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Title: Stage at diagnosis for childhood solid cancers in Australia: a population-based study

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Abbreviations: ACCR – Australian Childhood Cancer Registry; CNS – central nervous system; COG – Children's Oncology Group; ICCC-3 – International Classification of Childhood Cancers, 3rd edition; SIOP - International Society of Paediatric Oncology; TNM – tumour-node-metastasis; UICC – Union for International Cancer Control.

Abstract

Background: Stage of cancer at diagnosis is one of the strongest predictors of survival and is essential for population cancer surveillance, comparison of cancer outcomes and to guide national cancer control strategies. Our aim was to describe, for the first time, the distribution of cases by stage at diagnosis and differences in stage-specific survival on a population basis for a range of childhood solid cancers in Australia.

Methods: The study cohort was drawn from the population-based Australian Childhood Cancer Registry and comprised children (<15 years) diagnosed with one of 12 solid malignancies between 2006 and 2014. Stage at diagnosis was assigned according to the Toronto Paediatric Cancer Stage Guidelines. Observed (all cause) survival was calculated using the Kaplan-Meier method, with follow-up on mortality available to 31 December 2015.

Results: Almost three-quarters (1,256 of 1,760 cases, 71%) of children in the study had localised or regional disease at diagnosis, varying from 43% for neuroblastoma to 99% for retinoblastoma. Differences in 5-year observed survival by stage were greatest for osteosarcoma (localised 85% (95% CI=72%-93%) versus metastatic 37% (15%-59%)), neuroblastoma (localised 98% (91%-99%) versus metastatic 60% (52%-67%)), rhabdomyosarcoma (localised 85% (71%-93%) versus metastatic 53% (34%-69%)), and medulloblastoma (localised 69% (61%-75%) versus metastases to spine 42% (27%-57%)).

Conclusion: The stage-specific information presented here provides a basis for comparison with other international population cancer registries. Understanding variations in survival by stage at diagnosis will help with the targeted formation of initiatives to improve outcomes for children with cancer.

Keywords: childhood cancer; population cancer registry; solid tumours; stage at diagnosis; survival; Australia.

1. Introduction

Population-based cancer registries have an essential role in reporting on childhood cancer in that they provide ‘the whole picture’, as opposed to results from hospital series that only include a selected subset of cases or clinical trials that are based on patients treated under strictly-defined protocols. Data contained in cancer registries are thus crucial when studying outcomes at the population level to inform national cancer control plans. Further, information on cancer stage is essential for meaningful interpretation of these analyses, for example when comparing results over time and/or between jurisdictions. Yet for most countries, data on cancer stage are not available at a population level which has been identified as a “fundamental gap in population-based cancer registries”¹.

This is especially true for childhood cancers, in part because of the lack of an internationally recognised and uniform set of malignancy-specific staging systems suitable for use in cancer registries.² In Australia, as in most of the rest of the world, the only information on childhood cancer stage is primarily from clinical trials; however, as these results refer only to eligible trial patients, they are unlikely to represent the stage distribution or stage-specific outcomes of all patients.

The recent release,² successful testing³ and international endorsement⁴ of the consensus-based Toronto Paediatric Cancer Stage Guidelines has provided population cancer registries the means, for the first time, to assign childhood cancer stage using consistent staging systems and rules.⁵ Using the Toronto Guidelines, we aimed herein to assign and report the incident distribution and observed survival by stage at diagnosis of solid cancers for a population-based sample of childhood cancer patients in Australia, and to compare this information with published results from other areas where data were available.

2. Material and Methods

A complete register of all childhood cancer cases (<15 years) diagnosed in Australia since 1983 is maintained by the Australian Childhood Cancer Registry (ACCR). With appropriate ethics and legislative approvals, Australia's eight State and Territory Cancer Registries provide information to the ACCR each year on all incident childhood cancer cases diagnosed nationally. The ACCR Data Manager makes regular site visits to the major paediatric oncology hospitals to collect detailed treatment and other clinical information. The survival status of patients included in the ACCR is kept up-to-date by annual matching of the entire cohort against the National Death Index, a database that contains a record of every death registered in Australia at any age.

The study cohort comprised Australian residents who were diagnosed under the age of 15 and between the years 2006 and 2014 with one of the 12 types of solid cancers included in the Toronto Guidelines; namely 'medulloblastoma and other CNS embryonal tumours' (hereafter referred to as medulloblastoma), ependymoma, neuroblastoma, retinoblastoma, Wilms tumour, hepatoblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, testicular germ cell tumours and ovarian germ cell tumours. Almost all childhood cancer patients in Australia are treated at one of nine publicly-funded tertiary children's hospitals located throughout the country and the data required for assigning stage at diagnosis were collected from each of these hospitals.

