Wilms' Tumor at the Children's Hospital of Eastern Ontario: 1990-2001

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Background: *Wilms' Tumor is the most common malignant neoplasm of the urinary tract in children. Since 1969, the National Wilms' Tumor Study Group (NWTSG) has contributed to improving the clinical management and outcome of children affected by Wilms' Tumor. We have managed our patients according to NWTSG protocols and report our results herein.*

Methods: *Retrospective chart review of consecutive patients presenting at the Children's Hospital of Eastern Ontario (CHEO) with a diagnosis of Wilms' Tumor between April 1990 and March 2001.*

Results: *Forty patients with Wilms' Tumor (18 M/22 F) were diagnosed at CHEO during this interval. Mean age at diagnosis was 28.5 months. The most common presenting feature was a palpable abdominal mass in 85%. An overgrowth syndrome was noted in 10%. Metastatic disease was present at diagnosis in 20%, with the lungs (75%) the most common site of involvement. Distribution of clinical stage: I = 40%, II = 20%, III = 20%, IV = 15%, V = 5%. Favorable histology (FH) was diagnosed in 82.5%, anaplasia in 12.5% and clear cell sarcoma (CCSK) in 5%. Nephrogenic rests were present in 43% (perilobar (PL) = 20%, intralobar (IL) = 18%, PL + IL = 5%). Recurrence of disease occurred in 10%, with lungs (100%) the most frequent site of relapse. Survival was significantly greater in stage I disease and in those patients with FH. Patient 4-year survival data: stage I (FH), 100%; stage II (FH), 80%; stage III (FH), 100%, stage IV (FH), 67%; stages I-IV (CCSK), 100%; stage V, 0%. Overall 4-year survival rates of patients with FH were 92% and of all patients in the study was 86%.*

Conclusions: *The presentation of Wilms' Tumor at our institution mirrors that described in the literature. Importantly, by following NWTSG protocols we have achieved an outcome of overall 4-year patient survival comparable to the "gold standard". This demonstrates the utility of the NWTSG protocols as regards patient management of this relatively uncommon disease.*

Key Words: Wilms' Tumor (nephroblastoma), retrospective study, NWTSG, epidemiology, survival

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Introduction

Nephroblastoma, also known as Wilms' Tumor, is the most common primary malignant renal tumor of childhood.[1] It accounts for approximately 6%-7% of all childhood malignancies in North America. The annual incidence rate is seven cases per million in children less than 15 years of age.[2] Approximately 450

new cases are diagnosed each year in North America.[3] The peak age of presentation is during the third year of life with about 80% of patients presenting at less than 5 years of age.[4] The disease is seen worldwide with a similar age of onset and gender distribution.

Since 1969, virtually all children with Wilms' Tumor in the United States and Canada have been treated according to clinical trials developed by the National Wilms' Tumor Study Group (NWTSG).[5] The NWTSG has contributed to improving the clinical management of children affected by Wilms' Tumor. Based on a strategy of immediate nephrectomy, the NWTSG recommends early surgical resection of the tumor and affected kidney.[6] Subsequently, depending on the histology of the tumor and the clinico-pathologic stage patients receive chemotherapy. In addition, patients with advanced disease or specific adverse prognostic features receive radiotherapy. Utilizing this multimodal approach to therapy, overall survival of children with favorable histology Wilms' Tumor now approaches 90%.[7]

The objectives of this study were:

1) to compare the epidemiology of Wilms' Tumor at the Children's Hospital of Eastern Ontario (CHEO) to that described in the literature and
2) to compare the survival of patients with Wilms' Tumor diagnosed and managed at CHEO according to NWTSG protocol to the results of the NWTSG.

Materials and methods

After receiving approval from the hospital's ethics review board we retrospectively reviewed the charts of consecutive patients presenting at CHEO with a diagnosis of Wilms' Tumor between April 1990 and March 2001. In all cases the diagnosis of Wilms' Tumor was confirmed histopathologically, either from the nephrectomy specimen or by needle biopsy. Needle biopsy was performed in those patients whose tumors were deemed inoperable and for whom preoperative chemotherapy or radiotherapy was planned.

