Incidence and outcomes of neuroblastoma in Australian children: A population-based study (1983-2015)

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Abstract

Background: Neuroblastoma predominantly affects younger children and exhibits heterogeneous behaviour. This study describes incidence and outcomes for neuroblastoma using national population-based data from the Australian Childhood Cancer Registry.

Methods: Deidentified data for all children (0-14 years) diagnosed with neuroblastoma and ganglioneuroblastoma from 1983-2015 were extracted. Cause-specific (CSS) and event-free (EFS) survival were estimated using the cohort method. Adjusted hazard ratios (HRs) were calculated using a multivariable flexible parametric survival model. Other outcomes investigated included recurrence and second primary malignancies (SPMs).

Results: The study cohort comprised 1,269 patients. Age-standardised incidence rates remained steady across the study period at approximately 9.5 per million children per year. The proportion of patients with metastatic disease at diagnosis decreased from 63% in 1983-1995 to 42% by 2006-2015 ($p<0.001$). CSS and EFS both improved significantly over time and reached 75% (95% CI=71%-79%) and 71% (95% CI=66%-75%) at 5 years post-diagnosis, respectively, for children diagnosed between 2004-2013. Of patients achieving full remission, 28% relapsed with subsequent 5-year CSS of only 20%. Although SPMs were rare, neuroblastoma survivors carried a 5-fold increased risk compared to cancer rates in the general population (standardised incidence ratio [SIR]=5.18, 95% CI=3.01-8.91), with 7 of the 13 patients (54%) who were diagnosed with an SPM dying within 5 years.

Conclusions: CSS for childhood neuroblastoma has improved substantially over time in Australia, but still remains lower than for most other types of childhood cancer. SPMs are uncommon and carry a better prognosis than relapse of the primary tumour.

Keywords: neuroblastoma, childhood cancer, population-based cancer registry, incidence, survival

What is Known:

- Neuroblastoma is the most common extracranial solid tumour occurring in childhood.
- The biology and genomics associated with neuroblastoma point to clinical and biological differences between low- intermediate- and high-risk disease. Rather than one being a necessary precursor to the other, they behave more as different diseases.
- Population-based data are essential in providing a "real world" perspective that cannot be achieved from reporting on the subset of patients treated on specific clinical trials.

What This Study Adds:

- Although incidence rates have remained stable in Australia over the last three decades, the proportion of children with metastatic disease at diagnosis has decreased by one-third.
- Overall survival has improved markedly over time, even accounting for differences in stage at diagnosis.
- Survival is particularly poor for neuroblastoma patients aged >18 months with metastatic disease at diagnosis who suffer relapse.

Introduction

Neuroblastoma is an embryonal malignancy of neural crest cells, manifesting in the sympathetic nervous system. It is the most common paediatric solid tumour, accounting for approximately 7% of total cancer incidence worldwide among children aged 0-14.[1] The disease occurs almost exclusively during childhood[2] and most often before the age of five.[3]

Tumours can develop anywhere within the sympathetic nervous system, from neck to pelvis, but are most common in the adrenal glands.[2, 4] The primary tumour tends to wrap around vascular structures, rather than push them aside, making resection challenging. There is a high propensity to spread to many different sites (such as the bone marrow, liver or skin) with around half of patients presenting with metastatic disease.[5]

Because neuroblastoma can occur in many different sites, presentation is diverse. Symptoms may include a palpable abdominal mass, breathlessness, bladder or bowel dysfunction, fever, skeletal pain or failure to thrive.[2] The biology of neuroblastoma is as varied as its presentation. Age, stage, histology, and tumour biology all contribute to risk stratification, used to define treatment and prognosis.[6] Neuroblastoma does not inevitably progress from low- to high-risk, and the divergent genomics and biology of the various risk groups suggest they are clinically and biologically different diseases.

The purpose of this study is to use population-based registry data to describe incidence and survival for childhood neuroblastoma in Australia over the last three decades. Second primary malignancies and recurrence are also examined.

