Outcome of children with Wilms' tumor in Duhok city, Kurdistan region, North of Iraq

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Abstract

Wilms' tumor is a curable disease in most of the affected children. The treatment has been improved in the past two decades, with the aid of multimodal therapy protocols. The aims of this study were to evaluate the treatment results, and to assess the survival and the principal prognostic factors in children with Wilms' tumor in Duhok city, Kurdistan region, North of Iraq. Forty-two children diagnosed as having Wilms' tumor in the period between August 1999 and August 2006, who received their treatment at Hevi pediatric teaching Hospital, were studied. Information relating to the patients and the characteristics of the tumor were evaluated. All patients were treated surgically by nephrectomy, followed by postoperative chemotherapy, without radiotherapy (not available), depending on the stage of the tumor, and according to the National Wilms' Tumor Study (NWTS) protocols. Of these 42 patients, 25 were males and 17 were females (male-to-female ratio =1.47:1). The median age at the time of diagnosis was 33 months. The distribution of patients according to the surgical stage was: stage I: 30.9%, stage II: 26.2%, stage III: 35.7%, stage IV: 7.1%. Favorable histology was diagnosed in 69% and unfavorable histology (focal or diffuse anaplasia) in 31% of the patients. Tumor relapse was seen in 12 patients (28.5%). After 4 years follow up, 29 cases (69%) were alive free of disease, two cases (4.7%) were alive with disease and 11 cases (26.2%) had died. The disease-free survival and the overall survival rates at 4 years were 69% and 73.8%, respectively. As a developing country, with limited diagnostic facilities and inadequate facilities for standard management, we believe that our survival rates, although lesser than a number of similar studies survival, were acceptable. Further research with more comprehensive investigation is recommended to improve the treatment results.

Keywords: Wilms' tumor, nephroblastoma, prognostic factors, survival analysis, Duhok, Iraq.

Introduction

Wilms' tumor (WT) or nephroblastoma is an embryonal tumor of renal origin; it is the most common genitourinary malignancy of childhood with a peak occurrence between 3 and 6 years of age.1 It affects approximately one child per 10,000 worldwide before the age of 15, and ranks fifth in incidence among the solid tumors of childhood, following central nervous system tumors, lymphoma, neuroblastoma, and soft tissue sarcomas.2

There are racial and ethnic differences in the predisposition to WT. Most white populations have an age-adjusted incidence of 6 to 9 cases/million children/year. Black population in North America and some parts of Africa exceed 10 cases/million children/year. In Japan, the Philippines, and China, the incidence is less than 4 cases/million children/year.3

The most common presenting signs and symptoms of WT are an abdominal mass (75%), abdominal pain (28%), hypertension (26%), gross hematuria (18%), microscopic hematuria (24%), and fever (22%).4

Developments in surgical techniques and postoperative care, recognition of the sensitivity of WT to irradiation, and the availability of several active chemotherapeutic agents have led to a dramatic change in the prognosis for most patients with this once uniformly lethal malignancy.5

The aims of this study were to evaluate the characteristics of Wilms' tumor, to study the treatment results, and to assess the survival and the principal prognostic factors.

Methods

Between August 1999 and August 2006, 42 consecutively diagnosed and previously untreated children with Wilms' tumor admitted to the Hevi pediatric teaching Hospital were entered on the study, patients diagnosed after this date were not included because the period of follow up (4 years) has not completed.

Information relating to the patients and the characteristics of the tumor was obtained including age at the diagnosis, sex, mode of presentation, associated anomalies, involved kidney, staging, histology, investigations, preoperative treatment, postoperative treatment, and outcome.

Histopathologic classification and clinical staging were done according to the system used by the National Wilms' Tumor Study Group (NWTSG), (6,7).

All patients were treated surgically by nephrectomy, followed by postoperative chemotherapy, without radiotherapy (not available), depending on the stage of the tumor, and according to the NWTS protocols.8,9 Stage I and II-favorable histology and stage I focal and diffuse anaplasia-unfavorable histology disease were treated with actinomycin-D and vincristine for 18 weeks. Stage III and IV-favorable histology and stage II, III and IV focal anaplasia-unfavorable histology disease were treated with actinomycin-D, vincristine and doxorubicin for 24 weeks. Stage II, III and IV diffuse anaplasia-unfavorable histology disease and relapsing cases were treated with ICE therapy (ifosfamide with mesna, carboplatin and etoposide for 6 months). Stage V disease (bilateral WT) was not found in our patients.

