Atlas of Childhood Cancer in Ontario

1985-2004

POGO
PEDIATRIC ONCOLOGY GROUP OF ONTARIO

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PEDIATRIC ONCOLOGY GROUP OF ONTARIO

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PREFACE

When the concept of a provincial pediatric oncology group emerged in 1983 from discussions held in the attic of Ronald McDonald House in Toronto, the primary objective was deceptively simple: to ensure that every child with cancer in the vast Province of Ontario would have equal access to optimal care. Those of us present at that time had only a modest understanding of the challenges that lay ahead. Over the subsequent 3 decades, the Pediatric Oncology Group of Ontario (POGO) has grown into a sophisticated and highly professional organization with a $10 million annual budget, but the original objective has remained the cornerstone of our mission and vision, and the constant motivator to strive for that achievement.

Although we are justly proud of and enjoy the many fruits of our labours over more than 30 years, we have come to recognize the complexity inherent in the spectrum of cancer control in childhood and adolescence. This complexity has demanded investment in a broad array of endeavours that have contributed to the attainment of the principal goal, endeavours as disparate as these:

- The Pediatric Oncology Family Assistance Program and the Successful Academic and Vocational Training Initiative for cognitively challenged survivors
- The satellite clinic network in community hospitals and the aftercare system for comprehensive long-term follow up
- The research unit, with its distinctive focal "pillars" (epidemiology, health services, economics and survivorship/quality of life)
- POGO's networked information system (POGONIS) – one of the real jewels in our crown

Indeed, POGONIS facilitated the leadership role that POGO played in the national Childhood Cancer Surveillance and Control Program of the Public Health Agency of Canada, that program being co-chaired for a decade by two founding members of POGO.

All of these continuing activities have enjoyed the support of our major partner, the Ministry of Health and Long-Term Care (MOHLTC). At the request of the Ministry, and building on the first-ever needs assessment of Ontario's children with cancer and their families (undertaken by POGO in 1988), long-range plans for childhood cancer control were submitted in 1994 and 2005. It is small wonder that POGO became the MOHLTC's official source of advice on pediatric oncology in 1995. Spurred by the early development of staffing ratios, accepted by the Ministry and by other jurisdictions in Canada and beyond, and generating additional support for infrastructural development, POGO has catalyzed some $200 million into health care services and related activities devoted to the primary goal. Being headquartered within walking distance of the seat of provincial government has not hindered the journey to this success!

It is no accident that POGO's offices are located within the Discovery District of Canada's largest city. POGO's research unit is led by our medical director, who holds the endowed POGO Chair in Childhood Cancer Control at the University of Toronto. The unit sustains a fellowship program, seed funding and open operating grants with considerable support from the Canadian Cancer Society's Ontario Division. The work of the research unit is underpinned by the rich resource embedded in POGONIS. Moreover,

after POGO incorporated as a not-for-profit entity and achieved charitable institutional status in 2003, it was accorded the designation of a "45.1 entity" under federal-provincial privacy legislation, allowing POGO to hold detailed health information on patients and linkage to administrative databases.

These developments have contributed importantly to a longstanding undertaking: the creation of the *Atlas of Childhood Cancer in Ontario* that unfolds on the following pages. It paints a comprehensive picture over a considerable timeframe (up to 20 years) of an ever-changing landscape, yet another claim to distinction marking POGO as truly one of a kind in the worldwide community of pediatric oncology.

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ABOUT THE ORGANIZATIONS INVOLVED IN THIS ATLAS

POGO

Pediatric Oncology Group of Ontario (POGO) is the official source of advice on childhood cancer to the Ministry of Health and Long-Term Care; a trusted source of information among colleagues, parents, survivors and the public; and the long-standing leader of a collaboration among 5 academic pediatric oncology programs and other stakeholders. The result is a highly integrated childhood cancer system that delivers equitable care, accessible to families living across Ontario's vast geography.

Informed by POGO's unique database, expert analyses and the input of thought leaders, POGO delivers advice, recommendations and strategies; ensures implementation of solutions; and provides ongoing support and updates for childhood cancer programs. Together, these contributions ensure the evolution of the childhood cancer care system in response to constantly changing demands. POGO's programs have been deployed nationally and internationally and its work is published in peer-reviewed journals.

POGO collaborators include policy experts, researchers, epidemiologists, pediatric oncology clinical leaders, parents, childhood cancer survivors, Ministry and other stakeholders.

POGO receives core funding from the Ministry of Health and Long-Term Care. An engaged and supportive donor base provides additional funding for POGO research and family shield services, and granting agencies support the work of a focused POGO Research Unit.

ICES

The Institute for Clinical Evaluative Sciences (ICES) leads cutting-edge studies that evaluate health care delivery and outcomes. This research results in an evidence base that is published as atlases, investigative reports and peer-reviewed papers, and is used to guide decision-making and inform changes in health care policy and delivery.

ICES researchers, many of whom are practicing clinicians, have access to a vast array of Ontario's health-related data, including population-based health surveys, anonymous patient records and clinical and administrative databases. ICES is recognized as an international leader in maintaining the privacy and security of health information.

ICES receives core funding from the Ontario Ministry of Health and Long-Term Care. In addition, ICES scientists compete for peer-reviewed grants from federal funding agencies, such as the Canadian Institutes of Health Research, and receive project-specific funding from provincial and national organizations. The knowledge that arises from this research is always produced independent of the funding bodies, which is critical to ICES' reputation as a trusted, impartial source of high-quality health and health services research and evidence.

Photo by Tynan Studio

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Introduction

Introduction

Childhood cancer is a rare disease, but one with enormous implications for the child, the family and the health care system. In our Ontario and Canadian jurisdictions, childhood cancer (defined as cancer occurring in the 0–14 year age range) constitutes less than one half of 1 percent of new cases of cancer.[1] Because it is rare, it is not often described in detail, and because it is perceived to have a small impact on health care systems, it garners little attention from policy- and decision-makers. Childhood cancer, however, has a double impact on the health care system. It contributes the largest number of disease related deaths in this age group, while simultaneously contributing among the largest numbers of years of life saved by cancer treatment in all age groups. The management of childhood cancer is complex, intensive and costly. This care is delivered primarily in tertiary care institutions and thus has significant incremental social and financial impact on families who reside outside of large cities.

Childhood cancer treatment is one of the big success stories of contemporary medicine, with survival rates escalating dramatically over the last decades of the 20TH century. But because of the intensity of the treatment, the young age of many of the families and the uncertain outcome of treatment in terms of both survival and potential effects of treatment, the influence of the diagnosis and treatment of childhood cancer on families is disproportionately severe.

The impact on the health care system is similarly significant, and the funding necessary to support appropriate diagnostic, therapeutic and rehabilitation interventions is substantial. Over the past few decades, it has become apparent that the need for resources and funding does not end when treatment ends. The late effects of treatment for childhood cancer are significant for a proportion of survivors.

This Atlas encompasses a 20 year timeframe, from January 1985 to December 2004. Much change occurred over this period in the format of treatment, the use of different modalities of therapy and with the introduction of routine use of hematopoietic stem cell transplantation. During this period, more systematic organization of childhood cancer services has been achieved and thus systematic data were attainable. It is recognized that practice has changed further since the end of the study period; those changes will be the subject of a subsequent analysis. Nevertheless, the mature data for this cohort and the analytic approach used provide a substantive insight into the patterns of incidence and survival and their relationship to health care utilization.

Why Do We Need an Atlas of Childhood Cancer?

Most publications addressing childhood cancer report the results of patients treated on clinical trials. Planned, successive clinical trials, each predicated on the results of a prior trial, are the principal reason for the dramatic improvement in survival in this population. However, they capture only that proportion of the population for whom a trial is open, who are eligible for that particular trial and whose parents consent to trial participation. Additionally, the endpoints of clinical trials most often do not encompass post treatment events. Thus the larger picture of childhood cancer in terms of health services and health policy is obscured.

Ontario is fortunate to have a database that has, since 1985, actively recorded comprehensive data on all children treated in the 5 tertiary centres offering childhood cancer care. These data have created a natural population-based cohort, with data spanning demographic, diagnostic, treatment and outcome information. In addition, the Pediatric Oncology Group of Ontario (POGO) was accorded special status under the Personal Health Information Protection Act that permits it to link its database to a variety of administrative and registry databases, enabling certainty with respect to long term outcomes and access to health service utilization information.

Thus a comprehensive view of incidence, survival and health service use became possible, and it forms the backbone of this Atlas – describing for the first time in detail the scope of childhood cancer and the implications of a population-based childhood cancer cohort on our publically funded single payer health care system.

The Structure of This Atlas

The first 5 chapters describe the sources of data, the incidence of childhood cancer over the 20 year time span encompassed in the Atlas, the survival patterns over that period and the health service utilization patterns over time for the cohort as a whole and for subsets of patients. These chapters focus on the entire childhood cancer cohort.

The next 5 chapters address data on the 5 most numerous cancers as classified in the International Classification of Childhood Cancer (2005). These chapters set the Ontario experience in the context of world literature of similar scope. Leukemia is numerically the largest group, and along with lymphoma, is the category that most typically does not use surgery as one of the primary therapeutic modalities. Central nervous system tumours are the second most numerous group and over time have come to use all 3 therapeutic modalities – surgery, chemotherapy and radiation therapy. The non–CNS solid tumour group encompass 2 categories for which sample size is sufficient to identify trends in incidence, treatment and outcome. The rarity of childhood cancer is reflected in the relatively small numbers assembled over 20 years in the most populous province in Canada.

It is our hope that this volume will stimulate discussion, debate, policy consideration and, above all, more research from epidemiologists, clinicians, policy-makers, administrators and economists – all in the interests of improving both the understanding of childhood cancer and the policy and health care system in which it is managed.

[1] Canadian Cancer Society/National Cancer Institute of Canada. Canadian cancer statistics 2008. Toronto: The Society; 2008.

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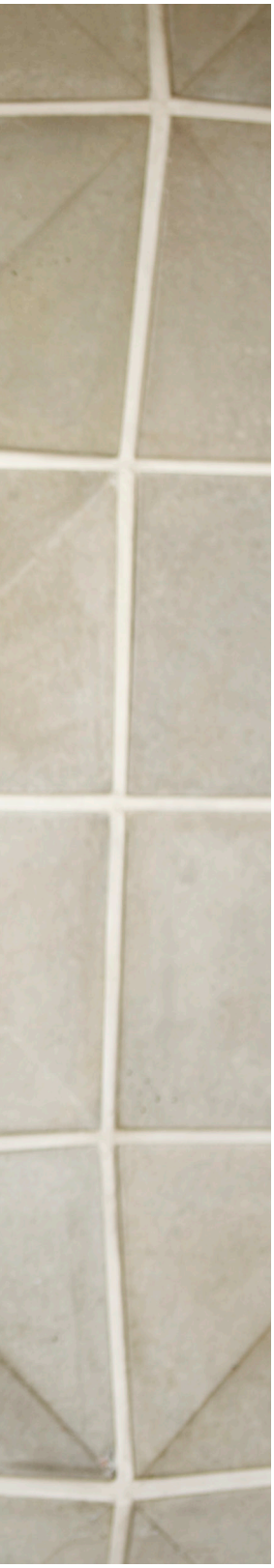

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POGONIS: Methods and Data Sources

Pediatric Oncology Group of Ontario Networked Information System (POGONIS)

History

In response to concern over published incidence rates of childhood cancer in Ontario, an early objective of the Pediatric Oncology Group of Ontario (POGO) was to clarify these rates.

A pediatric cancer registry, designed to record new incident cases by active registration, was created and began capturing data in 1985. The registry used a standardized paper registration form completed by a funded dedicated data manager in each tertiary care centre. Data elements were restricted to demographic and diagnostic information and were entered into a simple electronic database. Increased accuracy and specificity of diagnoses resulted. Comparison with the Ontario Cancer Registry revealed that a proportion of children were being treated at institutions other than the 5 pediatric tertiary centres.

In 1995, the data scope was extended to encompass key outcomes and standardized treatment information on all registered cases. The registry was converted to an electronic networked database, the Pediatric Oncology Group of Ontario Networked Information System (POGONIS). The system was developed in collaboration with Artificial Intelligence in Medicine Inc., a Canadian software engineering company with expertise in cancer informatics. POGONIS was structured as a relational database with meticulously defined data elements and architecture. The Ontario Ministry of Health and Long-Term Care financially supported the creation of POGONIS.

In 2008, POGONIS was reorganized as a patient/event driven model, enabling capture of key events in diagnosis, treatment and outcomes, including survival and other late effects, in a chronological record. The patient/event data model also provides specific data management tools that facilitate more timely, accurate and complete data capture.

The new POGONIS platform has enhanced functionality for retrieving and exporting data in various formats, which enhances inter-operability with other data management and analysis software systems, permitting increased utility for external researchers requesting data sets. POGONIS also provides enhanced management controls for data quality, accuracy and completeness and for data security to ensure compliance with provincial and federal privacy standards. Direct access to POGONIS is limited to a select group of authorized users and user actions. Any changes made in POGONIS are recorded in an audit log.

Between 2010 and 2013, POGO retrospectively collected treatment data not captured on the original cohort registered between 1985 and 1995. This effort was funded by operating grants from the Canadian Institutes of Health Research and the Canadian Cancer Society, Ontario Division. POGONIS now contains detailed demographic, diagnostic, treatment and outcome data for the entire cohort, starting in 1985, enhancing POGONIS's usefulness for the study of many population-based outcomes. The additional treatment data were not available for inclusion in this Atlas (hence all treatment information presented starts with diagnoses in 1995).

Prospective Data Collection

Funded, dedicated data managers/clinical research associates actively collect POGONIS-standardized data at each tertiary hospital using hospital chart review, internal hospital information systems and direct connections with the patient's health care team. The data are remotely entered into POGONIS via a virtual private network. POGONIS is physically housed on a dedicated server in the POGO office.

POGONIS also prospectively captures data on late effects for the population it encompasses. Although this component of the data is not used in this Atlas, the longitudinal commitment to the collection of expert-selected data elements and the data's availability

for research purposes make it a unique resource for studies of this population. These factors also create unique potential to improve both the care of future generations of childhood cancer patients and the ongoing care and quality of life of current patients and survivors and their families.

POGONIS Centralized Support

Beyond the physical hardware and information technology support required to operate POGONIS, POGO continues to provide oversight and resources for POGONIS, including the following:

- Clinical oversight, which ensures ongoing review and updating of all data element definitions, with resultant data standardization
- Continual (re)alignment of registration conventions to international cancer reporting schemas
- Continuity of the data via linkage to other databases to identify key events occurring either beyond the childhood age range or unrecorded in hospital charts, including death and development of subsequent primary cancers
- Ongoing knowledge transfer and education for data managers

Childhood Cancer Nomenclature and Classification System

A standardized system of tumour classification is at the heart of any cancer registry and is essential for the comparison of incidence and survival across countries and time periods. Classification systems for childhood cancers differ substantially from those used in adult cancer: the latter are anatomically classified, while the childhood classification is based on morphology of the tumour tissue.

Since its inception, POGONIS has used a common system for the classification of childhood cancer, based on morphology. As with all data elements in POGONIS, the classification system has been modified as needed as disease classifications have changed. Initially, POGONIS adopted the informal classification and nomenclature system developed internally by the former Childhood Cancer Study Group. The schema defined 10 diagnostic groups and assigned a 4 digit diagnosis code to each specific diagnosis. This classification system mapped onto other diagnostic schema, such as the one adopted by the International Agency for Research on Cancer and the subsequently developed International Classification of Childhood Cancer (ICCC).[1] The ICCC updated the widely used Birch and Marsden classification scheme to a schema defining 12 main diagnostic groups with multiple subgroups.[2] The ICCC first requires each tumour to be assigned to the appropriate International Classification of Diseases for Oncology (ICD-O) code,[3] after which the ICD-O codes are grouped into main and subgroups. In 2000, evolving diagnostic methods, including molecular, genetic and pathologic studies, prompted the development of the third edition of the ICD-O, which introduced numerous new morphology codes and revisions to the ICCC, now defined as ICCC-3.[4] POGONIS has adopted the ICCC-3 standard.

Data Quality

The accuracy and completeness of the data in a database, and the timeliness with which it is entered, can be measured and improved. The mechanisms POGO has in place to ensure the quality of the information stored in the POGONIS database are identified below.

Accuracy

- The standardized nomenclature and coding system for classification of childhood cancer entities is regularly adjusted to meet evolving standards for classification and is mapped to the ICCC system.
- POGONIS data are collected and entered only by designated data managers/clinical research associates, who are responsible for the collection, integrity, quality and transfer of data to POGONIS. POGO's senior database administrator provides this designated staff with detailed initial and ongoing training and support.

- Data managers are provided with written reference documents, policies and procedures to support their data gathering, entry and transfer responsibilities.
- Interactive and intelligent architecture with embedded data coding standards are in place to assist with option selection.
- A Data Quality Committee is in place to define the quantifiable measures for the evaluation of data quality and to report on the quality of the data in POGONIS.
- Random data audits are routinely conducted on a percentage of cases registered in POGONIS. Selective random re-verification is the preferred method for performing data audits. Such audit routines provide data quality surveillance by employing a variety of methodologies for identifying inaccuracies.
- POGO conducts annual comparison reviews of all registrations in POGONIS with Cancer Care Ontario's Cancer Registry under a data sharing agreement. These reviews assist in mutual data quality assurance.
- POGO routinely reviews specific disease events (e.g., relapses) and treatments (e.g., radiation) as a component of particular analytic projects. Algorithms have been written that specify mandatory correlations between treatment patterns and disease stage or clinical status. These reviews may reveal data that do not pass face validity tests and that therefore require data managers to re-verify the data against paper and electronic chart review.

The existing POGONIS structure and data policies and procedures are regularly reviewed to identify and introduce technical upgrades that will further enhance the data quality assessment process.

Completeness

The data managers/clinical research associates are responsible for ensuring the completeness of data transferred to POGO.

The POGO Data Quality Committee monitors the accuracy and completeness of the data by routinely identifying data fields with missing or improbable values. In POGONIS, data elements are organized within event-driven forms. For example, for a treatment event, there are forms for chemotherapy, surgery, radiation, bone marrow transplant, etc. Each form has required and optional data fields. On completion of a form, data managers are required to sign off on the form as complete, not applicable or pending completion. This step ensures that all required elements are entered for each form. Reports are generated to determine any errors or omissions and are provided to institutional data managers, along with a schedule of deadlines to populate the fields in which values are missing or corrections are required. In addition, embedded data edits identify fields with missing data elements, which are then brought to the attention of data managers.

Timeliness

Data on new incident cases, including demographic, diagnostic and an identified subset of treatment information, for each calendar year must be entered into POGONIS by March 31st of the following year.

Annual updates of information (diagnostic, treatment, outcome and service delivery) for each patient file are required by June 30th of the following year.

POGONIS Linkage with Other Data Sources

Under the *Ontario Personal Health Information Protection Act*, POGO is a "prescribed entity" and is authorized to collect, use and disclose personal health information (PHI) for the purposes of analysis or compiling of 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. PHI must be held, used and disclosed under the strict security specifications outlined and enforced by the office of Ontario's Information and Privacy Commissioner. POGO has created and operationalized detailed policies and procedures

that govern all aspects of the collection, use and disclosure of PHI. These are detailed in POGO's Privacy and Data Security Code and its Procedures.

Additionally, this designation permits POGO to establish linkages between POGONIS and other large designated administrative and purposed databases, creating the potential for more in-depth epidemiologic, outcome, service utilization and health economic studies than previously possible. Thus POGONIS's intrinsic potential can be amplified substantially by linkage to such databases as the Ontario Health Insurance Plan (OHIP) claims database, the Discharge Abstract Database (a record of all hospitalizations), the Registered Persons Database (which tracks eligibility for OHIP and related demographic data) and others.

To systematically capture deaths in the entire cohort regardless of location and age at death (specifically outside the pediatric period), death information is identified via annual record linkage to the Ontario Cancer Registry and the Ontario Registrar General Death File under a data sharing agreement with Cancer Care Ontario. This agreement also allows the identification of subsequent malignant neoplasms among the POGONIS cohort that develop after POGONIS patients have left the pediatric care system.

Potential Limitations of POGONIS

POGONIS is an active database, dependent on identification of all patients diagnosed and treated in pediatric hospitals. The capture of new cases in the 0–14 year age range has been cross validated against the Ontario Cancer Registry; the congruence is 98% in this age range.[5] By contrast, in the 15–19 year age range, completeness of ascertainment is substantially lower, with progressive decreases by successive years of age at diagnosis. On average POGONIS captures only 50% of patients diagnosed in this age range. This lower capture rate is the result of referral patterns in the community: older adolescents whom family practitioners suspect of having cancer are referred for diagnosis and treatment to adult cancer facilities. Accordingly, only the 0–14 years cohort is analyzed in this Atlas.

As indicated, classification of diseases in POGONIS follows the International Classification of Childhood Cancers, third edition.[4] This classification, updated in 2005, is related but not identical to the topography-based ICD-O 3 schema used for adult malignancies. Additionally, entities not included in ICD-O are included in the morphology-based ICCC. In particular, certain categories of brain neoplasms not identified in ICD-O 3 as malignant are included in the ICCC.

Advances in laboratory diagnostic techniques over the past 2 decades have been substantial and transformative. The evolution of immunohistochemistry (IHC), and more recently of molecular diagnostics, has confirmed the separate identity of clinically identified disease subsets and uncovered new diagnostic categories. An example is the identification of atypical teratoid/rhabdoid tumour (ATRT) within medulloblastoma and renal tumours, particularly in younger children. ATRT was originally suggested by the clinical observation of a lethal illness in younger patients diagnosed with medulloblastoma.[6] Atypical histology was then confirmed,[7] with the evolution of IHC, by the identification of polyphenotypic expression of epithelial, neurofibrillary and muscle elements. Ultimately, identification of somatic mutation in chromosome 22q11.2 and absence of expression of the INI 1 protein product[8] culminated in a specific diagnostic profile, now considered mandatory for the diagnosis.

This profile was not sought in the patients diagnosed in the early part of the period under consideration in this Atlas, and thus it is likely that some cases classified as either primitive neuroectodermal tumour/medulloblastoma or choroid plexus carcinoma might in reality have been examples of ATRT. The classification of lymphomas has similarly evolved with specific diagnostic translocations or molecular gene expression, such as *ALK 1* in anaplastic large cell lymphoma. Again, retrospective reclassification is not within the scope of this Atlas.

Research Applications

POGONIS has become a valuable tool for population-based planning, policy development and research in Ontario, across Canada and abroad. The richness of POGONIS's data supports POGO and its partners in planning for childhood cancer control in Ontario and is a critical resource for the work of the POGO Research Unit.

POGONIS is designed to routinely monitor

- The province-wide incidence and prevalence of childhood cancer
- The demand for care from and workload of pediatric oncology programs and staff
- The nature and specifics of treatment
- Patient outcomes
- Demography and the strategic placement of treatment facilities to enable care closer to home
- Long-term effects of childhood cancer and its treatment
- Health economics

In concert with this policy agenda, POGONIS is readily available for use by bona fide researchers to explore studies that would benefit from population-based data or from circumscribed subgroups in the database. To enable such research proposals, approval from a Research Ethics Board of record and a formal application process is required. Details can be found on the POGO website at www.pogo.ca.

References

1 Kramarova E, Stiller CA. The international classification of childhood cancer. Int J Cancer. 1996 Dec 11;68(6):759-65. [review]

2 Birch JMH. A classification scheme for childhood cancer. Int J Cancer. 1987 Nov 15;40(5):620-4.

3 Fritz A, Percy C, Jack A, Shanmugaratna K, Sobin L, Parkin MD, et al. International classification of diseases for oncology, 3rd ed. World Health Organization; 2000.

4 Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer. 2005 Apr 1;103(7):1457-67.

5 Greenberg ML, Barr RD, DiMonte B, McLaughlin E, Greenberg C. Childhood cancer registries in Ontario, Canada: lessons learned from a comparison of two registries. Int J Cancer. 2003 May 20;105(1):88-91.

6 Burger PC, Yu IT, Tihan T, Friedman HS, Strother DR, Kepner JL, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: a highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: a Pediatric Oncology Group study. Am J Surg Pathol. 1998 Sep;22(9):1083-92.

7 Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg. 1996 Jul;85(1):56-65.

8 Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res. 1999 Jan 1;59(1):74-9.

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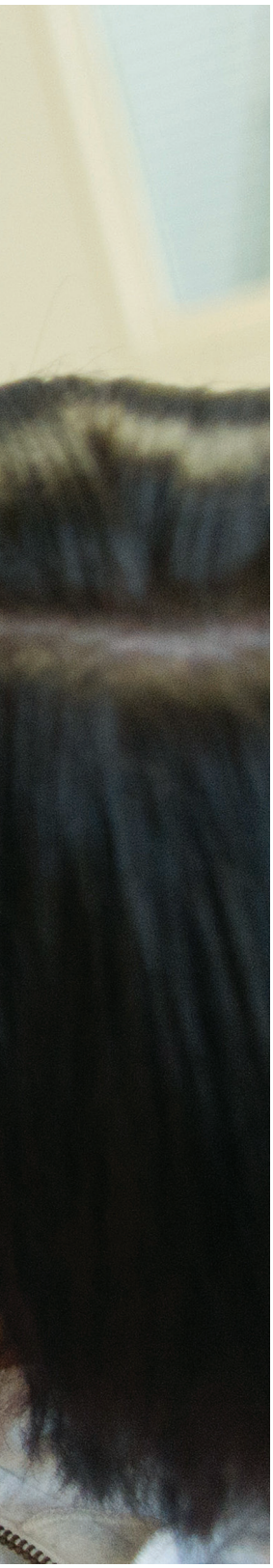


3

Incidence Patterns and Trends

Executive Summary

Data concerning 6,193 cases of childhood cancer (in the 0–14 year age group) diagnosed between 1985 and 2004, systematically recorded and grouped according to the International Classification of Childhood Cancer, third edition (ICCC-3), have been analyzed to describe the incidence patterns in Ontario.

Over the majority of the period analyzed, the incidence rate varied between 145 and 152.3 per million children. These incidence rates are comparable to those of most international jurisdictions, including those published in the Surveillance, Epidemiology and End Results (SEER) study and *Canadian Cancer Statistics*. The diseases with the highest incidence rates were leukemia (age standardized incidence rate [ASIR] of 45.5 per million), tumours of the central nervous system (CNS) (31.9 per million) and lymphoma and reticuloendothelial neoplasms (15.9 per million).

Age-specific incidence rates reveal the predominance of acute leukemia, specifically acute lymphoblastic leukemia (ALL), and CNS tumours, specifically astrocytomas, in the 1–4 year age group. By contrast, in children younger than 1 year, neuroblastoma and germ cell and soft tissue tumours predominate. In 10–14 year olds, lymphoma and bone tumours are most frequent. No significant change in incidence rate was detected for the major tumour categories, with the possible exception of astrocytomas, notably juvenile astrocytomas, seen in the late 1980s and early 1990s, after which the rate returned to baseline. This change is thought to represent a higher detection rate of astrocytomas related to neurofibromatosis type 1 resulting from the introduction of computed tomography (CT) and magnetic resonance imaging (MRI) screening.

Analysis of gender distribution reveals that for some malignancies there is male predominance (lymphoma and hepatoblastoma), with quite a remarkable male:female ratio of 4.56:1 in the case of Burkitt lymphoma. By contrast, for renal tumours and germ cell tumours the male:female ratio is reversed. Most remarkably, for thyroid cancers, the male:female ratio dropped dramatically over the observation period, from 0.95:1 in the earliest observation period to 0.22:1 for 2000–2004.

An exploratory mapping exercise tracking childhood cancer incidence across the census divisions of Ontario is presented. The mapping process used both the choropleth method and the Kriging procedure. While there is some variation of distribution across the province, no clear cut geographical pattern emerges.

Introduction

Childhood cancer differs from its adult counterpart in many respects. The spectrum of cancers is different, the biological behaviour is different and the treatment is very intense and most often occurs at a critical stage of physical, emotional and developmental evolution. Because of the severity of the disease and the intensity of treatment, childhood cancer, a relatively rare event, disproportionately affects the health care system.

Childhood cancer was the leading disease cause of death in Canada in the 0–14 year age range over the entire period covered in this Atlas; this continues to be true. While childhood cancer constitutes only 1–1.5% of incident cancers, the high cure rate and longevity of survivors renders it among the most significant contributors to potential years of life saved. Thus on 2 grounds, mortality rate and survival contribution, childhood cancer has impacts apparently disproportionate to its incidence rate.

Descriptive epidemiology may provide useful insights into patterns and trends of occurrence and may influence the study of causation, particularly when combined with contemporary molecular biology. Patterns of geographic distribution lend themselves to studies of etiology and socio-demographic influences on outcomes. Descriptive epidemiology may also enable understanding of health care utilization and system needs, prediction of future needs and health care resource planning.

Over the 20 years covered by this Atlas, 6,193 cases were registered in the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) database, with a consistent registration process over that time. This number reflects a population capture and is larger than many country-specific databases included in the European Automated Childhood Cancer Information System (ACCIS) project. Thus analysis of overall incidence of childhood cancer, and of specific subtypes in the delimited population of Ontario, may be of interest to a range of clinicians, scientists and health planners, in addition to epidemiologists. Combined with an understanding of treatment patterns and health care utilization, the nature of the impact on the current and future health of the population can be estimated. This chapter reports on the analysis of incidence and compares Ontario's incidence with that of other jurisdictions with the hope that doing so will stimulate further study and analysis by interested investigators and planners.

The POGONIS database classifies childhood cancer according to the International Classification of Childhood Cancer, third edition (ICCC-3).[1] This classification divides childhood cancer into 12 groups, each of which has subgroups. Only select subgroups are presented in detail in specific chapters in this Atlas. These subgroups become increasingly important as substantial differences in their basic biology are uncovered.

There is an important caveat, however, regarding the analysis of subgroups in any registry population. Shifts in classification and refining of specificity of diagnoses occur over time as a result of the advent of ever more sophisticated diagnostic tools, including immunohistochemistry and molecular diagnostics. These advances permit finer dissection of categories and re-assignment of some entities to other categories. Some disease entities had not been identified at the time of diagnosis of a proportion of cases in the database. If these cases were diagnosed today, they would be assigned to a different classification category, most frequently within the same major ICCC-3 group but occasionally to a completely different group.

Such reclassification cannot be achieved in retrospect without re-examining tissue specimens using contemporary methodology – an undertaking inappropriate for an Atlas but an opportunity awaiting eager investigators. Thus, as in all registries, individual cases are classified according to the definitive pathology report issued at the time of diagnosis of the malignancy. Since this is a universal practice, comparability among jurisdictions is possible.

Methodology

Incidence rates reported in this chapter are based on all childhood cancer patients (age 0–14 years at time of diagnosis) diagnosed between 1985 and 2004 and registered in POGONIS.

Every occurrence of childhood cancer is considered an incident "case." In subjects diagnosed with a subsequent, different primary cancer during follow up, each cancer was considered an incident case.

The malignancies reported are classified according to ICCC-3. It should be noted that 43 CNS low grade gliomas are included in the CNS chapter of this Atlas but not in the Incidence, Health Service Utilization or Survival chapters. This is because these cases were diagnosed radiologically, without pathologic confirmation, and were detected only by comparison with an imaging database. These cases are therefore not registered in the Ontario Cancer Registry and vital status cannot be confirmed.

Discussion

EXHIBIT 3.1: **Incidence rate (per million) of childhood cancer, by diagnosis, age 0–14 years, in Ontario, 1985–2004**

Diagnostic group	Sub-group	Total no. of cases	Incidence rate/million: Total (1985–2004)	1985–1989	1990–1994	1995–1999	2000–2004
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**2022**	**46.69**	**45.11**	**47.04**	**49.66**	**44.77**
	a. Lymphoid leukemias*	1591	36.73	36.59	36.49	36.33	36.73
	b. Acute myeloid leukemias†	319	7.37	8.21	9.19	6.08	7.37
	c. Chronic myeloproliferative diseases	22	0.51	0.56	0.35	0.43	0.51
	Other	90	—	—	—	—	—
II	**Lymphomas and reticuloendothelial neoplasms**	**650**	**15.01**	**12.68**	**14.84**	**14.40**	**17.56**
	a. Hodgkin lymphomas	256	5.91	6.16	5.48	6.35	5.91
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	219	5.06	5.41	5.30	5.56	5.06
	c. Burkitt lymphoma	110	2.54	2.52	1.77	3.22	2.54
	Other	65	—	—	—	—	—
III	**Central nervous system and miscellaneous intracranial and intraspinal neoplasms**	**1383**	**31.93**	**27.42**	**36.40**	**32.43**	**31.12**
	a. Ependymomas and choroid plexus tumours	119	2.75	2.61	2.21	2.96	2.75
	b. Astrocytomas	761	17.57	21.66	17.41	16.17	17.57
	c. Intracranial and intraspinal embryonal tumours	298	6.88	6.63	7.07	8.17	6.88
	Other	205	—	—	—	—	—
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**446**	**10.30**	**10.13**	**11.20**	**10.69**	**9.21**
	a. Neuroblastomas and ganglioneuroblastomas	438	10.11	11.11	10.43	9.04	10.11
	Other	8	—	—	—	—	—
V	**Retinoblastoma**	**169**	**3.90**	**3.27**	**3.62**	**4.52**	**3.90**
VI	**Renal tumours**	**362**	**8.36**	**8.59**	**8.96**	**9.37**	**6.61**
	a. Nephroblastomas and other nonepithelial renal tumours	339	7.83	8.39	8.49	8.66	5.91
	Other	23	—	—	—	—	—
VII	**Hepatic tumours**	**99**	**2.29**	**2.43**	**2.03**	**2.61**	**2.29**
VIII	**Malignant bone tumours**	**296**	**6.83**	**7.37**	**6.81**	**6.98**	**6.26**
	a. Osteosarcomas	146	3.37	3.27	3.27	2.87	3.37
	b. Ewing tumour and related sarcomas of bone	137	3.16	3.55	3.36	2.69	3.16
	Other	13	—	—	—	—	—

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia

continued on following page

EXHIBIT 3.1: **Incidence rate (per million) of childhood cancer, by diagnosis, age 0–14 years, in Ontario, 1985–2004** (cont'd)

Diagnostic group	Sub-group	Total no. of cases	Incidence rate/million: Total (1985–2004)	1985–1989	1990–1994	1995–1999	2000–2004
IX	**Soft tissue and other extraosseous sarcomas**	**393**	**9.07**	**7.67**	**8.40**	**8.92**	**11.04**
	a. Rhabdomyosarcomas	165	3.81	4.11	3.09	4.17	3.81
	Other	228	—	—	—	—	—
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**185**	**4.27**	**4.09**	**3.17**	**4.68**	**5.04**
	d. Gonadal carcinomas	74	1.71	1.40	1.86	2.35	1.71
	Other	111	—	—	—	—	—
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**128**	**2.96**	**2.86**	**1.12**	**3.18**	**4.52**
	b. Thyroid carcinomas	50	1.15	0.47	1.33	1.39	1.15
	d. Malignant melanomas	20	0.46	0.37	0.09	0.61	0.46
	Other	58	—	—	—	—	—
XII	**Other and unspecified malignant neoplasms**	**60**	**1.39**	**1.12**	**1.86**	**1.13**	**1.39**
	Total	6193					

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia

Exhibit 3.1

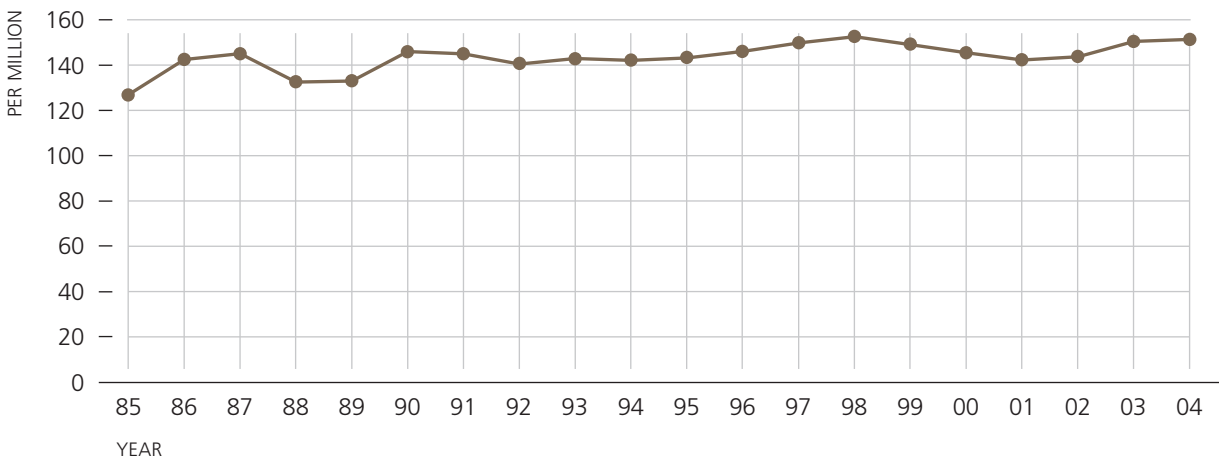
Type-specific incidence rates

Exhibit 3.1 provides the absolute numbers of cases in each of the 12 ICCC-3 categories and in the major subcategories, as well as the resultant incidence rates. The category "other" is used to denote all cases not identified in the major subcategories, and since it is a catch all grouping, incidence rates are not displayed.

For type-specific incidence rates, patients were grouped based on ICCC-3 into diagnosis groups. Patients were further grouped into 5 year intervals (1985–1989, 1990–1994, 1995–1999 and 2000–2004) and cumulative incidence rates are reported for each period.

For the denominator, we used the Ontario population age 0–14 years for the period 1985–2004. For each 5 year period, the 0–14 year old population for that period was determined and used as the denominator. The total number of cases of childhood cancer during the period was used as numerator. The same methodology was used for estimating the incidence rate for all years combined. Incidence rates are reported per million population.[2]

EXHIBIT 3.2: **Age-standardized smoothed incidence rate (per million) of childhood cancer, trend over time, age 0–14 years, in Ontario, 1985–2004**



The reader may note differences in the ASIRs reported in this chapter from those reported in the Survival chapter (Exhibit 4.1). These differences relate to the exclusion of cases from the data set used in the survival chapter that did not link to either the Ontario Cancer Registry or the Ontario Registrar General death file. The incidence rates identified in this chapter are the appropriate rates for quotation.

Exhibit 3.2

To reduce the effect of random variations on incidence trends, we used a 3 year moving average technique to smooth the trend. With this method, the moving average in each year is derived from averaging a weighted incidence value in the index year, the subsequent year and the prior year. The highest weight (0.5) was assigned to the index year and a weight of 0.25 was assigned to the prior and subsequent years. For the tail years, we used 0.75 for the index year and 0.25 for the year before or after it.

Age-specific and age-standardized incidence rates

EXHIBIT 3.3: **Age-specific and age-standardized incidence rates of childhood cancer, by diagnosis, age 0–14 years, in Ontario, 1985–2004**

Diagnostic group	Sub-group	Age-specific incidence rate per million per year, 1985–2004					
		Age < 1	Age 1–4	Age 5–9	Age 10–14	All ages	Age-standardized rate
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**38.13**	**87.44**	**38.01**	**24.94**	**46.69**	**45.50**
	a. Lymphoid leukemias*	18.34	74.41	30.67	16.67	36.73	35.70
	b. Acute myeloid leukemias†	13.67	10.23	5.28	5.99	7.37	7.46
	c. Chronic myeloproliferative diseases	—	0.44	0.34	0.83	0.51	1.18
II	**Lymphomas and reticuloendothelial neoplasms**	**4.32**	**8.13**	**14.27**	**23.08**	**14.96**	**15.93**
	a. Hodgkin lymphomas	—	0.96	3.36	13.50	5.91	7.44
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	0.72	3.41	6.17	6.06	5.06	5.41
	c. Burkitt lymphoma	—	2.45	3.50	2.14	2.54	2.91
III	**Central nervous system and miscellaneous intracranial and intraspinal neoplasms**	**28.42**	**39.17**	**32.38**	**26.45**	**31.93**	**31.94**
	a. Ependymomas and choroid plexus tumours	5.40	4.90	1.65	1.65	2.75	3.07
	b. Astrocytomas	10.79	21.51	18.45	14.88	17.57	17.73
	c. Intracranial and intraspinal embryonal tumours	7.55	9.01	7.75	4.20	6.90	7.08
IV	**Neuroblastoma and other peripheral nervous cell tumours**						
	a. Neuroblastomas and ganglioneuroblastomas	55.39	19.50	3.36	0.83	10.11	10.88
V	**Retinoblastoma**	**26.60**	**7.90**	**0.30**	—	**3.90**	**5.30**
VI	**Renal tumours**	**14.00**	**20.30**	**5.00**	**1.20**	**8.40**	**8.80**
	a. Nephroblastomas and other nonepithelial renal tumours	14.03	19.59	4.66	0.55	7.83	8.65
VII	**Hepatic tumours**	**11.15**	**3.50**	**1.10**	**0.83**	**2.29**	**2.86**
VIII	**Malignant bone tumours**	**1.08**	**1.49**	**5.90**	**13.09**	**6.80**	**8.06**
	a. Osteosarcomas		0.44	2.61	7.10	3.40	4.31
	b. Ewing tumour and related sarcomas of bone	0.36	0.96	3.16	5.44	3.20	3.83
IX	**Soft tissue and other extraosseous sarcomas**	**15.11**	**9.97**	**7.61**	**8.68**	**9.10**	**9.24**
	a. Rhabdomyosarcomas	3.24	5.77	4.18	2.00	3.81	4.10
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**12.95**	**4.02**	**2.13**	**4.96**	**4.30**	**4.61**
	d. Gonadal carcinomas	3.24	1.22	1.10	2.41	1.71	2.24
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**1.08**	**0.79**	**2.40**	**5.58**	**3.00**	**3.77**
	b. Thyroid carcinomas	—	0.09	1.10	2.27	1.15	1.83
	d. Malignant melanomas	0.72	0.09	0.21	0.96	0.46	1.15
XII	**Other and unspecified malignant neoplasms**	**4.00**	**1.00**	**0.80**	**1.80**	**1.40**	**1.90**

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia

Exhibit 3.3

The age-specific incidence rate is the number of cases found in a given age group divided by the number of children in that age group in the general population in the same time period, expressed as rate per million. The population used for each age group was the corresponding population for Ontario for the years 1985–2004. Age-specific incidence rates (ASIR) are reported for age groups of less than 1 year, 1–4, 5–9 and 10–14 years.

The ASIR is a weighted average of the age-specific incidence rate, where the weights are the proportions of persons in the corresponding age groups in a standard population. This statistic reduces the potential confounding effect of age. The standard populations used in the calculations were the Ontario population in 1996 and the world population in 2000. Since there was no substantive difference in these rates, only the Ontario adjusted rate is shown. Direct standardization was used in estimating ASIRs.

Between 1985 and 1990 the ASIR increased from 126.8 per million to 145.8 per million, an increase of 15%. A sharp increase occurs between 1985 and 1986 and while the data have been verified, some of this increase may represent underreporting in 1985. The subsequent rise between 1988 and 1990 may in part be accounted for by more ready access to CT and MRI screening for low grade gliomas in patients with neurofibromatosis.

Since 1990, the overall incidence rate of childhood cancer among 0–14 year olds in Ontario has remained stable, varying between 145.8 and 152.3 per million. This rate is very close to reported rates for Canada during the same period,[3] which ranged from 144 to 159 per million with an ASIR for 2000–2004 of 149.7 per million.[4] Since Ontario's population constitutes over 40% of the Canadian population, the impact of Ontario's incidence rate on the Canadian incidence data is substantial.

Comparative data from international jurisdictions include SEER, which reports ASIRs for the same age group from 1985 to 2002 ranging from 139 to 155 per million, comparable to Ontario data reported here.[5] Australian population-based data for 1997–2006 show an equivalent ASIR of 157.5 per million. The incidence rate for Europe as a whole between 1988 and 1997, derived from registries from many European countries from the ACCIS, is reported as 139 per million. Rates varied from 130 to 160 per million among regions and from 116 to 173 per million among countries.[6] Similar regional and geographic variations in incidence have been reported for different regions of the U.S.[7] using data from both SEER and the National Program of Cancer Registries for diagnoses during the period 2001–2003. French national data for the period 2000–2004 show an ASIR of 155 per million.[8]

Approaches to and reliability of registration procedures vary by region and over time. The degree of consistency of ASIRs across most registries is thus reassuring. It is acknowledged, however, that differences exist both in overall incidence rates among countries and regions and in distribution of specific diagnostic groups across geographic regions. An example of such a difference is the dramatically increased incidence of thyroid carcinoma documented in the Belarus registry in ACCIS.[9]

When adjusted for age, leukemia (45.5 per million), central nervous system tumours (CNS) tumours (31.9 per million) and lymphoma and reticuloendothelial neoplasms (15.9 per million) were the most common incident malignancies. With respect to age-specific rates, rates for leukemia, specifically ALL, and for CNS tumours peak in the 1–4 year age group. Within the CNS category, astrocytoma is the most frequent type, with the majority of cases occurring in the 1–4 year old group.

Peak incidence for neuroblastoma and germ cell and soft tissue tumours occurred in the less than 1 year age group. Lymphoma and bone tumours are most prevalent in the 10–14 year age group.

Both the age-specific and age standardized rates reported in Exhibit 3.3 are similar to incidence rates reported in other jurisdictions, such as the U.S.[10]

Disease-specific analyses are reported below for the 5 most frequently occurring cancers, for which sample size permits detailed analysis.

Leukemia

Leukemias, myeloproliferative diseases and myelodysplastic diseases have an ASIR of 45.5 per million for the entire period. This rate is comparable to rates in other reporting jurisdictions. The rate overwhelmingly represents ALL, with an ASIR of 35.7 per million, compared with 7.5 for acute myeloblastic leukemia (AML). Age-specific rates demonstrate an expected higher rate of 74.4 per million in the 1–4 year age group for ALL. The incidence rate for all leukemias over the period 1985–2004 differs little by 5 year period. While the incidence rate for AML fluctuates between 6.08 per million for 1995–1999 and 9.19 per million for 1990–1994, the total number of cases is small and the confidence intervals are wide.

Canadian national data reveal a marginally higher rate of 49.3 per million in the period 2000–2004.[4] SEER reports an ASIR over the period 1985–2002 of between 37 and 44 per million. The French ASIR for 2000–2004 was comparable at 45.9 per million,[8] as are Swiss data: 47.2 per million for all leukemias, 38.1 per million for ALL and 6.7 per million for AML in the period 1995–2004.[11] In Ontario there is a consistently elevated male:female ratio in the ASIR for ALL not seen in AML. Other jurisdictions report similar data.[8,12]

It is not possible on the basis of the Ontario data to determine subtypes of ALL by lineage classification.

A caveat to interpretation is important: the latest version of the International Classification of Diseases for Oncology (ICD-O),[13] implemented in 2001, incorporates myelodysplastic disorders of the bone marrow in the leukemia category and therefore assigns them a malignant behaviour code. Myelodysplastic disorders were not considered malignant in prior versions; comparison of data collected in earlier and later periods is therefore complicated by inclusion of these rare entities, the data for which are inconsistently collected.

Lymphoma and Reticuloendothelial Neoplasms

ICCC-3 group 2 includes Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma and miscellaneous reticuloendothelial neoplasms, limited to true malignant histiocytic entities and systemic variants of Langerhans histiocytosis. Since the inclusion of these latter entities in ICCC-3 is recent, there is inconsistency over the sequential time periods reported in the literature; comparability with reports from other jurisdictions is thus complicated. Additionally, nosology and classification systems of lymphoma have changed over the period reported here, further complicating comparison of subgroups.

The ASIR for lymphoma in Ontario over the 20 year period is 15.0 per million. The reported incidence in the U.S. in the period 2001–2003 is 15.6 per million.[7] National incidence data for France in the period 2000–2004 show a higher rate, at 17.1 per million.[8] The incidence in Ontario over the same period is equivalent at 17.6 per million (Exhibit 3.1). There is no obvious change in the Ontario incidence rate over the entire period (data not shown).

The ASIR for Hodgkin lymphoma is 7.4 per million, comparable to French and U.S. data for 1985–2002 (5 per million). The age-specific incidence is substantially higher in the 10–14 year age group at 13.5 per million, compared with 3.4 per million in the 5–9 year group. Equivalent incidence figures for the U.S. for 2001–2003 are 11.8 and 3.93 per million.

Non-Hodgkin lymphoma, excluding Burkitt lymphoma, has an incidence rate of 5.4 per million, with higher age-specific rates in the 2 older quartile age groups. No incidence trend over time is discernible. These incidence data are similar to French rates. U.S. data reported for 1985–2002, which do not separate Burkitt lymphoma, show rates ranging from 6 to 10 per million, with a rate of 10 per million for 1998–2002.

The ASIR for Burkitt lymphoma over the timeframe of the study is 2.9 per million. The French rate for the period 2000–2004 is substantially higher at 4 per million. Age-specific incidence rates show no differences across age groups.

Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms

The ASIR for this group is 31.9 per million, comparable to that reported for Germany (31.9), the U.S. (32.0) and Switzerland (30.4), but lower than that reported for France (36.2).

The ICCC-3 includes in this category certain neoplasms not considered malignant in adult populations. In particular, juvenile pilocytic astrocytoma and other low grade astrocytomas, classified in ICD-O as neoplasms of uncertain behaviour and allocated a behaviour code of 1, are included in the ICCC-3. (ICD-O assigns a behaviour code of 3 to malignant neoplasms, 0 to benign neoplasms and 1 to neoplasms of indeterminate behaviour.) This group constitutes about 45% of astrocytomas[14] among people under 20 years of age, and an active decision was made to include them in ICCC-3. Other included entities are craniopharyngioma and pituitary adenomata – the data collection for both is less reliable because these tumours are frequently treated by neurosurgical services only and not identified by pathology reports as malignant. They are thus incompletely recorded in the Ontario dataset, but in the French report constitute less than 2% of ICCC-3 group 3.

Astrocytomas, including juvenile astrocytomas, constitute by far the largest proportion of group 3 tumours, followed by intracranial and spinal embryonal tumours and ependymomas, with ASIRs of 17.7, 7.1 and 3.1 per million, respectively. The comparable ASIRs for the French group in its 2000–2004 data are 13.6, 7.8 and 3.8 per million. The difference in the ASIR for astrocytoma stands out. The increase in the absolute numbers of astrocytomas diagnosed in the late 1980s and early 1990s may account for this difference, postulated to be the consequence of the widespread introduction of screening CT and MRI in patients with neurofibromatosis type 1 during that period, resulting in the pre-symptomatic identification of juvenile astrocytomas.[15] These rates dropped to baseline levels by 1996 and have remained at that level since. Across the age quartiles, astrocytomas have the highest ASIR, maximal in the 1–4 year age group.

The ASIR for non-astrocytic tumours remained constant across the periods under analysis.

Embryonal tumours, including intracranial and spinal embryonal tumours, constitute approximately 20% of the cases recorded over the 20 year period.

Neuroblastoma and Other Peripheral Nervous Cell Tumours

The ASIR of 10.9 per million is in line with data reported from Germany (12.0), the U.S. (10.8)[7] and Switzerland (10.4).[11] The rate reported for France of 14.5 is higher than rates in most other jurisdictions.

As expected, the age-specific rate is substantially higher in the youngest age group than in any other – with a rate in the first year of life of 55.4 per million. No significant variation is noted over the successive periods, in contrast to reports from Piedmont, Italy,[16] and the French data, which demonstrate an increasing rate from the first year of life over time, suggesting the influence either of screening programs or of improved access to care. The Ontario rates are virtually identical to those reported for the U.S., suggesting that access to care is not the reason for rate increases in the early years of life.

Nephroblastoma and Other Nonepithelial Kidney Tumours

Since only a small number of renal cell carcinomas are represented in the renal tumour category, this discussion focuses on nephroblastoma and variants, as classified in ICCC-3.

Nephroblastoma, group 6a in ICCC-3, encompasses clear cell sarcoma and renal rhabdoid tumours, which together constitute less than 5% of renal tumours in most registries. The overall ASIR for the 20 year period of 8.7 per million is consistent across periods, with a small decline in the last 5 year period. This ASIR compares closely to the reported European incidence for all renal tumours of 8.5 per million[17,18] in the period 1988–1997. In the European study, the incidence demonstrated an annual increase of 0.8%, with variation by geographic zone. The sample size in Ontario does not permit such granular analysis. SEER data for 2001–2003 demonstrate an ASIR for this age group of 8.5 per million.[7]

The age-specific incidence data demonstrate a peak incidence in the 1–4 year age group, followed by the less than 1 year age group. Similar trends are seen in the European and SEER datasets.

EXHIBIT 3.4: **Incidence rate (per million) of childhood cancer, by diagnosis, males, age 0–14 years, in Ontario, 1985–2004**

Diagnostic group	Sub-group	Total (1985–2004) No. of cases	Incidence rate/million	95% CI	1985–1989 Incidence rate/million	95% CI
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**1114**	**50.21**	**47.74-52.69**	**48.46**	**43.35-53.57**
	a. Lymphoid leukemias*	892	40.21	37.99-42.42	40.88	36.19-45.58
	b. Acute myeloid leukemias†	166	7.48	6.53-8.44	6.18	4.36-8.01
	c. Chronic myeloproliferative diseases	8	0.36	0.15-0.57	0.60	0.03-1.17
	Other	48	—	—	—	—
II	**Lymphomas and reticuloendothelial neoplasms**	**415**	**18.70**	**17.15-20.17**	**16.80**	**13.75-19.76**
	a. Hodgkin lymphomas	143	6.45	5.56-7.33	5.78	4.02-7.55
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	147	6.63	5.73-7.53	5.98	4.19-7.78
	c. Burkitt lymphoma	91	4.10	3.39-4.81	4.19	2.68-5.69
	Other	34	—	—	—	—
III	**Central nervous system and miscellaneous intracranial and intraspinal neoplasms**	**772**	**34.80**	**32.74-36.86**	**30.71**	**26.64-34.78**
	a. Ependymomas and choroid plexus tumours	65	2.93	2.33-3.53	2.99	1.72-4.26
	b. Astrocytomas	401	18.08	16.59-19.56	15.95	13.02-18.89
	c. Intracranial and intraspinal embryonal tumours	202	9.11	8.05-10.16	7.18	5.21-9.15
	Other	104	—	—	—	—
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**255**	**11.49**	**10.31-12.68**	**11.57**	**9.07-14.07**
	a. Neuroblastomas and ganglioneuroblastomas	250	11.27	10.10-12.44	11.37	8.89-13.84
	Other	5	—	—	—	—
V	**Retinoblastoma**	**89**	**4.01**	**3.31-4.71**	**2.99**	**1.72-4.26**
VI	**Renal tumours**	**161**	**7.26**	**6.32-8.20**	**7.58**	**5.56-9.60**
	a. Nephroblastomas and other nonepithelial renal tumours	149	6.72	5.81-7.62	7.38	5.38-9.37
	Other	12	—	—	—	—
VII	**Hepatic tumours**	**61**	**2.75**	**2.17-3.33**	**2.79**	**1.56-4.02**
VIII	**Malignant bone tumours**	**155**	**6.99**	**6.06-7.91**	**8.77**	**6.60-10.95**
	a. Osteosarcomas	83	3.74	3.07-4.42	4.79	3.18-6.39
	b. Ewing tumour and related sarcomas of bone	69	3.11	2.49-3.73	3.79	2.36-5.22
	Other	3	—	—	—	—
IX	**Soft tissue and other extraosseous sarcomas**	**222**	**10.01**	**8.90-11.11**	**9.97**	**7.65-12.29**
	a. Rhabdomyosarcomas	99	4.46	3.72-5.20	5.19	3.51-6.86
	Other	123	—	—	—	—

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia
CI = confidence interval

1990–1994		1995–1999		2000–2004	
Incidence rate/million	95% CI	Incidence rate/million	95% CI	Incidence rate/million	95% CI
52.23	**47.16-57.30**	**51.03**	**46.15-55.91**	**49.02**	**44.27-53.77**
40.58	36.11-45.05	38.27	34.05-42.50	41.19	36.83-45.55
9.65	7.47-11.82	8.62	6.61-10.63	5.45	3.86-7.03
0.55	0.03-1.06	0.69	0.12-1.26	0.34	-0.06-0.74
—	—	—	—	—	—
18.90	**15.87-21.98**	**16.20**	**13.46-18.96**	**22.50**	**19.25-25.68**
7.10	5.23-8.97	6.21	4.50-7.91	6.64	4.89-8.39
7.10	5.23-8.97	6.03	4.36-7.71	7.32	5.48-9.16
3.82	2.45-5.19	3.10	1.90-4.31	5.28	3.72-6.84
—	—	—	—	—	—
37.13	**32.85-41.40**	**36.20**	**32.09-40.31**	**34.72**	**30.72-38.72**
2.37	1.29-3.45	2.24	1.22-3.26	4.09	2.71-5.46
21.29	18.05-24.53	18.27	15.35-21.19	16.68	13.91-19.45
8.74	6.66-10.81	10.00	7.84-12.16	10.21	8.04-12.38
—	—	—	—	—	—
11.10	**8.76-13.44**	**11.72**	**9.38-14.06**	**11.57**	**9.27-13.88**
10.92	8.60-13.24	11.38	9.07-13.68	11.40	9.11-13.70
—	—	—	—	—	—
4.73	**3.21-6.26**	**3.79**	**2.46-5.12**	**4.43**	**3.00-5.85**
9.28	**7.14-11.42**	**6.55**	**4.80-8.30**	**5.79**	**4.15-7.42**
8.92	6.82-11.01	5.86	4.21-7.52	4.94	3.43-6.44
—	—	—	—	—	—
3.09	**1.86-4.33**	**2.07**	**1.09-3.05**	**3.06**	**1.88-4.25**
6.55	**4.76-8.35**	**7.59**	**5.70-9.47**	**5.28**	**3.72-6.84**
3.46	2.15-4.76	3.79	2.46-5.12	3.06	1.88-4.25
3.09	1.86-4.33	3.62	2.32-4.92	2.04	1.07-3.01
—	—	—	—	—	—
9.28	**7.14-11.42**	**9.65**	**7.53-11.78**	**11.06**	**8.81-13.32**
4.91	3.36-6.47	3.79	2.46-5.12	4.09	2.71-5.46
—	—	—	—	—	—

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EXHIBIT 3.4: **Incidence rate (per million) of childhood cancer, by diagnosis, males, age 0–14 years, in Ontario, 1985–2004** (cont'd)

Diagnostic group	Sub-group	Total (1985–2004) No. of cases	Incidence rate/million	95% CI	1985–1989 Incidence rate/million	95% CI
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**83**	**3.74**	**3.07-4.42**	**4.19**	**2.68-5.69**
	d. Gonadal carcinomas	30	1.35	0.95-1.76	1.20	0.39-2.00
	Other	53	—	—	—	—
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**49**	**2.21**	**1.69-2.73**	**2.39**	**1.26-3.53**
	b. Thyroid carcinomas	16	0.72	0.42-1.02	1.40	0.53-2.26
	d. Malignant melanomas	6	0.27	0.09-0.45	0.40	-0.07-0.86
	Other	27	—	—	—	—
XII	**Other and unspecified malignant neoplasms**	**25**	**1.13**	**0.76-1.50**	**1.40**	**0.53-2.26**

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia
CI = confidence interval

EXHIBIT 3.5: **Incidence rate (per million) of childhood cancer, by diagnosis, females, age 0–14 years, in Ontario, 1985–2004**

Diagnostic group	Sub-group	Total (1985–2004) No. of cases	Incidence rate/million	95% CI	1985–1989 Incidence rate/million	95% CI
I	**Leukemias, myeloproliferative diseases and myelodysplastic diseases**	**908**	**42.98**	**40.63-45.33**	**41.59**	**36.72-46.45**
	a. Lymphoid leukemias*	699	33.09	31.03-35.15	34.23	29.82-38.65
	b. Acute myeloid leukemias†	153	7.24	6.28-8.21	5.46	3.70-7.22
	c. Chronic myeloproliferative diseases	14	0.66	0.37-0.95	0.84	0.15-1.53
	Other	42	—	—	—	—
II	**Lymphomas and reticuloendothelial neoplasms**	**235**	**11.08**	**9.89-12.27**	**8.40**	**6.22-10.59**
	a. Hodgkin lymphomas	113	5.35	4.52-6.18	5.46	3.70-7.22
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	72	3.41	2.75-4.07	1.47	0.56-2.38
	c. Burkitt lymphoma	19	0.90	0.56-1.24	1.05	0.28-1.82
	Other	31	—	—	—	—
III	**Central nervous system and miscellaneous intracranial and intraspinal neoplasms**	**611**	**28.92**	**27.00-30.85**	**23.94**	**20.25-27.63**
	a. Ependymomas and choroid plexus tumours	54	2.56	1.98-3.13	3.57	2.15-5.00
	b. Astrocytomas	360	17.04	15.56-18.52	13.86	11.06-16.67
	c. Intracranial and intraspinal embryonal tumours	96	4.54	3.78-5.31	3.57	2.15-5.00
	Other	101	—	—	—	—

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia
CI = confidence interval

	1990–1994		1995–1999		2000–2004	
	Incidence rate/million	95% CI	Incidence rate/million	95% CI	Incidence rate/million	95% CI
	2.73	**1.57-3.89**	**3.62**	**2.32-4.92**	**4.43**	**3.00-5.85**
	1.27	0.48-2.07	1.03	0.34-1.73	1.87	0.94-2.80
	—	—	—	—	—	—
	0.55	**0.03-1.06**	**2.07**	**1.09-3.05**	**3.74**	**2.43-5.06**
	0.18	-0.12-0.48	0.86	0.23-1.50	0.51	0.03-1.00
	0.73	0.13-1.33	0.17	-0.11-0.46	0.68	0.12-1.24
	—	—	—	—	—	—
	1.27	**0.48-2.07**	**1.03**	**0.34-1.73**	**0.85**	**0.22-1.48**

	1990–1994		1995–1999		2000–2004	
	Incidence rate/million	95% CI	Incidence rate/million	95% CI	Incidence rate/million	95% CI
	41.58	**36.94-46.23**	**48.21**	**43.35-53.07**	**40.33**	**35.92-44.73**
	32.38	28.29-36.48	34.62	30.50-38.74	31.27	27.39-35.14
	6.71	4.84-8.57	9.79	7.60-11.98	6.75	4.95-8.55
	0.57	0.03-1.12	0.72	0.13-1.32	0.53	0.03-1.04
	—	—	—	—	—	—
	10.54	**8.20-12.88**	**12.51**	**10.03-14.98**	**12.44**	**9.99-14.88**
	5.17	3.54-6.81	4.71	3.19-6.23	6.04	4.34-7.74
	3.64	2.27-5.01	4.53	3.04-6.02	3.73	2.39-5.07
	1.15	0.38-1.92	0.36	-0.06-0.78	1.07	0.35-1.78
	—	—	—	—	—	—
	35.64	**31.34-39.94**	**28.46**	**24.72-32.19**	**27.36**	**23.73-30.98**
	2.87	1.65-4.10	2.17	1.14-3.21	1.78	0.85-2.70
	22.04	18.66-25.42	16.49	13.65-19.34	15.63	12.89-18.37
	4.41	2.90-5.92	3.99	2.59-5.39	6.04	4.34-7.74
	—	—	—	—	—	—

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EXHIBIT 3.5: **Incidence rate (per million) of childhood cancer, by diagnosis, females, age 0–14 years, in Ontario, 1985–2004** (cont'd)

Diagnostic group	Sub-group	Total (1985–2004) No. of cases	Total (1985–2004) Incidence rate/million	Total (1985–2004) 95% CI	1985–1989 Incidence rate/million	1985–1989 95% CI
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**191**	**9.04**	**7.96-10.12**	**8.61**	**6.40-10.82**
	a. Neuroblastomas and ganglioneuroblastomas	188	8.90	7.83-9.97	8.40	6.22-10.59
	Other	3	—	—	—	—
V	**Retinoblastoma**	**80**	**3.79**	**3.09-4.48**	**5.46**	**3.70-7.22**
VI	**Renal tumours**	**201**	**9.51**	**8.41-10.62**	**9.66**	**7.32-12.00**
	a. Nephroblastomas and other nonepithelial renal tumours	190	9.00	7.90-10.10	9.50	7.10-11.80
	Other	11	—	—	—	—
VII	**Hepatic tumours**	**38**	**1.80**	**1.32-2.28**	**1.26**	**0.41-2.11**
VIII	**Malignant bone tumours**	**141**	**6.67**	**5.75-7.60**	**5.88**	**4.05-7.71**
	a. Osteosarcomas	63	2.98	2.36-3.60	3.57	2.15-5.00
	b. Ewing tumour and related sarcomas of bone	68	3.22	2.58-3.86	2.31	1.16-3.46
	Other	10	—	—	—	—
IX	**Soft tissue and other extraosseous sarcomas**	**171**	**8.09**	**7.08-9.11**	**5.25**	**3.52-6.98**
	a. Rhabdomyosarcomas	66	3.12	2.49-3.76	2.52	1.32-3.72
	Other	105	—	—	—	—
X	**Germ cell tumours, trophoblastic tumours and neoplasms of gonads**	**102**	**4.83**	**4.04-5.61**	**3.99**	**2.48-5.50**
	d. Gonadal carcinomas	44	2.08	1.57-2.60	1.05	0.28-1.82
	Other	58	—	—	—	—
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**79**	**3.74**	**3.05-4.43**	**3.36**	**1.98-4.74**
	b. Thyroid carcinomas	34	1.61	1.16-2.06	1.47	0.56-2.38
	d. Malignant melanomas	14	0.66	0.37-0.95	1.26	0.41-2.11
	Other	31	—	—	—	—
XII	**Other and unspecified malignant neoplasms**	**35**	**1.66**	**1.20-2.12**	**1.47**	**0.56-2.38**

*Almost exclusively acute lymphoblastic leukemia
†Including chronic myeloid leukemia
CI = confidence interval

Gender patterns in incidence

Exhibits 3.4 and 3.5

Overall, from 1985 to 2004 in Ontario, childhood cancers occurred more frequently in males than in females, with a male:female ratio of 1.16:1. The largest differences are seen in the lymphoma and reticuloendothelial neoplasms group, where the ratio is 1.69:1, and hepatic tumours, where the ratio is 1.53:1. Within the lymphoma and reticuloendothelial neoplasms grouping, sub-group differences in the male:female ratio are even more striking. Among the non-Hodgkin lymphoma group (not including Burkitt lymphoma) the male:female ratio is 1.94:1. Among those diagnosed with Burkitt lymphoma the male:female ratio is 4.56:1. U.S. and French data show equivalent gender ratios, as do data derived from the Berlin Frankfurt Munster Group. There is

	1990–1994		1995–1999		2000–2004	
	Incidence rate/million	95% CI	Incidence rate/million	95% CI	Incidence rate/million	95% CI
	11.31	**8.88-13.73**	**9.61**	**7.44-11.78**	**6.75**	**4.95-8.55**
	11.31	8.88-13.73	9.42	7.27-11.57	6.57	4.80-8.35
	—	—	—	—	—	—
	1.72	**0.78-2.67**	**3.44**	**2.14-4.74**	**4.62**	**3.13-6.11**
	8.62	**6.51-10.74**	**12.32**	**9.87-14.78**	**7.46**	**5.57-9.36**
	8.05	6.01-10.09	11.60	9.21-13.99	6.90	5.10-8.80
	—	—	—	—	—	—
	1.72	**0.78-2.67**	**1.99**	**1.00-2.98**	**2.13**	**1.12-3.14**
	7.09	**5.17-9.01**	**6.34**	**4.58-8.11**	**7.28**	**5.41-9.15**
	3.07	1.81-4.33	2.72	1.56-3.87	2.66	1.53-3.80
	4.02	2.58-5.47	3.08	1.85-4.31	3.38	2.10-4.65
	—	—	—	—	—	—
	7.47	**5.50-9.44**	**8.16**	**6.16-10.16**	**11.01**	**8.71-13.32**
	3.26	1.96-4.56	2.36	1.28-3.43	4.26	2.83-5.70
	—	—	—	—	—	—
	3.64	**2.27-5.01**	**5.80**	**4.11-7.49**	**5.68**	**4.03-7.34**
	1.53	0.64-2.42	2.72	1.56-3.87	2.84	1.67-4.01
	—	—	—	—	—	—
	1.72	**0.78-2.67**	**4.35**	**2.89-5.81**	**5.33**	**3.73-6.93**
	0.77	0.14-1.40	1.81	0.87-2.76	2.31	1.26-3.36
	0.77	0.14-1.40	0.18	-0.12-0.48	0.53	0.03-1.04
	—	—	—	—	—	—
	0.96	**0.25-1.66**	**2.72**	**1.56-3.87**	**1.42**	**0.59-2.25**

a less dramatic ratio of 2.5:1 for T cell lymphoblastic lymphoma in the latter series.[19] Similar data were observed for mature B cell leukemia in the French report. While there are no obvious explanations for this gender difference, it has been suggested that it may reflect a suppressor gene on the X chromosome.[19]

In several diagnostic groups females have higher incidence rates, including renal tumours (male:female ratio, 0.76:1). In the European data, sex differences were not noted. However, SEER data for 2001–2003 noted higher incidence rates in females than in males, with a male:female ratio of 0.87:1. Other tumours demonstrating female predominance include germ cell tumours (0.77:1) and other epithelial tumours (0.59:1).

