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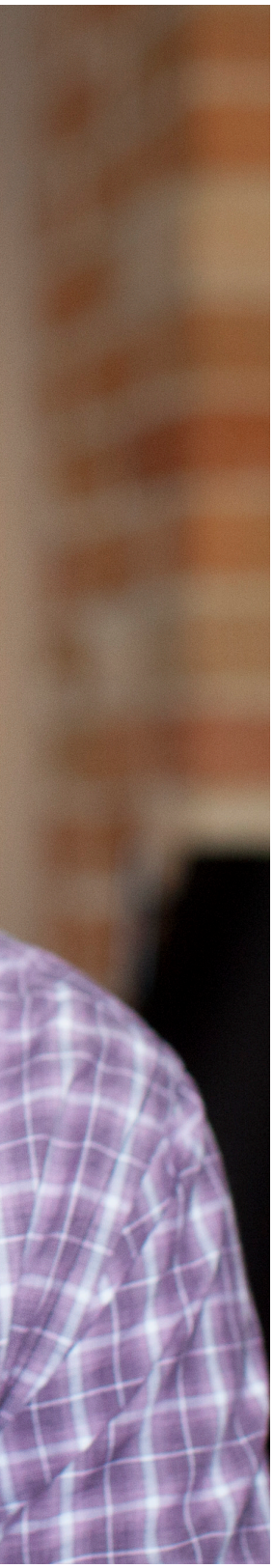

4

Survival

Executive Summary

Key findings

- Age standardized mortality rates for all cancers showed a progressive reduction in mortality over the 20 year period, although not all cancers had the same declines in mortality.
- While the decreasing trend in mortality started early in the 20 year period, the slope of the decline in recent years, especially from the late 1990s, was more pronounced.
- Over the 20 year period, age standardized mortality rates for all cancers decreased from 43.2 to 23.8 per million, a 45% overall decline.
- Over the 20 year period, the 5 year survival increased from 69% to 80%, reflecting an 11% overall increase in survival.
- Overall, 10 years after a cancer diagnosis, 69% of children in this cohort remain event free.

Implications

- The pattern of survival over the 20 year period among children diagnosed with cancer is encouraging.
- Although survival has improved, many children with cancer still die and cancer remains the second most common cause of death for Canadian children between 5 and 14 years of age and the leading disease cause of death for ages 0–19 years.
- Treatments have systematically improved over time, in large part because of sequential multinational cooperative group trials, such as those of the Children's Oncology Group.
- For almost all childhood malignancies, risk stratification has improved, resulting in rational intensification of therapy for those more likely to relapse and less intense therapy for those likely to be cured with standard therapy.
- Over the 20 year period, improved supportive care played an important role in enabling treatment intensification, where appropriate, and in reducing treatment-related mortality.
- Sustained survival beyond the first 5 years from diagnosis is evident in most cancer diagnostic groups. Still, decreases in survival after this point are noted and further work needs to be undertaken that compares survival relative to similar children not diagnosed with cancer.

Introduction

Background

Over the past 30 years, outcomes for pediatric cancer have improved remarkably, from 5 year survival rates in 1975 below 60% to current 5 year survival rates above 80%.[1,2] However, many children with cancer still die and cancer remains the second most common cause of death for Canadian children between 5 and 14 years of age[3] and the leading disease cause of death for ages 0–19 years.

For Canadian children aged 0–14 years with cancer, the most recently reported 5 year overall survival is 82% for those diagnosed between 2000 and 2004.[4] In a comparable period (diagnosed between 2000 and 2002), the Surveillance Epidemiology and End Results (SEER) program reported that 5 year survival for all children with cancer younger than 20 years of age in the United States was 79.1–80.9%.[5] These data suggest that survival is comparable in Canada and the United States. Overall survival proportions in both Canada and the United States are higher than in almost all low and middle income countries.

Among children aged 0–19 years at diagnosis, the 5 year overall survival proportion has improved over time, with survival of 71% for all children diagnosed with cancer from 1985 to 1988,[6] compared with survival of 82% for children diagnosed from 1999 to 2003.[7] Similarly, statistics available from the Canadian Cancer Society show that the age standardized mortality rate (ASMR) has decreased from 41.2 per million in 1985 to 20.6 per million in 2009.[4]

There are many reasons for this improvement in survival. First, treatments have systematically improved over time, in large part as a result of sequential multinational cooperative group trials, such as those of the Children's Oncology Group. Second, for almost all childhood malignancies, risk stratification has improved, resulting in rational intensification of therapy for those more likely to relapse and less intense therapy for those likely to be cured with standard therapy. Third, improved supportive care has played an important role in enabling treatment intensification, where appropriate, and reducing treatment-related mortality.

Causes of death among children with cancer can be broadly categorized as disease related or treatment related, although clear definitions for the latter do not exist. The balance between disease- and treatment-related causes of death is critical because it defines the potential limits of intensification of therapy, the role for further supportive care and where innovative therapy is necessary to improve survival rates.

There are likely to be differences between survival in population-based analyses and in clinical trials. More specifically, patients enrolled in clinical trials tend to have better outcomes than those who are not enrolled in trials.[8] Reasons behind this difference are protean and relate primarily to selection bias. Subjects with baseline comorbidities, organ dysfunction or poor performance status at presentation are often excluded from clinical trials. Patients who require urgent therapy may also not be enrolled in trials. Furthermore, even among those eligible for a trial, those who consent to enrollment are likely to be systematically different from those who refuse enrollment. Consequently, survival estimates derived from clinical trials do not accurately reflect survival of all patients diagnosed with cancer. This report is population-based.

The International Classification of Diseases (ICD) is a working classification maintained by the World Health Organization (WHO). The neoplasm section of ICD is a special adaptation created to classify oncologic diseases – the ICD-O. Although ICD-O is based on the ICD, the ICD describes only anatomic sites, while ICD-O describes anatomic site (topography), histology (morphology) and behaviour (e.g., malignant, benign or uncertain). Further refined histologic differentiation for leukemia and lymphoma is provided, based on the WHO Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues.

The latest iteration of ICD (ICD10) uses the ICD-O 3 version of the ICD-O classification schema. ICD-O 3 differs from ICD-O 2 in several respects:

- The addition of new morphologic codes
- Creation of a list of synonyms for morphologic codes
- A change in some descriptive morphologic codes
- A change from some entities classified as "tumour-like" to "neoplasm"
- Deletion of some terms
- A behaviour code (fifth digit) change for some terms, in either direction, moving some disease entities from malignant to benign and vice versa

Three other major changes occurred between the ICD-O 2 and 3: 1) the WHO classification of lymphoma supplanted the Revised European American Lymphoma classification, 2) the French-American-British classification of leukemia was incorporated and 3) the WHO classification of myeloid leukemia, incorporating morphology and cytogenetic abnormalities, was recognized.

The first International Classification of Childhood Cancer (ICCC), published in 1987,[9] recognized that in childhood cancers, morphology is much more relevant than topography. The ICCC was based on the ICD-O. As the ICD-O has evolved to incorporate evolving genetic and pathologic findings,[10] so has the ICCC. The ICCC-3, published in 2005,[11] is based on the ICD-O 3. Some disease entities recognized in the ICCC as malignant are not included in the ICD-O. These differences arise primarily because some tumours, although not histologically identified as malignant, manifest symptoms, prognosis and late effects similar to those of malignant tumours and are treated with interventions identical to those for other malignancies. An example of such a tumour group is low grade gliomas.[11] While a separate classification has been developed for adolescents and young adults,[12] all diagnoses in this chapter were classified according to ICCC-3.

The ICCC-3 classification scheme comprises 12 main diagnostic groups, with all but the retinoblastoma group having subgroups. The majority of exhibits are presented using the main groups and some subgroups. As a result of sample size limitations, several exhibits classify diagnoses into 4 consolidated categories: leukemia, lymphoma, central nervous system (CNS) tumours and solid tumours. The leukemia, lymphoma and CNS categories comprise the same main groups as outlined in the ICCC-3. The solid tumours category comprises the following ICCC-3 main groups:

- Neuroblastoma and other peripheral nervous cell tumours
- Retinoblastoma
- Renal tumours
- Hepatic tumours
- Malignant bone tumours
- Soft tissue and other extra-osseous sarcomas
- Germ cell tumours, trophoblastic tumours and neoplasms of the gonads

Methods

Data sources

Since 1985, the Pediatric Oncology Group of Ontario (POGO) has collected prospective data on all children diagnosed with and treated for cancer at each of the 5 tertiary pediatric oncology centres in the province: The Hospital for Sick Children (Toronto), McMaster Children's Hospital (Hamilton), Children's Hospital of Western Ontario (London), Kingston General Hospital (Kingston) and Children's Hospital of Eastern Ontario (Ottawa). In 1995, detailed treatment and diagnostic information was added to complement the cancer registry and hence the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) was created. Comparison studies with the Ontario Cancer Registry (OCR) indicate that POGONIS captures 96–98% of children aged 0–14 years who are diagnosed in Ontario.[13]

In 2004, POGO was designated a 45.1 Entity under the *Ontario Personal Health Information and Protection Act*. This designation enables POGO to collect, use and disclose personal health information for defined purposes of analysis and/or compiling statistical information with respect to the management, evaluation or monitoring of the allocation of resources to or planning for all or part of the health system, including the delivery of services, under strict privacy and security policies and procedures. It is this designation that allows POGO to link POGONIS to other data sources.