All patients were managed according to NWTSG protocols. Standard investigations for all patients included: abdominal ultrasound, chest x-ray and CT scan of the chest and abdomen. Patients with a diagnosis of clear cell sarcoma were also investigated with: imaging of the head (CT or MRI), bone scan, skeletal survey and bone marrow biopsy. Treatment of patients was based upon the histology and clinico-pathologic stage and involved a multimodal approach incorporating surgery, chemotherapy and radiotherapy as advocated by NWTSG. Tumor stage and histology was determined at CHEO according to NWTSG criteria.[8] In addition, the NWTS Pathology Center reviewed every pathological specimen.

The probability of survival after diagnosis was calculated by the method of Kaplan-Meier. The log-rank test was applied to evaluate the significance of established prognostic factors, stage and histological subtype. Survival time was defined as the time from diagnosis to death from any cause, or to date of last follow-up.

Results

A total of 40 children were diagnosed with Wilms' Tumor at CHEO between April 1990 and March 2001. Of the 40 children, five were diagnosed by percutaneous needle biopsy. The age and gender distribution of the 40 children is presented in Figure 1. The male:female ratio was 18:22 (0.82:1) and the age range at diagnosis was 4-108 months (median 23 months). Thirty-eight patients presented with unilateral tumors at diagnosis (18, right; 20, left) and two patients presented with synchronous bilateral tumors at diagnosis. The presenting signs and symptoms of the patients at diagnosis in order of frequency were as follows: palpable abdominal mass, 85%; abdominal distention, gross hematuria and anorexia, 30%; hypertension, 27.5%; abdominal pain and fever, 20%; nausea and vomiting, 12.5%; anemia and varicocele, 2.5%. The presence of metastatic disease at diagnosis occurred in eight patients (20%). Metastases were seen in lungs in 75%, liver in 25%, lungs and liver in 12.5% and peritoneum in 12.5%. Regional lymphatic spread was present in 17.5% of patients.

The presence of congenital anomalies at diagnosis of Wilms' Tumor occurred in four patients (10%). Each

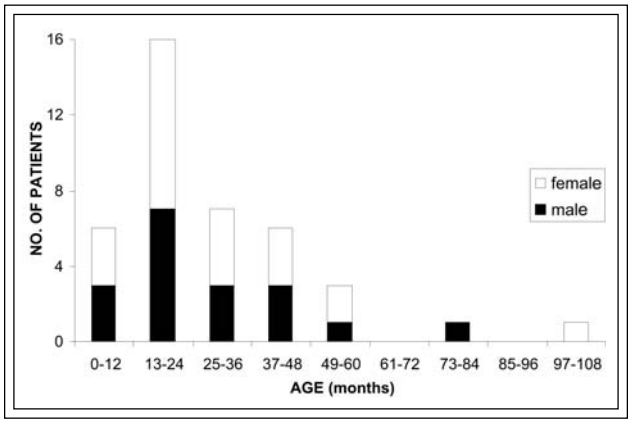

Figure 1. Distribution of 40 children with Wilms' Tumor by age and gender at diagnosis.

TABLE 1. **Patient population defined by histology and stage at presentation**

	Stage I	Stage II	Stage III	Stage IV	Stage V	n
Favorable histology	15 (0)	6 (1)	7 (0)	5 (1)	0	33 (2)
Unfavorable histology						
Focal anaplasia	0	0	1 (0)	1 (0)	0	2 (0)
Diffuse anaplasia	0	1 (0)	0	0	2 (2)	3 (2)
CCSK	1 (0)	1 (0)	0	0	0	2 (0)
Total						40 (4)

CCSK: Clear Cell Sarcoma of the Kidney
Values in parentheses represent number of patient deaths

of the patients had an overgrowth syndrome: two of the patients with Simpson-Golabi-Behmel Syndrome and the other two patients with Beckwith-Wiedemann Syndrome. Three patients were identified by screening through serial ultrasound every 6 months since the time of birth. All four patients survived to the time of last follow-up of this study. The two patients with Beckwith-Wiedemann Syndrome developed metachronous bilateral Wilms' Tumor.

Nephrogenic rests were present in 17 patients (43%). Perilobar NR (PLNR) were present in eight patients (20%), intralobar NR (ILNR) in seven patients (18%) and both PLNR and ILNR were present in two patients (5%). Recurrence of disease occurred in a total of four patients (10%). The most common sites of relapse were the lungs (100%), liver (50%), brain (25%) and peritoneum (25%).