Although the incidence trends by gender are generally stable over the entire period from 1985 to 2004, some changes have occurred. Among ependymoma and choroid plexus tumours the male:female ratio for the entire period is 1.15:1, although in the earliest period, 1985–1989, the male:female ratio was 0.84:1 and steadily climbed to the last period, 2000–2004, when it was 2.30:1. In contrast, among thyroid tumours the male:female ratio for the entire period was 0.45:1, although in the earliest period, 1985–1989, the ratio was 0.95:1 and steadily decreased to 2000–2004, when it was 0.22:1. A similar dramatic rise in average incidence rate of 5% per year between 1981 and 2009 has been described in young women aged 15–29 years between 1981 and 2009 in Ontario.[20]

Mapping and Spatial Distribution

The POGONIS database contains the 6 character postal code of the addresses of registered cases at the date of diagnosis. These postal codes can be linked to the 2001 Census Divisions for Ontario, permitting mapping of the variations of ASIRs across the province and exploration of differences in incidence.

A search of the literature revealed no reports of mapping of incidence rates for childhood cancer in Canada, either across provinces and territories or within any of these jurisdictions.

For the U.S., tables of incidence rates and maps displaying incidence rates are available for all cancers, including childhood cancers, across counties for each state.[21] We followed the methods described in this publication for reporting data by census division and mapping the incidence rates.

To obviate potential methodologic problems that would be caused by changes in population density and census definitions over the 20 years covered by this chapter, only the cases recorded in the 10 year period 1995–2004 were used for this exercise. For each census division we reviewed the number of incident cases of childhood cancer and recorded the incidence rate for the 10 years per 100,000 children, along with the lower and upper limits of the confidence intervals for the reported rates. The incidence rates are adjusted to the age distribution of children in Ontario as reported for the 2001 census.

We report the data for the 24 census divisions that had at least 30 incident cases of childhood cancer during the 10 year period. Census divisions with fewer than 30 incident cases were excluded for 2 reasons: 1) the estimates of incidence rates for census divisions with small numbers of cases may not be stable and 2) we wished to avoid the possibility of indirect identification of the individual children diagnosed with cancer.

EXHIBIT 3.6: **Ontario census divisions with ≥ 30 childhood cancer incident cases, age 0–14 years, in Ontario, 1995–2004**

Census division number	Census division name (alphabetically)	No. of children aged 0–14 years (2001)	No. of incident cases of cancer	Incidence rate per million	95% CI
57	Algoma District	21,025	35	166.50	114.10-221.60
28	Brant County	23,840	35	146.80	98.20-195.40
18	Durham Regional Municipality	115,565	170	147.10	125.00-169.20
37	Essex County	75,580	82	108.50	85.00-132.00
10	Frontenac County	23,235	62	255.80	192.20-319.40
53	General Sudbury Division	28,380	48	169.10	121.30-216.90
28	Haldimand-Norfolk Regional Municipality	20,970	45	214.60	152.00-277.20
24	Halton Regional Municipality	77,000	118	153.20	125.60-180.90
25	Hamilton Division	94,390	148	156.80	131.60-182.00
12	Hastings County	23,835	32	134.30	87.80-180.70
39	Middlesex County	78,780	125	158.70	130.90-186.50
26	Niagara Regional Municipality	74,915	114	152.20	124.30-180.10
48	Nipissing District	15,425	31	201.00	130.30-271.60
6	Ottawa Division	146,145	259	177.00	155.70-198.80
32	Oxford County	50,595	33	160.20	105.60-214.90
21	Peel Regional Municipality	217,290	367	168.90	151.60-186.20
15	Peterborough County	22,465	32	142.40	93.10-191.80
43	Simcoe County	80,245	125	155.80	128.50-183.10
1	Stormont, Dundas and Glengarry United Counties	21,395	30	140.20	90.10-190.40
58	Thunder Bay District	28,310	36	127.20	85.60-168.70
20	Toronto Division	433,810	662	152.60	141.00-164.20
30	Waterloo Regional Municipality	91,000	138	151.60	126.40-176.90
23	Wellington County	38,730	75	193.60	149.90-237.40
19	York Regional Municipality	155,715	255	163.80	143.70-183.80

CI = confidence interval

EXHIBIT 3.7: **Ontario census divisions with < 30 childhood cancer incident cases excluded from analysis, age 0–14 years, in Ontario, 1995–2004**

Census division number	Census division name (alphabetically)	No. of children aged 0–14 years (2001)
41	Bruce County	11,685
36	Chatham-Kent County	21,205
56	Cochrane District	17,730
22	Dufferin County	12,200
34	Elgin County	17,450
42	Grey County	16,315
40	Huron County	12,090
16	Kawartha Lakes Division	12,850
38	Lambton County	24,180
9	Lanark County	12,305
7	Leeds and Grenville United Counties	18,085
11	Lennox and Addington County	7,435
44	Muskoka District Municipality	9,180
14	Northumberland County	14,535
49	Parry Sound District	6,580
31	Perth County	15,435
2	Prescott and Russell United Counties	16,275
13	Prince Edward Division	4,170
47	Renfrew County	18,470
52	Sudbury District	4,220
54	Timiskaming District	6,410

Exhibits 3.6 and 3.7

Exhibit 3.6 displays the data of the 24 census divisions that had 30 or more incident cases of childhood cancer over the 10 year period, listed alphabetically. In the 2001 census data, the numbers of children ranged from just over 20,000 for Oxford County and Haldimand-Norfolk Regional Municipality to 433,810 in the Toronto Division. The numbers of incident cases ranged from 30 in Stormont, Dundas and Glengarry United Counties to 662 in the Toronto Division.

Exhibit 3.7 lists the census divisions with fewer than 30 incident cases of childhood cancer that were excluded from the analysis. They are located throughout Northern and Southern Ontario.

EXHIBIT 3.8: **Incidence rate of childhood cancer per 100,000, by census division, age 0-14 years, in Ontario by tertile,1995-2004**

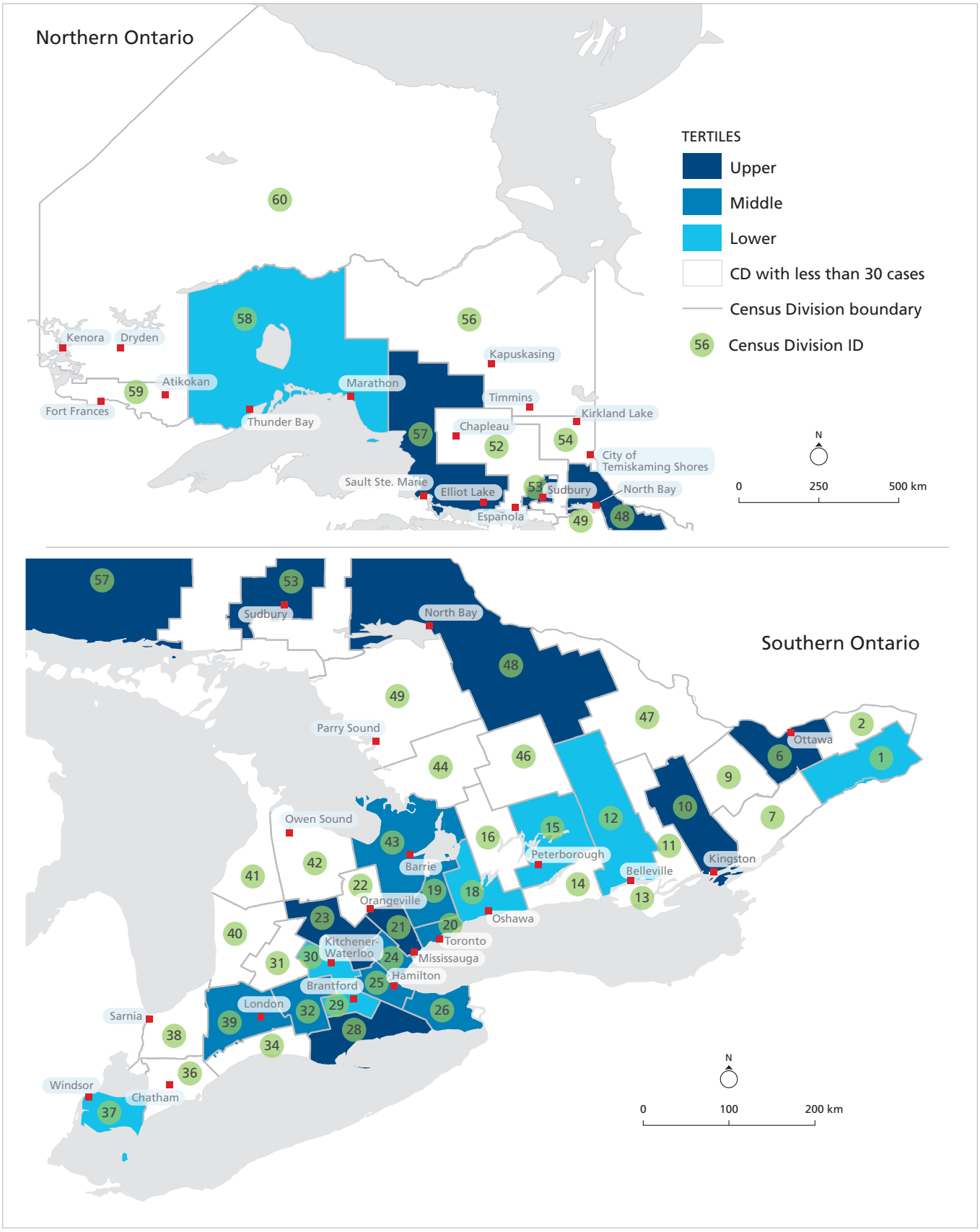

Exhibit 3.8

The incidence rates for the 24 census divisions were divided into lower, middle and upper tertiles; the rankings are displayed on a choropleth map (Exhibit 3.8). The census divisions in the lower and upper tertiles are located in Northern and Southern Ontario; the census divisions in the middle tertiles are located in Southern Ontario, west of Durham Region.

There are limitations to using choropleth maps for large areas, as exhibited on the map. First, the summary of regional variations assumes that if risk factors exist, they are common within each region. Second, there is a presumption that the rates are uniform within each census division, even though they likely vary across given units within divisions. Finally, shifts in colours across tertiles suggest that rates change abruptly between divisions, whereas the divisions are artificial and rates blend between divisions.

EXHIBIT 3.9: **Incidence rates by census division, age 0–14 years, in Ontario, 1995–2004**

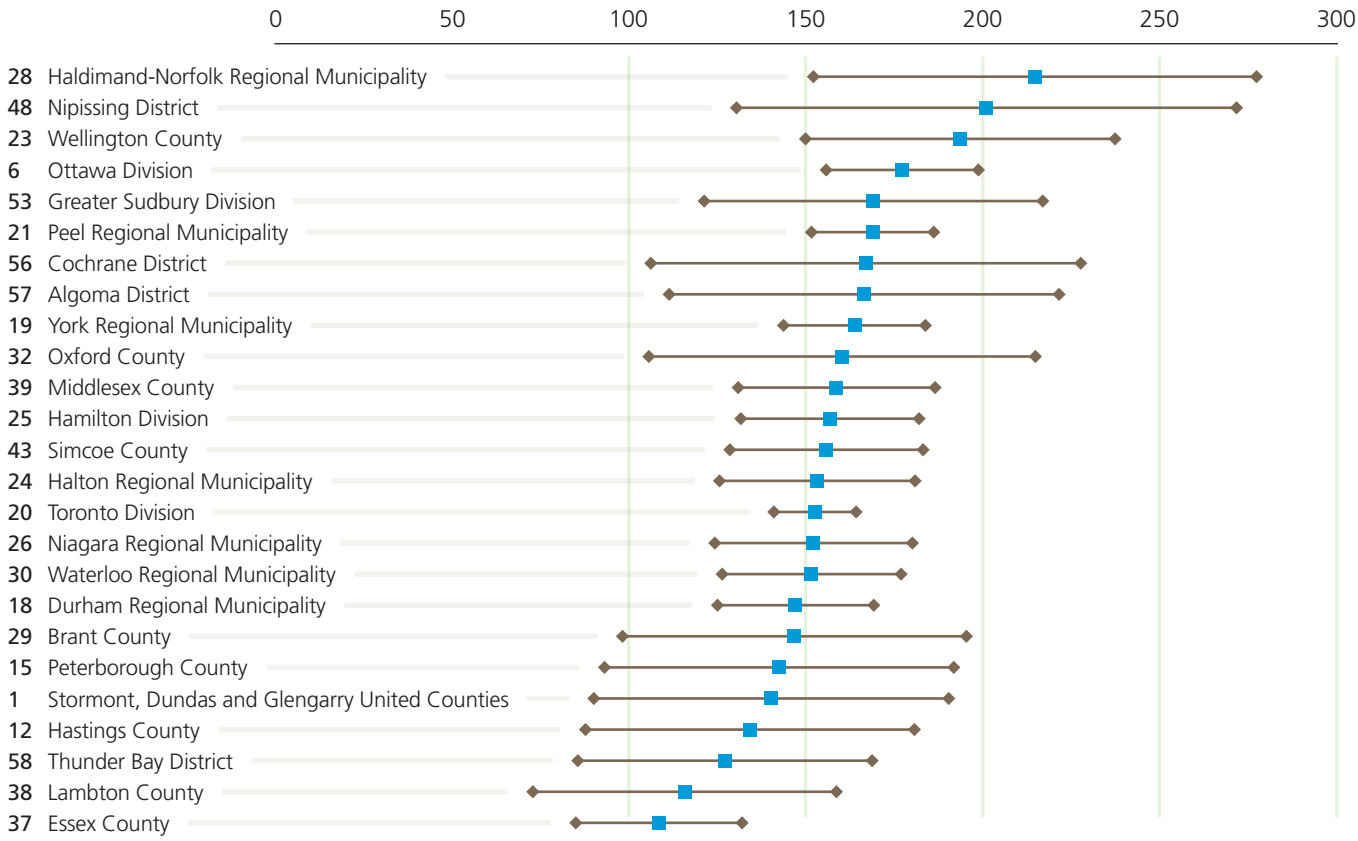

Exhibit 3.9

Exhibit 3.9 displays the variations in incidence rates of childhood cancer across the divisions and the corresponding confidence intervals. The range of the confidence intervals is determined in part by the number of children in each division. Census divisions with fewer children have larger confidence intervals. While the rates show an almost 2-fold difference between the minimum and maximum values, the confidence intervals overlap in most cases, rendering the differences not statistically significant. The variations in rates across the study area thus could have occurred by chance.

It should be noted that the results, statistics and regional variation in the map are comparable to the data and maps reported for Michigan, Ohio and Pennsylvania, the 3 U.S. states south of Ontario.

Another approach to mapping rates of rare cancer is to interpolate regional data onto a continuous surface for the estimating spatial risk function. Kriging is a geostatistical procedure for predicting values of incidence across the entire region from a scattered set of points with known values. The first step to achieving this was to use geographic information systems to define the census divisions as polygons and to place the known incidence rate at the centre of the geographic space for each census division.

The interpolation method for estimating the patterns for incidence rates across the province uses the concept of spatial autocorrelation or similarity of values of incidence rates in locations close to the known data points. The magnitude of the correlations for known points is inversely related to the distance between those points. The method fits a mathematical function for predicting a value (incidence rate) for each location within a specified search radius. Kriging is completed in 2 stages: the creation of variograms and covariance functions to estimate the statistical dependence called spatial correlation, and the prediction of unknown values.

EXHIBIT 3.10: **Incidence rate of childhood cancer per 100,000 by census division, age 0-14 years, in Ontario, 1995-2004**

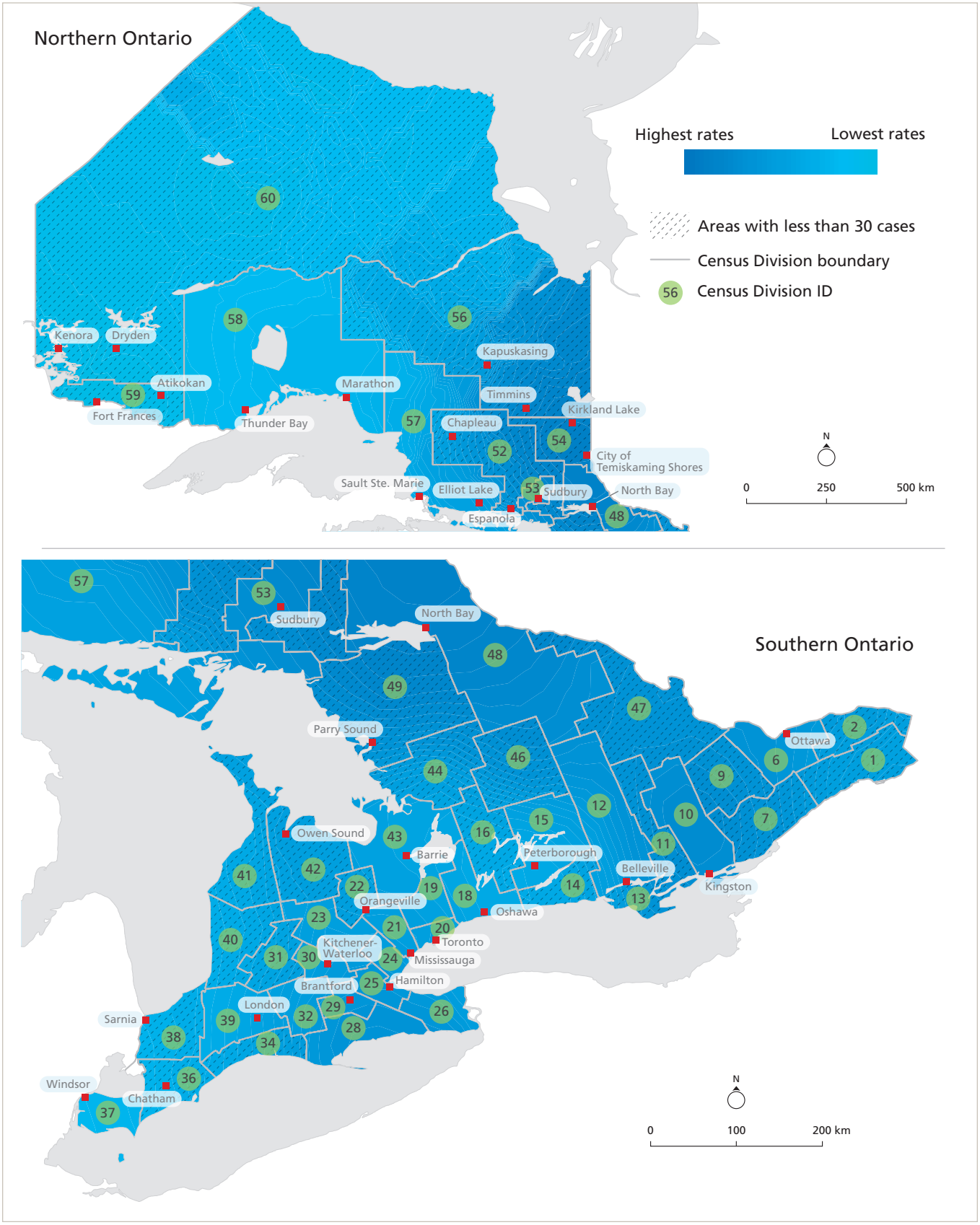

Exhibit 3.10

Exhibit 3.10 displays the map based on the Kriging procedure. To make the estimating of patterns for incidence rates across the province as complete as possible, we included all census divisions. The census divisions with dots are those with fewer than 30 incident cases.

The darkest shades for higher estimates spread from the lower part of Cochrane District down through Timiskaming District, through Nipissing District below North Bay to the Greater Sudbury Division and Parry Sound District. Dark shading is evident for Frontenac County as well. The light shades are evident primarily for census divisions in Northern Ontario and the southwestern parts of the province.

As Berke[22] notes, exploratory disease mapping provides insight into disease distribution, not specific precise estimates of location and spread. The Kriging map serves to generate questions and hypotheses about the epidemiology of childhood cancer.

Summary

A large geographically-defined population cohort of subjects aged 0–14 years diagnosed with childhood cancer in the Province of Ontario between 1985 and 2004, collected in an active database, was analyzed to assess trends in incidence, age distribution and gender. Efforts were made to map incidence rates across census divisions.

Incidence rates in Ontario were largely comparable both to pan-Canadian rates and to rates in international jurisdictions. By far the highest incidence rate was seen for acute leukemia, in particular ALL. This entity occurred predominantly in the 1–4 year age quartile and showed no change in incidence over the 20 year period. Similarly, tumours of the CNS, the second most common diagnostic group, demonstrate the highest rates in the 1–4 year group, largely comprising astrocytomas. While there was an increase in incidence rates in the late 1980s and early 1990s, this is thought to reflect the introduction of imaging screening for asymptomatic low grade gliomas in patients with neurofibromatosis type 1 over that period. Subsequent rates returned to baseline levels.

Lymphoma incidence rates did not demonstrate increases over the period of study. Burkitt lymphoma demonstrated a marked male predominance, a finding reported in other jurisdictions. No clear explanation is known. Substantial changes in male:female ratios were also demonstrated for ependymoma and choroid plexus tumours (which showed an increase in the male:female ratio) and thyroid cancer, which demonstrated both a significant increase in incidence and a steady reduction in the male:female ratio in this age group – a finding similar to that in the older adolescent and young adult group.

Despite meticulous efforts to identify differing geographic distribution, no such finding was established.

The presence of incidence rates similar to those of other jurisdictions both permits comparison and invites re-analysis using contemporary diagnostic tools to clarify sub-group distribution. As such techniques become more sophisticated, it may be possible to demonstrate differing incidence rate trends between molecularly-defined subgroups of childhood cancer acknowledged in the ICCC-3.

References

1 Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer. 2005 Apr 1;103(7):1457-67.

2 Statistics Canada. Table 051-0001-Estimates of popultaion, by age group and sex for July 1, Canada, provinces and territories, annual (person unless otherwise noted) CANSIM (database) [cited 2014 Nov 25].

3 Public Health Agency of Canada. Childhood cancer facts and figures. http://www.phac-aspc.gc.ca/cd-mc/cancer/childhood_cancer_figures-cancer_enfants-eng.php. 2013.

4 Canadian Cancer Society/National Cancer Institute of Canada. Canadian cancer statistics 2008. Toronto: The Society; 2008.

5 Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER cancer statistics review, 1975-2002. Pediatric Blood Cancer. Bethesda, MD: National Cancer Institute; 2005

6 Stiller CA, Marcos-Gragera R, Ardanaz E, Pannelli F, Almar Marqués E., Can˜ada MA, et al. Geographical patterns of childhood cancer incidence in Europe, 1988-1997. Report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):1952-60.

7 Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL. Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics. 2008 Jun;121(6):e1470-7.

8 Lacour B, Guyot-Goubin A, Guissou S, Bellec S, Desandes E, Clavel J. Incidence of childhood cancer in France: National Children Cancer Registries, 2000-2004. Eur J Cancer Prev. 2010 May;19(3):173-81.

9 Steliarova-Foucher E, Stiller CA, Pukkala E, Lacour B, Plesko I, Parkin DM. Thyroid cancer incidence and survival among European children and adolescents (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):2150-69.

10 Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. Bethesda, MD: National Cancer Institute; 2013.

11 Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MP, Kuehni CE, et al. Incidence of childhood cancer in Switzerland: the Swiss Childhood Cancer Registry. Pediatr Blood Cancer. 2008 Jan;50(1):46-51.

12 Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, et al. Trends in incidence of childhood cancer in Australia, 1983-2006. Br J Cancer. 2010 Feb 2;102(3):620-6.

13 Birch JMH. A classification scheme for childhood cancer. Int J Cancer. 1987 Nov 15;40(5):620-4.

14 Sievert AJ, Fisher MJ. Pediatric low-grade gliomas. J Child Neurol. 2009 Nov;24(11):1397-408.

15 Agha M, DiMonte B, Greenberg M, Greenberg C, Barr R, McLaughlin JR. Incidence trends and projections for childhood cancer in Ontario. Int J Cancer. 2006 Jun 1;118(11):2809-15. [Erratum appears in Int J Cancer. 2006 Nov 15;119(10):2503].

16 Dalmasso P, Pastore G, Zuccolo L, Maule MM, Pearce N, Merletti F, et al. Temporal trends in the incidence of childhood leukemia, lymphomas and solid tumors in north-west Italy, 1967-2001. A report of the Childhood Cancer Registry of Piedmont. Haematologica. 2005 Sep;90(9):1197-204.

17 Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev. 2010 Jun;36(4):277-85.

18 Pastore G, Znaor A, Spreafico F, Graf N, Pritchard-Jones K, Steliarova-Foucher E. Malignant renal tumours incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):2103-14.

19 Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005 Oct;131(1):39-49.

20 Cancer Care Ontario. Cancer fact: thyroid cancer driving the rise in cancers in young women. April 2013. https://www.cancercare.on.ca/cms/One.aspx?portalid=1377&pageid=274075 .

21 National Cancer Institute. State Cancer Profiles. http://statecancerprofiles.cancer.gov

22 Berke O. Exploratory disease mapping: Kriging the spatial risk function from regional count data. Int J Health Geog. 2004 Aug 26;3(1):18.

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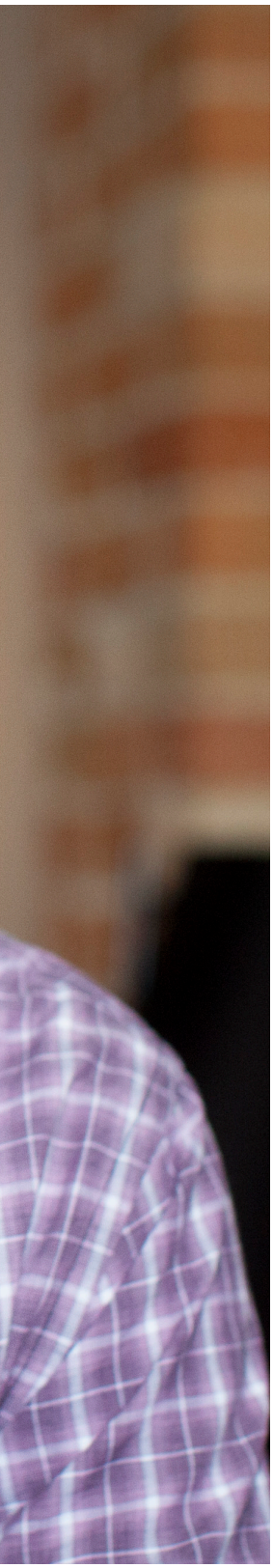

4

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**

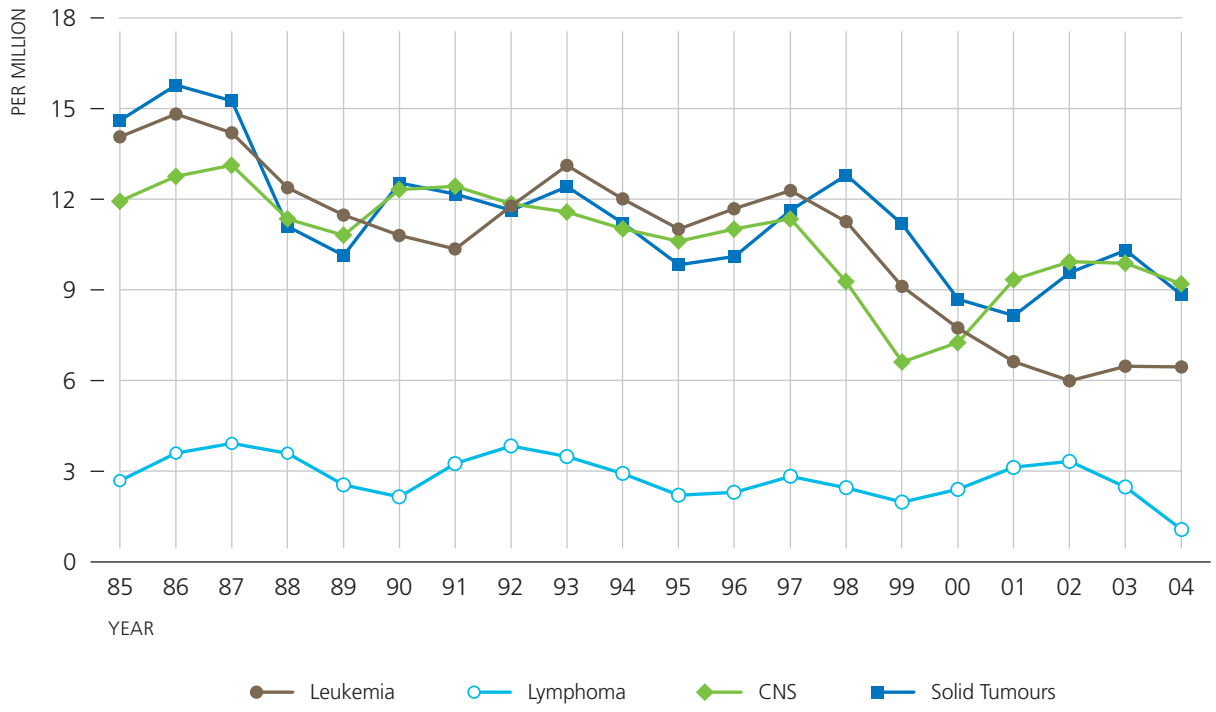

Exhibit 4.2

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.

References

1 Ries L, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda (MD): National Cancer Institute, SEER Program; 1999.

2 Craft AW. Childhood cancer—mainly curable so where next? Acta Paediatr. 2000;89(4):386-92.

3 Public Health Agency of Canada. Leading causes of death and hospitalization in Canada, 2010 [cited 2010 Oct 2]. Available from http://www.phac-aspc.gc.ca/publicat/lcd-pcd97/table1-eng.php.

4 Canadian Cancer Society/National Canadian Institute of Canada. Canadian cancer statistics 2008. Toronto: The Society; 2008.

5 National Cancer Institute. Statistics stratified by data type, 2010 [cited 2010 Oct 2]. Available from http://seer.cancer.gov/faststats/selections.php?#Output.

6 Villeneuve PJ, Raman S, Leclerc JM, Huchcroft S, Dryer D, Morrison H. Survival rates among Canadian children and teenagers with cancer diagnosed between 1985 and 1988. Cancer Prev Control. 1998;2(1):15-22.

7 Ellison LF, Pogany L, Mery LS. Childhood and adolescent cancer survival: a period analysis of data from the Canadian Cancer Registry. Eur J Cancer. 2007;43(13):1967-75.

8 Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. [Review] [52 refs]. Lancet. 2004;363(9405):263-70.

9 Birch JM, Marsden HB. A classification scheme for childhood cancer. Int J Cancer. 1987;40(5):620-4.

10 Fritz A, Percy C, Jack A. International classification of diseases for oncology. 3rd ed. Geneva: World Health Organization; 2000.

11 Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer. 2005;103(7):1457-67.

12 Birch JM, Alston RD, Kelsey AM, Quinn MJ, Babb P, McNally RJ. Classification and incidence of cancers in adolescents and young adults in England 1979-1997. Br J Cancer. 2002;87(11):1267-74.

13 Greenberg ML, Barr RD, DiMonte B, McLaughlin E, Greenberg C. Childhood cancer registries in Ontario, Canada: lessons learned from a comparison of two registries. Int J Cancer. 2003;105(1):88-91.

14 Fellegi IP, Sunter AB. A theory for record linkage. J Am Statist Assoc. 1969;64(328):1183-210.

15 Statistics Canada CANSIM Data. Website 2007 November 29 [cited 2008 Apr 27]. Available from http://www40.statcan.ca/l01/cst01/demo31a.htm?sdi=population.

16 Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer. 1996;78(9):2004-10.

17 Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. J Clin Epidemiol. 1997;50(2):211-6.

18 Ellison LF. An empirical evaluation of period survival analysis using data from the Canadian Cancer Registry. Ann Epidemiol. 2006;16(3):191-6.

19 Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. Eur J Cancer. 2004;40(3):326-35.

20 Brenner H, Hakulinen T. Period versus cohort modeling of up-to-date cancer survival. Int J Cancer. 2008;122(4):898-904.

21 Dickman P. Paul Dickman, 2009. Available from http://www.pauldickman.com/.

22 Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL. Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics. 2008;121(6):e1470-7.

23 Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, et al. Trends in incidence of childhood cancer in Australia, 1983-2006. Br J Cancer. 2010;102(3):620-6.

24 Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. J Nat Cancer Inst. 1998;90(17):1269-77.

25 Woods WG, Tuchman M, Robison LL, Bernstein M, Leclerc JM, Brisson LC, et al. A population-based study of the usefulness of screening for neuroblastoma. Lancet. 1996;348(9043):1682-7.

26 Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27(14):2328-38.

27 Reulen RC, Winter DL, Frobisher C, Lancashire ER, Stiller CA, Jenney ME, et al. Long-term cause-specific mortality among survivors of childhood cancer. JAMA. 2010;304(2):172-9.

28 Woods WG, Neudorf S, Gold S, Sanders J, Buckley JD, Barnard DR, et al. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission. Blood. 2001;97(1):56-62.

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5

Health Service Utilization

Executive Summary

Health care service utilized by a population-based cohort of children diagnosed with cancer between 1995 and 2004 was analyzed using a database held by the Pediatric Oncology Group of Ontario, linked to a series of administrative databases held by the Institute for Clinical Evaluative Sciences (ICES). The cohort was followed until death or the end of the study period in December 2008.

Health service utilization was assessed using hospital admissions, length of stay, physician encounters and selected imaging studies as indicators. Comparisons were made to an age, gender and geographically matched control population.

Rate ratios for hospital admissions and length of stay were elevated many hundredfold for cases in the first month after diagnosis and remained so for up to 6 months after diagnosis. While there was subsequently a steady drop in the rate ratios, even 2 years after diagnosis these ratios were in excess of 50-fold and persisted at approximately 20-fold beyond 3 years from diagnosis. Patients with leukemia contributed the highest proportion of admissions and days of stay for the first 6 months, followed by those with lymphoma.

Rate ratios for physician encounters were similarly elevated in cases compared with controls, notwithstanding the systematic underestimation of physician services as a result of alternative payment plans (APPs).

Since these evaluations do not encompass use of diagnostic services and most imaging, they are a minimal estimate. The results indicate, however, the extraordinarily high consumption of health services, persisting over long periods, that is one of the hallmarks of a diagnosis of childhood cancer. Imaging use rate ratios for cases compared with controls for ambulatory computed tomography (CT) and magnetic resonance imaging (MRI) ranged from 1,500-fold in the first month to several hundredfold in the third year after diagnosis and 25-fold thereafter.

These results have the following policy implications:

- Childhood cancer cure rates are one of the most remarkable successes of contemporary medicine. However, the health care cost of success is enormous.
- Resource allocation for the management of this population must necessarily be intensified.
- Intensified resource allocation must encompass human resources in directly involved disciplines, but also in such disciplines as diagnostic imaging, pathology and pharmacy, among others.
- There is no clear end to the duration of increased health care utilization, so appropriate resources must stretch into the post treatment and survivorship period.
- Beyond the period of active treatment and follow up, childhood cancer survivors continue to use substantial health care resources that are not accounted for in resource allocation.

Introduction

The pattern of illness, and therefore care, in childhood cancer has a particular blend of acute and chronic characteristics. Patients may present critically ill or with large tumours, symptomatic in some but not all cases. Early interventions are of high intensity and result in high acuity of illness. Treatment in most cases stretches over prolonged periods and follows a pattern of repeated high, albeit variable, intensity interventions using varying combinations of surgery, chemotherapy, stem cell transplant and radiation.

In the most common childhood cancer, acute lymphoblastic leukemia, protracted ambulatory maintenance therapy is employed, with primary cancer therapy continuing for up to 3 years after diagnosis. During the course of active therapy, unscheduled ambulatory visits and hospital admissions often occur as a result of complications of the aggressive therapy. Ambulatory visits often involve consultation with multiple specialties and extensive use of diagnostic, laboratory and physiologic monitoring services.

Completion of therapy dramatically reduces health care utilization but demands intensive surveillance for recurrence in the first 2 to 3 years – for some cancers even longer. Even after the period of highest risk for recurrence is over, the pattern of health care utilization does not revert to that of the non-cancer population.

As described in several sections of this Atlas, survival rates for children with cancer have risen substantially over the past 2 decades[1,2]. This survival improvement is the result of better understanding of the use of combinations of treatment modalities, more rational use of combinations of chemotherapy agents and more intensive therapy enabled by better supportive care. These shifts in treatment intensity have produced corresponding demands on the health care system; this chapter describes some dimensions of that demand.

This chapter addresses health care utilization by children aged 0–14 years at diagnosis who were treated for cancer in Ontario between 1995 and 2004, with follow up to December 2008. This cohort was selected because detailed treatment data are available and correlation with health care utilization is possible. Health care utilization from the time of diagnosis until death or the end of the follow up period has been analyzed. A separate analysis of utilization from the time therapy is completed is also presented. These latter analyses of health care utilization by off-treatment subjects encompass a different timeframe from other published descriptions of utilization by survivors, which focus on survivors of childhood cancer beyond 2 years from completion of therapy.[3] While there may be some overlap, the period after completion of therapy is not further analyzed in this chapter.

For the purposes of this chapter, health care utilization has been defined as

- Hospital admissions and duration of stay (in days), expressed as rates per person time by time period after diagnosis
- Physician visits, including inpatient and ambulatory visits, but excluding emergency room visits
- Utilization rates for selected high intensity imaging studies for which billing data are available

The documentation of physician visits is based on physician billing to the Ontario Health Insurance Plan (OHIP). In the academic health science centres, "shadow billing" has been used for many years – the funding process is an APP but physicians are required to shadow bill to justify APP expenditure on physician services. Because physician reimbursement does not directly depend on billing, it is known that shadow billing substantially underestimates the actual number and type of services delivered, with variation over time and by centre because APPs were introduced at different times in different centres. Thus the quantification of physician visits is considered a substantial underestimate of utilization, amplified by the fact that the majority of physician visits for the control population are actual billings for services delivered outside the academic health centre environment, tending to reduce the rate ratio.

Since rules governing billing for diagnostic imaging have varied over time depending on whether the imaging is conducted in the ambulatory or inpatient setting, only diagnostic imaging services for which allowable billing is consistent over the timeframe of the analysis were analyzed.

A further contribution to underestimation of actual service use relates to the observation made above that an ambulatory visit almost always involves substantial use of diagnostic, laboratory and physiologic monitoring services, which represent health care utilization but are funded through hospital global budgets and thus are not billed and cannot be tracked.

Analyses that focus on health care utilization during the period of active therapy include all cases newly diagnosed in the study period irrespective of subsequent disease status. This dataset is analyzed from the time of primary diagnosis to time of death or the end of the follow up period, broken down by month for the first 6 months and then by 6 month periods until more than 3 years from primary diagnosis. It should be noted that the date of diagnosis is defined in the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) database as "the date when definitive procedure confirming the diagnosis was carried out." For patients with solid tumours, including the central nervous system (CNS) group, a clinical diagnosis may have been made several days or more prior to this definitive procedure, and investigations, including diagnostic imaging, initiated. Such investigations would not have been captured since the starting point for the identification of health service utilization is the date of diagnosis. Similarly, days of hospitalization would have been systematically underestimated in this group. Thus all measures of utilization may be systematically underestimated, particularly with respect to inpatient stays.

Furthermore, significant delays in initial diagnosis in the primary care context and referral to the tertiary centre have been documented in the literature in a proportion of cases.[4–6] During this period, increased health care service utilization as a result of multiple visits and substantial use of diagnostic services, including extensive and costly use of imaging, laboratory and pathology resources, has often occurred. Such utilization prior to referral is not quantified in this chapter, thereby further underestimating true health care utilization.

The utilization for the period after completion of therapy is categorized monthly for the first 6 months to highlight immediate post therapy use and then by 6 month blocks until 24 months, yearly from 25 to 36 months and total visits beyond 36 months to the end of the follow up period. Completion of therapy is defined as a confirmed entry in the database indicating the end date of therapy. A small proportion of cases did not have a therapy end date, implying that they remained on therapy at the end of the follow up period and may thus have relapsed, or that they had died prior to the end of therapy.

Over the period analyzed, 20–25% of identified patients would have relapsed, either on treatment or after completion of treatment. A further, relatively small, number would have developed a second primary cancer. Health care utilization beyond 2 years from original diagnosis in these subgroups will be significantly higher but has been included in these analyses.

It is self-evident that children with chronic disease will use health care disproportionately compared with those without chronic disease. Data for health care utilization for chronic disease with episodic patterns of acute illness, such as asthma, demonstrate a substantial increase in hospitalization rates and ambulatory visits, albeit declining over the decades.[7] Data for children in Alberta with diabetes demonstrate 2.4 times the number of total physician visits in the youngest age group (aged < 5 years), compared with the equivalent age group in the general population, dropping to 1.5 and 1.8 times in the 5–9 year old and 10–14 year old groups, respectively.[8] Data for children with a developmental disability[9] also demonstrate substantial differences in hospital days compared with the general population (464 vs. 55 days per 1,000 population), non-physician professional visits (3.0 vs. 0.6) and home health provider days (3.8 vs. 0.04). In contrast to children with cancer, the highest consuming 10% of children with disabilities accounted for 65% of the total health care expenses of the cohort.

Patterns of care in all these categories differ from those in childhood cancer, however. Thus, we wished to identify how and to what degree patterns of health care utilization by childhood cancer patients differ from those of the non-cancer population. For this purpose, the childhood cancer population has been matched 5:1 to a cohort of non-cancer patients, as described below. Health care utilization over an identical timeframe has been used for comparison. It is acknowledged that this control group contains children with other chronic diseases.

Methods

Datasets

The cohorts were assembled and data collected as follows:

- Data on all children resident in Ontario diagnosed with cancer at age less than 15 years between 1995 and 2004, including demographic, diagnosis, treatment, relapses and death information, was obtained from POGONIS.
- Information on hospital admissions was obtained from the Discharge Abstract Database of the Canadian Institute for Health Information (CIHI-DAD), regardless of where in Ontario the hospitalization took place. This database includes admission dates and the diagnoses and procedures coded on hospital discharge.
- Information on physician visits was obtained from the OHIP database. This database includes date of service provision, service provision code and physician type.
- The Registered Persons Database (RPDB) is Ontario's population-based health care registry, which provides basic demographic information (date of birth, date of death, address changes) about individuals who have ever received an Ontario Health Insurance Number (OHIN).

These databases were linked using, a unique identifier, the OHIN assigned to each individual by the Ontario Ministry of Health and Long-Term Care. OHINs are scrambled and all identifying information stripped in the research version of these databases.

The dataset assembled from POGONIS was securely transferred to the ICES and then linked with the RPDB. Linkage was performed using the child's OHIN, name, date of birth, gender, postal code at the time of diagnosis and, where necessary, a probabilistic record linkage. Linkage was achieved for 3,256 of the 3,267 cases in the dataset (greater than 99%). These linked cases constituted the cohort followed for health service utilization.

Controls were selected using the RPDB based on the following matching criteria: month and year of birth, gender and forward sortation area, which is the first 3 characters of a postal code. Up to 5 controls were selected using either all 4 matching criteria or, when that was not possible, matches based on the first 3 criteria; 15,771 controls were selected.

The cancer diagnosis date of each case was assigned to the case's matched controls as the starting point for follow up. In the event of death of the index case, the matched controls were censored on the date of death of the cancer case. Person years of follow up were calculated for all cases and their matched controls from the date of diagnosis until either the time of death, censuring date or end of follow up (December 31, 2008).

All cases and controls were then linked to the CIHI and OHIP databases using encrypted OHINs to collect data on all admissions to hospitals and physician visits during the follow up period. The CIHI database was used to obtain data on admission dates, discharge dates and length of stay. The OHIP database was used to obtain data on each physician service received.

The comparative analyses are expressed for all children with cancer, encompassing all categories in the International Classification of Childhood Cancer, version 3 (ICCC-3), and compared with all children who did not have cancer. To dissect the contribution of different cancer types, further analyses were conducted for 4 groups of disease categories within ICCC-3 – leukemia, lymphoma, CNS tumours and "other," which combines all other groups. These subset analyses are not compared with control populations.

Discussion

EXHIBIT 5.1a: **Hospital separation* rate (per person month) and rate ratio by time since diagnosis, for cases and matched controls, age 0–14 years, in Ontario, 1995–2004**

	Cases				Controls		
Time since diagnosis	No. of patients	No. of separations	Person years	Separation rate/month	No. of separations	Person years	Separation rate/month
1 month	3256	3903	268.97	1.21	83	1295.64	0.005
2 months	3208	3074	266.61	0.96	55	1285.17	0.004
3 months	3191	2801	265.00	0.88	33	1277.26	0.002
4 months	3171	2522	263.41	0.80	34	1269.74	0.002
5 months	3151	2265	262.08	0.72	35	1263.16	0.002
6 months	3138	1946	260.34	0.62	39	1254.55	0.003
7–12 months	3113	7178	1523.36	0.39	190	7342.23	0.002
13–18 months	2982	3493	1459.90	0.20	197	7033.92	0.002
19–24 months	2868	2335	1415.26	0.14	154	6825.81	0.002
25–36 months	2795	3478	2755.12	0.11	284	13285.47	0.002
More than 3 years	2719	4803	12813.02	0.03	1425	61872.60	0.002

All rates are calculated per month (even for periods longer than 1 month).
CI = confidence interval
*Hospital separation = number of cases discharged plus the number of inpatient deaths

EXHIBIT 5.1b: **Hospital stay rate* (per person month) and rate ratio by time since diagnosis, for cases and matched controls, age 0–14 years, in Ontario, 1995–2004**

	Cases				Controls		
Time since diagnosis	No. of patients	Stay days	Person years	Stay rate/month	Stay days	Person years	Stay rate/month
1 month	3256	30341	268.97	9.40	242	1295.64	0.02
2 months	3208	15927	266.61	4.98	163	1285.17	0.01
3 months	3191	13988	265.00	4.40	82	1277.26	0.01
4 months	3171	12501	263.41	3.95	72	1269.74	0.00
5 months	3151	11068	262.08	3.52	162	1263.16	0.01
6 months	3138	9462	260.34	3.03	123	1254.55	0.01
7–12 months	3113	30346	1523.36	1.66	667	7342.23	0.01
13–18 months	2982	14684	1459.90	0.84	548	7033.92	0.01
19–24 months	2868	9488	1415.26	0.56	387	6825.81	0.00
25–36 months	2795	14089	2755.12	0.43	1171	13285.47	0.01
More than 3 years	2719	21923	12813.02	0.14	5148	61872.60	0.01

All rates are calculated per month (even for periods longer than 1 month).
*Stay rate is based on total number of days patient was hospitalized during each admission. Stay lengths were added for multiple admissions during same period.
Stay rate = (total stay length for all patients during period) / (12 × total person years of follow up).
CI = confidence interval

Separation rate ratio	
Rate ratio	95% CI
226.52	182.26-281.53
269.42	206.36-351.74
409.11	290.26-576.62
357.55	254.91-501.54
311.90	223.37-435.52
240.45	175.13-330.14
182.09	157.66-210.30
85.43	74.01-98.61
73.13	62.12-86.08
59.05	52.33-66.65
16.28	15.34-17.27

Stay rate ratio	
Rate ratio	95% CI
603.94	532.18-685.38
471.01	403.66-549.59
822.21	661.77-1021.55
836.93	663.87-1055.10
329.29	281.97-384.54
370.70	310.30-442.87
219.28	203.09-236.77
129.10	118.55-140.60
118.24	106.82-130.90
58.02	54.66-61.58
20.56	19.95-21.20

Exhibits 5.1a and 5.1b

Not surprisingly, the separation rate, the term used for discharge (reflecting admission rate), is highest in the first month after diagnosis, with a mean of more than 1 admission per person month. The rate ratio compared with that of controls is strikingly high, with reasonable confidence intervals, limited by the low number of events in the control group. The separation rates drop slowly over the first 6 months, with rate ratios maintained at greater than 300-fold higher for virtually this entire period.

Similarly, the days of hospital stay (designated in this chapter as stay rate) is strikingly high, with a nearly 600-fold higher rate ratio in the first month. Hospital stay rates are dictated by the acuity of illness in this period. These rates drop steeply in the second and subsequent months, but remain substantially higher than for the control population in the first 6 months (rate ratio range, 329.3–836.9). The admission and stay rates comprise planned admissions for therapy and unplanned admissions for complications of therapy.

While the admission and stay rates decline consistently after 6 months, they remain elevated to 24 months after initiation of therapy and beyond. Between 25 and 36 months, when the majority of patients (excluding those with a diagnosis of acute lymphoblastic leukemia) have completed therapy, the rate ratio for separations is 59.1 and for stay rates, 58.0.

Even for the follow up period beyond 3 years after diagnosis (median subsequent follow up, 4.7 years), the rate ratio for admissions (16.3) and stays (20.6) remained elevated. Because cases who relapsed during this time were not excluded from this analysis, they may make some contribution to this elevation. Of surviving patients, 43.7% contributed to hospital stays and days beyond 3 years. The leukemia group had the highest proportion (55.3%) of survivors with late hospital stays and lymphoma (30.4%) the lowest (data not shown).

The rate ratio for separations and stay rates demonstrated no trend for change over the two 5 year periods (1995–1999 and 2000–2004) analyzed, so the data have been combined. A recent practice shift toward providing more chemotherapy in an outpatient setting rather than during a hospital admission occurred after the period analyzed.

EXHIBIT 5.2: **Hospital separation* and hospital stay rate† (per person month) by time since diagnosis, by diagnosis group, age 0–14 years, in Ontario, 1995–2004**

	Time since diagnosis	No. of separations	Stay days	Person years	Separation rate/month	95% CI	Stay rate/month	95% CI
Leukemia	1 month	1483	16231	87.68	1.41	1.34-1.48	15.43	15.19-15.66
	2 months	1359	7286	86.85	1.30	1.24-1.38	6.99	6.83-7.15
	3 months	1280	6524	86.58	1.23	1.17-1.30	6.28	6.13-6.43
	4 months	1036	5452	86.26	1.00	0.94-1.06	5.27	5.13-5.41
	5 months	933	4591	86.09	0.90	0.85-0.96	4.44	4.32-4.57
	6 months	713	3522	85.73	0.69	0.64-0.75	3.42	3.31-3.54
	7–12 months	2358	10250	503.90	0.39	0.37-0.41	1.70	1.66-1.73
	13–18 months	1382	6275	485.79	0.24	0.22-0.25	1.08	1.05-1.10
	19–24 months	1189	4913	473.10	0.21	0.20-0.22	0.87	0.84-0.89
	25–36 months	1982	7866	926.73	0.18	0.17-0.19	0.71	0.69-0.72
	More than 3 years	2236	12853	4394.10	0.04	0.04-0.04	0.24	0.24-0.25
Lymphoma	1 month	477	2681	28.91	1.38	1.25-1.50	7.73	7.44-8.03
	2 months	337	1703	28.60	0.98	0.88-1.09	4.96	4.73-5.20
	3 months	290	1270	28.48	0.85	0.75-0.95	3.72	3.52-3.93
	4 months	251	1164	28.33	0.74	0.65-0.84	3.42	3.23-3.63
	5 months	175	888	28.17	0.52	0.44-0.60	2.63	2.46-2.81
	6 months	111	646	28.12	0.33	0.27-0.40	1.91	1.77-2.07
	7–12 months	562	2681	164.94	0.28	0.26-0.31	1.35	1.30-1.41
	13–18 months	341	1636	161.39	0.18	0.16-0.20	0.84	0.80-0.89
	19–24 months	194	1253	158.84	0.10	0.09-0.12	0.66	0.62-0.69
	25–36 months	241	1297	308.32	0.07	0.06-0.07	0.35	0.33-0.37
	More than 3 years	332	1703	1382.92	0.02	0.02-0.02	0.10	0.10-0.11
Central nervous system tumours	1 month	516	3885	58.67	0.73	0.67-0.80	5.52	5.35-5.69
	2 months	217	1308	57.93	0.31	0.27-0.36	1.88	1.78-1.99
	3 months	178	1032	57.04	0.26	0.22-0.30	1.51	1.42-1.60
	4 months	225	1016	56.35	0.33	0.29-0.38	1.50	1.41-1.60
	5 months	231	1009	55.86	0.34	0.30-0.39	1.51	1.41-1.60
	6 months	248	965	55.05	0.38	0.33-0.43	1.46	1.37-1.56
	7–12 months	1185	4026	315.46	0.31	0.30-0.33	1.06	1.03-1.10
	13–18 months	602	2102	294.39	0.17	0.16-0.18	0.60	0.57-0.62
	19–24 months	235	796	283.28	0.07	0.06-0.08	0.23	0.22-0.25
	25–36 months	286	1062	553.99	0.04	0.04-0.05	0.16	0.15-0.17
	More than 3 years	875	2834	2667.72	0.03	0.03-0.03	0.09	0.09-0.09

All rates are calculated per month (even for periods longer than 1 month).
†Stay rate is based on total number of days patient was hospitalized during each admission. Stay lengths were added for multiple admissions during same period.
Stay rate = (total stay length for all patients during period) / (12 × total person years of follow up).
CI = confidence interval
*Hospital separation = number of cases discharged plus the number of inpatient deaths

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EXHIBIT 5.2: **Hospital separation* and hospital stay rate† (per person month) by time since diagnosis, by diagnosis group, age 0–14 years, in Ontario, 1995–2004** (cont'd)

	Time since diagnosis	No. of separations	Stay days	Person years	Separation rate/ month	95% CI	Stay rate/ month	95% CI
Other	1 month	1427	7544	93.70	1.27	1.20-1.34	6.71	6.56-6.86
	2 months	1161	5630	93.20	1.04	0.98-1.10	5.03	4.90-5.17
	3 months	1053	5162	92.90	0.94	0.89-1.00	4.63	4.50-4.76
	4 months	1010	4869	92.50	0.91	0.85-0.97	4.39	4.26-4.51
	5 months	926	4580	91.96	0.84	0.79-0.89	4.15	4.03-4.27
	6 months	874	4329	91.45	0.80	0.74-0.85	3.94	3.83-4.06
	7–12 months	3073	13389	539.05	0.48	0.46-0.49	2.07	2.03-2.11
	13–18 months	1168	4671	518.33	0.19	0.18-0.20	0.75	0.73-0.77
	19–24 months	717	2526	500.04	0.12	0.11-0.13	0.42	0.40-0.44
	25–36 months	969	3864	966.08	0.08	0.08-0.09	0.33	0.32-0.34
	More than 3 years	1360	4533	4368.28	0.03	0.02-0.03	0.09	0.08-0.09

All rates are calculated per month (even for periods longer than 1 month).
†Stay rate is based on total number of days patient was hospitalized during each admission. Stay lengths were added for multiple admissions during same period.
Stay rate = (total stay length for all patients during period) / (12 × total person years of follow up).
CI = confidence interval
*Hospital separation = number of cases discharged plus the number of inpatient deaths

Exhibit 5.2

Leukemia demonstrates the highest admission rate and by a large margin the highest stay rate in the first month, reflecting the intensity of initial therapy in this group of diseases. The leukemia group includes both myeloid and lymphoid leukemia, and hospital stays are known to be particularly long for the former. There is little difference between the other 3 groups in this first month. Both admission and stay rates for lymphoma are lower than those for leukemia, possibly reflecting the more frequent treatment of Hodgkin lymphoma in the ambulatory context.

Admission and stay rates generally remain higher for leukemia for the first 6 months than in the other 3 disease groups. Admission and particularly stay rates for CNS tumours are lower and decline more rapidly than those for lymphoma and other tumours, probably reflecting the ambulatory nature of therapy for a portion of this group of diseases. For all 3 groups (leukemia, lymphoma and CNS tumours), the admission and stay rates remain a log order higher than for the control group as a whole beyond 3 years from diagnosis (Exhibit 5.1). Of the leukemia population, 86% remained in the cohort beyond 3 years, as did 87% of the lymphoma population and 76% of the CNS population.

EXHIBIT 5.3a: **Hospital separation* rate (per person month) and rate ratio for cases completing primary therapy without relapse followed to death or end of study or censored at time of relapse† if no relapse after end of therapy, age 0–14 years, in Ontario, 1995–2004**

	Cases				Controls		
Time since end of treatment	No. of patients	No. of separations	Person years	Separation rate/month	No. of separations	Person years	Separation rate/month
1 month	2309	1133	186.89	0.505	44	917.01	0.004
2 months	2217	387	183.60	0.176	31	916.68	0.003
3 months	2189	340	181.73	0.156	20	916.60	0.002
4 months	2171	305	180.15	0.141	25	916.60	0.002
5 months	2154	266	178.89	0.124	14	916.60	0.001
6 months	2141	235	178.04	0.110	19	916.59	0.002
7–12 months	2130	861	1055.85	0.068	116	5499.10	0.002
13–18 months	2100	507	1045.77	0.040	107	5499.10	0.002
19–24 months	2088	313	1043.30	0.025	97	5499.03	0.001
25–36 months	2083	453	2079.48	0.018	171	10994.23	0.001
More than 3 years	2074	974	7851.58	0.010	807	42271.24	0.002

All rates are calculated per month (even for periods longer than 1 month).
Controls are censored at the same point as their matched cases (death, post therapy relapse or end of follow up).
†Relapsed cases contribute from the end of their primary therapy to the date of their relapse. If relapses occurred before completion of primary therapy, they are not included in this table.
CI = confidence interval
*Hospital separation = number of cases discharged plus the number of inpatient deaths

EXHIBIT 5.3b: **Hospital stay rate* (per person month) and rate ratio for cases completing primary therapy without relapse followed to death or end of study or censored at time of relapse† if no relapse after end of therapy, age 0–14 years, in Ontario, 1995–2004**

	Cases				Controls		
Time since end of treatment	No. of patients	Stay days	Person years	Stay rate/month	Stay days	Person years	Stay rate/month
1 month	2309	4717	186.89	2.103	78	917.01	0.007
2 months	2217	1714	183.60	0.778	73	916.68	0.007
3 months	2189	1357	181.73	0.622	61	916.60	0.006
4 months	2171	958	180.15	0.443	71	916.60	0.006
5 months	2154	968	178.89	0.451	53	916.60	0.005
6 months	2141	646	178.04	0.302	76	916.59	0.007
7–12 months	2130	2785	1055.85	0.220	439	5499.10	0.007
13–18 months	2100	1514	1045.77	0.121	383	5499.10	0.006
19–24 months	2088	765	1043.30	0.061	368	5499.03	0.006
25–36 months	2083	1180	2079.48	0.047	382	10994.23	0.003
More than 3 years	2074	2903	7851.58	0.031	369	42271.24	0.001

All rates are calculated per month (even for periods longer than 1 month).
Controls are censored at the same point as their matched cases (death, post therapy relapse or end of follow up).
*Stay rate is based on total number of days patient was hospitalized during each admission. Stay lengths were added for multiple admissions during same period.
Stay rate = (total stay length for all patients during period) / (12 × total person years of follow up).
†Relapsed cases contribute from the end of their primary therapy to the date of their relapse. If relapses occurred before completion of primary therapy, they are not included in this table.
CI = confidence interval

	Separation rate ratio	
	Rate ratio	95% CI
	126.35	93.49-170.75
	62.33	43.23-89.86
	85.74	54.62-134.60
	62.07	41.29-93.92
	97.35	56.88-166.63
	63.68	39.90-101.63
	38.66	31.85-46.93
	24.92	20.23-30.69
	17.01	13.54-21.36
	14.01	11.75-16.70
	6.50	5.92-7.13

	Stay rate ratio	
	Rate ratio	95% CI
	296.74	237.24-371.15
	117.23	92.75-148.17
	112.20	86.81-145.01
	68.65	53.95-87.37
	93.58	70.98-123.39
	43.76	34.50-55.50
	33.04	29.88-36.54
	20.79	18.58-23.25
	10.96	9.68-12.41
	16.33	14.55-18.33
	42.36	38.01-47.20

Exhibits 5.3a and 5.3b

Exhibits 5.3a and 5.3b depict the utilization pattern of patients whose course was not complicated by relapse and thus reflects a best case scenario. Patients who relapsed during their primary therapy are excluded and patients who relapsed after the end of therapy are censored at the time of their relapse. All others are followed to death or the end of the study period. The exhibits document hospital admission rates and stay rates beyond the end of therapy.

Both admission and stay rates are substantially higher than the rates for controls in the month after the end of therapy, reflecting the complications of the last cycle of chemotherapy or surgery as the final therapy. Rate ratios are greatly elevated – 126.4 and 296.7, respectively – although the confidence intervals are wide because of the smaller numbers of events. The rates then decline dramatically, but rate ratios remain significantly elevated even more than 3 years after the end of treatment – 6.5-fold for separation rate and 42.4-fold for stay rate. Median follow up duration is 3.6 years beyond the end of therapy.

