to collect consistent, standardized information on stage at diagnosis for most childhood cancers. It is important to note that the Toronto Guidelines and associated algorithms are not intended to be static and we anticipate they will continue to improve following testing in other populations.

While some population registries indicate that they collect data on childhood cancer stage, there is little published information available.(15, 16) Consistent with our finding that 27% of

children with solid tumours for whom stage could be assigned had advanced/metastatic disease, 24% of childhood solid tumours in Singapore(17), and 25% of non-central nervous system solid tumours in the United States are diagnosed with distant metastases(18). It is unclear, however, what staging systems were used in these studies.

There are many practical and legitimate reasons why cancer stage may not be noted in the patient's medical record. In this study, stage recorded by the treating clinician could be located for fewer than 40% of patients. We are not aware whether this applies in other countries, however, even if stage were always documented, there is still the problem that staging criteria for the same malignancies vary between cooperative trial groups around the world. Further, staging by the medical team is for the purpose of an individual patient's risk categorization and treatment planning. On a population level, this information is unlikely to be complete or consistent over time and it is therefore not suitable for population comparisons or cancer surveillance. Our results thus represent a considerable advance in achieving population-wide stage information for childhood cancer compared to what is currently possible.

A potential limitation in generalizing these findings is that the sample comprised cases diagnosed some years ago, between 2006 and 2010. At the time of sampling, Australia's state-based population cancer registries varied widely in terms of the currency of their data. To ensure a national sample with consistency across states, the sampling frame was limited to cases diagnosed during the five years from 2006 to 2010, the most recent year for which national data was available. Given that the completeness of medical records for more recent years is, if anything, likely to be better than the records used in this study, the results reported here should be regarded as the lower limit for the percentage of cases that can be staged in this way.

This study was conducted in a single high income country with virtually complete ascertainment of cancer (notification of cancer is a statutory requirement in Australia) and high data quality (approximately 95% of all childhood cancer cases are histologically verified). The results presented here for Tier 2 staging systems are likely to be applicable to population registries in other high income countries. We are, however, unable to comment on the practical application of the Tier 1 staging systems in low and middle income countries, and feasibility testing in such settings will be needed.

A further limitation in regard to the comparison with expert reviewers is that the number of categories for stage varied from cancer to cancer. Thus, the extent of agreement between the computer algorithms and expert reviewers may not be directly comparable across cancer types.

While survival rates are high and improving over time for many childhood malignancies, there are wide variations by malignancy type and large inequities in childhood cancer outcomes between countries.(19, 20) In adult cancers, geographical and other disparities in survival are due in part to differences in stage at diagnosis.(21, 22) Comparison of robust population-based stage data across jurisdictions would determine whether the same is true for childhood cancer, in turn informing interventions targeting improved diagnosis and outcomes. Our findings suggest that collecting such data is feasible. The Toronto Childhood Cancer Stage Guidelines, and associated staging algorithms developed and tested in this study, have the clear potential to facilitate evidence-based population cancer control for childhood cancer.

Declarations

Ethics approval: The study was approved by the following ethics committees -

- University of Queensland Behavioural and Social Sciences Ethical Review Committee
- QIMR Berghofer Medical Research Institute Human Research Ethics Committee
- Children's Health Queensland Hospital and Health Service Human Research Ethics Committee
- Australian Capital Territory Health, Human Research Ethics Committee
- Cancer Council Victoria Human Research Ethics Committee
- The Royal Children's Hospital Human Research Ethics Committee
- Monash Health Human Research Ethics Committee
- The Tasmanian Health and Medical Human Research Ethics Committee
- Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research
- Princess Margaret Hospital Human Research Ethics Committee
- The Australian Institute of Health and Welfare Ethics Committee
- New South Wales Population and Health Services Research Ethics Committee
- NSW Population and Health Services Research Ethics Committee
- Government of Western Australia Department of Health Human Research Ethics Committee
- South Australian Health Human Research Ethics Committee
- Women's and Children's Health Network Human Research Ethics Committee