Methods

Data

Deidentified unit record data used in this study were from the Australian Childhood Cancer Registry (ACCR), a national population-based registry containing detailed demographic and clinical information on every child diagnosed with cancer in Australia between the ages of 0 to 14 years, inclusive. Cases in the ACCR are categorised according to the 3rd edition of the International Classification of Childhood Cancer (ICCC-3).[7] The diagnostic subgroup of 'neuroblastoma & ganglioneuroblastoma' as defined in the ICCC-3 forms the basis for this study (hereafter referred to as 'neuroblastoma'). Children with other peripheral nervous cell tumours are not included in this report.

All State and Territory cancer registries in Australia supply routine data on incident cases to the ACCR on an annual basis. At the time of this study, cases were available for the period from 1983 to 2015. Detailed clinical information is collected by the ACCR Data Manager from medical records during site visits to the treating hospital. Mortality status is updated by regular linkage with the National Death Index, and information on second primary malignancies is obtained by linkage with the Australian Cancer Database.

Analyses

Incidence rates were directly age-standardised to the 2001 Australian Standard Population and reported per million children per year. Estimated resident population data used as the denominator in rate calculations were sourced from the Australian Bureau of Statistics.[8] Trends for incidence counts and rates were calculated over the entire study period (1983-2015) using joinpoint regression. Models were specified with a maximum of 3 joinpoints and

a minimum of 6 years between joinpoints. Results were reported in terms of the annual percentage change (APC).

All remaining analyses were restricted to patients diagnosed between 1983 and 2013 to allow a minimum of two years of follow-up through to 31 Dec 2015. Where feasible, analyses were stratified into three groups according to patients' age and metastatic status: non-metastatic disease; metastatic and aged <18 months at diagnosis; and metastatic disease and patient aged 18 months or older at diagnosis.

The cohort method was used to calculate cause-specific survival (CSS) estimates up to 20 years from the date of diagnosis. Survival time was censored at the end of the follow-up period for patients who remained alive. Adjusted hazard ratios (HRs) within five years of diagnosis were obtained from a multivariable flexible parametric survival model[9]. Covariates included in the model were sex, age group, year of diagnosis, metastatic status at diagnosis and type of treatment received (surgery with curative intent, chemotherapy and radiotherapy, each classified as a binary variable). Exclusions were applied for patients with missing data for any of these variables, and for those where the basis of diagnosis was autopsy or death certificate only. The procedure was repeated for five-year event free survival (EFS), where an event was defined as cause-specific death, relapse, or diagnosis of a second primary malignancy (SPM).

Standardised incidence ratios (SIRs), obtained by dividing the observed number of SPMs in the study cohort by the expected number, were used to approximate the relative risk of SPMs. To exclude synchronous cancers, time at risk was accumulated from two months after diagnosis of neuroblastoma until date of death, date of diagnosis of a SPM or the end of the

study period, whichever occurred first. The expected number of cancers was then derived by multiplying the time at risk (in person-years) by the incidence rate of cancer (excluding neuroblastoma) in the general population,[10] matched by sex, age and calendar year. Maximum attained age at the end of follow-up was 47 years.

Details of relapses among children with neuroblastoma following full remission were also examined. Time to relapse was measured from both date of diagnosis and date of last recorded treatment (surgery, chemotherapy or radiotherapy); however, time from full remission to relapse could not be evaluated as date of remission is not recorded in the ACCR.

The study complied with all of the ethics approvals under which the ACCR operates. All analyses were conducted using Stata/SE for Windows v14.2 (StataCorp, College Station, TX).

Results

Incidence

Details of the study cohort (n=1,269) are shown in Table 1. A small majority (54%) were boys and the median age at diagnosis was 19 months. The proportion of girls diagnosed with neuroblastoma over time appeared to increase over time, from 41% between 1983-1995 to 49% between 2006-2015, but this observation may be due to chance (p=0.05). Distribution of the age at diagnosis remained static across the study period (p=0.51). More than half (53%) of all neuroblastoma patients in Australia were reported to have metastatic disease at the time of diagnosis, including 61% of those aged 18 months or older. Notably, the proportion of patients with metastatic disease at diagnosis decreased from 63% to 42% (p<0.001) between 1983-1995 and 2006-2015, respectively.