POGONIS captures information pertaining to the timing and definitive diagnosis of cancer. In 1995, in-hospital mortality information was added as part of the routine systematic data collection. To systematically capture all deaths, regardless of location, including in-hospital deaths, from 1985 to 2004 inclusive, death information was identified via record linkage to the OCR and the Ontario Registrar General Death File (ORGDF).

The OCR is a population-based tumour registry operated by Cancer Care Ontario. The OCR began in 1964 and consists of computerized information on all new cases of cancer in Ontario, except non-melanoma skin cancers. The OCR is a passive registry based on pathology reports on all cases in which there is a diagnosis of cancer, electronic patient records from the regional cancer centres, electronic hospital discharge records from all Ontario hospital admissions with a diagnosis of cancer (including day surgery) and electronic reports of deaths in Ontario from the ORGDF.

This chapter is based on patients aged 0–14 years who were diagnosed with one or more malignant neoplasms in the period 1985–2004 inclusive, who were Ontario residents at the time of diagnosis and who were treated in one of the POGO affiliated centres. The year of diagnosis and diagnostic group are based on the first recorded neoplasm in POGONIS.

Record linkage

The linkage between the OCR and POGONIS was generated both deterministically by the Ontario Health Insurance Number (OHIN) and probabilistically. OHINs were assigned to Ontario residents in 1991. Any records that did not match exactly based on the OHIN were considered for probabilistic linkage. For the probabilistic linkage, the individual's first, middle and last name; sex; birth date; and 6 character postal code at the time of diagnosis were used as identifiers. With every probabilistic link, exact matches on name identifiers were undertaken, followed by fuzzy matches using the New York State Identification and Intelligence System phonetic coding system to account for minor typographical errors, misspellings and hyphenated names. Alternate matching was also employed for matching the date of birth, assessing the separate components of the date (day, month and year) and transposition of date components or missing values. For every probabilistic record linkage, a weight based on the theoretical framework developed by Fellegi and Sunter was calculated.[14] A higher weight denotes a higher likelihood of accurate matching. Matches with acceptable weights were considered linked, while matches with lower than acceptable weights were considered not linked.

Results of record linkage

Overall, 95.1% of subjects were successfully linked to the OCR, the ORGDF or both (note that as described above, some entities are not recognized by ICD-O as malignant and thus some malignancies captured by POGONIS are not captured by the OCR. Hence some subjects are linked only to the ORGDF). Of those subjects who were linked, 63.1% were linked deterministically based on the OHIN and 30.3% were linked based on surname and date of birth. The remainder (6.6%) were linked based on date of birth, postal code at time of diagnosis and the first initial of both the given name and surname. As expected, subjects diagnosed in the early part of the cohort had lower linkage proportions than did subjects diagnosed in the later part. Subjects diagnosed in 1985 had the lowest linkage proportion, at 83.0%, while approximately 90% of subjects diagnosed between 1986 and 1990 were linked. From 1991 to 2004, subjects diagnosed had an average linkage rate of 97.2%.

Of the 4.9% of subjects who did not link, half were diagnosed from the early part of the cohort (1985–1989 inclusive). A sensitivity analysis was performed on the early part of the cohort to examine the impact of subject linkage proportions on overall survival proportions (OSP) at 5 years. The sensitivity analysis considers 3 scenarios:

1. An analysis in which non-linked subjects are assumed to be alive
2. An analysis that uses only those subjects who linked (and for whom follow up information is known)
3. An analysis in which non-linked subjects are assumed to have died 2.5 years after diagnosis

Scenario 1 was selected to represent the situation with the highest number of survivors, or best-case situation. Scenario 2 was selected to represent known outcomes and therefore was thought to be the least biased result. Scenario 3 was selected to represent the situation with the lowest possible number of survivors, or the worst-case situation. The result of this sensitivity analysis is presented in Exhibit 4.7.

As expected, scenario 1 provided the highest OSP at 5 years: 0.72 (95% confidence interval: 0.68–0.76), while scenario 3 provided the lowest OSP at 5 years: 0.61 (95% CI: 0.57–0.66) and scenario 2 provided an OSP at 5 years of 0.69 (95% CI: 0.64–0.73), which is between the estimates of the other scenarios. The pattern observed in OSP for all cancers combined (scenario 1 highest, scenario 3 lowest and scenario 2 in between) remains consistent when examining various individual diagnostic groups and subgroups, although the range in estimates generated for each sensitivity analysis can be large when sub-group sample sizes are small, such as in the case in lymphoma.

Since the assumptions used in scenarios 1 and 3 are considered extreme and scenario 2 was considered to provide the least biased estimate (the fewest assumptions), all subsequent survival analyses in this chapter have been undertaken with the subset of subjects who linked to either the OCR or ORGDF (scenario 2). Although there is still potential for residual bias, specifically in the early years of the cohort, this scenario does not use any assumptions and from the sensitivity analysis, any bias that may result is considered minimal. Still, readers should use caution when interpreting survival estimates from the early part of the cohort, especially when considering sub-group analysis with small sample sizes. For example, those who died prior to 1991 would never have received an OHIN and thus may be at higher risk of remaining unlinked. Readers can refer to Exhibit 4.7 when interpreting various OSPs to assist with interpretation.

Calculation of age-standardized mortality rates

ASMRs were calculated stratifying by diagnostic group, diagnosis year and age at time of diagnosis (grouped into a 4 category age variable: less than 1 year, 1–4 years, 5–9 years and 10–14 years) and then standardized to the 2001 Ontario population.

Estimates for the Ontario population in each year, stratified by 1 year age groups, were obtained from CANSIM Table 051-00011, "Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual," which is available from Statistics Canada.[15] Estimates are final intercensal up to 2005, final postcensal for 2006 and 2007 and updated postcensal for 2008. Intercensal estimates correspond to estimates between censuses, whereas postcensal estimates correspond to non-census years after the most recent census. The production of intercensal estimates involves the retrospective adjustment of past figures

with the availability of new census data. These estimates are used by Statistics Canada in the calculation of demographic, social and economic indicators in which the population, or part of it, serves as the denominator and is also used in the calculation of weights for use in Statistics Canada's Surveys.

Calculation of overall survival proportions

In 1996, Brenner and Gefeller proposed a new method for monitoring cancer patient survival.[16] Survival analyses in this chapter were conducted using period analysis methodology.

Period analysis uses the survival experience of people in a recent time interval to estimate survival. Briefly, for patients diagnosed at time T, one would have to wait until T + 5 years to calculate an actual 5 year survival estimate. For practical reasons, traditional reporting of survival is based on cohort analysis whereby the proportion of patients surviving for the specified time interval is T – 5 years. If one has survival data complete up to time T, those diagnosed at T – 5 represent the subjects in the cohort who have complete follow up and provide 5 years of person-time. Subjects who were diagnosed in the years T – 4, T – 3, T – 2 and T – 1 provide partial person-time and are censored at time T. With this method, changes in survival are disclosed with considerable delay (those diagnosed at T – 5 have their 5 year survival reported at time T, 5 years later).

The Brenner method, modelled after period life tables, uses period analysis to provide a more up to date representation of the survival probability at the time the latest mortality information was available.[17] Appendix 4.1 provides a graphical representation of actual, cohort, complete and period survival methods.[18]

Although the use of synthetic cohorts to calculate survival is conceptually more difficult to understand than the traditional "real" cohorts, the advantage related to timelier prognosis warrants the increased complexity, given the rapidly changing prognosis of childhood cancer survivors. Several empirical comparisons have been undertaken to show the increased timeliness of reporting advances.[18-20]

This methodology has been employed by many provincial and national cancer publications and hence permits the estimates in this chapter to be compared with other published data.[4]

For overall survival calculations, person-time was calculated in months from the date of a subject's first diagnosis to the date of death, or if the subject survived, to December 31, 2006. Subjects were censored at the time of death or the end of the follow up period (December 31, 2006).