EXHIBIT 5.4: **Hospital separation* and hospital stay rates† (per person month) for cases completing primary therapy without relapse by diagnosis and time since end of treatment followed to death or end of study or censored at time of relapse‡ if relapsed after end of therapy, age 0–14 years, in Ontario, 1995–2004**

	Time since end of treatment	No. of separations	Stay days	Person years	Separation rate/month	95% CI	Stay rate/month	95% CI
Leukemia	1 month	295	818	62.17	0.40	0.35-0.44	1.10	1.02-1.17
	2 months	118	524	61.34	0.16	0.13-0.19	0.71	0.65-0.78
	3 months	105	444	61.01	0.14	0.12-0.17	0.61	0.55-0.67
	4 months	98	260	60.69	0.13	0.11-0.16	0.36	0.31-0.40
	5 months	84	391	60.66	0.12	0.09-0.14	0.54	0.49-0.59
	6 months	73	264	60.47	0.10	0.08-0.13	0.36	0.32-0.41
	7–12 months	218	964	361.09	0.05	0.04-0.06	0.22	0.21-0.24
	13–18 months	121	526	358.59	0.03	0.02-0.03	0.12	0.11-0.13
	19–24 months	66	202	357.89	0.02	0.01-0.02	0.05	0.04-0.05
	25–36 months	90	387	714.85	0.01	0.01-0.01	0.05	0.04-0.05
	More than 3 years	258	740	2105.79	0.01	0.01-0.01	0.03	0.03-0.03
Lymphoma	1 month	75	352	21.67	0.29	0.23-0.36	1.35	1.22-1.50
	2 months	29	140	21.37	0.11	0.08-0.16	0.55	0.46-0.64
	3 months	30	147	21.25	0.12	0.08-0.17	0.58	0.49-0.68
	4 months	35	67	21.20	0.14	0.10-0.19	0.26	0.20-0.33
	5 months	37	96	21.17	0.15	0.10-0.20	0.38	0.31-0.46
	6 months	26	46	21.12	0.10	0.07-0.15	0.18	0.13-0.24
	7–12 months	113	434	126.51	0.07	0.06-0.09	0.29	0.26-0.31
	13–18 months	47	171	126.15	0.03	0.02-0.04	0.11	0.10-0.13
	19–24 months	25	127	126.01	0.02	0.01-0.02	0.08	0.07-0.10
	25–36 months	45	172	252.00	0.01	0.01-0.02	0.06	0.05-0.07
	More than 3 years	78	206	962.56	0.01	0.01-0.01	0.02	0.02-0.02
Central nervous system tumours	1 month	228	1404	35.94	0.53	0.46-0.60	3.26	3.09-3.43
	2 months	62	222	34.66	0.15	0.11-0.19	0.53	0.47-0.61
	3 months	46	222	33.92	0.11	0.08-0.15	0.55	0.48-0.62
	4 months	44	195	33.58	0.11	0.08-0.15	0.48	0.42-0.56
	5 months	40	164	33.18	0.10	0.07-0.14	0.41	0.35-0.48
	6 months	27	112	32.98	0.07	0.04-0.10	0.28	0.23-0.34
	7–12 months	116	448	190.91	0.05	0.04-0.06	0.20	0.18-0.21
	13–18 months	91	288	185.92	0.04	0.03-0.05	0.13	0.11-0.14
	19–24 months	41	102	185.52	0.02	0.01-0.02	0.05	0.04-0.06
	25–36 months	89	239	369.64	0.02	0.02-0.02	0.05	0.05-0.06
	More than 3 years	226	1103	1550.64	0.01	0.01-0.01	0.06	0.06-0.06

All rates are calculated per month (even for periods longer than 1 month).
†Stay rate is based on total number of days patient was hospitalized during each admission. Stay lengths were added for multiple admissions during same period.
Stay rate = (total stay length for all patients during period) / (12 × total person years of follow up).
CI = confidence interval
*Hospital separation = number of cases discharged plus the number of inpatient deaths
‡Relapsed cases contribute from the end of their primary therapy to the date of their relapse. If relapses occurred before completion of primary therapy, they are not included in this table.

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EXHIBIT 5.4: **Hospital separation* and hospital stay rates† (per person month) for cases completing primary therapy without relapse by diagnosis and time since end of treatment followed to death or end of study or censored at time of relapse‡ if relapsed after end of therapy, age 0–14 years, in Ontario, 1995–2004** (cont'd)

	Time since end of treatment	No. of separations	Stay days	Person years	Separation rate/month	95% CI	Stay rate/month	95% CI
Other	1 month	535	2143	67.68	0.66	0.60-0.72	2.64	2.53-2.75
	2 months	178	828	66.81	0.22	0.19-0.26	1.03	0.96-1.11
	3 months	159	544	66.13	0.20	0.17-0.23	0.69	0.63-0.75
	4 months	128	436	65.25	0.16	0.14-0.19	0.56	0.51-0.61
	5 months	105	317	64.47	0.14	0.11-0.16	0.41	0.37-0.46
	6 months	109	224	64.05	0.14	0.12-0.17	0.29	0.25-0.33
	7–12 months	414	939	380.60	0.09	0.08-0.10	0.21	0.19-0.22
	13–18 months	248	529	377.89	0.05	0.05-0.06	0.12	0.11-0.13
	19–24 months	181	334	376.38	0.04	0.03-0.05	0.07	0.07-0.08
	25–36 months	229	382	747.12	0.03	0.02-0.03	0.04	0.04-0.05
	More than 3 years	412	854	3275.58	0.01	0.01-0.01	0.02	0.02-0.02

All rates are calculated per month (even for periods longer than 1 month).
†Stay rate is based on total number of days patient was hospitalized during each admission. Stay lengths were added for multiple admissions during same period.
Stay rate = (total stay length for all patients during period) / (12 × total person years of follow up).
CI = confidence interval
*Hospital separation = number of cases discharged plus the number of inpatient deaths
‡Relapsed cases contribute from the end of their primary therapy to the date of their relapse. If relapses occurred before completion of primary therapy, they are not included in this table.

Exhibit 5.4

CNS tumours and the "other tumours" group have higher late admission and stay rates than the other disease groups, particularly in the first month after completion of therapy but maintained over the first 4 months. For all disease groups, the admission and stay rates appear to be a log order greater, even at the longest follow up time, than the rates for the entire control population used to generate Exhibits 5.3a and 5.3b.

An analysis of separation and stay rates for cases of acute lymphoblastic leukemia who relapsed, compared with rates for age matched leukemia patients who did not relapse, demonstrates significant elevation, most notably in the first 6 months after relapse but persisting until 24 months from relapse (data not shown).

EXHIBIT 5.5: **Ontario Health Insurance Plan service rate* (per person month) by time since diagnosis, for cases and controls, age 0–14 years, in Ontario, 1995–2004**

	Cases			Controls				
Time since diagnosis	No. of OHIP services	Person years	Service rate/month	No. of OHIP services	Person years	Service rate/month	Service rate ratio	95% CI
1 month	102459	268.97	31.74	8387	1295.64	0.54	58.8	57.55-60.17
2 months	57785	266.61	18.06	7998	1285.17	0.52	34.8	34.02-35.65
3 months	47793	265.00	15.03	7737	1277.26	0.50	29.8	29.07-30.50
4 months	42488	263.41	13.44	7730	1269.74	0.51	26.5	25.86-27.14
5 months	39129	262.08	12.44	8055	1263.16	0.53	23.4	22.86-23.98
6 months	36021	260.34	11.53	8021	1254.55	0.53	21.6	21.12-22.17
7–12 months	147635	1523.36	8.08	44262	7342.23	0.50	16.1	15.91-16.25
13–18 months	96605	1459.90	5.51	41716	7033.92	0.49	11.2	11.03-11.29
19–24 months	80262	1415.26	4.73	40296	6825.81	0.49	9.6	9.49-9.72
25–36 months	119906	2755.12	3.63	78041	13285.47	0.49	7.4	7.34-7.48
More than 3 years	344784	12813.02	2.24	547479	61872.60	0.74	3.0	3.03-3.05

OHIP = Ontario Health Insurance Plan
All rates are calculated per month (even for periods longer than 1 month).
*A service is a single service billed by a physician (or other health care professional entitled to bill OHIP).
CI = confidence interval

Exhibit 5.5

Physician visits, derived from OHIP service billings, are nearly 60-fold those of the control group in the first month after diagnosis. This difference reflects the acuity of illness and the frequent need for medical services. These encounters represent both inpatient and ambulatory contacts with physicians and are probably a substantial underestimate since inpatient shadow billing may be at least as erratic as outpatient billing.

The physician visit rate ratio does not diminish below a 10-fold elevation until beyond 18 months from diagnosis and remains 3 times that of controls until the end of the follow up period.

EXHIBIT 5.6: **Ontario Health Insurance Plan service rate* (per person month) by time since diagnosis, for cases, by diagnosis group, age 0–14 years, in Ontario, 1995–2004**

	Time since diagnosis	No. of OHIP services	Person years	Service rates/month	95% CI
Leukemia	1 month	43915	87.68	41.74	41.35-42.13
	2 months	24179	86.85	23.20	22.91-23.49
	3 months	18672	86.58	17.97	17.72-18.23
	4 months	16848	86.26	16.28	16.03-16.52
	5 months	15737	86.09	15.23	15.00-15.47
	6 months	13871	85.73	13.48	13.26-13.71
	7–12 months	55860	503.90	9.24	9.16-9.31
	13–18 months	40853	485.79	7.01	6.94-7.08
	19–24 months	37916	473.10	6.68	6.61-6.75
	25–36 months	56791	926.73	5.11	5.06-5.15
	More than 3 years	128099	4394.10	2.43	2.41-2.44
Lymphoma	1 month	13396	28.91	38.62	37.97-39.28
	2 months	8558	28.60	24.93	24.41-25.47
	3 months	6600	28.48	19.31	18.85-19.79
	4 months	5449	28.33	16.03	15.60-16.46
	5 months	4161	28.17	12.31	11.94-12.69
	6 months	3704	28.12	10.98	10.63-11.34
	7–12 months	15749	164.94	7.96	7.83-8.08
	13–18 months	11136	161.39	5.75	5.64-5.86
	19–24 months	9124	158.84	4.79	4.69-4.89
	25–36 months	12387	308.32	3.35	3.29-3.41
	More than 3 years	38525	1382.92	2.32	2.30-2.34
Central nervous system tumours	1 month	14776	58.67	20.99	20.65-21.33
	2 months	7268	57.93	10.46	10.22-10.70
	3 months	5470	57.04	7.99	7.78-8.21
	4 months	4678	56.35	6.92	6.72-7.12
	5 months	4460	55.86	6.65	6.46-6.85
	6 months	4208	55.05	6.37	6.18-6.57
	7–12 months	20381	315.46	5.38	5.31-5.46
	13–18 months	14281	294.39	4.04	3.98-4.11
	19–24 months	10024	283.28	2.95	2.89-3.01
	25–36 months	15817	553.99	2.38	2.34-2.42
	More than 3 years	67399	2667.72	2.11	2.09-2.12

OHIP = Ontario Health Insurance Plan
All rates are calculated per month (even for periods longer than 1 month).
*A service is a single service billed by a physician (or other health care professional entitled to bill OHIP).
CI = confidence interval

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EXHIBIT 5.6: **Ontario Health Insurance Plan service rate* (per person month) by time since diagnosis, for cases, by diagnosis group, age 0–14 years, in Ontario, 1995–2004** (cont'd)

	Time since diagnosis	No. of OHIP services	Person years	Service rates/month	95% CI
Other	1 month	30372	93.70	27.01	26.71-27.32
	2 months	17780	93.20	15.90	15.66-16.13
	3 months	17051	92.90	15.30	15.07-15.53
	4 months	15513	92.50	13.98	13.76-14.20
	5 months	14771	91.96	13.39	13.17-13.60
	6 months	14238	91.45	12.97	12.76-13.19
	7–12 months	55645	539.05	8.60	8.53-8.67
	13–18 months	30335	518.33	4.88	4.82-4.93
	19–24 months	23198	500.04	3.87	3.82-3.92
	25–36 months	34911	966.08	3.01	2.98-3.04
	More than 3 years	110761	4368.28	2.11	2.10-2.13

OHIP = Ontario Health Insurance Plan
All rates are calculated per month (even for periods longer than 1 month).
*A service is a single service billed by a physician (or other health care professional entitled to bill OHIP).
CI = confidence interval

Exhibit 5.6

The "front end loading" of physician encounters is observed in each diagnosis group. Surprisingly, the encounter rate for all other categories exceeds that for CNS tumours, with leukemia manifesting the most intense physician encounter rate, followed by lymphoma; this pattern persists throughout the entire follow up period. The physician encounter rate for CNS tumours drops faster and more profoundly from 3 to 6 months and then plateaus at a level comparable to that of leukemia and lymphoma. This pattern probably reflects the shorter duration of high intensity treatment during the period of the study, which largely precedes the introduction of multiple tandem hematopoietic stem cell transplants for medulloblastoma.

EXHIBIT 5.7: **Number and rate (per person month) of inpatient and outpatient computed tomography scans and outpatient magnetic resonance imaging scans, by time since diagnosis, for cases and matched controls, age 0–14 years, in Ontario, 1995–2004**

	Cases				Controls				
Time since diagnosis	No. of patients	No. of scans	Person years	Rate/ month	No. of scans	Person years	Rate/ month	Rate ratio	95% CI
1 month	3256	4645	268.97	1.44	14	1295.64	0.001	1598.23	1005.52-2857.28
2 months	3208	1904	266.61	0.60	28	1285.17	0.002	327.79	232.89-490.54
3 months	3191	1902	265.00	0.60	24	1277.26	0.002	381.98	264.84-591.46
4 months	3171	1747	263.41	0.55	11	1269.74	0.001	765.56	456.81-1483.61
5 months	3151	1333	262.08	0.42	23	1263.16	0.002	279.33	192.07-437.21
6 months	3138	1415	260.34	0.45	26	1254.55	0.002	262.26	183.99-399.11
7–12 months	3113	6926	1523.36	0.38	92	7342.23	0.001	362.84	298.33-450.10
13–18 months	2982	5405	1459.90	0.31	93	7033.92	0.001	280.02	230.36-347.06
19–24 months	2868	4285	1415.26	0.25	80	6825.81	0.001	258.33	209.43-325.89
25–36 months	2795	6348	2755.12	0.19	212	13285.47	0.001	144.39	126.47-166.27
More than 3 years	2719	14858	12813.02	0.10	2917	61872.60	0.004	24.60	23.65-25.60

All rates are calculated per month (even for periods longer than 1 month).
CI = confidence interval

EXHIBIT 5.8: **Number and rate (per person month) of inpatient and outpatient computed tomography scans and outpatient magnetic resonance imaging scans, by time since diagnosis, for cases by diagnosis group, age 0–14 years, in Ontario 1995–2004**

	Time since diagnosis	No. of patients	No. of scans	Person years	Rate/month	95% CI
Leukemia	1 month	1483	561	87.7	0.53	0.49-0.58
	2 months	1359	270	86.8	0.26	0.23-0.29
	3 months	1280	194	86.6	0.19	0.16-0.21
	4 months	1036	146	86.3	0.14	0.12-0.17
	5 months	933	127	86.1	0.12	0.10-0.15
	6 months	713	149	85.7	0.14	0.12-0.17
	7–12 months	2358	517	503.9	0.09	0.08-0.09
	13–18 months	1382	377	485.8	0.06	0.06-0.07
	19–24 months	1189	294	473.1	0.05	0.05-0.06
	25–36 months	1982	466	926.7	0.04	0.04-0.05
	More than 3 years	2236	1505	4394.1	0.03	0.03-0.03
Lymphoma	1 month	477	1043	28.9	3.01	2.83-3.20
	2 months	337	473	28.6	1.38	1.26-1.51
	3 months	290	469	28.5	1.37	1.25-1.50
	4 months	251	403	28.3	1.19	1.07-1.31
	5 months	175	298	28.2	0.88	0.78-0.99
	6 months	111	319	28.1	0.95	0.84-1.06
	7–12 months	562	1493	164.9	0.75	0.72-0.79
	13–18 months	341	1169	161.4	0.6	0.57-0.64
	19–24 months	194	854	158.8	0.45	0.42-0.48
	25–36 months	241	1195	308.3	0.32	0.30-0.34
	More than 3 years	332	1709	1382.9	0.1	0.10-0.11
Central nervous system tumours	1 month	516	1478	58.7	2.1	1.99-2.21
	2 months	217	326	57.9	0.47	0.42-0.52
	3 months	178	283	57	0.41	0.37-0.46
	4 months	225	304	56.3	0.45	0.40-0.50
	5 months	231	231	55.9	0.34	0.30-0.39
	6 months	248	252	55	0.38	0.34-0.43
	7–12 months	1185	1215	315.5	0.32	0.30-0.34
	13–18 months	602	963	294.4	0.27	0.26-0.29
	19–24 months	235	824	283.3	0.24	0.23-0.26
	25–36 months	286	1349	554	0.2	0.19-0.21
	More than 3 years	875	5074	2667.7	0.16	0.15-0.16

All rates are calculated per month (even for periods longer than 1 month).
CI = confidence interval

continued on following page

EXHIBIT 5.8: **Number and rate (per person month) of inpatient and outpatient computed tomography scans and outpatient magnetic resonance imaging scans, by time since diagnosis, for cases by diagnosis group, age 0–14 years, in Ontario 1995–2004** (cont'd)

	Time since diagnosis	No. of patients	No. of scans	Person years	Rate/month	95% CI
Other	1 month	1427	1563	93.7	1.39	1.32-1.46
	2 months	1161	835	93.2	0.75	0.70-0.80
	3 months	1053	956	92.9	0.86	0.80-0.91
	4 months	1010	894	92.5	0.81	0.75-0.86
	5 months	926	677	92	0.61	0.57-0.66
	6 months	874	695	91.5	0.63	0.59-0.68
	7–12 months	3073	3701	539.1	0.57	0.55-0.59
	13–18 months	1168	2896	518.3	0.47	0.45-0.48
	19–24 months	717	2313	500	0.39	0.37-0.40
	25–36 months	969	3338	966.1	0.29	0.28-0.30
	More than 3 years	1360	6570	4368.3	0.13	0.12-0.13

All rates are calculated per month (even for periods longer than 1 month).
CI = confidence interval

Exhibits 5.7 and 5.8

Imaging utilization

The majority of imaging studies carried out on this patient population are undertaken at the tertiary hospitals. In this context, many categories of imaging studies are funded by the hospital's global budget and are not identified in the OHIP billing claims since no physician bill is submitted. However, data are available through OHIP for ambulatory and inpatient CT scans and ambulatory MRI studies. The data reveal a substantial number of such investigations in the first month following diagnosis, with rates exceeding 1 study per month per person year. The rate ratios are enormously elevated – approximately 1600-fold – in the first month after diagnosis, remaining several hundredfold higher until the 36th month and then dropping to 25 times higher until the end of follow up. Analysis by disease group indicates that the rates are substantially higher for CNS tumours, lymphoma and the "other" malignancy category, with rates 3- to 6-fold higher than those for leukemia in the first month. Importantly, these rates remain elevated in similar proportions even through the longest follow up period.

Summary

The pattern of illness and resultant care required in childhood cancer differs from other childhood conditions that demonstrate high rates of health care service utilization. Excellent survival rates have been achieved, but the use of health care services required to achieve those outcomes is intense.

The use of these services by a population-based cohort of children diagnosed with cancer between 1995 and 2004 was studied using a standardized database held by the Pediatric Oncology Group of Ontario, linked to a series of administrative databases. The cohort was followed until death or the end of the study period in December 2008. Indicators of utilization studied included hospital admissions and length of stay, physician encounters based on physician billing records and rates of selected high intensity imaging studies.

Rate ratios for admissions and hospital days for the cohort were calculated, comparing them to matched controls drawn from the general population. Rate ratios were many hundredfold higher in the first month after diagnosis and remained elevated several hundredfold for up to 6 months after diagnosis. While there was subsequently a steady drop in the rate ratios, even 2 years after diagnosis these ratios were in excess of 50-fold, and they persisted at approximately 20-fold beyond 3 years from diagnosis. The leukemia population contributes the highest proportion of admissions and stay days for the first 6 months, followed by lymphoma.

Physician visits are acknowledged to be systematically underestimated by virtue of APPs introduced into the academic health science centres during the period of study. Notwithstanding, the rate ratio for physician visits is 60-fold in the first month after diagnosis, remains markedly elevated at more than 20-fold for the first 6 months and is dramatically elevated until the end of the follow up period. The leukemia group again contributes the highest proportion of visits. The use of specialized imaging is elevated several hundredfold in the first months after diagnosis, peaking in the first month at nearly 1600-fold.

While other dimensions of health care utilization, such as pathology and laboratory services, could not be quantified for this analysis because they are funded by hospital global budgets and are not identifiable in administrative data, they are intensely used by this population.

Based on this analysis, the childhood cancer population uses vastly greater amounts of health service during active therapy. This pattern continues, albeit at lower intensity, over at least the duration of this study, which followed the cohort for a mean duration of 3.6 years beyond the end of therapy. The cohort represents a low volume but high cost group of children for whom treatment is enormously successful but very resource intensive. Provision of appropriate resources, human and material, both in the immediately related disciplines and in other supportive disciplines, is critical to the maintenance of these exceptional survival outcomes.

References

1 Canadian Cancer Society/national Cancer Institute of Canada.Canadian cancer statistics 2008.Toronto:The Society; 2008.

2 Howlader N, Noone AM, Krapacho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. Bethesda, MD: National Cancer Institute; 2013.

3 Bradley NM, Lorenzi MF, Abanto Z, Sheps S, Broemeling AM, Spinelli JJ, et al. Hospitalisations 1998-2000 in a British Columbia population-based cohort of young cancer survivors: report of the Childhood/Adolescent/Young Adult Cancer Survivors (CAYACS) Research Program. Eur J Cancer 2010 Sep;46(13):2441-8.

4 Dang-Tan T, Trottier H, Mery LS, Morrison HI, Barr RD, Greenberg ML, et al. Determinants of delays in treatment initiation in children and adolescents diagnosed with leukemia or lymphoma in Canada. Int J Cancer 2010 Apr 15;126(8):1936-43.

5 Dang-Tan T, Trottier H, Mery LS, Morrison HI, Barr RD, Greenberg ML, et al. Delays in diagnosis and treatment among children and adolescents with cancer in Canada. Pediatr Blood Cancer 2008 Oct;51(4):468-74.

6 Klein-Geltink J, Pogany L, Mery LS, Barr RD, Greenberg ML. Impact of age and diagnosis on waiting times between important healthcare events among children 0 to 19 years cared for in pediatric units: the Canadian Childhood Cancer Surveillance and Control Program. J Pediatr Hematol Oncol 2006 Jul;28(7):433-9.

7 To T, Dell S, Dick P, Cicutto L. The burden of illness experienced by young children associated with asthma: a population-based cohort study. J Asthma 2008 Jan;45(1):45-9.

8 Johnston JA, Rabi DM, Edwards AL, Balko SU. Diabetes and health care utilization in Alberta: Johnson JA, editor. Alberta Diabetes Atlas 2009. Edmonton: Instutite of Health Economics 2009; Available from: http://www.albertadiabetes.ca/

9 Newacheck PW, Inkelas M, Kim SE. Health services use and health care expenditures for children with disabilities. Pediatrics 2004 Jul;114(1):79-85.

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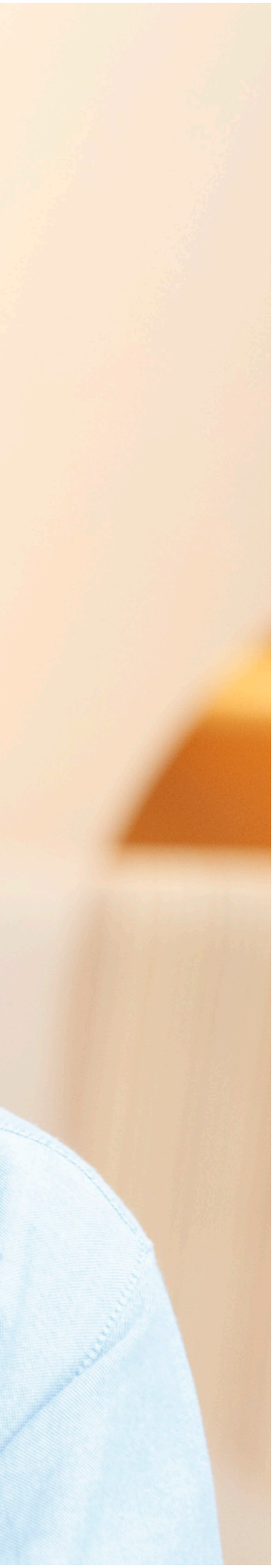

6

Leukemia

Executive Summary

This chapter provides population-based information about the incidence of different forms of leukemia, the frequency of relapse, the use of hematopoietic stem cell transplantation (HSCT) and the probability of long term survival among children in Ontario diagnosed between 1985 and 2004.

Acute lymphoblastic leukemia (ALL) was the most common form of childhood leukemia (80.4% of all cases), followed by acute myeloid leukemia (AML) (15.6%). The age standardized incidence rate (ASIR) for any form of childhood leukemia was 44.4 cases per 1 million population per year (36.0 for ALL and 7.3 for AML). The incidence of leukemia was higher among males (56.0% of cases for ALL and 52.8% of cases for AML).

The age standardized mortality rate (ASMR) for any form of childhood leukemia was 10.7 deaths per 1 million population per year (6.4 for ALL and 3.6 for AML). Mortality rates were higher for males than females with ALL but were similar for AML. Mortality rates for leukemia decreased over time, particularly during the most recent reporting period (from 11.1 to 6.6 in 2000–2004). Mortality, expressed as the number of deaths per number of cases diagnosed, particularly improved for childhood AML (59.5% in 1990–1994, compared with 29.4% in 2000–2004), likely reflecting intensified chemotherapy and supportive care.

The proportions for event free survival (EFS) and overall survival were 0.71 and 0.81 for all children with leukemia diagnosed between 1995 and 2004. There was no significant difference between the 2 most recent treatment periods (1995–1999 and 2000–2004). As expected, EFS and overall survival were higher for children with ALL (0.77 and 0.87, respectively) than for AML (0.50 and 0.59, respectively). EFS after a diagnosis of ALL was lowest in infants (younger than 1 year of age; 0.37), intermediate for children 10 years or older (0.79) and highest in the age group 1–9 years (0.90). Stratified by risk group, the proportion of survival after 5 years among children with ALL was 0.95 for children with standard risk ALL and 0.82 for high risk ALL during the entire reporting period (1995–2004).

HSCT was a part of leukemia treatment for 18.7% of all children (45.8% of all patients with AML and 11.2% of those with ALL). Most recipients received stem cells from an allogeneic donor (97.4% during the most recent treatment period, 2000–2004). The majority of transplants for AML were carried out as part of a patient's initial treatment for leukemia (in first remission, 74.0%). In contrast, transplantation for ALL was most commonly used after a first relapse (in second remission, 59.6%). The probability of 5 year overall survival after allogeneic HSCT for children with any form of leukemia was 0.64; for ALL it was 0.66 and for AML, 0.68. The proportion of children treated for leukemia with a stem cell transplant decreased over time (from 22.2% to 14.9%) because there were fewer transplants for children with AML.

A relapse of leukemia developed in 21.0% of children (in 17.8% of those with ALL and 36.9% of those with AML). Relapse occurred more often in males than females. The proportion of children who relapsed decreased over time (by 24.7% for ALL and 30.0% for AML). Most (41.3%) relapses of ALL occurred late (more than 36 months after the initial diagnosis of leukemia) but early (within 18 months of initial diagnosis) in 71.0% of AML relapses. The proportion of children who survived at least 5 years after a relapse was significantly higher for ALL (0.58) than for AML (0.27).

Introduction

The term leukemia ("white blood" according to its etymology) encompasses the malignancies of the hematopoietic system, which present with disseminated involvement of blood and bone marrow. During childhood, leukemia is the most common form of cancer (31% of all new diagnoses of cancer[1]). Overall, it is a rare disease (48 new cases per year per 1 million population aged 0–14 years[1]).

Forms of childhood leukemia

There are 4 main types of leukemia affecting children. Acute lymphoblastic leukemia is by far the predominant form of childhood leukemia (approximately 80% of new cases[1]). ALL is subdivided according to the lymphoid lineage of the leukemic cell population (also termed blast cells) into B-precursor ALL (85% of ALL) and T-cell ALL (15% of ALL).[2] ALL occurs particularly frequently among young children and has a characteristic peak in its age distribution between 2 and 7 years.[3] Treatment consists of multi-agent chemotherapy administered mostly in the out-patient setting over approximately 2.5–3.5 years (longer in males). Prognosis depends on increasingly refined risk groups (see below); survival with current therapy ranges between 80% (high risk) and 90% (standard risk) for B-precursor ALL.

Acute myeloid leukemia is the second most common form of childhood leukemia (7 cases per 1 million population per year, or 15% of all new cases of leukemia per year[1]) and after a peak during the first year of life[4] it occurs with a constant incidence throughout childhood. Treatment consists of a series of highly intense multi-agent chemotherapy courses delivered in the in-patient setting over less than 6 months. Leukemic relapse and to a lesser degree treatment related mortality, mostly due to infections, result in long term survival rates of approximately 50–60%.[5-7]

Chronic myeloid leukemia (CML) is rare in children and more common in adults.[8] Prior to the introduction of tyrosine kinase inhibitors as a mechanism-specific treatment for CML, HSCT was the treatment of choice for pediatric patients. The role of HSCT in the treatment of children with CML is currently being redefined.[9]

Juvenile myelomonocytic leukemia (JMML) is a very rare type of leukemia found only in children.[10,11] HSCT currently is the only treatment associated with long term survival.[12,13]

Disease mechanisms

What causes childhood leukemia remains to be determined. Genome-wide analyses of leukemic blasts are defining the genetic mutations underlying ALL[14] and AML.[15,16] These mutations accumulate during a multi-step process and, by inducing increased cell proliferation, abnormal cell survival and impaired differentiation, result in the transformation of normal blood cells into the malignant cells that manifest as leukemia.[17] Strikingly, this process of leukemic transformation may be initiated before birth.[18,19] This was demonstrated by the detection of leukemia-specific fusion genes, for example ETV6-RUNX1 (TEL-AML1), in neonatal blood samples of children who years later developed leukemia, in this case B-precursor ALL. The observation that leukemic transformation is completed only in a small fraction of individuals in whom the process is initiated suggests that cooperating events are necessary; these may include environmental cues.[20]

Identification of specific acquired genetic abnormalities in leukemic blasts allows prognostic stratification of B-precursor ALL[21] and AML[22] and confirms the diagnosis in CML[8] and JMML.[10,11] Detection of the BCR-ABL1 fusion gene in CML, for example, and therapeutic inhibition of the encoded tyrosine kinase has established the feasibility of targeted chemotherapy and a new paradigm of drug development.

Leukemia is a disease that results from the accumulation of leukemic blasts that if left unchecked will interfere with normal organ function and survival. Based on seminal work in AML it is now clear that leukemic cell populations, although morphologically homogeneous, are functionally organized into a hierarchy.[23-25] Thus, a small fraction of leukemia-initiating cells (also termed cancer stem cells) within the leukemic cell population is capable of maintaining the malignant clone and must be eradicated to achieve long term cure.

Prognostic factors

Diagnostic investigation of childhood leukemia focuses on an increasingly refined set of prognostic criteria that allow the classification of a patient's leukemia as, for example, standard or high risk and determine the selection of the appropriate treatment intensity (e.g., lower vs. higher intensity chemotherapy protocols in ALL; chemotherapy vs. chemotherapy followed by HSCT in AML). Prognostic criteria in ALL include age, white blood cell count at diagnosis, lineage phenotype of the leukemic blasts and involvement of the central nervous system (CNS). Analysis of leukemic cells with cytogenetic (karyotype, fluorescence in situ hybridization) and molecular methods to detect fusion genes and specific gene mutations has refined the stratification of childhood leukemia into prognostic groups. It is anticipated that current genome-wide characterization of leukemic cells[14-16] will further expand and improve the prognostic algorithm.

In addition to the morphologic and genetic analysis of leukemic cells in the laboratory, the assessment of an individual patient's early response to treatment in his or her blood and bone marrow has proven prognostic. Initially, clearance of ALL cells in the blood of individual patients to either below or above a threshold level after 1 week of preliminary treatment (mainly with oral prednisone[26]) was used to select treatment intensity (higher intensity for those with slower clearance).

In the late 1990s, methods became available that allowed the detection of residual leukemia cells at the submicroscopic level, termed minimal residual disease (MRD),[27] in the bone marrow of children considered "in remission" (free of detectable leukemia) after the first 4 weeks of ALL treatment (i.e., the end of the induction phase). MRD assays detect either a pattern of cell surface markers or genetic, DNA-based markers that are uniquely present in an individual patient's leukemic cells. As few as 1 leukemic cell in 10,000 bone marrow cells can be detected by MRD testing, compared with 1 in 20 using standard microscopy. Thus, treatment can be intensified early on to maximize the probability of survival and decrease the risk of relapse for those patients whose MRD levels in the bone marrow remain high after the first treatment course. In AML, treatment response assessments after the first course of chemotherapy, initially by routine microscopy and recently by MRD testing, help determine which patients will require HSCT as part of their treatment. Conversely, patients with minimal or absent levels of MRD can expect a highly favourable prognosis and may be candidates for a reduction of treatment intensity.

Treatment

The intensity of treatment for childhood leukemia is stratified according to the estimated risk of leukemic relapse. Higher intensity treatment protocols, which are associated with more acute life threatening side effects (e.g., infection) and late effects (see below), are reserved for patients at high risk of relapse. Relapse of leukemia has a poor prognosis, with a probability of survival as low as 30–40%.[28-31] Treatment for leukemia in most cases consists of multi-agent chemotherapy. The use of cranial irradiation as CNS-directed therapy is increasingly avoided because of the development of significant late neurocognitive and endocrine effects in survivors and an increased risk of second malignancies (13.3% after 30 years), particularly malignant brain tumours, which may become apparent more than 25 years after treatment for leukemia.[32]

HSCT is used as part of the treatment for ultra high risk subsets of childhood leukemia patients during initial therapy (during first remission, CR1) and after a relapse (during second remission, CR2). HSCT allows the administration of anti-leukemic drug and irradiation doses that exceed the tolerance of the recipient's normal bone marrow, by subsequently supplying normal hematopoietic stem cells from a suitable donor. Long term survival rates after HSCT for ALL and AML are between 50% and 60%.[33,34]

There have been significant advances in leukemia treatment during the reporting period covered by this atlas. For childhood AML, a successful approach that includes intensified chemotherapy protocols and use of HSCT according to cytogenetic risk groups and early treatment response was pioneered by the United Kingdom Medical Research Council Study Group and has now been widely adopted.[6] In ALL, the use of a high intensity treatment element (delayed intensification therapy) was found to be beneficial for all risk groups.[26] Treatment for CML in children has been revolutionized with the introduction of oral tyrosine kinase inhibitors, which can achieve molecular remissions and have prompted an ongoing reassessment of the role of HSCT for this leukemia in childhood.[8]

The increased probability of long term survival for children with leukemia has brought the late adverse effects of leukemia treatment into focus. Lasting adverse neurocognitive late effects following cranial irradiation in subgroups of ALL, osteonecrosis in adolescents treated with high doses of glucocorticoids and cardiomyopathy, which may follow the use of anthracyclines during chemotherapy for both ALL and AML, serve as examples of the challenges facing survivors of childhood leukemia.[35,36] There is hope that the current era of genomic leukemia research and the new paradigm of chemotherapy targeting mechanisms, such as cell signaling pathways specific to leukemic cells, will not only enhance the efficacy of leukemia treatment, but also lower the frequency of lasting adverse effects.

Data collection

Monitoring progress requires basic data about how many children are affected per unit of population and year (incidence), the distribution of various forms of leukemia, the mortality rates associated with childhood leukemia, event free survival (time free of relapse, a second cancer or death) and overall survival after a diagnosis of leukemia. These data are essential for further analyses to identify the barriers to successful outcomes of leukemia treatment (e.g., leukemic relapse, treatment related mortality, late effects of treatment) and for effective policy decisions aimed at overcoming these barriers.

One principal source for these data is clinical trials conducted by large study groups such as the Children's Oncology Group, the Dana-Farber Cancer Institute Consortium and St. Jude Children's Research Hospital in North America, and European groups such as the Berlin-Frankfurt-Münster Study Group and the U.K. Medical Research Council Study Group. The strength of clinical trial data lies in the homogeneity of the underlying patient populations, as defined by study eligibility criteria and the use of uniform treatment protocols. Disadvantages are that trial-based data may not seamlessly cover a period of time if clinical studies accrued patients only during limited time intervals. Further, enrollment in clinical trials represents selected samples, which do not include patients who had leukemia but did not meet eligibility criteria, did not consent or did not complete the study.

A complementary data source is the population-based collection and analysis of information on childhood leukemia such as the one presented in the following discussion. Data captured on unselected cases in the entire population of children in a geographic area over a long period provide a valuable basis for the analysis of trends over time and the planning of resource allocation. As a trade-off, data collected in this fashion are influenced by differences in diagnostic and treatment approaches within and among participating centres. Population-based data collection may be broader but also limited to fewer items than clinical studies and may depend on linkage to other databases. The database that underlies the exhibits presented here, for example, does not completely capture out-of-hospital and late deaths before 1995 and therefore depends on linkage to other registries for the period 1985–1994. Thirty-six of 1,967 (1.8%) cases in the entire leukemia cohort did not link. As a result, estimates of overall survival and EFS were based on cohort members with a positive link (see Chapter 4: Survival).

The following exhibits provide a population-based perspective on the incidence of leukemia and associated mortality, the distribution of leukemia types, the use of HSCT, the incidence of leukemic relapse and survival for children in Ontario between 1985 and 2004.

Discussion

EXHIBIT 6.1a: **Age-standardized incidence rate and age-standardized mortality rate by period, age 0–14 years, in Ontario, 1985–2004**

			Total (1985–2004)					Year of diagnosis: 1985–1989				
			New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR
Total	**All leukemia**	**Overall**	**1967**	**44.43**	**467**	**10.67**	**0.24**	**414**	**41.12**	**136**	**13.46**	**0.33**
	Lymphoid	Overall	1582	35.78	278	6.39	0.18	348	34.54	95	9.40	0.27
	Acute myeloid	Overall	307	6.92	148	3.37	0.49	53	5.30	32	3.19	0.60
		APL	23	0.51	6	0.14	0.28	2	0.21	2	0.21	1.00
		Down	29	0.62	8	0.17	0.28	3	0.29	1	0.10	0.34
		Other	255	5.78	134	3.06	0.53	48	4.79	29	2.88	0.60
	Chronic myeloid	Overall	22	0.52	8	0.20	0.38	6	0.63	4	0.43	0.67
	JMML	Overall	18	0.38	13	0.28	0.73	3	0.27	3	0.27	1.00
	Leukemia NOS	Overall	38	0.83	20	0.43	0.52	4	0.38	2	0.18	0.47
Females	**All leukemia**	**Overall**	**877**	**19.8**	**198**	**4.49**	**0.23**	**184**	**18.34**	**55**	**5.38**	**0.29**
	Lymphoid	Overall	696	15.72	109	2.47	0.16	153	15.25	32	3.12	0.20
	Acute myeloid	Overall	145	3.26	69	1.57	0.48	24	2.40	18	1.78	0.74
		APL	14	0.32	3	0.08	0.24	2	0.21	2	0.21	1.00
		Down	9	0.19	2	0.04	0.22	0		0		
		Other	122	2.75	64	1.45	0.53	22	2.18	16	1.56	0.71
	Chronic myeloid	Overall	14	0.33	6	0.15	0.45	3	0.32	2	0.21	0.68
	JMML	Overall	4	0.09	4	0.09	1.00	1	0.09	1	0.09	1.00
	Leukemia NOS	Overall	18	0.40	10	0.22	0.54	3	0.29	2	0.18	0.61
Males	**All leukemia**	**Overall**	**1090**	**24.63**	**269**	**6.18**	**0.25**	**230**	**22.78**	**81**	**8.08**	**0.35**
	Lymphoid	Overall	886	20.06	169	3.92	0.20	195	19.30	63	6.28	0.33
	Acute myeloid	Overall	162	3.66	79	1.80	0.49	29	2.90	14	1.42	0.49
		APL	9	0.19	3	0.06	0.33					
		Down	20	0.43	6	0.13	0.30	3	0.29	1	0.10	0.34
		Other	133	3.04	70	1.61	0.53	26	2.61	13	1.32	0.51
	Chronic myeloid	Overall	8	0.19	2	0.05	0.27	3	0.32	2	0.21	0.67
	JMML	Overall	14	0.29	9	0.19	0.65	2	0.17	2	0.17	1.00
	Leukemia NOS	Overall	20	0.43	10	0.21	0.50	1	0.09	0		0.00

ASIR = age standardized incidence rate; ASMR = age standardized mortality rate; APL = acute promyelocytic leukemia; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified; Down = Down syndrome

	1990–1994					1995–1999					2000–2004				
	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR
	494	**44.52**	**128**	**11.55**	**0.26**	**549**	**47.43**	**127**	**11.06**	**0.23**	**510**	**44.63**	**76**	**6.63**	**0.15**
	393	35.40	71	6.39	0.18	423	36.51	71	6.18	0.17	418	36.65	41	3.58	0.10
	86	7.79	51	4.63	0.60	100	8.69	45	3.93	0.45	68	5.90	20	1.74	0.29
	6	0.55	1	0.09	0.16	6	0.52	2	0.18	0.35	9	0.77	1	0.09	0.11
	13	1.09	4	0.34	0.31	7	0.58	1	0.08	0.14	6	0.52	2	0.17	0.33
	67	6.15	46	4.21	0.68	87	7.59	42	3.67	0.48	53	4.61	17	1.48	0.32
	7	0.68	2	0.20	0.30	4	0.35	1	0.08	0.24	5	0.42	1	0.09	0.21
	5	0.40	3	0.24	0.61	6	0.50	4	0.34	0.67	4	0.35	3	0.26	0.75
	3	0.26	1	0.08	0.31	16	1.38	6	0.52	0.38	15	1.31	11	0.96	0.74
	210	**18.93**	**56**	**5.00**	**0.26**	**260**	**22.43**	**55**	**4.80**	**0.21**	**223**	**19.49**	**32**	**2.78**	**0.14**
	171	15.39	35	3.11	0.20	196	16.84	28	2.42	0.14	176	15.40	14	1.21	0.08
	33	2.99	18	1.61	0.54	52	4.52	22	1.94	0.43	36	3.13	11	0.96	0.31
	2	0.20	0		0.00	4	0.35	1	0.10	0.27	6	0.51	0		0.00
	4	0.33	2	0.17	0.51	3	0.25	0		0.00	2	0.18	0		0.00
	27	2.45	16	1.44	0.59	45	3.92	21	1.84	0.47	28	2.44	11	0.96	0.39
	4	0.39	2	0.20	0.52	4	0.35	1	0.08	0.24	3	0.26	1	0.09	0.35
	0		0			2	0.17	2	0.17	1.00	1	0.09	1	0.09	1.00
	2	0.16	1	0.08	0.49	6	0.55	2	0.18	0.33	7	0.62	5	0.44	0.72
	284	**25.60**	**72**	**6.54**	**0.26**	**289**	**25.00**	**72**	**6.26**	**0.25**	**287**	**25.15**	**44**	**3.85**	**0.15**
	222	20.01	36	3.27	0.16	227	19.67	43	3.76	0.19	242	21.25	27	2.37	0.11
	53	4.80	33	3.03	0.63	48	4.17	23	1.99	0.48	32	2.77	9	0.78	0.28
	4	0.35	1	0.09	0.25	2	0.17	1	0.09	0.51	3	0.26	1	0.09	0.34
	9	0.76	2	0.17	0.22	4	0.33	1	0.08	0.25	4	0.35	2	0.17	0.50
	40	3.70	30	2.77	0.75	42	3.67	21	1.82	0.50	25	2.17	6	0.52	0.24
	3	0.29	0		0.00	0		0			2	0.17	0		0.00
	5	0.40	3	0.24	0.61	4	0.33	2	0.17	0.50	3	0.26	2	0.18	0.66
	1	0.10	0		0.00	10	0.83	4	0.34	0.41	8	0.69	6	0.52	0.75

Exhibit 6.1a

Incidence

A total of 1,967 children under 15 years of age were diagnosed with leukemia in Ontario between 1985 and 2004. Age standardized incidence rates are reported for 5 year intervals. Lymphoid leukemia, referred to in the following as acute lymphoblastic leukemia, accounted for the majority of cases (80.4%), followed by AML (15.5% of cases). All other forms of leukemia were rare (CML, 1.1%; JMML, 0.9%). A total of 38 cases (1.9% of the total) could not be further classified (leukemia not otherwise specified/NOS). Among children with AML, the proportions of those subgroups that are treated with distinct approaches were in keeping with reports based on clinical trials both for acute promyelocytic leukemia (APL, or French-American-British/FAB-M3, 9.8% vs. 7.5–9.0%[6]) and AML in children with Down syndrome (9.4% vs. 3.5–9.8%[37]). The higher incidence among males of ALL (56.0%) and AML (52.8%) was identical to the rate in recent trial-based reports.[2,6] The higher incidence of Down syndrome AML among males (69.0% vs. 48–52%[38]) and APL among females (60.9% vs. 45.6–59.5%[39]) was unexpected but is based on a small number of cases.

The ASIRs were 44.4 per 1 million population per year for any form of childhood leukemia, 35.8 for ALL and 6.9 for AML and were consistent with corresponding values (48, 38 and 7, respectively) reported for the age adjusted (ages 0–14 years) U.S. standard population (2000).[1]

Mortality

The ASMRs were 10.7 deaths per 1 million per year for any form of leukemia, 6.4 for ALL and 3.4 for AML from 1985 to 2004 based on the standard Ontario population (2001). To estimate the mortality among children diagnosed with leukemia, ratios of ASMR to ASIR were calculated.

Taking all forms of childhood leukemia together, the incidence of leukemia was approximately 4 times higher than the mortality from leukemia (ASMR/ASIR, 0.24).

The mortality/incidence ratio was lowest for ALL (0.18) and markedly higher for AML (0.49). The low ASMR/ASIR ratios for the prognostically favourable subsets APL (0.27), which is associated with a reported survival rate of 78.1%,[39] and AML in Down syndrome (0.28) were expected.[38]

Mortality expressed as the ASMR/ASIR ratio was lower in females with ALL (0.16) than in males (0.20), while no gender associated difference was observed for AML (0.49 in males, 0.48 in females), despite a larger number of males in the prognostically favourable subset of Down syndrome AML.

Mortality rates for leukemia NOS resembled those of AML more than those of ALL.

Trends

In a comparison of 5 year intervals, the incidence of all forms of childhood leukemia increased from 41.1 to 47.4 per 1 million between 1985 and 1999 before decreasing during the most recent reporting period (2000–2004) to 44.6, a value similar to that observed during 1990–1994 (44.5). The same pattern was observed for the ASIR of AML (an increase from 5.3 to 8.7 between 1985 and 1999 followed by a decrease to 5.9 during the most recent reporting period). In contrast, the ASIR of ALL increased from 34.5 to 36.7 from 1985 to 2004 and remained constant (36.5 and 36.7) during the 2 most recent reporting periods (1995–1999 and 2000–2004).

For all leukemia, mortality as measured by ASMR decreased over time. This decrease was gradual during 1985–1999 (from 13.5 to 11.1) and more accelerated during the most recent reporting period (11.1 to 6.6 between 2000 and 2004).

In relative terms, the ASMR decreased by 43.8% for ALL (from 6.4 to 3.6) and 62.4% for AML (from 4.6 to 1.8) between 1994 and 2004. The ratio of leukemia-associated mortality to incidence of leukemia (ASMR/ASIR) for ALL first decreased after 1989 (from 0.27 to 0.18), remained stable at this lower level until 1999 and then decreased further (to 0.10 for 2000–2004), reflecting improved survival. For AML the decrease began in 1995 and was both marked and sustained (from 0.60 in 1994 to 0.29 in 2004; decreasing by approximately 0.15 every 5 years), and illustrates the significant improvement of survival for children with AML since 1995.

Owing to methodologic limitations (see Chapter 4: Survival among Children Diagnosed with Cancer in Ontario from 1985 to 2004), longitudinal comparisons of ASMRs are most reliable after 1991. For both genders the ASMR for leukemia decreased by a similar degree (by 41.1% for males and 44.4% for females) between 1990 and 2004. Relative decreases in ASMRs in males were greater for AML (a 74.3% decrease) than for ALL (27.5%), whereas in females the ASMR showed a greater relative decrease for ALL (a 61.1% decrease) than for AML (40.4%). Available data showed no detectable improvement in ASMR over time for APL (FAB-M3) or Down syndrome AML, suggesting that the improved ASMR for AML occurred in the majority of AML patients who are not part of these specific prognostically favourable subsets.

EXHIBIT 6.1b: **Incidence and mortality by period for acute myeloid leukemia by French-American-British classification, age 0–14 years, in Ontario, 1985–2004**

			Total (1985–2004)				Year of diagnosis: 1985–1989			
			New cases		Deaths		New cases		Deaths	
			n	%	n	%	n	%	n	%
Total		Overall	**307**	**100.00**	**148**	**48.21**	**53**	**17.26**	**32**	**60.38**
	Non-Down acute myeloid leukemia	M0	9	2.93	6	66.67	0	0.00	0	
		M1	30	9.77	20	66.67	5	9.43	3	60.00
		M2	44	14.33	19	43.18	3	5.66	1	33.33
		APL	23	7.49	6	26.09	2	3.77	2	100.00
		M4	48	15.64	22	45.83	7	13.21	4	57.14
		M5	35	11.40	16	45.71	8	15.09	6	75.00
		M6	8	2.61	6	75.00	2	3.77	1	50.00
		M7	23	7.49	13	56.52	0	0.00	0	
		Unknown	58	18.89	32	55.17	23	43.40	14	60.87
	Down syndrome*		29	9.45	8	27.59	3	5.66	1	33.33

*72.4% (21/29) of the Down syndrome patients were M7.

Exhibit 6.1b

Based on a classification of AML according to blast morphology, the most common forms of childhood AML were myeloblastic (FAB-M2), myelo- and monoblastic (FAB-M4) and monoblastic (FAB-M5). Among children with Down syndrome, the predominant blast phenotype was megakaryoblastic (FAB-M7, 72.4%). These distributions are consistent with data collected in recent clinical trials.[6]

The mortality (expressed as number of deaths per number of cases diagnosed) due to childhood AML markedly decreased from 59.3% in 1990–1994 to 29.4% in 2000–2004. This trend highlights a significant improvement in AML therapy for children, which is likely the result of intensified chemotherapy[6] and supportive care. Compared with the mortality in the entire group of children with AML (48.2%), lower death rates, as expected, were observed for APL (FAB-M3, 26.1%) and Down syndrome AML (27.6%).[38,39] These data confirm the favourable prognosis and support the current use of distinct treatment approaches for these subtypes of AML.

During the most recent period (2000–2004) mortality proportions for all children with AML (29.4%) had decreased to those observed for these favourable subgroups over the entire reporting period (26.1% and 27.6% for APL and Down syndrome AML, respectively). In the latter sub-groups recent mortality (2000–2004) was lower for APL (11.1%) than for the entire reporting period (26.1%) but unchanged for Down syndrome AML (33.3% in 2000–2004 vs. 27.6% in 1985–2004). This observation may reflect the introduction of all-trans retinoic acid, improving management of acute hemorrhagic complications of APL, and at the same time may highlight room for further improvement in the treatment of Down syndrome AML.[40]

	1990–1994				1995–1999				2000–2004			
	New cases		Deaths		New cases		Deaths		New cases		Deaths	
	n	%	n	%	n	%	n	%	n	%	n	%
	86	**28.01**	**51**	**59.30**	**100**	**32.57**	**45**	**45.00**	**68**	**22.15**	**20**	**29.41**
	2	2.33	1	50.00	4	4.00	4	100.00	3	4.41	1	33.33
	11	12.79	9	81.82	10	10.00	5	50.00	4	5.88	3	75.00
	13	15.12	9	69.23	14	14.00	6	42.86	14	20.59	3	21.43
	6	6.98	1	16.67	6	6.00	2	33.33	9	13.24	1	11.11
	12	13.95	7	58.33	18	18.00	7	38.89	11	16.18	4	36.36
	5	5.81	4	80.00	12	12.00	3	25.00	10	14.71	3	30.00
	3	3.49	2	66.67	3	3.00	3	100.00	0	0.00	0	—
	7	8.14	7	100.00	10	10.00	6	60.00	6	8.82	0	0.00
	14	16.28	7	50.00	16	16.00	8	50.00	5	7.35	3	60.00
	13	15.12	4	30.77	7	7.00	1	14.29	6	8.82	2	33.33

EXHIBIT 6.2: **5 year overall and event free survival proportions by age group and period, age 0–14 years, in Ontario, 1985–2004**

			1985–2004		1995–2004				1985–1989	
	Age (years)	N	OSP	95% CI	OSP	95% CI	EFSP	95% CI	OSP	95% CI
All leukemia	**Overall**	**1967**	**0.79**	**0.77-0.80**	**0.81**	**0.78-0.83**	**0.71**	**0.69-0.74**	**0.72**	**0.64-0.79**
	< 1	94	0.37	0.26-0.47	0.40	0.28-0.53	0.35	0.23-0.47	0.21	0.06-0.42
	1–4	790	0.84	0.81-0.86	0.85	0.82-0.88	0.75	0.70-0.78	0.82	0.72-0.88
	5–9	730	0.83	0.79-0.85	0.85	0.81-0.88	0.76	0.72-0.80	0.75	0.55-0.87
	10–14	353	0.69	0.64-0.74	0.72	0.65-0.77	0.62	0.54-0.68	0.69	0.57-0.79
Lymphoid	**Overall**	**1582**	**0.85**	**0.83-0.87**	**0.87**	**0.85-0.89**	**0.77**	**0.75-0.80**	**0.78**	**0.68-0.86**
	< 1	47	0.38	0.24-0.52	0.37	0.20-0.54	0.32	0.17-0.49	0.28	0.05-0.57
	1–4	659	0.90	0.87-0.92	0.91	0.88-0.94	0.80	0.76-0.84	0.87	0.77-0.93
	5–9	630	0.87	0.83-0.89	0.90	0.86-0.92	0.81	0.76-0.84	0.79	0.52-0.92
	10–14	246	0.78	0.72-0.83	0.79	0.71-0.85	0.70	0.62-0.77	0.75	0.60-0.85
Acute myeloid	**Overall**	**307**	**0.52**	**0.46-0.57**	**0.59**	**0.52-0.66**	**0.50**	**0.43-0.57**	**0.42**	**0.26-0.57**
	< 1	32	0.39	0.22-0.56	0.54	0.29-0.73	0.48	0.25-0.67	0.28	0.03-0.64
	1–4	107	0.55	0.45-0.64	0.62	0.49-0.73	0.52	0.40-0.64		
	5–9	83	0.55	0.43-0.66	0.58	0.44-0.69	0.52	0.38-0.64	0.49	0.13-0.78
	10–14	85	0.47	0.36-0.58	0.56	0.40-0.69	0.43	0.29-0.57	0.48	0.23-0.70
Chronic myeloid	**Overall**	**22**	**0.77**	**0.51-0.91**	**0.72**	**0.29-0.92**	**0.56**	**0.24-0.79**	**1.00**	
	< 1	0								
	1–4	3	0.67	0.05-0.95	0.51	0.00-0.92	0.51	0.00-0.92		
	5–9	6	1.00		1.00		1.00			
	10–14	13	0.66	0.29-0.87	0.77	0.25-0.95	0.53	0.14-0.81	1.00	
JMML	**Overall**	**18**	**0.24**	**0.08-0.45**	**0.27**	**0.08-0.50**	**0.20**	**0.05-0.43**		
	< 1	12	0.38	0.12-0.64	0.37	0.11-0.64	0.27	0.06-0.55		
	1–4	5								
	5–9	1								
	10–14	0								
Leukemia NOS	**Overall**	**38**	**0.54**	**0.37-0.69**	**0.56**	**0.36-0.72**	**0.44**	**0.26-0.60**	**0.27**	**0.01-0.68**
	< 1	3								
	1–4	16	0.68	0.39-0.85	0.68	0.36-0.86	0.49	0.22-0.71		
	5–9	10	0.52	0.16-0.79	0.44	0.10-0.74	0.44	0.10-0.75	1.00	
	10–14	9	0.52	0.17-0.78	0.52	0.17-0.78	0.37	0.09-0.66		

If blank, number is not estimable.
OSP = overall survival proportion; CI = confidence interval; EFSP = event free survival proportion; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified
*Although OSP is reported as lower than EFSP, it is an artifact of the small sample size.

1990–1994		1995–1999				2000–2004			
OSP	95% CI	OSP	95% CI	EFSP	95% CI	OSP	95% CI	EFSP	95% CI
0.77	**0.73-0.80**	**0.78**	**0.74-0.81**	**0.68**	**0.64-0.72**	**0.84**	**0.81-0.87**	**0.75**	**0.71-0.78**
0.39	0.18-0.60	0.40	0.24-0.55	0.31	0.17-0.46	0.42	0.22-0.61	0.40	0.20-0.59
0.82	0.76-0.86	0.81	0.76-0.85	0.73	0.67-0.78	0.90	0.85-0.93	0.76	0.70-0.81
0.79	0.72-0.84	0.83	0.77-0.87	0.71	0.65-0.77	0.87	0.81-0.90	0.82	0.76-0.86
0.69	0.59-0.78	0.69	0.59-0.77	0.59	0.49-0.68	0.75	0.65-0.82	0.64	0.54-0.72
0.84	**0.80-0.87**	**0.85**	**0.81-0.88**	**0.75**	**0.71-0.79**	**0.89**	**0.86-0.92**	**0.79**	**0.76-0.83**
0.49	0.20-0.73	0.39	0.19-0.59	0.28	0.12-0.47	0.35	0.10-0.61	0.39	0.12-0.67*
0.89	0.83-0.92	0.88	0.83-0.92	0.81	0.75-0.86	0.94	0.89-0.97	0.79	0.73-0.84
0.81	0.75-0.87	0.89	0.83-0.93	0.76	0.69-0.82	0.90	0.85-0.93	0.85	0.79-0.89
0.83	0.71-0.90	0.77	0.65-0.85	0.69	0.58-0.79	0.81	0.70-0.89	0.71	0.59-0.80
0.40	**0.29-0.50**	**0.53**	**0.44-0.62**	**0.45**	**0.36-0.54**	**0.67**	**0.56-0.76**	**0.56**	**0.45-0.66**
0.19	0.01-0.53	0.49	0.18-0.74	0.49	0.18-0.74	0.65	0.28-0.87	0.40	0.08-0.72
0.44	0.27-0.60	0.60	0.43-0.73	0.52	0.36-0.66	0.65	0.42-0.81	0.53	0.33-0.70
0.53	0.26-0.75	0.47	0.32-0.60	0.40	0.25-0.55	0.69	0.46-0.84	0.66	0.42-0.82
0.30	0.14-0.48	0.48	0.27-0.66	0.35	0.18-0.54	0.64	0.42-0.80	0.51	0.31-0.68
0.74	**0.28-0.93**	**0.57**	**0.12-0.86**	**0.39**	**0.10-0.68**	**1.00**		**1.00**	
		0.51	0.00-0.92	0.51	0.00-0.92	0.64	0.42-0.80	0.51	0.31-0.68
1.00		0.51	0.00-0.92	0.51	0.00-0.92				
0.43	0.06-0.78	0.68	0.12-0.93	0.37	0.06-0.70	1.00		1.00	
		0.24	**0.04-0.53**	**0.12**	**0.01-0.41**	**0.25**	**0.04-0.55**	**0.22**	**0.04-0.50**
		0.48	0.07-0.82	0.25	0.01-0.65	0.29	0.04-0.63	0.28	0.05-0.59
0.66	**0.06-0.94**	**0.65**	**0.35-0.84**	**0.48**	**0.21-0.71**	**0.43**	**0.21-0.64**	**0.35**	**0.16-0.55**
0.50	0.01-0.91	0.77	0.32-0.94	0.39	0.04-0.75	0.48	0.18-0.73	0.39	0.16-0.62
1.00		0.53	0.11-0.83	0.59	0.13-0.88*	0.21	0.00-0.75	0.21	0.00-0.75
		1.00		1.00		0.45	0.11-0.74	0.28	0.05-0.59

Exhibit 6.2

The proportions of 5 year EFS and overall survival for all children with leukemia were 0.71 and 0.81, respectively, between 1995 and 2004. There was no significant difference between the 2 most recent treatment periods (1995–1999 and 2000–2004). Both EFS and overall survival were higher for children with ALL (0.77 and 0.87, respectively) than for those with AML (0.50 and 0.59, respectively) and were within the range reported by clinical trials.[2,6,7,41,42] The proportion of overall survival for children with any leukemia, ALL and AML, which was calculated after including linkage-based mortality data for out-of-hospital and late deaths between 1985 and 1994, was similar to results based only on directly captured mortality data (1995–2004).

Age at diagnosis has a significant impact on the prognosis of ALL.[43] EFS was lowest in infants with ALL (younger than 1 year of age; EFS proportion, 0.37), intermediate for children 10 years or older (0.79) and highest in the age group 1–9 years (0.90). The same pattern applied to overall survival (0.37 for infants less than 1 year of age; 0.79 for children 10 years or older; 0.90 for the most favourable age group, 1–9 years). These results are as expected and reflect a widespread risk classification of childhood ALL.[43] Whereas all children 10 or older are considered to have high risk ALL by virtue of their age alone, not all children in the 1–9 year age group are expected to have standard risk ALL – some would be classified as having high risk ALL if their white blood cell count at diagnosis was 50 × 10^9/L or more. In contrast, EFS and overall survival of children with AML was not significantly different among age groups, consistent with data reported by clinical study groups.[5,6]

EXHIBIT 6.3: **Hematopoietic stem cell transplantation by relapse status and period, age 0–14 years, in Ontario, 1995–2004**

	1995–2004							1995–1999		
		HSCT			Timing of HSCT (%)				HSCT	
	Total patients	n	%	Allogeneic (%)	CR1	CR2	CR3	Total patients	n	%
All leukemia	**1059**	**198**	**18.70**	**86.36**	**54.55**	**38.89**	**6.57**	**549**	**122**	**22.22**
Lymphoid	841	94	11.18	100.00	27.66	59.57	12.77	423	52	12.29
Acute myeloid	168	77	45.83	64.94	74.03	25.97	0.00	100	58	58.00
Chronic myeloid	9	6	66.67	100.00	100.00	0.00	0.00	4	3	75.00
JMML	10	5	50.00	100.00	100.00	0.00	0.00	6	2	33.33
Leukemia NOS	31	16	51.61	100.00	87.50	6.25	6.25	16	7	43.75

HSCT = hematopoietic stem cell transplantation; CR1 = first remission (prior to relapse); CR2 = second remission (after first relapse); CR3 = third remission (after second relapse); JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Infants (less than 1 year of age) with ALL had consistently worse EFS and overall survival than other age groups in both periods (1995–1999 and 2000–2004). No other significant age-based differences were apparent in EFS or overall survival in children with ALL and AML over time. EFS (0.44) and overall survival (0.56) for leukemia NOS resembled more closely the proportions for AML than for ALL, without significant differences among age groups or treatment periods.

CML and JMML are rare forms of childhood leukemia and in this cohort accounted for 1.1% of cases (compared with the 3% expected[8]) and 0.9% of cases (compared with the 2–3% expected[12]), respectively. JMML is found predominantly in young children – half of all patients are diagnosed before 2 years of age[11,44] – and long term cure requires HSCT. The observed 5 year EFS (0.20) and overall survival (0.27) proportions were lower than reported for larger series (EFS 49–55% and overall survival 57.9%[12,13]) and likely result from the small number of cases analyzed. Treatment for CML has undergone a significant transformation since the use of oral tyrosine kinase inhibitors began to decrease the use of HSCT.[8] A first phase I study of imatinib in pediatric patients with Philadelphia chromosome positive leukemia was reported in 2004.[45] The EFS (0.56) and overall survival (0.72) observed between 1995 and 2004 are therefore likely to change significantly during future treatment periods.

				2000–2004						
	Timing of HSCT (%)				HSCT			Timing of HSCT (%)		
Allogeneic (%)	CR1	CR2	CR3	Total patients	n	%	Allogeneic (%)	CR1	CR2	CR3
79.51	**59.02**	**35.25**	**5.74**	**510**	**76**	**14.90**	**97.37**	**47.37**	**46.05**	**6.58**
100.00	30.77	55.77	13.46	418	42	10.05	100.00	23.81	64.29	11.90
56.90	77.59	22.41	0.00	68	19	27.94	89.47	63.16	36.84	0.00
100.00	100.00	0.00	0.00	5	3	60.00	100.00	100.00	0.00	0.00
100.00	100.00	0.00	0.00	4	3	75.00	100.00	100.00	0.00	0.00
100.00	85.71	14.29	0.00	15	9	60.00	100.00	88.89	11.11	0.00

Exhibit 6.3

Among 1,059 children with leukemia, 18.7% underwent HSCT between 1995 and 2004. They included 45.8% of all patients with AML and 11.2% of all patients with ALL. Because of the higher overall number of patients with ALL, the largest number of HSCT procedures was carried out for ALL (47.4% of all transplants, compared with 38.9% for AML). The majority of transplant recipients received allogeneic grafts (86.3%). Non-allogeneic grafts were used only for a subset of AML patients (35.1%). The majority of transplants for AML were carried out as part of the initial treatment for leukemia (in first remission; 74.0% of transplants for AML). In contrast, transplantation in second remission (after a first relapse) was the most common indication in children with ALL (59.6% of transplants for ALL). These findings are consistent with the current use of HSCT in the treatment of childhood leukemia.

From the earlier (1995–1999) to the more recent (2000–2004) period the proportion of patients undergoing HSCT as part of leukemia treatment decreased from 22.2% to 14.9%. This decrease was accounted for largely by a lower proportion of children with AML (27.9% vs. 58.0% during the earlier period), whereas the proportion of patients with ALL remained similar (12.2% in 1995–1999 and 10.0% in 2000–2004). The use of allogeneic donors for AML patients increased over time (from 56.9% to 89.5%), raising the overall proportion of allogeneic transplants from 79.5% to 97.4%.