The Toronto Guidelines incorporate a two-tiered approach to defining stage,² in which the Tier 2 staging systems are generally the more detailed and intended for use in higher resource settings. This study uses the Tier 2 staging definitions, as summarised in Table 1. Full details of the Tier 1 and Tier 2 staging criteria for each cancer type are available elsewhere.^{2, 5}

To assign stage, the required data items were manually extracted from medical records and recorded in a customised online application during hospital site visits by ACCR staff. Algorithms within the application (formulated directly from the staging rules⁵) were passed over the raw data and stage was assigned automatically. The staging application and algorithms have been extensively tested and validated³ and are available on request from the authors.

Kaplan-Meier estimates of observed (all-cause) survival by cancer stage were calculated using the cohort method, with follow-up to 31 December 2015. Survival time for each patient accumulated from the date of diagnosis to either the date of death, the end of the follow-up period, or five years after diagnosis, whichever occurred first. For patients who remained alive, censoring was applied either five years after diagnosis or at the study end date for those with less than 5 years of follow-up. The equality of survivor functions by cancer stage were evaluated using the log-rank test. Stage categories were combined for some cancers where necessary to allow a somewhat larger pool of cases when estimating survival. Even so, there were an insufficient number of cases and/or deaths to stratify survival by stage at diagnosis for ependymoma, retinoblastoma, testicular germ cell tumours and ovarian germ cell tumours.

The study was approved by 16 independent ethics committees representing each of the State/Territory cancer registries and major paediatric treating hospitals in Australia. Analysis was conducted using Stata/SE version 15.1 for Windows (StataCorp LLC, College Station, TX).

3. Results

The study cohort included 1,760 children who had sufficient information in the medical record to enable Tier 2 stage to be assigned. These cases represented 94% (N=1,878) of patients for whom medical records were located at one of the in-scope hospitals and 88%

(N=2,009) of all Australian children aged <15 years who were diagnosed with one of the 12 types of childhood solid cancers between 2006 and 2014, ranging from 65% for ovarian germ cell tumours and 66% for non-rhabdomyosarcoma soft tissue sarcomas to 96% for retinoblastoma.

As shown in Table 2, the most common cancers in the study cohort were neuroblastoma (n=383, 22%), medulloblastoma (n=261, 15%) and Wilms tumour (n=241, 14%). Boys accounted for 53% of the overall study cohort, varying from 46% for Wilms tumour to 62% for medulloblastoma (aside from sex-specific cancers). Median age at diagnosis was 3 years, ranging from 1 year old for several cancers including neuroblastoma, retinoblastoma and hepatoblastoma up to 12 years old for osteosarcoma. There were no significant differences in the sex or age composition of the study cohort compared against all children with one of the 12 in-scope cancers (52% of all these patients being boys with a median age of 3 years).

3.1. Cases by stage at diagnosis

Approximately three-quarters (n=1,256, 71%) of the children in the study had localised or regional disease at diagnosis and the remaining 504 children (29%) were diagnosed with metastatic cancer. This distribution varied widely by the type of cancer; less than half (43%) of children with neuroblastoma had localised or regional disease at diagnosis, compared to 95% with ovarian germ cell tumours and 99% with retinoblastoma (Table 3).

The proportion of neuroblastoma patients diagnosed with localised or locoregional disease varied according to age, with 58% of patients under 18 months having localised or locoregional disease versus 31% of those aged 18 months and over (p<0.001). Further, of the 70 neuroblastoma patients under 18 months at diagnosis who had metastatic disease, 24 (34%) were classified as stage MS (i.e. metastases confined to the skin, liver and/or bone marrow).

Children with Wilms tumour were treated under the COG (post-operative chemotherapy) or SIOF (pre-operative chemotherapy) protocols,⁶ with similar numbers overall in both groups (49% and 51%, respectively). Although the majority (29 of 42, 69%) of children diagnosed with Stage IV Wilms tumours were treated with SIOF protocols, the difference in stage distribution by treatment protocol was only of borderline statistical significance ($p=0.07$).

Just over a quarter (28%) of children with retinoblastoma had bilateral disease; they were more likely to be treated conservatively (focal therapies or chemotherapy without enucleation being performed, stage 0) than those with unilateral disease (50% and 22%, respectively, $p=0.001$). There was an insufficient number of cases ($n=9$) to establish any pattern in stage distribution for children with bilateral Wilms tumours. No bilateral cases were recorded for either testicular or ovarian germ cell tumours.