For event free survival calculations, person-time was calculated in months from the date of a subject's first diagnosis to the date of death, relapse or diagnosis of a second primary tumour, whichever came first. If the subject did not experience death, relapse or a second primary tumour, person-time was calculated to December 31, 2006. Subjects were censored at the time of death, relapse or diagnosis of a second cancer or the end of the follow up period (December 31, 2006). Disease progression (distinguished from relapse by the absence of any remission) is difficult to capture and is not contained in the POGONIS database and therefore not considered here. However, this condition applies to only a small proportion of patients.

For exhibits that examine OSPs after relapse, person-time was calculated in months from the date of a subject's relapse of their first diagnosis to the date of death, or if the subject survived, to December 31, 2006. Subjects were censored at the time of death or the end of the follow up period (December 31, 2006).

All survival analyses were performed using an algorithm, with minor modifications, designed by Dickman.[21] The estimates are based on 0.25 year increments in the first year of person-time, 0.5 year increments in years 2 through 5 of person-time and 1 year increments beyond year 5 of person-time.

Limitations

Given that this chapter focuses on survival, the occurrence and date of death are important elements of all data presented. POGO has been capturing these data for in-hospital deaths since January 1995, and with the linkage to the OCR and the ORGDF, a nearly complete capture of deaths across the entire cohort was obtained. Still, linkage proportions are lower in the early period of the cohort. A sensitivity analysis was undertaken, the results of which have already been discussed. It is recognized that the decision to base all analyses in this chapter on those individuals who achieved positive linkage could introduce bias and that this bias would have a greater impact in the early period of the cohort and potentially be exaggerated by the small sample sizes in some diagnostic subgroups examined. For this reason, readers should use caution when interpreting survival estimates from the early part of the cohort, especially when considering sub-group analysis.

The utility of the POGONIS database and death certificate data in determining the cause of death was examined and found to be low. Although a cause of death is registered on the death record, its reliability is poor. Thus, attempts to distinguish cause using data available in POGONIS were made, but ultimately, it was decided that it was not possible to assign cause of death using the POGONIS data and therefore no discussion of cause of death or assignment of cause of death to treatment- or disease-related factors is presented.

EXHIBIT 4.1: **Age-standardized incidence rate and age-standardized mortality rate (per million) by period and diagnosis, age 0–14 years, in Ontario, 1985–2004**

		Year of diagnosis									
		Total (1985–2004)		1985–1989		1990–1994		1995–1999		2000–2004	
		ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year
	Total	**134.23**	**36.45**	**117.48**	**42.76**	**135.65**	**39.66**	**142.25**	**35.53**	**141.55**	**27.86**
Diagnostic group	Sub-group										
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**44.43**	**10.67**	**41.12**	**13.46**	**44.52**	**11.55**	**47.43**	**11.06**	**44.63**	**6.63**
	a. Lymphoid leukemias	35.28	6.34	34.54	9.40	34.73	6.39	35.27	6.00	36.56	3.58
	b. Acute myeloid leukemias	6.89	3.35	5.30	3.19	7.79	4.63	8.59	3.84	5.90	1.74
	c. Chronic myeloproliferative disease*†	0.50	0.17	—	—	—	—	—	—	—	—
II	**Lymphoma and reticuloendothelial neoplasms**	**14.32**	**2.81**	**11.21**	**3.34**	**15.08**	**3.12**	**14.04**	**2.26**	**16.94**	**2.50**
	a. Hodgkin lymphomas	5.83	0.74	5.03	1.08	6.54	0.81	5.57	0.47	6.16	0.60
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	4.85	1.29	3.35	1.35	5.41	1.77	5.17	1.08	5.46	0.95
	c. Burkitt lymphoma	2.34	0.38	2.24	0.71	2.39	0.28	1.70	0.19	3.05	0.34
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**29.89**	**10.68**	**24.57**	**11.79**	**33.44**	**11.96**	**30.96**	**9.85**	**30.59**	**9.10**
	a. Ependymoma and choroid plexus tumour	2.58	1.28	2.86	1.85	2.44	1.57	2.04	0.84	2.96	0.87
	b. Astrocytomas	16.41	4.88	13.15	5.12	19.87	5.75	16.69	4.62	15.94	4.01
	c. Intracranial and intraspinal embryonal tumours	6.64	3.59	5.30	3.48	6.43	3.59	6.80	3.45	8.03	3.85
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**9.36**	**3.73**	**8.39**	**3.95**	**9.78**	**4.35**	**10.20**	**3.87**	**9.06**	**2.73**
	a. Neuroblastoma and ganglioneuroblastoma	9.17	3.68	8.18	3.85	9.68	4.35	9.94	3.87	8.88	2.64
V	**Retinoblastoma**	**3.46**	**0.11**	**3.24**	**0.18**	**2.72**	**0.08**	**3.40**	**0.00**	**4.47**	**0.17**

ASIR = age standardized incidence rate; ASMR = age standardized mortality rate; CNS = central nervous system

*Including chronic myeloid leukemia

†Because of small sample sizes, rates are not provided for 5 year periods.

The reader may note that there are differences in the ASIR reported in this chapter from that reported in the Incidence chapter (Exhibit 3.2). These differences relate to the exclusion of cases from the data set used in this chapter that did not link to either the Ontario Cancer Registry or the Ontario Registrar General death file, as described in the chapter. The true incidence rates for quotation purposes can be found in the Incidence chapter and exhibits.

continued on following page

EXHIBIT 4.1: **Age-standardized incidence rate and age-standardized mortality rate (per million) by period and diagnosis, age 0–14 years, in Ontario, 1985–2004** (cont'd)

		Year of diagnosis									
		Total (1985–2004)		1985–1989		1990–1994		1995–1999		2000–2004	
		ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year	ASIR per million per year	ASMR per million per year
	Total	134.23	36.45	117.48	42.76	135.65	39.66	142.25	35.53	141.55	27.86
Diagnostic group	Sub-group										
VI Renal tumours		**7.58**	**0.91**	**6.99**	**0.99**	**8.17**	**0.85**	**8.76**	**1.20**	**6.41**	**0.61**
	a. Nephroblastoma and other nonepithelial renal tumours	7.11	0.82	6.79	0.89	7.71	0.85	8.05	1.11	5.89	0.44
VII Hepatic tumours		**2.10**	**0.76**	**1.71**	**0.67**	**2.13**	**0.99**	**1.94**	**0.86**	**2.64**	**0.53**
VIII Malignant bone tumours		**6.80**	**2.69**	**6.97**	**3.54**	**6.96**	**2.48**	**7.08**	**2.45**	**6.19**	**2.30**
	a. Osteosarcomas	3.33	1.34	3.99	2.04	3.27	1.38	3.29	1.01	2.76	0.95
	b. Ewing tumour and related sarcomas of bone	3.18	1.31	2.89	1.50	3.69	1.11	3.42	1.44	2.73	1.19
IX Soft tissue and other extraosseous sarcomas		**8.51**	**2.51**	**6.85**	**2.58**	**7.66**	**2.85**	**8.85**	**2.45**	**10.69**	**2.17**
	a. Rhabdomyosarcomas	3.68	1.10	3.60	1.31	3.90	1.46	3.04	0.68	4.19	0.96
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads		**3.97**	**0.68**	**3.37**	**1.20**	**3.01**	**0.63**	**4.68**	**0.46**	**4.84**	**0.42**
	d. Gonadal carcinomas	1.59	0.11	0.70	0.00	1.40	0.00	1.99	0.28	2.26	0.17
XI Other malignant epithelial neoplasms and malignant melanomas		**2.67**	**0.43**	**2.32**	**0.63**	**1.17**	**0.40**	**3.06**	**0.27**	**4.12**	**0.44**
	b. Thyroid carcinomas	1.06	0.05	1.18	0.21	0.49	0.00	1.18	0.00	1.38	0.00
	d. Malignant melanomas†	0.45	0.17	—	—	—	—	—	—	—	—
XII Other unspecified malignant neoplasms		**1.14**	**0.47**	**0.73**	**0.43**	**1.02**	**0.40**	**1.85**	**0.81**	**0.96**	**0.26**

ASIR = age standardized incidence rate; ASMR = age standardized mortality rate; CNS = central nervous system

*Including chronic myeloid leukemia

†Because of small sample sizes, rates are not provided for 5 year periods.

