

Kidney tumors in children: A single centre experience from a developing country

ZEHRA FADOO, SAMIA HUSSAIN, SUKAINA PANJU, SAIMA ALVI

Aga Khan University, Department of Pediatrics, Karachi-Pakistan

ABSTRACT

The outcome of children with kidney tumors has significantly improved in the last two decades in the developed world but not in resource poor countries. We share our ten years experience from a single institution of Pakistan. Records of 23 children with kidney tumors were reviewed for demographics, presenting features, staging work-up and outcome. There were 21 (91%) children with Wilms tumor and one each of clear cell sarcoma of kidney and rhabdoid tumor of kidney. Median age of presentation was 4 years with male predominance. Abdominal mass was the commonest presenting feature. Advanced stage was seen in 17 (74%) patients. Eighteen children agreed for therapy and were treated according to National Wilms Tumor Study Guidelines. The overall relapse free survival for children with Wilms Tumor was 56%. Both children with other histopathological subtypes died. Further improvement in survival of these children can only be achieved by increasing awareness, early recognition, appropriate referral, and multidisciplinary approach. [Turk J Cancer 2009;39(1):131-135]

KEY WORDS: Childhood, developing country, kidney tumors, outcome

INTRODUCTION

Kidney tumors comprise almost 6% of all cancers in children below 15 years of age with a wide spectrum of morphological and histopathological types. Wilms Tumor (WT) also known as nephroblastoma or renal embryoma accounts for 95% of all malignant neoplasms of the kidney, the rest being renal cell carcinoma (RCC, 2.6%), clear cell sarcoma of the kidney (CCSK, 1.6%), and rhabdoid tumor of the kidney (RTK, 1%). Other rarer forms of childhood renal tumors include congenital mesoblastic nephroma (CMN), multilocular cystic renal tumor and angiomyolipoma. Wilms tumor is more common in children below 5 years of age. The peak age of presentation is between 3-4 years with no sex predilection (1,2). Remarkable progress has been achieved in the management and outcome of nephroblastoma during the last two decades (3,4). This has largely been the result of multidisciplinary approach by the large collaborative groups namely National Wilms Tumor Study Group (NWTSG) and International Society of Pediatric Oncology (SIOP). However the outcome continues to remain poor in most of the developing countries (5-7). Late presentation with advanced stage disease, delayed referrals, socioeconomic constraints, treatment abandonment, and lack of education are the factors responsible for poor outcome (8). Pakistan being a developing country has similar problems. There is no population based tumor registry in Pakistan, therefore, the exact incidence and outcome of different cancers in children remains unknown. We present here our experi-

ence of kidney tumors in children seen at a single centre over a period of ten years. The focus has been on identification of the demographic features, clinical presentations, and treatment outcome.

PATIENTS AND METHODS

A retrospective chart analysis of children less than 15 years of age admitted to the Aga Khan University Hospital from 1999-2008 with the diagnosis of kidney tumors was carried out. A total of 24 patients were identified and 23 records were available for review of demographics, presenting features, staging workup and outcome. The staging and treatment was carried out according to NWTSG guidelines (9). All inoperable tumors were considered Stage III and treated accordingly. The treatment included 2 drugs (vincristine and actinomycin D) over 18 weeks for Stage I/II favorable histology WT. Stage II-IV focal anaplasia and Stage III/IV received 3 drugs (vincristine, actinomycin-D and doxorubicin) over 24 weeks with radiation therapy (XRT). Radiation was given to the flank for Stage III disease, to whole abdomen if there was tumor rupture during surgery or gross residual disease was present. The lungs were radiated if pulmonary nodules were present at initial diagnosis. The child with CCSK received vincristine, doxorubicin, cyclophosphamide and etoposide over 24 weeks with XRT to the flank. The child with RTK received carboplatin, etoposide and cyclophosphamide with XRT. The laboratory workup for all patients included complete blood count, urinalysis, renal and liver function tests. The radiological assessment included computed tomography (CT) scan of abdomen, X-ray and/or CT scan of the chest, ultrasound of abdomen, and an echocardiogram. Magnetic resonance imaging (MRI) scan of brain and ⁹⁹Tc bone scan were performed in children with CCSK and RTK. The histopathological diagnosis was confirmed in all cases either by core needle biopsy or upfront nephrectomy (UN). Descriptive statistical analyses were performed using SPSS version 16.0. Relapse free survival was estimated by the method of Kaplan and Meier.

RESULTS

There were 14 (61%) boys with a male to female ratio of 1.5:1. The median age of presentation was 4 years (range 1-9 years). The histopathological types seen were

21 (91%) WT including one extra renal, and one each of CCSK and RTK. All children except one with relapsed disease presented as new diagnoses.