3.2. Observed survival by stage at diagnosis

A total of 353 deaths (20%) were recorded among patients in the study cohort to 31 Dec 2015 (Table 2). Nearly all of these deaths ($n=339$, 96%) were related to the original cancer. Children with medulloblastoma ($n=99$, 38%), ependymoma ($n=30$, 29%) and osteosarcoma ($n=22$, 28%) had the highest proportions of deaths due to any cause, while in contrast all children in the study cohort with testicular germ cell tumours and nearly all with either retinoblastoma or ovarian germ cell tumours remained alive by the end of the study period.

The largest differences in five-year observed survival by stage at diagnosis were observed for osteosarcoma (86% for localised cases versus 37% for children with metastatic disease), neuroblastoma (98% for stage L1 versus 60% for metastatic (excluding stage MS)), rhabdomyosarcoma (85% for stage I versus 53% for stage IV), non-rhabdomyosarcoma soft tissue sarcoma (89% for stages I and II combined versus 47% for stage IV) and medulloblastoma (69% for stage M0 versus 42% for stage M3) – see Table 4

and Figure 1. Among children with neuroblastoma, the survival estimate of 60% for stage M contrasted with 5-year observed survival of 92% for stage MS, although the latter result was based on only a small number of cases (n=24). Excluding children under 18 months of age, the estimate for 5-year observed survival for children with stage M neuroblastoma dropped to 52% (95% CI = 42%-60%). Smaller, but nonetheless significant, differences by stage were also demonstrated for each of the other childhood solid cancers included in the survival analysis: Ewing sarcoma (91% for localised versus 73% for metastatic), hepatoblastoma (88% for localised versus 64% for metastatic) and Wilms tumour (varying from 97% for stage III/yIII to 83% for stage IV).

4. Discussion

We report here the first national study, conducted within the setting of a population-based childhood cancer registry, describing the incident distribution and survival by stage at diagnosis for a range of the most common types of childhood solid cancers. Well over 90% of the eligible study cohort were able to be staged from first principles using the Toronto Guidelines.⁵ Earlier work has demonstrated that only approximately 40% of childhood cancer cases in Australia have stage recorded by the treating clinician in the medical record.³ We found that around three out of every four children with a solid cancer were diagnosed at a lower stage and that, when there were a sufficient number of cases, all of these cancers exhibited highly significant differences in stage-specific survival. While this latter finding may be expected, quantifying the extent of the differences is nonetheless important as it demonstrates the capability of the systems included in the Toronto Guidelines to clearly discriminate survival by stage. Reporting on outcomes by stage for childhood cancers had not been possible until now due to the previous lack of information on stage at diagnosis within the Australian Childhood Cancer Registry, as in most other cancer registries, thus hampering the interpretation of results.

There is a notable paucity of published information on the stage-specific distribution and survival of solid childhood tumours; what is available comes mainly from clinical trials, with varying eligibility criteria, and not from population cancer registries, making comparisons with the present results difficult unless recruitment rates to the trial are high across all patients. Importantly, our study has been conducted within the setting of a population-based childhood cancer registry and the results presented here will provide a comparison point for similar analyses in other countries as the Toronto Guidelines⁵ are implemented more broadly in cancer registries around the world.

4.1. International comparisons for the distribution of stage at diagnosis

Based on the Chang M staging system⁷ that classifies stage according to the anatomic location of metastases in the central nervous system, 44% of children aged 3 to 18 years in a randomised trial for medulloblastoma in Germany, Austria, and Switzerland had some form of metastatic disease at diagnosis,⁸ somewhat higher than the 31% from our study. This variation may partly reflect the different age groups under consideration and also that the study conducted in Europe is somewhat older (patients registered between 1991 and 1997). The Australian distribution of stage at diagnosis for Wilms tumour (29% stage I/II and 17% stage IV) more closely resembled recent results from the United Kingdom (36% and 18%) than from Germany (55% and 16%), noting that the results for both of these countries were from an international randomised trial of patients who were all treated with pre-operative chemotherapy. The trial did have a very high recruitment rate however (>90% in the United Kingdom) and so was likely to represent the stage distribution at the population level.⁹ It was postulated that the smaller proportion of lower stage tumours in the United Kingdom may reflect differences in the healthcare system compared to Germany, leading to delays in the detection of Wilms tumours.⁹ Among children with osteosarcoma, 26% in Australia had metastatic disease, similar to contemporary data from Argentina (31%)¹⁰ but somewhat higher compared to Finnish children between 1991 and 2005 (18%).¹¹