The reader may note that there are differences in the ASIR reported in this chapter from that reported in the Incidence chapter (Exhibit 3.2). These differences relate to the exclusion of cases from the data set used in this chapter that did not link to either the Ontario Cancer Registry or the Ontario Registrar General death file, as described in the chapter. The true incidence rates for quotation purposes can be found in the Incidence chapter and exhibits.

Exhibit 4.1

The age standardized incidence rates (ASIRs) reported here for the period are influenced downward by apparently lower ASIRs during 1985–1989. These lower rates may reflect lower capture rates at the beginning of this period. The ASIR for the last two time periods has remained constant and suggests a slight increase in the ASIR over the period 1990–1994.

ASIRs are compared with those published for other international jurisdictions. SEER data report on persons aged 0–19 years for 2001–2003[22] by the 12 ICCC categories, standardized to the United States population in 2000. Australian data are population-based for 1997–2006 for the 0–14 year age group, standardized to the WHO world standard population in 2001.[23]

The ASIR for all cancers presented here (134.2 per million per year) is somewhat lower for the entire period. However, comparisons with the U.S. for an equivalent period (2000–2004) are not substantially different (141.6 vs. 151.0), while Australian ASIRs are higher, at 157.5 per million.

The ASIRs for the major ICCC disease groups vary. For group I, the leukemia ASIR (44.4) has been stable and slightly lower than the U.S. or Australian rates (48.1 and 53.1, respectively). The ASIR for acute lymphoblastic leukemia, the largest sub-group, is comparable to the U.S. rates (34.3 for males and 27.9 for females) and lower than the Australian rate (40.8). Group II, lymphoma, has shown a rising ASIR; the ASIR of 16.9 in the last period appears to be higher than both the U.S. and Australian rates (15.6 and 15.4).

ASIRs for subgroups are not stable enough for commentary. For group III, CNS tumours, ASIRs rose in the period 1990–1994; this increase was particularly apparent for the astrocytoma sub-group (the ASIR increased from 13.2 to 19.9). The timing of the increase coincides with widespread availability of computed tomography (CT) and magnetic resonance (MR) imaging and the screening of patients with neurofibromatosis type 1, as has been reported in the U.S.[24] The ASIR then dropped somewhat (to 16.7 in the subsequent period). The ASIR for group IV (neuroblastoma and peripheral nervous cell tumours) demonstrates fluctuation around a base rate of 9.5 per million, comparable with Australian and U.S. data. It is unclear whether the apparent increase in ASIR during 1995–1999 reflects a halo effect from the neuroblastoma screening study[25] or is incidental. For group VI, renal tumours, the ASIR is comparable to both U.S. and Australian reports in the relevant period but is substantially higher in the earlier periods.

The age-standardized mortality rate for all cancers shows a progressive reduction in mortality over the successive periods, reflecting better supportive care that permits more aggressive therapy over time and better understanding of multi-agent therapy. This improvement is true for groups I and II and each of their subgroups and is present but less dramatic for group III. In particular, the change in ASMR for intracranial and intraspinal embryonal tumours over this timeframe is less evident. For group IV, the ASMR decreases predominantly in the last time period, possibly reflecting improvements in duration of survival resulting from intensified therapy, including the consistent application of high dose therapy and stem cell rescue. For group VI, an already low ASMR continued to improve over the reporting period.

EXHIBIT 4.2: **Age-standardized mortality rates (per million) by diagnosis group and year, age 0–14 years, in Ontario, 1985–2004**

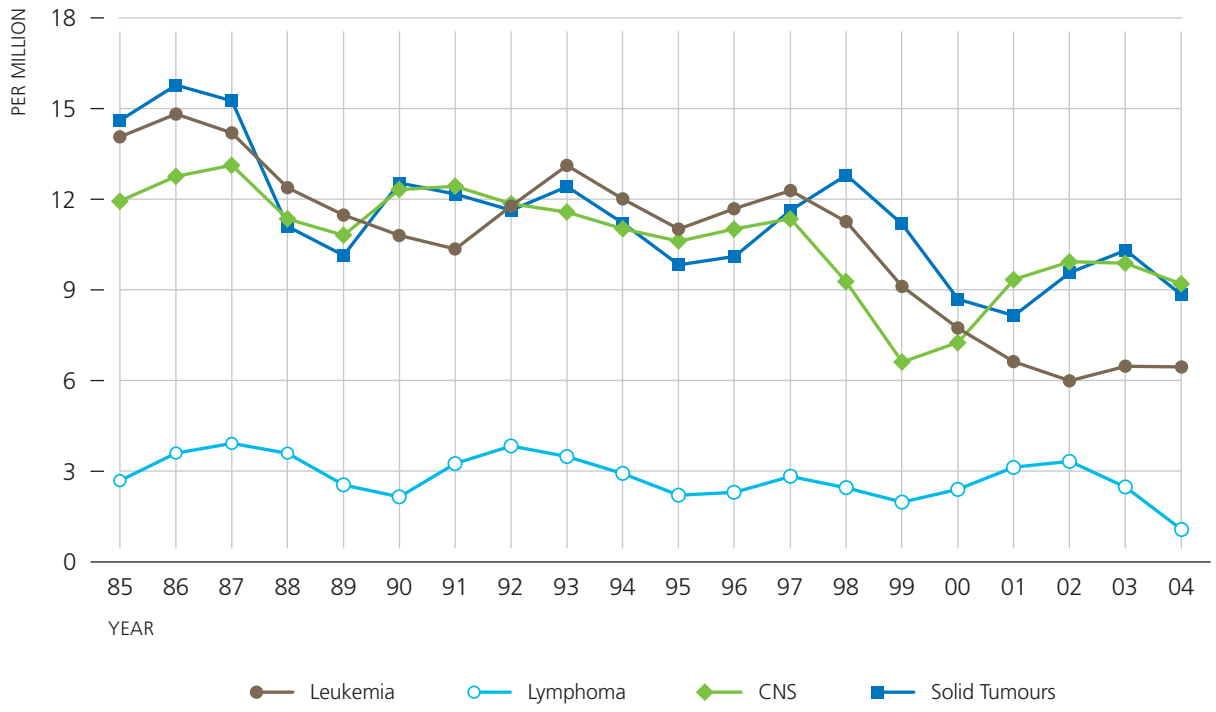

Exhibit 4.2

The exhibit shows the trend over time for the ASMR for all childhood cancers, leukemia, lymphoma, CNS and solid tumours. For all childhood cancers, trend analysis indicates a significant 2.3% average decline in ASMR every year ($P < 0.001$). While the decreasing trend started from the early years of the period, the slope of the decline in recent years, especially from the late 1990s, was more significant. During this period, the ASMR for all cancers decreased from 42.9 per million in 1985 to 23.1 per million in 2004, a 46% overall decline.

The trend over time for the ASMR in leukemia was similar to that for all cancers (a 2.4% decline per year, $P < 0.001$). The mortality rate for leukemia declined by more than 55% during this 20 year period in Ontario. Children diagnosed with lymphoma demonstrated a large decline in their ASMR over time. Compared with those diagnosed with leukemia, children diagnosed with CNS tumours demonstrated smaller decreases in their ASMRs. Trend analysis indicates a 1.4% average yearly decline in mortality among patients with CNS tumours ($P < 0.007$). Although smaller than the decrease for leukemia, the decrease for CNS tumours is still a significant 29% decline over the 20 year period.

Children diagnosed with solid tumours also show a declining trend in mortality. In spite of observed fluctuations, even in smoothed rates, the overall pattern indicates a declining trend in the ASMR for solid tumours. Regression analysis indicates an overall 2.4% average yearly decline in the ASMR for solid tumours ($P = 0.017$).