The distribution of patients by clinical stage and histology is presented in Table 1. The probability of survival by stage and by histology is illustrated in Figure 2 and Figure 3 respectively. A significant difference in survival was present between stage I and stage II (p=0.0108) and between stage I and stage IV or higher (p=0.0050). There was no statistical difference between stage II and stage III (p=0.2367). The comparison between stage III and stage IV or higher showed a trend but did not reach statistical significance (p=0.0628). A significant difference in survival was present between patients with favorable versus unfavorable histology tumors (p=0.0220).

Patient 4-year survival rates by clinico-pathologic stage and histology at our institution and the results of the NWTS-4 is given in Table 2. The 4-year overall survival rate for patients at our institution with favorable histology was 92% and the 4-year overall survival rate for all patients in our study was 86%.

Discussion

The Children's Hospital of Eastern Ontario is a pediatric hospital serving a population of approximately 1.5 million in the city of Ottawa and

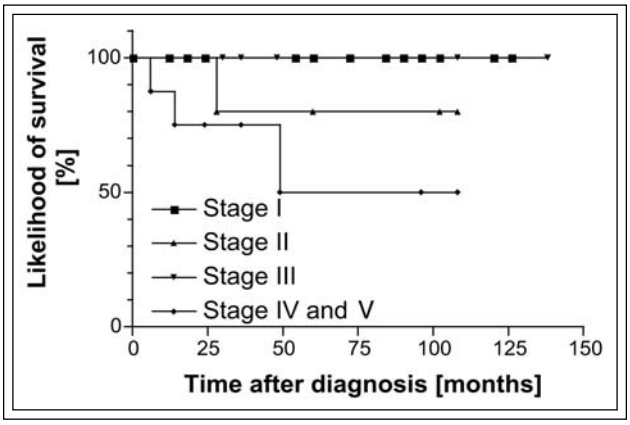

Figure 2. The probability of survival after diagnosis using the Kaplan-Meier method for all patients by clinical stage.

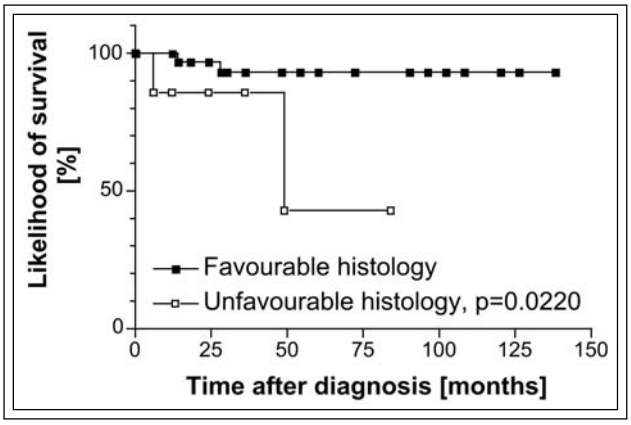

Figure 3. The probability of survival after diagnosis using the Kaplan-Meier method for favorable versus unfavorable histology.

TABLE 2. **Patient 4-year survival rates at CHEO and the NWTS-4**

Stage	Histology	CHEO	NWTS-4
I	Favorable	100.0%	95.6%
II	Favorable	80.0%	91.1%
III	Favorable	100.0%	90.9%
IV	Favorable	66.6%	80.9%
I-IV	CCSK	100.0%	74.8%
All patients		86.0%	89.1%**

CCSK: Clear Cell Sarcoma of the Kidney
NWTS-4 results (1987-1994): Green DM, Thomas PRM, Shochat S. The Treatment of Wilms' Tumor: Results of the National Wilms' Tumor Studies. *Hematology/Oncology Clinics of North America* 1995;9:1267-1274.
** NWTS-3 results (1979-1986): D'Angio GJ, Breslow NE, Beckwith JB et al. Treatment of Wilms' Tumor: Results of the Third National Wilms' Tumor Study. *Cancer* 1989;64:349-360.