***Declaration of interests*:** The authors have no competing interests to disclose.

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***Authors' contributions*:** JFA, SG and ALF were responsible for the study concept and design. JFA, DRY, LJW, SG and ALF developed the staging manual (available at https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf) with input from the other authors. LJW collected the data and DRY wrote the staging algorithms and performed the data analysis. All authors were responsible for data interpretation. JFA and DRY wrote the draft manuscript. All authors read and edited the draft manuscripts and approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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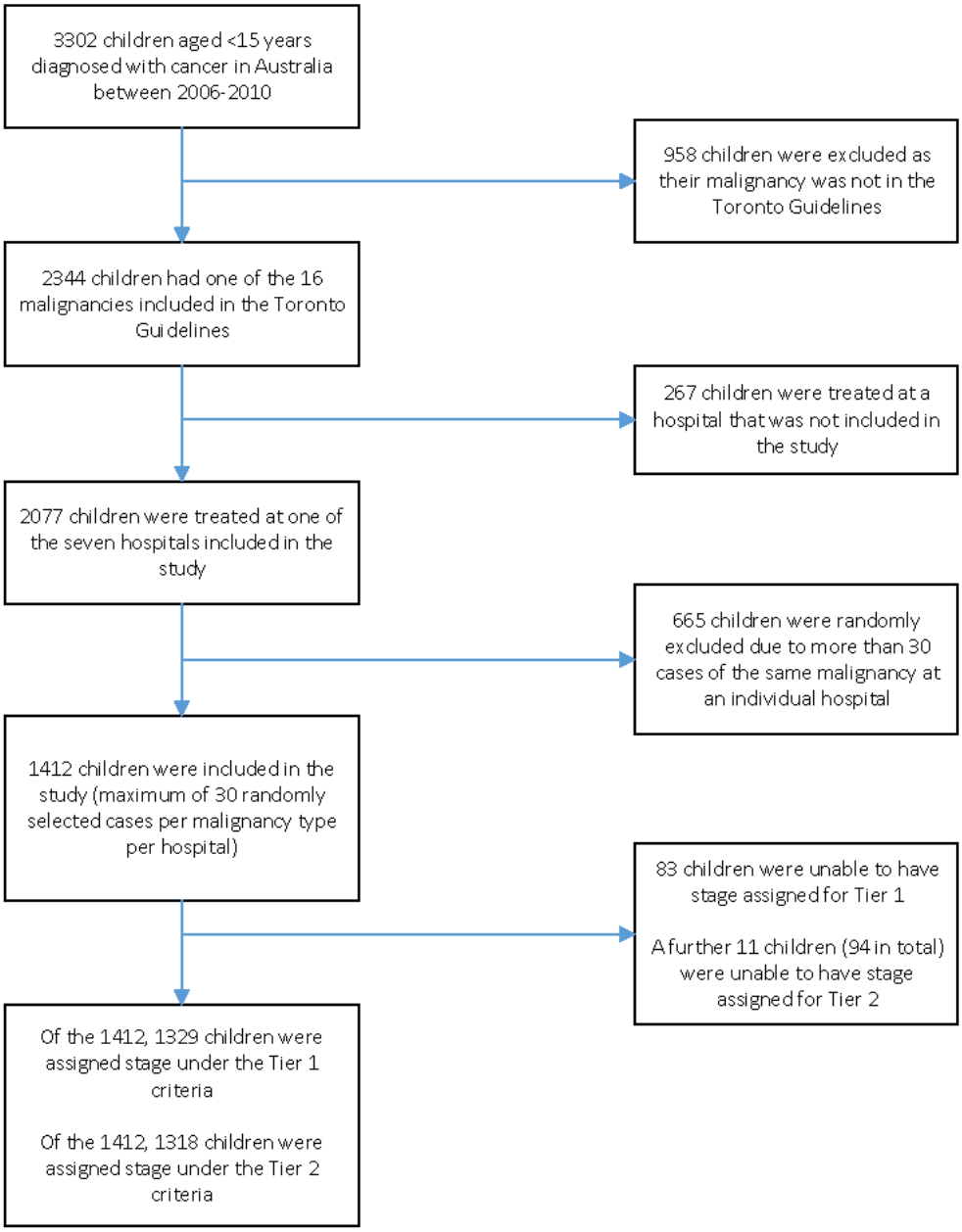