EXHIBIT 4.3: **Overall survival proportions and survival duration by diagnosis, age 0–14 years, in Ontario, 1985–2004**

		Proportion survived									
		1 year		3 year		5 year		7 year		10 year	
		OSP	95% CI	OSP	95% CI	OSP	95% CI	OSP	95% CI	OSP	95% CI
	Overall	**0.90**	**0.89-0.91**	**0.80**	**0.79-0.81**	**0.76**	**0.75-0.77**	**0.74**	**0.73-0.75**	**0.73**	**0.72-0.74**
Diagnostic group	Sub-group										
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**0.91**	**0.90-0.93**	**0.83**	**0.81-0.85**	**0.79**	**0.77-0.80**	**0.77**	**0.74-0.79**	**0.75**	**0.73-0.77**
	a. Lymphoid leukemias	0.95	0.94-0.96	0.89	0.88-0.91	0.85	0.83-0.87	0.83	0.81-0.85	0.81	0.79-0.83
	b. Acute myeloid leukemias	0.73	0.68-0.78	0.56	0.50-0.61	0.52	0.46-0.57	0.51	0.45-0.57	0.50	0.44-0.55
	c. Chronic myeloproliferative disease*	0.95	0.70-0.99	0.89	0.63-0.97	0.76	0.48-0.90	0.63	0.36-0.81	0.63	0.36-0.81
II	**Lymphoma and reticuloendothelial neoplasms**	**0.91**	**0.89-0.93**	**0.85**	**0.82-0.88**	**0.83**	**0.80-0.86**	**0.82**	**0.78-0.85**	**0.81**	**0.77-0.84**
	a. Hodgkin lymphomas	1.00	0.97-1.00	0.94	0.90-0.96	0.93	0.88-0.95	0.91	0.86-0.94	0.89	0.84-0.93
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	0.88	0.82-0.92	0.78	0.71-0.83	0.75	0.69-0.81	0.74	0.67-0.80	0.72	0.64-0.78
	c. Burkitt lymphoma	0.84	0.75-0.90	0.84	0.75-0.90	0.84	0.75-0.90	0.84	0.75-0.90	0.84	0.75-0.90
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**0.84**	**0.82-0.86**	**0.73**	**0.70-0.75**	**0.69**	**0.66-0.71**	**0.67**	**0.64-0.70**	**0.65**	**0.62-0.68**
	a. Ependymoma and choroid plexus tumour	0.84	0.76-0.89	0.62	0.52-0.71	0.51	0.41-0.60	0.48	0.38-0.58	0.43	0.32-0.53
	b. Astrocytomas	0.84	0.81-0.86	0.76	0.72-0.79	0.74	0.71-0.77	0.74	0.70-0.77	0.73	0.69-0.76
	c. Intracranial and intraspinal embryonal tumours	0.81	0.76-0.85	0.60	0.53-0.65	0.51	0.45-0.57	0.47	0.40-0.53	0.45	0.38-0.51
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**0.88**	**0.84-0.90**	**0.71**	**0.66-0.75**	**0.64**	**0.59-0.68**	**0.62**	**0.57-0.67**	**0.61**	**0.56-0.66**
	a. Neuroblastoma and ganglioneuroblastoma	0.88	0.84-0.90	0.71	0.66-0.75	0.64	0.59-0.68	0.62	0.56-0.66	0.61	0.56-0.66
V	**Retinoblastoma**	**0.99**	**0.95-1.00**	**0.98**	**0.94-0.99**	**0.98**	**0.94-0.99**	**0.98**	**0.94-0.99**	**0.98**	**0.94-0.99**
VI	**Renal tumours**	**0.99**	**0.96-0.99**	**0.91**	**0.87-0.94**	**0.90**	**0.86-0.92**	**0.89**	**0.85-0.92**	**0.89**	**0.84-0.92**
	a. Nephroblastoma and other nonepithelial renal tumours	0.99	0.97-1.00	0.91	0.87-0.94	0.90	0.86-0.93	0.89	0.85-0.92	0.89	0.84-0.92
VII	**Hepatic tumours**	**0.74**	**0.64-0.82**	**0.65**	**0.54-0.74**	**0.63**	**0.52-0.72**	**0.63**	**0.52-0.72**	**0.63**	**0.52-0.72**
VIII	**Malignant bone tumours**	**0.90**	**0.86-0.93**	**0.71**	**0.65-0.76**	**0.63**	**0.57-0.69**	**0.62**	**0.56-0.68**	**0.60**	**0.53-0.66**
	a. Osteosarcomas	0.89	0.82-0.93	0.72	0.64-0.79	0.63	0.54-0.71	0.62	0.52-0.70	0.59	0.50-0.67
	b. Ewing tumour and related sarcomas of bone	0.92	0.85-0.95	0.68	0.59-0.75	0.63	0.54-0.70	0.62	0.52-0.70	0.59	0.49-0.67
IX	**Soft tissue and other extraosseous sarcomas**	**0.90**	**0.86-0.93**	**0.76**	**0.71-0.80**	**0.72**	**0.67-0.76**	**0.71**	**0.66-0.76**	**0.70**	**0.64-0.75**
	a. Rhabdomyosarcomas	0.92	0.86-0.95	0.79	0.72-0.85	0.74	0.66-0.80	0.73	0.65-0.79	0.70	0.62-0.78
X	**Germ cell tumours, trophoblastic tumours, and neoplasms of gonads**	**0.96**	**0.91-0.98**	**0.88**	**0.82-0.92**	**0.86**	**0.79-0.90**	**0.85**	**0.78-0.90**	**0.85**	**0.78-0.90**
	d. Gonadal carcinomas	0.97	0.88-0.99	0.93	0.83-0.97	0.91	0.80-0.96	0.91	0.80-0.96	0.91	0.80-0.96
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**0.95**	**0.88-0.98**	**0.90**	**0.82-0.94**	**0.87**	**0.79-0.92**	**0.85**	**0.76-0.91**	**0.83**	**0.73-0.90**
	b. Thyroid carcinomas	1.00		1.00		1.00		1.00		0.96	0.71-0.99
	d. Malignant melanomas	0.83	0.57-0.94	0.62	0.34-0.81	0.53	0.25-0.74	0.53	0.25-0.74	0.53	0.25-0.74
XII	**Other unspecified malignant neoplasms**	**0.80**	**0.66-0.89**	**0.69**	**0.53-0.80**	**0.64**	**0.48-0.76**	**0.61**	**0.45-0.74**	**0.61**	**0.45-0.74**

OSP = overall survival proportion; CI = confidence interval; CNS = central nervous system
*Including chronic myeloid leukemia

Exhibit 4.3

In the first 5 years following diagnosis, retinoblastoma and thyroid cancer had the highest survival proportions, with 100% of children diagnosed with thyroid cancer and 98% of children diagnosed with retinoblastoma surviving for 5 years. In contrast, children diagnosed with acute myeloid leukemia, ependymoma, intracranial and intraspinal tumours, CNS tumours or malignant melanoma experienced the worst survival 5 years following diagnosis, ranging from 51% to 53% (although the survival of those children diagnosed with malignant melanoma should be interpreted with caution owing to the small number of diagnoses and evidenced by the large confidence interval).

As expected, the overall survival proportion declines as longer follow up periods are considered. Overall, in this cohort, 1 year OSP was 0.90 and 10 year OSP was 0.73. The largest declines are in the early period, with a 14% decline in the first 5 years following diagnosis and then only a 3% decline from 5 years up to 10 years after diagnosis. Longer follow up will be important because some studies show continuing deviation of mortality rates for survivors from those of normative populations.[26,27]

For most cancer diagnoses, this stability in survival from 5 to 10 years post diagnosis holds, with decreases in OSP ranging from 0% to 6%, with the exception of chronic myeloid leukemia, which had the largest decline in OSP from 5 to 10 years (13%), followed by ependymoma, which had an 8% decline in the same period.

EXHIBIT 4.4: **5 year overall survival proportions by period and diagnosis, age 0–14 years, in Ontario, 1985–2004**