Radiological examination included chest X-ray, ultrasonography, and abdomeno-pelvic CT scan, and laboratory examination included complete blood picture, urinalysis, renal and liver function tests.

The patients who achieved complete remission were followed up every 3 months for 4 years by chest X-ray, abdominal ultrasonography and renal function tests, with assessment of overall survival (from the date of diagnosis to the date of death or the date of last follow-up) and disease-free survival (duration of time from complete remission to clinical and radiological progression of disease). No patient was lost to follow up.

Results

Males constituted 59.5% (25/42 cases), and females 40.5% (17/42 cases), with male-to-female ratio of 1.47:1. Age at the time of

diagnosis was divided into three levels: 0-23 months, 24-47 months and 48 or more months.

The median age at the time of diagnosis was 33 months and ranged between 2 to 68 months. Twenty-one (50%) patients were under 24 months of age, 16 (38%) were between 24 and 47 months and only 5 (12%) patients were above 48 months of age.

Only two patients were found to have associated hypospadias.

The most frequent presentation was abdominal mass and distension found by the parents or physicians. The modes of presentation are shown in table (1).

The left kidney was affected in 24 (57%), and the right one in 18 (43%) cases.

Nephrectomy was performed in all cases, and 5 patients received chemotherapy prior to nephrectomy, because they presented tumors that were considered by the surgeon to be too large and therefore inoperable at the time of diagnosis.

Favorable histology was found in 29 cases (69%), while unfavorable histology (focal or diffuse anaplasia) was found in 13 cases (31%). Table (2) summarizes the general characteristics of patients.

The distribution of the staging in relation to age groups (Table 3) showed that stage I and II were the most frequent stages in children under 24 months old, while stage III and IV were predominant in patients aged 48 months and over. No child under 24 months old presented stage IV of the disease. Three patients presented metastatic disease to the lungs at the time of diagnosis.

There were ten recorded complications of chemotherapy. In six children the complications were directly attributable to myelosuppression, and one of the patients died due to severe neutropenia and septic shock. One of the patients developed peripheral neuropathy after receiving vincristine. Drug induced hepatitis occurred in 3 patients.

Tumor relapse was seen in 12 patients (28.5%), three in stage II, six in stage III and three in stage IV. Of these 12 patients, nine had unfavorable histology and three had favorable histology. Sites of relapse were lungs 6 cases (50%), abdomen 4 cases (33.3%) and lungs and abdomen 2 cases (16.6%).

The mean time for relapse after surgery was 15 months, and ten patients died within six months to one year of the relapse.

After 4 years follow up, 29 cases (69%) were alive free of disease, two cases (4.7%) were alive with disease and 11 cases (26.2%) had died.

The 4-year disease free survival and the overall survival rate were 69% and 73.8% respectively.

Discussion

The present study is the first long-term prospective analysis of the results of treatment of pediatric WT in Kurdistan region, North of Iraq.

The male-to-female ratio in our series was 1.47:1, which was similar to Europe but different from the USA, where there is female predominance.10,11 In a similar study conducted by Hisham et al., males constituted 61.3% of the cases.12

The median age of the patients in our study (33 months) was lower than most of other countries. Hisham et al. and Seyed-Ahadi et al. showed that the median age of patients with WT in Egypt and Iran was 60 months and 45.2 months,

respectively.12,13 In North America, the average age of diagnosis for unilateral WT is 42 months for boys and 47 months for girls.2 The younger age incidence in our patients indicates racial and ethnic differences in the predisposition to WT.

Most children with WT are brought to medical attention because of abdominal swelling or the presence of an abdominal mass. Usually this is noticed by a parent while bathing or dressing the child.4 In this study, the most frequent presentation was abdominal swelling (92.8%), followed by abdominal pain (26.2%), hematuria (21.4%), and finally fever (16.6%). This coincides with the work of Hisham et al.,12 Seyed-Ahadi *et al.*,13 and Pianezza *et al*., 14 where an abdominal mass was the most common presenting feature (82.3%, 90.9% and 85%, respectively). The United Kingdom Children's Cancer Study Group (UKCCSG) in their WT trial reported this rate to be 74%.15 The reason that the abdominal mass had been most frequently seen in our study may be because of delayed presentation of our patients.