Among children with AML, HSCT was not only used less frequently during the recent treatment period but also less frequently during first remission (i.e., as part of initial leukemia therapy) than before (63.1% vs. 77.6% of AML). Fewer HSCT procedures in first remission were also observed for ALL (23.8% vs. 30.8%). Possible explanations include refined risk stratification (by cytogenetics and treatment response) and improved treatment outcomes after chemotherapy.

EXHIBIT 6.4: **5 year overall survival proportion from diagnosis among children who received hematopoietic stem cell transplantation by period, age 0–14 years, in Ontario, 1995–2004**

		1995–2004				1995–1999				2000–2004			
		Received HSCT				Received HSCT				Received HSCT			
HSCT type	Diagnosis	Total patients	n	OSP	95% CI	Total patients	n	%	95% CI	Total patients	n	%	95% CI
All	**All leukemia**	**1059**	**198**	**0.63**	**0.55-0.70**	**549**	**122**	**0.66**	**0.55-0.76**	**510**	**76**	**0.62**	**0.52-0.71**
	Lymphoid	841	94	0.66	0.53-0.75	423	52	0.76	0.56-0.88	418	42	0.61	0.47-0.72
	Acute myeloid	168	77	0.64	0.52-0.74	100	58	0.62	0.47-0.74	68	19	0.76	0.58-0.87
	Chronic myeloid	9	6	1.00		4	3	1.00		5	3	1.00	
	JMML	10	5	0.30	0.03-0.66	6	2			4	3	0.22	0.00-0.73
	Leukemia NOS	31	16	0.37	0.14-0.61	16	7			15	9	0.32	0.10-0.58
Allogeneic	**All leukemia**		**171**	**0.64**	**0.55-0.71**		**97**	**0.69**	**0.55-0.80**		**74**	**0.61**	**0.51-0.70**
	Lymphoid		94	0.66	0.53-0.75		52	0.76	0.56-0.88		42	0.61	0.47-0.72
	Acute myeloid		50	0.68	0.52-0.80		33	0.68	0.47-0.83		17	0.75	0.55-0.87
	Chronic myeloid		6	1.00			3	1.00			3	1.00	
	JMML		5	0.30	0.03-0.66		2				3	0.22	0.00-0.73
	Leukemia NOS		16	0.37	0.14-0.61		7				9	0.32	0.10-0.58
Autologous	**All leukemia**		**27**	**0.56**	**0.36-0.72**		**25**	**0.56**	**0.35-0.73**		**2**	**0.78**	**0.35-0.95**
	Lymphoid		0				0				0		
	Acute myeloid		27	0.56	0.36-0.72		25	0.56	0.35-0.73		2	0.78	0.35-0.95
	Chronic myeloid		0				0				0		
	JMML		0				0				0		
	Leukemia NOS		0				0				0		

If blank, number is not estimable.
HSCT = hematopoietic stem cell transplantation; OSP = overall survival proportion; CI = confidence interval; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.4

For the entire period (1995–2004) the proportion of 5 year overall survival after allogeneic HSCT for all forms of pediatric leukemia was 0.64; for ALL it was 0.66 and for AML, 0.68. Autologous transplantation, which was confined to AML, resulted in an overall survival of 0.56. While the frequency of non-allogeneic HSCT markedly decreased during the most recent treatment period (see also Exhibit 6.3), no significant change in overall survival after HSCT over time was apparent.

EXHIBIT 6.5: **Leukemia relapse according to interval from initial diagnosis, by period, age 0–14 years, in Ontario, 1995–2004**

		1995–2004					
		Relapse			Time to relapse in months from diagnosis (%)		
		Total (n)	Yes				
			n	%	0–17	18–35	36+
All	**All leukemia**	**1059**	**222**	**20.96**	**42.34**	**25.23**	**32.43**
	Lymphoid	841	150	17.84	29.33	29.33	41.33
	Acute myeloid	168	62	36.90	70.97	17.74	11.29
	Chronic myeloid	9	1	11.11	0.00	0.00	100.00
	JMML	10	1	10.00	100.00	0.00	0.00
	Leukemia NOS	31	8	25.81	62.50	12.50	25.00
Females	**All leukemia**	**483**	**88**	**18.22**	**46.59**	**19.32**	**34.09**
	Lymphoid	372	56	15.05	30.36	25.00	44.64
	Acute myeloid	88	29	32.95	82.76	6.90	10.34
	Chronic myeloid	7	1	14.29	0.00	0.00	100.00
	JMML	3	0	0.00			
	Leukemia NOS	13	2	15.38	0.00	50.00	50.00
Males	**All leukemia**	**575**	**133**	**23.13**	**39.10**	**29.32**	**31.58**
	Lymphoid	469	94	20.04	28.72	31.91	39.36
	Acute myeloid	80	33	41.25	60.61	27.27	12.12
	Chronic myeloid	2	0	0.00			
	JMML	7	1	14.29	100.00	0.00	0.00
	Leukemia NOS	18	6	33.33	83.33	0.00	16.67

JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.5

The prognosis for survival after a relapse of leukemia depends mainly on 2 prognostic factors: the time between initial diagnosis of leukemia and relapse (see Exhibit 6.5) and the site of relapse (see Exhibit 6.6).

Between 1995 and 2004 a relapse of leukemia developed in 21.0% of children with leukemia (including 17.8% of those with ALL and 36.9% of those with AML). Males had a higher proportion of cases with relapse (23.2% of males had a relapse of leukemia, 20.0% a relapse of ALL and 41.3% a relapse of AML) than did females (18.2% of females with leukemia had a relapse, 15.1% a relapse of ALL and 33.0% a relapse of AML), in keeping with trial-based results.[30,31] There was a marked decrease in the proportion of children who relapsed between the earlier period (1995–1999) and the more recent period (2000–2004). The proportion of children who relapsed decreased for any leukemia from 24.4% to 17.3% (a 29.1% decrease), for ALL from 20.3% to 15.3% (a 24.6% decrease) and for AML from 42.0% to 29.4% (a 30.0% decrease). The decrease was larger among females (36.5%; from 21.9% to 13.9%) than males (25.2%; from 26.6% to 19.9%) and slightly larger for AML than ALL.

In ALL, a late relapse, defined as occurring more than 36 months after initial diagnosis of leukemia, is more favourable than an early relapse (18–35 months from diagnosis). Very early relapse (within 18 months of initial diagnosis) has the least favourable prognosis.[28–31,46] For AML, relapse occurring more than 1 year after initial diagnosis is considered more favourable than relapse prior to this point.[47,48]

1995–1999						2000–2004					
Relapse			Time to relapse in months from diagnosis (%)			Relapse			Time to relapse in months from diagnosis (%)		
Total (n)	Yes					Total (n)	Yes				
	n	%	0–17	18–35	36+		n	%	0–17	18–35	36+
549	**134**	**24.41**	**40.30**	**24.63**	**35.07**	**510**	**88**	**17.25**	**45.45**	**26.14**	**28.41**
423	86	20.33	24.42	26.74	48.84	418	64	15.31	35.94	32.81	31.25
100	42	42.00	71.43	21.43	7.14	68	20	29.41	70.00	10.00	20.00
4	1	25.00	0.00	0.00	100.00	5	0	0.00			
6	0	0.00				4	1	25.00	100.00	0.00	0.00
16	5	31.25	60.00	20.00	20.00	15	3	20.00	66.67	0.00	33.33
260	**57**	**21.92**	**47.37**	**17.54**	**35.09**	**223**	**31**	**13.90**	**45.16**	**22.58**	**32.26**
196	35	17.86	28.57	22.86	48.57	176	21	11.93	33.33	28.57	38.10
52	20	38.46	85.00	5.00	10.00	36	9	25.00	77.78	11.11	11.11
4	1	25.00	0.00	0.00	100.00	3	0	0.00			
2	0	0.00				1	0	0.00			
6	1	16.67	0.00	100.00	0.00	7	1	14.29	0.00	0.00	100.00
289	**77**	**26.64**	**35.06**	**29.87**	**35.06**	**287**	**57**	**19.86**	**45.61**	**28.07**	**26.32**
227	51	22.47	21.57	29.41	49.02	242	43	17.77	37.21	34.88	27.91
48	22	45.83	59.09	36.36	4.55	32	11	34.38	63.64	9.09	27.27
0	0					2	0	0.00			
4	0	0.00				3	1	33.33	100.00	0.00	0.00
10	4	40.00	75.00	0.00	25.00	8	2	25.00	100.00	0.00	0.00

Using this grouping based on time to relapse, the majority of relapses in children with ALL occurred late (41.3%). In contrast, relapses in AML occurred predominantly within the first 18 months after diagnosis (71.0%). This pattern applied to both males and females in the entire cohort (1995–2004). Over time – that is, comparing the periods 1995–1999 and 2000–2004 – late relapse of ALL (more than 36 months from diagnosis) and relapse of AML less than 18 months from diagnosis remained the most common forms of relapse among females, while their overall relapse rates markedly decreased. Among males with ALL, however, the proportion of (prognostically favourable) late relapse decreased while (prognostically unfavourable) very early relapse increased (from 21.6% to 37.2%).

The proportion of AML relapses was lower in females than in males and decreased in both over time. AML relapse within the first 18 months from diagnosis, however, accounted for a larger share of relapse cases among females than males during both time periods. This suggests that relapse of AML in females overall was less frequent but of a higher risk type when it did occur.

Lower relapse rates for ALL in females than in males have been observed consistently.[30,31] Although the overall decrease of ALL relapse during the recent treatment period occurred in parallel with improvements in the risk stratification and intensification of ALL therapy, it is not possible to deduce specific causes of this trend.

EXHIBIT 6.6a: **Leukemia relapse according to site of relapse by period, ages 0–14 years, Ontario, 1995–2004**

	1995–2004								1995–1999		
		Relapse		Relapse site (%)						Relapse	
	Total patients	n	%	Bone marrow only	Isolated CNS	Testes	Bone marrow and CNS or testes	Other	Total patients	n	%
Percentage for relapse site based on those who relapsed											
All leukemia	**1059**	**222**	**20.96**	**71.17**	**14.41**	**3.60**	**6.76**	**4.05**	**549**	**134**	**24.41**
Lymphoid	841	150	17.84	62.00	20.67	5.33	8.67	3.33	423	86	20.33
Acute myeloid	168	62	36.90	91.94	1.61	0.00	1.61	4.84	100	42	42.00
Chronic myeloid	9	1	11.11	100.00	0.00	0.00	0.00	0.00	4	1	25.00
JMML	10	1	10.00	100.00	0.00	0.00	0.00	0.00	6	0	0.00
Leukemia NOS	31	8	25.81	75.00	0.00	0.00	12.50	12.50	16	5	31.25
Percentage for relapse site based on total patients											
All leukemia	**1059**	**222**	**20.96**	**14.92**	**3.02**	**0.76**	**1.42**	**0.85**	**549**	**134**	**24.41**
Lymphoid	841	150	17.84	11.06	3.69	0.95	1.55	0.59	423	86	20.33
Acute myeloid	168	62	36.90	33.93	0.60	0.00	0.60	1.79	100	42	42.00
Chronic myeloid	9	1	11.11	11.11	0.00	0.00	0.00	0.00	4	1	25.00
JMML	10	1	10.00	10.00	0.00	0.00	0.00	0.00	6	0	0.00
Leukemia NOS	31	8	25.81	19.35	0.00	0.00	3.23	3.23	16	5	31.25

CNS = central nervous system; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.6a

Leukemic relapse may occur in the bone marrow, outside the bone marrow (such as in the central nervous system, testes or, less frequently, other organs) or both. The majority of relapsed ALL involved the bone marrow as the only site (62.0%), followed by isolated involvement of the CNS (20.7%) and testicular tissue (5.3%). These observations are consistent with data derived from clinical trials for relapse of childhood ALL.[31]

In AML the predominance of relapse in the bone marrow was even more pronounced (91.9% bone marrow alone and 93.6% for bone marrow combined with other sites, vs. reported proportions of 79.4% for bone marrow alone and 89.2% for bone marrow combined with other sites[47]). The distribution of sites of leukemic relapse in children is in keeping with available reports and appeared stable for both ALL and AML during the 2 reporting periods (1995–1999 and 2000–2004).

2000–2004												
Relapse site (%)						Relapse			Relapse site (%)			
Bone marrow only	Isolated CNS	Testes	Bone marrow and CNS or testes	Other	Total patients	n	%	Bone marrow only	Isolated CNS	Testes	Bone marrow and CNS or testes	Other
74.63	**12.69**	**3.73**	**6.72**	**2.24**	**510**	**88**	**17.25**	**65.91**	**17.05**	**3.41**	**6.82**	**6.82**
63.95	18.60	5.81	9.30	2.33	418	64	15.31	59.38	23.44	4.69	7.81	4.69
95.24	2.38	0.00	0.00	2.38	68	20	29.41	85.00	0.00	0.00	5.00	10.00
100.00	0.00	0.00	0.00	0.00	5	0	0.00					
					4	1	25.00	100.00	0.00	0.00	0.00	0.00
80.00	0.00	0.00	20.00	0.00	15	3	20.00	66.67	0.00	0.00	0.00	33.33
18.21	**3.10**	**0.91**	**1.64**	**0.55**	**510**	**88**	**17.25**	**11.37**	**2.94**	**0.59**	**1.18**	**1.18**
13.00	3.78	1.18	1.89	0.47	418	64	15.31	9.09	3.59	0.72	1.20	0.72
40.00	1.00	0.00	0.00	1.00	68	20	29.41	25.00	0.00	0.00	1.47	2.94
25.00	0.00	0.00	0.00	0.00	5	0	0.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00	4	1	25.00	25.00	0.00	0.00	0.00	0.00
25.00	0.00	0.00	6.25	0.00	15	3	20.00	13.33	0.00	0.00	0.00	6.67

EXHIBIT 6.6b: **5 year overall survival proportions by relapse status and period, age 0–14 years, in Ontario, 1995–2004**

Diagnosis	1995–2004							1995–1999			
	Total patients	Relapse			No relapse			Total patients	Relapse		
		n	OSP	95% CI	n	OSP	95% CI		n	OSP	95% CI
All leukemia	**1059**	**222**	**0.48**	**0.41-0.56**	**837**	**0.91**	**0.89-0.93**	**549**	**134**	**0.50**	**0.39-0.60**
Lymphoid	841	150	0.58	0.48-0.66	691	0.95	0.93-0.97	423	86	0.63	0.48-0.75
Acute myeloid	168	62	0.27	0.16-0.39	106	0.80	0.71-0.87	100	42	0.26	0.14-0.40
Chronic myeloid	9	1	1.00		8	0.87	0.35-0.98	4	1		
JMML	10	1			9	0.29	0.05-0.60	6	0		
Leukemia NOS	31	8	0.39	0.09-0.70	23	0.61	0.36-0.78	16	5	0.38	0.03-0.76

If blank, number is not estimable.
OSP = overall survival proportion; CI = confidence interval; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.6b

The proportion of children who survived at least 5 years was significantly higher after a relapse of ALL (0.58) than after a relapse of AML (0.27). Among patients who did not experience a leukemic relapse, a higher proportion of those with ALL survived (0.95) than of those with AML (0.80). This observation is consistent with the higher mortality associated with AML therapy, likely resulting from the use of more intense chemotherapy protocols and the more frequent use of HSCT. This pattern remained stable during the 2 reporting periods (1995–1999 and 2000–2004).

While the 5 year overall survival proportion was significantly lower for children with relapsed AML during the early treatment period, this difference was not apparent during the more recent period. Possible explanations lie in improvements in survival for children with relapsed AML – for example, due to improved indications and outcomes for first or second HSCT.

			2000–2004						
No relapse			Total patients	Relapse			No relapse		
n	OSP	95% CI		n	OSP	95% CI	n	OSP	95% CI
415	**0.89**	**0.85-0.92**	**510**	**88**	**0.50**	**0.41-0.59**	**422**	**0.92**	**0.90-0.95**
337	0.93	0.87-0.96	418	64	0.57	0.46-0.66	354	0.96	0.94-0.98
58	0.79	0.66-0.88	68	20	0.35	0.18-0.52	48	0.82	0.68-0.90
3	0.67	0.05-0.95	5	0			5	1.00	
6			4	1			3	0.28	0.05-0.59
11	0.76	0.34-0.94	15	3	0.47	0.00-0.91	12	0.45	0.20-0.67

EXHIBIT 6.7: **5 year overall survival proportions for lymphoid leukemia patients by risk group and period, age 0–14 years, in Ontario, 1995–2004**

	5 year survival proportion by risk group								
	1995–2004						1995–1999		
Age (years)	Standard			High			Standard		
	n	OSP	95% CI	n	OSP	95% CI	n	OSP	95% CI
Overall	**425**	**0.95**	**0.91-0.97**	**411**	**0.82**	**0.78-0.86**	**179**	**0.94**	**0.86-0.98**
< 1				20	0.34	0.14-0.56			
1–4	212	0.96	0.91-0.98	124	0.87	0.79-0.92	96	0.95	0.84-0.98
5–9	213	0.93	0.88-0.97	142	0.87	0.79-0.91	83	0.93	0.74-0.99
10–14				125	0.79	0.68-0.86			

Risk group was unknown for 5 patients.
OSP = overall survival proportion; CI = confidence interval

Exhibit 6.7

Survival outcomes for ALL according to prognostic risk group were available for 836 children aged 0–14 years between 1995 and 2004. The classification of standard risk vs. high risk groups within pediatric ALL was based on the prognostic criteria used at the start of treatment and therapeutic protocol. The interpretation of the data has to take into account that the basis of this prognostic classification has expanded from age, presenting white blood cell count, immunophenotype and CNS involvement to increasingly refined cytogenetic characterization of the blasts and evaluation of early treatment responses (see Introduction).

In the entire cohort of children with ALL included in this analysis, the standard risk and high risk groups each made up half of the cohort (infant ALL in this analysis was classified as high risk). In fact, the high risk group accounted for the majority of ALL patients during 1995–1999 (57.4%) before decreasing to 40.9% during 2000–2004. This distribution of ALL risk groups differs from trial-based data, which show that approximately 25% of all children with B-precursor ALL enrolled in clinical trials are classified as having high risk ALL.[26] It is likely that the introduction of risk classification based on early treatment response (MRD; see Introduction) will affect the distribution of ALL risk groups in subsequent treatment periods.

Treatment approaches were heterogeneous and included study protocols of 2 groups (Children's Oncology Group or predecessors and Dana-Farber Cancer Institute Consortium) as well as treatment protocols adopted by individual centres as standards of care.

				2000–2004					
	High			Standard			High		
	n	OSP	95% CI	n	OSP	95% CI	n	OSP	95% CI
	241	**0.81**	**0.73-0.87**	**246**	**0.95**	**0.91-0.97**	**170**	**0.83**	**0.78-0.88**
	11	0.42	0.14-0.69				9	0.35	0.10-0.61
	79	0.84	0.72-0.91	116	0.96	0.91-0.99	45	0.90	0.79-0.96
	97	0.86	0.72-0.94	130	0.93	0.87-0.96	45	0.85	0.74-0.91
	54	0.76	0.56-0.88				71	0.81	0.70-0.89

The proportion of overall survival after 5 years was 0.95 for children with standard risk ALL and 0.82 for high risk ALL during the entire reporting period (1995–2004). Survival proportions in the age groups 1–4/5–9 years were higher in the standard risk group (0.96/0.93) and lower for high risk patients (0.87/0.87) than in the entire group of children with ALL between the ages of 1 and 9 years (0.91/0.90) (see also Exhibit 6.2). These results are expected because the latter group contains both patients with standard risk and high risk ALL.

In the more recent period (2000–2004), overall survival for standard risk ALL was significantly higher than for all children with high risk ALL (including infant ALL) or children with high risk ALL older than 10 years, suggesting that further improvements in therapeutic efficacy, particularly in the high risk group, remain to be achieved.

Summary

Incidence

ALL was the most common form of childhood leukemia (80.4%), followed by AML (15.6%). ASIRs were 44.4 cases for any form of childhood leukemia, 36.0 for ALL and 7.3 for AML per 1 million population per year. The incidence of leukemia was higher among males (56.0% of ALL, 52.8% of AML).

Mortality

The ASMRs were 10.7 deaths due to any form of childhood leukemia, 6.4 due to ALL and 3.6 due to AML per 1 million population per year. Males with ALL had a higher mortality rate than females; there was no difference for AML. Mortality rates decreased for all leukemias over time, particularly during the most recent reporting period (2000–2004). Mortality, expressed as the number of deaths per number of cases diagnosed, improved particularly for childhood AML (from 59.3% in 1990–1994 to 29.4% in 2000–2004), likely reflecting intensified chemotherapy and supportive care.

Event free and overall survival

EFS and overall survival were 0.71 and 0.81 for all children with leukemia. As expected, EFS and overall survival were higher for children with ALL (0.77 and 0.87, respectively) than for those with AML (0.50 and 0.59, respectively). EFS was lowest in infants (younger than 1 year of age) with ALL (0.37), intermediate for children aged 10 years or older (0.79) and highest in the age group 1–9 years (0.90). The proportion of survival after 5 years was 0.95 for children with standard risk ALL and 0.82 for high risk ALL during the entire reporting period (1995–2004).

Hematopoietic stem cell transplantation

HSCT was part of treatment for 18.7% of children with leukemia (45.8% of those with AML and 11.2% of those with ALL). Most recipients received allografts (97.4% between 2000 and 2004). Most transplants for AML were carried out in first remission. In contrast, transplantation for ALL was most commonly used in second remission. The probability of survival after allogeneic HSCT for all pediatric leukemias was 0.64, for ALL it was 0.66 and for AML, 0.68. The proportion of patients treated for leukemia with HSCT decreased over time as a result of a lower proportion of all children with AML undergoing HSCT.

Relapse

Among children with leukemia, 20.0% developed a relapse (17.8% of those with ALL and 36.9% of those with AML). Relapse occurred more often in males than females. The proportion of children who relapsed decreased over time (by 24.6% for ALL and 30.0% for AML). Most relapses occurred late (more than 36 months from initial diagnosis) in ALL (41.3%) but early (within 18 months of diagnosis) in AML (71.0%). The proportion of children who survived at least 5 years after a relapse was significantly higher for ALL (0.58) than for AML (0.27).

References

1 Group USCSW. United States cancer statistics. 1999–2008 incidence and mortality web-based report, 2012. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Available at http://www.cdc.gov/uscs.

2 Pui C-H, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treatment of childhood acute lymphoblastic leukemia without prophylactic cranial irradiation. N Engl J Med. 2009;360:2730-41.

3 Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer. 2000;88:2398-424.

4 Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet. 2000;355:165-9.

5 Creutzig U, Zimmermann M, Lehrnbecher T, Graf N, Hermann J, Niemeyer CM, et al. Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: results of AML-BFM 98. J Clin Oncol. 2006;24:4499-506.

6 Gibson BE, Wheatley K, Hann IM, Stevens RF, Webb D, Hills RK, et al. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. Leukemia. 2005;19:2130-8.

7 Rubnitz JE, Raimondi SC, Tong X, Srivastava DK, Razzouk BI, Shurtleff SA, et al. Favorable impact of the t(9;11) in childhood acute myeloid leukemia. J Clin Oncol. 2002;20:2302-9.

8 Andolina JR, Neudorf SM, Corey SJ. How I treat childhood CML. Blood. 2012;119:1821-30.

9 Pulsipher MA. Treatment of CML in pediatric patients: should imatinib mesylate (STI-571, Gleevec) or allogeneic hematopoietic cell transplant be front-line therapy? Pediatr Blood Cancer. 2004;43:523-33.

10 Loh ML. Recent advances in the pathogenesis and treatment of juvenile myelomonocytic leukaemia. Br J Haematol. 2001;152:677-87.

11 Niemeyer CM, Kratz CP. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia: molecular classification and treatment options. Br J Haematol. 2008;140:610-24.

12 Locatelli F, Nollke P, Zecca M, Korthof E, Lanino E, Peters C, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood. 2005;105:410-9.

13 Manabe A, Okamura J, Yumura-Yagi K, Akiyama Y, Sako M, Uchiyama H, et al. Allogeneic hematopoietic stem cell transplantation for 27 children with juvenile myelomonocytic leukemia diagnosed based on the criteria of the International JMML Working Group. Leukemia. 2002;16:645-9.

14 Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446:758-64.

15 Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009;361(11):1058-66.

16 Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, et al. The origin and evolution of mutations in acute myeloid leukemia. Cell. 2012;150:264-78.

17 Speck NA, Gilliland DG. Core-binding factors in haematopoiesis and leukaemia. Nat Rev Cancer. 2002;2:502-13.

18 Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: lessons in natural history. Blood. 2003;102:2321-33.

19 Greaves MF, Wiemel J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer. 2003;3:639-49.

20 Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer. 2006;6:193-203.

21 Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350:1535-48.

22 Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol. 2001;29:487-94.

23 Dick JE. Stem cell concepts renew cancer research. Blood. 2008;112:4793-807.

24 Wang JC, Dick JE. Cancer stem cells: lessons from leukemia. Trends Cell Biol. 2005;15:494-501.

25 Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997;3:730-7.

26 Schrappe M, Stanulla M. Treatment of childhood acute lymphoblastic leukemia. In Pui C-H, editor. Treatment of acute leukemias. Totowa (NJ): Humana Press; 2003, pp. 87-104.

27 Cave H, van der Werff ten Bosch J, Suciu S, Guidal C, Waterkeyn C, Otten J, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer—Childhood Leukemia Cooperative Group. N Engl J Med. 1998;339:591-8.

28 Einsiedel HG, von Stackelberg A, Hartmann R, Fengler R, Schrappe M, Janka-Schaub G, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia—relapse study of the Berlin-Frankfurt-Munster Group 87. J Clin Oncol. 2005;23:7942-50.

29 Gaynon PS. Childhood acute lymphoblastic leukaemia and relapse. Br J Haematol. 2005;131:579-87.

30 Ko RH, Ji L, Barnette P, Bostrom B, Hutchinson R, Raetz E, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia consortium study. J Clin Oncol. 2010;28:648-54.

31 Tallen G, Ratei R, Mann G, Kaspers G, Niggli F, Karachunsky A, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol. 2010;28:2339-47.

32 Pui CH, Cheng C, Leung W, Rai SN, Rivera GK, Sandlund JT, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med. 2003;349:640-9.

33 Dini G, Zecca M, Balduzzi A, Messina C, Masetti R, Fagioli F, et al. No difference in outcome between children and adolescents transplanted for acute lymphoblastic leukemia in second remission. Blood. 2011;118:6683-90.

34 Shaw PJ, Kan F, Woo Ahn K, Spellman SR, Aljurf M, Ayas M, et al. Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors. Blood. 2010;116:4007-15.

35 Lipshultz SE. Exposure to anthracyclines during childhood causes cardiac injury. Semin Oncol. 2006;33:S8-14.

36 Pui CH. Toward optimal central nervous system-directed treatment in childhood acute lymphoblastic leukemia. J Clin Oncol. 2003;21:179-81.

37 Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. Br J Haematol. 2000;110:512-24.

38 Sorrell AD, Alonzo TA, Hilden JM, Gerbing RB, Loew TW, Hathaway L, et al. Favorable survival maintained in children who have myeloid leukemia associated with Down syndrome using reduced-dose chemotherapy on Children's Oncology Group trial A2971: a report from the Children's Oncology Group. Cancer. 2012;118(19):4806-14.

39 Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood. 2010; 116:3171-9.

40 Gamis AS. Acute myeloid leukemia and Down syndrome evolution of modern therapy—state of the art review. Pediatr Blood Cancer. 2005;44:13-20.

41 Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111:5477-85.

42 Creutzig U, Zimmermann M, Ritter J, Reinhardt D, Hermann J, Henze G, et al. Treatment strategies and long-term results in paediatric patients treated in four consecutive AML-BFM trials. Leukemia. 2005;19:2030-42.

43 Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14:18-24.

44 Koike K, Matsuda K. Recent advances in the pathogenesis and management of juvenile myelomonocytic leukaemia. Br J Haematol. 2008;141:567-75.

45 Champagne MA, Capdeville R, Krailo M, Qu W, Peng B, Rosamilia M, et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood. 2004;104:2655-60.

46 Nguyen K, Devidas M, Cheng SC, La M, Raetz EA, Carroll WL, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22:2142-50.

47 Sander A, Zimmermann M, Dworzak M, Fleischhack G, von Neuhoff C, Reinhardt D, et al. Consequent and intensified relapse therapy improved survival in pediatric AML: results of relapse treatment in 379 patients of three consecutive AML-BFM trials. Leukemia. 2010;24:1422-8.

48 Webb DK. Management of relapsed acute myeloid leukaemia. Br J Haematol. 1999;106:851-9.

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7

Lymphoma

Executive Summary

In Canada approximately 850 children under the age of 14 years are diagnosed with cancer annually, reflecting an annual age standardized incidence rate (ASIR) of 144–159 per 1 million children.[1] Of these cancers, 12.0% are lymphomas, which represents an ASIR of 16.9 per million. Hodgkin lymphoma (HL) accounts for about 40.0% of the lymphomas diagnosed; non-Hodgkin lymphoma (NHL) accounts for the remainder.

Ontario's statistics reflect the national numbers. Over a period of 20 years (1985–2004), lymphoma incidence data for Ontario were collected and entered into the database of the Pediatric Oncology Group of Ontario Networked Information System (POGONIS). The ASIR of pediatric cancer in Ontario was between 145 and 152.3 per 1 million over that period. During this time, 646 children were diagnosed with lymphoma – 12.0% of all pediatric cancers captured in the database. Approximately 39.5% (255 cases) were HL, and 57.1% (369 cases) were NHL. Age standardized incidence increased with age for all lymphomas, with an increase in particular in the NHL 5–9 year age group. There is also an indication that the incidence for NHL increased overall. There was no increase in the incidence of HL in the younger age groups.

Consistent with the literature, there was a male predominance in lymphoma overall for all age groups combined, with an increasing proportion of females in the older age groups. Overall survival for pediatric lymphoma remains high, with HL survival stable over time. While there was some overall improvement in survival in the NHL group, survival varies across the subtypes. Recognizing that numbers are small in each NHL category, survival for Burkitt lymphoma increased over time, as it did for the mixed category of "other," possibly reflecting the improvement in management of post transplant lymphoproliferative disorder (PTLD). The numbers are small, but patients with anaplastic large cell lymphoma (ALCL) fared less well over time, while lymphoblastic lymphoma (LL) patients had variable survival rates at each of the noted time points.

The trend in therapy showed a decrease in the use of radiation, especially for HL. Reviewing incidence, survival, therapy and development of second malignancies is an important part of overall cancer care and reflecting on these statistics can help in the planning of cancer care services in the province.

Introduction

In Canada almost 850 children 0–14 years of age are diagnosed with cancer every year and around 135 die from their disease. Lymphomas constitute about 12.0% of all cancers in this age group in Canada and are third in frequency after acute leukemias and brain tumours.[1] Lymphomas are clinically and biologically heterogeneous. Approximately 60.0% of newly diagnosed cases are NHL and the rest are HL.[2]

Non-Hodgkin lymphomas

The non-Hodgkin lymphomas are a heterogeneous group of diseases that reflect the differentiation stages of the lymphoid cells from which they originate.[3] Overall, they are rare, with an estimated incidence of 8 or 9 new cases per 1 million children per year.[1] The incidence of NHL increases steadily with age; age-specific incidence varies among the subtypes. The incidence of NHL in male children is almost twice that of female children. NHLs are categorized as low, intermediate or high grade based on their clinical aggressiveness. More than 90% of pediatric NHL cases are considered high grade tumours and comprise 4 main histologic subtypes: Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), ALCL and LL.[4] With effective combination chemotherapy and better supportive care, overall survival at 5 years is about 85% for all NHL.[5]

Hodgkin lymphomas

Hodgkin lymphomas are characterized by the presence of rare multinucleated giant cells, or Reed-Sternberg cells, almost always of B-cell derivation. The majority of the tumour is composed of inflammatory cells and fibrosis. The estimated incidence of HL is about 5–6 new cases per 1 million per year.[1] Childhood HL typically affects children 10–14 years of age and has a significant male predominance. HL has a bimodal age peak, occurring in the adolescent/young adult years and at age 55 and over.

Recent large trials report long term survival rates of 85–95% for childhood HL.[6] The main focus of these trials, however, has been to prevent late complications of therapy, including second malignancies, abnormal bone and soft tissue development, sterility and late cardiac and pulmonary disease. Current risk- and response-adapted therapies aim to minimize treatment intensity, therefore reducing toxicity, by omitting involved field radiotherapy among patients who are either at low risk or are rapid early responders.[6]

Classification

The third edition of the International Classification of Childhood Cancer (ICCC-3) classifies tumours coded according to the International Classification of Diseases for Oncology (ICD-O-3) and was designed for use in international population-based cancer registries.[7] The ICCC-3 maintains the division of lymphomas into the 2 major groups, Hodgkin lymphomas (IIa) and non-Hodgkin lymphomas (IIb). NHL in the ICCC-3 includes 4 categories:

- II(b) non-Hodgkin lymphomas (except Burkitt lymphoma)
- II(c) Burkitt lymphoma (including Burkitt-like and other variants)
- II(d) miscellaneous lymphoreticular neoplasms
- II(e) unspecified lymphomas

The ICD-O codes used to classify lymphomas in the ICCC classification have been mapped to the POGONIS fields, ensuring compatibility with ICCC while allowing finer dissection of group IIb as follows:

- Lymphoblastic lymphoma
- Anaplastic large cell lymphoma
- Other, which includes
    a. Large cell lymphoma, B-cell, diffuse not otherwise specified (NOS) and diffuse large cell B-cell lymphoma (DLBCL) [n=47]
    b. Post transplant lymphoproliferative disease [n=23]
    c. Lymphoma non-B non-T cell [n=4]
    d. Primary central nervous system lymphoma [n=5]
    e. Miscellaneous lymphoma (follicular lymphoma, mucosa-associated lymphoid tissue lymphoma and grey zone lymphoma) [n=22]

The reticuloendothelial neoplasms included in the ICCC, disseminated Langerhans cell histiocytosis and identified reticuloendothelial sarcomas (including histiocytic, interdigitating dendritic and follicular dendritic) are included and described in the incidence table and included in all analyses specifying all lymphomas in the following tables, but are not further discussed in this chapter.

Data collection

Lymphoma incidence data for Ontario were obtained from the POGONIS database. Registration in POGONIS is an active process, with cases being registered on confirmation of pathologic diagnosis by the 5 participating institutions that treat all children diagnosed with cancer in Ontario. The database captures 98% of children identified with cancer in the province.

All children aged 0–14 years diagnosed with lymphoma and registered in POGONIS in the categories corresponding to the ICCC definitions during the period 1985–2004 were captured in this analysis. For more information on data sources and methods, refer to Chapter 2 (Survival). The ICCC-defined category comprises 646 cases, including 22 cases of reticuloendothelial neoplasms. The latter are included in all analyses that specify all lymphomas but are not expanded on further. Vital status is based on linkage to Cancer Care Ontario mortality data.

Limitations

Classification systems have changed over time, and cases diagnosed earlier in the cohort will not have been classified according to the latest iteration of the ICD-O. While the POGONIS codes have been mapped to the ICD-O codes used in the ICCC-3 classification, a residual group of miscellaneous cases and cases identified as NOS is found in the category "other"; they do not conform to ICCC-3. However, incidence and mortality data for the NHL group as a whole are compatible with ICCC-3. For example, the subtype currently known as mature B-cell lymphoma should be considered its own category, while in the POGONIS database it is included in the "other" category. Another limitation is that 3.8% of patients did not link in the mortality analysis because they did not have Ontario Health Insurance Numbers, thereby excluding them from the final analyses of survival.

The following discussion provides a population-based overview for Ontario on the age-specific incidence of Hodgkin and non-Hodgkin lymphomas; incidence by NHL subtype and stage; the use of chemotherapy, radiation therapy and hematopoietic stem cell transplantation (HSCT); overall and event free survival (EFS) rates; relapse and survival after relapse; and the incidence of second malignancies for children in Ontario between 1985 and 2004.

Discussion

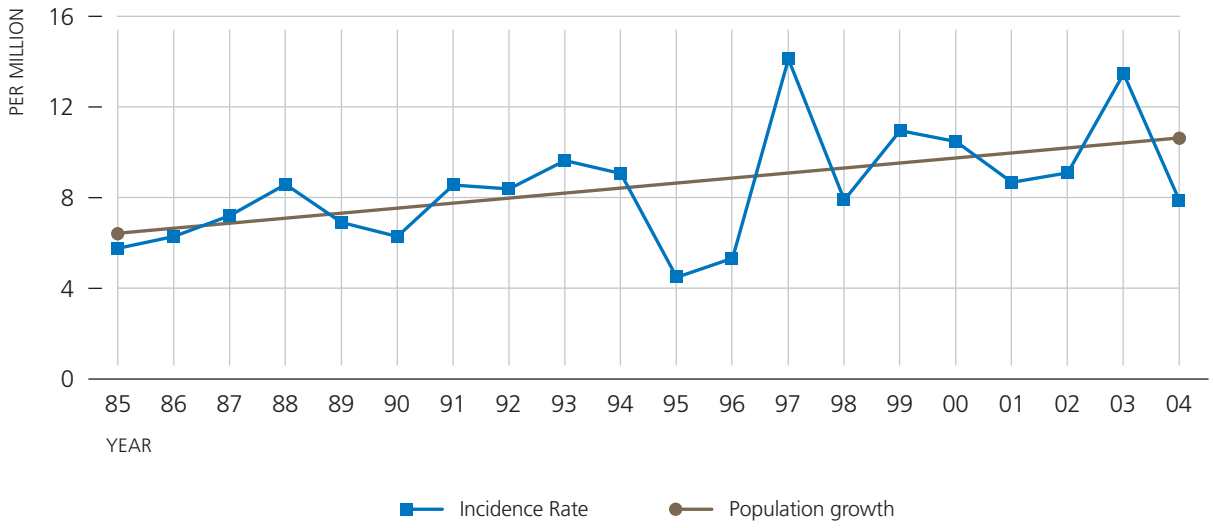
EXHIBIT 7.1a: **Incidence rate per 1 million for all lymphomas by age and period, age 0–14 years, in Ontario, 1985–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis: All years N	%	IR	% Female	1985–1989 N	%	IR	% Female
All lymphoma	Overall	**646**	**100.00**	**14.5**	**35.76**	**124**	**100.00**	**12.7**	**32.26**
	0–4	110	17.03	6.9	22.73	18	14.52	5.4	x
	5–9	206	31.89	13.9	31.07	43	34.68	13.4	x
	10–14	330	51.08	22.5	41.21	63	50.81	19.4	41.27
Hodgkin	Overall	**255**	**39.47**	**5.9**	**44.31**	**55**	**44.35**	**5.6**	**47.27**
	0–4	11	4.31	0.8	x	2	3.64	0.6	x
	5–9	49	19.22	3.4	x	14	25.45	4.4	x
	10–14	195	76.47	13.5	48.72	39	70.91	12.0	51.28
Non-Hodgkin	Overall	**369**	**57.12**	**8.7**	**30.35**	**68**	**54.84**	**7.0**	**20.59**
	0–4	86	23.31	6.3	27.91	16	23.53	4.8	x
	5–9	153	41.46	10.7	30.72	28	41.18	8.7	x
	10–14	130	35.23	9.1	31.54	24	35.29	7.4	25.00
Burkitt/Burkitt-like*	Overall	**133**	**36.04**	**3.1**	**18.05**	**33**	**48.53**	**3.4**	**x**
	0–4	30	22.56	2.1	20.00	9	27.27	2.7	x
	5–9	60	45.11	4.1	16.67	11	33.33	3.4	x
	10–14	43	32.33	3.0	18.60	13	39.39	4.0	x
Lymphoblastic	Overall	**95**	**25.75**	**2.2**	**30.53**	**15**	**22.06**	**1.5**	**x**
	0–4	24	25.26	1.7	25.00	3	20.00	0.9	x
	5–9	44	46.32	3.0	36.36	9	60.00	2.8	x
	10–14	27	28.42	1.9	25.93	3	20.00	0.9	x
Anaplastic large cell	Overall	**40**	**10.84**	**0.9**	**40.00**	**2**	**2.94**	**0.2**	**x**
	0–4	7	17.50	0.5	x	0	0.00	0.0	x
	5–9	17	42.50	1.2	41.18	1	50.00	0.3	x
	10–14	16	40.00	1.1	x	1	50.00	0.3	x
Other†	Overall	**101**	**27.37**	**2.3**	**42.57**	**18**	**26.47**	**1.8**	**x**
	0–4	25	24.75	1.8	44.00	4	22.22	1.2	x
	5–9	32	31.68	2.2	43.75	7	38.89	2.2	x
	10–14	44	43.56	3.0	40.91	7	38.89	2.2	x
Miscellaneous reticuloendothelial neoplasms‡	Overall	**22**	**3.41**	**—**	**27.27**	**1**	**0.81**	**—**	**x**
	0–4	13	59.09	—	x	0	0.00	—	x
	5–9	4	18.18	—	x	1	100.00	—	x
	10–14	5	22.73	—	x	0	0.00	—	x

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.
‡Miscellaneous reticuloendothelial neoplasms include Langerhans cell histiocytosis/systemic Letterer-Siwe disease, hemophagocytic macrophage related syndrome (familial erythrophagocytic lymphohistiocytosis) and histiocytic lymphoma.
x: For privacy reasons some data have not been reported.

	1990–1994				1995–1999				2000–2004			
	N	%	IR	% Female	N	%	IR	% Female	N	%	IR	% Female
All Cancers	**161**	**100.00**	**15**	**34.16**	**163**	**100.00**	**14.4**	**41.10**	**198**	**100.00**	**17.5**	**31.82**
Leukemias	27	16.77	7.3	x	27	16.56	7.3	33.33	38	19.19	11.3	21.05
Lymphomas	45	27.95	12.6	x	59	36.20	15.3	40.68	59	29.80	15.1	18.64
CNS Tumours	89	55.28	26.1	35.96	77	47.24	20.5	44.16	101	51.01	24.8	43.56
Epithelial Neoplasms	**66**	**40.99**	**6.2**	**40.91**	**62**	**38.04**	**5.4**	**43.55**	**72**	**36.36**	**6.4**	**45.83**
Adrenocortical Carcinoma	2	3.03	0.5	x	5	8.06	1.4	x	2	2.78	0.6	x
Thyroid Carcinoma	10	15.15	2.8	x	14	22.58	3.6	x	11	15.28	2.8	x
Other Epithelial Neoplasms	54	81.82	15.8	42.59	43	69.35	11.5	48.84	59	81.94	14.7	52.54
Germ Cell Tumours	**90**	**55.90**	**8.5**	**31.11**	**97**	**59.51**	**8.9**	**41.24**	**114**	**57.58**	**10.3**	**26.32**
Intracranial Germ Cell Tumours	23	25.56	6.2	x	19	19.59	5.7	42.11	28	24.56	8.7	28.57
Extracranial Germ Cell Tumours	34	37.78	9.8	41.18	45	46.39	11.9	42.22	46	40.35	12.0	19.57
Gonadal Germ Cell Tumours	33	36.67	9.7	x	33	34.02	9.1	39.39	40	35.09	10.1	32.50
Other Neoplasms	**32**	**35.56**	**3.0**	**31.25**	**30**	**30.93**	**2.7**	**x**	**38**	**33.33**	**3.4**	**15.79**
Hepatic Tumours	10	31.25	2.7	x	3	10.00	0.8	x	8	21.05	2.4	x
Bone Tumours	13	40.63	3.6	x	16	53.33	4.1	x	20	52.63	5.1	x
Soft Tissue Sarcomas	9	28.13	2.6	x	11	36.67	2.9	x	10	26.32	2.5	x
Miscellaneous	**22**	**24.44**	**2.1**	**x**	**27**	**27.84**	**2.4**	**40.74**	**31**	**27.19**	**2.7**	**29.03**
Neuroblastoma	6	27.27	1.6	x	6	22.22	1.6	x	9	29.03	2.7	x
Retinoblastoma	8	36.36	2.2	x	14	51.85	3.6	64.29	13	41.94	3.6	x
Other Miscellaneous	8	36.36	2.3	x	7	25.93	1.9	x	9	29.03	2.2	x
Unspecified	**11**	**12.22**	**1.0**	**x**	**9**	**9.28**	**0.8**	**x**	**18**	**15.79**	**1.6**	**38.89**
Unspecified Malignant Tumours	2	18.18	0.5	x	3	33.33	0.8	x	2	11.11	0.6	x
Unspecified Benign Tumours	6	54.55	1.7	x	3	33.33	0.8	x	7	38.89	1.8	x
Unspecified Neoplasms	3	27.27	0.9	x	3	33.33	0.8	x	9	50.00	2.2	x
Non-Neoplastic Disorders	**25**	**27.78**	**2.3**	**x**	**31**	**31.96**	**2.7**	**67.74**	**27**	**23.68**	**2.4**	**29.63**
Histiocytic Disorders	5	20.00	1.3	x	7	22.58	1.9	x	9	33.33	2.7	x
Other Non-Neoplastic Disorders	7	28.00	2.0	x	12	38.71	3.1	x	6	22.22	1.5	x
Unspecified Non-Neoplastic Disorders	13	52.00	3.8	x	12	38.71	3.2	x	12	44.44	2.9	x
Unknown	**5**	**3.11**	**—**	**x**	**4**	**2.45**	**—**	**x**	**12**	**6.06**	**—**	**x**
Unknown Malignant Tumours	2	40.00	—	x	3	75.00	—	x	8	66.67	—	x
Unknown Benign Tumours	1	20.00	—	x	0	0.00	—	x	2	16.67	—	x
Unknown Neoplasms	2	40.00	—	x	1	25.00	—	x	2	16.67	—	x

EXHIBIT 7.2: **Incidence rate per 1 million of non-Hodgkin lymphoma, trend over time, age 0–14 years, in Ontario, 1985–2004**



P-value for trend <0.0001

Exhibits 7.1–7.2

Incidence

The diagnosis of lymphoma accounted for 12% of all cancer cases in children 0–14 years of age between 1985 and 2004 in Ontario, with a total of 646 cases. Incidence rates are reported for each 5 year interval. NHL accounted for the majority of cases (369, or 57.1%), while HL was less common (255 cases, 39.5%). The incidence rate was 14.5 per 1 million per year for all childhood lymphoma – 8.7 for NHL and 5.9 for HL. The incidence rate of all lymphomas increased from 12.7 per 1 million per year in the first reporting period (1985–1989) to 17.5 in the most recent period (2000–2004) (Exhibit 7.1a). This increase was more significant in the NHL group during the last period, with a *P*-value for trend of < 0.0001 (incidence rate increasing from 7.0 in 1985–1989 to 10.3 in the last period) (Exhibit 7.2). The increase was consistent and notable in the 5–9 year age group (Exhibit 7.1a). HL had a modest increase in incidence rate from 5.6 in 1985–1989 to 6.4 in the last period. Although the numbers are small, there was a trend toward an increasing number of stage 4 HL and NHL cases over the 20 year period, possibly reflecting higher detection rates of diffuse disease as a result of better and more sensitive diagnostic tests (data not shown).

EXHIBIT 7.1b: **Incidence rate per 1 million of Hodgkin lymphoma by stage and gender, age 0–14 years, in Ontario, 1985–2004**

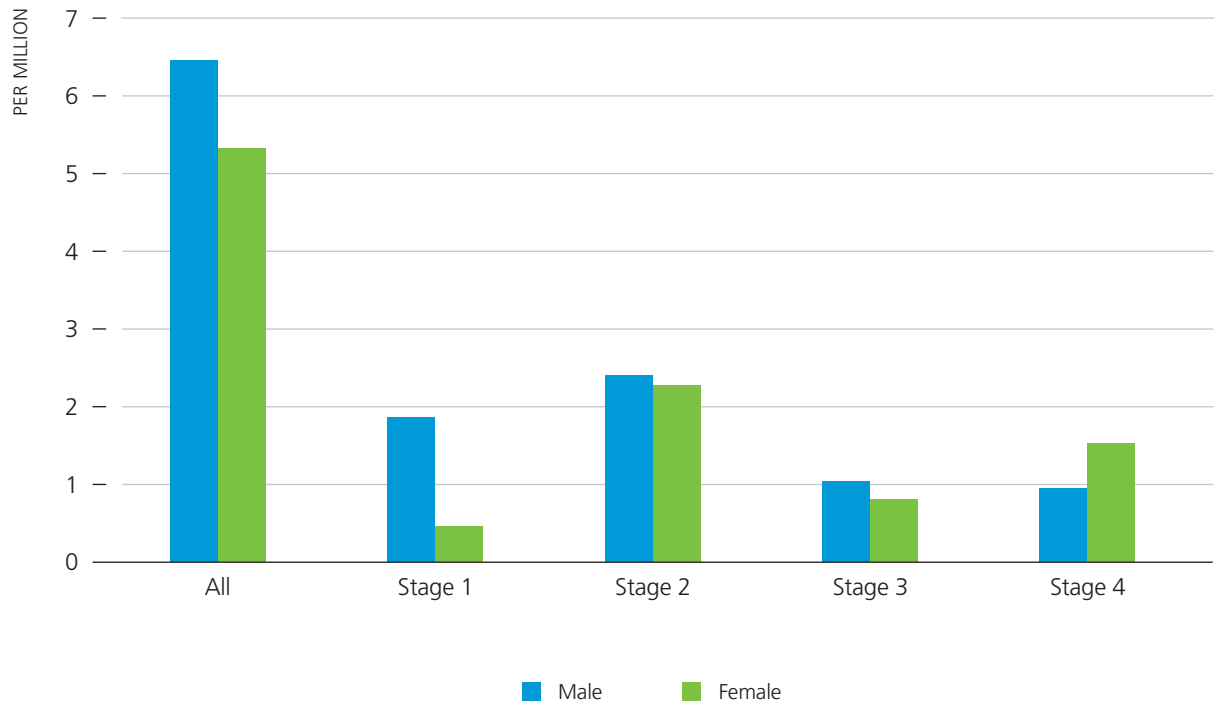


EXHIBIT 7.1c: **Incidence rate per 1 million of non-Hodgkin lymphoma by stage and gender, age 0–14 years, in Ontario, 1985–2004**

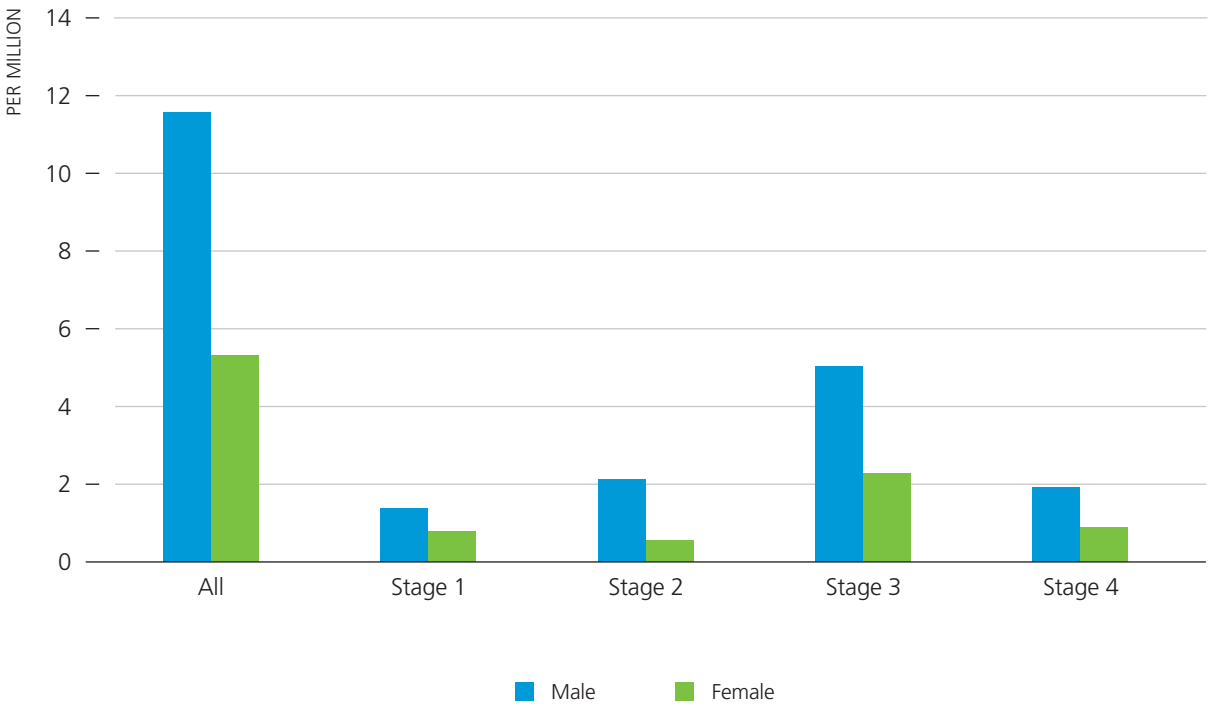
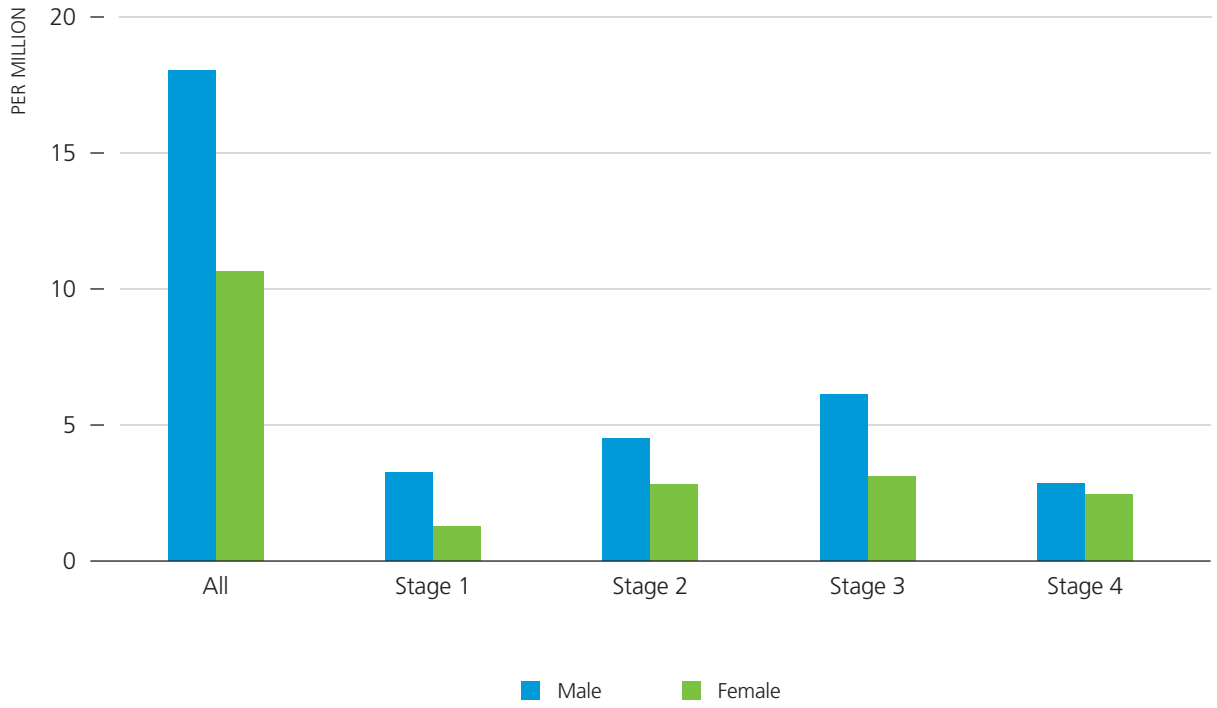


EXHIBIT 7.1d: **Incidence rate per 1 million of Hodgkin and non-Hodgkin lymphoma by stage and gender, age 0–14 years, in Ontario, 1985–2004**



Age-specific incidence

Average incidence increased with age for all lymphomas, with the greatest gradient between age groups in the HL group (incidence rate of 0.8 in children aged 0–4 years, compared with 13.5 in children aged 10–14 years). The incidence pattern of HL is in keeping with that seen in developed countries, where it tends to be more common in adolescents aged 15–19 years. Despite the increase in immigration to Ontario in recent years and recognizing that HL develops at a younger age in less privileged societies, HL was rare among children younger than 5 years. Among the NHL group, the greatest difference was between the 5–9 year group (incidence rate, 10.7) and the 0–4 year group (incidence rate, 6.3) (Exhibit 7.1a).

Gender-specific incidence

Male incidence of lymphoma was predominant in all age groups, particularly in very young children (0–4 years). The overall incidence of lymphoma in females appeared to increase with age. The incidence of stage 4 HL was higher in females, especially in the 10–14 year group (data not shown). In NHL, male incidence was higher for all age groups and among all stages (Exhibit 7.1c). ALCL, however, was more common in females, particularly in children aged 5–14 years (Exhibit 7.1a).

Subtype-specific incidence

When analyzed according to NHL histologic subtype, BL/BL-like were the most frequently diagnosed subtype (133 patients, 36.0%), followed by "other" NHL (101 cases, 27.4%), LL (95 cases, 25.8%) and ALCL (40 cases, 10.8%). BL/BL-like had a peak incidence in the 5–9 year age group, with 60 of 133 (45.1%) patients with BL being diagnosed in this age group. The most striking change over the 20 year period was the appearance of PTLD and primary central nervous system (CNS) lymphoma, which were not reported to the POGONIS database prior to 1995. Regarding ALCL, the number of cases in 1990–1994 was significantly different from the numbers in other periods (chi square = 12.5, $P < 0.01$) and there was a trend toward an increased incidence in children 10–14 years of age.

Regarding NHL subtypes, the incidence rate for BL was stable over the 20 year period, whereas there was a modest increase for both LL (from 1.5 to 2.7) and the "other" category (from 1.8 to 2.4). The increased number of patients diagnosed with ALCL throughout the 20 year period (incidence rate increasing from 0.2 to 1.6) is the result of improved detection of this entity rather than an absolute increase (Exhibit 7.1a).

Risk factors

The reasons for the increasing incidence of NHL are likely a combination of changes in risk factors and improved detection and classification of these lymphomas. The most common risk factor for NHL is immune insufficiency, related to a congenital immunodeficiency syndrome (e.g., X-linked lymphoproliferative disease, ataxia-telangiectasia or Wiskott-Aldrich syndrome), immunosuppressive therapy (e.g., in recipients of solid organ or bone marrow transplants), the human immunodeficiency virus[4] or autoimmune lymphoproliferative syndrome.[8] Although various organic solvents such as pesticides, dioxins and benzene have been implicated in the etiology of NHL, there is no convincing evidence that they represent significant risk factors for childhood lymphomas.[9,10]

Exhibits 7.3a–7.3b

Survival

Overall survival

Among all lymphomas, 1 year overall survival was 91.6% and 3 year overall survival was 85.9%. There was no significant change by 5 years (overall survival, 84.2%). The 1 year overall survival was 87.9% in the first period (1985–1989), improving to 91.9% in the last period (2000–2004); 3 year survival improved from 82.3% in the first period to 87.9% in the last, and 5 year survival improved from 79.8% to 86.4%. Mortality was relatively higher in the 10–14 year age group across all lymphomas. In HL patients (255 in total), overall survival at 1 year was 99.6% (1 death), while 3 and 5 year survival remained stable at approximately 93–94% across the 4 time periods. (One year survival data are not shown.)

Among NHL patients, mortality was higher in the 10–14 year age group, particularly in the BL/BL-like and "other" categories. There was a trend toward improved overall survival in all NHL patients across the 4 periods: 1 year overall survival increased from 77.9% in the first period to 88.6% in the last, 3 year survival from 72.1% to 86.0% and 5 year survival from 69.1% to 84.2%.

Overall survival at 1 year for all BL patients over the 20 year period was 86.4%; as expected, it plateaued at 85.0% at 3 years. The 1, 3 and 5 year overall survival for BL patients was essentially constant at 72.7–69.7% in the first period, increasing to a stable 5 year survival of 89.5% during the last period.

For all patients with LL over the 20 year period, overall survival dropped slightly from 94.7% at 1 year to 86.3% at 5 years. Over the 4 consecutive periods, there was no substantial change in 1, 3 or 5 year overall survival. There is a suggestion that mortality was higher in younger children with LL, with 3 of 5 deaths by 1 year occurring in children under 4 years of age, and 8 of 12 deaths by 3 years occurring in children younger than 10 years.

The 5 year overall survival for ALCL throughout the 20 year period was 70.0% and remained relatively stable at 66.7% during the last 2 periods. In the "other" category, overall survival improved significantly from 50.0% to 85.2% at 3 years and from 44.4% to 81.5% at 5 years (Exhibits 7.3a and 7.3b).

Across all lymphoma types, mortality was, not surprisingly, higher in patients with stage 3 or 4 disease (with 66 deceased out of 314, or 21.0%) as opposed to those with stage 1 or 2 cancer (19 deceased out of 257, or 7.4%). Overall survival for stages 1 and 2 remained the same (92.1%–95.7%) throughout the 4 periods, while survival for stages 3 and 4 improved from 73.4% in the first period to 84.5% in the last.

EXHIBIT 7.3a: **3 year survival rates for lymphoma by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1985–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis: All years N	All years Deaths	All years % Survived	1985–1989 N	1985–1989 Deaths	1985–1989 % Survived
All lymphoma	Overall	**646**	**91**	**85.91**	**124**	**22**	**82.26**
	0–4	110	18	83.64	18	5	72.22
	5–9	206	29	85.92	43	9	79.07
	10–14	330	44	86.67	63	8	87.30
Hodgkin	Overall	**255**	**15**	**94.12**	**55**	**3**	**94.55**
	0–4	11	0	100.00	2	0	100.00
	5–9	49	2	95.92	14	1	92.86
	10–14	195	13	93.33	39	2	94.87
Non-Hodgkin	Overall	**369**	**69**	**81.30**	**68**	**19**	**72.06**
	0–4	86	14	83.72	16	5	68.75
	5–9	153	26	83.01	28	8	71.43
	10–14	130	29	77.69	24	6	75.00
Burkitt/Burkitt-like*	Overall	**133**	**20**	**84.96**	**33**	**9**	**72.73**
	0–4	30	4	86.67	9	3	66.67
	5–9	60	6	90.00	11	3	72.73
	10–14	43	10	76.74	13	3	76.92
Lymphoblastic	Overall	**95**	**12**	**87.37**	**15**	**1**	**93.33**
	0–4	24	3	87.50	3	0	100.00
	5–9	44	5	88.64	9	1	88.89
	10–14	27	4	85.19	3	0	100.00
Anaplastic large cell	Overall	**40**	**10**	**75.00**	**2**	**0**	**100.00**
	0–4	7	1	85.71	0	0	—
	5–9	17	5	70.59	1	0	100.00
	10–14	16	4	75.00	1	0	100.00
Other†	Overall	**101**	**27**	**73.27**	**18**	**9**	**50.00**
	0–4	25	6	76.00	4	2	50.00
	5–9	32	10	68.75	7	4	42.86
	10–14	44	11	75.00	7	3	57.14
All		**576**	**76**	**86.81**	**115**	**21**	**81.74**
Stage 1 & 2		258	15	94.19	51	4	92.16
Stage 3 & 4		318	61	80.82	64	17	73.44

The total for stages may not be the same as reported in Exhibit 7.3b because all individuals may not have linked successfully to Cancer Care Ontario mortality data.
*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

22 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.
7 deaths occurred in this group and are included in the survival calculations for the "all lymphomas" category.