Clinical features

Abdominal mass was the chief presenting feature in 17 (74%) patients followed by abdominal pain in 14 (61%), fever in 13 (56%), and gross hematuria in 4 (17%). Vomiting and urinary retention was seen in 2 (9%) patients. One child with extra renal WT presented with acute renal failure secondary to urinary tract obstruction. Hypertension was observed in 13 (56%) cases while developmental delay and hypospadias was seen in one child each. Two children presented with thrombi in inferior vena cava and renal vein with extension up to the right atrium in one case.

Diagnosis and staging

CT scan of abdomen and pelvis was performed at diagnosis on all cases, whereas ultrasound of abdomen was done in 15 (65%) patients. Metastases to the chest were evaluated by X-ray only in 5 (22%), CT scan in 6 (26%), and by both modalities in 12 (52%) cases. All children had unilateral disease, 15 (65%) had right sided and 8 (35%) had left sided disease. There were 3 patients (13%) each of Stage I and II, 13 (57%) with Stage III, and 4 (17%) with Stage IV disease. One patient had metastatic deposits in the liver and another in the lungs, while two had involvement of both organs. Eighteen of 23 (78%) children received treatment at our centre. Upfront nephrectomy (UN) was done in 6 (33%) patients, one with Stage III (RTK), while the rest had Stage I/II disease (WT). The remaining 12 (67%) children received preoperative chemotherapy (PC) and thus were treated as Stage III. However, these patients had a core needle biopsy prior to starting treatment. All but one patient with WT had favorable histology. Both patients with CCSK and RTK had Stage III disease.

Patients and outcome

Eighteen of 23 (78%) children with renal tumors opted for treatment at our center. Five patients left after the initial diagnosis and staging workup, including the patient who presented as relapsed disease. The therapy was given as per NWTSG guidelines. Sixteen children with WT received treatment, with the relapse free survival of 56% (Figure 1). The follow up period after treatment ranged from 1-63 months (average 16 months). The details of

five relapsed patients of WT and one with CCSK are given in Table 1. Three of the relapsed patients with WT had Stage III, one had Stage I and one had Stage IV disease. The one patient with Stage I/favorable histology WT had tumor size <550 gr and initially received no therapy but was salvaged with chemotherapy and XRT after relapse. The rest of relapsed patients had pre-operative chemotherapy with delayed surgery/XRT. The overall survival could not be calculated because a significant proportion of relapsed patients were lost to follow up. The child with CCSK relapsed after 2 years of initial diagnosis with CNS metastasis while the one with RTK succumbed to infection during chemotherapy.

DISCUSSION

Kidney tumors comprise approximately 6% of all childhood cancers. WT is the most common primary renal neoplasm in children. The exact incidence and outcome of these tumors in Pakistan is unknown. Although our study is a single institution experience, biases regarding patient selection have to be considered. In the absence of larger cohorts this may represent some of our patient characteristics and help promote better understanding of our population. In our study the most common histopathological subtype was WT (91%). The median age at the time of diagnosis was 4 years, which is slightly higher than reported from developed countries but similar to the data reported from Sudan, Nigeria and other developing countries (2,6, 10-13). Boys outnumbered girls with a ratio of

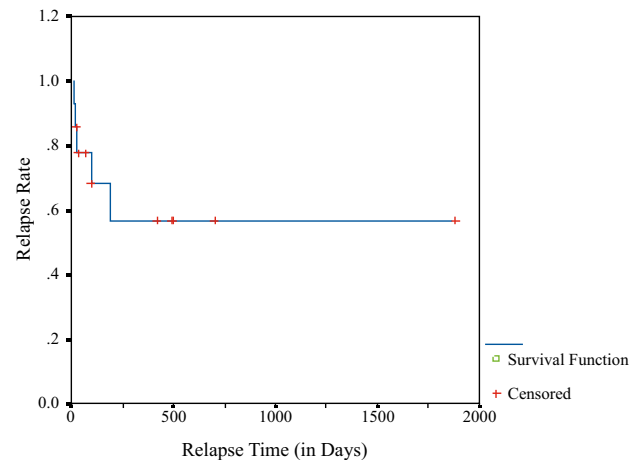


Fig 1. Relapse free survival of sixteen children with WT receiving treatment

1.5:1, again consistent with literature from other resource poor countries (14-16). This may either be a true reflection of sex predilection for the disease or a gender bias in our culture where males are brought preferentially to medical attention than females.

The first Wilms tumor trial from the United Kingdom Children Cancer Study Group (UKCCSG) reported abdominal mass as the most common presenting symptom with comparable reports from other studies (6,13,17,18). Fever, abdominal pain, gross hematuria, and hypertension are other frequently seen symptoms in these children (2). Similar observations were seen in our study population.

