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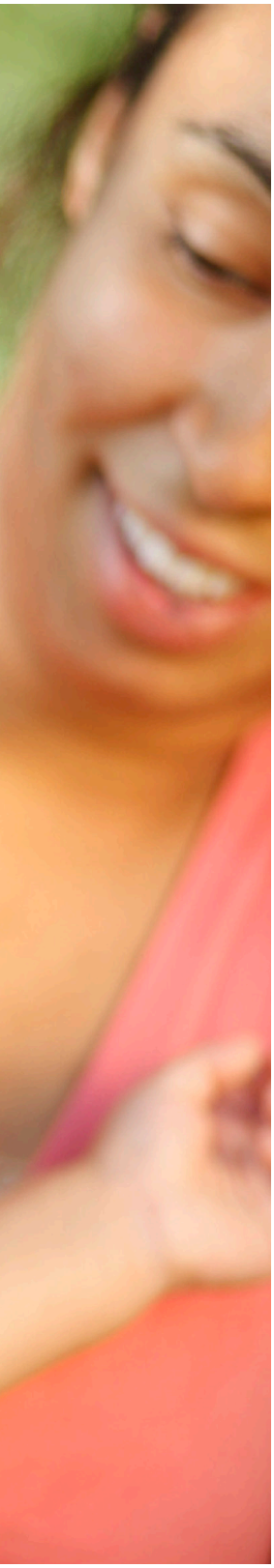

10

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%**	**—**	**—**	**—**	**—**

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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.

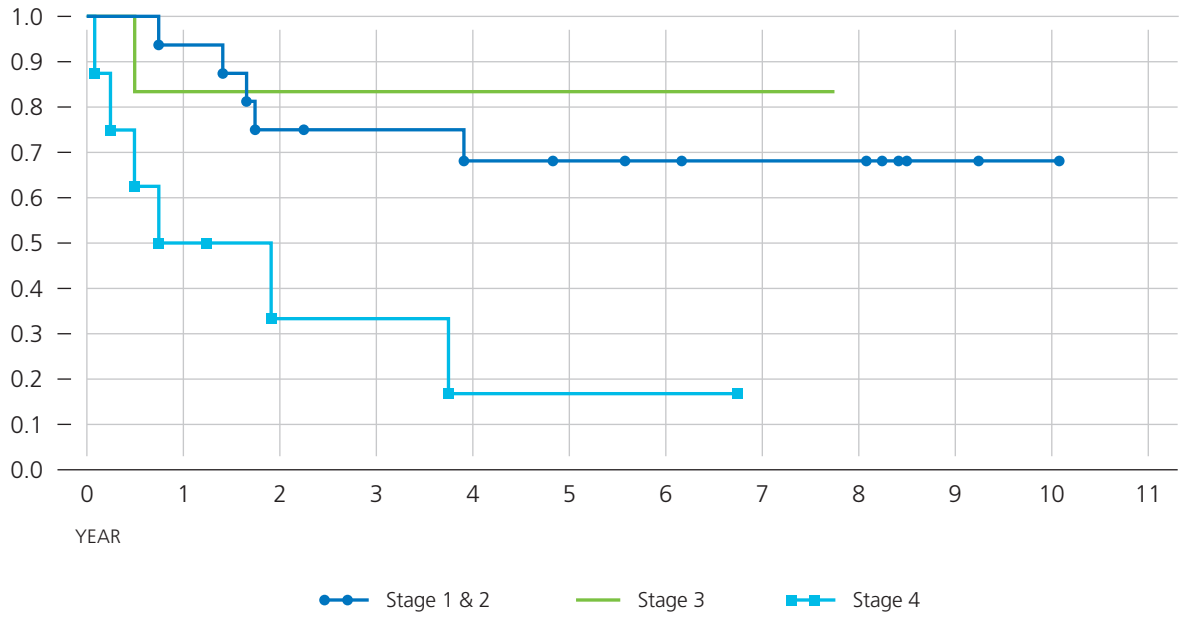
For Wilms tumour patients, 5 year OSPs were as follows: 0.68 for early stage disease (stages 1 and 2 combined), 0.83 for advanced stage non-metastatic disease (stage 3) and 0.17 for metastatic disease (stage 4). It is surprising that OSP was better for stage 3 disease than for low stage disease, for 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.

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