		Year of diagnosis									
		All years		1985–1989		1990–1994		1995–1999		2000–2004	
		OSP	95% CI	OSP	95% CI	OSP	95% CI	OSP	95% CI	OSP	95% CI
	Overall	**0.76**	**0.75-0.77**	**0.69**	**0.64-0.73**	**0.74**	**0.72-0.76**	**0.77**	**0.75-0.78**	**0.80**	**0.78-0.82**
Diagnostic group	Sub-group										
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**0.79**	**0.77-0.80**	**0.72**	**0.64-0.79**	**0.77**	**0.73-0.80**	**0.78**	**0.74-0.81**	**0.84**	**0.81-0.87**
	a. Lymphoid leukemias	0.85	0.83-0.87	0.78	0.68-0.86	0.84	0.80-0.87	0.85	0.81-0.88	0.89	0.86-0.92
	b. Acute myeloid leukemias	0.52	0.46-0.57	0.42	0.26-0.57	0.40	0.29-0.50	0.54	0.44-0.62	0.67	0.56-0.76
	c. Chronic myeloproliferative disease*†	0.76	0.48-0.90	—		—		—		—	
II	**Lymphoma and reticuloendothelial neoplasms**	**0.83**	**0.80-0.86**	**0.8**	**0.70-0.87**	**0.82**	**0.75-0.87**	**0.84**	**0.78-0.89**	**0.86**	**0.80-0.90**
	a. Hodgkin lymphomas	0.93	0.88-0.95	0.93	0.77-0.98	0.90	0.79-0.95	0.93	0.85-0.97	0.94	0.86-0.98
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	0.75	0.69-0.81	0.68	0.48-0.82	0.74	0.60-0.84	0.78	0.66-0.87	0.78	0.67-0.86
	c. Burkitt lymphoma	0.84	0.75-0.90	0.62	0.38-0.79	0.92	0.73-0.98	0.84	0.60-0.94	0.88	0.73-0.95
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**0.69**	**0.66-0.71**	**0.51**	**0.38-0.62**	**0.68**	**0.63-0.72**	**0.70**	**0.66-0.74**	**0.72**	**0.67-0.76**
	a. Ependymoma and choroid plexus tumour	0.51	0.41-0.60	0.56	0.31-0.75	0.45	0.28-0.60	0.53	0.33-0.70	0.55	0.37-0.69
	b. Astrocytomas	0.74	0.71-0.77	0.68	0.58-0.76	0.74	0.67-0.79	0.74	0.68-0.79	0.79	0.73-0.84
	c. Intracranial and intraspinal embryonal tumours	0.51	0.45-0.57	0.16	0.00-0.60	0.46	0.34-0.57	0.52	0.41-0.62	0.57	0.46-0.66
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**0.64**	**0.59-0.68**	**0.59**	**0.47-0.69**	**0.61**	**0.51-0.69**	**0.70**	**0.61-0.77**	**0.67**	**0.59-0.75**
	a. Neuroblastoma and ganglioneuroblastoma	0.64	0.59-0.68	0.59	0.47-0.70	0.6	0.51-0.69	0.69	0.60-0.77	0.67	0.58-0.75
V	**Retinoblastoma**	**0.98**	**0.94-0.99**	**0.95**	**0.72-0.99**	**0.97**	**0.84-1.00**	**1.00**		**0.98**	**0.88-1.00**
VI	**Renal tumours**	**0.90**	**0.86-0.92**	**0.85**	**0.71-0.93**	**0.94**	**0.88-0.98**	**0.86**	**0.78-0.91**	**0.91**	**0.84-0.95**
	a. Nephroblastoma and other nonepithelial renal tumours	0.90	0.86-0.93	0.84	0.70-0.92	0.95	0.89-0.98	0.86	0.78-0.92	0.92	0.84-0.96
VII	**Hepatic tumours†**	**0.63**	**0.52-0.72**	—		**0.59**	**0.37-0.76**	**0.59**	**0.38-0.74**	**0.75**	**0.55-0.87**
VIII	**Malignant bone tumours**	**0.63**	**0.57-0.69**	**0.60**	**0.43-0.73**	**0.62**	**0.50-0.72**	**0.69**	**0.59-0.78**	**0.63**	**0.53-0.72**
	a. Osteosarcomas	0.63	0.54-0.71	0.74	0.55-0.86	0.56	0.39-0.69	0.66	0.50-0.78	0.65	0.49-0.77
	b. Ewing tumour and related sarcomas of bone	0.63	0.54-0.70	0.33	0.12-0.56	0.68	0.49-0.82	0.70	0.55-0.81	0.61	0.46-0.73
IX	**Soft tissue and other extraosseous sarcomas**	**0.72**	**0.67-0.76**	**0.69**	**0.53-0.81**	**0.66**	**0.55-0.75**	**0.68**	**0.59-0.76**	**0.79**	**0.71-0.85**
	a. Rhabdomyosarcomas	0.74	0.66-0.80	0.75	0.51-0.88	0.67	0.51-0.79	0.76	0.61-0.85	0.79	0.65-0.88
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**0.86**	**0.79-0.90**	**0.81**	**0.61-0.92**	**0.77**	**0.60-0.88**	**0.90**	**0.77-0.96**	**0.89**	**0.78-0.95**
	d. Gonadal carcinomas†	0.91	0.80-0.96	—		1.00		0.95	0.75-0.99	0.83	0.63-0.92
XI	**Other malignant epithelial neoplasms and malignant melanomas†**	**0.87**	**0.79-0.92**	—		**0.75**	**0.52-0.88**	**0.86**	**0.61-0.95**	**0.92**	**0.81-0.97**
	b. Thyroid carcinomas†	1.00		—		1.00		1.00		1.00	
	d. Malignant melanomas†	0.53	0.25-0.74	—		—		—		—	
XII	**Other unspecified malignant neoplasms**	**0.64**	**0.48-0.76**	**0.58**	**0.17-0.84**	**0.62**	**0.30-0.83**	**0.73**	**0.47-0.87**	**0.55**	**0.28-0.76**

OSP = overall survival proportion; CI = confidence interval; CNS = central nervous system
*Including chronic myeloid leukemia
†Because of small sample sizes, rates are not provided for 5 year periods.

Exhibit 4.4

Overall, between 1985 and 2004, the 5 year survival proportions for patients aged 0–14 years increased from 69% to 80%, reflecting an 11% overall increase in survival over the 20 year period. Specifically, from 1985 to 1989 the survival rate was 69%, for 1990–1994 it was 74%, for 1995–1995 it was 77% and for 2000–2004 it was 80%.

Much of the overall improved survival has been driven by survival improvements in leukemia (12% increase in survival), lymphoma (6% increase) and CNS tumours (21% increase). These 3 major diagnostic groups represent the largest proportion of childhood cancer diagnoses. The other major diagnostic groups had an average increase in survival of 5% (range: –3% to 10%) over the 20 year period, far below increases seen in the major leukemia, lymphoma and CNS diagnostic groups.

Although acute lymphoblastic leukemia had a 12% increase in survival over the 20 year period, acute myeloid leukemia had a 25% increase in survival over the same period, most likely as a result of advances in treatments and supportive care[28] and the low OSP at the start of the period.

Within the lymphoma group, Hodgkin lymphoma had only a 1% increase in survival over the 20 year period, while non-Hodgkin and Burkitt lymphoma had 10% and 26% increases, respectively. Note that there is a potential ceiling effect when considering the high OSP for Hodgkin lymphoma at the start of the 20 year period and the comparably lower OSP for non-Hodgkin and Burkitt lymphoma.

Over the 20 year period, survival proportions for retinoblastoma remained the highest of all childhood cancer diagnoses, with an overall survival rate of 98%, which remained relatively unchanged across the period.

With the exception of the "Other" major diagnostic category, bone cancers had the lowest overall survival at 63% in the latest period (2000–2004) with little progress in survival over the 20 year period.

EXHIBIT 4.5: **Event free survival proportion and survival duration by diagnosis, age 0–14 years, in Ontario, 1995–2004**