	1990–1994			1995–1999			2000–2004		
	N	Deaths	% Survived	N	Deaths	% Survived	N	Deaths	% Survived
	161	**22**	**86.34**	**163**	**23**	**85.89**	**198**	**24**	**87.88**
	27	3	88.89	27	6	77.78	38	4	89.47
	45	8	82.22	59	7	88.14	59	5	91.53
	89	11	87.64	77	10	87.01	101	15	85.15
	66	**4**	**93.94**	**62**	**3**	**95.16**	**72**	**5**	**93.06**
	2	0	100.00	5	0	100.00	2	0	100.00
	10	0	100.00	14	1	92.86	11	0	100.00
	54	4	92.59	43	2	95.35	59	5	91.53
	90	**16**	**82.22**	**97**	**18**	**81.44**	**114**	**16**	**85.96**
	23	2	91.30	19	4	78.95	28	3	89.29
	34	7	79.41	45	6	86.67	46	5	89.13
	33	7	78.79	33	8	75.76	40	8	80.00
	32	**4**	**87.50**	**30**	**3**	**90.00**	**38**	**4**	**89.47**
	10	1	90.00	3	0	100.00	8	0	100.00
	13	2	84.62	16	0	100.00	20	1	95.00
	9	1	88.89	11	3	72.73	10	3	70.00
	22	**3**	**86.36**	**27**	**5**	**81.48**	**31**	**3**	**90.32**
	6	0	100.00	6	1	83.33	9	2	77.78
	8	1	87.50	14	3	78.57	13	0	100.00
	8	2	75.00	7	1	85.71	9	1	88.89
	11	**2**	**81.82**	**9**	**3**	**66.67**	**18**	**5**	**72.22**
	2	0	100.00	3	1	66.67	2	0	100.00
	6	2	66.67	3	1	66.67	7	2	71.43
	3	0	100.00	3	1	66.67	9	3	66.67
	25	**7**	**72.00**	**31**	**7**	**77.42**	**27**	**4**	**85.19**
	5	1	80.00	7	2	71.43	9	1	88.89
	7	2	71.43	12	2	83.33	6	2	66.67
	13	4	69.23	12	3	75.00	12	1	91.67
	147	**19**	**87.07**	**141**	**17**	**87.94**	**173**	**19**	**89.01**
	77	5	93.51	60	3	95.00	70	3	95.71
	70	14	80.00	81	14	82.72	103	16	84.47

EXHIBIT 7.3b: **5 year survival rates for lymphoma by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1985–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis: All years N	All years Deaths	All years % Survived	1985–1989 N	1985–1989 Deaths	1985–1989 % Survived
All lymphoma	Overall	**646**	**102**	**84.21**	**124**	**25**	**79.84**
	0–4	110	22	80.00	18	6	66.67
	5–9	206	31	84.95	43	10	76.74
	10–14	330	49	85.15	63	9	85.71
Hodgkin	Overall	**255**	**18**	**92.94**	**55**	**4**	**92.73**
	0–4	11	0	100.00	2	0	100.00
	5–9	49	2	95.92	14	1	92.86
	10–14	195	16	91.79	39	3	92.31
Non-Hodgkin	Overall	**369**	**76**	**79.40**	**68**	**21**	**69.12**
	0–4	86	17	80.23	16	6	62.50
	5–9	153	28	81.70	28	9	67.86
	10–14	130	31	76.15	24	6	75.00
Burkitt/Burkitt-like*	Overall	**133**	**21**	**84.21**	**33**	**10**	**69.70**
	0–4	30	5	83.33	9	4	55.56
	5–9	60	6	90.00	11	3	72.73
	10–14	43	10	76.74	13	3	76.92
Lymphoblastic	Overall	**95**	**13**	**86.32**	**15**	**1**	**93.33**
	0–4	24	3	87.50	3	0	100.00
	5–9	44	5	88.64	9	1	88.89
	10–14	27	5	81.48	3	0	100.00
Anaplastic large cell	Overall	**40**	**12**	**70.00**	**2**	**0**	**100.00**
	0–4	7	1	85.71	0	0	—
	5–9	17	6	64.71	1	0	100.00
	10–14	16	5	68.75	1	0	100.00
Other†	Overall	**101**	**30**	**70.30**	**18**	**10**	**44.44**
	0–4	25	8	68.00	4	2	50.00
	5–9	32	11	65.63	7	5	28.57
	10–14	44	11	75.00	7	3	57.14
All		**571**	**85**	**85.11**	**115**	**24**	**79.13**
Stage 1 & 2		257	19	92.61	51	5	90.20
Stage 3 & 4		314	66	78.98	64	19	70.31

The total for stages may not be the same as reported in Exhibit 7.3a because all individuals may not have linked successfully to Cancer Care Ontario mortality data.
*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

22 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.
8 deaths occurred in this group and are included in the survival calculations for the "all lymphomas" category.

	1990–1994			1995–1999			2000–2004		
	N	Deaths	% Survived	N	Deaths	% Survived	N	Deaths	% Survived
	161	**26**	**83.85**	**163**	**24**	**85.28**	**198**	**27**	**86.36**
	27	5	81.48	27	6	77.78	38	5	86.84
	45	9	80.00	59	7	88.14	59	5	91.53
	89	12	86.52	77	11	85.71	101	17	83.17
	66	**5**	**92.42**	**62**	**3**	**95.16**	**72**	**6**	**91.67**
	2	0	100.00	5	0	100.00	2	0	100.00
	10	0	100.00	14	1	92.86	11	0	100.00
	54	5	90.74	43	2	95.35	59	6	89.83
	90	**18**	**80.00**	**97**	**19**	**80.41**	**114**	**18**	**84.21**
	23	3	86.96	19	4	78.95	28	4	85.71
	34	8	76.47	45	6	86.67	46	5	89.13
	33	7	78.79	33	9	72.73	40	9	77.50
	32	**4**	**87.50**	**30**	**3**	**90.00**	**38**	**4**	**89.47**
	10	1	90.00	3	0	100.00	8	0	100.00
	13	2	84.62	16	0	100.00	20	1	95.00
	9	1	88.89	11	3	72.73	10	3	70.00
	22	**3**	**86.36**	**27**	**6**	**77.78**	**31**	**3**	**90.32**
	6	0	100.00	6	1	83.33	9	2	77.78
	8	1	87.50	14	3	78.57	13		100.00
	8	2	75.00	7	2	71.43	9	1	88.89
	11	**3**	**72.73**	**9**	**3**	**66.67**	**18**	**6**	**66.67**
	2	0	100.00	3	1	66.67	2	0	100.00
	6	3	50.00	3	1	66.67	7	2	71.43
	3	0	100.00	3	1	66.67	9	4	55.56
	25	**8**	**68.00**	**31**	**7**	**77.42**	**27**	**5**	**81.48**
	5	2	60.00	7	2	71.43	9	2	77.78
	7	2	71.43	12	2	83.33	6	2	66.67
	13	4	69.23	12	3	75.00	12	1	91.67
	146	**22**	**84.93**	**139**	**18**	**87.05**	**171**	**21**	**87.72**
	77	7	90.91	59	3	94.92	70	4	94.29
	69	15	78.26	80	15	81.25	101	17	83.17

EXHIBIT 7.3c: **5 year survival rates for lymphoma by tumour type, sex and year of diagnosis, age 0–14 years, in Ontario, 1985–2004**

	Year of diagnosis					
	All years			1985–1989		
Cancer type	N	Deaths	% Survived	N	Deaths	% Survived
Female						
All lymphoma	**235**	**44**	**81.28**	**40**	**11**	**72.50**
Hodgkin	113	12	89.38	26	4	84.62
Non-Hodgkin	112	28	75.00	14	7	50.00
Burkitt/Burkitt-like*	24	4	83.33	5	2	60.00
Lymphoblastic	29	5	82.76	4	0	100.00
Anaplastic large cell	16	4	75.00	0	0	—
Other†	43	15	65.12	5	5	0.00
Male						
All lymphoma	**411**	**58**	**85.89**	**84**	**14**	**83.33**
Hodgkin	142	6	95.77	29	0	100.00
Non-Hodgkin	257	48	81.32	54	14	74.07
Burkitt/Burkitt-like*	109	17	84.40	28	8	71.43
Lymphoblastic	66	8	87.88	11	1	90.91
Anaplastic large cell	24	8	66.67	2	0	100.00
Other†	58	15	74.14	13	5	61.54

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

22 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.
8 deaths occurred in this group and are included in the survival calculations for the "all lymphomas" category.

Exhibit 7.3c

Gender-specific overall survival

The 5 year overall survival in females with any lymphoma was 81.3% during the 20 year period, compared with 85.9% for males. Females showed a trend toward improved overall survival from 72.5% in the first period to 81.2% in the last. Among HL patients, survival in females improved marginally from 84.6% in the first period to 87.9% in the last. In the NHL group, females had a significant increase in survival from 50.0% in the first period to 76.7% in the last. The greatest improvement for females was among BL/BL-like cases, which saw overall survival increase from 60.0% in the first period to 83.3% in the last.

Among males with any lymphoma, 5 year overall survival improved equivalently, from 83.3% in the earliest period to 89.1% in the most recent one. The 5 year survival in males with HL was better, at 100.0% in the first period and 94.9% in the most recent one. Overall survival in males with NHL improved from 74.1% to 86.9%; more specifically, in BL it rose from 71.4% to 90.6% and in ALCL from 57.1% in 1990–1994 to 72.7% in the last period (Exhibit 7.3c).

	1990–1994			1995–1999			2000–2004		
	N	Deaths	% Survived	N	Deaths	% Survived	N	Deaths	% Survived
	56	**9**	**83.93**	**70**	**11**	**84.29**	**69**	**13**	**81.16**
	27	2	92.59	27	2	92.59	33	4	87.88
	28	6	78.57	40	8	80.00	30	7	76.67
	10	1	90.00	3	0	100.00	6	1	83.33
	5	1	80.00	11	3	72.73	9	1	88.89
	4	0	100.00	5	1	80.00	7	3	57.14
	9	4	55.56	21	4	80.95	8	2	75.00
	105	**17**	**83.81**	**93**	**13**	**86.02**	**129**	**14**	**89.15**
	39	3	92.31	35	1	97.14	39	2	94.87
	62	12	80.65	57	11	80.70	84	11	86.90
	22	3	86.36	27	3	88.89	32	3	90.63
	17	2	88.24	16	3	81.25	22	2	90.91
	7	3	57.14	4	2	50.00	11	3	72.73
	16	4	75.00	10	3	70.00	19	3	84.21

EXHIBIT 7.4a: **3 year event free survival rates for lymphoma by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1995–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis								
		All years			1995–1999			2000–2004		
		N	Event	% Event free survival	N	Event	% Event free survival	N	Event	% Event free survival
All lymphoma	Overall	**361**	**85**	**76.45**	**163**	**36**	**77.91**	**198**	**49**	**75.25**
	0–4	54	13	75.93	27	8	70.37	38	12	68.42
	5–9	116	25	78.45	59	15	74.58	59	11	81.36
	10–14	175	37	78.86	77	13	83.12	101	26	74.26
Hodgkin	Overall	**134**	**19**	**85.82**	**62**	**6**	**90.32**	**72**	**13**	**81.94**
	0–4	7	0	100.00	5	0	100.00	2	0	100.00
	5–9	25	3	88.00	14	2	85.71	11	1	90.91
	10–14	102	16	84.31	43	4	90.70	59	12	79.66
Non-Hodgkin	Overall	**211**	**56**	**73.46**	**98**	**27**	**72.45**	**114**	**29**	**74.56**
	0–4	47	13	72.34	19	5	73.68	28	8	71.43
	5–9	91	22	75.82	46	13	71.74	46	9	80.43
	10–14	73	21	71.23	33	9	72.73	40	12	70.00
Burkitt/ Burkitt-like*	Overall	**68**	**9**	**86.76**	**30**	**3**	**90.00**	**38**	**6**	**84.21**
	0–4	11	1	90.91	3	0	100.00	8	1	87.50
	5–9	36	2	94.44	16	0	100.00	20	2	90.00
	10–14	21	6	71.43	11	3	72.73	10	3	70.00
Lymphoblastic	Overall	**58**	**16**	**72.41**	**27**	**7**	**74.07**	**31**	**9**	**70.97**
	0–4	15	5	66.67	6	1	83.33	9	4	55.56
	5–9	27	6	77.78	14	4	71.43	13	2	84.62
	10–14	16	5	68.75	7	2	71.43	9	3	66.67
Anaplastic large cell	Overall	**27**	**12**	**55.56**	**9**	**4**	**55.56**	**18**	**8**	**55.56**
	0–4	5	3	40.00	3	2	33.33	2	1	50.00
	5–9	10	4	60.00	3	1	66.67	7	3	57.14
	10–14	12	5	58.33	3	1	66.67	9	4	55.56
Other†	Overall	**58**	**19**	**67.24**	**31**	**13**	**58.06**	**27**	**6**	**77.78**
	0–4	16	4	75.00	7	2	71.43	9	2	77.78
	5–9	18	10	44.44	12	8	33.33	6	2	66.67
	10–14	24	5	79.17	12	3	75.00	12	2	83.33

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

16 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.

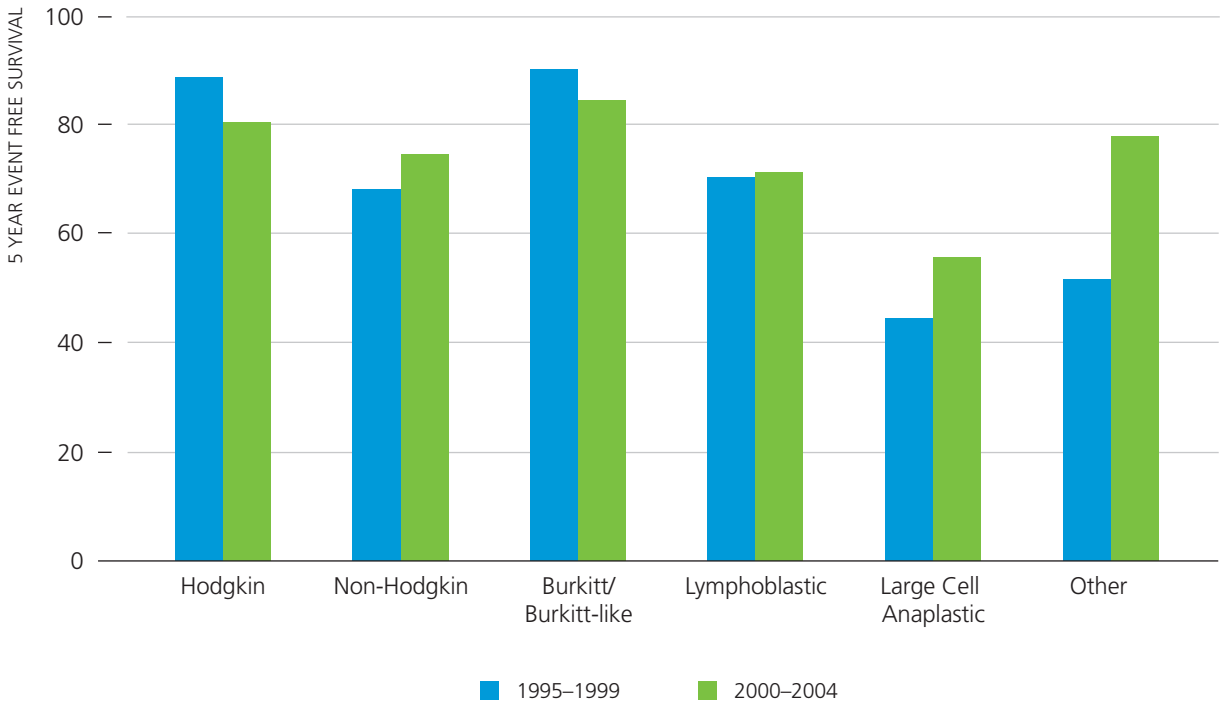
EXHIBIT 7.4b: **5 year event free survival rates for lymphoma by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1995–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis								
		All years			1995–1999			2000–2004		
		N	Event	% Event free survival	N	Event	% Event free survival	N	Event	% Event free survival
All lymphoma	**Overall**	**361**	**91**	**74.79**	**163**	**41**	**74.85**	**198**	**50**	**74.75**
	0–4	54	15	72.22	27	10	62.96	38	12	68.42
	5–9	116	25	78.45	59	15	74.58	59	11	81.36
	10–14	175	41	76.57	77	16	79.22	101	27	73.27
Hodgkin	**Overall**	**134**	**21**	**84.33**	**62**	**7**	**88.71**	**72**	**14**	**80.56**
	0–4	7	0	100.00	5	0	100.00	2	0	100.00
	5–9	25	3	88.00	14	2	85.71	11	1	90.91
	10–14	102	18	82.35	43	5	88.37	59	13	77.97
Non-Hodgkin	**Overall**	**211**	**60**	**71.56**	**98**	**31**	**68.37**	**114**	**29**	**74.56**
	0–4	47	15	68.09	19	7	63.16	28	8	71.43
	5–9	91	22	75.82	46	13	71.74	46	9	80.43
	10–14	73	23	68.49	33	11	66.67	40	12	70.00
Burkitt/ Burkitt-like*	**Overall**	**68**	**9**	**86.76**	**30**	**3**	**90.00**	**38**	**6**	**84.21**
	0–4	11	1	90.91	3	0	100.00	8	1	87.50
	5–9	36	2	94.44	16	0	100.00	20	2	90.00
	10–14	21	6	71.43	11	3	72.73	10	3	70.00
Lymphoblastic	**Overall**	**58**	**17**	**70.69**	**27**	**8**	**70.37**	**31**	**9**	**70.97**
	0–4	15	6	60.00	6	2	66.67	9	4	55.56
	5–9	27	6	77.78	14	4	71.43	13	2	84.62
	10–14	16	5	68.75	7	2	71.43	9	3	66.67
Anaplastic large cell	**Overall**	**27**	**13**	**51.85**	**9**	**5**	**44.44**	**18**	**8**	**55.56**
	0–4	5	3	40.00	3	2	33.33	2	1	50.00
	5–9	10	4	60.00	3	1	66.67	7	3	57.14
	10–14	12	6	50.00	3	2	33.33	9	4	55.56
Other†	**Overall**	**58**	**21**	**63.79**	**31**	**15**	**51.61**	**27**	**6**	**77.78**
	0–4	16	5	68.75	7	3	57.14	9	2	77.78
	5–9	18	10	44.44	12	8	33.33	6	2	66.67
	10–14	24	6	75.00	12	4	66.67	12	2	83.33

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

16 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.

EXHIBIT 7.4c: **5 year event free survival among lymphoma cases, by type and period, age 0–14 years, in Ontario, 1995–2004**



Exhibits 7.4a – 7.4c

Event free survival

EFS rates were reportable for only the 1995–2004 period. The 3 and 5 year EFS rates for all lymphomas were very similar at 76.5% and 74.8%, respectively, and were relatively stable from 1995–1999 to the most recent period (77.9 % and 75.3% for 3 year EFS in the 2 periods, and 74.8% throughout the 10 year period for 5 year EFS) (Exhibits 7.4a and 7.4b). HL patients had 3 and 5 year EFS that was stable at 85.8% and 84.3%, respectively. The 3 year EFS for HL decreased from 90.3% during the 1995–1999 period to 81.9% in the most recent one, while 5 year EFS decreased from 88.7% to 80.6%. Interestingly, the small number (7) of younger patients with HL (age 0–4 years) had 100.0% 3 and 5 year EFS. The drop in EFS was more obvious among teenagers with HL, with 3 year EFS dropping from 90.7% in the first period to 79.7% in the last, and 5 year EFS dropping from 88.4% to 78.0%.

Among NHL patients, 3 and 5 year EFS was very similar at 73.5% and 71.5%, respectively, again implying that any significant events occurred within the first 3 years. The 3 year EFS was 72.5% in 1995–1999 and remained relatively stable at 74.6% in the most recent period, while 5 year EFS was 68.4% in 1995–1999 and 74.6% in 2000–2004. From 1995 until 2004, the 3 and 5 year EFS rates for patients with BL/BL-like disease were identical at 86.8%, with a mild decrease in EFS from 90.0% to 84.2% in the most recent period. Patients with BL/BL-like disease aged 0–4 and 5–9 years had 5 year EFS of 90.9% and 94.4%, respectively, compared with 71.4% for patients aged 10–14 years (Exhibits 7.4a and 7.4b).

Overall 5 year EFS for LL patients was 70.7%, with younger and older children having worse EFS (60.0% and 68.8%, respectively) while the 5–9 year old group had better EFS at 77.8%. In addition, 5 year EFS decreased from 66.7% during 1995–1999 to 55.6% in the most recent period for younger patients (0–4 years) and from 71.4% to 66.7% in the 10–14 year group. EFS improved from 71.4% to 84.6% for the 5–9 year group. Throughout the 1995–2004 period, 5 year EFS for ALCL patients was only 51.9%, with a slight improvement from 44.4% in the first period to 55.6% in the last. The sample size, however, is small. The 5 year EFS for the "other" group was 51.6% in 1995–1999, improving to 77.8% in 2000–2004 (Exhibits 7.4a–c).

EXHIBIT 7.5a: **3 year relapse free survival rates for lymphoma by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1995–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis								
		All years			1995–1999			2000–2004		
		N	Relapse	% Relapse free survival	N	Relapse	% Relapse free survival	N	Relapse	% Relapse free survival
All lymphoma	**Overall**	**361**	**53**	**85.32**	**163**	**21**	**87.12**	**198**	**32**	**83.84**
	0–4	54	11	79.63	27	4	85.19	38	7	81.58
	5–9	116	16	86.21	59	11	81.36	59	5	91.53
	10–14	175	26	85.14	77	6	92.21	101	20	80.20
Hodgkin	**Overall**	**134**	**17**	**87.31**	**62**	**5**	**91.94**	**72**	**12**	**83.33**
	0–4	7	0	100.00	5	0	100.00	2	0	100.00
	5–9	25	2	92.00	14	1	92.86	11	1	90.91
	10–14	102	15	85.29	43	4	90.70	59	11	81.36
Non-Hodgkin	**Overall**	**211**	**30**	**85.78**	**101**	**15**	**85.15**	**114**	**15**	**86.84**
	0–4	47	7	85.11	21	3	85.71	28	4	85.71
	5–9	91	13	85.71	46	10	78.26	46	3	93.48
	10–14	73	10	86.30	34	2	94.12	40	8	80.00
Burkitt/ Burkitt-like*	**Overall**	**68**	**5**	**92.65**	**30**	**0**	**100.00**	**38**	**5**	**86.84**
	0–4	11	1	90.91	3	0	100.00	8	1	87.50
	5–9	36	2	94.44	16	0	100.00	20	2	90.00
	10–14	21	2	90.48	11	0	100.00	10	2	80.00
Lymphoblastic	**Overall**	**58**	**8**	**86.21**	**27**	**6**	**77.78**	**31**	**2**	**93.55**
	0–4	15	1	93.33	6	0	100.00	9	1	88.89
	5–9	27	4	85.19	14	4	71.43	13	0	100.00
	10–14	16	3	81.25	7	2	71.43	9	1	88.89
Anaplastic large cell	**Overall**	**27**	**7**	**74.07**	**9**	**3**	**66.67**	**18**	**4**	**77.78**
	0–4	5	2	60.00	3	2	33.33	2	0	100.00
	5–9	10	2	80.00	3	1	66.67	7	1	85.71
	10–14	12	3	75.00	3	0	100.00	9	3	66.67
Other†	**Overall**	**58**	**10**	**82.76**	**31**	**6**	**80.65**	**27**	**4**	**85.19**
	0–4	16	3	81.25	7	1	85.71	9	2	77.78
	5–9	18	5	72.22	12	5	58.33	6	0	100.00
	10–14	24	2	91.67	12	0	100.00	12	2	83.33

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

16 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.

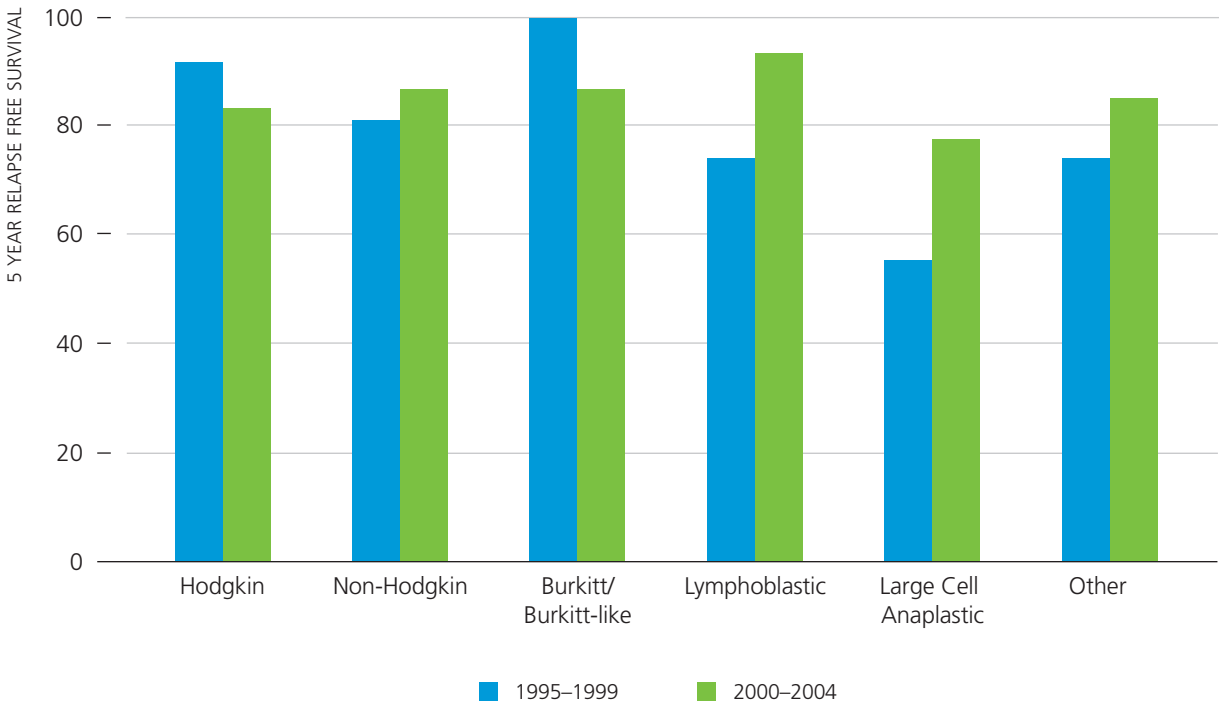
EXHIBIT 7.5b: **5 year relapse free survival rates for lymphoma by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1995–2004**

Cancer type	Age group at time of diagnosis (years)	Year of diagnosis								
		All years			1995–1999			2000–2004		
		N	Relapse	% Relapse free survival	N	Relapse	% Relapse free survivall	N	Relapse	% Relapse free survival
All lymphoma	Overall	**361**	**57**	**84.21**	**163**	**25**	**84.66**	**198**	**32**	**83.84**
	0–4	54	13	75.93	27	6	77.78	38	7	81.58
	5–9	116	16	86.21	59	11	81.36	59	5	91.53
	10–14	175	28	84.00	77	8	89.61	101	20	80.20
Hodgkin	Overall	**134**	**17**	**87.31**	**62**	**5**	**91.94**	**72**	**12**	**83.33**
	0–4	7	0	100.00	5	0	100.00	2	0	100.00
	5–9	25	2	92.00	14	1	92.86	11	1	90.91
	10–14	102	15	85.29	43	4	90.70	59	11	81.36
Non-Hodgkin	Overall	**211**	**34**	**83.89**	**97**	**19**	**80.41**	**114**	**15**	**86.84**
	0–4	47	9	80.85	19	5	73.68	28	4	85.71
	5–9	91	13	85.71	45	10	77.78	46	3	93.48
	10–14	73	12	83.56	33	4	87.88	40	8	80.00
Burkitt/ Burkitt-like*	Overall	**68**	**5**	**92.65**	**30**	**0**	**100.00**	**38**	**5**	**86.84**
	0–4	11	1	90.91	3	0	100.00	8	1	87.50
	5–9	36	2	94.44	16	0	100.00	20	2	90.00
	10–14	21	2	90.48	11	0	100.00	10	2	80.00
Lymphoblastic	Overall	**58**	**9**	**84.48**	**27**	**7**	**74.07**	**31**	**2**	**93.55**
	0–4	15	2	86.67	6	1	83.33	9	1	88.89
	5–9	27	4	85.19	14	4	71.43	13	0	100.00
	10–14	16	3	81.25	7	2	71.43	9	1	88.89
Anaplastic large cell	Overall	**27**	**8**	**70.37**	**9**	**4**	**55.56**	**18**	**4**	**77.78**
	0–4	5	2	60.00	3	2	33.33	2	0	100.00
	5–9	10	2	80.00	3	1	66.67	7	1	85.71
	10–14	12	4	66.67	3	1	66.67	9	3	66.67
Other†	Overall	**58**	**12**	**79.31**	**31**	**8**	**74.19**	**27**	**4**	**85.19**
	0–4	16	4	75.00	7	2	71.43	9	2	77.78
	5–9	18	5	72.22	12	5	58.33	6	0	100.00
	10–14	24	3	87.50	12	1	91.67	12	2	83.33

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

16 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.

EXHIBIT 7.5c: **5 year relapse free survival rates among lymphoma cases by tumour type, and period, age 0–14 years, in Ontario, 1995–2004**



Exhibits 7.5a–7.5c

Relapse free survival

The 3 and 5 year relapse free survival (RFS) rates for all lymphomas were almost identical, at 85.3% and 84.2%, respectively, from 1995 to 2004 (Exhibits 7.5a and 7.5b). Children with HL had similar 3 and 5 year RFS of 87.3% during 1995–2004, while there was a slight decrease in 5 year RFS from 91.9% during 1995–1999 to 83.3% during 2000–2004 (Exhibit 7.5a–c). Children with NHL had 3 year RFS of 85.8% and 5 year RFS of 83.9% for the 10 year period. The 5 year RFS improved from 80.4% during 1995–1999 to 86.8% during the most recent period. For BL patients 1, 3 and 5 year RFS remained stable at 92.7% during 1995–2004, with all events occurring during the first year, as expected; RFS at 5 years was 100.0% for BL patients during 1995–1999 but decreased to 86.8% during 2000–2004 (Exhibit 7.5c). For patients with LL, there was a notable improvement in 5 year RFS from 74.1% during 1995–1999 to 93.6% during 2000–2004. Similarly, patients with ALCL had improved 5 year RFS of 77.8% during 2000–2004, compared with 55.6% during 1995–1999. Those with "other" lymphomas had 5 year RFS of 85.2% in the most recent period and 74.2% during 1995–1999.

EXHIBIT 7.6: **Proportion of patients who received hematopoietic stem cell transplantation, chemotherapy and radiation treatment among lymphoma cases by tumour type, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1995–2004**

Cancer type	Age group at time of diagnosis (years)	Number of cases			Hematopoietic stem cell transplantation					
		1995–2004	1995–1999	2000–2004	All years		1995–1999		2000–2004	
					N	%	N	%	N	%
All lymphoma	Overall	**361**	**163**	**198**	**46**	**12.74**	**19**	**11.66**	**27**	**13.64**
	0–4	65	27	38	10	15.38	4	14.81	6	15.79
	5–9	118	59	59	14	11.86	9	15.25	5	8.47
	10–14	178	77	101	22	12.36	6	7.79	16	15.84
Hodgkin	Overall	**134**	**62**	**72**	**15**	**11.19**	**4**	**6.45**	**11**	**15.28**
	0–4	7	5	2	0	0.00	0	0.00	0	0.00
	5–9	25	14	11	2	8.00	1	7.14	1	9.09
	10–14	102	43	59	13	12.75	3	6.98	10	16.95
Non-Hodgkin	Overall	**211**	**97**	**114**	**28**	**13.27**	**14**	**14.43**	**14**	**12.28**
	0–4	47	19	28	8	17.02	3	15.79	5	17.86
	5–9	91	45	46	12	13.19	8	17.78	4	8.70
	10–14	73	33	40	8	10.96	3	9.09	5	12.50
Burkitt/Burkitt-like*	Overall	**68**	**30**	**38**	**6**	**8.82**	**1**	**3.33**	**5**	**13.16**
	0–4	11	3	8	2	18.18	0	0.00	2	25.00
	5–9	36	16	20	2	5.56	0	0.00	2	10.00
	10–14	21	11	10	2	9.52	1	9.09	1	10.00
Lymphoblastic	Overall	**58**	**27**	**31**	**7**	**12.07**	**6**	**22.22**	**1**	**3.23**
	0–4	15	6	9	2	13.33	1	16.67	1	11.11
	5–9	27	14	13	4	14.81	4	28.57	0	0.00
	10–14	16	7	9	1	6.25	1	14.29	0	0.00
Anaplastic large cell	Overall	**27**	**9**	**18**	**5**	**18.52**	**2**	**22.22**	**3**	**16.67**
	0–4	5	3	2	1	20.00	1	33.33	0	0.00
	5–9	10	3	7	1	10.00	0	0.00	1	14.29
	10–14	12	3	9	3	25.00	1	33.33	2	22.22
Other†	Overall	**58**	**31**	**27**	**10**	**17.24**	**5**	**16.13**	**5**	**18.52**
	0–4	16	7	9	3	18.75	1	14.29	2	22.22
	5–9	18	12	6	5	27.78	4	33.33	1	16.67
	10–14	24	12	12	2	8.33	0	0.00	2	16.67

*Burkitt/Burkitt-like includes Burkitt and small non-cleaved cell, non-Burkitt pleomorphic undifferentiated.
†Other includes large cell lymphoma not otherwise specified, post transplant lymphoproliferative disorder, lymphomas not otherwise specified or miscellaneous lymphoma, and central nervous system lymphoma.

16 reticuloendothelial neoplasms not shown separately on this table are included in the overall total for all lymphomas.

	Chemotherapy						Radiation						Radiation + chemotherapy					
	All years		1995–1999		2000–2004		All years		1995–1999		2000–2004		All years		1995–1999		2000–2004	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	344	**95.29**	**152**	**93.25**	**192**	**96.97**	**143**	**39.61**	**77**	**47.24**	**66**	**33.33**	**142**	**39.34**	**76**	**46.63**	**66**	**33.33**
	59	90.77	24	88.89	35	92.11	14	21.54	9	33.33	5	13.16	14	21.54	9	33.33	5	13.16
	114	96.61	57	96.61	57	96.61	31	26.27	21	35.59	10	16.95	31	26.27	21	35.59	10	16.95
	171	96.07	71	92.21	100	99.01	98	55.06	47	61.04	51	50.50	97	54.49	46	59.74	51	50.50
	131	**97.76**	**60**	**96.77**	**71**	**98.61**	**100**	**74.63**	**55**	**88.71**	**45**	**62.50**	**99**	**73.88**	**54**	**87.10**	**45**	**62.50**
	7	100.00	5	100.00	2	100.00	6	85.71	5	100.00	1	50.00	6	85.71	5	100.00	1	50.00
	25	100.00	14	100.00	11	100.00	16	64.00	11	78.57	5	45.45	16	64.00	11	78.57	5	45.45
	99	97.06	41	95.35	58	98.31	78	76.47	39	90.70	39	66.10	77	75.49	38	88.37	39	66.10
	191	**90.52**	**86**	**88.66**	**105**	**92.11**	**37**	**17.54**	**19**	**19.59**	**18**	**15.79**	**37**	**17.54**	**19**	**19.59**	**18**	**15.79**
	39	82.98	15	78.95	24	85.71	6	12.77	3	15.79	3	10.71	6	12.77	3	15.79	3	10.71
	85	93.41	42	93.33	43	93.48	14	15.38	9	20.00	5	10.87	14	15.38	9	20.00	5	10.87
	67	91.78	29	87.88	38	95.00	17	23.29	7	21.21	10	25.00	17	23.29	7	21.21	10	25.00
	66	**97.06**	**28**	**93.33**	**38**	**100.00**	**1**	**1.47**	**1**	**3.33**	**0**	**0.00**	**1**	**1.47**	**1**	**3.33**	**0**	**0.00**
	11	100.00	3	100.00	8	100.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	35	97.22	15	93.75	20	100.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	20	95.24	10	90.91	10	100.00	1	4.76	1	9.09	0	0.00	1	4.76	1	9.09	0	0.00
	58	**100.00**	**27**	**100.00**	**31**	**100.00**	**22**	**37.93**	**14**	**51.85**	**8**	**25.81**	**22**	**37.93**	**14**	**51.85**	**8**	**25.81**
	15	100.00	6	100.00	9	100.00	3	20.00	1	16.67	2	22.22	3	20.00	1	16.67	2	22.22
	27	100.00	14	100.00	13	100.00	10	37.04	8	57.14	2	15.38	10	37.04	8	57.14	2	15.38
	16	100.00	7	100.00	9	100.00	9	56.25	5	71.43	4	44.44	9	56.25	5	71.43	4	44.44
	23	**85.19**	**9**	**100.00**	**14**	**77.78**	**4**	**14.81**	**1**	**11.11**	**3**	**16.67**	**4**	**14.81**	**1**	**11.11**	**3**	**16.67**
	4	80.00	3	100.00	1	50.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	8	80.00	3	100.00	5	71.43	2	20.00	0	0.00	2	28.57	2	20.00	0	0.00	2	28.57
	11	91.67	3	100.00	8	88.89	2	16.67	1	33.33	1	11.11	2	16.67	1	33.33	1	11.11
	44	**75.86**	**22**	**70.97**	**22**	**81.48**	**10**	**17.24**	**3**	**9.68**	**7**	**25.93**	**10**	**17.24**	**3**	**9.68**	**7**	**25.93**
	9	56.25	3	42.86	6	66.67	3	18.75	2	28.57	1	11.11	3	18.75	2	28.57	1	11.11
	15	83.33	10	83.33	5	83.33	2	11.11	1	8.33	1	16.67	2	11.11	1	8.33	1	16.67
	20	83.33	9	75.00	11	91.67	5	20.83	0	0.00	5	41.67	5	20.83	—	0.00	5	41.67

Exhibit 7.6

Type of Treatment

Lymphoma is treated with chemotherapy, radiation, HSCT or a combination of these therapies. For all lymphomas over all years combined, 12.7% were treated with HSCT, 95.3% with chemotherapy and 39.6% with radiation. All but 1 (39.3%) patient undergoing radiation treatment received a combination of radiation and chemotherapy. The use of radiation alone and the combined use of radiation and chemotherapy decreased in the lymphoma group between 1995–1999 and 2000–2004, largely as a result of the reduction in the use of radiation for HL. For all HL patients the proportion receiving radiation dropped from 88.7% to 62.5% between the 2 periods. The NHL group received less radiation than the HL group either alone or in combination with chemotherapy, but the percentages of patients receiving radiation remained constant over time.

Looking at the NHL subtypes, although numbers are small, ALCL patients in the 10–14 year age group were most likely to undergo HSCT (3 of 12, or 25.0%). Virtually all LL patients received chemotherapy or chemotherapy and radiation, but the use of radiation decreased from 51.9% in 1995–1999 to 25.8% in 2000–2004. All patients with BL received chemotherapy and only 1 of 68 patients (1.5%) received radiotherapy during the 1995–1999 period. No BL patient received radiation during 2000–2004 (Exhibit 7.6).

Second Malignancies

The cumulative incidence of second malignancies was 4.3%, or 27 of 624 lymphoma patients, with a median duration of follow up of 10.0 years. Among long term survivors of HL 14 second cancers occurred, for a cumulative rate of 5.4% (3 secondary leukemias, 2 CNS tumours, 2 bone tumours, 1 solid tumour, 1 germ cell tumour and 5 miscellaneous tumours). In survivors of BL, 2 secondary lymphomas and 1 miscellaneous tumour occurred, and 1 miscellaneous secondary tumour developed in a survivor of LL. Eight secondary cancers developed among survivors of "other" lymphomas (2 secondary leukemias, 1 lymphoma, 2 CNS tumours, 2 solid tumours and 2 miscellaneous cancers). The cumulative rate of second malignancies for the entire NHL group was lower than for HL, at 3.5% (data not shown).

Summary

While the overall incidence of pediatric cancer has remained stable over several decades, it is important to assess trends of incidence and patterns of treatment over time to better address the future health needs of the patients and to assess the successes and shortcomings of the care provided. Cancer control mandates that we continue to evaluate outcomes so that future cancer care strategies will be effective.

Ontario has developed a database through POGO that facilitates such endeavours. While the database is not a perfect measure because of changes in categorization over time, it is clear that pediatric lymphoma accounts for 10% of all pediatric cancers in Ontario, which is on par with the rest of the nation. Survival curves and treatment trends parallel reports in the literature and despite an increasing and diverse immigration pattern, there does not seem to be a significant change in the reported numbers and trends. Such statistical analysis remains important in directing future research and appropriately allocating health care resources.

References

1 Canadian Cancer Society, National Cancer Institute of Canada. Canadian cancer statistics 2008. Toronto: CCS/NCIC; 2008.

2 Magrath IT. Malignant non-Hodgkin's lymphoma in children. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 2nd ed. Philadelphia: J.B. Lippincott; 1993. p. 537-75.

3 Greaves MF. Differentiation-linked leukemogenesis in lymphocytes. Science. 1986 Nov;234(4777):697-704.

4 Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med. 1996 May;334(19):1238-48.

5 Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005 Oct;131(1):39-49.

6 Hodgson DC, Hudson MM, Constine LS: Pediatric Hodgkin lymphoma: maximizing efficacy and minimizing toxicity. Semin Radiat Oncol. 2007 Jul;17(3):230-42.

7 Sterialova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer. 2005 Apr;103(7):1457-67.

8 Straus SE, Sneller M, Lenardo MJ, Puck JM, Strober W. An inherited disorder of lymphocyte apoptosis: the autoimmune lymphoproliferative syndrome. Ann Intern Med. 1999 Apr;130(7):591-601.

9 Persson B. Occupational exposure and malignant lymphoma. Int J Occup Med Environ Health. 1996;9(4):309-21.

10 Bertazzi PA, Pesatori AC, Bernucci I, Landi MT, Consonni D. Dioxin exposure and human leukemias and lymphomas. Lessons from the Seveso accident and studies on industrial workers. Leukemia. 1999 Apr;13(Suppl 1):S72-4.

Photo by Vivid Eye Photography

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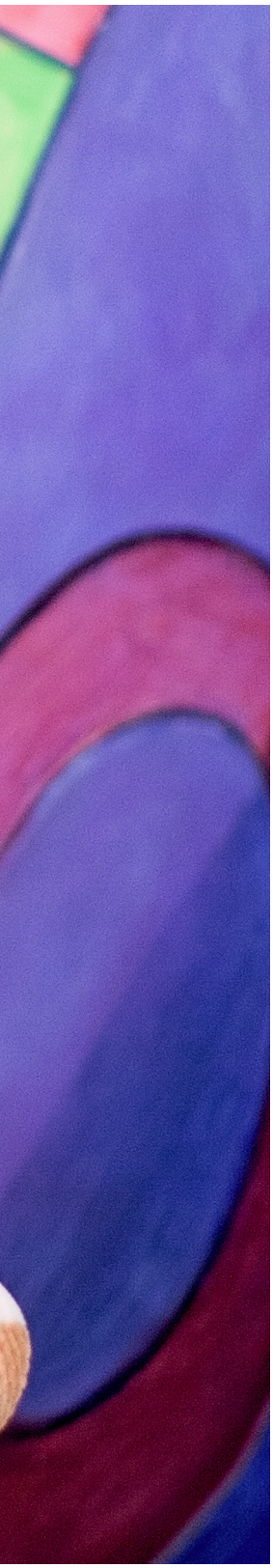


8

Central Nervous System Tumours

Executive Summary

Brain tumours are rare in children, with an overall cumulative age standardized incidence rate (ASIR) of 33.6 per million per year for children 14 years of age or younger in the Province of Ontario. This rate did not significantly change from 1990 to 2004. During this period, central nervous system (CNS) tumours were slightly more common in males than females (male:female ratio, 1.3:1). The age distribution remained fairly constant over the period (20.9% under 3 years of age at diagnosis, 45.2% aged 4–9 years, 33.8% aged 10–14 years). The most common histopathologic diagnosis was low grade astrocytoma (50.6%), followed by medulloblastoma (15.8%) and high grade glial tumours (14.7%). Ependymoma accounted for 6.6%, germ cell tumours for 2.5% and supratentorial primitive neuroectodermal tumours (PNETs) for 4.2%. Therapeutic modalities vary with age, with radiotherapy tending to be less commonly used in children 3 years of age and under. Though therapeutic options advanced over the study period, the 5 year survival rates remained relatively stable (69% in 1990; 73% by 2004). The only exceptions were for patients with the histologic diagnosis of medulloblastoma or germ cell tumours, for which there was a steady improvement in survival.

Introduction

Central nervous system tumours occur at all ages. They are more predominant in the posterior fossa (infratentorial) region.[1] The incidence is 49.7 per million person years for children aged less than 15 years in the United States.[2] An increase in the incidence rate was reported in the late 1970s and early 1980s.[3] Because the greatest increase occurred in the diagnosis of benign tumours, the increase was felt to be secondary to the availability of new investigational tools (i.e., cranial tomography and magnetic resonance imaging [MRI]).

Limitations in information obtained from cancer registries include incompleteness resulting from the surveillance techniques used.[4] This limitation may result in the populations included in the different registries not being comparable. The completeness of case ascertainment across reporting regions, provinces and countries may vary for several reasons. The registry may include cases for which the diagnosis was made at autopsy. Additionally, case definitions may vary. For example, only malignant tumours might be included and not benign tumours, resulting in an underestimate of persons at risk of developing a CNS tumour.

A second limitation is the histologic classification of the tumours at time of diagnosis. These tumours often demonstrate significant heterogeneity and different regions may show different characteristics. The histologic diagnosis can be limited by the amount of tissue available for analysis. This is particularly the case when only biopsy material is available: the smaller the sample size, the greater the risk of missing important changes that may be present within the tumour. These missed findings could lead to a misclassification (e.g., benign rather than malignant variant or combined tumour tissue types). Classification is often further complicated by a lack of universal agreement on the histologic criteria necessary for a given pathologic diagnosis and the changing of these criteria with time. Finally, multiple centres may be submitting cases to a central registry and patients may be seen in different centres at different times during treatment, resulting in duplicate case reporting in the registries.

Ontario has a unique medical system. Not only is universal medical and hospital care centrally funded by the provincial ministry of health, the care of children with CNS tumours is carried out in one of the 5 university affiliated hospitals. Thus all children under 14 years of age with a suspected CNS tumour are referred to one of these centres for diagnosis and treatment. The histologic classification system used in each of these centres is similar. All the centres are active participants in the Pediatric Oncology Group of Ontario Networked Information System (POGONIS), registering all newly diagnosed cases. This chapter provides a summary, based on the data from this registry, of CNS tumours occurring in children aged 14 years or less in Ontario between 1985 and 2004.

Discussion

The histology groupings used in this report are based on the International Classification of Childhood Cancer, third edition (ICCC-3), diagnostic group III, with exceptions. This chapter includes germ cell tumours, which are not included in the ICCC-3 categorization. CNS lymphoma is not included in this chapter because it is included in the chapter on lymphomas. Anaplastic gangliomas are included in the high grade glial tumour group. Desmoplastic neuroepithelial tumours and pituitary adenomas, if benign, are not included.

Incidence

EXHIBIT 8.1a: **Incidence of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**

		Period of diagnosis								
		All years			1985–1989			1990–1994		
Tumour type	Age (years)	Total N	%	Female (%)	Total N	%	Female (%)	Total N	%	Female (%)
All central nervous system tumours	Overall	**1448**	**100.00**	**43.16**	**274**	**100.00**	**41.61**	**394**	**100.00**	**47.21**
	0–3	303	20.93	45.54	70	25.55	48.57	83	21.07	50.60
	4–9	655	45.23	42.60	127	46.35	39.37	166	42.13	42.77
	10–14	490	33.84	42.45	77	28.10	38.96	145	36.80	50.34
Low grade glial tumours	Overall	**733**	**50.62**	**46.11**	**118**	**43.07**	**44.92**	**224**	**56.85**	**50.45**
	0–3	129	17.60	n/a	24	20.34	n/a	44	19.64	n/a
	4–9	330	45.02	n/a	57	48.31	n/a	95	42.41	n/a
	10–14	274	37.38	n/a	37	31.36	n/a	85	37.95	n/a
High grade glial tumours	Overall	**213**	**14.71**	**50.23**	**52**	**18.98**	**44.23**	**59**	**14.97**	**47.46**
	0–3	35	16.43	n/a	8	15.38	n/a	9	15.25	n/a
	4–9	110	51.64	n/a	28	53.85	n/a	27	45.76	n/a
	10–14	68	31.92	n/a	16	30.77	n/a	23	38.98	n/a
Ependymoma	Overall	**96**	**6.63**	**45.83**	**25**	**9.12**	**52.00**	**22**	**5.58**	**54.55**
	0–3	41	42.71	n/a	10	40.00	n/a	12	54.55	n/a
	4–9	28	29.17	n/a	10	40.00	n/a	4	18.18	n/a
	10–14	27	28.13	n/a	5	20.00	n/a	6	27.27	n/a
Medulloblastoma	Overall	**228**	**15.75**	**28.07**	**39**	**14.23**	**25.64**	**58**	**14.72**	**27.59**
	0–3	43	18.86	n/a	13	33.33	n/a	6	10.34	n/a
	4–9	120	52.63	n/a	18	46.15	n/a	31	53.45	n/a
	10–14	65	28.51	n/a	8	20.51	n/a	21	36.21	n/a
Supratentorial PNET	Overall	**61**	**4.21**	**45.90**	**12**	**4.38**	**58.33**	**9**	**2.28**	**55.56**
	0–3	24	39.34	n/a	5	41.67	n/a	4	44.44	n/a
	4–9	32	52.46	n/a	7	58.33	n/a	5	55.56	n/a
	10–14	5	8.20	n/a	0	0.00	n/a	0	0.00	n/a

PNET = primitive neuroectodermal tumour
n/a For privacy reasons percent female has been reported only overall and not by age group.

The terms used to describe the regions of the CNS are based on commonly used terms in neurologic anatomy. The supratentorial region includes the cerebral hemispheres (i.e., occipital, parietal, temporal and frontal lobes) and/or the midline axial structures (i.e., diencephalon, thalamus, basal ganglia, optic chiasm, optic nerves, pituitary fossa, olfactory nerves and tectal plate region). The infratentorial region includes the brain stem, cerebellum and/or the floor of the fourth ventricle. The meninges include the covering of the supratentorial region, the infratentorial region and/or the spinal cord.

1995–1999			2000–2004		
Total N	%	Female (%)	Total N	%	Female (%)
392	**100.00**	**41.33**	**388**	**100.00**	**42.01**
81	20.66	43.21	69	17.78	39.13
174	44.39	43.10	188	48.45	44.15
137	34.95	37.96	131	33.76	40.46
197	**50.26**	**43.15**	**194**	**50.00**	**44.85**
32	16.24	n/a	29	14.95	n/a
85	43.15	n/a	93	47.94	n/a
80	40.61	n/a	72	37.11	n/a
58	**14.80**	**56.90**	**44**	**11.34**	**52.27**
11	18.97	n/a	7	15.91	n/a
29	50.00	n/a	26	59.09	n/a
18	31.03	n/a	11	25.00	n/a
19	**4.85**	**52.63**	**30**	**7.73**	**30.00**
9	47.37	n/a	10	33.33	n/a
7	36.84	n/a	7	23.33	n/a
3	15.79	n/a	13	43.33	n/a
57	**14.54**	**24.56**	**74**	**19.07**	**32.43**
9	15.79	n/a	15	20.27	n/a
29	50.88	n/a	42	56.76	n/a
19	33.33	n/a	17	22.97	n/a
21	**5.36**	**28.57**	**19**	**4.90**	**52.63**
10	47.62	n/a	5	26.32	n/a
9	42.86	n/a	11	57.89	n/a
2	9.52	n/a	3	15.79	n/a

continued on following page

EXHIBIT 8.1a: **Incidence of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**

		Period of diagnosis								
		All years			1985–1989			1990–1994		
Tumour type	Age (years)	Total N	%	Female (%)	Total N	%	Female (%)	Total N	%	Female (%)
Germ cell tumours	Overall	**36**	**2.49**	**25.00**	**10**	**3.65**	**20.00**	**4**	**1.02**	**50.00**
	0–3	2	5.56	n/a	1	10.00	n/a	0	0.00	n/a
	4–9	8	22.22	n/a	1	10.00	n/a	3	75.00	n/a
	10–14	26	72.22	n/a	8	80.00	n/a	1	25.00	n/a
Other central nervous system tumours	Overall	**81**	**5.59**	**43.21**	**18**	**6.57**	**33.33**	**18**	**4.57**	**55.56**
	0–3	29	35.80	n/a	9	50.00	n/a	8	44.44	n/a
	4–9	27	33.33	n/a	6	33.33	n/a	1	5.56	n/a
	10–14	25	30.86	n/a	3	16.67	n/a	9	50.00	n/a

PNET = primitive neuroectodermal tumour
n/a For privacy reasons percent female has been reported only overall and not by age group.

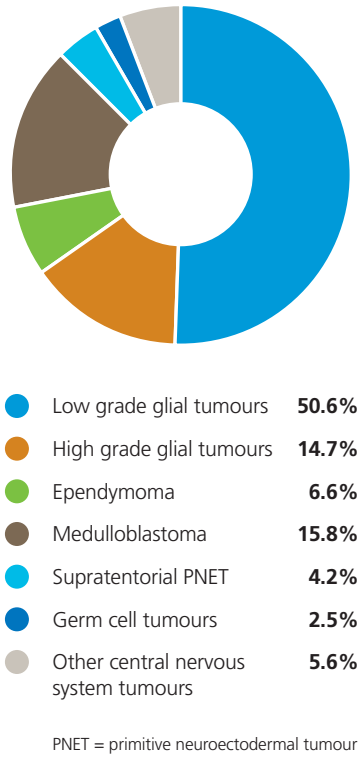
Exhibits 8.1a and 8.1b

During the period 1985–2004, a total of 1,448 cases of primary CNS tumours were reported in Ontario.

There was a male predominance (male:female ratio, 1.31:1). The commonest tumour histology was low grade glial, which accounted for 50.6% of tumours. Medulloblastoma and high grade glial tumours were almost equally distributed and together accounted for one-third of all tumours (medulloblastoma, 15.8%; high grade glial tumours, 14.7%), while ependymomas accounted for 6.6% of all tumours, supratentorial PNETs for 4.2% and germ cell tumours for 2.5%.

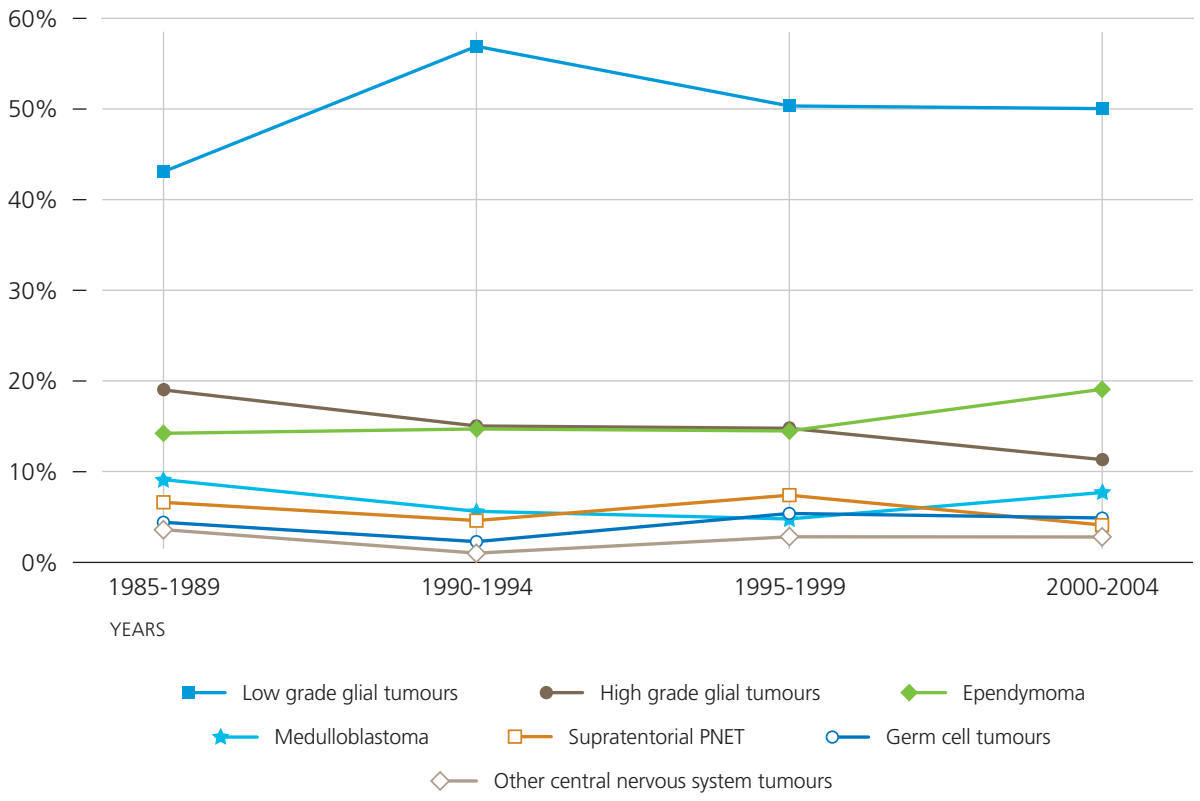
1995–1999			2000–2004		
Total N	%	Female (%)	Total N	%	Female (%)
11	**2.81**	**9.09**	**11**	**2.84**	**36.36**
0	0.00	n/a	1	9.09	n/a
4	36.36	n/a	0	0.00	n/a
7	63.64	n/a	10	90.91	n/a
29	**7.40**	**44.83**	**16**	**4.12**	**37.50**
10	34.48	n/a	2	12.50	n/a
11	37.93	n/a	9	56.25	n/a
8	27.59	n/a	5	31.25	n/a

EXHIBIT 8.1b: **Distribution of central nervous system tumours, by histology, age 0–14 years, in Ontario, 1985–2004**



PNET = primitive neuroectodermal tumour

EXHIBIT 8.2: **Distribution of CNS tumours by histology and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**



PNET = primitive neuroectodermal tumour

Exhibit 8.2

With the exception of the histologic diagnosis of medulloblastoma, the distribution of diagnoses remained relatively stable over the survey time periods. The proportion of total tumours with the histologic diagnosis of medulloblastoma increased from 14.2% in the 1985–1989 period to 19.1% in 2000–2004, with the increase being largely in the 4–9 year old group. There was an increase in the proportion of low grade glial tumours in 1990–1994, but this returned to baseline levels in subsequent study periods. However, the proportion of tumours diagnosed as high grade glial tumours decreased steadily from 19.0% in the 1985–1990 period to 11.3% in 2000–2004. The proportion of tumours diagnosed as PNET, ependymoma or germ cell was relatively constant over the different periods.

EXHIBIT 8.3: **Age-standardized incidence of primary central nervous system tumours by tumour type and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**

	Period of diagnosis										
	Total (1985–2004)		1985–1989		1990–1994		1995–1999		2000–2004		
Tumour type	ASIR/ million/ year	95% CI	ASIR/ million/ year	95% CI	ASIR/ million/ year	95% CI	ASIR/ million/ year	95% CI	ASIR/ million/ year	95% CI	Test for trend (p value)
All central nervous system tumours	**33.16**	**24.92-41.39**	**27.68**	**13.95-41.42**	**36.57**	**18.69-54.44**	**34.58**	**17.70-51.46**	**33.80**	**16.68-50.92**	**0.72**
Low grade glial tumours	16.78	12.45-21.11	11.94	5.84-18.05	20.81	10.45-31.17	17.48	8.66-26.29	16.90	8.11-25.69	0.50
High grade glial tumours	4.96	3.56-6.36	5.31	2.41-8.22	5.54	2.40-8.68	5.14	2.23-8.04	3.84	1.66-6.01	0.95
Ependymoma	2.18	1.51-2.84	2.51	1.00-4.01	1.96	0.78-3.14	1.62	0.54-2.71	2.61	1.11-4.11	0.96
Medulloblastoma	5.22	3.65-6.79	3.92	1.75-6.09	5.48	2.04-8.93	5.02	2.25-7.79	6.45	2.55-10.35	0.89
Supratentorial PNET	1.35	0.88-1.83	1.18	0.46-1.90	0.77	0.13-1.42	1.80	0.51-3.08	1.67	0.67-2.66	0.92
Germ cell tumours	0.84	0.48-1.21	1.05	0.22-1.89	0.39	0.01-0.77	1.00	0.17-1.83	0.94	0.18-1.70	0.95
Other central nervous system tumours	1.82	1.25-2.40	1.77	0.76-2.78	1.61	0.39-2.82	2.53	1.09-3.97	1.39	0.52-2.26	0.94

ASIR = age standardized incidence rate; PNET = primitive neuroectodermal tumour; CI = confidence interval

Exhibit 8.3

The overall cumulative ASIR of CNS tumours was 33.2 per million per year (95% confidence interval [CI], 24.92–41.39).

The age-standardized tumour incidence rates for the group as a whole, as well as when broken into histologic diagnoses, remained stable over the review period, with the exception of low grade glial tumours. The age-standardized tumour incidence rate for low grade glial tumours increased from 11.94 per million persons per year in 1985–1989 to 20.81 per million persons per year in 1990–1994. The incidence declined in the following 2 study periods (1995–1999 and 2000–2004) but did not return to the rate reported for 1985–1989.

Exhibit 8.4

At the time of diagnosis, 45.2% of the children were age 4–9 years, 33.8% were age 10–14 years and 20.9% were age 3 years or less. The diagnosis was rarely made in the first 60 days of life (1.5%, data not shown). The age at diagnosis based on histology followed a similar pattern except for ependymoma and germ cell tumours. Children with a diagnosis of ependymoma were more often age 3 years or younger (42.7%), whereas the majority of children diagnosed with a germ cell tumour were over age 10 years (72.2%) (Exhibit 8.1a).

EXHIBIT 8.4: **Distribution of CNS tumours by age at diagnosis, age 0–14 years, in Ontario, 1985–2004**

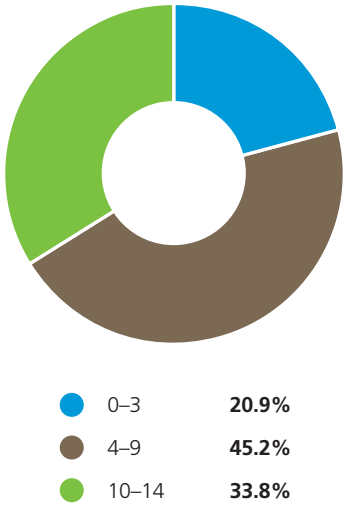


EXHIBIT 8.5: **Distribution of CNS tumours by age and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**

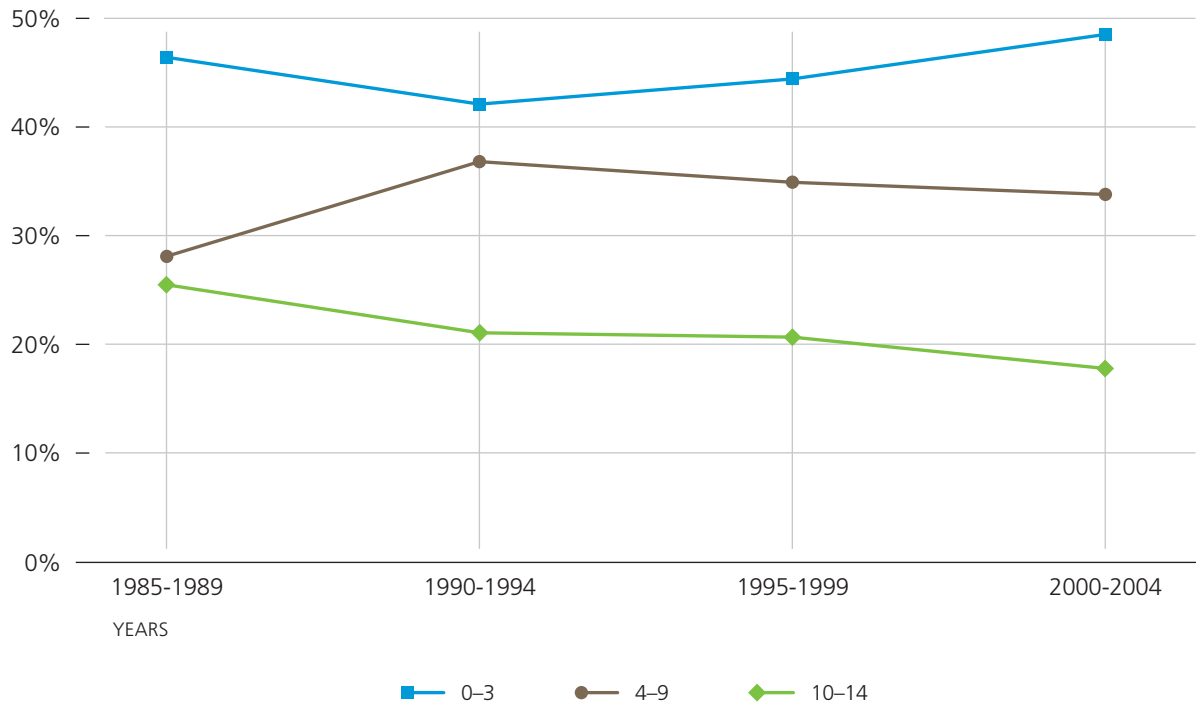
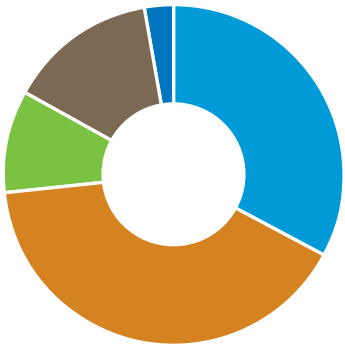


Exhibit 8.5

When the proportion of children diagnosed in each age group over the period 1985–2004 was examined, the proportion diagnosed at age 3 years or younger decreased from 25.6% in 1985–1989 to 17.8% in 2000–2004. For children aged 10–14 years, there was a small increase in the proportion from 1985–1989 (28.1%) to 1990–1994 (36.8%); however, after the 1990–1994 period, the proportion remained relatively constant (35.0–33.8%). For children aged 4–9 years, the proportion diagnosed remained relatively stable (46.4–48.5%) over the period 1985–2004.