Two patients (4.7%) in our series were found to have associated hypospadias, which is lower than that reported by NWTS group and Seyed-Ahadi et al. (7.3% and 10.9%, respectively),7,13 this may be related to limited number of patients in our series. Miller et al. were the first to describe the association between congenital anomalies (or syndromes) and WT.16

In this study, the left kidney was mostly affected (57%). It was compatible with the report of Seyed-Ahadi et al. and Lemerle *et al.*,13,17 but in contrast to the result reported by Mott with similar right and left kidney involvement.18

In relation to histopathology, favorable histology was seen in 69% of cases and unfavorable histology (focal and diffuse anaplasia) in 31%. This rate is similar to that reported by Seyed-Ahadi et al. where 54.5% of patients had favorable and 43.6% had unfavorable histology.13 The percentage of patients with unfavorable histology in our series was higher than that in NWTS3, where only 11.12% of patients had unfavorable histology,7 suggesting the existence of a more aggressive form of WT in our region.

Having compared the surgical stages of our patients with NWTS3 results, we found that in NWTS3, stage I patients constituted 42% of all patients,7 while it was 30.9% in our study. Stage III patients constituted 35.7% of our study population compared with 23% in NWTS3 patients.7 Our results are comparable with that of Zaghloul et al.,19 who reported 112 children with pathological diagnosis of WT that were treated during the period 1979-1989. They were postoperatively staged as follows: stage I, 25 (22.3%) patients; stage II, 27 (24.1%) patients; stage III, 48 (42.8%) patients; stage IV, 9 (8%) patients; and stage V, 3 (2.6%) patients, whereas Hung et al.,20 who conducted a similar study noticed the following: Stage I constituted 43.2% of the cases, stage II 19.3%, stage III 23.9%, stage IV 6.8% and stage V 6.8% of the cases, indicating delayed presentation and delayed diagnosis of our patients. The age at the time of diagnosis deserves attention. Patients aged over 48 months presented greater frequency of stage III and stage IV tumors. This greater frequency of disease at more advanced stages in our patients may be explainable, at least in part, by the delay in diagnosing it. A study from the NWTS showed that children older than 48 months at the time of diagnosis had a higher probability of relapse and

death. This association was attributed to the delay in the diagnosis, which is more frequently found among older children.21 This result showed the importance of establishing the diagnosis at an early stage.

The overall recurrence rate in the present study was 28.5% (12/42) and the majorities were of stage III and IV, and in those with unfavorable histology. The recurrence was more frequently seen in age groups ≥ 48 months and 24-47 months (80% and 31.2%, respectively). Six cases (50%) recurred distantly (lungs), 4 cases (33.3%) recurred locally (abdomen), and 2 cases (16.6%) recurred locally and distantly. Our current study results coincide with the work of Hisham *et al.* and Spurrier et al., where recurrence rate was 24.2% and 20%, respectively, and the lung was the most common site of metastases.12,22 In contrast, Seyed-Ahadi et al. reported tumor relapse in only four patients (7%), three in stage III and one in stage IV.13 The high rate of recurrence in our series may be due to the high percentage of patients with unfavorable histology.

The disease-free survival rate and overall survival rate at 4 years in our study were 69% and 73.8% respectively. The similar rates in NWTS3 were 81% and 89%, respectively.7 Our survival indices were somewhat higher than that reported by Hisham et al. (58% and 70.1%, respectively) but lesser than that reported by Seyed-Ahadi *et al.* (71% and 86% respectively).12,13 Also Pianezza e*t al*. and Marilia *et al.* reported 4-year survival rates superior to ours (86% and 84.6%, respectively).14,23 The results presented allow the conclusion that the staging and histology remained as prognostic factors associated with higher risk of death. Similarly, Zaghloul *et al.* and Hung et al reported that tumor histology and clinical stage significantly affected the disease-free survival.19,24 In the various clinical trials carried out by NWTSG and International Society of Pediatric Oncology (SIOP), factors associated with the prognosis for WT cases were identified. Among these, the most prominent were the staging (particularly the compromising of lymph nodes), rupture of the tumor and histology.7,24 These results showed that the histology and staging are fundamental for guiding the appropriate therapy.

Wilms' tumor is radiosensitive, and radiation therapy is the mainstay of treatment. Initially used in all patients with WT, successive studies from the NWTSG and SIOP have demonstrated that only patients with stage III or IV disease require radiation therapy.4 It is likely that the availability of radiation therapy in our region might improve the survival of our patients, particularly those with advanced stage disease.