Incidence counts for neuroblastoma increased by 1.3% per year (p=0.003) between 1983 and 2015 (total increase of 49%; Figure 1). The corresponding trend for incidence rates was not statistically significant (p=0.22), however, with an average age-adjusted rate of 9.5 per million children per year across the study period.

Mortality

Of the 1,148 children who were diagnosed with neuroblastoma between 1983-2013, 432 (37%) died by 31 Dec 2015. Only a small proportion of these deaths (n=21, 5%) were due to causes other than neuroblastoma, including 6 deaths that were attributed to other cancers. Nearly all of the deaths (n=400, 93%) occurred within 5 years of neuroblastoma diagnosis, although this varied from 95% of deaths due to neuroblastoma versus 43% of deaths due to other causes.

Survival

Significant differences in CSS were found for several covariates (Table 2 and Figure 2). In particular, 5-year CSS improved dramatically from 53% to 75% for children diagnosed between 1983-1993 and 2004-2013, respectively. This improvement in CSS over time was observed irrespective of age or stage at diagnosis, from 78% to 91% for patients with non-metastatic disease (p=0.002), 63% to 85% for those with metastatic disease and aged <18 months (p=0.008) and 27% to 46% for patients with metastatic disease who were 18 months or older (p<0.001).

After multivariable adjustment, the risk of mortality due to neuroblastoma for all children diagnosed between 2004-2013 was less than half compared to those diagnosed between 1983-1993 (HR=0.46, p<0.001). CSS was also much better for children under 18 months of age and those with non-metastatic disease, with adjusted HRs around three times higher for each of the other age groups and for those with metastatic stage in comparison.

Similar relationships held true for EFS (Supplementary Table 1). Five-year EFS was 71% for children diagnosed between 2004-2013.

Relapse

Full remission was obtained for 863 of 1,148 children with neuroblastoma (75%) during the study period, of whom 241 (28%) suffered a relapse. Two-thirds (n=158, 66%) of relapses were to distant/multiple sites, while the remainder (n=83, 34%) occurred at the primary site or local lymph nodes. Median times to first relapse were 458 days (IQR = 302-694 days) from date of diagnosis or 287 days (IQR = 146-511 days) from date of last recorded treatment prior to first relapse. Although children under 18 months of age were less likely to relapse (14%) compared to older patients (>40% in each of the other age groups), they also

had a substantially shorter median time to relapse of 167 days from date of last recorded treatment (Table 3).

Cause-specific survival for childhood neuroblastoma patients who relapsed was 20% (95% CI = 15%-25%) five years after first relapse. Survival following relapse was, however, heavily dependent on age and stage at initial diagnosis, varying from 46% (95% CI = 33%-59%) at 5 years after relapse for patients with non-metastatic disease at diagnosis compared to only 4% (95% CI = 1%-9%) for patients aged >18 months with metastatic disease at diagnosis.

Secondary primary malignancies

Survivors of childhood neuroblastoma were estimated to be over 5 times more likely to be diagnosed with a second cancer than expected (SIR = 5.18, 95% CI = 3.01-8.91, $p<0.001$), based on 13 patients who were diagnosed with a SPM. The corresponding absolute excess risk was 9.2 SPMs per 10,000 person-years at risk (95% CI = 7.6-10.2) and the cumulative incidence of SPMs after 20 years was 1.4% (95% CI = 0.7%-2.4%). Patients aged >18 months with metastatic disease carried a considerably greater relative risk, accounting for 7 of the SPMs with an SIR of 13.57 (95% CI = 6.47-28.46).

Median time between first and second diagnosis was around 4.5 years, ranging from 8 months to 21 years. Eleven of the SPMs (85%) were diagnosed before 15 years of age and the oldest reported age at second diagnosis was 23. Leukaemia was the most common type of SPM (6 cases, mostly acute myeloid leukaemia). Seven of the 13 patients (54%) with a SPM died prior to the end of 2015.