Diagnostic group	Sub-group	Proportion event free survival									
		1 year		3 year		5 year		7 year		10 year	
		EFSP	95% CI	EFSP	95% CI	EFSP	95% CI	EFSP	95% CI	EFSP	95% CI
	Overall	**0.86**	**0.85-0.87**	**0.75**	**0.73-0.76**	**0.70**	**0.69-0.72**	**0.68**	**0.67-0.67**	**0.67**	**0.66-0.69**
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**0.89**	**0.87-0.91**	**0.79**	**0.76-0.81**	**0.71**	**0.68-0.74**	**0.69**	**0.66-0.72**	**0.68**	**0.65-0.71**
	a. Lymphoid leukemias	0.94	0.92-0.95	0.86	0.83-0.88	0.77	0.74-0.80	0.75	0.72-0.77	0.74	0.71-0.77
	b. Acute myeloid leukemias	0.68	0.61-0.75	0.54	0.46-0.60	0.50	0.43-0.57	0.49	0.42-0.56	0.49	0.41-0.56
	c. Chronic myeloproliferative disease*	0.89	0.40-0.98	0.68	0.24-0.90	0.68	0.24-0.90	0.60	0.22-0.84	0.60	0.22-0.84
II	**Lymphoma and reticuloendothelial neoplasms**	**0.84**	**0.80-0.88**	**0.77**	**0.72-0.81**	**0.74**	**0.70-0.79**	**0.74**	**0.69-0.78**	**0.73**	**0.68-0.77**
	a. Hodgkin lymphomas	0.92	0.85-0.95	0.85	0.78-0.90	0.84	0.77-0.89	0.84	0.77-0.89	0.83	0.76-0.88
	b. Non-Hodgkin (except Burkitt lymphoma)	0.82	0.74-0.88	0.72	0.64-0.79	0.70	0.61-0.77	0.68	0.59-0.75	0.67	0.57-0.74
	c. Burkitt lymphoma	0.85	0.73-0.92	0.85	0.73-0.92	0.85	0.73-0.92	0.85	0.73-0.92	0.83	0.70-0.91
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**0.81**	**0.78-0.83**	**0.70**	**0.66-0.73**	**0.65**	**0.62-0.69**	**0.63**	**0.59-0.66**	**0.61**	**0.57-0.64**
	a. Ependymoma and choroid plexus tumour	0.77	0.64-0.86	0.53	0.39-0.65	0.49	0.35-0.61	0.40	0.28-0.53	0.40	0.28-0.53
	b. Astrocytomas	0.82	0.78-0.86	0.75	0.70-0.79	0.72	0.67-0.76	0.70	0.65-0.74	0.67	0.63-0.72
	c. Intracranial and intraspinal embryonal tumours	0.74	0.67-0.80	0.54	0.47-0.62	0.47	0.40-0.55	0.45	0.37-0.53	0.44	0.37-0.52
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**0.84**	**0.79-0.88**	**0.64**	**0.58-0.70**	**0.62**	**0.56-0.68**	**0.61**	**0.55-0.67**	**0.61**	**0.54-0.67**
	a. Neuroblastoma and ganglioneuroblastoma	0.84	0.78-0.88	0.64	0.57-0.69	0.62	0.55-0.68	0.61	0.54-0.67	0.60	0.54-0.66
V	**Retinoblastoma**	**1.00**		**0.97**	**0.90-0.99**	**0.92**	**0.84-0.96**	**0.92**	**0.84-0.96**	**0.92**	**0.84-0.96**
VI	**Renal tumours**	**0.89**	**0.84-0.93**	**0.79**	**0.72-0.84**	**0.78**	**0.72-0.83**	**0.77**	**0.71-0.83**	**0.77**	**0.71-0.83**
	a. Nephroblastoma and other nonepithelial renal tumours	0.90	0.84-0.93	0.79	0.72-0.84	0.78	0.72-0.84	0.77	0.70-0.83	0.77	0.70-0.83
VII	**Hepatic tumours**	**0.76**	**0.62-0.85**	**0.66**	**0.51-0.76**	**0.63**	**0.49-0.75**	**0.63**	**0.49-0.75**	**0.63**	**0.49-0.75**
VIII	**Malignant bone tumours**	**0.88**	**0.82-0.92**	**0.63**	**0.55-0.70**	**0.58**	**0.50-0.65**	**0.56**	**0.48-0.63**	**0.53**	**0.46-0.61**
	a. Osteosarcomas	0.87	0.76-0.93	0.61	0.50-0.71	0.56	0.44-0.66	0.52	0.40-0.63	0.50	0.39-0.61
	b. Ewing tumour and related sarcomas of bone	0.89	0.79-0.94	0.62	0.51-0.71	0.57	0.46-0.67	0.56	0.45-0.65	0.53	0.42-0.63
IX	**Soft tissue and other extraosseous sarcomas**	**0.86**	**0.81-0.90**	**0.69**	**0.63-0.75**	**0.68**	**0.61-0.73**	**0.67**	**0.60-0.73**	**0.66**	**0.60-0.72**
	a. Rhabdomyosarcomas	0.89	0.81-0.94	0.71	0.61-0.79	0.69	0.58-0.77	0.68	0.57-0.76	0.66	0.55-0.75
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**0.93**	**0.87-0.97**	**0.87**	**0.80-0.92**	**0.85**	**0.77-0.91**	**0.85**	**0.77-0.91**	**0.85**	**0.77-0.91**
	d. Gonadal carcinomas	0.89	0.76-0.95	0.85	0.71-0.92	0.85	0.71-0.92	0.85	0.71-0.92	0.85	0.71-0.92
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**0.91**	**0.82-0.96**	**0.84**	**0.73-0.90**	**0.82**	**0.71-0.89**	**0.77**	**0.64-0.85**	**0.74**	**0.61-0.84**
	b. Thyroid carcinomas	0.96	0.77-0.99	0.88	0.68-0.96	0.88	0.68-0.96	0.88	0.68-0.96	0.83	0.61-0.94
	d. Malignant melanomas	0.86	0.32-0.98	0.56	0.08-0.87	0.56	0.08-0.87	0.56	0.08-0.87	0.56	0.08-0.87
XII	**Other unspecified malignant neoplasms**	**0.82**	**0.64-0.91**	**0.69**	**0.51-0.82**	**0.60**	**0.41-0.74**	**0.56**	**0.38-0.71**	**0.56**	**0.38-0.71**

EFSP = event free survival proportion; CI = confidence interval; CNS = central nervous system
Note: EFSP is the length of time between the date of diagnosis and progression or relapse or second malignancy or death.
*Including chronic myeloid leukemia

Exhibit 4.5

Event free survival proportion (EFSP) was defined as the period between the date of diagnosis and the date of either relapse, the development of a second malignancy in childhood (diagnosed at a POGO affiliated centre) or death, whichever occurred first. Some limitations apply to this information, typical of registry data. In particular, disease progression is difficult to capture, is not contained in the POGONIS database and is thus not considered. However, disease progression applies to a small proportion of patients. Additionally, the capture of second cancers is limited to those identified in the pediatric age range, reflecting a significant underestimate since latency times for second solid tumours are long. Finally, late relapse beyond the pediatric age range is not available and thus is not considered. Readers should exercise appropriate caution when interpreting this table.

Overall, 10 years after a cancer diagnosis, 67% of children in this cohort remain event free. The biggest decline occurs within the first year after the diagnosis of cancer, where the EFSP is 86%. Children diagnosed with retinoblastoma experienced the highest 10 year EFSP at 92%, while those with ependymoma experienced the lowest 10 year EFSP at 40%.

In the first year after diagnosis, those diagnosed with acute myeloid leukemia experienced the highest proportion of events, with a 1 year EFSP of 68%.

EXHIBIT 4.6: **Overall survival proportions by selected survival durations among patients who relapsed by diagnosis, age 0–14 years, in Ontario, 1995–2004**

		Proportion overall survival from first relapse					
		1 year		3 year		5 year	
		OSP	95% CI	OSP	95% CI	OSP	95% CI
	Overall	**0.62**	**0.58-0.65**	**0.42**	**0.38-0.46**	**0.39**	**0.35-0.43**
Diagnostic group	Sub-group						
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**0.59**	**0.52-0.65**	**0.43**	**0.37-0.50**	**0.41**	**0.35-0.48**
	a. Lymphoid leukemias	0.68	0.60-0.75	0.50	0.43-0.58	0.48	0.40-0.56
	b. Acute myeloid leukemias	0.37	0.25-0.49	0.25	0.15-0.37	0.23	0.13-0.34
	c. Chronic myeloproliferative disease*†	—		—		—	
II	**Lymphoma and reticuloendothelial neoplasms**	**0.63**	**0.50-0.74**	**0.51**	**0.38-0.62**	**0.46**	**0.33-0.58**
	a. Hodgkin lymphoms	0.73	0.47-0.88	0.59	0.35-0.77	0.42	0.20-0.63
	b. Non-Hodgkin (except Burkitt lymphoma)	0.55	0.35-0.71	0.41	0.24-0.58	0.41	0.24-0.58
	c. Burkitt lymphoma*†	—		—		—	
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**0.61**	**0.52-0.69**	**0.40**	**0.32-0.49**	**0.38**	**0.30-0.46**
	a. Ependymoma and choroid plexus tumour	0.68	0.43-0.84	0.26	0.10-0.45	0.14	0.03-0.32
	b. Astrocytomas	0.70	0.54-0.81	0.65	0.50-0.77	0.65	0.50-0.77
	c. Intracranial and intraspinal embryonal tumours	0.42	0.28-0.56	0.11	0.04-0.21	0.08	0.02-0.18
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**0.54**	**0.40-0.66**	**0.22**	**0.12-0.34**	**0.14**	**0.06-0.24**
	a. Neuroblastoma and ganglioneuroblastoma	0.55	0.41-0.67	0.22	0.12-0.35	0.14	0.06-0.24
V	**Retinoblastoma†**	—		—		—	
VI	**Renal tumours**	**0.79**	**0.61-0.89**	**0.59**	**0.41-0.73**	**0.53**	**0.35-0.68**
	a. Nephroblastoma and other nonepithelial renal tumours	0.81	0.62-0.91	0.59	0.41-0.74	0.54	0.35-0.69
VII	**Hepatic tumours†**	—		—		—	
VIII	**Malignant bone tumours**	**0.55**	**0.39-0.69**	**0.26**	**0.14-0.40**	**0.26**	**0.14-0.40**
	a. Osteosarcomas	0.73	0.50-0.87	0.34	0.16-0.52	0.34	0.16-0.52
	b. Ewing tumour and related sarcomas of bone	0.31	0.12-0.52	0.15	0.03-0.34	0.15	0.03-0.34
IX	**Soft tissue and other extraosseous sarcomas**	**0.72**	**0.53-0.84**	**0.40**	**0.24-0.56**	**0.40**	**0.24-0.56**
	a. Rhabdomyosarcomas	0.81	0.51-0.94	0.38	0.16-0.60	0.38	0.16-0.60
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**0.62**	**0.26-0.85**	**0.36**	**0.09-0.65**	**0.36**	**0.09-0.65**
	d. Gonadal carcinomas†	—		—		—	
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**0.80**	**0.41-0.95**	**0.71**	**0.35-0.90**	**0.71**	**0.35-0.90**
	b. Thyroid carcinomas†	—		—		—	
	d. Malignant melanomas†	—		—		—	
XII	**Other unspecified malignant neoplasms†**	—		—		—	

OSP = overall survival proportion; CI = confidence interval; CNS = central nervous system
*Including chronic myeloid leukemia
†Diagnostic groups or subgroups with 5 or fewer relapses have been suppressed.