4.2. International comparisons of survival by stage

The ability of Chang's M staging system to differentiate survival for childhood medulloblastoma appears mixed. Dufour et. al.¹² did not find a significant difference in survival by stage for children with metastatic medulloblastoma treated at a single institution in France during the period 1988-2008, with 5-year overall survival of 47%, 51% and 42% for stages M1, M2 and M3, respectively (very similar to our results of 47% for M1 and M2 combined and 42% for M3). They suggested that the phenotype of metastasis (nodular or laminar) was a better predictor of survival than stage.¹² A population-based study of 628 children diagnosed with medulloblastoma in Canada between 1990 and 2009 also reported a lack of difference in survival by stage.¹³ In contrast, and reinforcing our findings, researchers in Switzerland (1972-1991),¹⁴ Germany (1991-1997)⁸ and the United States (1969-1997)¹⁵ have previously shown a significant difference in survival between children with non-metastatic and metastatic medulloblastoma based on a clinical series of patients.

The International Neuroblastoma Risk Group reported 5-year overall survival of 96% for patients diagnosed at stage L1 and 89% for stage L2,¹⁶ providing a good match with the outcomes shown here (98% and 87%, respectively). For children diagnosed with metastatic neuroblastoma in the United States between 1973 and 2010, 10-year overall survival was 39% for those aged between 2 and 17 years old at diagnosis,¹⁷ somewhat lower than our result of 52% for 5-year observed survival among children with metastatic disease who were aged 18 months or older. Our finding of a favourable prognosis for infants under 18 months old with metastatic neuroblastoma confined to the skin, liver and/or bone marrow also replicates findings from other countries.¹⁸⁻²⁰ These particular tumours have a tendency to spontaneously regress even without chemotherapy; while there are several plausible genomic, biological and immunological reasons for regression, the exact mechanisms remain unknown.^{21, 22}

Wilms tumour is treated under either the SIOP or COG protocols, which differ in the use of neoadjuvant chemotherapy.⁶ Both approaches are used fairly evenly in Australia and were found to achieve similar survival outcomes. Based on 3,559 children treated on the SIOP 2001 protocol for Wilms tumour in Europe from 2001 onwards, Brok et. al.²³ reported 5-year overall survival varied from 98% for stage I down to 82% for stage IV, corresponding quite well with our results.

A population-based study from the United States²⁴ on patients with rhabdomyosarcoma aged 0-19 at diagnosis between 1973 and 2005 found that stage was a strong predictor of mortality, with 5-year survival ranging from 83% for localised disease to 33% for those with distant metastases. Survival for children with stage IV rhabdomyosarcoma appeared to be somewhat better within the Australian cohort at 53%, although our point estimate was accompanied by a wide confidence interval (95% CI = 34%-69%) due to the small number of cases (n=36). The different age criteria in the two datasets combined with the lower survival experienced by rhabdomyosarcoma patients aged over 10 years old at diagnosis²⁴ may also have contributed to this potential disparity.

We reported a much higher survival rate for localised osteosarcoma (86%) compared to a recent paper from Argentina (52%),¹⁰ but consistent with 10-year overall survival in Finland (82%) for the period 1991-2005.¹¹ Five-year survival for metastatic stage was also higher in Australia than for Argentina (37% and 22%, respectively),¹⁰ but our result was comparable to population data reported in the United States (1973-2010) and Finland, where 10-year overall survival for metastatic osteosarcoma was 29%¹⁷ and 36%¹¹, respectively.

While several childhood solid cancers in this study were characterised by very large differences in survival between patients with localised versus metastatic disease at diagnosis, the disparity in survival by stage at diagnosis (although still statistically significant) was somewhat slighter for children with Wilms tumour, hepatoblastoma or

Ewing sarcoma. A possible reason for the smaller difference observed in survival by stage for children with Wilms tumour or hepatoblastoma in our study is the higher cure rates for metastatic disease compared to other solid cancers. For example, the International Childhood Liver Tumours Strategy Group (SIOPEL) reported that advances in the treatment regime resulted in 74% of metastatic hepatoblastoma patients on the SIOPEL-4 trial achieving complete remission at the end of therapy.²⁵ Trials for Ewing sarcoma have shown that metastatic disease (especially to bone and bone marrow) has a very poor prognosis (5-year overall survival <30%),²⁶ but the age inclusion criteria for these trials typically extend into older adolescents and young adults, which may in part explain the much higher survival (73%) reported here given that age at diagnosis >14 years is associated with poorer prognosis.²⁶