Discussion

The ACCR is a unique, high-quality database of diagnostic, clinical and outcome information on every case of childhood cancer diagnosed in Australia. The data presented here therefore represent a population-based summary of the descriptive epidemiology of childhood neuroblastoma over the last three decades for all Australian patients under the age of 15.

Internationally, the incidence rate of sympathetic nervous cell tumours among children aged 0-14 (of which neuroblastoma accounts for the vast majority) was reported to vary between 3.2 to 14.9 per million person-years in India and Canada, respectively, between 2001-2010.[1] The Australian average of 9.5 cases per million person-years reported here is therefore mid-range and consistent with a reported incidence rate of 10.1 in Northern Europe.[1] In contrast to our finding of stable incidence rates, significant increases in neuroblastoma have been documented for children in Spain (APC=1.4% between 1983-2007)[11] and Italy (APC=1.9% between 1988-2008)[12] and for the 1-4 age group in Canada (APC=1.7% between 1992-2010).[13] Improvements over time in diagnostic techniques have been cited as a possible reason for these apparent increases,[11, 13] including a rise in the detection of latent or asymptomatic tumours. If this were true in Australia then we would expect to see an increase in incidence over time, and/or an increase in the proportion of younger children. Neither were observed, so the concomitant finding of a decrease in those children metastatic at diagnosis remains unexplained.

Survival following a diagnosis of neuroblastoma is generally inferior to many other forms of childhood cancer.[14] Tumour behaviour for neuroblastoma varies widely, from rapid progression through to spontaneous regression.[15] Outcomes are not easy to forecast, and are influenced by genomic and biological features in addition to age and stage at diagnosis.

Imaging alone is insufficient to confidently predict behaviour and must therefore be supplemented with tissue for tumour biology in order to risk stratify.

Our estimate of 75% 5-year CSS for children diagnosed with neuroblastoma between 2004 and 2013 compares favourably to 5-year observed survival of 71% reported across Europe for the period 1999-2007[16] but was somewhat lower than the result of 80% for the United States between 2008 and 2014[17]. The large gains in survival over time in Australia have coincided with a shift towards lower stage at diagnosis, combined with advances in understanding of the biology of neuroblastoma that have led to refinements in risk-based treatment.[5, 18] In contrast to our finding, a study from Denmark reported no difference in stage for children with neuroblastoma diagnosed between 1981-1990 compared to 1991-2000.[19] Possible reasons underlying the observed change in the distribution of stage cannot be determined from ACCR data. Improvements in survival from our data are apparent even allowing for lower stage disease over time and do not appear to have plateaued. Prognosis remains poor, however, for post-infant children with metastatic neuroblastoma and particularly for those who suffer relapse, with only one in five relapsed patients in the study cohort surviving for five years.

Although rare, SPMs pose another serious danger to neuroblastoma survivors. The relative risk was greater for older children with metastatic disease, and acute myeloid leukaemia accounted for the majority of these SPMs, suggesting a therapy-related aetiology among these patients. In comparison to the overall SIR of 5.2 estimated here, a population-based SIR of 5.3 has been reported using registry data from the United States and Canada.[20] The greater than expected number of SPMs compared to the general population is primarily linked to the late effects of treatment, including alkylating agents, topoisomerase II inhibitors, platinum

compounds and radiotherapy.[5] Indeed, treatment intensity has a clear effect on the likelihood of developing a SPM, with Applebaum et. al.[21] demonstrating that SIRs varied from 3.1 to 17.5 for neuroblastoma patients with low- and high-risk disease, respectively, although it should be noted that this study was limited to children treated on specific clinical trials. Genetic susceptibility may also have a role in the development of SPMs following neuroblastoma.[21]

A limitation of this analysis was the lack of information on pre-treatment risk group. For example, the details necessary to stratify neuroblastoma patients by the International Neuroblastoma Risk Group Staging System (INRGSS)[22] into low-, intermediate- and high-risk disease were not available for all patients. These data are currently being added to the ACCR database to allow risk stratification for future reports.[23]

To conclude, incidence rates of neuroblastoma have remained fairly stable in Australia over the previous three decades, with an unexplained decrease in the proportion of patients with metastatic disease at diagnosis. CSS has improved substantially over time irrespective of age and stage at diagnosis, but mortality remains elevated for children 18 months or older with metastatic disease at diagnosis. SPMs are uncommon and carry a somewhat better prognosis than a relapse of the primary tumour, but new therapies for neuroblastoma are on the horizon that may offer a more positive outcome for all patients.