Figure 1: Flow chart of the sample selection process

Table 1: Details of the study cohort by type of childhood cancer, Australian Childhood Cancer Registry, 2006-2010

Type of cancer[1]	Sample size	Boys n (%)	Girls n (%)	Median age at diagnosis in years (IQR)
Acute lymphoblastic leukaemia	194	102 (53)	92 (47)	4·0 (2·0-8·0)
Acute myeloid leukaemia	151	76 (50)	75 (50)	5·0 (1·0-10·0)
Hodgkin lymphoma	101	58 (57)	43 (43)	12·0 (10·0-13·0)
Non-Hodgkin lymphoma	132	95 (72)	37 (28)	9·0 (5·5-12·0)
Neuroblastoma	166	96 (58)	70 (42)	1·0 (0·0-3·0)
Wilms tumour	126	55 (44)	71 (56)	3·0 (1·0-5·0)
Rhabdomyosarcoma	92	54 (59)	38 (41)	4·0 (2·5-8·5)
Non-rhabdomyosarcoma soft tissue sarcomas	57	34 (60)	23 (40)	7·0 (1·0-12·0)
Osteosarcoma	40	17 (42)	23 (58)	12·5 (10·0-14·0)
Ewing sarcoma	55	31 (56)	24 (43)	9·0 (6·0-12·0)
Retinoblastoma	76	42 (55)	34 (45)	1·0 (0·0-2·0)
Hepatoblastoma	46	27 (59)	19 (41)	1·0 (0·0-2·0)
Testicular cancer	16	16 (100)	0 (0)	1·0 (0·5-2·0)
Ovarian cancer	18	0 (0)	18 (100)	11·5 (10·0-13·0)
Medulloblastoma	92	59 (64)	33 (36)	5·0 (4·0-8·0)
Ependymoma	50	32 (64)	18 (36)	3·5 (2·0-7·0)
TOTAL	**1,412**	**794 (56)**	**618 (44)**	**4·0 (1·0-10·0)**

Abbreviations: IQR = interquartile range.
Notes: 1. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).(23)

Table 2: Childhood cancer cases that could be staged according to Tier 1 and Tier 2 Toronto Childhood Cancer Stage Guidelines by type of cancer, Australian Childhood Cancer Registry, 2006-2010

Type of cancer[1]	Sample size	Able to be staged			
		Tier 1[2]		Tier 2[2]	
		n	%	n	%
Acute lymphoid leukaemia	194	181	93	180	93
Acute myeloid leukaemia	151	131	87	131	87
Hodgkin lymphoma	101	95	94	95	94
Non-Hodgkin lymphoma	132	128	97	128	97
Neuroblastoma	166	159	96	159	96
Wilms tumour	126	115	91	115	91
Rhabdomyosarcoma	92	89	97	82	89
Non-rhabdomyosarcoma	57	51	89	48	84
Osteosarcoma	40	37	93	37	93
Ewing sarcoma	55	53	96	53	96
Retinoblastoma	76	75	99	75	99
Hepatoblastoma	46	46	100	46	100
Testicular	16	15	94	15	94
Ovarian	18	17	94	17	94
Medulloblastoma	92	89	97	89	97
Ependymoma	50	48	96	48	96
TOTAL	**1,412**	**1,329**	**94**	**1,318**	**93**

Notes: 1. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).(23) 2. Tier 1 is a basic staging system for use in low and middle income countries where resources devoted to cancer registration are generally limited. Tier 2 is a more detailed staging system designed for use in high income countries.