4.3. Strengths and limitations

A strength of the current study is that it utilises data from the Australian Childhood Cancer Registry allowing us to report national population-based estimates of survival. Even so, due to the rarity of some cancers, the small number of patients available meant confidence intervals were wide for some of the stage-specific results. While recognising that other key variables, such as age and treatment received, might influence the relationship between stage and survival, the small numbers available within the various staging categories for most cancers in the study also precluded multivariate adjustment of survival estimates for other known prognostic factors. The lower proportion (approximately two-thirds) of patients in the study compared to the population for either non-rhabdomyosarcoma soft tissue sarcomas or ovarian germ cell tumours potentially calls into question the representativeness of the results for these cancers; we hasten to note, however, that there were no apparent biases in the age and sex distribution between the study cohort and patients with any of the 12 cancers who did not have medical records at an in-scope hospital.

4.4. Conclusions

As the first childhood cancer registry to implement the Toronto Guidelines across a broad range of solid cancers, these results represent an important step towards consistent and reliable information on stage for childhood cancers within Australia. Further, they demonstrate that it is feasible to achieve robust, national population-based information stratified by stage. Such data, if available internationally, have the potential to contribute to improved epidemiological reporting for childhood cancers globally,²⁷ help to shed light on the factors underlying the marked international inequity in outcomes,²⁸ and inform interventions to reduce these disparities.

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Table 1: Summary of the staging systems in the Toronto Guidelines by type of solid tumour

| Type of solid tumour ^a | Staging system | Stage category | Summary definition ^b |
|---|-------------------------------------|----------------|--|
| Ependymoma, medulloblastoma | Chang M ⁷ | M0 | No visible disease on imaging beyond primary site of disease and no tumour cells in the CSF. |
| | | M1 | Tumour cells in the CSF. |
| | | M2 | Visible metastasis in brain. |
| | | M3 | Visible metastasis in spine or cervico-medullary junction. |
| | | M4 | Visible metastasis outside of the CNS. |
| Neuroblastoma | INRGSS ¹⁶ | L1 | Localized tumour that does not involve any vital structures as defined by the list of IDRFs and the tumour must be confined within one body compartment (neck, chest, abdomen, or pelvis). |
| | | L2 | Locoregional tumour with one or more IDRFs. |
| | | MS | Metastatic disease confined to skin, liver, and/or bone marrow, in a patient less than 18 months old. |
| | | M | Distant metastatic disease (not contiguous with the primary tumour) except as defined for stage MS. |
| Retinoblastoma | IRSS ²⁹ | 0 | The tumour is confined to the globe and enucleation has not been performed. |
| | | I | Enucleation with negative margins. |
| | | II | Enucleation with microscopic residual disease. |
| | | III | Regional extension. |
| | | IV | Distant metastatic disease. |
| Wilms tumour | COG/ NWTSG ⁶ | I | Tumour limited to kidney and completely resected. |
| | | II | Tumour extends beyond kidney but completely resected. |
| | | III | Residual tumour or non-haematogenous metastases confined to abdomen. |
| | | IV | Haematogenous metastases or spread beyond abdomen at diagnosis. |
| | SIOP ⁶ | yI | Tumour limited to kidney and completely resected. |
| | | yII | Tumour extends beyond kidney but completely resected. |
| | | yIII | Incomplete excision of the tumour (gross or microscopic extension beyond the resection margins). |
| | | IV | Haematogenous metastases or spread beyond abdomen at diagnosis. |
| Hepatoblastoma, osteosarcoma, Ewing sarcoma | Localised/ metastatic | L | Tumour confined to the organ or area of origin, including regional lymph nodes. |
| | | M | Distant metastatic disease. |
| Rhabdomyosarcoma | Anatomic site and TNM ³⁰ | I | Favourable site, any T, any N, M0. |
| | | II | Unfavourable site, T1a or T2a, N0, M0. |
| | | III | Unfavourable site and (T1a or T2a, N1, M0) or (T1b or T2b, any N, M0). |
| | | IV | Any site, any T, any N, M1. |