EXHIBIT 8.6: **Distribution of central nervous system tumours, by location, age 0–14 years, in Ontario, 1985-2004**



Supratentorial	**43.0%**
Infratentorial	**52.6%**
Brain Stem	**12.8%**
Cerebellar	**18.4%**
Spinal Cord	**3.5%**

Footnote for Exhibit 8.6

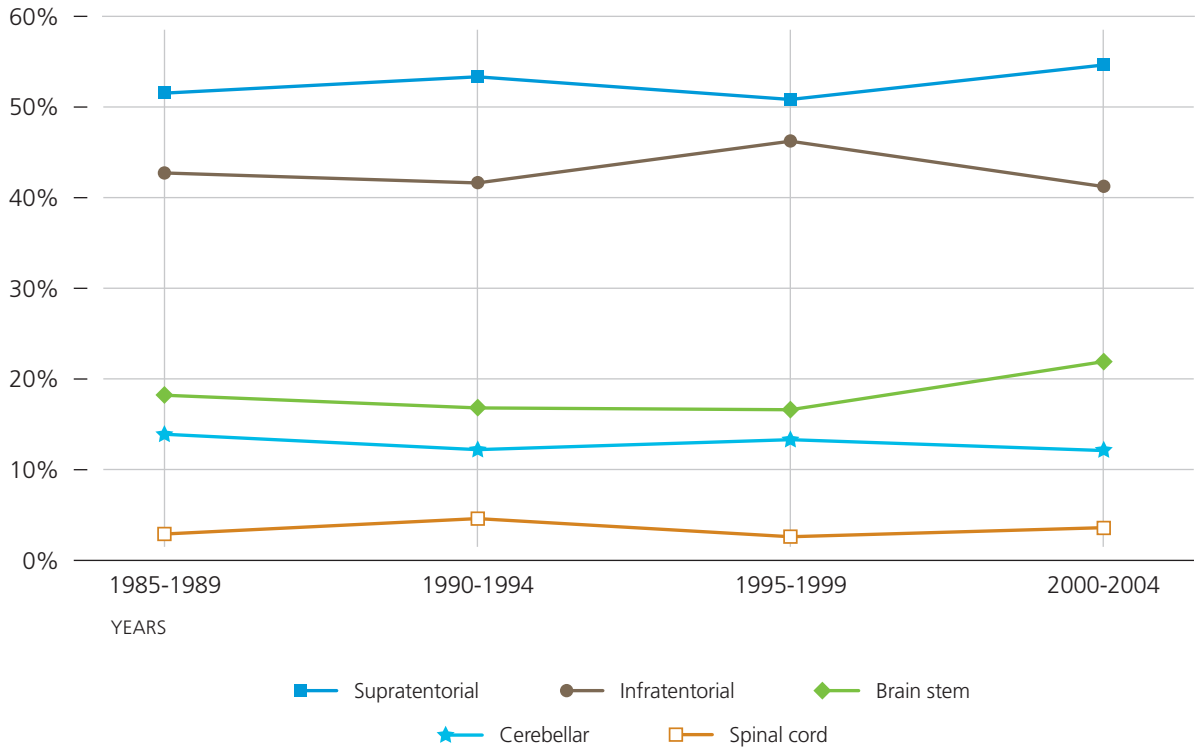
Locations as grouped are not mutually exclusive.

Supratentorial includes tumours in the hemispheric, midline axial, thalamic and 3rd ventricle regions.

Infratentorial includes tumours in the brain stem, cerebellum, 4th ventricle and posterior fossa (not otherwise specified) regions.

Cerebellar includes tumours in the 4th ventricle and posterior fossa (not otherwise specified) regions.

EXHIBIT 8.7: **Distribution of CNS tumours by location and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**



Exhibits 8.6 and 8.7

In terms of tumour location, there was a slight predominance of tumours in the infratentorial region (52.6%) over the supratentorial region (43.0%). The distribution of the supratentorial tumours was as follows: 41.0% involved principally the cerebral hemispheres, 51.0% involved mainly the midline axial structures and 8.0% arose from the third ventricle (data not shown). Tumours in the infratentorial region were mainly located in the cerebellum (75.7%), with only 24.3% involving primarily the brain stem region (data not shown).

Over successive 5 year intervals between 1985 and 2004, the proportion of tumours arising in the different anatomic regions (i.e., supratentorial, infratentorial, meninges and spinal cord) remained relatively stable.

Treatment

EXHIBIT 8.8a: First surgery for primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1995–2004

		Period of diagnosis					
		Total patients (1995–2004)		All years (1995–2004)			
Tumour type	Age (years)			No surgery		Biopsy or resection	
		Total N	%	No. of cases	%	No. of cases	%
All central nervous system tumours	**Overall**	**780**	**100.00**	**187**	**23.97**	**593**	**76.03**
	0–3	150	19.23	35	23.33	115	76.67
	4–9	362	46.41	97	26.80	265	73.20
	10–14	268	34.36	55	20.52	213	79.48
Low grade glial tumours	**Overall**	**391**	**100.00**	**96**	**24.55**	**295**	**75.45**
	0–3	61	15.60	24	39.34	37	60.66
	4–9	178	45.52	47	26.40	131	73.60
	10–14	152	38.87	25	16.45	127	83.55
High grade glial tumours	**Overall**	**102**	**100.00**	**59**	**57.84**	**43**	**42.16**
	0–3	18	17.65	6	33.33	12	66.67
	4–9	55	53.92	39	70.91	16	29.09
	10–14	29	28.43	14	48.28	15	51.72
Ependymoma	**Overall**	**49**	**100.00**	**1**	**2.04**	**48**	**97.96**
	0–3	19	38.78	0	0.00	19	100.00
	4–9	14	28.57	0	0.00	14	100.00
	10–14	16	32.65	1	6.25	15	93.75
Medulloblastoma	**Overall**	**131**	**100.00**	**8**	**6.11**	**123**	**93.89**
	0–3	24	18.32	1	4.17	23	95.83
	4–9	71	54.20	5	7.04	66	92.96
	10–14	36	27.48	2	5.56	34	94.44
Supratentorial PNET	**Overall**	**40**	**100.00**	**5**	**12.50**	**35**	**87.50**
	0–3	15	37.50	1	6.67	14	93.33
	4–9	20	50.00	2	10.00	18	90.00
	10–14	5	12.50	2	40.00	3	60.00
Germ cell tumours	**Overall**	**22**	**100.00**	**13**	**59.09**	**9**	**40.91**
	0–3	1	4.55	1	100.00	0	0.00
	4–9	4	18.18	2	50.00	2	50.00
	10–14	17	77.27	10	58.82	7	41.18
Other central nervous system tumours	**Overall**	**45**	**100.00**	**5**	**11.11**	**40**	**88.89**
	0–3	12	26.67	2	16.67	10	83.33
	4–9	20	44.44	2	10.00	18	90.00
	10–14	13	28.89	1	7.69	12	92.31

PNET = primitive neuroectodermal tumour

1995–1999				2000–2004			
No surgery		Biopsy or resection		No surgery		Biopsy or resection	
No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
85	**21.68**	**307**	**78.32**	**102**	**26.29**	**286**	**73.71**
15	18.52	66	81.48	20	28.99	49	71.01
46	26.44	128	73.56	51	27.13	137	72.87
24	17.52	113	82.48	31	23.66	100	76.34
43	**21.83**	**154**	**78.17**	**53**	**27.32**	**141**	**72.68**
11	34.38	21	65.63	13	44.83	16	55.17
21	24.71	64	75.29	26	27.96	67	72.04
11	13.75	69	86.25	14	19.44	58	80.56
28	**48.28**	**30**	**51.72**	**31**	**70.45**	**13**	**29.55**
2	18.18	9	81.82	4	57.14	3	42.86
20	68.97	9	31.03	19	73.08	7	26.92
6	33.33	12	66.67	8	72.73	3	27.27
0	**0.00**	**19**	**100.00**	**1**	**3.33**	**29**	**96.67**
0	0.00	9	100.00	0	0.00	10	100.00
0	0.00	7	100.00	0	0.00	7	100.00
0	0.00	3	100.00	1	7.69	12	92.31
1	**1.75**	**56**	**98.25**	**7**	**9.46**	**67**	**90.54**
0	0.00	9	100.00	1	6.67	14	93.33
0	0.00	29	100.00	5	11.90	37	88.10
1	5.26	18	94.74	1	5.88	16	94.12
3	**14.29**	**18**	**85.71**	**2**	**10.53**	**17**	**89.47**
1	10.00	9	90.00	0	0.00	5	100.00
1	11.11	8	88.89	1	9.09	10	90.91
1	50.00	1	50.00	1	33.33	2	66.67
6	**54.55**	**5**	**45.45**	**7**	**63.64**	**4**	**36.36**
0	—	0	—	1	100.00	0	0.00
2	50.00	2	50.00	0	—	0	—
4	57.14	3	42.86	6	60.00	4	40.00
4	**13.79**	**25**	**86.21**	**1**	**6.25**	**15**	**93.75**
1	10.00	9	90.00	1	50.00	1	50.00
2	18.18	9	81.82	0	0.00	9	100.00
1	12.50	7	87.50	0	0.00	5	100.00

EXHIBIT 8.8b: **Treatment with chemotherapy of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1995–2004**

		Period of diagnosis								
		All years (1995–2004)			1995–1999			2000–2004		
Tumour type	Age (years)	Total	Chemotherapy		Total	Chemotherapy		Total	Chemotherapy	
		N	Yes (n)	%	N	Yes (n)	%	N	Yes (n)	%
All central nervous system tumours	Overall	**780**	**317**	**40.64**	**392**	**142**	**36.22**	**388**	**175**	**45.10**
	0–3	150	91	60.67	81	52	64.20	69	39	56.52
	4–9	362	147	40.61	174	57	32.76	188	90	47.87
	10–14	268	79	29.48	137	33	24.09	131	46	35.11
Low grade glial tumours	Overall	**391**	**74**	**18.93**	**197**	**28**	**14.21**	**194**	**46**	**23.71**
	0–3	61	27	44.26	32	15	46.88	29	12	41.38
	4–9	178	35	19.66	85	10	11.76	93	25	26.88
	10–14	152	12	7.89	80	3	3.75	72	9	12.50
High grade glial tumours	Overall	**102**	**45**	**44.12**	**58**	**21**	**36.21**	**44**	**24**	**54.55**
	0–3	18	9	50.00	11	5	45.45	7	4	57.14
	4–9	55	22	40.00	29	8	27.59	26	14	53.85
	10–14	29	14	48.28	18	8	44.44	11	6	54.55
Ependymoma	Overall	**49**	**24**	**48.98**	**19**	**13**	**68.42**	**30**	**11**	**36.67**
	0–3	19	14	73.68	9	9	100.00	10	5	50.00
	4–9	14	4	28.57	7	3	42.86	7	1	14.29
	10–14	16	6	37.50	3	1	33.33	13	5	38.46
Medulloblastoma	Overall	**131**	**114**	**87.02**	**57**	**45**	**78.95**	**74**	**69**	**93.24**
	0–3	24	23	95.83	9	9	100.00	15	14	93.33
	4–9	71	63	88.73	29	23	79.31	42	40	95.24
	10–14	36	28	77.78	19	13	68.42	17	15	88.24
Supratentorial PNET	Overall	**40**	**31**	**77.50**	**21**	**18**	**85.71**	**19**	**13**	**68.42**
	0–3	15	10	66.67	10	8	80.00	5	2	40.00
	4–9	20	16	80.00	9	8	88.89	11	8	72.73
	10–14	5	5	100.00	2	2	100.00	3	3	100.00
Germ cell tumours	Overall	**22**	**17**	**77.27**	**11**	**8**	**72.73**	**11**	**9**	**81.82**
	0–3	1	1	100.00	0	0	—	1	1	100.00
	4–9	4	2	50.00	4	2	50.00	0	0	—
	10–14	17	14	82.35	7	6	85.71	10	8	80.00
Other central nervous system tumours	Overall	**45**	**12**	**26.67**	**29**	**9**	**31.03**	**16**	**3**	**18.75**
	0–3	12	7	58.33	10	6	60.00	2	1	50.00
	4–9	20	5	25.00	11	3	27.27	9	2	22.22
	10–14	13	0	0.00	8	0	0.00	5	0	0.00

PNET = primitive neuroectodermal tumour

EXHIBIT 8.8c: **Treatment with radiotherapy of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1995–2004**

		Period of diagnosis										
		All years (1995–2004)										
Tumour type	Age (years)	Total	None		Received any		0–90 days		91–180 days		≥ 181 days	
		N	Yes (n)	%	Yes (n)	%	Yes (n)	%	Yes (n)	%	Yes (n)	%
All central nervous system tumours	Overall	**780**	**435**	**55.77**	**304**	**38.97**	**231**	**75.99**	**34**	**11.18**	**39**	**12.83**
	0–3	150	113	75.33	27	18.00	3	11.11	7	25.93	17	62.96
	4–9	362	175	48.34	160	44.20	145	90.63	6	3.75	9	5.63
	10–14	268	147	54.85	117	43.66	83	70.94	21	17.95	13	11.11
Low grade glial tumours	Overall	**391**	**312**	**79.80**	**41**	**10.49**	**18**	**43.90**	**6**	**14.63**	**17**	**41.46**
	0–3	61	48	78.69	3	4.92	0	0.00	1	33.33	2	66.67
	4–9	178	136	76.40	18	10.11	9	50.00	1	5.56	8	44.44
	10–14	152	128	84.21	20	13.16	9	45.00	4	20.00	7	35.00
High grade glial tumours	Overall	**102**	**30**	**29.41**	**69**	**67.65**	**63**	**91.30**	**2**	**2.90**	**4**	**5.80**
	0–3	18	14	77.78	4	22.22	1	25.00	1	25.00	2	50.00
	4–9	55	11	20.00	41	74.55	40	97.56	1	2.44	0	0.00
	10–14	29	5	17.24	24	82.76	22	91.67	0	0.00	2	8.33
Ependymoma	Overall	**49**	**13**	**26.53**	**36**	**73.47**	**22**	**61.11**	**6**	**16.67**	**8**	**22.22**
	0–3	19	10	52.63	9	47.37	1	11.11	2	22.22	6	66.67
	4–9	14	1	7.14	13	92.86	13	100.00	0	0.00	0	0.00
	10–14	16	2	12.50	14	87.50	8	57.14	4	28.57	2	14.29
Medulloblastoma	Overall	**131**	**21**	**16.03**	**110**	**83.97**	**104**	**94.55**	**1**	**0.91**	**5**	**4.55**
	0–3	24	19	79.17	5	20.83	1	20.00	0	0.00	4	80.00
	4–9	71	2	2.82	69	97.18	67	97.10	1	1.45	1	1.45
	10–14	36	0	0.00	36	100.00	36	100.00	0	0.00	0	0.00
Supratentorial PNET	Overall	**40**	**17**	**42.50**	**23**	**57.50**	**17**	**73.91**	**3**	**13.04**	**3**	**13.04**
	0–3	15	10	66.67	5	33.33	0	0.00	2	40.00	3	60.00
	4–9	20	5	25.00	15	75.00	14	93.33	1	6.67	0	0.00
	10–14	5	2	40.00	3	60.00	3	100.00	0	0.00	0	0.00
Germ cell tumours	Overall	**22**	**1**	**4.55**	**21**	**95.45**	**4**	**19.05**	**16**	**76.19**	**1**	**4.76**
	0–3	1	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00
	4–9	4	1	25.00	3	75.00	1	33.33	2	66.67	0	0.00
	10–14	17	0	0.00	17	100.00	3	17.65	13	76.47	1	5.88
Other central nervous system tumours	Overall	**45**	**41**	**91.11**	**4**	**8.89**	**3**	**75.00**	**0**	**0.00**	**1**	**25.00**
	0–3	12	12	100.00	0	0.00	0	—	0	—	0	—
	4–9	20	19	95.00	1	5.00	1	100.00	0	0.00	0	0.00
	10–14	13	10	76.92	3	23.08	2	66.67	0	0.00	1	33.33

PNET = primitive neuroectodermal tumour

continued on following page

EXHIBIT 8.8c: **Treatment with radiotherapy of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1995–2004** (cont'd)

		Period of diagnosis										
		1995–1999										
Tumour type	Age (years)	Total	None		Received any		0–90 days		91–180 days		≥ 181 days	
		N	Yes (n)	%	Yes (n)	%	Yes (n)	%	Yes (n)	%	Yes (n)	%
All central nervous system tumours	Overall	**392**	**224**	**57.14**	**150**	**38.27**	**111**	**74.00**	**15**	**10.00**	**24**	**16.00**
	0–3	81	63	77.78	15	18.52	1	6.67	3	20.00	11	73.33
	4–9	174	84	48.28	76	43.68	66	86.84	4	5.26	6	7.89
	10–14	137	77	56.20	59	43.07	44	74.58	8	13.56	7	11.86
Low grade glial tumours	**Overall**	**197**	**157**	**79.70**	**23**	**11.68**	**10**	**43.48**	**2**	**8.70**	**11**	**47.83**
	0–3	32	27	84.38	2	6.25	0	0.00	0	0.00	2	100.00
	4–9	85	62	72.94	10	11.76	5	50.00	0	0.00	5	50.00
	10–14	80	68	85.00	11	13.75	5	45.45	2	18.18	4	36.36
High grade glial tumours	**Overall**	**58**	**18**	**31.03**	**39**	**67.24**	**34**	**87.18**	**2**	**5.13**	**3**	**7.69**
	0–3	11	8	72.73	3	27.27	1	33.33	1	33.33	1	33.33
	4–9	29	8	27.59	20	68.97	19	95.00	1	5.00	0	0.00
	10–14	18	2	11.11	16	88.89	14	87.50	0	0.00	2	12.50
Ependymoma	**Overall**	**19**	**6**	**31.58**	**13**	**68.42**	**7**	**53.85**	**2**	**15.38**	**4**	**30.77**
	0–3	9	4	44.44	5	55.56	0	0.00	1	20.00	4	80.00
	4–9	7	1	14.29	6	85.71	6	100.00	0	0.00	0	0.00
	10–14	3	1	33.33	2	66.67	1	50.00	1	50.00	0	0.00
Medulloblastoma	**Overall**	**57**	**8**	**14.04**	**49**	**85.96**	**47**	**95.92**	**0**	**0.00**	**2**	**4.08**
	0–3	9	8	88.89	1	11.11	0	0.00	0	0.00	1	100.00
	4–9	29	0	0.00	29	100.00	28	96.55	0	0.00	1	3.45
	10–14	19	0	0.00	19	100.00	19	100.00	0	0.00	0	0.00
Supratentorial PNET	**Overall**	**21**	**9**	**42.86**	**12**	**57.14**	**7**	**58.33**	**2**	**16.67**	**3**	**25.00**
	0–3	10	6	60.00	4	40.00	0	0.00	1	25.00	3	75.00
	4–9	9	2	22.22	7	77.78	6	85.71	1	14.29	0	0.00
	10–14	2	1	50.00	1	50.00	1	100.00	0	0.00	0	0.00
Germ cell tumours	**Overall**	**11**	**1**	**9.09**	**10**	**90.91**	**3**	**30.00**	**7**	**70.00**	**0**	**0.00**
	0–3	0	0	—	0	—	0	—	0	—	0	—
	4–9	4	1	25.00	3	75.00	1	33.33	2	66.67	0	0.00
	10–14	7	0	0.00	7	100.00	2	28.57	5	71.43	0	0.00
Other central nervous system tumours	**Overall**	**29**	**25**	**86.21**	**4**	**13.79**	**3**	**75.00**	**0**	**0.00**	**1**	**25.00**
	0–3	10	10	100.00	0	0.00	0	—	0	—	0	—
	4–9	11	10	90.91	1	9.09	1	100.00	0	0.00	0	0.00
	10–14	8	5	62.50	3	37.50	2	66.67	0	0.00	1	33.33

PNET = primitive neuroectodermal tumour

	2000–2004										
	Total	None		Received any		0–90 days		91–180 days		≥ 181 days	
	N	Yes (n)	%	Yes (n)	%	Yes (n)	%	Yes (n)	%	Yes (n)	%
	388	**211**	**54.38**	**154**	**39.69**	**120**	**77.92**	**19**	**12.34**	**15**	**9.74**
	69	50	72.46	12	17.39	2	16.67	4	33.33	6	50.00
	188	91	48.40	84	44.68	79	94.05	2	2.38	3	3.57
	131	70	53.44	58	44.27	39	67.24	13	22.41	6	10.34
	194	**155**	**79.90**	**18**	**9.28**	**8**	**44.44**	**4**	**22.22**	**6**	**33.33**
	29	21	72.41	1	3.45	0	0.00	1	100.00	0	0.00
	93	74	79.57	8	8.60	4	50.00	1	12.50	3	37.50
	72	60	83.33	9	12.50	4	44.44	2	22.22	3	33.33
	44	**12**	**27.27**	**30**	**68.18**	**29**	**96.67**	**0**	**0.00**	**1**	**3.33**
	7	6	85.71	1	14.29	0	0.00	0	0.00	1	100.00
	26	3	11.54	21	80.77	21	100.00	0	0.00	0	0.00
	11	3	27.27	8	72.73	8	100.00	0	0.00	0	0.00
	30	**7**	**23.33**	**23**	**76.67**	**15**	**65.22**	**4**	**17.39**	**4**	**17.39**
	10	6	60.00	4	40.00	1	25.00	1	25.00	2	50.00
	7	0	0.00	7	100.00	7	100.00	0	0.00	0	0.00
	13	1	7.69	12	92.31	7	58.33	3	25.00	2	16.67
	74	**13**	**17.57**	**61**	**82.43**	**57**	**93.44**	**1**	**1.64**	**3**	**4.92**
	15	11	73.33	4	26.67	1	25.00	0	0.00	3	75.00
	42	2	4.76	40	95.24	39	97.50	1	2.50	0	0.00
	17	0	0.00	17	100.00	17	100.00	0	0.00	0	0.00
	19	**8**	**42.11**	**11**	**57.89**	**10**	**90.91**	**1**	**9.09**	**0**	**0.00**
	5	4	80.00	1	20.00	0	0.00	1	100.00	0	0.00
	11	3	27.27	8	72.73	8	100.00	0	0.00	0	0.00
	3	1	33.33	2	66.67	2	100.00	0	0.00	0	0.00
	11	**0**	**0.00**	**11**	**100.00**	**1**	**9.09**	**9**	**81.82**	**1**	**9.09**
	1	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00
	0	0	—	0	—	0	—	0	—	0	—
	10	0	0.00	10	100.00	1	10.00	8	80.00	1	10.00
	16	**16**	**100.00**	**0**	**0.00**	**0**	**—**	**0**	**—**	**0**	**—**
	2	2	100.00	0	0.00	0	—	0	—	0	—
	9	9	100.00	0	0.00	0	—	0	—	0	—
	5	5	100.00	0	0.00	0	—	0	—	0	—

Exhibits 8.8a–8.8c

Complete information on treatment modalities employed was available for the period 1995–2004 only. Over this period treatment modalities evolved. These changes include advances in imaging technology (i.e., the availability of MRI) and surgical techniques, the availability of chemotherapeutic agents, differing combinations and dosages of chemotherapeutic agents, the changing knowledge of the effectiveness of therapeutic agents and an increased understanding of basic tumour biology. These factors make it difficult to provide an accurate overview of the treatment modalities used. Considering these limitations, Exhibits 8.8a-8.8c provide an overview of the different treatment modalities employed for the different age groups.

The number of children who did not undergo first look surgery did not vary greatly with age (0–3 years, 23.3%; 4–9 years, 26.8%; and 10–14 years, 20.5%). For low grade glioma, 24.6% did not undergo surgical intervention, suggesting that the diagnosis was based on radiologic findings or known predisposing circumstances (e.g., neurofibromatosis type 1). With respect to high grade glial tumours, the 57.8% who did not undergo surgery encompass a high proportion of diffuse intrinsic pontine glioma, which was treated nonsurgically (data not shown).

The relative frequency with which different modalities were used within treatment protocols has also changed with time. There has been an increase in the proportion of children who receive chemotherapy, both upfront and overall, as part of their initial treatment regimen. This increase is particularly evident in the 4–9 year and 10–14 year age groups and is true for all tumours except ependymoma. However, as Exhibit 8.8c demonstrates, the proportion of children who received upfront radiotherapy remained stable.

When the data were broken down into treatment by age group and examined over the same time periods, no significant changes were observed between the age groups.

The treatment protocols used are different for the different tumour types. As well, the components of the treatment protocol have changed over time. Between the 2 time periods (1995–1999 and 2000–2004), upfront surgical intervention was less frequently performed for germ cell tumours. Chemotherapy became more commonly used in the treatment of high grade glial tumours, medulloblastoma and germ cell tumours. There was a trend to decreased use of chemotherapy and increased use of radiotherapy in the treatment of children with ependymoma. In the low grade glioma group, the proportion of patients who received radiotherapy dropped from 11.7% to 9.3% from the early period to the later period. The drop is more dramatic in 0–3 and 4–9 year olds than in the 10–14 year age group (Exhibit 8.8c).

Survival

EXHIBIT 8.9: **5 year overall survival of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1985–2004**

		Period of diagnosis										
		All years (1985–2004)		1985–1989		1990–1994		1995–1999		2000–2004		
Tumour type	Age (years)	OSP	95% CI	OSP	95% CI	OSP	95% CI	OSP	95% CI	OSP	95% CI	Test for trend (p value)*
All central nervous system tumours	Overall	**0.69**	**0.66-0.72**	**0.51**	**0.40-0.62**	**0.68**	**0.63-0.73**	**0.71**	**0.66-0.75**	**0.73**	**0.68-0.77**	**0.00**
	0–3	0.57	0.50-0.62	0.32	0.09-0.59	0.68	0.57-0.77	0.59	0.48-0.68	0.46	0.35-0.57	0.21
	4–9	0.69	0.65-0.73	0.63	0.50-0.73	0.68	0.60-0.75	0.70	0.63-0.76	0.73	0.66-0.79	0.08
	10–14	0.76	0.72-0.80	0.66	0.51-0.77	0.68	0.58-0.76	0.77	0.70-0.83	0.86	0.79-0.91	0.00
Low grade glial tumours	Overall	**0.94**	**0.91-0.95**	**0.89**	**0.78-0.94**	**0.95**	**0.91-0.98**	**0.95**	**0.91-0.97**	**0.93**	**0.88-0.95**	**0.49**
	0–3	0.95	0.89-0.98	0.85	0.59-0.95	1.00	—	1.00	—	0.92	0.71-0.98	0.61
	4–9	0.94	0.90-0.96	0.91	0.75-0.97	0.96	0.90-0.99	0.96	0.88-0.99	0.91	0.83-0.96	0.59
	10–14	0.93	0.89-0.95	0.90	0.64-0.98	0.91	0.81-0.96	0.93	0.85-0.96	0.94	0.86-0.98	0.39
High grade glial tumours	Overall	**0.22**	**0.17-0.28**	**0.30**	**0.17-0.45**	**0.23**	**0.14-0.33**	**0.20**	**0.11-0.30**	**0.23**	**0.12-0.36**	**0.39**
	0–3†	0.45	0.28-0.60	—	—	0.55	0.21-0.80	0.50	0.23-0.73	0.29	0.04-0.62	—
	4–9†	0.19	0.12-0.27	—	—	0.23	0.11-0.38	0.14	0.06-0.27	0.17	0.04-0.39	—
	10–14	0.16	0.08-0.26	0.28	0.08-0.52	0.15	0.04-0.31	0.10	0.01-0.37	0.30	0.09-0.55	0.90
Ependymoma	Overall	**0.54**	**0.42-0.64**	**0.60**	**0.33-0.79**	**0.59**	**0.38-0.75**	**0.50**	**0.29-0.68**	**0.51**	**0.32-0.66**	**0.35**
	0–3†	0.33	0.18-0.48	—	—	0.50	0.23-0.72	0.15	0.03-0.36	0.19	0.06-0.39	—
	4–9	0.62	0.41-0.78	0.50	0.16-0.77	0.46	0.15-0.73	0.85	0.36-0.97	0.80	0.38-0.95	0.06
	10–14	0.84	0.59-0.94	1.00	—	1.00	—	0.72	0.23-0.93	0.69	0.29-0.90	0.07
Medulloblastoma	Overall	**0.58**	**0.51-0.65**	**0.20**	**0.00-0.69**	**0.48**	**0.34-0.60**	**0.59**	**0.46-0.69**	**0.68**	**0.56-0.78**	**0.00**
	0–3	0.36	0.21-0.50	0.12	0.00-0.51	0.36	0.09-0.65	0.38	0.12-0.64	0.44	0.18-0.68	0.11
	4–9†	0.61	0.51-0.70	—	—	0.51	0.33-0.67	0.60	0.42-0.74	0.69	0.52-0.81	—
	10–14†	0.67	0.52-0.78	—	—	0.41	0.13-0.68	0.67	0.43-0.83	0.85	0.61-0.95	—
Supratentorial PNET	Overall†	**0.20**	**0.11-0.32**	**—**	**—**	**0.25**	**0.08-0.47**	**0.00**	**0.00-0.00**	**0.19**	**0.07-0.35**	**—**
	0–3†	0.13	0.03-0.29	—	—	0.20	0.01-0.57	—	—	0.01	0.00-0.04	—
	4–9†	0.25	0.11-0.42	—	—	0.33	0.07-0.63	0.32	0.06-0.62	0.26	0.06-0.52	—
	10–14†	—	—	—	—	—	—	—	—	—	—	—
Germ cell tumours	Overall†	**0.85**	**0.68-0.93**	**0.60**	**0.22-0.84**	**1.00**	**—**	**0.89**	**0.52-0.98**	**0.92**	**0.56-0.99**	**0.05**
	0–3†	—	—	—	—	—	—	—	—	—	—	—
	4–9†	1.00	—	—	—	1.00	—	1.00	—	1.00	—	—
	10–14	0.87	0.66-0.95	0.71	0.25-0.92	1.00	—	0.82	0.30-0.97	1.00	—	0.12
Other central nervous system tumours	Overall	**0.62**	**0.49-0.72**	**0.28**	**0.04-0.61**	**0.37**	**0.15-0.60**	**0.82**	**0.62-0.92**	**0.82**	**0.58-0.93**	**0.00**
	0–3	0.28	0.13-0.45	0.41	0.10-0.71	0.17	0.02-0.43	0.47	0.16-0.74	0.36	0.05-0.71	0.68
	4–9†	0.87	0.62-0.96	—	—	0.75	0.05-0.97	1.00	—	1.00	—	—
	10–14†	0.82	0.55-0.94	—	—	0.21	0.02-0.53	1.00	—	1.00	—	—

OSP = overall survival proportion; PNET = primitive neuroectodermal tumour; CI = confidence interval
*Test for trend not calculated if any period specific OSP is missing.
†Owing to small sample sizes, rates are not provided for some time periods.

EXHIBIT 8.10: **5 year event free survival of primary central nervous system tumours, by tumour type, age at diagnosis and period of diagnosis, age 0–14 years, in Ontario, 1995–2004**

		Period of diagnosis					
		All years (1995–2004)		1995–1999		2000–2004	
Tumour type	Age (years)	EFSP	95% CI	EFSP	95% CI	EFSP	95% CI
All central nervous system tumours	Overall	**0.66**	**0.62-0.69**	**0.65**	**0.60-0.69**	**0.67**	**0.62-0.71**
	0–3	0.45	0.37-0.52	0.50	0.39-0.60	0.39	0.28-0.49
	4–9	0.66	0.61-0.71	0.64	0.57-0.71	0.67	0.60-0.74
	10–14	0.77	0.72-0.82	0.74	0.66-0.80	0.81	0.73-0.86
Low grade glial tumours	Overall	**0.89**	**0.85-0.91**	**0.90**	**0.86-0.94**	**0.87**	**0.81-0.91**
	0–3	0.85	0.74-0.92	0.86	0.71-0.93	0.84	0.63-0.93
	4–9	0.89	0.83-0.93	0.92	0.84-0.96	0.86	0.77-0.92
	10–14	0.90	0.84-0.93	0.90	0.82-0.95	0.89	0.80-0.94
High grade glial tumours	Overall	**0.18**	**0.12-0.26**	**0.19**	**0.11-0.30**	**0.18**	**0.08-0.31**
	0–3	0.35	0.16-0.55	0.50	0.22-0.73	0.08	0.00-0.39
	4–9	0.15	0.07-0.25	0.14	0.05-0.26	0.19	0.05-0.40
	10–14	0.12	0.04-0.25	0.10	0.01-0.37	0.23	0.05-0.48
Ependymoma	Overall	**0.44**	**0.30-0.57**	**0.48**	**0.28-0.66**	**0.42**	**0.24-0.58**
	0–3	0.17	0.06-0.33	0.18	0.04-0.40	0.18	0.04-0.40
	4–9	0.66	0.35-0.85	0.85	0.36-0.97	0.53	0.17-0.80
	10–14	0.64	0.36-0.82	0.72	0.23-0.93	0.61	0.28-0.82
Medulloblastoma	Overall	**0.54**	**0.45-0.62**	**0.50**	**0.37-0.60**	**0.58**	**0.46-0.69**
	0–3	0.24	0.09-0.43	0.27	0.05-0.55	0.21	0.05-0.45
	4–9	0.55	0.43-0.66	0.48	0.32-0.63	0.61	0.44-0.74
	10–14	0.70	0.53-0.82	0.61	0.38-0.77	0.81	0.56-0.93
Supratentorial PNET	Overall	**0.19**	**0.07-0.34**	**0.32**	**0.13-0.53**	**0.18**	**0.06-0.35**
	0–3*	0.07	0.00-0.27	—	—	0.01	0.00-0.06
	4–9	0.25	0.07-0.48	0.32	0.07-0.62	0.27	0.06-0.56
	10–14*	—	—	—	—	—	—
Germ cell tumours	Overall	**0.81**	**0.58-0.92**	**0.69**	**0.34-0.88**	**0.92**	**0.56-0.99**
	0–3*	—	—	—	—	—	—
	4–9*	0.65	0.20-0.89	0.45	0.07-0.78	1.00	—
	10–14*	0.94	0.66-0.99	0.82	0.35-0.96	1.00	—
Other central nervous system tumours	Overall	**0.71**	**0.55-0.82**	**0.60**	**0.37-0.78**	**0.82**	**0.58-0.93**
	0–3	0.31	0.10-0.56	0.37	0.10-0.65	0.36	0.05-0.71
	4–9*	0.93	0.59-0.99	0.86	0.26-0.98	1.00	—
	10–14*	0.85	0.50-0.96	0.72	0.26-0.92	1.00	—

EFSP = event free survival proportion; PNET = primitive neuroectodermal tumour; CI = confidence interval
*Owing to small sample sizes, rates are not provided for some time periods.

Exhibits 8.9 and 8.10

Survival information was available for 1,342 of the 1,448 cases contained in this registry.

The overall 5 year survival rate for all children diagnosed with a CNS tumour between 1985 and 2004 was 69% (95% CI, 66–72%). The survival rate varied with age. In children 3 years of age or less at initial diagnosis, the survival rate was 57% (95% CI, 50–62%), compared with 76% (95% CI, 72–80%) for children 10–14 years of age. Children 4–9 years of age at diagnosis had a 5 year survival rate between that of the other 2 age groups (i.e., 69% [95% CI, 65–73%]). The difference in survival rates based on age probably reflects the different distribution of tumour types by age and the treatment of the tumour based on the age of the child at diagnosis.

For the period 1990–2004, there was a progressive increase in the overall 5 year survival rate in each successive 5 year interval for all ages combined (from 68% to 73%). This improvement was most obvious in children over 10 years of age at the time of diagnosis (from 68% to 86%). It was also notable for children 4–9 years of age at the time of diagnosis (from 68% to 73%). However, overall survival for children aged 0–3 years at diagnosis declined (from 68% to 46%), although the confidence intervals are wide, reflecting the small sample size.

The reasons for the differences in 5 year survival rates between the different age groups are complex. They include differences in distribution by tumour type and thus therapy. Changes in treatment approaches may also have a role. The limitation of use of radiation therapy in the youngest age group may also have a significant impact.

As expected, children with a histologic diagnosis of low grade glial tumour did well (5 year survival rate of 94% [95% CI, 91–95%]), with no significant change in survival over the 20 year period. Children with a diagnosis of germ cell tumour had an 85% 5 year survival rate (95% CI, 68–93%), with appreciable improvement over successive time periods. Children with either medulloblastoma or ependymoma had similar 5 year survival rates: 58% (95% CI, 51–65%) and 54% (95% CI, 42–64%), respectively, with substantial improvement in overall survival for the former over successive periods and no change in survival for the latter. The poorest outcomes were seen in patients with either PNETs or high grade glial tumours (5 year survival of 20% [95% CI, 11–32%] and 22% [95% CI, 17–28%], respectively).

From 1990 to 2004, based on histologic diagnosis, 5 year survival rates remained constant, except for the medulloblastoma group. For this group of patients, the 5 year survival rate steadily increased, from 48% (95% CI, 34–60%) for 1990–1995 to 68% (95% CI, 56–78%) for 2000–2004. Similar improvements were seen in germ cell tumours, with survival rates increasing from 60% (95% CI, 22–84%) in the first 5 year period to 92% (95% CI, 56–99%) in the last.

For completeness, the event (progression) free survival rates for the subset diagnosed and treated between 1995 and 2004 are included in Exhibit 8.10; however, caution is needed in interpreting these data. At progression, a change in therapies being offered, including second look surgery, use of radiotherapy in children previously felt to be at risk of secondary cognitive impairment owing to age or change in chemotherapy regimen, may be the reason for this change in overall survival.

The proportion of children with different tumour histologies in this cohort varied with age. The number of children in each group was relatively small. Small shifts in outcome for a small number of children within a sub-group could affect the overall outcome. For similar reasons, a change in therapeutic strategies in 1 sub-group that resulted in increased 5 year survival rates for that tumour group could also affect the outcome for a certain age group if the proportion of the tumour type was great enough within that group.

Summary

Brain tumours are rare in children, with an annual incidence rate of 33.2 per million children 14 years of age or younger in the Province of Ontario. This rate did not change significantly over the study period. CNS tumours are slightly more common in males than females and in children over 3 years of age. Therapeutic modalities vary with age, with radiotherapy tending to be less commonly used in children 3 years of age or younger. Though therapeutic options advanced over the study period, the 5 year survival rates remained relatively stable, except for medulloblastoma and germ cell tumours, where there was a steady improvement in survival.

References

1 Bestak M. Epidemiology of brain tumors. In: Keating RF, Goodrich JT, Packer RJ, editors. Tumors of the pediatric central nervous system, 1st ed. New York & Stuttgart: Thieme; 2001.

2 Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol. 2012 Nov;14(Suppl 5):1-49. [Erratum in Neuro Oncol. 2013 May;15(5):646-7.]

3 Davis F. Current epidemiological trends and surveillance issues in brain tumors. Expert Rev Anticancer Ther. 2001;1:335-407.

4 Davis F, McCarthy B, Beyers M. Centralized databases available for describing primary brain tumor incidence, survival, and treatment: Central Brain Tumor Registry of United States; Surveillance, Epidemiology, and End Results; and National Cancer Data Base. Neuro Oncol. 1999 Jul;1(3):206-11.

Photo by Vivid Eye Photography

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9

Neuroblastoma

Executive Summary

Neuroblastoma is the most common extracranial tumour of childhood and the third most common pediatric cancer. The age standardized incidence in North America is 8.9–12.5 per million with a slightly higher incidence in males. The median age at diagnosis is 18 months, with the highest incidence in infants aged less than 6 months. Diagnosis is very rare after age 10 years. The most common sites of primary tumours are the thorax and abdomen. Approximately 50% of patients present with metastases, most commonly to the lymph nodes, bone or bone marrow.

Patients with neuroblastoma can be classified into 3 risk categories: low, intermediate and high risk based on clinical (age and stage) and biologic (molecular and genetic) factors. Low risk cases most commonly include localized tumours that can be observed or surgically resected and rarely require chemotherapy treatment. Intermediate risk tumours are biologically favourable unresectable large tumours that cross the midline and often invade the spinal cord, vessels or organs. These patients often receive moderate doses of chemotherapy followed by surgical resection. In contrast, most high risk patients have metastatic disease and require intensive treatment with chemotherapy, radiation, surgery, autologous stem cell transplant (since the mid- to late 1990s) and, more recently, immunotherapy. Five year overall survival rates for low and intermediate risk patients are more than 90%, while rates for high risk patients are less than 50%.

For patients treated in Ontario during the study period, data collected in the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) included stage, age and treatment modalities (chemotherapy, stem cell transplant). A total of 435 cases of neuroblastoma were diagnosed in Ontario from 1985 to 2004 with an average of 21 cases per year. Interestingly, the incidence of neuroblastoma increased 9.5% from the 1985–1989 period to the 2000–2004 period. The increase was most significant for infants less than 1 year of age with stage 1 disease and was most likely due to increased detection of small, low risk tumours. The numbers of patients diagnosed with stage 2, 3 and 4 disease was essentially stable during 1985–2004.

Overall survival was 64.6% for all patients with neuroblastoma in Ontario during the 20 year study period, improving from 58.6% in 1985–1989 to 73.5% in 2000–2004. Event free survival (EFS), for which data were collected only during the latter 10 years of the study, improved from 58.1% (1995–1999) to 68.6% (2000–2004). Age and stage are 2 highly prognostic factors. Notably, 2 of 115 patients with localized neuroblastoma (stage 1 and 2) died of their disease. Among patients with metastatic (stage 4) neuroblastoma over 18 months of age in the most recent period (2000–2004), the 5 year EFS and overall survival were 39.3% and 48.5%, respectively. These rates represent an improvement of 170% since the 1985–1989 period. Since the mid-1990s, autologous bone marrow transplants (BMT) or stem cell transplants have become the standard of care – the use of BMT increased from 78.0% (1995–1999) to 90.9% (2000–2004).

More than one third of patients with neuroblastoma experience 1 or more relapses. The proportion of patients whose disease recurred decreased from 41.0% (1995–1999) to 26.4% (2000–2004). The majority of relapses occurred in patients with stage 4 disease. Of the total recurrences, 83.3% and 77.7% were stage 4 at initial diagnosis in the 1995–1999 and 2000–2004 periods, respectively. The incidence of recurrence may decrease further in the post-2004 periods as a result of increased use of immunotherapy with anti-GD2 antibodies and cytokines. Five year overall survival post relapse is only 20%, which is similar to outcomes reported for other registries. The improvements in survival post relapse may be due to increased use of chemotherapies and other treatments. Increasing use of targeted inhibitors and high dose metaiodobenzylguanidine (MIBG) therapy for relapsed neuroblastoma may lead to improved survival rates, response duration or both in future cohorts of patients.

Introduction

Neuroblastoma is the most common extracranial pediatric solid tumour and the most frequently diagnosed cancer in infants. Neuroblastoma includes a spectrum of neural crest tumours that range from benign, self-resolving tumours to disseminated malignant tumours that account for more deaths than any other pediatric solid tumour.

Epidemiology

The incidence of neuroblastoma varies significantly in different countries, with frequency generally associated with the medical resources available. Lower frequency of diagnosis has been observed in countries with fewer medical resources. In North America and Europe, national incidences have been estimated at between 8.9 and 12.5 cases per million population.[1–4] Most studies suggest a slight male predominance, similar to other common childhood solid tumours. Notably, a 1997 review from the Canadian National Cancer Incidence Reporting System reported a higher incidence in males (11.0 vs. 9.6 per million).[2]

Neuroblastoma is primarily a disease of infants and toddlers, with a median age at diagnosis of approximately 18 months. The reported age-specific incidence rates for infants less than 6 months of age range from 52.3 to 72.5 cases per million. In children aged 1–4 years, the incidence falls to 18.1–19.5 cases per million. The incidence continues to fall with increasing age to approximately 1 per million in children aged 10–14 years.[1]

Clinical Presentation

Presenting symptoms vary depending on the location of the primary tumour, which may occur anywhere along the course of the sympathetic chain from the brain to the pelvis, and on the extent of the disease. Many symptoms are a direct result of local effects of the tumour mass on organs, vessels or nerves; symptoms occasionally may be secondary to a paraneoplastic process. The primary tumour site for more than 65% of patients is the abdomen, most commonly the adrenal gland. Related symptoms can include hypertension, abdominal pain and constipation. In infants thoracic tumours are more common and symptoms may include Horner syndrome (unilateral ptosis, anhydrosis and myosis) and respiratory symptoms.[5–7] Spinal cord compression presenting as paraplegia and loss of bladder function can result from centrally-located paraspinal tumours. In more than 50% of patients, neuroblastoma metastasizes to bone, bone marrow, lymph nodes or the liver, and less commonly, in infants, to skin. Although uncommon, metastases to the orbital bone result in peri-orbital bruising, proptosis and potentially visual impairment. Metastases to the liver in infants can result in hepatomegaly and secondary renal failure and respiratory compromise. Metastases to the lung and brain are rare at diagnosis, but central nervous system disease at relapse is increasingly common.[5–7]

Diagnosis and Staging

Many investigations are required to confirm the diagnosis of neuroblastoma and evaluate disease extent. In most cases, tumour tissue is required to obtain pathologic, biologic and molecular information to determine prognosis and choice of therapy. The choice between biopsy or upfront resection depends on patient characteristics and, most importantly, the presence of metastatic disease. Diagnosis of neuroblastoma can be confirmed either by histologic diagnosis on biopsy or resection specimen, or by elevated urinary catecholamines together with tumour cells detected in the bone marrow.

Urinary catecholamines

Neuroblastomas are characterized by abnormal catecholamine synthesis resulting in increased levels of metabolites, including homovanillic acid (HVA) and vanillylmandelic acid (VMA). Elevated urinary HVA and VMA can be detected in approximately 90% of patients and provides a non-invasive, inexpensive, rapid method for disease detection and surveillance.[8-10] Most laboratories can now analyze levels in "spot" samples of approximately 10 mL.

Imaging assessment

As part of initial assessment of disease burden and assessment of surgical risks and resectability, patients require imaging of their primary tumour site and potential sites of metastases. Cross-sectional imaging modalities such as computed tomography and magnetic resonance imaging (MRI) are used to assess the primary tumour; lymph node involvement; and local invasion of vessels, nerves and organs at diagnosis, during therapy and for surveillance following completion of therapy. Urgent MRI is required if intraspinal invasion and cord compression are suspected.

Nuclear medicine scans are routinely used to identify metastatic disease. Technetium-99m-MDP bone scans have been used to detect cortical bony metastases of many types of solid tumours, including neuroblastoma. Since the late 1990s, however, technetium bone scans have been slowly replaced by scans using radiolabelled MIBG, a norepinephrine analogue specific to neural crest tumours. Of neuroblastomas, 90% are MIBG-avid and MIBG can identify soft tissue, bone and bone marrow metastases. Scoring systems (e.g., the Curie score) are now being incorporated to quantitate disease at diagnosis and during treatment.[11] In the 10% of patients with non-MIBG-avid disease, bone scans have been used for metastatic evaluation; however, evidence suggests that positron emission tomography (PET) provides more sensitive detection of metastatic bone and soft tissue lesions. Routine use of PET scans in these rare MIBG-negative patients will likely be recommended in the next set of international response criteria guidelines.[12,13]

Bone marrow

Advanced neuroblastoma typically metastasizes to bone marrow. Bone marrow aspirations and biopsies from at least 2 sites are required for staging. In certain cases in which bone marrow evaluation is positive, bone marrow neuroblasts may provide sufficient material for diagnosis and can be used to determine molecular and genetic markers (e.g., *MYCN* amplification; see below).

Upfront surgical resection

For localized, non-metastatic lesions, upfront surgery is often the approach of choice.[14] Factors influencing the resectability of the lesion include its size, location and relation to vital structures. Surgical resection alone may be the optimal form of therapy for patients with low stage disease. Any involved or potentially involved lymph nodes are resected or sampled at the time of surgery for staging.

Recent data from the International Neuroblastoma Risk Group (INRG) and the International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) have demonstrated that a system to standardize image defined risk factors (IDRFs), including direct organ involvement, invasion of spinal cord and vascular encasement, can be used pre-operatively to determine which subsets of patients should have pre-operative chemotherapy.[15,16]

Tumour biopsy

Although upfront surgical resection is usually preferred for localized disease without IDRFs, many children will present with metastatic disease or large, unresectable lesions with IDRFs. In these cases, biopsy is performed to confirm the histologic diagnosis and to acquire tissue to test for specific molecular and genetic characteristics. Although traditionally most biopsies were performed by surgical incision ("open"), more recently at some institutions biopsies have been obtained by laparoscopy or by image guided needle core biopsies. However, it is critical that sufficient biopsy tissue be obtained to test molecular and genetic markers required for risk stratification (see below).[17]

Prognostic Factors and Risk Stratification

Large cooperative group studies and international databases have resulted in the identification of statistically robust clinical and biologic (molecular and genetic) factors that predict prognosis and can be used to define clinical risk groups to tailor the intensity of adjuvant therapy. For patients treated in Ontario during the study period, the main risk factors for which data were collected included International Neuroblastoma Staging System (INSS),[18] stage and age. The biologic predictors were identified over the timeframe of this sample and were either not known or not collected throughout most of the timeframe covered, and thus are not available in the current POGONIS dataset.

Factors Determining Risk Assignment

Age

Age has long been recognized as an important predictor of outcome in neuroblastoma.[19] Historically, age of less than 12 months was considered a favourable prognostic factor, and compared with patients older than 12 months these infants were often treated with less intensive therapy. More recently, large retrospective studies have demonstrated that age is a continuous variable and that the cutoff for favourable prognosis could be extended to age 18 months for the subset of patients with biologically favourable tumours.[20–22]

Stage

A variety of systems have been used internationally to stage disease in patients with neuroblastoma. In an attempt to facilitate comparison of results across various international cooperative groups, a consensus system, the INSS, was first published in 1988 and updated in 1993; it has been used for the POGONIS data (Appendix 1).[23,18]

INSS staging is by definition post surgical. It can vary depending on surgical experience and aggressiveness. Stages 1 and 2 represent completely and incompletely resected tumours with or without local lymph node involvement, respectively. Stage 3 tumours cross the midline and stage 4 involves distant metastases. Stage 4s (4 special) represents a distinct subset of metastatic neuroblastoma, defined as presentation at less than 12 months of age and with metastatic spread limited to skin, liver and/or bone marrow, but not bone. Although these patients usually have biologically favourable tumours, infants with stage 4s disease, especially those less than 2 months of age, experience significant morbidity and mortality due to hepatomegaly, infection and respiratory and renal failure.[24,25]

A newer, pre-surgical staging system, the International Neuroblastoma Risk Group Staging System (INRGSS), was developed in Europe to stage tumours based on IDRFs, independent of whether the tumour crosses the midline, its size or individual surgical preferences.[26] The INRGSS is being prospectively studied in North American cooperative group trials.

Histology

In 1984, Shimada et al. published an age-based prognostic pathologic classification system of neuroblastic tumours that factored in Schwannian stromal proportion and the mitosis-karyorrhexis index, a surrogate marker for proliferation.[27] The International Neuroblastoma Pathology Classification (INPC) updated the original Shimada classification to incorporate other prognostic histologic factors, including mitotic rate, calcification and differentiation.[28,29]

MYCN amplification

Increased copies (more than 10) of the *MYCN* oncogene is the most powerful biologic predictor of poor outcome.[30] Approximately 20% of all neuroblastoma tumours demonstrate *MYCN* amplification (MYCNA); the incidence is higher (40%) in stage 4 patients. Several studies in North America and Europe have demonstrated that even for infants *MYCN* status can discriminate recurrence risk. For example, the Children's Cancer Group (CCG) reported that infants with stage 4 disease had 3 year EFS of 93% in the absence of *MYCN* amplification, compared with 10% for those with *MYCN* amplification tumours.[31] Although in older children (over 18 months) with metastatic disease *MYCN* amplification is not an independent predictor of long term outcome, in studies of patients with INSS stage 2 or 3 disease *MYCN* status may predict prognosis.[32,33]

The current standard technique for detecting *MYCN* amplification is fluorescence in situ hybridization (FISH). Genetic techniques that can simultaneously detect gain and loss at multiple genetic loci may soon replace FISH, however.

DNA ploidy

Ploidy, or tumour DNA content (chromosome number), is a powerful predictor of relapse free survival and is especially informative for the subset of patients younger than 18 months or patients with low stage disease. Hyperdiploid tumours (DNA index greater than 1) with an increased amount of DNA compared with diploid tumours (DNA index = 1) as determined by flow cytometry are associated with a more favourable prognosis.[34,35]

Other chromosomal alterations

Over the past decade the presence of segmental chromosome aberrations (small losses and gains of chromosomal material), including allelic losses at 1p and 11q and additional chromosomal gains and losses, have been shown to predict poor prognosis.[36,37] Based on these studies, current and future clinical trials are likely to include the presence of segmental aberrations (as detected by FISH or newer technologies such as array comparative genomic hybridization and single nucleotide polymorphism analyses) as a prognostic factor to inform risk group assignment and tailor therapies.

Contemporary data suggest that for children older than 18 months at diagnosis who present with metastatic disease (stage 4), additional tumour biomarkers are not independently prognostic. In contrast, for children younger than 18 months with metastatic disease, and for patients who present with localized disease, the identification of specific biologic and clinical risk factors has enabled more precise prediction of prognosis and determination of the most appropriate treatment intensity.

Risk Groups and Treatment

Currently the majority of North American pediatric oncology centres use the Children's Oncology Group (COG) criteria to establish risk groups (Appendix 2). The COG risk stratification uses age, stage, *MYCN* status, tumour ploidy and INPC histologic classification. In future studies the system will likely include the status of specific chromosomal losses and gains. Currently, in North America centralized laboratories supported by the COG and the U.S. National Cancer Institute perform some of these studies for patients on clinical trials. However, a systematic approach to the development of Ontario's capacity and funding to perform and interpret these assays needs to be developed.

Low risk disease

The majority of patients with low risk disease have localized tumours (INSS stage 1 or 2) with favourable biology. Patients with low risk disease may receive only initial diagnostic or definitive surgery, or both, with no chemotherapy. Furthermore, over the past decade some studies have supported observation only for small, biologically favourable tumours, which often spontaneously regress or differentiate. Asymptomatic infants with small tumours detected incidentally, such as on prenatal and neonatal ultrasounds, are followed with frequent imaging studies (optimally ultrasounds) and urinary catecholamine measurement to confirm resolution over time. This approach may allow a high percentage of infants to avoid surgery and surgical morbidity.[38-40]

Low risk patients who are symptomatic (i.e., with spinal cord compression or large hepatomegaly) often require chemotherapy to relieve their symptoms. These approaches have recently been reported to result in EFS of 87% and overall survival of 96%.[14]

Intermediate risk disease

The majority of intermediate risk neuroblastoma patients are characterized by unresectable large masses (usually INSS stage 3). Over the past decade the intermediate risk group has expanded to include INSS stage 4 patients younger than 18 months with favourable biology, a group of patients previously treated as high risk. The identification of a diverse group at intermediate risk, defined in multiple ways and treated with multiple chemotherapy regimens, has resulted in excellent reported survival rates (greater than 75–80%) by a variety of cooperative groups.[41,42] The COG recently reported that overall survival of above 90% could be maintained by using a risk-stratified approach to therapy that reduces chemotherapy for patients with biologically favourable

tumours.[43] Based on these results, current strategies are aimed at reducing intensity and duration of chemotherapy in the majority of patients with more favourable intermediate risk disease, while identifying clinical and biologic characteristics of intermediate risk patients at the highest risk for relapse in an effort to maintain excellent survival while reducing short and long term toxicities.

High risk disease

In contrast to the excellent survival associated with low risk and intermediate risk neuroblastoma, EFS for high risk disease remains poor. For patients treated in the 1990s and most of the 2000–2010 period, EFS for high risk disease was approximately 40%.[44-48]

Therapy for high risk disease involves 3 phases of treatment: induction, consolidation and maintenance. For induction, patients receive 5–7 cycles of dose intense chemotherapy and undergo surgical resection of the primary tumour (usually after cycle 4 or 5); 85–90% of patients initially respond to this chemotherapy. However, there are both acute and long term toxicities, including infections, multi-organ dysfunction and hearing and renal morbidities.

Following induction therapy, current protocols for high risk disease include consolidation therapy with high dose myeloablative chemotherapy followed by autologous BMT or stem cell transplant. Transplants for neuroblastoma patients were initially performed using harvested bone marrow cells. Over the past decade autologous peripheral blood stem cells have been routinely used to repopulate the marrow. In contrast to bone marrow and peripheral blood stem cell transplants for hematopoietic malignancies, for neuroblastoma stem cells are re-infused as a rescue to enable the use of high dose myeloablative chemotherapy.

The use of autologous stem cell transplant or rescue has consistently shown short and long term survival advantages. A prospective randomized clinical trial by the CCG confirmed the improved long term survival for stem cell transplant compared with chemotherapy (5 year EFS, 30% vs. 19%).[46,47] Similar results have been reported from the German Paediatric Oncology and Haematology Society (GPOH).[45,49] No advantage has been demonstrated for methods that attempt to purge contaminating neuroblastoma cells from the peripheral blood stem cells.[48] Current and future trials will be aimed at improving the efficacy of consolidation regimens with increased intensity, such as double autologous transplants, or modifications in conditioning strategies.

Despite intensive induction chemotherapy and consolidation with BMT or peripheral blood stem cell transplant, recurrence rates remained high, with more than 60% of patients experiencing relapse, presumably owing to the presence of clinically undetectable minimum residual disease. Oral cis-retinoic acid (cis-RA) administered following transplant consolidation therapy has been shown to significantly improve outcomes and is now the standard of care for maintenance therapy.[46]

During the past 10 years additional agents for high risk patients in the post consolidation or maintenance phases of therapy have been examined, including immunotherapies that target the disialoganglioside GD2 that is almost universally expressed on the surface of neuroblastoma cells. A COG phase 3 randomized controlled trial demonstrated that the addition of anti-GD2 chimeric (human-mouse) Ch14.18, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) to cis-RA produced outcomes superior to that of cis-RA alone (2 year EFS of 66% vs. 46%).[48] Similar long term data from the GPOH demonstrated improved EFS almost 10 years following administration of Ch14.18 post transplant.[50] Immunotherapy with Ch14.18, interleukin-2 and GM-CSF is now considered the standard of care for all high risk neuroblastoma patients as part of their upfront post consolidation treatment. The production of Ch14.18 in North America will move from the U.S. National Cancer Institute to a commercial pharmaceutical company and the cost will not be covered by clinical trials once commercially licensed. Thus it will be critical to obtain national regulatory approvals and provincial funding for the approximately 8–10 high risk patients treated annually with immunotherapy in Ontario.

Relapsed disease

Despite the recent treatment advances for high risk neuroblastoma, relapsed or refractory disease is often fatal.[51,52] If relapse is localized, surgery, radiation therapy or both can be curative; however, for patients with recurrent metastatic disease, particularly following upfront intensive high risk therapy, current salvage therapies can prolong survival but cure only a minority of patients.

Importantly, a variety of second line therapies palliate symptoms and prolong life for many years.[53-56] Several retrospective studies have reported the survival for patients following relapse or progression of neuroblastoma. The largest analysis (of 8,800 patients from the INRG) reported that the 5 year overall survival for the 2,266 patients who relapsed between 1990 and 2002 was 20%.[57] Agents in clinical trials include immunotherapies and tyrosine kinase inhibitors, including inhibitors of the anaplastic lymphoma kinase, which is mutated in 10% of sporadic neuroblastoma tumours.[58] Targeted radiotherapy with high dose MIBG has shown a response rate of 37% in the refractory disease setting and in 2014 is available to patients in Ontario.[59]

Future Directions

With contemporary therapy, approximately 50% of patients with high risk neuroblastoma still experience recurrence and those that are cured have significant late effects. With traditional chemotherapeutic agents now approaching maximal intensity, new targeted therapies are required. One such strategy will involve the addition of high dose MIBG therapy to upfront treatment for subsets of high risk neuroblastoma patients. Approaches to improve the efficacy and decrease the toxicity of immunotherapy are also active areas of investigation. In contrast, for patients with low or intermediate risk neuroblastoma, recent North American and European trials support continued reduction in chemotherapy for subsets of patients based on favourable clinical and biologic risk factors.

For all patients with neuroblastoma it is expected that there will be integration of additional molecular and genetic features to further refine risk stratification. For example, specific signatures of gene expression in tumours can predict outcome among patients with high risk neuroblastoma to distinguish an ultra high risk group with EFS below 20%.[60,61] Whole-genome sequencing strategies will likely help identify novel tumour targets as well as host (patient) genetic sequences that predict the development of toxicities to specific therapies, such as hearing loss.[62] These advances will lead to further personalized or precision medicine for patients with neuroblastoma.

Data Collection

The slow but steady improvement in neuroblastoma survival in the past 3 decades is the result of sequential clinical trials performed by cooperative groups such as the COG in North America, the SIOPEN and the GPOH. Clinical trial participation requires patient or family consent and results therefore may not truly represent population outcomes, since many patients do not enter studies because of parental choice, severity of presenting disease, eligibility or timing criteria and study availability.

POGONIS provides an opportunity to capture trends in incidence and outcome of neuroblastoma on a population basis, independent of clinical trial participation. This population-based sample allows assessment of the translation of successful clinical trials to real world results in a population. One caveat specifically related to outcomes for the neuroblastoma population, however, is that information on many of the contemporary prognostic factors and biomarkers used to stratify therapy in recent international cooperative group studies was either not available during the period under consideration or POGONIS did not collect it, thus limiting some of the potential comparisons. Nevertheless, the presence of stage and age data allows for basic risk stratification and comparison of trends and outcomes for many of the relevant risk groups with larger cohorts of patients in Ontario.

Discussion

EXHIBIT 9.1: **Incidence of primary neuroblastoma by age at diagnosis and year of diagnosis, age 0–14, in Ontario, 1985–2004**

		All years 1985–2004	1985–1989	1990–1994	1995–1999	2000–2004
Stage	Age group at time of diagnosis	N	N	N	N	N
All	Overall	**435**	**95**	**118**	**118**	**104**
	< 1 year	154	34	40	38	42
	1–4 years	185	38	55	49	43
	≥ 5 years	96	23	23	31	19
1	Overall	**58**	**8**	**15**	**15**	**20**
	< 1 year	32	4	5	10	13
	1–4 years	19	3	8	2	6
	≥ 5 years	7	1	2	3	1
2	Overall	**64**	**14**	**19**	**17**	**14**
	< 1 year	35	8	11	9	7
	1–4 years	23	5	8	5	5
	≥ 5 years	6	1	0	3	2
3	Overall	**87**	**21**	**25**	**23**	**18**
	< 1 year	38	8	10	11	9
	1–4 years	34	8	12	7	7
	≥ 5 years	15	5	3	5	2
4	Overall	**192**	**42**	**46**	**61**	**43**
	< 1 year	23	7	4	7	5
	1–4 years	107	22	25	35	25
	≥ 5 years	62	13	17	19	13
4s	Overall	**27**	**7**	**11**	**1**	**8**
	< 1 year	26	7	10	1	8
	1–4 years	1	0	1	0	0
	≥ 5 years	0	0	0	0	0
Missing stage	Overall	**7**	**3**	**2**	**1**	**1**

Exhibit 9.1

There were 435 cases of neuroblastoma diagnosed in Ontario from 1985 to 2004. The average number of cases per year was 22. The overall number of neuroblastoma cases has increased at a rate comparable to the increase in total population in Ontario. The absolute number of cases per 5 year period increased 9.5% from 1985–1989 to 2000–2004. This difference was caused primarily by the marked (150%) increase in stage 1 disease, particularly among children less than 1 year of age. A greater than 3-fold increase in incidence was detected for infants with stage 1 disease diagnosed in the most recent period (2000–2004) compared with the earliest period (1985–1989). This increase may be attributed to increased recognition of low stage asymptomatic masses incidentally detected by imaging investigations ordered to investigate unrelated symptoms, such as chest x-ray for cough or abdominal ultrasound for urinary tract infection. In addition, the increased use of prenatal ultrasounds has likely contributed to the detection of adrenal masses in the third trimester.