In conclusion, our survival indices were lesser than a number of similar studies survival figures; this may be related to the existence of a more aggressive form of WT in our region and delayed presentation and delayed diagnosis of our patients. As a developing country, with limited diagnostic facilities and inadequate facilities for standard management, we believe that our survival indices were acceptable. We recommend further research with more comprehensive investigation to improve the treatment results of patients with high stage unfavorable histology as drug intensification, or trials involving new investigational therapy.

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Table 1 Modes of presentation of patients

Presenting signs and symptoms	No. (%)
Abdominal mass	39 (92.8)
Abdominal pain	11 (26.2)
Hematuria	9 (21.4)
Fever	7 (16.6)

N.B. Some patients had more than one presentation.

Table 2 General characteristics of patients studied

Variable	No. (%)	Death No. (%)
Gender		
Males	25 (59.5)	8 (25)
Females	17 (40.5)	3 (17.6)
Age groups		
0-23 months	21 (50)	2 (9.5)
24-47 months	16 (38)	5 (31.2)
≥ 48 months	5 (12)	4 (80)
Staging		
I	13 (30.9)	1 (7.7)
II	11 (26.2)	1 (9)
III	15 (35.7)	6 (40)
IV	3 (7.1)	3 (100)
Histopathology		
Favorable	29 (69)	3 (10.3)
Unfavorable	13 (31)	8 (61.5)

Table 3 The distribution of the staging in relation to age groups

Age groups	Stage I	Stage II	Stage III	Stage IV
0-23 months	**9**	**6**	**6**	**0**
24-47 months	**4**	**5**	**7**	**0**
≥ 48 months	**0**	**0**	**2**	**3**

الخلاصة

مصيرالأطفال المصابين بورم ويلمز في مدينة دهوك / إقليم كردستان / شمال العراق

ورم ويلمز من الأمراض الخبيثة التي يمكن الشفاء منه، خصوصا في العقدين الأخيرين بعد إتباع الطرق الحديثة في العلاج. الهدف من هذا البحث هو دراسة نتائج العلاج ومعدل البقاء على قيد الحياة، والعوامل المؤثرة في مصير المرضى .

تمت دراسة اثنتين وأربعين حالة من الأطفال المصابين بورم ويلمز في الفترة من شهر آب ١٩٩٩- إلى آب٢٠٠٦ الذين عولجوا في مستشفى هيفي التعليمي، حيث سُجلت المعلومات الخاصة بالمريض والورم.

جميع المرضى عُولجوا جراحيا بإزالة الكلية المصابة واتبعه العلاج الكيمياوي (بدون إشعاع لعدم توفره) اعتمادا على البروتوكولات العالمية المتعارف عليها.

من بين اثنين وأربعين مريضا، شكل الذكور خمسة وعشرون حالة والإناث سبعة عشرة حالة، ونسبة الذكور إلى الإناث كانت ١,٤٧ : ١، معدل أعمار المرضى عند التشخيص كان ثلاث وثلاثون شهرا .

مراحل الورم كانت على النحو التالي:

٣٠,٩% كانوا في المرحلة الأولى من المرض، ٢٦,٢% في المرحلة الثانية، ٣٥,٧ % في المرحلة الثالثة، و٧,١% في المرحلة الرابعة. في ٦٩% من المرضى كان النسيج ايجابيا (مبشرا بالنجاح) وفي ٣١% كان غير ايجابي (غير مبشر بالنجاح). حصل انتكاس الحالة في اثنا عشر مريضا (٢٨,٥%). بعد أربع سنوات من المتابعة فإن ٢٩مريضا (٦٩%) مازالوا على قيد الحياة بدون مرض، ومريضين (٤,٧%) على قيد الحياة مع وجود المرض، وحصلت الوفاة في أحد عشر مريضا (٢٦,٢%). معدل البقاء بدون مرض ومعدل البقاء على قيد الحياة بعد أربع سنوات كانت ٦٩% و ٧٣,٨% على الترتيب.

كدولة نامية مع محدودية الوسائل التشخيصية وعدم كفاية الطرق العلاجية الحديثة فإننا نعتقد بأن نسبة البقاء على قيد الحياة مقبولة رغم أنها أقل مما هو في الدول الأخرى، وننصح بإجراء بحوث أوسع لتحسين علاج المرضى.