Table 1 (cont.): Summary of the staging systems in the Toronto Guidelines by type of solid tumour

| | | | |
|---|-----------------------------|-----|--|
| Non-rhabdomyosarcoma soft tissue sarcomas | TNM ³⁰ and grade | I | Any T, N0, M0, G1 or Gx. |
| | | II | T1, N0, M0, G2 or G3. |
| | | III | (T2 or T3 or T4, N0, M0, G2 or G3) or (any T, N1, M0, any G). |
| | | IV | Any T, any N, M1, any G. |
| Testicular germ cell tumours | TNM ³⁰ | I | Any T, N0, M0. |
| | | II | Any T, any N, M0. |
| | | III | Any T, any N, M1. |
| Ovarian germ cell tumours | FIGO ³¹ | I | Tumour confined to ovaries (one or both). |
| | | II | Tumour involves one or both ovaries with pelvic extension (below the pelvic brim). |
| | | III | Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes. |
| | | IV | Distant metastasis (excluding peritoneal metastases). |

Abbreviations: CFS = cerebrospinal fluid; CNS = central nervous system; COG = Children's Oncology Group; IDRFs = image-defined risk factors; INRGSS = International Neuroblastoma Risk Group Staging System; IRSS = International Retinoblastoma Staging System; G = tumour grade; NWTSG = National Wilms Tumour Study Group; SIOP = International Society of Paediatric Oncology; TNM = tumour size/regional lymph node involvement/metastasis.

Notes: a. Classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).³² b. For the full definitions, see <https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf>.

Table 2: Characteristics of the study cohort by type of solid tumour, Australian Childhood Cancer Registry, 2006-2014

| Cancer type^a | Study cohort (n) | % of all relevant cases in the ACCR | Boys (%) | Median age at diagnosis (years) | Deaths prior to 31 Dec 2015 (%) |
|---|-------------------------|--|-----------------|--|--|
| Total study cohort | 1,760 | 87.4 | 52.7 | 3 | 20.1 |
| Ependymoma | 102 | 87.9 | 57.8 | 3.5 | 29.4 |
| Medulloblastoma | 261 | 94.3 | 61.7 | 5 | 37.9 |
| Neuroblastoma | 383 | 91.9 | 50.7 | 1 | 23.2 |
| Retinoblastoma | 148 | 96.1 | 52.7 | 1 | 0.7 |
| Wilms tumour | 241 | 90.6 | 45.6 | 3 | 7.1 |
| Hepatoblastoma | 80 | 93.2 | 57.5 | 1 | 18.8 |
| Osteosarcoma | 80 | 83.3 | 51.3 | 12 | 27.5 |
| Ewing sarcoma | 109 | 92.4 | 46.8 | 9 | 13.8 |
| Rhabdomyosarcoma | 159 | 86.9 | 55.4 | 4 | 22.6 |
| Non-rhabdomyosarcoma soft tissue sarcomas | 124 | 66.0 | 54.8 | 7 | 22.6 |
| Testicular germ cell tumours | 31 | 81.6 | 100.0 | 1 | 0.0 |
| Ovarian germ cell tumours | 42 | 64.6 | 0.0 | 11 | 2.4 |

Notes: a. Classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).³²

Table 3: Incident distribution of stage^a by type of solid tumour^b, Australian Childhood Cancer Registry, 2006-2014

| Type of solid tumour ^b | Staging category ^a | | | | |
|--|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| | M0 | M1 | M2 | M3 | M4 |
| Ependymoma (n=102) | | | | | |
| n | 92 | <5 ^c | <5 ^c | 6 | <5 ^c |
| % | 90.2 | - ^c | - ^c | 5.9 | - ^c |
| Medulloblastoma (n=261) | M0 | M1 | M2 | M3 | M4 |
| n | 179 | 5 | 19 | 58 | 0 |
| % | 68.6 | 1.9 | 7.3 | 22.2 | 0.0 |
| Neuroblastoma (n=383) | L1 | L2 | MS | M | |
| n | 98 | 67 | 24 | 194 | |
| % | 25.6 | 17.5 | 6.3 | 50.7 | |
| Retinoblastoma (n=148) | 0 | I | II | III | IV |
| n | 45 | 99 | <5 ^c | <5 ^c | <5 ^c |
| % | 30.4 | 66.9 | - ^c | - ^c | - ^c |
| Wilms tumour (n=241) | I/yI | II/yII | III/yIII | IV | |
| n | 69 | 55 | 75 | 42 | |
| % | 28.6 | 22.8 | 31.1 | 17.4 | |
| Hepatoblastoma (n=80) | L | M | | | |
| n | 53 | 27 | | | |
| % | 66.3 | 33.8 | | | |
| Osteosarcoma (n=80) | L | M | | | |
| n | 59 | 21 | | | |
| % | 73.8 | 26.3 | | | |
| Ewing sarcoma (n=109) | L | M | | | |
| n | 73 | 36 | | | |
| % | 67.0 | 33.0 | | | |
| Rhabdomyosarcoma (n=159) | I | II | III | IV | |
| n | 52 | 21 | 50 | 36 | |
| % | 32.7 | 13.2 | 31.5 | 22.6 | |
| Non-rhabdomyosarcoma (n=124) | I | II | III | IV | |
| n | 58 | 14 | 26 | 26 | |
| % | 46.8 | 11.3 | 21.0 | 21.0 | |
| Testicular germ cell tumours (n=31) | I | II | III | | |
| n | 25 | <5 ^c | <5 ^c | | |
| % | 80.7 | - ^c | - ^c | | |
| Ovarian germ cell tumours (n=42) | I | II | III | IV | |
| n | 21 | <5 ^c | 13 | <5 ^c | |
| % | 50.0 | - ^c | 31.0 | - ^c | |