The number of stage 2, 3, 4 and 4s cases remained essentially stable over all 4 study periods. Approximately half of all cases involved infants or toddlers aged less than 18 months, a proportion similar to that of other groups, including a report of the Italian Registry from a similar period (1979–2005): 45% of that study's 2,216 patients were younger than 18 months.[63] It should be noted that while many of these incidentally detected localized neuroblastoma masses were historically treated by surgical resection, chemotherapy or both during the periods under study, more recent studies support observation for a subset of these patients with small adrenal masses.[40] Current COG and SIOPEN trials are also investigating the role of any intervention in a subset of larger localized masses with favourable biology in children under 18 months.[64]

EXHIBIT 9.2: **5 year overall survival with primary neuroblastoma tumours by stage, age of diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1985–2004**

		All years 1985–2004			1985–1989		
Stage	Age group at time of diagnosis	N	Overall survival	%	N	Overall survival	%
All	Overall	**421**	**272**	**64.61**	**87**	**51**	**58.62**
	0–28 days	21	17	80.95	4	3	75.00
	0–12 months	151	139	92.05	34	29	85.29
	12–18 months	41	25	60.98	10	6	60.00
	18+ months	229	108	47.16	43	16	37.21
1	Overall	**53**	**52**	**98.11**	**7**	**7**	**100.00**
	0–28 days	5	5	100.00	1	1	100.00
	0–12 months	30	30	100.00	4	4	100.00
	12–18 months	4	4	100.00	0	0	—
	18+ months	19	18	94.74	3	3	100.00
2	Overall	**62**	**61**	**98.39**	**12**	**12**	**100.00**
	0–28 days	2	2	100.00	0	0	—
	0–12 months	35	35	100.00	8	8	100.00
	12–18 months	5	5	100.00	1	1	100.00
	18+ months	22	21	95.45	3	3	100.00
3	Overall	**84**	**68**	**80.95**	**20**	**15**	**75.00**
	0–28 days	3	3	100.00	0	0	—
	0–12 months	37	35	94.59	8	7	87.50
	12–18 months	11	8	72.73	4	4	100.00
	18+ months	36	25	69.44	8	4	50.00
4	Overall	**190**	**64**	**33.68**	**40**	**11**	**27.50**
	0–28 days	3	1	33.33	0	0	—
	0–12 months	23	17	73.91	7	5	71.43
	12–18 months	19	7	36.84	5	1	20.00
	18+ months	148	40	27.03	28	5	17.86
4s	Overall	**27**	**23**	**85.19**	**7**	**5**	**71.43**
	0–28 days	8	6	75.00	3	2	66.67
	0–12 months	26	22	84.62	7	5	71.43
	12–18 months	1	1	100.00	0	0	—
	18+ months	0	0	—	0	0	—
Missing stage	Overall	**5**	**4**	**80.00**	**1**	**1**	**100.00**

	1990–1994			1995–1999			2000–2004			1995–2004		
	N	Overall survival	%	N	Overall survival	%	N	Overall survival	%	N	Overall survival	%
Total	**115**	**72**	**62.61**	**117**	**74**	**63.25**	**102**	**75**	**73.53**	**219**	**149**	**68.04**
Eye	5	4	80.00	3	3	100.00	9	7	77.78	12	10	83.33
Head and neck	38	36	94.74	38	37	97.37	41	37	90.24	79	74	93.67
Thorax	18	12	66.67	5	4	80.00	8	3	37.50	13	7	53.85
Abdomen	59	24	40.68	74	33	44.59	53	35	66.04	127	68	53.54
Stage 1	**12**	**12**	**100.00**	**15**	**14**	**93.33**	**19**	**19**	**100.00**	**34**	**33**	**97.06**
Eye	0	0	—	0	0	—	4	4	100.00	4	4	100.00
Head and neck	3	3	100.00	10	10	100.00	13	13	100.00	23	23	100.00
Thorax	3	3	100.00	0	0	—	1	1	100.00	1	1	100.00
Abdomen	6	6	100.00	5	4	80.00	5	5	100.00	10	9	90.00
Stage 2	**19**	**18**	**94.74**	**17**	**17**	**100.00**	**14**	**14**	**100.00**	**31**	**31**	**100.00**
Eye	1	1	100.00	0	0	—	1	1	100.00	1	1	100.00
Head and neck	11	11	100.00	9	9	100.00	7	7	100.00	16	16	100.00
Thorax	3	3	100.00	1	1	100.00	0	0	—	1	1	100.00
Abdomen	5	4	80.00	7	7	100.00	7	7	100.00	14	14	100.00
Stage 3	**25**	**19**	**76.00**	**22**	**20**	**90.91**	**17**	**14**	**82.35**	**39**	**34**	**87.18**
Eye	0	0	—	2	2	100.00	1	1	100.00	3	3	100.00
Head and neck	10	10	100.00	11	11	100.00	8	7	87.50	19	18	94.74
Thorax	5	3	60.00				2	1	50.00	2	1	50.00
Abdomen	10	6	60.00	11	9	81.82	7	6	85.71	18	15	83.33
Stage 4	**46**	**11**	**23.91**	**61**	**21**	**34.43**	**43**	**21**	**48.84**	**104**	**42**	**40.38**
Eye	1	0	0	1	1	100.00	1	0	0	2	1	50.00
Head and neck	4	2	50.00	7	6	85.71	5	4	80.00	12	10	83.33
Thorax	5	2	40.00	4	3	75.00	5	1	20.00	9	4	44.44
Abdomen	37	7	18.92	50	12	24.00	33	16	48.48	83	28	33.73
Stage 4S	**11**	**11**	**100.00**	**1**	**1**	**100.00**	**8**	**6**	**75.00**	**9**	**7**	**77.78**
Eye	3	3	100.00	0	0	—	2	1	50.00	2	1	50.00
Head and neck	10	10	100.00	1	1	100.00	8	6	75.00	9	7	77.78
Thorax	1	1	100.00	0	0	—	0	0	—	0	0	—
Abdomen	0	0	—	0	0	—	0	0	—	0	0	—
Unstaged	**2**	**1**	**50.00**	**1**	**1**	**100.00**	**1**	**1**	**100.00**	**2**	**2**	**100.00**

Exhibit 9.2

Overall survival

Survival data are available for all periods from 1985 to 2004. The cohort comprised 421 patients whose 5 year overall survival during that period was 64.6%. There is evidence of improved outcome with time. The 5 year overall survival for 2000–2004 was 73.5%, compared with 58.6% in the earliest period (1985–1989).

Localized disease

Similar to those in published international cohorts, patients recorded in POGONIS with INSS stage 1 or 2 disease had excellent overall survival in all time periods, with only a single death in each stage group reported for the entire review period.[14,26] This excellent survival rate justifies the development of trials aimed at decreasing treatment for this group to lessen exposure to chemotherapies and surgery and thus decrease the incidence of acute and long term effects.

Metastatic disease

The most striking improvements in outcome were observed for stage 4 patients. The 5 year overall survival for stage 4 patients improved almost 2-fold, from 27.5% in 1985–1999 to 48.8% in 2000–2004. The improvement in survival was most pronounced in stage 4 patients older than 18 months (overall survival 17.9% vs. 48.5%).

Age and biomarkers in metastatic neuroblastoma

Age is a well-known prognostic factor in neuroblastoma. Specifically, the outcome for patients older than 18 months is significantly worse than that for those younger than 18 months.[65] The overall survival for Ontario patients over 18 months improved by 77.5% in the most recent period compared with 1985–1989. The use of myeloablative chemotherapy with autologous BMT and more recently stem cell transplant became the standard of care starting in the latter part of the 1990s[45,46] and thus we hypothesize that this improvement in survival is due to adoption of protocols in Ontario that include consolidation with bone marrow or stem cell transplant. In support of this hypothesis, the percentage of stage 4 patients older than 18 months who underwent transplant in Ontario increased from 78.0% (1995–1999) to 90.9% (2000–2004) (data not shown).

Although data on the use of BMT are not available before 1995, the majority of protocols did not include BMT as the standard approach in the early 1990s. The most recent COG study for high risk neuroblastoma conducted between 2001 and 2006 included 6 cycles of induction chemotherapy, surgery and autologous stem cell transplant following high dose chemotherapy with cyclophosphamide, etoposide and melphalan. The 5 year overall survival and EFS were 50% and 38%, respectively.[45]

The 5 year overall survival for stage 4 patients older than 18 months in Ontario in 2000–2004 was similar to the 50% survival rate for the COG study (study A3973) that was open during this period.[45] That study enrolled patients who met criteria for high risk disease (other than stage 4 patients who were over 18 months); thus, 14% of patients were under 18 months owing to the presence of unfavourable biology (usually *MYCN* amplification) and 14% were stage 3 (because of *MYCN* amplification, unfavourable histology or both). Since biomarker data are not available we can compare only the entire stage 4 population over age 18 months in Ontario with the overall A3973 cohort of 495 patients.

Historically all patients with stage 4 disease were treated as high risk and received similar treatment. Data from the late 1990s demonstrated that infants (under 12 months) with stage 4 disease in the absence of *MYCN* amplification had a significantly better outcome and thus, most centres in North America (including Ontario) have been treating these patients with intermediate risk protocols, which include moderate dose chemotherapy and no stem cell transplant. In a CCG study, the EFS for stage 4 infants with *MYCN* amplification treated with intermediate risk therapy was 10%, compared with 93% for those without *MYCN* amplification. In Ontario the 5 year overall survival for stage 4 patients younger than 12 months was above 80% for the period 1995–2004. This suggests that the majority of these patients had favourable biology and specifically were less likely to have had tumours with *MYCN* amplification. COG study A3961, which enrolled patients with intermediate risk neuroblastoma between 1997 and 2005, included 176 infants with stage 4 non-*MYCN* amplification disease. These patients received moderate dose intermediate risk therapy; their EFS and overall survival were 81% and 93%, respectively.[43]

EXHIBIT 9.3: **5 year event free survival with primary neuroblastoma tumours by stage, age at diagnosis and year of diagnosis, age 0–14 years, in Ontario, 1995–2004**

		All years: 1995–2004			1995–1999			2000–2004		
Stage	Age group at time of diagnosis	N	Event free survival	%	N	Event free survival	%	N	Event free survival	%
All	**Overall**	**219**	**138**	**63.01**	**117**	**68**	**58.12**	**102**	**70**	**68.63**
	0–28 days	12	9	75.00	3	3	100.00	9	6	66.67
	0–12 months	79	69	87.34	38	34	89.47	41	35	85.37
	12–18 months	13	7	53.85	5	4	80.00	8	3	37.50
	18+ months	127	62	48.82	74	30	40.54	53	32	60.38
1	**Overall**	**34**	**32**	**94.12**	**15**	**14**	**93.33**	**19**	**18**	**94.74**
	0–28 days	4	3	75.00	0	0	0	4	3	75.00
	0–12 months	23	22	95.65	10	10	100.00	13	12	92.31
	12–18 months	1	1	100.00	0	0	—	1	1	100.00
	18+ months	10	9	90.00	5	4	80.00	5	5	100.00
2	**Overall**	**31**	**30**	**96.77**	**17**	**17**	**100.00**	**14**	**13**	**92.86**
	0–28 days	1	1	100.00	0	0	0	1	1	100.00
	0–12 months	16	14	87.50	9	9	100.00	7	6	85.71
	12–18 months	1	1	100.00	1	1	100.00	—	—	—
	18+ months	14	14	100.00	7	7	100.00	7	7	100.00
3	**Overall**	**39**	**31**	**79.49**	**22**	**17**	**77.27**	**17**	**14**	**82.35**
	0–28 days	3	3	100.00	2	2	100.00	1	1	100.00
	0–12 months	19	16	84.21	11	9	81.82	8	7	87.50
	12–18 months	2	1	50.00	0	0	—	2	1	50.00
	18+ months	18	14	77.78	11	8	72.73	7	6	85.71
4	**Overall**	**104**	**37**	**35.58**	**61**	**19**	**31.15**	**43**	**18**	**41.86**
	0–28 days	2	1	50.00	1	1	100.00	1	—	0.00
	0–12 months	12	10	83.33	7	6	85.71	5	4	80.00
	12–18 months	9	4	44.44	4	3	75.00	5	1	20.00
	18+ months	83	23	27.71	50	10	20.00	33	13	39.39
4s	**Overall**	**9**	**7**	**77.78**	**1**	**1**	**100.00**	**8**	**6**	**75.00**
	0–28 days	2	1	50.00	0	0	—	2	1	50.00
	0–12 months	9	7	77.78	1	1	100.00	8	6	75.00
	12–18 months	0	0	—	0	0	—	0	0	—
	18+ months	0	0	—	0	0	—	0	0	—
Missing stage	**Overall**	**2**	**2**	**100.00**	**1**	**1**	**100.00**	**1**	**1**	**100.00**

Exhibit 9.3

The POGONIS data for the most recent 10-year period (1995–2004) allow for the calculation of EFS in addition to overall survival. The 5 year EFS for all patients in that period was 63.0%, with superior outcomes noted in the most recent 5 year period (68.6% vs. 58.1%). The INRG database includes clinical outcome, stage, age and biomarker data for 8,800 patients diagnosed with neuroblastoma between 1990 and 2002 from Europe, North America and Japan.[66] The 5 year EFS and overall survival in the INRG cohort were 63% and 70%, respectively, which is very similar to the POGONIS data for this period. The majority of events (55) were recurrences. The Italian Neuroblastoma Registry reported that only 10% of deaths were due to toxicity, surgical complications or second malignancies.[63]

Relapsed disease

Relapse data have been collected in POGONIS for the 2 most recent 5 year periods (1995–1999 and 2000–2004). As expected based on the improved survival rates, the relapse rates were lower in 2000–2004 than in 1995–1999. Of 118 patients, 48 (40.6%) experienced at least one relapse of neuroblastoma in 1995–1999, compared with 27 of 104 (25.9%) in 2000–2004. As expected, the majority of relapses occurred in the higher stages (3 and 4, non-4s). Stage 4 patients accounted for 83.3% of the recurrences in 1995–1999 and 77.7% in 2000–2004 (data not shown). Our data are very similar to those published by the INRG, in which 2,266 of 8,800 (25.7%) patients experienced recurrence and 72% had stage 4 disease.[57] Similarly, in the Italian Registry 40% of 2,216 patients developed a relapse or progression.[64] The patients studied in these publications, much like those covered by the POGONIS data, were treated pre-2005 and thus the majority would have been unlikely to have received immunotherapy. The addition of anti-GD2 antibody (Ch14.18), interleukin-2 and GM-CSF in the post transplant setting is likely to improve the relapse free survival of high risk patients.[48]

EXHIBIT 9.4a: **1 year overall survival after relapse**

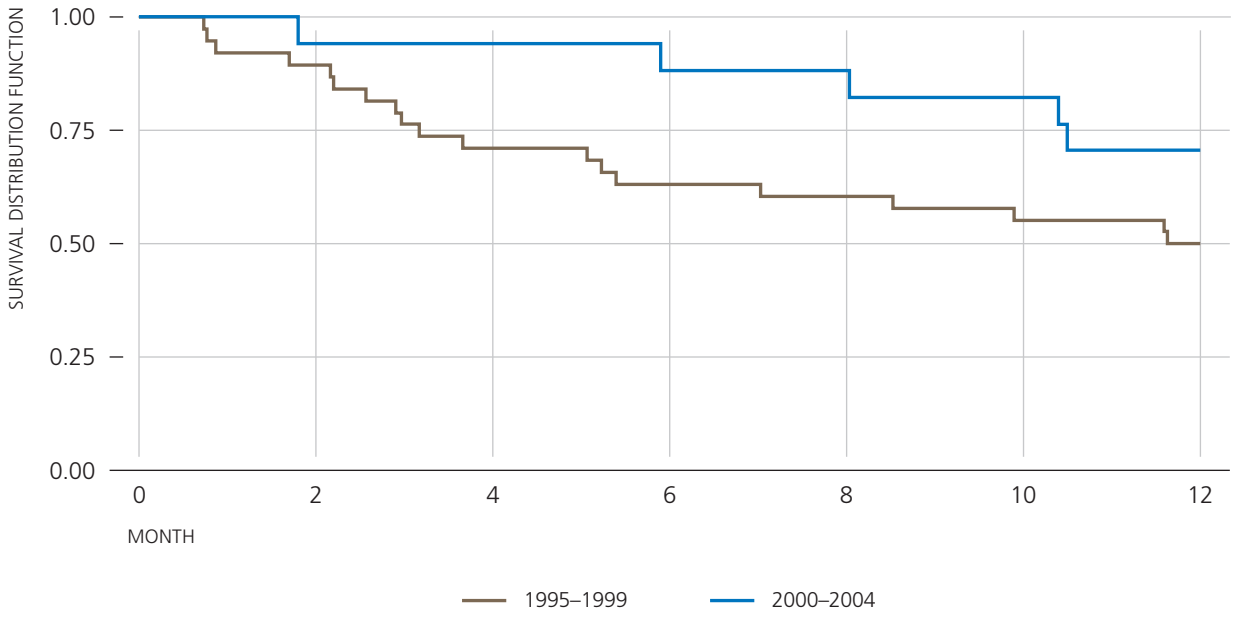

EXHIBIT 9.4b: **3 year overall survival after relapse**

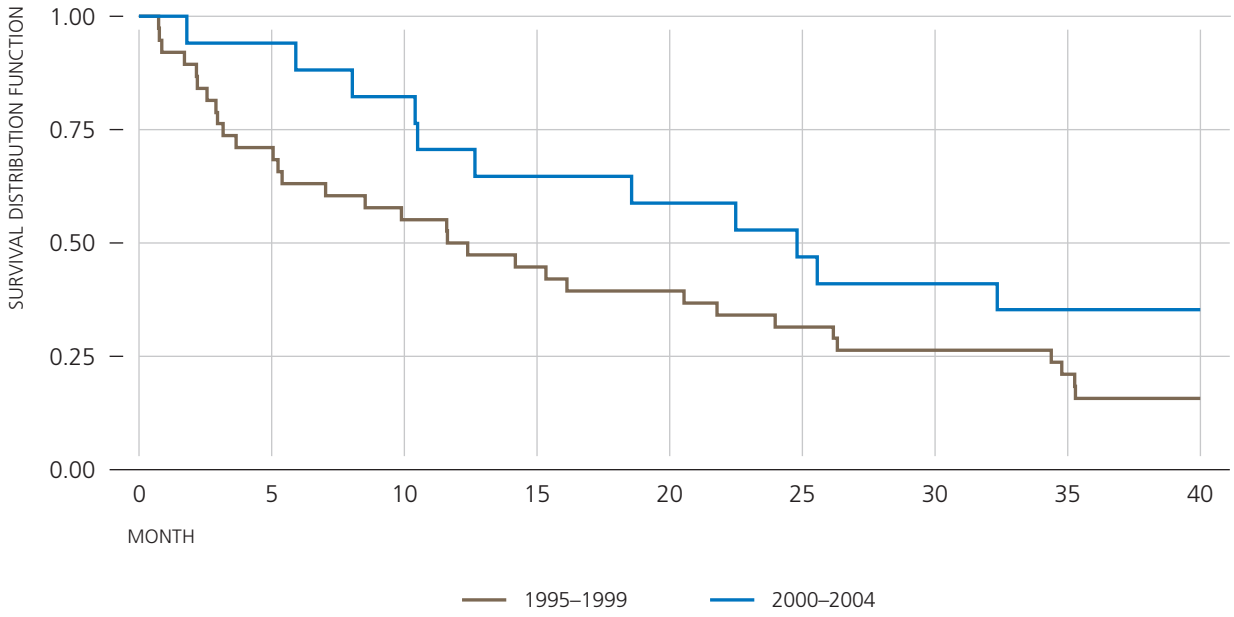

EXHIBIT 9.4c: **5 year overall survival after relapse**

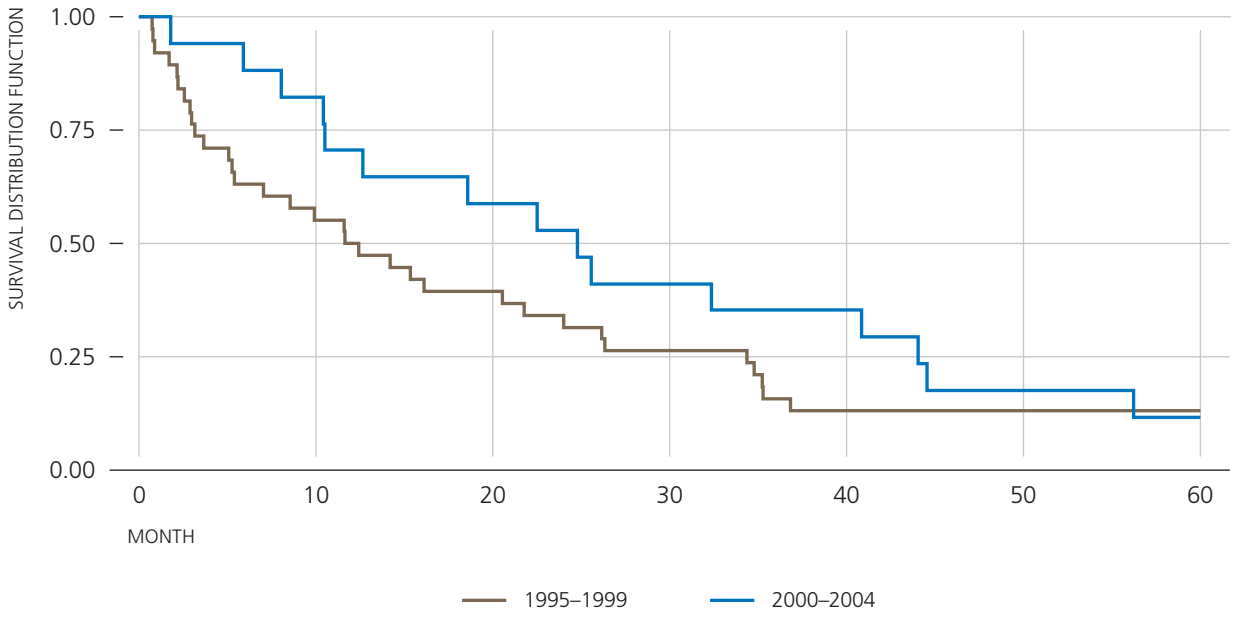

Exhibit 9.4a–9.4c

Survival post relapse

There were fewer relapses in 2000–2004 than in 1995–1999 (data not shown). For those patients who experienced a relapse, the overall survival at 1, 3 and 5 years post relapse was much higher in the 2000–2004 period, suggesting improvements in salvage therapy and illustrating that a significant portion of relapsed patients live for many years following relapse. This supposition is supported by the data from INRG, which show that patients with relapsed neuroblastoma had a 5 year overall survival of 20%, though outcome was significantly worse for patients who had initially presented with metastatic disease.[57] Increasing use of targeted inhibitors and high dose MIBG therapy may result in improved salvage rates and prolonged survival for patients with recurrent neuroblastoma.

References

1 Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, et al. (eds). SEER cancer statistics review, 1975-2006. Bathesda (MD): National Cancer Institute; 2009.

2 Gao RN, Levy IG, Woods WG, Coombs BA, Gaudette LA, Hill GB. Incidence and mortality of neuroblastoma in Canada compared with other childhood cancers. Cancer Causes Control. 1997 Sep;8(5):745-54.

3 Heck JE, Ritz B, Hung RJ, Hashibe M, Boffetta P. The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol. 2009 Mar;23(2):125-43.

4 Spix C, Pastore G, Sankila R, Stiller CA, Steliarova-Foucher E. Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):2081-91.

5 Dubois SG, London WB, Zhang Y, Matthay KK, Monclair T, Ambros PF, et al. Lung metastases in neuroblastoma at initial diagnosis: a report from the International Neuroblastoma Risk Group (INRG) project. Pediatr Blood Cancer. 2008 Nov;51(5):589-92.

6 Kramer K, Kushner BH, Modak S, Pandit-Taskar N, Smith-Jones P, Zanzonico P, et al. Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma. J Neurooncol. 2010 May;97(3):409-18.

7 Matthay KK, Brisse H, Couanet D, Couturier J, Bénard J, Mosseri V, et al. Central nervous system metastases in neuroblastoma: radiologic, clinical, and biologic features in 23 patients. Cancer. 2003 Jul;98(1):155-65.

8 LaBrosse EH, Com-Nougué C, Zucker JM, Comoy E, Bohuon C, Lemerle J, Schweisguth O. Urinary excretion of 3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxyphenylacetic acid by 288 patients with neuroblastoma and related neural crest tumors. Cancer Res. 1980 Jun;40(6):1995-2001.

9 Graham-Pole J, Salmi T, Anton AH, Abramowsky C, Gross S. Tumor and urine catecholamines (CATs) in neurogenic tumors. Correlations with other prognostic factors and survival. Cancer. 1983 Mar;51(5):834-9.

10 Tuchman M, Morris CL, Ramnaraine ML, Bowers LD, Krivit W. Value of random urinary homovanillic acid and vanillylmandelic acid levels in the diagnosis and management of patients with neuroblastoma: comparison with 24-hour urine collections. Pediatrics. 1985 Feb;75(2):324-8.

11 Ady N, Zucker JM, Asselain B, Edeline V, Bonnin F, Michon J, et al. A new 123I-MIBG whole body scan scoring method—application to the prediction of the response of metastases to induction chemotherapy in stage IV neuroblastoma. Eur J Cancer. 1995;31A(2):256-61.

12 Lopci E, Piccardo A, Nanni C, Altrinetti V, Garaventa A, Pession A, et al. 18F-DOPA PET/CT in neuroblastoma: comparison of conventional imaging with CT/MR. Clin Nucl Med. 2012 Apr;37(4):e73-8.

13 Piccardo A, Lopci E, Conte M, Garaventa A, Foppiani L, Altrinetti V, et al. Comparison of 18F-dopa PET/CT and 123I-MIBG scintigraphy in stage 3 and 4 neuroblastoma: a pilot study. Eur J Nucl Med Mol Imaging. 2012 Jan;39(1):57-71.

14 Strother DR, London WB, Schmidt ML, Brodeur GM, Shimada H, Thorner P, et al. Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: results of Children's Oncology Group study P9641. J Clin Oncol. 2012 May;30(15):1842-8.

15 Cecchetto G, Mosseri V, De Bernardi B, Helardot P, Monclair T, Costa E, et al. Surgical risk factors in primary surgery for localized neuroblastoma: the LNESG1 study of the European International Society of Pediatric Oncology Neuroblastoma Group. J Clin Oncol. 2005 Nov;23(33):8483-9.

16 Simon T, Hero B, Benz-Bohm G, von Schweinitz D, Berthold F. Review of image defined risk factors in localized neuroblastoma patients: results of the GPOH NB97 trial. Pediatr Blood Cancer. 2008 May;50(5):965-9.

17 Gupta A, Kumar A, Walters S, Chait P, Irwin MS, Gerstle JT. Analysis of needle versus open biopsy for the diagnosis of advanced stage pediatric neuroblastoma. Pediatr Blood Cancer. 2006 Dec;47(7):875-9.

18 Brodeur GM, Seeger RC, Barrett A, Berthold F, Castleberry RP, D'Angio G, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. J Clin Oncol. 1988 Dec;6(12):1874-81.

19 Breslow N, McCann B. Statistical estimation of prognosis for children with neuroblastoma. Cancer Res. 1971 Dec;31(12):2098-103.

20 George RE, London WB, Cohn SL, Maris JM, Kretschmar C, Diller L, et al. Hyperdiploidy plus nonamplified MYCN confers a favorable prognosis in children 12 to 18 months old with disseminated neuroblastoma: a Pediatric Oncology Group study. J Clin Oncol. 2005 Sep;23(27):6466-73.

21 Schmidt ML, Lal A, Seeger RC, Maris JM, Shimada H, O'Leary M, et al. Favorable prognosis for patients 12 to 18 months of age with stage 4 nonamplified MYCN neuroblastoma: a Children's Cancer Group Study. J Clin Oncol. 2005 Sep;23(27):6474-80.

22 London WB, Castleberry RP, Matthay KK, Look AT, Seeger RC, Shimada H, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. J Clin Oncol. 2005 Sep;23(27):6459-65.

23 Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol. 1993 Aug;11(8):1466-77.

24 Nickerson HJ, Matthay KK, Seeger RC, Brodeur GM, Shimada H, Perez C, et al. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: a Children's Cancer Group study. J Clin Oncol. 2000 Feb;18(3):477-86.

25 Taggart DR, London WB, Schmidt ML, DuBois SG, Monclair TF, Nakagawara A, et al. Prognostic value of the stage 4S metastatic pattern and tumor biology in patients with metastatic neuroblastoma diagnosed between birth and 18 months of age. J Clin Oncol. 2011 Nov;29(33):4358-64.

26 Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol. 2009 Jan;27(2):298-303.

27 Shimada H, Chatten J, Newton WA Jr, Sachs N, Hamoudi AB, Chiba T, et al. Histopathologic prognostic factors in neuroblastic tumors: definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblastomas. J Natl Cancer Inst. 1984 Aug;73(2):405-16.

28 Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B, et al. The International Neuroblastoma Pathology Classification (the Shimada system). Cancer. 1999 Jul;86(2):364-72.

29 Shimada H, Umehara S, Monobe Y, Hachitanda Y, Nakagawa A, Goto S, et al. International neuroblastoma pathology classification for prognostic evaluation of patients with peripheral neuroblastic tumors: a report from the Children's Cancer Group. Cancer. 2001 Nov;92(9):2451-61.

30 Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY, Hammond D. Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. N Engl J Med. 1985 Oct;313(18):1111-6.

31 Schmidt ML, Lukens JN, Seeger RC, Brodeur GM, Shimada H, Gerbing RB, et al. Biologic factors determine prognosis in infants with stage IV neuroblastoma: a prospective Children's Cancer Group study. J Clin Oncol. 2000 Mar;18(6):1260-8.

32 Bagatell R, Beck-Popovic M, London WB, Zhang Y, Pearson AD, Matthay KK, et al. Significance of MYCN amplification in international neuroblastoma staging system stage 1 and 2 neuroblastoma: a report from the International Neuroblastoma Risk Group database. J Clin Oncol. 2009 Jan;27(3):365-70.

33 Tonini GP, Boni L, Pession A, Rogers D, Iolascon A, Basso G, et al. MYCN oncogene amplification in neuroblastoma is associated with worse prognosis, except in stage 4s: the Italian experience with 295 children. J Clin Oncol. 1997 Jan;15(1):85-93.

34 Katzenstein HM, Bowman LC, Brodeur GM, Thorner PS, Joshi VV, Smith EI, et al. Prognostic significance of age, MYCN oncogene amplification, tumor cell ploidy, and histology in 110 infants with stage D(S) neuroblastoma: the Pediatric Oncology Group experience—a Pediatric Oncology Group study. J Clin Oncol. 1998 Jun;16(6):2007-17.

35 Look AT, Hayes FA, Nitschke R, McWilliams NB, Green AA. Cellular DNA content as a predictor of response to chemotherapy in infants with unresectable neuroblastoma. N Engl J Med. 1984 Jul;311(4):231-5.

36 Schleiermacher G, Michon J, Ribeiro A, Pierron G, Mosseri V, Rubie H, et al. Segmental chromosomal alterations lead to a higher risk of relapse in infants with MYCN-non-amplified localised unresectable/disseminated neuroblastoma (a SIOPEN collaborative study). Br J Cancer. 2011 Dec;105(12):1940-8.

37 Oberthuer A, Hero B, Berthold F, Juraeva D, Faldum A, Kahlert Y, et al. Prognostic impact of gene expression-based classification for neuroblastoma. J Clin Oncol. 2010 Jul;28(21):3506-15.

38 Oue T, Inoue M, Yoneda A, Kubota A, Okuyama H, Kawahara H, et al. Profile of neuroblastoma detected by mass screening, resected after observation without treatment: results of the Wait and See pilot study. J Pediatr Surg. 2005 Feb;40(2):359-63.

39 Fritsch P, Kerbl R, Lackner H, Urban C. "Wait and see" strategy in localized neuroblastoma in infants: an option not only for cases detected by mass screening. Pediatr Blood Cancer., 2004 Nov;43(6):679-82.

40 Nuchtern JG, London WB, Barnewolt CE, Naranjo A, McGrady PW, Geiger JD, et al. A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: a Children's Oncology Group study. Ann Surg. 2012 Oct;256(4):573-80.

41 Matthay KK, Perez C, Seeger RC, Brodeur GM, Shimada H, Atkinson JB, et al. Successful treatment of stage III neuroblastoma based on prospective biologic staging: a Children's Cancer Group study. J Clin Oncol. 1998 Apr;16(4):1256-64.

42 Bagatell R, Rumcheva P, London WB, Cohn SL, Look AT, Brodeur GM, et al. Outcomes of children with intermediate-risk neuroblastoma after treatment stratified by MYCN status and tumor cell ploidy. J Clin Oncol. 2005 Dec;23(34):8819-27.

43 Baker DL, Schmidt ML, Cohn SL, Maris JM, London WB, Buxton A, et al. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med. 2010 Sep;363(14):1313-23.

44 Berthold F, Boos J, Burdach S, Erttmann R, Henze G, Hermann J, et al. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial. Lancet Oncol. 2005 Sep;6(9):649-58.

45 Kreissman SG, Seeger RC, Matthay KK, London WB, Sposto R, Grupp SA, et al. Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): a randomised phase 3 trial. Lancet Oncol. 2013 Sep;14(10):999-1008.

46 Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a Children's Oncology Group study. J Clin Oncol. 2009 Mar;27(7): 1007-13.

47 Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Engl J Med. 1999 Oct;341(16):1165-73.

48 Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep;363(14):1324-34.

49 Yalcin B, Kremer LC, Caron HN, van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev. 2013 Aug;8: p. CD006301.

50 Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Klingebiel T, Berthold F. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer. 2011 Jan;18(11):21.

51 Lau L, Tai D, Weitzman S, Grant R, Baruchel S, Malkin D. Factors influencing survival in children with recurrent neuroblastoma. J Pediatr Hematol Oncol. 2004 Apr;26(4):227-32.

52 Garaventa A, Parodi S, De Bernardi B, Dau D, Manzitti C, Conte M, et al. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer. 2009 Nov;45(16):2835-42.

53 Dubois SG, Chesler L, Groshen S, Hawkins R, Goodarzian F, Shimada H, et al. Phase I study of vincristine, irinotecan, and 131I-metaiodobenzylguanidine for patients with relapsed or refractory neuroblastoma: a New Approaches to Neuroblastoma Therapy Trial. Clin Cancer Res. 2012 May;18(9):2679-86.

54 London WB, Frantz CN, Campbell LA, Seeger RC, Brumback BA, Cohn SL, et al. Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. J Clin Oncol. 2010 Aug;28(24):3808-15.

55 Bagatell R, London WB, Wagner LM, Voss SD, Stewart CF, Maris JM, et al. Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: a Children's Oncology Group study. J Clin Oncol. 2011 Jan;29(2):208-13.

56 Kushner BH, Kramer K, Modak S, Cheung NK. Irinotecan plus temozolomide for relapsed or refractory neuroblastoma. J Clin Oncol. 2006 Nov;24(33):5271-6.

57 London WB, Castel V, Monclair T, Ambros PF, Pearson AD, Cohn SL, et al. Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group project. J Clin Oncol. 2011 Aug;29(24):3286-92.

58 Morgenstern DA, Baruchel S, Irwin MS. Current and future strategies for relapsed neuroblastoma: challenges on the road to precision therapy. J Pediatr Hematol Oncol. 2013 Jul;35(5):337-47.

59 Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, et al. Phase I dose escalation of 131I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. J Clin Oncol. 1998 Jan;16(1):229-36.

60 Asgharzadeh S, Pique-Regi R, Sposto R, Wang H, Yang Y, Shimada H, et al. Prognostic significance of gene expression profiles of metastatic neuroblastomas lacking MYCN gene amplification. J Natl Cancer Inst. 2006 Sep;98(17):1193-203.

61 Asgharzadeh S, Salo JA, Ji L, Oberthuer A, Fischer M, Berthold F, et al. Clinical significance of tumor-associated inflammatory cells in metastatic neuroblastoma. J Clin Oncol. 2012 Oct;30(28):3525-32.

62 Ross CJ, Katzov-Eckert H, Dubé MP, Brooks B, Rassekh SR, Barhdadi A, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet. 2009 Dec;41(12):1345-9.

63 Haupt R, Garaventa A, Gambini C, Parodi S, Cangemi G, Casale F, et al. Improved survival of children with neuroblastoma between 1979 and 2005: a report of the Italian Neuroblastoma Registry. J Clin Oncol. 2010 May;28(14):2331-8.

64 Park JR, Bagatell R, London WB, Maris JM, Cohn SL, Matthay KK, et al. Children's Oncology Group's 2013 blueprint for research: neuroblastoma. Pediatr Blood Cancer. 2013 Jun;60(6):985-93.

65 London WB, Boni L, Simon T, Berthold F, Twist C, Schmidt ML, et al. The role of age in neuroblastoma risk stratification: the German, Italian, and Children's Oncology Group perspectives. Cancer Lett. 2005 Oct;228(1-2):257-66.

66 Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009 Jan;27(2):289-97.

67 Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. Hematol Oncol Clin North Am. 2010 Feb;24(1):65-86.

Appendices

APPENDIX 1: **International Neuroblastoma Staging System (INSS)[23]**

Stage 1	Localized tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive).
Stage 2a	Localized tumour with incomplete gross resection; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically.
Stage 2b	Localized tumour with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumour; enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement, or localized unilateral tumour with contralateral regional lymph node involvement, or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4s).
Stage 4s	Localized primary tumour (as defined for stage 1, 2a or 2b) with dissemination limited to skin, liver and/or bone marrow (limited to infants < 1 year of age).

APPENDIX 2: **Children's Oncology Group Risk Group and Protocol Assignment Schema[67]**

INSS stage	Age	MYCN status	Shimada histology	DNA ploidy	Risk group
1	0–21 yr	Any[a]	Any[b]	Any[c]	Low
2A/2B	<365 d	Any[a]	Any[b]	Any[c]	Low
	>365 d–21 yr	Non-amp	Any[b]	—	Low
	>365 d–21 yr	Amp	Fav	—	Low
	>365 d–21 yr	Amp	Unfav	—	High
3	<365 d	Non-amp	Any[b]	Any[c]	Intermediate
	<365 d	Amp	Any[b]	Any[c]	High
	>365 d–21 yr	Non-amp	Fav	—	Intermediate
	>365 d–21 yr	Non-amp	Unfav	—	High
	>365 d–21 yr	Amp	Any	—	High
4	<365 d	Non-amp	Any[b]	Any[c]	Intermediate
	<365 d	Amp	Any	Any	High
	>365 d–21 yr	Any	Any	—	High
4S	<365 d	Non-amp	Fav	>1	Low
	<365 d	Non-amp	Any[b]	=1	Intermediate
	<365 d	Non-amp	Unfav	Any[c]	Intermediate
	<365 d	Amp	Any	Any	High

Biology defined by MYCN status: amplified (Amp) vs. non-amplified (non-amp); Shimada histopathology: favourable (Fav) vs. unfavourable (Unfav); DNA ploidy: DNA index (DI) >1 or = 1; hypodiploid tumours (with DI <1) will be treated as a tumour with a DI >1.
[a]Must be "not amplified" or "amplified" cannot be unsatisfactory.
[b]Must be "favourable" or "unfavourable" cannot be inadequate.
[c]Must be >1 or = 1 (for patients <365 d) cannot be unsatisfactory.

Courtesy of Children's Oncology Group

Photo by Tynan Studio

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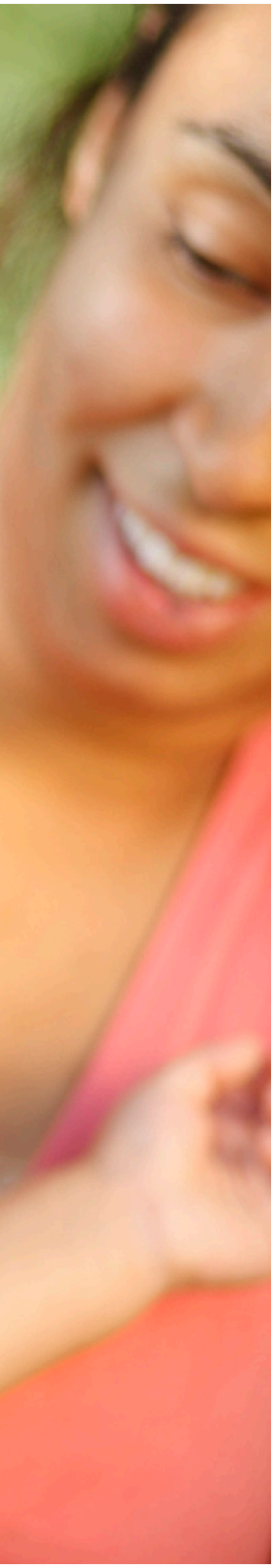

10

Renal Tumours

Executive Summary

This chapter provides population-based information regarding the incidence of pediatric renal tumours, frequency of relapse, probability of long term survival and treatment modalities used among children aged 0–14 years resident in Ontario, diagnosed between 1985 and 2004.

Key Findings

Nephroblastoma, defined for the purposes of this Atlas according to the International Classification of Childhood Cancer, third edition (ICCC-3), was the most common form of renal tumour in children (94.7%), followed by renal carcinoma (4.7%) and unspecified malignant renal tumours (0.6%). Nephroblastoma as defined by ICCC-3 includes Wilms tumour, rhabdoid tumour and clear cell sarcoma. Wilms tumour was the most common type of nephroblastoma, comprising 89.4% of all renal tumours. The incidence of renal tumours was higher among females (55.6% for nephroblastoma, 57.0% for Wilms tumour and 58.8% for renal carcinoma).

The age standardized incidence rate (ASIR) for all renal tumours was 7.9 per 1 million population per year (7.5 for nephroblastoma, 7.1 for Wilms tumour and 0.4 for renal carcinoma). The age standardized mortality rate (ASMR) for all renal tumours was 0.89 deaths per 1 million population per year (0.82 for nephroblastoma, 0.76 for Wilms tumour and 0.07 for renal carcinoma). ASMRs for all renal tumours, nephroblastoma and Wilms tumour were lowest during the most recent 5 year reporting period (2000–2004).

For all children with Wilms tumours, the 5 and 10 year overall survival proportions (OSPs) were 0.90 and 0.89 for the 1985–2004 reporting period and 0.90 and 0.88 for the 1995–2004 period. For all children with Wilms tumours, from 1995 to 2004, the 5 and 10 year event free survival proportions (EFSPs) were 0.78 and 0.75. OSP improved from 0.86 to 0.92 and EFSP from 0.74 to 0.82 in the 1995–1999 and 2000–2004 periods, respectively.

For the 1995–2004 period, stages 1 through 5 Wilms tumour had a 5 year OSP of 0.90, 0.94, 0.97, 0.78 and 0.84, respectively, better for stage 2 and 3 disease than for stage 1 disease. Five year EFSPs for stages 1 through 5 were 0.79, 0.75, 0.86, 0.76 and 0.83, respectively. There was no change in the 5 and 10 year OSP or EFSP for any stage except stage 3. For stage 3 patients, there was a decrease in the 10 year EFSP (0.75) compared with the 5 year EFSP (0.86), with a parallel reduction in the 10 year OSP (0.90) compared with the 5 year OSP (0.97).

For Wilms tumours diagnosed from 1995 to 2004, 5 year OSP was highest in the 1–3 year age group at 0.97, followed by the 4–7 year group at 0.88 and the less than 1 year group at 0.83. The 8–14 year group had the worst OSP at 0.64. Five year EFSP was highest for Wilms tumours in the 1–3 year group at 0.83, followed by the 4–7 year group at 0.78 and the 8–14 year group at 0.73. The less than 1 year group had the worst EFSP at 0.63.

Of patients with Wilms tumour diagnosed between 1995 and 2004, 21.9% relapsed. For the relapsed group, 5 year OSP from the time of relapse was 0.56 for all stages combined, 0.68 for early stage disease (stages 1 and 2 combined), 0.83 for advanced stage non-metastatic disease (stage 3) and 0.17 for metastatic disease (stage 4). Five year OSP from the time of relapse was best for the 1–3 year age group (0.83), followed by the less than 1 year group (0.53) and the 4–7 year group (0.49), with none of the 4 patients in the 8–14 year group still alive 3 years from relapse.

The majority of patients with Wilms tumour received immediate surgery (within 6 weeks of diagnosis), with a larger number receiving immediate surgery in the most recent reporting period (86.4% in 2000–2004) than in the previous 5 years (73.9% in 1995–1999). For the 1995–2004 period, half of all patients with an initial diagnosis of Wilms tumour were treated with a combination of surgery and chemotherapy only; an additional 45.7% received a combination of surgery, chemotherapy and radiation and 4.0% were treated with surgery only.

Introduction

In Canada, renal tumours account for 5.1% of all malignancies in children up to 14 years of age, inclusive, with an ASIR of 8.1 per 1 million population per year and an ASMR of 1.2 deaths per 1 million per year.[1]

In children younger than 15 years, nephroblastoma accounts for 97.3% and renal cell carcinoma (RCC) for 2.6% of all renal tumours.[2] Within the nephroblastoma group, Wilms tumour accounts for the vast majority of tumours, with clear cell sarcoma of the kidney (CCSK) and rhabdoid tumours comprising 1.6 % and 1.0% of nephroblastomas, respectively.[2] Despite their relatively low prevalence, rhabdoid tumours account for a disproportionately high number of relapses and deaths.

Wilms tumour is diagnosed predominantly in children less than 5 years of age, with a mean age of 41.5 months for males and 46.9 months for females with unilateral disease, and 29.5 months for males and 32.6 months for females with bilateral disease. The male:female ratio is 0.92:1.00 for unilateral and 0.60:1.00 for bilateral disease.[3] In a small percentage of patients, Wilms tumour is associated with other congenital abnormalities and specific syndromes.

CCSK is also a disease of young children. The mean age of diagnosis was 36 months in the National Wilms Tumour Study Group trials 1–4, with a male:female ratio of 2:1.[4] Rhabdoid tumours are seen predominantly in infants and toddlers, with a mean age of 18 months and more than 75% of cases occurring in the first 2 years of life. The male:female ratio is 1.37:1.[5] In contrast, renal carcinoma occurs predominantly in older children and adolescents. In a relatively large study looking at patients younger than 16 years with RCC, the median age at diagnosis was 10.6 years, with a male:female ratio of 1:1.[6]

Prognostic factors

Since the 1980s, the 5 year survival rate for Wilms tumour has been consistently above 90%,[7] despite reductions in the length of therapy, dose of radiation, extent of fields irradiated and the percentage of patients receiving radiation therapy.[8] The main prognostic factors for Wilms tumour are the stage, age, histology and genetics of the tumour. Lower stage disease, younger age, favourable (as opposed to anaplastic) histology and absence of loss of heterozygosity at chromosomes 1p and 16q are associated with a better prognosis.[9-11] With intensification of treatment, however, even advanced stage disease with poor prognostic features is curable in the majority of patients with Wilms tumours.

Prognosis for CCSK is good, with 5 year event free and overall survival of 79% and 89%, respectively, for stages 1–4.[12] Favourable prognostic factors for CCSK are low stage, age between 2 and 4 years at diagnosis, absence of tumour necrosis and treatment with doxorubicin.[4] RCC in children differs histologically and molecularly from its adult counterpart. It has a better prognosis when the disease is localized and amenable to surgical resection but prognosis is poor in metastatic disease. Rhabdoid tumours are highly aggressive tumours that have a very poor prognosis, with advanced stage and patients less than 2 years of age having a particularly poor outcome.[13]

Genetic factors and disease mechanisms associated with childhood renal tumours

In a small percentage of patients, Wilms tumour is associated with other congenital abnormalities and specific syndromes, such as aniridia, genitourinary anomalies and mental retardation (WAGR syndrome); Denys-Drash syndrome; Beckwith-Wiedemann syndrome; sporadic hemihypertrophy and other overgrowth syndromes; and cryptorchidism and hypospadias in males. Both WAGR and Denys-Drash syndromes are associated with deletions or mutations in the *WT1* gene located on chromosome 11p13.[14–16] In about 15% of cases, Beckwith-Wiedemann syndrome is associated with abnormalities in the *WT2* gene, located on chromosome 11p15.[17,18]

Both renal and extrarenal rhabdoid tumours are associated with abnormalities in the *hSNF5/INI1* gene on chromosome 22q11.2.[19] A proportion of rhabdoid tumours are associated with a familial germline mutation or deletion in this gene.

Pediatric RCC differs from its adult counterpart.[20-22] There are three subgroups of pediatric RCC. The first group is characterized by a clear cell appearance. In this sub-group, some lesions are associated with the *TFE3* gene located at Xp11.2; these lesions constitute a distinctive subtype of RCC found in adolescents and young adults.[23-26] The second group is the classic papillary renal carcinoma (similar to adult disease) with gains in chromosome 7 and 17. The third group includes renal medullary carcinoma, which is a very aggressive malignancy associated with the sickle cell trait.[27]

Genetically linked conditions that increase the risk of RCC include von Hippel-Lindau disease, tuberous sclerosis, hereditary papillary renal carcinoma, hereditary leiomyomatosis, Birt-Hogg-Dubé syndrome, hyperparathyroidism-jaw tumour syndrome and familial papillary thyroid carcinoma. The mutation of the von Hippel-Lindau tumour suppressor gene (*VHL*) is found on chromosome 3p25-26 and the tuberous sclerosis gene is located at either chromosome 9q34 (*TSC1* gene) or chromosome 16p13.3 (*TSC2* gene).

Bilateral Wilms tumour

Bilateral Wilms tumours account for 4–5% of all Wilms tumours. They may be synchronous (occur at the same time) or metachronous (occur sequentially). In the National Wilms Tumour Study Group data from 1969–1994, 15% of patients with bilateral Wilms tumour had developed end stage renal disease at 20 years from diagnosis, compared with 1.3% of children treated for unilateral disease.[28] This finding has prompted the development of management strategies aimed at preserving renal parenchyma in these patients whenever possible.

Treatment

Given the relatively favourable prognosis for Wilms tumour, treatment strategies have focused on refining stratification based on the estimated risk of relapse, with reduction in treatment intensity wherever feasible to reduce late effects of treatment. Strategies under investigation include 1) increasing the intensity of treatment and adding radiation for patients with low stage Wilms tumour with poor prognostic features, such as anaplasia or loss of heterozygosity at 1p and 16 q, and 2) reducing treatment for Wilms tumour with favourable histology and metastatic lung disease and good response to chemotherapy (where lung radiation is omitted).

Patients with CCSK have shown improved survival with the addition of doxorubicin and radiation to surgical resection. Given the very poor prognosis of rhabdoid tumours, strategies under investigation are focused on intensifying treatment for this group of patients. For RCC, the mainstay of treatment is complete surgical resection of disease. This disease does not respond to chemotherapy or radiation. Other adjuvant treatments, such as immunotherapy and molecularly targeted treatment, have been used with limited success in advanced disease.[29]

Methods

Data collection and identification of the cohort

The Ontario cohort consists of patients diagnosed with a first primary renal malignant neoplasm, aged up to 14 years, from January 1, 1985, to December 31, 2004, inclusive, who were Ontario residents at the time of diagnosis and were treated in 1 of 5 tertiary programs in Ontario affiliated with the Pediatric Oncology Group of Ontario (POGO). The cohort was identified through the POGO Networked Information System. Data were grouped into 5 year periods of diagnosis and categorized by age and stage at diagnosis. Diagnoses were classified according to ICCC-3[30] as nephroblastoma and other nonepithelial renal tumours, renal carcinomas and unspecified malignant renal tumours.[30] Nephroblastoma includes Wilms tumour, CCSK and rhabdoid tumours. Sub-group analyses were also conducted for Wilms tumour patients. Information is provided on the types of pediatric renal tumours diagnosed, incidence, mortality and relapse rates, and treatment modalities used, both at initial diagnosis and at relapse.

Calculation of age standardized incidence and mortality rates

ASIRS and ASMRs were calculated according to the methodology described in Chapter 2 (Survival).

Calculation of observed survival proportions

Survival analyses for primary renal tumours were conducted using Brenner's period analysis methodology.[31,32] For more information regarding their survival methodology, see Chapter 2. Survival analyses for relapsed patients were conducted using the Kaplan-Meier methodology.

For OSPs, person-time was calculated in months from the date of a subject's first renal tumour diagnosis to the date of death or, if the subject survived, to December 31, 2006. OSPs were calculated for subjects who linked with the Ontario Registrar General Mortality Registry both for the entire cohort, 1985–2004 (346 of 359 patients) and for the subset of patients diagnosed between 1995 and 2004 (176 of 179). The period 1995–2004 was selected to allow for comparability to the cohort included in event free survival analyses. This latter group was used for the calculation of EFSP because availability of relapse data was limited to this group. Person-time was calculated in months from the date of diagnosis of the first renal tumour to the date of death, relapse or diagnosis of a second primary malignant neoplasm, or to the end of the study period (December 31, 2006).

For observed survival proportions after relapse, the subset of patients diagnosed with primary renal tumours between 1995 and 2004 who relapsed and linked with the Ontario Registrar General Mortality Registry (all 37 relapsed patients) was analyzed. Person-time was calculated in months from the date of first relapse of the primary renal tumour to the date of death or to December 31, 2006.

Advantages and limitations

The advantages of population-based data collection are that it captures a complete, unselected group of all patients in a specific geographic location over a specified period of time and allows monitoring of trends over time. In distinction to clinical trial cohorts, population cohorts do not exclude patients who, for whatever reason, do not enter clinical trials. A potential disadvantage of population-based databases, however, is that classification systems may change over time. For example, in this chapter, the "nephroblastoma and other non-epithelial" diagnostic category includes Wilms tumour, CCSK and rhabdoid tumours because these tumours are classified as 1 entity in ICCC-3. Evolution of immunohistochemistry and molecular pathology has allowed the identification of discrete entities, such as rhabdoid tumours. However, these tumours cannot be identified retrospectively within the population-based database; therefore, the true incidence of rhabdoid tumours in the population cohort is likely underestimated. All registries using ICCC-3 as their classification system that have accrued patients over a long time span are subject to similar limitations, and thus comparisons between registries are best limited to those that encompass similar time spans.

Discussion

EXHIBIT 10.1: **Incidence of first primary renal tumours, by diagnostic group, year of diagnosis, stage and age at diagnosis, age 0–14 years, in Ontario, 1985–2004**

		5 year of diagnosis									
		Total (1985–2004)								1985–1989	
Diagnostic group	Stage at diagnosis			Age (months)				Female			
		N	%	Mean	Median	SD	Range	N	%	N	%
6. Renal tumours*	Overall†	**359**	**100.00%**	**46.11**	**38.00**	**35.52**	**2-178**	**199**	**55.43%**	**84**	**23.40%**
	1	121	33.70%	36.79	28.00	33.06	2-170	62	51.24%	34	40.48%
	2	83	23.12%	46.96	40.00	33.63	4-173	51	61.45%	15	17.86%
	3	79	22.01%	54.52	42.00	39.00	3-178	47	59.49%	15	17.86%
	4	51	14.21%	63.43	58.00	34.86	14-177	24	47.06%	11	13.10%
	5‡	19	5.29%	25.95	25.00	15.58	6-56	13	68.42%	7	8.33%
6a. Nephroblastoma*	Overall†	**340**	**94.71%**	**42.79**	**36.00**	**30.85**	**2-177**	**189**	**55.59%**	**82**	**97.62%**
	1	113	33.24%	32.42	26.00	26.54	2-170	59	52.21%	34	41.46%
	2	80	23.53%	44.04	39.50	27.61	4-137	49	61.25%	15	18.29%
	3	75	22.06%	51.47	41.00	35.47	3-175	43	57.33%	15	18.29%
	4	48	14.12%	59.48	57.00	31.30	14-177	23	47.92%	10	12.20%
	5‡	19	5.59%	25.95	25.00	15.58	6-56	13	68.42%	7	8.54%
6a. i) Wilms tumour*§	Overall†	**321**	**89.42%**	**42.54**	**36.00**	**30.79**	**2-177**	**183**	**57.01%**	**81**	**96.43%**
	1	111	34.58%	32.49	26.00	26.75	2-170	59	53.15%	34	41.98%
	2	71	22.12%	43.21	39.00	26.31	4-121	45	63.38%	14	17.28%
	3	69	21.50%	52.42	41.00	35.72	3-175	41	59.42%	15	18.52%
	4	47	14.64%	59.26	57.00	31.60	14-177	23	48.94%	10	12.35%
	5	19	5.92%	25.95	25.00	15.58	6-56	13	68.42%	7	8.64%
6b. Renal carcinomas	Overall	**17**	**4.74%**	**116.18**	**135.00**	**49.86**	**30-178**	**10**	**58.82%**	**1**	**1.19%**
	1	7	41.18%	110.43	129.00	44.11	44-157	3	42.86%	0	0.00%
	2	3	17.65%	125.00	172.00	82.27	30-173	2	66.67%	0	0.00%
	3	4	23.53%	111.75	112.00	62.54	45-178	4	100.00%	0	0.00%
	4	3	17.65%	126.67	140.00	31.21	91-149	1	33.33%	1	100.00%
6c. Unspecified malignant renal tumours	Overall†	**2**	**0.56%**	**15.00**	**15.00**	**0.00**	**15-15**	**0**	**0.00%**	**1**	**1.19%**

SD = standard deviation
*Includes 5 cases of cystic nephroblastoma.
†Patients with missing or not applicable stage information (n=6) have been included in the Overall total.
‡Stage 5 renal tumours include patients with Wilms tumour only.
§Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

					1990–1994					
	Age (months)						Age (months)			
	Mean	Median	SD	Range	N	%	Mean	Median	SD	Range
	37.25	**33.50**	**26.74**	**3-149**	**96**	**26.74%**	**46.08**	**38.00**	**36.84**	**4-178**
	32.32	30.50	21.77	3-99	40	41.67%	35.00	26.00	28.86	4-135
	29.20	25.00	17.21	4-58	20	20.83%	45.45	47.50	27.10	7-105
	44.47	38.00	25.42	15-108	20	20.83%	72.90	55.50	52.14	13-178
	66.00	69.00	38.67	22-149	12	12.50%	48.00	43.00	27.27	14-92
	25.14	25.00	15.92	6-44	4	4.17%	20.25	13.50	14.52	12-42
	36.16	**33.50**	**23.90**	**3-108**	**91**	**94.79%**	**43.38**	**36.00**	**33.69**	**4-175**
	32.32	30.50	21.77	3-99	38	41.76%	32.13	26.00	24.43	4-95
	29.20	25.00	17.21	4-58	20	21.98%	45.45	47.50	27.10	7-105
	44.47	38.00	25.42	15-108	17	18.68%	68.29	55.00	49.66	13-175
	57.70	56.00	28.62	22-95	12	13.19%	48.00	43.00	27.27	14-92
	25.14	25.00	15.92	6-44	4	4.40%	20.25	13.50	14.52	12-42
	35.89	**33.00**	**23.92**	**3-108**	**89**	**92.71%**	**43.30**	**36.00**	**34.04**	**4-175**
	32.32	30.50	21.77	3-99	37	41.57%	31.97	26.00	24.75	4-95
	27.14	25.00	15.83	4-51	19	21.35%	44.89	45.00	27.72	7-105
	44.47	38.00	25.42	15-108	17	19.10%	68.29	55.00	49.66	13-175
	57.70	56.00	28.62	22-95	12	13.48%	48.00	43.00	27.27	14-92
	25.14	25.00	15.92	6-44	4	4.49%	20.25	13.50	14.52	12-42
	149.00	**149.00**	**—**	**149-149**	**5**	**5.21%**	**95.20**	**74.00**	**59.23**	**44-178**
	—	—	—	—	2	40.00%	89.50	89.50	64.35	44-135
	—	—	—	—	0	0.00%	—	—	—	—
	—	—	—	—	3	60.00%	99.00	74.00	69.94	45-178
	149.00	149.00	—	149-149	0	0.00%	—	—	—	—
	15.00	**15.00**	**—**	**15-15**	**0**	**0.00%**	**—**	**—**	**—**	**—**

continued on following page

EXHIBIT 10.1: **Incidence of first primary renal tumours, by diagnostic group, year of diagnosis, stage and age at diagnosis, age 0–14 years, in Ontario, 1985–2004** (cont'd)

		5 year of diagnosis											
		1995–1999						2000–2004					
Diagnostic group	Stage at diagnosis			Age (months)						Age (months)			
		N	%	Mean	Median	SD	Range	N	%	Mean	Median	SD	Range
6. Renal tumours*	Overall†	104	28.97%	49.03	42.50	35.07	5-173	75	20.89%	52.00	36.00	41.36	2-177
	1	31	29.81%	36.94	24.00	36.67	7-157	16	21.33%	50.44	30.00	50.96	2-170
	2	27	25.96%	51.15	43.00	35.77	5-173	21	28.00%	55.71	37.00	41.52	15-172
	3	27	25.96%	53.81	50.00	35.06	9-150	17	22.67%	42.88	32.00	30.98	3-113
	4	15	14.42%	64.80	58.00	26.90	29-137	13	17.33%	73.92	69.00	43.87	22-177
	5‡	3	2.88%	34.33	41.00	25.66	6-56	5	6.67%	26.60	25.00	11.72	14-41
6a. Nephroblastoma*	Overall†	98	94.23%	44.63	42.00	28.23	5-137	69	92.00%	47.25	35.00	36.70	2-177
	1	27	27.55%	27.52	21.00	20.06	7-83	14	20.29%	42.86	26.00	46.87	2-170
	2	26	26.53%	46.46	42.50	26.72	5-121	19	27.54%	50.95	37.00	33.22	15-137
	3	26	26.53%	50.12	48.00	29.91	9-108	17	24.64%	42.88	32.00	30.98	3-113
	4	15	15.31%	64.80	58.00	26.90	29-137	11	15.94%	66.36	61.00	42.20	22-177
	5‡	3	3.06%	34.33	41.00	25.66	6-56	5	7.25%	26.60	25.00	11.72	14-41
6a. i) Wilms tumour*§	Overall†	92	88.46%	45.11	42.00	27.93	5-137	59	78.67%	46.51	35.00	36.99	2-177
	1	26	28.26%	27.85	22.50	20.38	7-83	14	23.73%	42.86	26.00	46.87	2-170
	2	24	26.09%	48.63	43.00	26.63	5-121	14	23.73%	47.71	37.00	28.27	15-117
	3	23	25.00%	49.52	46.00	28.77	9-108	14	23.73%	46.43	34.00	32.93	3-113
	4	15	16.30%	64.80	58.00	26.90	29-137	10	16.95%	66.00	59.00	44.46	22-177
	5	3	3.26%	34.33	41.00	25.66	6-56	5	8.47%	26.60	25.00	11.72	14-41
6b. Renal carcinomas	Overall	5	4.81%	142.00	150.00	27.84	101-173	6	8.00%	106.67	115.50	55.65	30-172
	1	3	60.00%	129.00	129.00	28.00	101-157	2	33.33%	103.50	103.50	62.93	59-148
	2	1	20.00%	173.00	173.00	—	173-173	2	33.33%	101.00	101.00	100.41	30-172
	3	1	20.00%	150.00	150.00	—	150-150	0	0.00%	—	—	—	—
	4	0	0.00%	—	—	—	—	2	33.33%	115.50	115.50	34.65	91-140
6c. Unspecified malignant renal tumours	Overall†	1	0.96%	15.00	15.00	N/A	15-15	0	0.00%	—	—	—	—

SD = standard deviation

*Includes 5 cases of cystic nephroblastoma.

†Patients with missing or not applicable stage information (n=6) have been included in the Overall total.

‡Stage 5 renal tumours include patients with Wilms tumour only.

§Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

Exhibit 10.1

A total of 359 patients under the age of 15 years were diagnosed with a first primary renal tumour in this time period, with a mean age at diagnosis of 3.8 years. Over half of all cases of primary renal tumours (55.4%) were female. The percentage was 55.6% for nephroblastoma, 57.0% for Wilms tumour and 58.8% for renal carcinoma.

Nephroblastoma, at 340 cases (94.7%), accounted for the vast majority of cases; 17 (4.7%) were renal carcinomas and 2 (0.6%) were unspecified malignant renal tumours. For all primary renal tumours, over half had early stage disease (stages 1 and 2 combined, 56.8%). Advanced stage non-metastatic disease (stage 3) accounted for 79 cases (22.0%) and metastatic disease (stage 4) was present in 51 cases (14.2%). Stage 5 (bilateral renal tumours) was rare, accounting for 19 cases with Wilms tumour (5.9%). By age at diagnosis, 38 cases (10.6%) were younger than 1 year, 188 (52.4%) were 1–3 years, 100 (27.9%) were 4–7 years and 33 (9.2%) were 8–14 years (data not shown).

During 1985–2004, Wilms tumour accounted for 321 patients (89.4% of all renal tumours). For patients with Wilms tumour, stages 1 through to 5 accounted for 111 (34.6%), 71 (22.1%), 69 (21.5%), 47 (14.6%) and 19 (5.9%) patients, respectively (data were missing for 4 patients). The median age of stage 1 patients with Wilms tumour (26 months) was substantially lower than that of stage 4 patients (57 months).

When divided into 5 year periods, the incidence of Wilms tumour appears to be decreasing. The proportion was 96.4% of all primary renal tumours in the 1985–1989 period, declining steadily over time to 78.7% in 2000–2004. The proportion of stage 1 Wilms tumour relative to the other stages decreased significantly over time, accounting for 42.0% of all Wilms tumours during 1985–1989 and 23.7% for 2000–2004 ($P = 0.0450$). This decrease occurred in spite of increased screening for Beckwith-Wiedemann syndrome in the more recent periods aimed at increasing the proportion of patients diagnosed at early stages. One reason for this phenomenon may be better imaging in more recent years, which would better detect the extent of disease previously missed, resulting in upstaging of tumours previously reported as stage 1. If this is the case, patients will have received more intensive treatment in recent years than in earlier periods. Alternatively, changes in environmental risk factors may be contributing to some of these observed changes.[33]

Wilms tumour patients were significantly younger (mean age, 3.5 years) than patients with RCC (mean age, 9.7 years). The incidence of renal carcinomas appears to be increasing over the study period, from 1.2% in 1985–1989 to 8.0% in 2000–2004. The numbers of cases are very small, however, and this trend should therefore be interpreted with caution.

Non-Wilms nephroblastoma cases comprised 19 patients during 1985–2004 (5.6% of nephroblastoma cases), of which 17 (5.0%) were CCSK and 2 (0.6%) were rhabdoid tumours. The mean and median age of the non-Wilms nephroblastoma group was 47 and 38 months, respectively, with an age range of 1–12 years; 31.6% were female. The incidence of non-Wilms nephroblastoma appears to increase over time, from 1 case (1.2% of nephroblastoma cases) in 1985–1989 to 10 cases (14.5% of nephroblastoma cases) in 2000–2004 (data not shown). However, the accuracy with which the diagnosis of rhabdoid tumour could be made improved significantly after the mid-1990s, when the deletion or mutation of the *hSNF5/INI1* gene was identified in rhabdoid tumours. This resulted in the ability to detect reduced expression at the protein level with *INI1* immunohistochemistry. This development helped to distinguish rhabdoid tumours from other pediatric soft tissue tumours and likely increased the number of cases correctly diagnosed as rhabdoid tumour that may have been previously misclassified as a Wilms or other pediatric soft tissue tumour. Thus we are not able to accurately identify the incidence, or obtain true population capture, of rhabdoid tumours, especially before the mid-1990s. Review of all cases registered as Wilms tumour has not yielded descriptive comments suggesting rhabdoid tumour in any other cases.