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Table 1: Incidence distribution for childhood neuroblastoma[a] by key demographic and clinical characteristics, Australia, 1983-2015

	Incidence count	(%)
Total	1,269	100.0
Sex		
Boys	689	54.3
Girls	580	45.7
Age group		
< 18 months	596	47.0
18 months-4 years	519	40.9
5-14 years	125	9.9
10-14 years	29	2.3
Metastatic status at diagnosis		
Non-metastatic	541	42.6
Metastatic	668	52.6
< 18 months old	*257*	*20.3*
>= 18 months old	*411*	*32.4*
Not stated	60	4.7

Abbreviations: 95% CI = 95% confidence interval.

Notes: a.) Defined using diagnostic subgroup IVa "Neuroblastoma and ganglioneuroblastoma" from the International Classification of Childhood Cancers (ICCC-3).

Table 2: Five-year cause-specific survival and adjusted hazard ratios by selected characteristics for childhood neuroblastoma[a], Australia, 1983-2013

	Number of cases	Five-year cause-specific survival[b] (95% CI)	Adjusted hazard ratio (95% CI)	p-value
Total	1,148	65.4 (62.5-68.1)	n.a.	n.a.
Sex			p=0.25	
Boys	631	65.0 (61.1-68.7)	1.00	
Girls	517	65.8 (61.5-69.7)	1.13 (0.92-1.38)	0.25
Age group at diagnosis			p<0.001	
< 18 months	534	84.5 (81.2-87.3)	1.00	
18 months-4 years	469	47.5 (42.8-52.0)	3.18 (2.45-4.12)	<0.001
5-9 years	116	50.4 (40.7-59.3)	2.86 (2.01-4.06)	<0.001
10-14 years	29	57.0 (36.6-73.1)	2.72 (1.47-5.03)	0.001
Year of diagnosis			p<0.001	
1983-1993	363	53.1 (47.8-58.1)	1.00	
1994-2003	358	65.8 (60.6-70.4)	0.79 (0.62-1.00)	0.05
2004-2013	427	75.4 (70.8-79.3)	0.46 (0.35-0.59)	<0.001
Metastatic status at diagnosis			p<0.001	
Non-metastatic	493	86.9 (83.5-89.6)	1.00	
Metastatic	655	49.5 (45.5-53.2)	2.71 (2.00-3.68)	<0.001
Surgery[c]			p<0.001	
Yes	734	72.5 (69.1-75.6)	1.00	
No	414	52.4 (47.3-57.2)	2.06 (1.67-2.53)	p<0.001
Chemotherapy			p<0.001	
Yes	777	54.4 (50.8-57.9)	1.00	
No	371	89.0 (85.3-91.8)	0.48 (0.33-0.70)	p<0.001
Radiotherapy			p=0.57	
Yes	275	48.2 (42.1-54.0)	1.00	
No	873	70.9 (67.7-73.8)	1.07 (0.85-1.34)	0.57

Abbreviations: 95% CI = 95% confidence interval; n.a. = not applicable.

Notes: a.) Excludes cases with unspecified metastatic status at diagnosis. b.) Survival was calculated using the cohort method, with follow-up on mortality status to 31 Dec 2015. c.) Includes surgery with curative intent (complete or incomplete removal of tumour).