Table 3: Agreement between Tier 2 stage assigned by the computer algorithm and expert reviewers in a subsample[1] by type of childhood cancer, Australian Childhood Cancer Registry, 2006-2010

Type of cancer[2]	Number of staging categories	Number of cases	Number of cases for whom		
			algorithm matched all reviewers (n, 95% CI)[3]	algorithm matched some reviewers (n, 95% CI)[3]	algorithm matched no reviewers (n, 95% CI)[3]
Three reviewers per case					
Acute lymphoblastic leukaemia	4	10	9 (6·7-10·0)	1 (0·0-3·3)	0
Acute myeloid leukaemia	3	10	9 (6·7-10·0)	1 (0·0-3·3)	0
Hodgkin lymphoma	5	10	7 (3·5-10·0)	2 (0·0-5·0)	1 (0·0-3·3)
Non-Hodgkin lymphoma	5	10	8 (5·0-10·0)	2 (0·0-5·0)	0
Two reviewers per case					
Neuroblastoma	5	10	8 (5·0-10·0)	2 (0·0-5·0)	0
Wilms tumour	5	10	9 (6·7-10·0)	1 (0·0-3·3)	0
Rhabdomyosarcoma	5	10	4 (0·3-7·7)	5 (1·2-8·8)	1 (0·0-3·3)
Non-rhabdomyosarcoma	5	10	5 (1·2-8·8)	4 (0·3-7·7)	1 (0·0-3·3)
Osteosarcoma	3	10	8 (5·0-10·0)	2 (0·0-5·0)	0
Ewing sarcoma	3	10	9 (6·7-10·0)	1 (0·0-3·3)	0
Retinoblastoma	6	10	10	0	0
Hepatoblastoma	3	10	9 (6·7-10·0)	0	1 (0·0-3·3)
Testicular cancer	4	10	10	0	0
Ovarian cancer	5	10	8 (5·0-10·0)	1 (0·0-3·3)	1 (0·0-3·3)
Medulloblastoma	6	10	9 (6·7-10·0)	1 (0·0-3·3)	0
Ependymoma	6	10	10	0	0
Total cancers		**160**	**132 (122·5-141·5)**	**23 (14·2-31·8)**	**5 (0·6-9·4)**

Abbreviations: 95% CI = 95% confidence interval.
Notes: 1. There were ten cases for each type of cancer in the subsample, for a total of 160 cases. Three expert reviewers each independently assigned stage for acute lymphoblastic leukaemia, acute myeloid leukaemia, Hodgkin lymphoma and non-Hodgkin lymphoma and two expert reviewers independently assigned stage for each of the remaining 12 types of cancer. 2. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).(23) 3. Confidence intervals were not applicable where agreement was all or none.

Table 4: Mean time per case to collect data for staging by type of childhood cancer

Type of cancer[1]	Sample size (n)	Mean time per case in minutes (std dev)
Acute lymphoid leukaemia	194	14·4 (8·6)
Acute myeloid leukaemia	151	13·6 (7·2)
Hodgkin lymphoma	101	21·0 (7·4)
Non-Hodgkin lymphoma	132	20·8 (8·9)
Neuroblastoma	166	21·8 (9·6)
Wilms tumour	126	21·6 (11·9)
Rhabdomyosarcoma	92	22·2 (8·5)
Non-rhabdomyosarcoma	57	20·5 (9·0)
Osteosarcoma	40	17·3 (9·3)
Ewing sarcoma	55	17·5 (10·2)
Retinoblastoma	76	11·2 (4·3)
Hepatoblastoma	46	16·8 (12·7)
Testicular cancer	16	15·8 (7·1)
Ovarian cancer	18	17·8 (9·8)
Medulloblastoma	92	17·2 (7·6)
Ependymoma	50	14·2 (7·0)
Total	**1,412**	**18·0 (9·5)**

Notes: 1. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).(23)