EXHIBIT 10.2: **Age standardized incidence and mortality rates of first primary renal tumours, per 1 million population per year, by year of diagnosis, diagnostic group and stage at diagnosis, age 0–14 years, in Ontario, 1985–2004***

		Year of diagnosis							
		Total (1985–2004)				1985–1989			
Diagnostic group	Stage at diagnosis	New cases	ASIR per million per year	Deaths	ASMR per million per year	New cases	ASIR per million per year	Deaths	ASMR per million per year
6. Renal tumours†	**Overall‖**	**359**	**7.91**	**40**	**0.89**	**84**	**7.95**	**9**	**0.90**
	1	121	2.64	6	0.13	34	3.18	1	0.09
	2	83	1.80	5	0.11	15	1.35	0	0.00
	3	79	1.77	8	0.18	15	1.48	2	0.20
	4	51	1.15	16	0.37	11	1.12	5	0.52
	5‡	19	0.42	3	0.07	7	0.64	1	0.09
6a. Nephroblastoma†	**Overall‖**	**340**	**7.48**	**37**	**0.82**	**82**	**7.75**	**8**	**0.80**
	1	113	2.46	6	0.13	34	3.18	1	0.09
	2	80	1.74	5	0.11	15	1.35	0	0.00
	3	75	1.68	8	0.18	15	1.48	2	0.20
	4	48	1.08	13	0.30	10	1.01	4	0.41
	5‡	19	0.42	3	0.07	7	0.64	1	0.09
6a. i) Wilms tumours†§	**Overall‖**	**321**	**7.07**	**34**	**0.76**	**81**	**7.65**	**8**	**0.80**
	1	111	2.42	6	0.13	34	3.18	1	0.09
	2	71	1.54	5	0.11	14	1.25	0	0.00
	3	69	1.55	7	0.16	15	1.48	2	0.20
	4	47	1.05	12	0.27	10	1.01	4	0.41
	5	19	0.42	3	0.07	7	0.64	1	0.09
6b. Renal carcinomas	**Overall‖**	**17**	**0.39**	**3**	**0.07**	**1**	**0.11**	**1**	**0.11**
	1	7	0.16	0	0.00	0	—	0	—
	2	3	0.07	0	0.00	0	—	0	—
	3	4	0.09	0	0.00	0	—	0	—
	4	3	0.07	3	0.07	1	0.11	1	0.11
6c. Unspecified malignant renal tumours	**Overall‖**	**2**	**0.04**	**0**	**0.00**	**1**	**0.10**	**0**	**0.00**

ASIR = age standardized incidence rate; ASMR = age standardized mortality rate

*Rates are age standardized to 2001 Ontario population, ages 0–14 years (based on the following age strata: <1, 1–4, 5–9 and 10–14 years), 1985–2008, and are expressed per million population per year because of disease rarity. ASMRs are calculated based on the subset of the cohort of patients diagnosed with renal tumours 1985–2004 (n=359) who linked with the Ontario Registrar General Mortality Registry (n=346); 13 patients who did not link have been excluded from all survival related analyses. Subjects were censored at time of death or at the end of follow up (Dec. 31, 2006).

†Includes 5 cases of cystic nephroblastoma.

‡Stage 5 renal tumours include patients with Wilms tumour only.

§Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

‖Patients with missing or not applicable stage information (n=6) have been included in the "Overall Total"

	1990–1994				1995–1999				2000–2004			
	New cases	ASIR per million per year	Deaths	ASMR per million per year	New cases	ASIR per million per year	Deaths	ASMR per million per year	New cases	ASIR per million per year	Deaths	ASMR per million per year
	96	**8.28**	**10**	**0.85**	**104**	**8.83**	**13**	**1.11**	**75**	**6.59**	**8**	**0.70**
	40	3.37	2	0.17	31	2.60	3	0.26	16	1.40	0	0.00
	20	1.73	3	0.27	27	2.29	1	0.08	21	1.83	1	0.09
	20	1.79	3	0.26	27	2.32	3	0.26	17	1.50	0	0.00
	12	1.05	2	0.16	15	1.27	4	0.35	13	1.14	5	0.43
	4	0.34	0	0.00	3	0.25	1	0.08	5	0.44	1	0.09
	91	**7.82**	**10**	**0.85**	**98**	**8.29**	**13**	**1.11**	**69**	**6.07**	**6**	**0.53**
	38	3.18	2	0.17	27	2.25	3	0.26	14	1.23	0	0.00
	20	1.73	3	0.27	26	2.20	1	0.08	19	1.66	1	0.09
	17	1.52	3	0.26	26	2.23	3	0.26	17	1.50	0	0.00
	12	1.05	2	0.16	15	1.27	4	0.35	11	0.97	3	0.26
	4	0.34	0	0.00	3	0.25	1	0.08	5	0.44	1	0.09
	89	**7.65**	**10**	**0.85**	**92**	**7.78**	**12**	**1.03**	**59**	**5.19**	**4**	**0.35**
	37	3.10	2	0.17	26	2.16	3	0.26	14	1.23	0	0.00
	19	1.65	3	0.27	24	2.03	1	0.08	14	1.23	1	0.09
	17	1.52	3	0.26	23	1.97	2	0.17	14	1.23	0	0.00
	12	1.05	2	0.16	15	1.27	4	0.35	10	0.88	2	0.17
	4	0.34	0	0.00	3	0.25	1	0.08	5	0.44	1	0.09
	5	**0.46**	**0**	**0.00**	**5**	**0.46**	**0**	**0.00**	**6**	**0.52**	**2**	**0.17**
	2	0.19	0	0.00	3	0.27	0	0.00	2	0.17	0	0.00
	0	—	0	—	1	0.09	0	0.00	2	0.17	0	0.00
	3	0.28	0	0.00	1	0.09	0	0.00	0	—	0	—
	0	—	0	—	0	—	0	—	2	0.17	2	0.17
	0	**—**	**0**	**—**	**1**	**0.08**	**0**	**0.00**	**0**	**—**	**0**	**—**

Exhibit 10.2

ASIRs and ASMRs are reported for 5 year intervals for 1985–2004 based on the standard Ontario population (2001). ASIRs were 7.91 per 1 million population per year for all primary renal tumours, 7.48 for nephroblastoma, 7.07 for Wilms tumour (a sub-group of nephroblastoma) and 0.39 for renal carcinoma. For all primary renal tumours and nephroblastoma, the observed rates in Ontario are consistent with corresponding rates (8.1 and 7.5, respectively) reported for the age standardized (ages 0–14 years) Canadian population (2001–2005).[34]

The ASMRs were 0.89 deaths per 1 million population per year for any first primary renal tumour, 0.82 for nephroblastoma, 0.76 for Wilms tumour and 0.07 for renal carcinoma. For all primary renal tumours and nephroblastoma in the 2000–2004 period, Ontario ASMRs (0.7 and 0.53, respectively) were better than corresponding rates (1.2 and 0.9, respectively) reported for the age standardized Canadian population over the same period.[33]

Trends in age standardized incidence and mortality rates

In a comparison of 5 year intervals, the incidence of primary renal tumours initially increased before decreasing in the most recent reporting period. ASIR per million per year was 7.95 in 1985–1989, 8.28 in 1990–1994, 8.83 in 1995–2000 and 6.59 in 2000–2004. Corresponding national data for the same age group, available for the 1990–1994 and 2000–2004 period, show slightly higher ASIRs of 9.06 and 8.5, respectively.[34,35]

ASIRs for nephroblastoma showed a similar trend, initially increasing to a maximum of 8.29 per million per year in the 1995–1999 period before showing a decline in the 2000–2004 period to 6.07. The national ASIR for 2000–2004 was slightly higher at 7.9 per million per year.[35] Not surprisingly, the trend for Wilms tumour, which constituted the vast majority of cases of nephroblastoma, reflected the trend for nephroblastoma. ASIR for Wilms tumour was 7.65 in 1985–1989 and 1990–1994, 7.78 in 1995–2000 and 5.19 in 2000–2004. It is unclear whether the drop in ASIR in the most recent reporting period is part of a trend or an anomaly. Review of ASIR data in subsequent years will help to determine this.

The ASIR for renal carcinoma increased from 0.11 per 1 million population per year to 0.52 from 1985–1989 to 2000–2004 and remained constant in the 2 middle reporting periods (1990–1994 and 1995–1999) at 0.46. This rate is a striking 4.7-fold increase from the first to the last reporting period for renal carcinomas. The number of cases is very small, however, so this finding needs to be interpreted with caution.

For all primary renal tumours, the ASMR declined between the first and last reporting period. The ASMR per million per year was 0.90 in 1985–1989, 0.85 in 1990–1994, 1.11 in 1995–1999 and 0.70 in 2000–2004. For nephroblastoma, there was an initial increase before a major decline in the last reporting period: the ASMR was 0.80 in 1985–1989, 0.85 in 1990–1994, 1.11 in 1995–1999 and 0.53 in 2000–2004. This pattern was also seen in Wilms tumour, where the ASMR was 0.80 in 1985–1989, 0.85 in 1990–1994, 1.03 in 1995–1999 and 0.35 in 2000–2004. For renal carcinoma, the ASMR was 0.11 in 1985–1989, 0 in 1990–1994 and 1995–1999 and 0.17 in 2000–2004.

In relative terms, the ASMR for all primary renal tumours decreased by 22% (from 0.90 to 0.70) between the 1985–1989 and 2000–2004 reporting periods, mainly as a result of a reduction in ASMR for Wilms tumour (from 0.80 to 0.35). This decrease is in contrast to national data, which showed a 38% increase in the ASMR between 1990–1994 and 2000–2004 (from 0.87 to 1.2) for the same age group.[34,35]

For nephroblastoma, the ASMR decreased by 34% (from 0.80 to 0.53) between the 1985–1989 and 2000–2004 periods. National ASMR data for nephroblastoma, available for 2000–2004 only, showed a much higher rate, at 0.9.[35]

For RCC, the ASMR increased by 54% (from 0.11 to 0.17) between 1985–1989 and 2000–2004. The number of cases is very small, however, so this finding needs to be interpreted with caution. Both pathological and clinical differences have been reported between adult and pediatric RCC, with pediatric disease having better event free and overall survival rates, especially if all disease is surgically resected.

EXHIBIT 10.3a: **5 and 10 year overall survival proportions for patients diagnosed with a primary renal tumour, by year of diagnosis, diagnostic group and stage at diagnosis, ages 0–14 years, in Ontario, 1985–2004**

		Year of diagnosis					
		Overall (1985–2004)				1985–1989	
Diagnostic group	Stage at diagnosis	5 year OSP	95% CI	10 year OSP	95% CI	5 year OSP	95% CI
6. Renal tumours*	Overall	**0.90**	**0.86-0.93**	**0.89**	**0.85-0.93**	**0.85**	**0.71-0.93**
	1	0.94	0.88-0.97	0.92	0.76-0.97	0.95	0.69-0.99
	2	0.93	0.84-0.97	0.95	0.81-0.99	—	—
	3	0.91	0.82-0.96	0.90	0.70-0.97	0.80	0.44-0.94
	4	0.71	0.55-0.83	0.76	0.51-0.89	—	—
	5†	0.88	0.60-0.97	—	—	0.81	0.18-0.98
6a. Nephroblastoma*	Overall	**0.90**	**0.86-0.93**	**0.89**	**0.85-0.92**	**0.85**	**0.71-0.93**
	1	0.94	0.87-0.97	0.90	0.72-0.97	0.95	0.69-0.99
	2	0.93	0.84-0.97	0.95	0.81-0.99	—	—
	3	0.91	0.81-0.96	0.89	0.69-0.97	0.80	0.44-0.94
	4	0.74	0.58-0.85	0.79	0.53-0.91	—	—
	5	0.88	0.60-0.97	—	—	0.81	0.18-0.98
6a. i) Wilms tumours*‡	Overall	**0.90**	**0.86-0.93**	**0.89**	**0.84-0.92**	**0.84**	**0.70-0.92**
	1	0.94	0.87-0.97	0.90	0.71-0.97	0.95	0.69-0.99
	2	0.92	0.82-0.97	0.94	0.78-0.98	—	—
	3	0.92	0.81-0.97	0.90	0.66-0.98	0.80	0.44-0.94
	4	0.74	0.58-0.85	0.78	0.52-0.91	—	—
	5	0.88	0.60-0.97	—	—	0.81	0.18-0.98
6b. Renal carcinomas	Overall	**0.88**	**0.60-0.97**	**0.88**	**0.60-0.97**	—	—

OSP = overall survival proportion; CI = confidence interval
*Includes 3 cases of cystic nephroblastoma.
†Stage 5 renal tumours include patients with Wilms tumour only.
‡Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

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EXHIBIT 10.3a: **5 and 10 year overall survival proportions for patients diagnosed with a primary renal tumour, by year of diagnosis, diagnostic group and stage at diagnosis, ages 0–14 years, in Ontario, 1985–2004** (cont'd)

		Year of diagnosis					
		1990–1994		1995–1999		2000–2004	
Diagnostic group	Stage at diagnosis	5 year OSP	95% CI	5 year OSP	95% CI	5 year OSP	95% CI
6. Renal tumours*	**Overall**	**0.94**	**0.88-0.98**	**0.86**	**0.78-0.91**	**0.92**	**0.85-0.96**
	1	0.95	0.83-0.99	0.94	0.80-0.98	0.96	0.80-0.99
	2	0.96	0.75-0.99	0.83	0.58-0.94	0.97	0.79-0.99
	3	1.00	—	0.89	0.72-0.96	0.95	0.74-0.99
	4	0.80	0.42-0.95	0.63	0.34-0.82	0.78	0.50-0.91
	5†	1.00	—	1.00	—	0.84	0.25-0.98
6a. Nephroblastoma*	**Overall**	**0.95**	**0.89-0.98**	**0.85**	**0.77-0.91**	**0.93**	**0.86-0.97**
	1	0.95	0.82-0.99	0.93	0.78-0.98	0.96	0.77-0.99
	2	0.96	0.75-0.99	0.83	0.58-0.94	0.96	0.79-0.99
	3	1.00	—	0.88	0.70-0.96	0.95	0.74-0.99
	4	0.87	0.40-0.98	0.63	0.34-0.82	0.84	0.55-0.95
	5	1.00	—	1.00	—	0.84	0.25-0.98
6a. i) Wilms tumours*‡	**Overall**	**0.95**	**0.88-0.98**	**0.86**	**0.77-0.91**	**0.92**	**0.85-0.96**
	1	0.95	0.82-0.99	0.93	0.77-0.98	0.95	0.76-0.99
	2	0.96	0.74-0.99	0.83	0.58-0.94	0.95	0.75-0.99
	3	1.00	—	0.91	0.72-0.97	0.95	0.72-0.99
	4	0.87	0.40-0.98	0.63	0.34-0.82	0.84	0.54-0.95
	5	1.00	—	1.00	—	0.84	0.25-0.98
6b. Renal carcinomas	**Overall**	**0.83**	**0.29-0.97**	**1.00**	—	**0.88**	**0.42-0.98**

OSP = overall survival proportion; CI = confidence interval
*Includes 3 cases of cystic nephroblastoma.
†Stage 5 renal tumours include patients with Wilms tumour only.
‡Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

Exhibit 10.3a

For all children with primary renal tumours from 1985 to 2004, the 5 and 10 year OSPs were 0.90 and 0.89, respectively, suggesting that very few patients died beyond 5 years from diagnosis.

For children with primary Wilms tumours, the 5 and 10 year OSPs were 0.90 and 0.89, respectively. By reporting period, the 5 year OSPs were 0.84, 0.95, 0.86 and 0.92 for 1985–1989, 1990–1994, 1995–1999 and 2000–2004, respectively. Stage at diagnosis affected prognosis. For Wilms tumours diagnosed from 1985 to 2004, stages 1 through 5 had 5 year OSPs of 0.94, 0.92, 0.92, 0.74 and 0.88, respectively.

The 5 year OSP for non-Wilms nephroblastoma patients diagnosed during 1985–2004 was 0.94 (95% CI: 0.65–0.99) (data not shown). For RCC, 5 year OSP was 0.88.

EXHIBIT 10.3b: **5 and 10 year overall survival proportions for patients diagnosed with a primary renal tumour, by year of diagnosis, diagnostic group and age at diagnosis, ages 0–14 years, in Ontario, 1985–2004**

		Year of diagnosis					
		Overall (1985–2004)				1985–1989	
Diagnostic group	Age at diagnosis (years)	5 year OSP	95% CI	10 year OSP	95% CI	5 year OSP	95% CI
6. Renal tumours*	**Overall**	**0.90**	**0.86-0.93**	**0.89**	**0.85-0.92**	**0.85**	**0.71-0.93**
	<1	0.94	0.78-0.98	0.90	0.73-0.97	1.00	—
	1–3	0.95	0.90-0.97	0.94	0.89-0.97	0.91	0.75-0.97
	4–7	0.82	0.72-0.89	0.82	0.72-0.89	0.59	0.25-0.82
	8–14	0.81	0.60-0.92	0.81	0.60-0.92	—	—
6a. Nephroblastoma*	**Overall**	**0.90**	**0.86-0.93**	**0.89**	**0.85-0.92**	**0.85**	**0.71-0.93**
	<1	0.94	0.78-0.98	0.90	0.73-0.97	1.00	—
	1–3	0.94	0.90-0.97	0.94	0.88-0.96	0.91	0.75-0.97
	4–7	0.83	0.73-0.89	0.83	0.73-0.89	0.59	0.25-0.82
	8–14	0.76	0.49-0.90	0.76	0.49-0.90	—	—
6a. i) Wilms tumours*†	**Overall**	**0.90**	**0.86-0.93**	**0.89**	**0.84-0.92**	**0.84**	**0.70-0.92**
	<1	0.94	0.78-0.98	0.90	0.73-0.97	1.00	—
	1–3	0.95	0.90-0.97	0.94	0.88-0.97	0.91	0.75-0.97
	4–7	0.81	0.71-0.88	0.81	0.71-0.88	0.54	0.19-0.79
	8–14	0.74	0.46-0.89	0.74	0.46-0.89	—	—
6b. Renal carcinomas	**Overall**	**0.88**	**0.60-0.97**	**0.88**	**0.60-0.97**	**—**	**—**
	<1	—	—	—	—	—	—
	1–3	1.00	—	1.00	—	—	—
	4–7	0.71	0.03-0.97	0.71	0.03-0.97	—	—
	8–14	0.91	0.51-0.99	0.91	0.51-0.99	—	—

OSP = overall survival proportion; CI = confidence interval
*Includes 3 cases of cystic nephroblastoma.
†Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

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EXHIBIT 10.3b: **5 and 10 year overall survival proportions for patients diagnosed with a primary renal tumour, by year of diagnosis, diagnostic group and age at diagnosis, ages 0–14 years, in Ontario, 1985–2004** (cont'd)

		Year of diagnosis					
		1990–1994		1995–1999		2000–2004	
Diagnostic group	Age at diagnosis (years)	5 year OSP	95% CI	5 year OSP	95% CI	5 year OSP	95% CI
6. Renal tumours*	**Overall**	**0.94**	**0.88-0.98**	**0.86**	**0.78-0.91**	**0.92**	**0.85-0.96**
	<1	1.00	—	0.85	0.30-0.98	0.90	0.46-0.99
	1–3	0.96	0.86-0.99	0.94	0.83-0.98	0.98	0.86-1.00
	4–7	0.92	0.72-0.98	0.76	0.59-0.87	0.89	0.72-0.96
	8–14	0.85	0.35-0.98	0.80	0.48-0.93	0.80	0.47-0.94
6a. Nephroblastoma*	**Overall**	**0.95**	**0.89-0.98**	**0.85**	**0.77-0.91**	**0.93**	**0.86-0.97**
	<1	1.00	—	0.85	0.30-0.98	0.90	0.46-0.99
	1–3	0.96	0.85-0.99	0.93	0.82-0.98	0.98	0.86-1.00
	4–7	0.92	0.71-0.98	0.76	0.58-0.87	0.93	0.78-0.98
	8–14	1.00	—	0.73	0.36-0.91	0.67	0.29-0.88
6a. i) Wilms tumours*†	**Overall**	**0.95**	**0.88-0.98**	**0.86**	**0.77-0.91**	**0.92**	**0.85-0.96**
	<1	1.00	—	0.85	0.30-0.98	0.90	0.46-0.99
	1–3	0.96	0.85-0.99	0.95	0.84-0.99	0.97	0.85-0.99
	4–7	0.91	0.70-0.98	0.75	0.57-0.86	0.93	0.77-0.98
	8–14	1.00	—	0.69	0.30-0.89	0.65	0.24-0.88
6b. Renal carcinomas	**Overall**	**0.83**	**0.29-0.97**	**1.00**	**—**	**0.88**	**0.42-0.98**
	<1	—	—	—	—	—	—
	1–3	—	—	0.73	0.36-0.91	—	—
	4–7	—	—	0.73	0.36-0.91	0.59	0.00-0.96
	8–14	0.65	0.07-0.93	1.00	—	1.00	—

OSP = overall survival proportion; CI = confidence interval
*Includes 3 cases of cystic nephroblastoma.
†Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

Exhibit 10.3b

For Wilms tumours, age at diagnosis appeared to affect prognosis. In the 1985–2004 period, 5 year OSP was highest in the 1–3 year age group at 0.95, followed by the less than 1 year group at 0.94 and the 4–7 year group at 0.81. The 8–14 year group had the poorest OSP at 0.74. Apart from the under 1 year group, where the OSP fell from 0.94 at 5 years to 0.90 at 10 years, 5 and 10 year OSPs were essentially the same.

Exhibit 10.3c

There was a trend for increasing stage by age, in which 29 (80.6%) Wilms tumour patients aged less than 1 year had stages 1 and 2 combined, compared with only 46 (43.8%) patients age 4 year or older.

Furthermore, Wilms tumour patients younger than 4 years accounted for 81.1% (n = 86) of stage 1 patients, 62.9% (n = 44) of stage 2, 53.8% (n = 35) of stage 3, 37.8% (n = 17) of stage 4 and 94.7% (n = 18) of stage 5. Almost all patients with bilateral Wilms tumour developed the disease before age 4, likely reflecting an underlying predisposition – for example, conditions such as Beckwith-Wiedemann syndrome.

EXHIBIT 10.3c: **5 and 10 year overall survival proportions for patients diagnosed with a primary Wilms tumour, by stage and age at diagnosis, age 0–14 years, in Ontario, 1985–2004***

Stage at diagnosis	Age at diagnosis (years)	N	%	Overall (1985–2004) 5 year OSP	95% CI	10 year OSP	95% CI
Overall†	Overall	**308**	**100.00%**	**0.90**	**0.86-0.93**	**0.89**	**0.84-0.92**
	<1	36	11.69%	0.94	0.78-0.98	0.90	0.73-0.97
	1–3	167	54.22%	0.95	0.90-0.97	0.94	0.88-0.97
	4–7	86	27.92%	0.81	0.71-0.88	0.81	0.71-0.88
	8–14	19	6.17%	0.74	0.46-0.89	0.74	0.46-0.89
1	Overall	**106**	**34.42%**	**0.94**	**0.87-0.97**	**0.90**	**0.71-0.97**
	<1	22	20.75%	0.95	0.69-0.99	0.95	0.69-0.99
	1–3	64	60.38%	0.98	0.89-1.00	0.98	0.89-1.00
	4–7	17	16.04%	0.76	0.47-0.90	0.76	0.47-0.90
	8–14	3	2.83%	1.00	—	1.00	—
2	Overall	**70**	**22.73%**	**0.92**	**0.82-0.97**	**0.94**	**0.78-0.98**
	<1	7	10.00%	0.85	0.34-0.98	0.85	0.34-0.98
	1–3	37	52.86%	0.97	0.81-1.00	0.97	0.81-1.00
	4–7	22	31.43%	0.90	0.66-0.97	0.90	0.66-0.97
	8–14	4	5.71%	0.73	0.15-0.95	0.73	0.15-0.95
3	Overall	**65**	**61.32%**	**0.92**	**0.81-0.97**	**0.90**	**0.66-0.98**
	<1	2	3.08%	1.00	—	—	—
	1–3	33	50.77%	0.97	0.79-1.00	0.91	0.69-0.98
	4–7	21	32.31%	0.86	0.62-0.95	0.86	0.62-0.95
	8–14	9	13.85%	0.89	0.39-0.98	0.89	0.39-0.98
4	Overall	**45**	**64.29%**	**0.74**	**0.58-0.85**	**0.78**	**0.52-0.91**
	<1	0	0.00%	—	—	—	—
	1–3	17	37.78%	0.85	0.52-0.96	0.85	0.52-0.96
	4–7	25	55.56%	0.73	0.50-0.87	0.73	0.50-0.87
	8–14	3	6.67%	—	—	—	—
5	Overall	**19**	**29.23%**	**0.88**	**0.60-0.97**	—	—
	<1	3	15.79%	1.00	—	1.00	—
	1–3	15	78.95%	0.85	0.51-0.96	0.85	0.51-0.96
	4–7	1	5.26%	1.00	—	—	—
	8–14	0	0.00%	—	—	—	—

OSP = overall survival proportion; CI = confidence interval

*Includes 3 cases of cystic nephroblastoma. Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

†Patients with missing or not applicable stage information (n=3) have been included in the Overall stage group.

The effects of stage by age at diagnosis on 5 and 10 year OSP for Wilms tumour patients over the period 1985–2004 are presented. Age at diagnosis appears to affect prognosis: the 5 and 10 year OSPs were highest among patients younger than 4 years of age. However, the stage distribution is skewed toward lower stages for younger ages; we therefore speculate that the poorer OSP for older patients is related to the higher stages of disease.

EXHIBIT 10.4a: **5 and 10 year overall and event free survival proportions for patients diagnosed with a primary renal tumour, by year of diagnosis, diagnostic group and stage at diagnosis, age 0–14 years, in Ontario, 1995–2004***

		Year of diagnosis							
		Overall (1995–2004)							
Diagnostic group	Stage at diagnosis	5 year OSP	95% CI	5 year EFSP	95% CI	10 year OSP	95% CI	10 year EFSP	95% CI
6. Renal tumours†	Overall	**0.90**	**0.84-0.94**	**0.79**	**0.72-0.85**	**0.88**	**0.81-0.93**	**0.76**	**0.68-0.82**
	1	0.92	0.76-0.97	0.83	0.67-0.91	0.92	0.76-0.97	0.83	0.67-0.91
	2	0.95	0.81-0.99	0.77	0.61-0.87	0.95	0.81-0.99	0.77	0.61-0.87
	3	0.95	0.82-0.99	0.86	0.71-0.93	0.90	0.70-0.97	0.77	0.57-0.88
	4	0.76	0.51-0.89	0.70	0.48-0.84	0.76	0.51-0.89	0.70	0.48-0.84
	5‡	0.84	0.25-0.98	0.83	0.29-0.97	—	—	—	—
6a. Nephroblastoma†	Overall	**0.90**	**0.83-0.94**	**0.79**	**0.71-0.85**	**0.88**	**0.81-0.93**	**0.76**	**0.67-0.82**
	1	0.90	0.72-0.97	0.80	0.62-0.90	0.90	0.72-0.97	0.80	0.62-0.90
	2	0.95	0.81-0.99	0.78	0.63-0.88	0.95	0.81-0.99	0.78	0.63-0.88
	3	0.95	0.81-0.99	0.86	0.70-0.93	0.89	0.69-0.97	0.76	0.55-0.88
	4	0.79	0.53-0.91	0.73	0.50-0.86	0.79	0.53-0.91	0.73	0.50-0.86
	5‡	0.84	0.25-0.98	0.83	0.29-0.97	—	—	—	—
6a. i) Wilms tumours†§	Overall	**0.90**	**0.83-0.94**	**0.78**	**0.70-0.84**	**0.88**	**0.80-0.93**	**0.75**	**0.66-0.82**
	1	0.90	0.71-0.97	0.79	0.61-0.89	0.90	0.71-0.97	0.79	0.61-0.89
	2	0.94	0.78-0.98	0.75	0.57-0.86	0.94	0.78-0.98	0.75	0.57-0.86
	3	0.97	0.80-1.00	0.86	0.69-0.94	0.90	0.66-0.98	0.75	0.52-0.88
	4	0.78	0.52-0.91	0.76	0.53-0.89	0.78	0.52-0.91	0.76	0.53-0.89
	5	0.84	0.25-0.98	0.83	0.29-0.97	—	—	—	—
6b. Renal carcinomas	Overall	**0.91**	**0.46-0.99**	**0.77**	**0.35-0.94**	**0.91**	**0.46-0.99**	**0.77**	**0.35-0.94**

OSP = overall survival proportion; CI = confidence interval; EFSP = event free survival proportion

*The reporting period 1995–2004 was selected to allow for comparability with event free survival analyses (availability of relapse data was limited to this group). Overall, there were no second malignant neoplasms observed 1995–2004.

†Includes 3 cases of cystic nephroblastoma.

‡Stage 5 renal tumours include patients with Wilms tumour only.

§Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

Exhibit 10.4a

For all children with primary Wilms tumours diagnosed during 1995–2004, the 5 and 10 year OSPs were stable at 0.90 and 0.88, respectively, similar to the 20 year period between 1985 and 2004. For 1995–2004, the 5 and 10 year EFSPs for Wilms tumour patients were 0.78 and 0.75, respectively, suggesting ongoing significant events for a small proportion of patients beyond 5 years from diagnosis.

There was a rise in both 5 year OSP and 5 year EFSP when the 2 most recent treatment periods (1995–1999 and 2000–2004) were compared. For Wilms tumours, OSP increased from 0.86 to 0.92 and EFSP from 0.74 to 0.82 in 1995–1999 and 2000–2004, respectively. This increase occurred despite a reduction in the intensity of treatment in more recent years in an attempt to reduce late effects of treatment.

Stages 1 through 5 Wilms tumour had a 5 year OSP of 0.90, 0.94, 0.97, 0.78 and 0.84, respectively, and a 5 year EFSP of 0.79, 0.75, 0.86, 0.76 and 0.83, respectively. These rates suggest that for patients with lower stage disease, retrieval therapy is more

1995–1999				2000–2004			
5 year OSP	95% CI	5 year EFSP	95% CI	5 year OSP	95% CI	5 year EFSP	95% CI
0.86	**0.78-0.91**	**0.75**	**0.64-0.84**	**0.92**	**0.85-0.96**	**0.82**	**0.72-0.88**
0.94	0.80-0.98	0.77	0.52-0.90	0.96	0.80-0.99	0.90	0.66-0.97
0.83	0.58-0.94	0.72	0.40-0.89	0.97	0.79-0.99	0.79	0.59-0.91
0.89	0.72-0.96	0.88	0.66-0.96	0.95	0.74-0.99	0.84	0.60-0.94
0.63	0.34-0.82	0.57	0.25-0.79	0.78	0.50-0.91	0.78	0.49-0.91
1.00	—	—	—	0.84	0.25-0.98	0.81	0.32-0.96
0.85	**0.77-0.91**	**0.74**	**0.62-0.83**	**0.93**	**0.86-0.97**	**0.83**	**0.73-0.89**
0.93	0.78-0.98	0.74	0.48-0.89	0.96	0.77-0.99	0.87	0.59-0.96
0.83	0.58-0.94	0.72	0.39-0.89	0.96	0.79-0.99	0.82	0.60-0.92
0.88	0.70-0.96	0.87	0.65-0.96	0.95	0.74-0.99	0.84	0.60-0.94
0.63	0.34-0.82	0.57	0.25-0.79	0.84	0.55-0.95	0.84	0.53-0.95
1.00	—	—	—	0.84	0.25-0.98	0.81	0.32-0.96
0.86	**0.77-0.91**	**0.74**	**0.62-0.83**	**0.92**	**0.85-0.96**	**0.82**	**0.71-0.89**
0.93	0.77-0.98	0.74	0.48-0.88	0.95	0.76-0.99	0.86	0.57-0.96
0.83	0.58-0.94	0.72	0.39-0.89	0.95	0.75-0.99	0.75	0.50-0.89
0.91	0.72-0.97	0.90	0.65-0.97	0.95	0.72-0.99	0.82	0.55-0.93
0.63	0.34-0.82	0.57	0.25-0.79	0.84	0.54-0.95	0.91	0.61-0.98
1.00	—	—	—	0.84	0.25-0.98	0.81	0.32-0.96
1.00	**—**	**1.00**	**—**	**0.88**	**0.42-0.98**	**0.69**	**0.24-0.91**

effective than it is in those with stage 4 disease. The better 5 year EFSP for stage 3 than for stage 1 and 2 was surprising. It could be a result of more intensive treatment for stage 3 than for stage 1 and 2. Alternatively, it may reflect a period in which routine pre-operative chemotherapy was used, which may have resulted in down staging of what was really stage 3 disease.

There was no change in the 5 and 10 year OSP or EFSP for any stage except stage 3. For stage 3 patients, there was a decrease in the 10 year EFSP (0.75) from the 5 year EFSP (0.86), with a parallel reduction in the 10 year OSP (0.90) compared with the 5 year OSP (0.97). Unlike local stage 1 and 2 disease, patients with stage 3 disease would have received flank or whole abdominal radiation and anthracycline therapy. One possible reason for the late drop in EFSP and OSP for stage 3 may be late effects from this additional treatment.

The 5 year EFSP for non-Wilms nephroblastoma patients diagnosed between 1995 and 2004 was 0.86 (95% CI: 0.53–0.97) (data not shown).

For renal carcinoma for the 10 year period 1995–2004, 5 year EFSP was 0.77 and 5 year OSP was 0.91. This OSP was higher than for the 20 year period 1985–2004, which was 0.88 (Exhibit 10.3b). This reflects improvement in 5 year OSP in more recent years. Both clinical and pathological differences between adult and pediatric renal carcinoma have been reported, with pediatric RCC having higher event free and overall survival rates, at greater than 90%.[36]

EXHIBIT 10.4b: **5 and 10 year overall and event free survival proportions for patients diagnosed with a primary renal tumour, by year of diagnosis, diagnostic group and age at diagnosis, age 0–14 years, in Ontario, 1995–2004***

		Year of diagnosis							
		Overall (1995–2004)							
Diagnostic group	Age at diagnosis (years)	5 year OSP	95% CI	5 year EFSP	95% CI	10 year OSP	95% CI	10 year EFSP	95% CI
6. Renal tumours[†‡]	Overall	**0.90**	**0.84-0.94**	**0.79**	**0.72-0.85**	**0.88**	**0.81-0.93**	**0.76**	**0.68-0.82**
	<1	0.83	0.47-0.96	0.63	0.33-0.82	—	—	—	—
	1–3	0.96	0.87-0.99	0.84	0.73-0.91	0.96	0.87-0.99	0.84	0.73-0.91
	4–7	0.87	0.74-0.94	0.77	0.63-0.86	0.87	0.74-0.94	0.73	0.58-0.84
	8–14	0.81	0.52-0.93	0.77	0.49-0.91	0.81	0.52-0.93	0.77	0.49-0.91
6a. Nephroblastoma[†§]	Overall	**0.90**	**0.83-0.94**	**0.79**	**0.71-0.85**	**0.88**	**0.81-0.93**	**0.76**	**0.67-0.82**
	<1	0.83	0.47-0.96	0.63	0.33-0.82	—	—	—	—
	1–3	0.96	0.87-0.99	0.84	0.73-0.90	0.96	0.87-0.99	0.84	0.73-0.90
	4–7	0.89	0.75-0.95	0.78	0.64-0.87	0.89	0.75-0.95	0.74	0.59-0.85
	8–14	0.68	0.32-0.88	0.75	0.41-0.92	0.68	0.32-0.88	0.75	0.41-0.92
6a. i) Wilms tumours[†§]	Overall	**0.90**	**0.83-0.94**	**0.78**	**0.70-0.84**	**0.88**	**0.80-0.93**	**0.75**	**0.66-0.82**
	<1	0.83	0.47-0.96	0.63	0.33-0.82	—	—	—	—
	1–3	0.97	0.87-0.99	0.83	0.71-0.90	0.97	0.87-0.99	0.83	0.71-0.90
	4–7	0.88	0.74-0.95	0.78	0.63-0.87	0.88	0.74-0.95	0.74	0.58-0.85
	8–14	0.64	0.27-0.86	0.73	0.37-0.91	0.64	0.27-0.86	0.73	0.37-0.91
6b. Renal carcinomas	Overall	**0.91**	**0.46-0.99**	**0.77**	**0.35-0.94**	**0.91**	**0.46-0.99**	**0.77**	**0.35-0.94**

OSP = overall survival proportion; CI = confidence interval; EFSP = event free survival proportion

*The reporting period 1995–2004 was selected to allow for comparability with event free survival analyses (availability of relapse data was limited to this group). Overall, there were no second malignant neoplasms observed 1995–2004.

[†]Includes 3 cases of cystic nephroblastoma.

[‡]Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

[§]Owing to small sample size, a statistical anomaly occurs resulting in the reported 5 year OSP being lower than the 5 year EFSP for nephroblastoma and Wilms tumour patients aged 8–14 years.

Exhibit 10.4b

For Wilms tumours diagnosed from 1995 to 2004, 5 year OSP was highest in the 1–3 year age group at 0.97, followed by the 4–7 year group at 0.88 and the less than 1 year group at 0.83. The 8–14 year group had the worst OSP at 0.64. Five year OSP was worse in the more recent 10 year period (1995–2004) for patients younger than 1 year (0.83) than in the 20 year period 1985–2004 (0.94) (Exhibit 10.3b). This may be a result of rhabdoid tumours being misclassified as other tumour types in the earlier decade (1985–1994) and therefore not being included in the OSPs. Similarly, for the 8–14 year age group, the 5 year OSP was 0.64 in the more recent 10 year period (1995–2004), compared with 0.74 in the 20 year period 1985–2004. The reason for the poorer results in the more recent decade is unclear but may be a statistical aberration due to the small numbers.

For 1995–2004, 5 year EFSP was highest for Wilms tumours in the 1–3 year group at 0.83, followed by the 4–7 year group at 0.78 and the 8–14 year group at 0.73. The less than 1 year group had the worst EFSP at 0.63. The relatively poor EFSP prognosis in patients younger than 1 year may be due to reluctance to treat very young patients aggressively. Some of these patients were salvageable at relapse, however, reflected by the higher 5 year OSP of 0.83.

1995–1999				2000–2004			
5 year OSP	95% CI	5 year EFSP	95% CI	5 year OSP	95% CI	5 year EFSP	95% CI
0.86	**0.78-0.91**	**0.75**	**0.64-0.84**	**0.92**	**0.85-0.96**	**0.82**	**0.72-0.88**
0.85	0.30-0.98	—	—	0.90	0.46-0.99	0.60	0.25-0.82
0.94	0.83-0.98	0.76	0.58-0.88	0.98	0.86-1.00	0.90	0.76-0.96
0.76	0.59-0.87	0.74	0.53-0.87	0.89	0.72-0.96	0.77	0.57-0.88
0.80	0.48-0.93	0.76	0.31-0.94	0.80	0.47-0.94	0.79	0.42-0.94
0.85	**0.77-0.91**	**0.74**	**0.62-0.83**	**0.93**	**0.86-0.97**	**0.83**	**0.73-0.89**
0.85	0.30-0.98	—	—	0.90	0.46-0.99	0.60	0.25-0.82
0.93	0.82-0.98	0.76	0.56-0.87	0.98	0.86-1.00	0.90	0.75-0.96
0.76	0.58-0.87	0.74	0.53-0.87	0.93	0.78-0.98	0.79	0.60-0.90
0.73	0.36-0.91	0.68	0.18-0.92	0.67	0.29-0.88	0.83	0.27-0.97
0.86	**0.77-0.91**	**0.74**	**0.62-0.83**	**0.92**	**0.85-0.96**	**0.82**	**0.71-0.89**
0.85	0.30-0.98	—	—	0.90	0.46-0.99	0.60	0.25-0.82
0.95	0.84-0.99	0.77	0.58-0.89	0.97	0.85-0.99	0.87	0.70-0.95
0.75	0.57-0.86	0.73	0.51-0.86	0.93	0.77-0.98	0.81	0.61-0.92
0.69	0.30-0.89	0.63	0.12-0.90	0.65	0.24-0.88	0.83	0.27-0.97
1.00	—	**1.00**	—	**0.88**	**0.42-0.98**	**0.69**	**0.24-0.91**

EXHIBIT 10.4c: **5 and 10 year overall and event free survival proportions for patients diagnosed with a primary Wilms tumour, by stage and age at diagnosis, age 0–14 years, in Ontario, 1995–2004***

Stage at diagnosis	Age at diagnosis (years)	N	%	Overall (1995–2004) 5 year OSP	95% CI	5 year EFSP	95% CI	10 year OSP	95% CI	10 year EFSP	95% CI
Overall†	Overall	148	100.00%	0.90	0.83-0.94	0.78	0.70-0.84	0.88	0.80-0.93	0.75	0.66-0.82
	<1	15	10.14%	0.83	0.47-0.96	0.63	0.33-0.82	—	—	—	—
	1–3	73	49.32%	0.97	0.87-0.99	0.83	0.71-0.90	0.97	0.87-0.99	0.83	0.71-0.90
	4–7	48	32.43%	0.88	0.74-0.95	0.78	0.63-0.87	0.88	0.74-0.95	0.74	0.58-0.85
	8–14	12	8.11%	0.64	0.27-0.86	0.73	0.37-0.91	0.64	0.27-0.86	0.73	0.37-0.91
1	Overall	39	100.00%	0.90	0.71-0.97	0.79	0.61-0.89	0.90	0.71-0.97	0.79	0.61-0.89
	<1	9	23.08%	0.86	0.31-0.98	0.76	0.31-0.94	—	—	—	—
	1–3	22	56.41%	1.00	—	0.95	0.67-0.99	1.00	—	0.95	0.67-0.99
	4–7	6	15.38%	0.63	0.13-0.90	0.35	0.05-0.70	0.63	0.13-0.90	0.35	0.05-0.70
	8–14	2	5.13%	—	—	—		—	—	—	—
2	Overall	38	100.00%	0.94	0.78-0.98	0.75	0.57-0.86	0.94	0.78-0.98	0.75	0.57-0.86
	<1	2	5.26%	0.48	0.01-0.89	—	—	—	—	—	—
	1–3	21	55.26%	1.00	—	0.68	0.43-0.84	1.00	—	0.68	0.43-0.84
	4–7	12	31.58%	1.00	—	1.00	.	.	—	—	—
	8–14	3	7.89%	0.63	0.08-0.92	0.67	0.05-0.94	0.63	0.08-0.92	0.67	0.05-0.94
3	Overall	36	100.00%	0.97	0.80-1.00	0.86	0.69-0.94	0.90	0.66-0.98	0.75	0.52-0.88
	<1	2	5.56%	1.00	—	1.00	—	—	—	—	—
	1–3	17	47.22%	1.00	—	0.88	0.61-0.97	1.00	—	0.88	0.61-0.97
	4–7	13	36.11%	0.92	0.58-0.99	0.77	0.44-0.92	0.92	0.58-0.99	0.65	0.30-0.86
	8–14	4	11.11%	1.00	—	1.00	—	—	—	—	—
4	Overall	25	100.00%	0.78	0.52-0.91	0.76	0.53-0.89	0.78	0.52-0.91	0.76	0.53-0.89
	<1	0	0.00%	—	—	—	—	—	—	—	—
	1–3	6	24.00%	1.00	—	1.00	—	1.00	—	1.00	—
	4–7	16	64.00%	0.84	0.50-0.96	0.77	0.49-0.91	—	—	—	—
	8–14	3	12.00%	—	—	—		—	—	—	—
5	Overall	8	100.00%	0.84	0.25-0.98	0.83	0.29-0.97	—	—	—	—
	<1	1	12.50%	1.00	—	1.00	—	—	—	—	—
	1–3	6	75.00%	0.77	0.10-0.97	0.74	0.14-0.95	—	—	—	—
	4–7	1	12.50%	1.00	—	1.00	—	—	—	—	—
	8–14	0	0.00%	—	—	—	—	—	—	—	—

OSP = overall survival proportion; CI = confidence interval

*Includes 3 cases of cystic nephroblastoma. Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

†Patients with missing or not applicable stage information (n=2) have been included in the Overall stage group.

Exhibit 10.4c

The effects of stage by age at diagnosis on 5 and 10 year OSP and EFSP over the period 1995–2004 are presented. Analysis across stages demonstrated that age did not affect OSP or EFSP. Similar to the 20 year period, the age distribution was skewed across stage groups, whereby older patients (age 4 and up) tended to have more advanced disease (stages 3 and 4) (60.0%, 36 of 60), while the majority (61.4%, 54 of 88) of patients younger than 4 years had early disease (stages 1 and 2).

Exhibit 10.5

Exhibit 10.5 focuses on patients with Wilms tumour who relapsed in the period for which relapse data were available (1995–2004). Overall numbers were small, so the data should be interpreted with caution. However, some interesting observations can be made.

For patients with Wilms tumour diagnosed between 1995 and 2004, 33 of 151 (21.9%) relapsed (data not shown). For the relapsed Wilms tumour group, 5 year OSP from the time of relapse was 0.56 for all stages combined. Therefore, almost half of all patients with relapsed Wilms tumour did not survive. This suggests that the general perception among clinicians that patients with relapsed Wilms tumour are usually salvageable is erroneous. Consideration should therefore be given to ensuring that upfront treatment is aggressive enough to prevent relapse in as many patients as possible and that relapse therapy needs to be more aggressive.

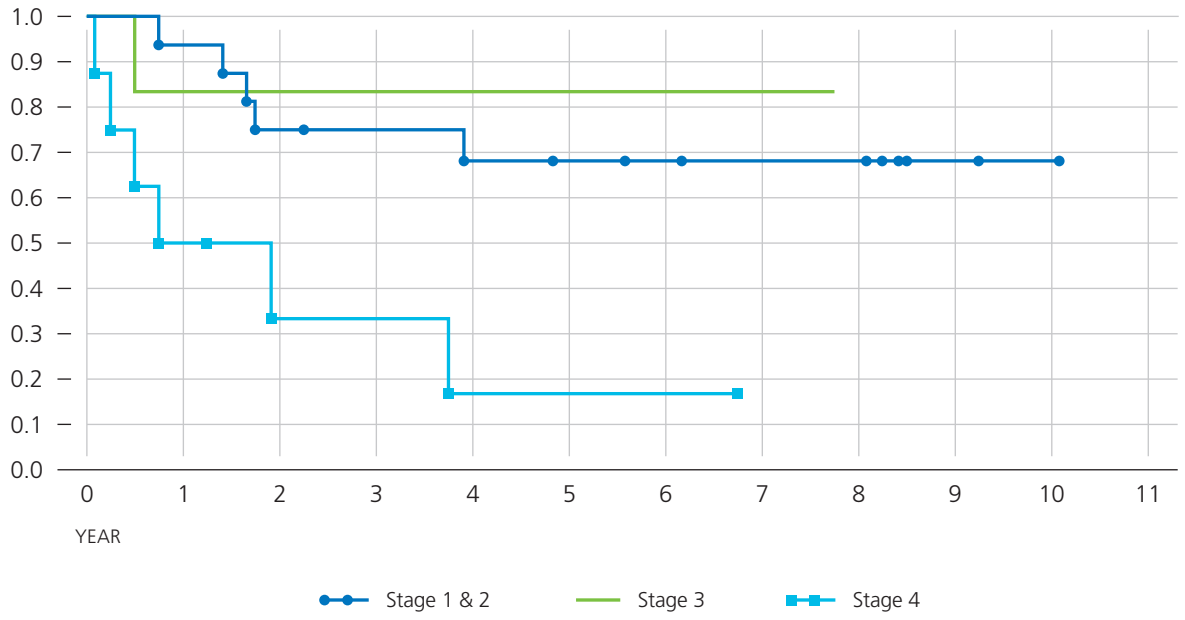
For Wilms tumour patients, 5 year OSPs were as follows: 0.68 for early stage disease (stages 1 and 2 combined), 0.83 for advanced stage non-metastatic disease (stage 3) and 0.17 for metastatic disease (stage 4). It is surprising that OSP was better for stage 3 disease than for low stage disease, for which initial treatment would have been of lower intensity and therefore more options for salvage would have been available. In the future, determining the predictors of high risk of relapse (independent of initial stage of diagnosis) will allow for more aggressive treatment upfront, which will likely further reduce relapse rates.

An example of a marker that has already been identified is loss of heterozygosity at chromosomes 1p and 16q, that confers a poorer prognosis in some Wilms tumours. A Children's Oncology Group study is investigating whether more intensive treatment for this group of patients reduces relapse rates.

For Wilms tumour, 5 year OSP from the time of relapse was best for the 1–3 year age group (0.83), followed by the less than 1 year group (0.53) and the 4–7 year group (0.49). None of the 4 patients in the 8–14 year group was still alive 3 years from relapse (data not shown).

Of the 33 patients with Wilms tumour who relapsed, 6.0% received no further treatment, 39.3% received chemotherapy, 72.7% received radiation, 60.6% received surgery and 21.2% received all 3 treatment modalities (data not shown).

EXHIBIT 10.5: **Overall survival proportions among patients diagnosed with a primary Wilms tumour who relapsed, by stage at diagnosis, age 0–14 years, in Ontario, 1995–2004***



*The reporting period 1995–2004 was selected because availability of relapse data was limited to this period. Data for stages other than 1–4 (i.e., stage 5 and missing stages) have been supressed. Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.

EXHIBIT 10.6: **Treatment of first primary Wilms tumour with chemotherapy, radiotherapy or surgery, by stage at diagnosis, age 0–14 years, in Ontario, 1995–2004***

Stage at diagnosis	Overall (1995–2004)												
	Total	Surgery		Chemotherapy		Radiotherapy†		Chemo + RT + surgery		Chemo + surgery		Surgery only‡	
	N	n	%	n	%	n	%	n	%	n	%	n	%
Overall	**151**	**151**	**100.00%**	**145**	**96.03%**	**69**	**45.70%**	**69**	**45.70%**	**76**	**50.33%**	**6**	**3.97%**
1	40	40	100.00%	34	85.00%	1	2.50%	1	2.50%	33	82.50%	6	15.00%
2	38	38	100.00%	38	100.00%	4	10.53%	4	10.53%	34	89.47%	0	0.00%
3	37	37	100.00%	37	100.00%	36	97.30%	36	97.30%	1	2.70%	0	0.00%
4	25	25	100.00%	25	100.00%	23	92.00%	23	92.00%	2	8.00%	0	0.00%
5	8	8	100.00%	8	100.00%	4	50.00%	4	50.00%	4	50.00%	0	0.00%

Chemo = chemotherapy; RT = radiotherapy
*Includes 3 cases of cystic nephroblastoma. The reporting period 1995–2004 was selected because availability of treatment data was limited to this period. Incidence and population capture of rhabdoid tumours cannot be obtained owing to changes in diagnostic techniques.
†All 5 stage 1 and 2 Wilms tumour patients who received radiotherapy had diffuse anaplasia, unfavourable histology or progressive disease.
One stage 3 Wilms tumour (cystic nephroblastoma) case did not receive radiotherapy.
‡Patients who received surgery only included 4 Wilms tumour cases on surgery only protocols and 2 cases of cystic nephroblastoma.

Exhibit 10.6

Treatment for renal tumours consists of surgery with or without chemotherapy and radiation, depending on the type and stage of the tumour. Wilms tumours usually require surgery and chemotherapy, with radiation reserved for the more advanced stages. CCSK and rhabdoid tumours are usually treated with all 3 therapeutic modalities. RCC requires surgery and does not respond to radiation or chemotherapy.

In the period for which complete treatment data are available (1995–2004), 6 patients with Wilms tumour (4.0%) were treated with surgery only and the remainder had surgery combined with additional treatment modalities: 145 (96.0%) received chemotherapy and 69 (45.7%) received radiation as part of their treatment; 76 (50.3%) received a combination of chemotherapy and surgery and 69 (45.7%) received all 3 treatment modalities.

For patients with stage 1 Wilms tumour, 6 (15.0%) had surgery only. The remainder had surgery combined with additional treatment modalities: 33 (82.5%) patients received a combination of chemotherapy and surgery and 1 (2.5%) received chemotherapy, radiation and surgery. All stages 2–5 Wilms tumour patients had surgery and chemotherapy as part of their treatment regimen, and none had surgery as the only treatment modality. A combination of chemotherapy and surgery was given to 34 (89.5%) stage 2, 1 (2.7%) stage 3, 2 (8.0%) stage 4 and 4 (50.0%) stage 5 Wilms tumour patients. A combination of surgery, chemotherapy and radiation was given to 4 (10.5%) stage 2, 36 (97.3%) stage 3, 23 (92.0%) stage 4 and 4 (50.0%) stage 5 patients. Of patients with stage 1 or 2 Wilms tumour who received radiotherapy, 5 were confirmed to have diffuse anaplasia, unfavourable histology or progressive disease. Furthermore, only 1 stage 3 patient (who had cystic nephroblastoma) did not receive radiotherapy.

Surgery as the only treatment modality was given to 26.6% of Wilms tumour patients less than 1 year of age, 2.3% who were 1–3 years of age and no patients 4 years or older. Chemotherapy was administered to 73.3% of Wilms tumour patients less than 1 year of age, 97.3% of patients 1–3 years of age and all patients 4 years or older. Treatment with a combination of chemotherapy and surgery was given to 60.0% of patients younger than 1 year, 60.5% of those 1–3 years old, 33.3% of those aged 4–7 years and 41.6% of those aged 8–14 years. Treatment with chemotherapy, surgery and radiation was given to 13.3% of patients less than 1 year of age, 36.8% of those aged 1–3, 66.6% of those aged 4–7 and 58.3% of those aged 8–14. Radiation was given to the majority of patients aged 4–14 years (66.6% of those aged 4–7 and 58.3% of those aged 8–14), to 36.8% of those aged 1–4 and to 13.3% of those younger than 1 year (data not shown).

Of the 151 patients with Wilms tumour, 78.8% received surgery within 6 weeks of diagnosis (immediate surgery), 18.5% within 6–12 weeks and 3% beyond 12 weeks. More patients received immediate surgery in the 2000–2004 period (86.4%) than in 1995–1999 (73.9%), reflecting a change in treatment protocol (data not shown). The current North American practice is to provide immediate surgery for patients with Wilms tumour when safely possible to maximize the ability to make an accurate pathological and genetic diagnosis, including identifying factors for relapse, such as anaplasia and loss of heterozygosity at 1p and 16q.

Of the 16 patients diagnosed with non-Wilms nephroblastoma from 1995 to 2004, 14 (87.5%) were treated with a combination of surgery, chemotherapy and radiotherapy, while 2 (12.5%) received chemotherapy and surgery (data not shown).

Summary

Incidence

Nephroblastoma was the most common form of renal tumour in children (94.7%), followed by renal carcinomas (4.7%). Wilms tumour accounted for 89% of all renal tumours. ASIRs were 7.9 for all renal tumours, 7.5 for nephroblastoma, 7.1 for Wilms tumour and 0.4 for renal carcinoma per 1 million population per year. The incidence of renal tumours was higher among females (55.6% for nephroblastoma, 57.0% for Wilms tumour and 58.8% for renal carcinomas).

Mortality

The ASMRs were 0.89 deaths for all renal tumours, 0.82 for nephroblastoma, 0.76 for Wilms tumour and 0.07 for renal carcinomas per 1 million population per year. Mortality rates for all renal tumours, Wilms tumour and nephroblastoma were lowest during the most recent reporting period (2000–2004). For all primary renal tumours and nephroblastoma in 2000–2004, Ontario ASMRs (0.70 and 0.53, respectively) were lower than corresponding rates (1.2 and 0.9, respectively) reported for the age standardized (ages 0–14) Canadian population over the same period.[33] Mortality declined between the first (1995–1999) and last (2000–2004) periods for all renal tumours, Wilms tumour and nephroblastoma over the 4 periods.

Event free survival and overall survival

For the 1995–2004 period, 5 year EFSP and OSP were 0.78 and 0.90 for Wilms tumour and 0.77 and 0.91 for RCC, respectively. Stage 3 Wilms tumour patients had better EFSP and OSP than stage 1 patients, likely reflecting more intensive treatment. For Wilms tumour, 5 year EFSP was lowest in patients younger than 1 year (0.63), and 5 year OSP was lowest in patients aged 8–14 years (0.64).

Relapse

A relapse of Wilms tumour occurred in 21.9% of patients; the 5 year OSP in this relapsed group was 0.56, meaning almost half of all patients with relapsed Wilms tumour did not survive. Five year OSP was worst in the 8–14 year age group, with none of 4 patients still alive 5 years from relapse. For low stage disease (stage 1 and 2), 5 year OSP was 0.68; it was 0.83 for advanced stage non-metastatic disease (stage 3) and 0.17 for metastatic disease (stage 4).

Of the 33 patients with Wilms tumour who relapsed, 6.0% received no further treatment, 39.3% received chemotherapy, 72.7% received radiation, 60.6% received surgery and 21.2% received all 3 treatment modalities.

Treatment

The majority of patients with Wilms tumour received immediate surgery (within 6 weeks of diagnosis). Half of all patients with an initial diagnosis of Wilms tumour were treated with a combination of surgery and chemotherapy and an additional 45.7% received a combination of surgery, chemotherapy and radiation.

References

1 Canadian Cancer Society's Steering Committee. Canadian cancer statistics 2009. Toronto: The Society; 2009.

2 Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, MD: National Cancer Institute; 1999.

3 Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumor. Med Pediatr Oncol 1993;21(3):172-81.

4 Argani P, Perlman EJ, Breslow NE, Browning NG, Green DM, D'Angio GJ, Beckwith JB. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumor Study Group Pathology Center. Am J Surg Pathol 2000 Jan;24(1):4-18.

5 Palmer NF, Sutow W. Clinical aspects of the rhabdoid tumor of the kidney: a report of the National Wilms' Tumor Study Group. Med Pediatr Oncol 1983;11(4):242-5.

6 Selle B, Furtwangler R, Graf N, Kaatsch P, Bruder E, Leuschner I. Population-based study of renal cell carcinoma in children in Germany, 1980-2005: more frequently localized tumors and underlying disorders compared with adult counterparts. Cancer 2006 Dec;107(12):2906-14.

7 Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010 May;28(15):2625-34.

8 Green DM, Breslow NE, Beckwith JB, Finklestein JZ, Grundy P, Thomas PR, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 1998 Dec;16(12):3744-51.

9 Popov SD, Sebire NJ, Pritchard-Jones K, Vujanic GM. Renal tumors in children aged 10-16 years: a report from the United Kingdom Children's Cancer and Leukaemia Group. Pediatr Dev Pathol 2011 May;14(3):189-93.

10 Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey ML, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol 2005 Oct;23(29):7312-21.

11 Dome JS, Cotton CA, Perlman EJ, Breslow NE, Kalapurakal JA, Ritchey ML, et al. Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. J Clin Oncol 2006 May;24(15):2352-8.

12 Seibel NL, Sun J, Anderson JR, Breslow NE, Perlman EJ, Ritchey ML, et al. Outcome of clear cell sarcoma of the kidney (CCSK) treated on the National Wilms Tumor Study-5 (NWTS) [Abstract]. J Clin Oncol 2006;24(18S):A-9000, 502s.

13 Tomlinson GE, Breslow NE, Dome J, Guthrie KA, Norkool P, Li S, et al. Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: age at diagnosis as a prognostic factor. J Clin Oncol 2005 Oct;23(30):7641-5.

14 Riccardi VM, Sujansky E, Smith AC, Francke U. Chromosomal imbalance in the aniridia-Wilms' tumor association: 11p interstitial deletion. Pediatrics 1978 Apr;61(4):604-10.

15 Pelletier J, Bruening W, Kashtan CE, Mauer SM, Manivel JC, Striegel JE, et al. Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell 1991 Oct;67(2):437-47.

16 Coppes MJ, Campbell CE, Williams BR. The role of WT1 in Wilms tumorigenesis. FASEB J 1993 Jul;7(10):886-95.

17 Koufos A, Grundy P, Morgan K, Aleck KA, Hadro T, Lampkin BC, et al. Familial Wiedemann-Beckwith syndrome and a second Wilms tumor locus both map to 11p15.5. Am J Hum Genet 1989 May;44(5):711-9.

18 Ping AJ, Reeve AE, Law DJ, Young MR, Boehnke M, Feinberg AP. Genetic linkage of Beckwith-Wiedemann syndrome to 11p15. Am J Hum Genet 1989 May;44(5):720-3.

19 Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res 1999 Jan;59(1):74-9.

20 Carcao MD, Taylor GP, Greenberg ML, Bernstein ML, Champagne M, Hershon L, Baruchel S. Renal-cell carcinoma in children: a different disorder from its adult counterpart? Med Pediatr Oncol 1998 Sep;31(3):153-8.

21 Spreafico F, Collini P, Terenziani M, Marchiano A, Piva L. Renal cell carcinoma in children and adolescents. Expert Rev Anticancer Ther 2010 Dec;10(12):1967-78.

22 Perlman EJ. Pediatric renal cell carcinoma. Surg Pathol Clin 2010 Sep;3(3):641-51.

23 Dal Cin P, Stas M, Sciot R, De Wever I, Van Damme B, Van den Berghe H. Translocation (X;1) reveals metastasis 31 years after renal cell carcinoma. Cancer Genet Cytogenet 1998 Feb;101(1):58-61.

24 Meloni AM, Dobbs RM, Pontes JE, Sandberg AA. Translocation (X;1) in papillary renal cell carcinoma. A new cytogenetic subtype. Cancer Genet Cytogenet 1993 Jan;65(1):1-6.

25 Tonk V, Wilson KS, Timmons CF, Schneider NR, Tomlinson GE. Renal cell carcinoma with translocation (X;1). Further evidence for a cytogenetically defined subtype. Cancer Genet Cytogenet 1995 May;81(1):72-5.

26 Tomlinson GE, Nisen PD, Timmons CF, Schneider NR. Cytogenetics of a renal cell carcinoma in a 17-month-old child. Evidence for Xp11.2 as a recurring breakpoint. Cancer Genet Cytogenet 1991 Nov;57(1):11-7.

27 Warren KE, Gidvani-Diaz V, Duval-Arnould B. Renal medullary carcinoma in an adolescent with sickle cell trait. Pediatrics 1999 Feb;103(2):E22.

28 Breslow NE, Collins AJ, Ritchey ML, Grigoriev YA, Peterson SM, Green DM. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 2005 Nov;174(5):1972-5.

29 Bruce J, Gough DC. Long-term follow-up of children with renal carcinoma. Br J Urol 1990 May;65(5):446-8.

30 Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer. 3rd ed. Cancer 2005 Apr;103(7):1457-67.

31 Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer 1996 Nov;78(9):2004-10.

32 Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. J Clin Epidemiol 1997 Feb;50(2):211-6.

33 Chu A, Heck JE, Ribeiro KB, Brennan P, Boffetta P, Buffler P, Hung RJ. Wilms' tumour: a systematic review of risk factors and meta-analysis. Paediatr Perinat Epidemiol 2010 Sep;24(5):449-69.

34 National Cancer Institute of Canada. Canadian cancer statistics 1999. Toronto: The Society/The Institute; 1999.

35 Canadian Cancer Society/National Cancer Institute of Canada. Canadian cancer statistics 2008. Toronto: The Society; 2008.

36 Ramphal R, Pappo A, Zielenska M, Grant R, Ngan BY. Pediatric renal cell carcinoma: clinical, pathologic, and molecular abnormalities associated with the members of the mit transcription factor family. Am J Clin Pathol 2006 Sep;126(3):349-64.

Conclusions

The existence of a comprehensive database with population capture has permitted a holistic overview of patterns of incidence, survival and health care utilization that mirror the reality of the entire childhood cancer population. The advantages of the population-based dataset are self-evident, more particularly in the context of the ability to link to other databases. This unique dataset has yielded insights into areas of key importance as we strive to improve the cancer journey for all children – in terms of not only survival rates, but also the quality of the journey.

Childhood cancer contributes a small proportion of incident cases – but a very large number of life years gained as a result of successful treatment. In distinction to adults with cancer, virtually all children with cancer are treated primarily at 1 of 5 Ontario Academic Health Sciences Centres, enabling accurate tracking of the diseases, treatments, outcomes and health care utilization.

The reader will, we hope, have a better perspective on childhood cancer issues, albeit a perspective that we believe can be improved by further research, which we hope readers will be interested in sharing with us – the database is available for use by qualified investigators with appropriate Ethics Board approval. It is our intent to publish updates on this cohort as it ages, but also to update the Atlas cohort with the next cohort, diagnosed between 2005 and 2009, as 5 year follow up becomes possible.

As demonstrated in the Incidence chapter, readers can be reassured that the incidence of cancer in children is not rising in Ontario, nor are there pockets of increased incidence at any location in the province. Of interest is the changing gender ratio for some tumours and the peculiar gender distribution for such tumours as Burkitt lymphoma and thyroid carcinoma – areas for further research.

The Survival chapter demonstrates the value of population capture, showing a clear overall steady increase in survival rates across all categories of malignancy. It also demonstrates that relapse of the primary disease, while devastating, is not a harbinger of fatality – survival rates are appreciable, albeit with very aggressive and resource-intense therapy.

And overall, the diagnosis of childhood cancer invokes a resource use pattern that is intensive, stretching over long periods of active treatment. Beyond the period of active treatment, resource use for pediatric cancer patients remains log orders greater than for the general childhood population. The resource use captured in this Atlas does not account for the considerable resources necessary in pathology and molecular diagnosis, in diagnostic imaging or in any of the psychosocial disciplines – all of which are critical to accurate diagnosis, appropriate therapy and optimal long term outcomes, physical and emotional. It will be imperative, in our single payer health care system, for resources, in all disciplines and modalities, to match utilization to ensure not only the best survival rates, but survival with good quality of life and a journey made as tolerable as possible – a matter that the government has kept, and must continue to keep, top of mind as we produce an ever increasing population of survivors of childhood cancer.

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