Table 3: Relapse following full remission for childhood neuroblastoma[a] by key demographic and clinical characteristics, Australia, 1983-2013[b]

	Full remission	Relapse	(%)	Median time from date of last treatment[c] to relapse in days (IQR)
Total	863	241	27.9	287 (146-511)
Sex				
Boys	481	139	28.9	289 (149-526)
Girls	382	102	26.7	279 (132-444)
Age group				
< 18 months	458	63	13.8	167 (101-429)
18 months-4 years	313	137	43.8	297 (157-546)
5-14 years	75	34	45.3	327 (207-596)
10-14 years	17	7	41.2	551 (180-1034)
Metastatic status at diagnosis				
Non-metastatic	397	57	14.4	264 (140-488)
Metastatic < 18 months	206	40	19.4	203 (84-429)
Metastatic >= 18 months	260	144	55.4	305 (168-568)

Abbreviations: IQR = interquartile range.

Notes: a.) Excludes cases with unspecified metastatic status at diagnosis. b.) Cases diagnosed 1983 to 2012 with follow-up on relapse status to 31 Dec 2015. c.) Calculated from date of last recorded curative surgery, chemotherapy or radiotherapy prior to date of first relapse.

Supplementary Table 1: Five-year event-free survival[a] and adjusted hazard ratios by selected characteristics for childhood neuroblastoma[b], Australia, 1983-2013

	Number of cases	Five-year event-free survival[a] (95% CI)	Adjusted hazard ratio (95% CI)	p-value
Total	1,148	60.2 (57.3-63.0)	n.a.	n.a.
Sex			p=0.49	
Boys	631	59.7 (55.8-63.5)	1.00	
Girls	517	60.9 (56.5-65.0)	1.07 (0.89-1.29)	0.49
Age group at diagnosis			p<0.001	
< 18 months	534	78.5 (74.8-81.8)	1.00	
18 months-4 years	469	43.1 (38.5-47.6)	2.57 (2.04-3.23)	<0.001
5-9 years	116	48.0 (38.7-56.8)	2.33 (1.69-3.23)	<0.001
10-14 years	29	46.7 (27.5-63.8)	2.50 (1.45-4.32)	0.001
Year of diagnosis			p<0.001	
1983-1993	363	47.9 (42.7-53.0)	1.00	
1994-2003	358	60.3 (55.0-65.1)	0.80 (0.64-1.00)	0.05
2004-2013	427	70.8 (66.2-75.0)	0.49 (0.39-0.62)	<0.001
Metastatic status at diagnosis			p<0.001	
Non-metastatic	493	81.1 (77.4-84.3)	1.00	
Metastatic	655	44.7 (40.8-48.4)	2.40 (1.84-3.13)	<0.001
Surgery[c]			p<0.001	
Yes	734	65.6 (62.1-69.0)	1.00	
No	414	50.7 (45.7-55.5)	1.69 (1.39-2.05)	p<0.001
Chemotherapy			p=0.003	
Yes	777	50.0 (46.4-53.5)	1.00	
No	371	82.1 (77.8-85.6)	0.63 (0.46-0.85)	0.003
Radiotherapy			p=0.36	
Yes	275	43.2 (37.3-49.0)	1.00	
No	873	65.7 (62.4-68.8)	1.11 (0.89-1.37)	0.36

Abbreviations: 95% CI = 95% confidence interval; n.a. = not applicable.

Notes: a.) Events were defined as cause-specific death, relapse or diagnosis of second malignancy. Survival was calculated using the cohort method, with follow-up on mortality status to 31 Dec 2015. b.) Excludes cases with unspecified metastatic status at diagnosis. c.) Includes surgery with curative intent (complete or incomplete removal of tumour).

Figure legends

Figure 1: Incidence count and rate trends for childhood neuroblastoma, Australia, 1983-2015. APC = annual percentage change. Rates were age-standardised to the 2001 Australian Standard Population. Trends modelled using joinpoint regression (http://surveillance.cancer.gov/joinpoint/).

Figure 2: Five-year unadjusted cause-specific survival for childhood neuroblastoma patients by selected characteristics, Australia, 1983-2013. Survival was calculated using the cohort method, with follow-up on mortality status to 31 Dec 2015.