Abbreviations: L = localised; M = metastatic; MS = metastatic disease in patients aged < 18 months at diagnosis with metastases confined to skin, liver and/or bone marrow; M0 = no visible disease on imaging beyond primary site and no tumour cells in the cerebrospinal fluid; M1 = tumour cells in the cerebrospinal fluid; M2 = visible metastasis in the brain; M3 = visible metastasis in spine or cervicomedullary junction; M4 = metastasis outside of the central nervous system.

Notes: a. Cases were staged using Tier 2 of the Toronto Paediatric Cancer Stage Guidelines.²

b. Classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).³² c. Result withheld (cell count < 5 or insufficient data).

Table 4: Five-year observed survival estimates by type of childhood solid tumour and stage^b, Australian Childhood Cancer Registry, 2006-2014^a

| Type of solid tumour ^b | Tier 2 Stage ^c | n | Five-year observed survival estimate (%) ^d | p-value ^e |
|--|---------------------------|-----|---|----------------------|
| Medulloblastoma | M0 | 179 | 68.6 (60.8-75.1) | <0.001 |
| | M1/M2 | 24 | 47.2 (25.7-66.1) | |
| | M3 | 58 | 42.5 (27.5-56.7) | |
| | M4 | 0 | n.a. | |
| Neuroblastoma | L1 | 98 | 97.7 (91.0-99.4) | <0.001 |
| | L2 | 67 | 86.5 (73.4-93.4) | |
| | MS | 24 | 91.7 (70.6-97.9) | |
| | M | 194 | 60.0 (51.8-67.2) | |
| Wilms tumour | I/yI | 69 | 93.2 (82.4-97.4) | 0.03 |
| | II/yII | 55 | 91.3 (78.4-96.6) | |
| | III/yIII | 75 | 97.2 (89.1-99.3) | |
| | IV | 42 | 83.2 (68.0-91.6) | |
| Hepatoblastoma | L | 53 | 87.7 (74.5-94.3) | 0.02 |
| | M | 27 | 63.9 (41.5-79.6) | |
| Osteosarcoma | L | 59 | 85.5 (71.7-92.8) | <0.001 |
| | M | 21 | 36.7 (14.8-59.1) | |
| Ewing sarcoma | L | 73 | 90.9 (78.7-96.3) | 0.02 |
| | M | 36 | 72.8 (51.5-86.0) | |
| Rhabdomyosarcoma | I | 52 | 85.3 (71.5-92.7) | 0.005 |
| | II | 21 | 84.4 (58.8-94.8) | |
| | III | 50 | 77.6 (62.3-87.4) | |
| | IV | 36 | 53.2 (34.2-69.0) | |
| Non-rhabdomyosarcoma soft tissue sarcoma | I/II | 72 | 89.3 (78.6-94.8) | <0.001 |
| | III | 26 | 76.9 (55.7-88.9) | |
| | IV | 26 | 46.7 (25.4-65.5) | |

Abbreviations: L = localised; M = metastatic; MS = metastatic disease in patients aged ≤ 18 months at diagnosis with metastases confined to skin, liver and/or bone marrow.; M0 = no visible disease on imaging beyond primary site and no tumour cells in the cerebrospinal fluid; M1 = tumour cells in the cerebrospinal fluid; M2 = visible metastasis in the brain; M3 = visible metastasis in spine or cervicomedullary junction; M4 = metastasis outside of the central nervous system; n.a. = not applicable.

Notes: a. Survival was followed up to 31 Dec 2015. b. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).³² c. Stage was defined by the Toronto Paediatric Cancer Stage Guidelines.² d. Values shown in brackets are the 95% confidence interval. e. P-values were derived using a log-rank test.