surrounding area. Our frequency of 40 cases diagnosed with Wilms' Tumor over an 11-year period is lower than the incidence observed by NWTS of seven cases per million. Of the 40 patients, 38 (95%) presented under 5 years of age. Studies have shown that more than 80% of Wilms' Tumor cases present under the age of 5.[4] We observed a male-to-female ratio of 0.88:1 that resembles studies demonstrating a 22% higher rate of Wilms' Tumor in girls compared to boys in the United States.[9] In our study, the median age of presentation was 23 months for both boys and girls with unilateral tumors. Data from the NWTS demonstrate female registrants with unilateral disease to have a median age of onset of 42 months versus 35 months for males.[8] We observed a 5% frequency of patients presenting with bilateral disease (synchronous Wilms' Tumor) as compared to a frequency of 6% of patients participating in the NWTS.[9] Of the 38 patients with unilateral disease at presentation, 18 presented in the right kidney and 20 in the left kidney (0.9:1) supporting the notion that Wilms' Tumor occurs in either kidney with equal frequency.

Wilms' Tumor usually arise in young children with no unusual physical features or family history and are considered to be "sporadic." Wilms' Tumor may also appear as a feature of a specific genetic disorder or be associated with a familial predisposition.[10] Approximately 10% of children with Wilms' Tumor have recognized congenital malformations.[11] Among the more common disorders associated with Wilms' Tumor are the overgrowth syndromes, such as the Beckwith-Wiedemann syndrome and the Simpson-Golabi-Behmel syndrome.[12] We observed two patients with Beckwith-Wiedemann syndrome and two patients with Simpson-Golabi-Behmel syndrome (total = 10%). The median age at diagnosis for these four patients was 20 months. This demonstrates at our institution that the median age at diagnosis for patients with overgrowth syndromes is similar to that of the general Wilms' Tumor population in keeping with the literature.[13]

The most common presenting feature of Wilms' Tumor at CHEO was a palpable abdominal mass in 85% of patients, which is consistent with the literature.[8] Hypertension was present in 27.5% of our patients at presentation. Studies have shown hypertension to be present in 25% of cases.[14] Macroscopic hematuria was present in 30% of patients at initial presentation resembling a 10%-25% frequency observed in the literature.[15]

Metastatic disease was present at diagnosis in 20% of patients at our institution. The most commonly affected site was the lung (75%), followed by liver (25%), lungs and liver (12.5%) and peritoneum (12.5%). Studies have shown hematogenous metastasis to be present at diagnosis in 10%-15% of patients with the most commonly affected sites being the lung (85%), liver (10%-15%) and lungs and liver (8%).[16]

The presence of nephrogenic rests (NR) at our institution occurred in 43% of patients. NR are known to be remnants of embryonic tissue that are considered precursor lesions to Wilms' Tumor. NR were found in 30%-40% of surgically removed kidneys in patients in the NWTS.[8] In our study, the mean age at diagnosis for patients with ILNR was 17.6 months compared to 28.5 months for all the patients. This is in support of data showing ILNR to be associated with a younger age at diagnosis.[17] Of the four patients with overgrowth syndromes, the two patients with Beckwith-Wiedemann syndrome both had PLNR and one of the two patients with Simpson-Golabi-Behmel syndrome had ILNR. It is known that patients with Beckwith-Wiedemann syndrome have an increased incidence of PLNR, in comparison with patients with unilateral

tumors not associated with congenital anomalies.[18] In addition, of the two patients with synchronous bilateral Wilms' Tumor both had PLNR. This finding is in agreement with the literature demonstrating an increased incidence of PLNR versus ILNR in patients with synchronous bilateral Wilms' Tumor.[19]

Recurrence of disease occurred in 10% of patients, with lungs (100%) the most frequent site of relapse. The NWTS also reports the lungs to be the most frequent site of relapse.[20] Patients with unfavorable histology tumors (diffuse anaplasia) accounted for 50% of the relapses. This finding is in support of the NWTS which show that tumors classified as unfavorable behave more aggressively and are associated with a poorer outcome.[7]