Exhibit 4.6

Exhibit 4.6 describes the OSP by diagnosis group among those who relapsed and effectively describes the efficacy of salvage therapy in terms of success and durability of treatment for relapse salvage. One year OSP is 60% or more among those with relapsed acute lymphoblastic leukemia, Hodgkin lymphoma, astrocytoma, nephroblastoma, osteosarcoma and rhabdomyosarcoma. However, OSP at 5 years is much less encouraging and remains at less than 60% for all of these malignancies, although 3 year OSP is 50% (95% CI: 43–58%) for acute lymphoblastic leukemia, 59% (95% CI: 35–77%) for Hodgkin lymphoma, 65% (95% CI: 50–77%) for astrocytoma, 59% (95% CI: 41–74%) for nephroblastoma and 38% (95% CI: 16–60%) for rhabdomyosarcoma. Particularly poor 3 and 5 year OSP (less than 20–25%) was seen for children with relapsed acute myeloid leukemia, intracranial and intraspinal CNS tumours, neuroblastoma and Ewing sarcoma, reflecting disease refractory to available treatments.

EXHIBIT 4.7: **5 year overall survival proportions by linkage status and diagnosis, age 0–14 years, in Ontario, 1985–1989**

		Proportion survived					
		All subjects (assumes survival if not linked)		Linked only (removes those who did not link)		Assumed dead (if not linked, assumed died at 2.5 years after diagnosis)	
		OSP	95% CI	OSP	95% CI	OSP	95% CI
	Overall	**0.72**	**0.68-0.76**	**0.69**	**0.64-0.73**	**0.61**	**0.57-0.66**
Diagnostic group	Sub-group						
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**0.74**	**0.66-0.81**	**0.72**	**0.64-0.79**	**0.67**	**0.59-0.74**
	a. Lymphoid leukemias	0.80	0.70-0.87	0.78	0.68-0.86	0.73	0.63-0.81
	b. Acute myeloid leukemias	0.43	0.27-0.58	0.42	0.26-0.57	0.40	0.24-0.56
	c. Chronic myeloproliferative disease*†	—		—		—	
II	**Lymphoma and reticuloendothelial neoplasms**	**0.83**	**0.74-0.89**	**0.80**	**0.70-0.87**	**0.65**	**0.52-0.75**
	a. Hodgkin lymphomas	0.94	0.80-0.98	0.93	0.77-0.98	0.83	0.62-0.93
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	0.73	0.54-0.85	0.68	0.48-0.82	0.55	0.33-0.73
	c. Burkitt lymphoma	0.69	0.46-0.84	0.62	0.38-0.79	0.39	0.17-0.60
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**0.58**	**0.46-0.68**	**0.51**	**0.38-0.62**	**0.46**	**0.34-0.57**
	a. Ependymoma and choroid plexus tumour	0.58	0.34-0.76	0.56	0.31-0.75	0.58	0.34-0.76
	b. Astrocytomas	0.72	0.62-0.79	0.68	0.58-0.76	0.57	0.46-0.67
	c. Intracranial and intraspinal embryonal tumours	0.16	0.00-0.60	0.16	0.00-0.60	0.16	0.00-0.60
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**0.62**	**0.50-0.71**	**0.59**	**0.47-0.69**	**0.54**	**0.42-0.64**
	a. Neuroblastoma and ganglioneuroblastoma	0.62	0.50-0.72	0.59	0.47-0.70	0.54	0.42-0.64
V	**Retinoblastoma**	**0.96**	**0.76-0.99**	**0.95**	**0.72-0.99**	**0.83**	**0.57-0.94**
VI	**Renal tumours**	**0.87**	**0.74-0.94**	**0.85**	**0.71-0.93**	**0.72**	**0.57-0.83**
	a. Nephroblastoma and other nonepithelial renal tumours	0.87	0.74-0.93	0.84	0.70-0.92	0.71	0.56-0.82
VII	**Hepatic tumours†**	—		—		—	
VIII	**Malignant bone tumours**	**0.64**	**0.48-0.76**	**0.60**	**0.43-0.73**	**0.52**	**0.36-0.66**
	a. Osteosarcomas	0.76	0.58-0.87	0.74	0.55-0.86	0.65	0.45-0.79
	b. Ewing tumour and related sarcomas of bone	0.41	0.18-0.63	0.33	0.12-0.56	0.28	0.10-0.50
IX	**Soft tissue and other extraosseous sarcomas**	**0.73**	**0.57-0.83**	**0.69**	**0.53-0.81**	**0.63**	**0.46-0.75**
	a. Rhabdomyosarcomas	0.76	0.53-0.89	0.75	0.51-0.88	0.76	0.53-0.89
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**0.84**	**0.66-0.93**	**0.81**	**0.61-0.92**	**0.74**	**0.53-0.87**
	d. Gonadal carcinomas†	—		—		—	
XI	**Other malignant epithelial neoplasms and malignant melanomas†**	—		—		—	
	b. Thyroid carcinomas†	—		—		—	
	d. Malignant melanomas†	—		—		—	
XII	**Other unspecified malignant neoplasms**	**0.73**	**0.38-0.91**	**0.58**	**0.17-0.84**	**0.46**	**0.08-0.78**

OSP = overall survival proportion; CI = confidence interval; CNS = central nervous system
*Including chronic myeloid leukemia
†Because of small sample sizes, rates are not provided for 5 year periods.

APPENDIX 4.1: **Graphical representation of actual, cohort, complete and period survival methods**

		Follow up year										
	Diagnosis year	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Actual	1997						1	1/2	2/3	3/4	4/5	5
Cohort	1992	1	1/2	2/3	3/4	4/5	5					
Complete	1992	1	1/2	2/3	3/4	4/5	5					
	1993		1	1/2	2/3	3/4	4/5					
	1994			1	1/2	2/3	3/4					
	1995				1	1/2	2/3					
	1996					1	1/2					
	1997						1					
Period	1992						5					
	1993						4/5					
	1994						3/4					
	1995						2/3					
	1996						1/2					
	1997						1					

Summary

Over a 20 year period, age standardized mortality among children aged 0–14 years diagnosed with cancer in Ontario has decreased from 42.76 to 27.86 per million population per year, a 35% decrease. Still, in 2004, nearly 1 in 5 children diagnosed with cancer in Ontario would not survive 5 years after their diagnosis.

Differences in survival by specific diagnosis exist. For example, children diagnosed with retinoblastoma experience low mortality and excellent long term survival compared with children diagnosed with acute myeloid leukemia, who have high mortality and poor long term survival.

Sustained survival beyond the first 5 years from diagnosis is evident in most cancer diagnostic groups, supporting the standard presentation of 5 year overall survival proportions in many publications. Still, decreases after this point are noted and further work needs to be undertaken that compares the relative survival of children with cancer to similar children not diagnosed with cancer.

Children who relapse generally experience low survival rates, although some disease groups experience better survival than others. Clearly, further research to improve survival in these children with poor prognosis is urgently needed. Minimizing relapse rates with initial treatment is critical, with a further focus on optimizing outcomes for those who do relapse.

The pattern of survival over the past 20 years among children diagnosed with cancer is encouraging. Continued advances in treatments and care are targeted at improving survival, but as the survival proportion continues to climb, a ceiling effect will occur and the rate of improvement is likely to decline. Only continued surveillance will detect rates of change and determine the true long term impact of a childhood cancer diagnosis.

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