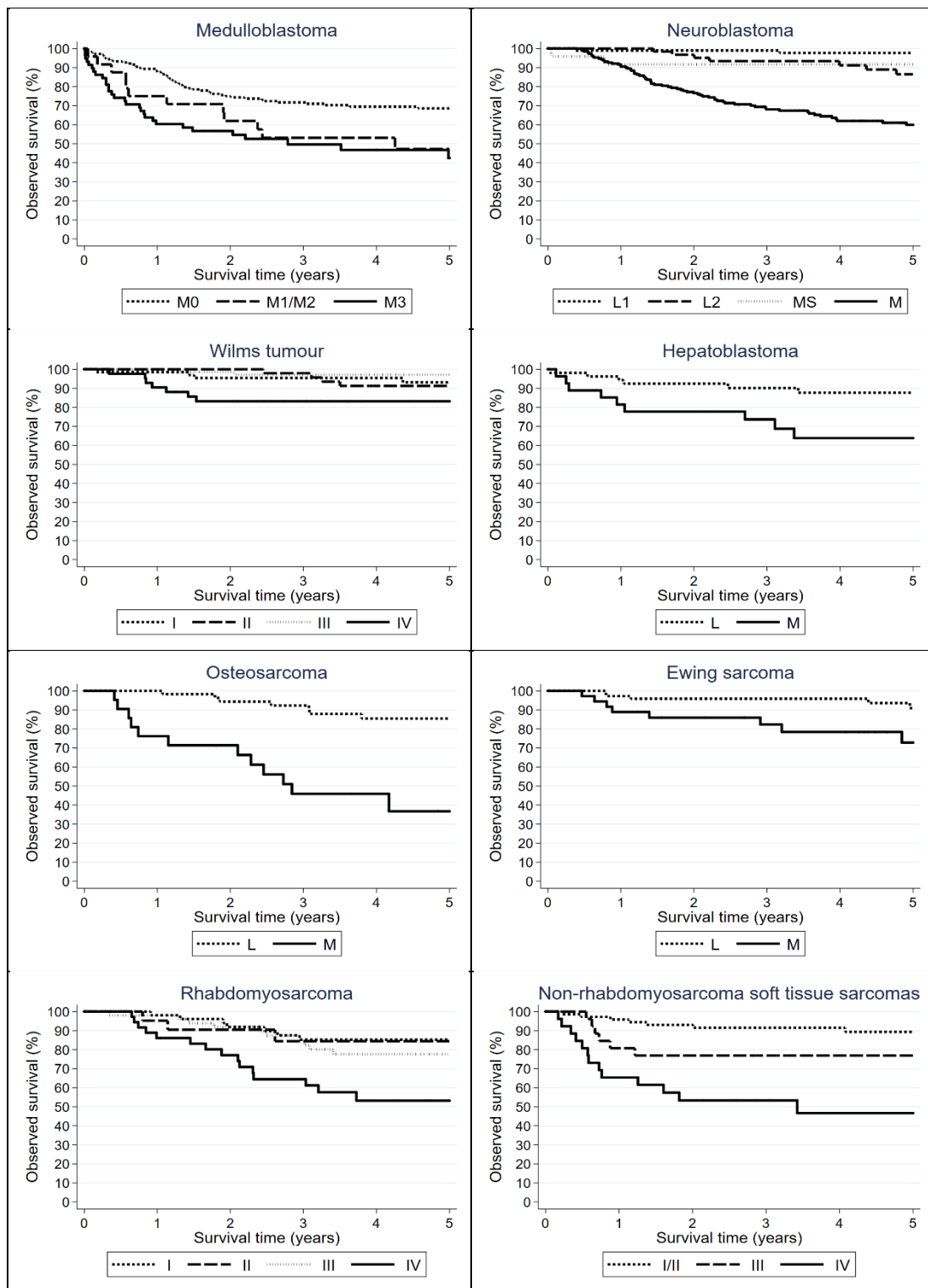


Figure 1: Kaplan-Meier observed survival curves by type of childhood solid tumour and stage, Australian Childhood Cancer Registry, 2006-2014.

Survival was followed up to 31 Dec 2015. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).³² Stage was defined by the Toronto Paediatric Cancer Stage Guidelines.² Abbreviations: CNS = central nervous system; L = localised; M = metastatic; MS = metastatic disease in patients aged ≤ 18 months at diagnosis with metastases confined to skin, liver and/or bone marrow.; M0 = no visible disease on imaging beyond primary site and no tumour cells in the cerebrospinal fluid; M1 = tumour cells in the cerebrospinal fluid; M2 = visible metastasis in the brain; M3 = visible metastasis in spine or cervicomedullary junction.