The NWTSG study has shown a definite relationship between the response to treatment, recurrence rate and the grade of tumor.[21] Classification of Wilms' Tumor by the NWTSG includes two broad prognostic groups: a large group of "favorable" histology comprising about 85% of cases and a small group of "unfavorable" histology.[8] The prior definition of unfavorable histology included tumors with nuclear atypia (anaplasia, focal or diffuse) and sarcomatous tumors (rhabdoid tumor of the kidney, RTK and clear cell sarcoma of the kidney, CCSK).[7] The latter two tumor types, however, are currently considered tumor types distinct from Wilms' Tumor[7]. Anaplasia is present in approximately 5% of Wilms' Tumor cases.[22] The presence of anaplasia has been closely linked to decreased tumor responsiveness to adjuvant chemotherapy and is associated with a poor prognosis.[21] In addition, both RTK and CCSK are associated with a markedly poorer outcome.[7]

In our study, 82.5% of patients were diagnosed with favorable histology, 12.5% with anaplasia (focal + diffuse) and 5% with CCSK. We were able to demonstrate a statistically significant difference in survival for patients with favorable versus unfavorable histology. This result supports studies of the NWTSG in which patients with unfavorable histology tumors have a poorer clinical outcome compared to patients with favorable histology tumors.[23] In addition, of the patients with anaplasia in our study, those with focal anaplasia had a 100% survival compared to those patients with diffuse anaplasia who had a survival of 33.3%. The NWTSG have shown that patients with focal as opposed to diffuse anaplasia seem to have a more favorable outcome.[24]

The distribution of patients by stage with favorable histology tumors was stage I in 37.5%, stage II in 15%, stage III in 17.5% and stage IV in 12.5%. In NWTS-3, the distribution of patients by stage with favorable histology tumors was stage I in 47%, stage II in 22%, stage III in 22% and stage IV in 9%.[25] We were able to demonstrate that stage of disease was important in predicting survival irrespective of histology. A statistically significant difference in survival was observed between patients with stage I versus stage II disease and between patients with stage I versus stage IV or higher disease. This result supports the NWTSG in which clinico-pathologic stage is an important prognostic factor in patients with Wilms' Tumor.[8] A significant difference however was not observed between patients with stage II and stage III disease or between patients with stage III and higher disease. Our inability to demonstrate a statistical difference in survival based on stage in these groups was probably related to the smaller number of patients within these groups compared to the larger stage I group.

Of the 40 patients in our study, five were diagnosed by percutaneous needle biopsy. Of the five patients, two had synchronous bilateral Wilms' Tumor (stage V) and three patients had stage IV disease with FH at diagnosis. Each of the three patients with stage IV disease were deemed inoperable and had tumor extension to the IVC. Only two of the five patients diagnosed by needle biopsy survived and both patients had stage IV disease with lung and lymph node metastasis and no tumor recurrence. Both of these patients underwent preoperative chemotherapy, radical nephrectomy and postoperative radiotherapy and chemotherapy. The patient with stage IV disease who did not survive had metastasis to the liver at diagnosis, underwent preoperative chemotherapy, radical nephrectomy and excisional biopsy of the liver and postoperative radiotherapy and chemotherapy. This patient had tumor recurrence to the liver, lungs and peritoneum. The current recommendations from the NWTSG are that preoperative chemotherapy is of benefit for patients with bilateral involvement,[26] those with inoperable disease at surgical exploration[27] and those with IVC extension above the hepatic veins.[28]

Our 4-year survival data is similar to that of the NWTS-4. We obtained an overall 4-year survival rate for patients with favorable histology of 92%. The NWTSG achieved an overall 4-year survival rate for patients with favorable histology approaching 90%.[7] In addition, our overall 4-year survival rate for all 40 patients in the study was 86%. Data from the NWTS-3 reports an overall 4-year survival of all 1439 patients to be 89.1%.[25] The large differences in 4-year survival between CHEO and the NWTSG with respect to stage II and IV FH and stages I-IV CCSK most likely is a result of the small number of patients in our study

compared to the much larger NWTSG trials. In the NWTS-3, the number of patients who had stage II FH, stage IV FH, and stages I-IV CCSK were 278, 120 and 50 patients respectively.[25]

Conclusions

Our results closely resemble those of the literature with respect to the presentation of Wilms' Tumor. In support of the NWSTG, the importance of clinico-pathologic stage and grade of tumor as it applies to prognosis and clinical outcome was shown. By following NWTSG protocols we were able to achieve overall 4-year survival rates comparable to the "gold standard." This demonstrates the utility of the NWTSG protocols as regards patient management for children affected by Wilms' Tumor. □

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