A substantial proportion (74%) of our patients presented as advanced stage disease (Stage III and IV). This

Table 1
Characteristics of relapsed patients

Patient	Type of Renal Tumor	Primary tumor sites	Stage of disease at diagnosis	Treatment received	Site of Relapse	Time To Relapse from end of treatment (months)	Therapy after relapse	Outcome
01	WT	Kidney	III	PC,A,V,D/XRT	Primary site/ Lungs	03	No	Lost to follow up
02	WT	Kidney	I	Only surgery	Primary site/ Liver	<1	Yes	Alive without disease
03	CCSK	Kidney	III	PC,V,C,D,E/XRT	Brain	24	No	Lost to follow up
04	WT	Kidney/lung	IV	PC,A,V,D/XRT	Primary site/Liver	<1	No	Lost to follow up
05	WT	Kidney	III	PC,A,V,D/XRT	Primary site/ Liver	<1	No	Expired
06	WT	kidney	III	PC,A,V,D/XRT	Primary site/Lungs/Liver	06	No	Expired

WT: Wilms tumor, CCSK: clear cell sarcoma of the kidney

PC: preoperative chemotherapy, A: actinomycin-D, V: vincristine, D: doxorubicin, XRT: radiation, C: cyclophosphamide, E: etoposide

is another significant factor that determines the outcome. Davidson and others (19) have reported a similar pattern of advanced stage disease in developing countries. In our study the relapse free survival of children with WT was 56% that compares with the reported figures from developing countries but still far less than the developed countries (4,6,13,20). Older age and advanced stage of the disease found in our children at presentation might have contributed to the poorer outcome. The outcome in five children is unknown as they were lost to follow-up, two of them just after completion of therapy and 3 after relapse. Loss to follow-up and abandonment of treatment are factors known to contribute to poor survival (8,21). All relapses seen in our children with WT were seen within 6 months of completion of therapy. Early relapses have been associated with poor outcome and may reflect more aggressive nature of disease seen in children residing in developing countries (22). The most frequent sites of relapse reported in children with WT are the lungs, while original tumor bed, liver, brain and bone are less frequently involved (23). In our observation primary tumor bed was the predominant site of relapse seen in all patients with combination of lung and/or liver metastasis. The relapses were seen more in children who had pre-operative chemotherapy (PC). Under staging because of difficulty of assessing nodal spread and alteration in histology with PC has been known to increase local relapses as shown in SIOP 6 trial (24). All 5 NWTS trials have been based on upfront nephrectomy (UN) with risk adapted chemotherapy/radiotherapy and recommendation that all children who had inoperable tumors at diagnosis be treated as Stage III to overcome the above mentioned issues. The International Society of Pediatric Oncology (SIOP) on the other hand uses PC to decrease the risk of tumor spillage. With the excellent outcome of children treated on either of the two regimens the aim is now to decrease the risk of potential long term sequelae without altering the efficacy. Cardiotoxicity secondary to anthracyclines and effects on growth and fertility after abdominal irradiation are the major long term sequelae seen in these patients (25).

In our patients advanced disease at diagnosis resulting in inadequate local control even with delayed nephrectomy, further delay in radiation because of parental anxiety

and concerns, intra-operative tumor spillage and intolerance to chemotherapy could be some of the risk factors for relapses in our patients. Multidisciplinary team approach comprising of surgeons, radiation and pediatric oncologist with development of expertise in their respective fields is essential for improving the outcome of these children. Uniform protocols need to be established to give standard of care to all and to evaluate the outcome in a more significant manner. Collaborative efforts also need to be established between the caregivers and different centres involved in the care of these children as all facilities may not be available at a single institute.

In contrast to WT, recurrences in CCSK are usually seen 3 years after completion of treatment. The most preferential sites of recurrences are bone and local bed of tumor followed by brain and liver (26). The only child with CCSK diagnosed and treated at our hospital relapsed after 24 months. Another unusual finding in our study was a child with RTK who presented at 8 years of age. The NWTS reported RTK being more frequently seen in children less than 2 years of age with only one out of 142 children above 8 years of age (27). Although the prognosis is better for older children, our patient died early during chemotherapy secondary to infection.

A significant proportion (22%) of our children left after the establishment of diagnosis. The exact reasons for leaving were not ascertained but inadequate finances, ignorance, lack of support in terms of lodging and misconceptions about the disease as reported in other studies, were the most probable factors (6,7,13,19).

CONCLUSION

The outcome of children with kidney tumors continues to remain poor in developing countries. Improvement in the survival of these children can only be achieved by early recognition and referral, multidisciplinary approach with close collaboration of surgeons, pathologist, radiation and pediatric oncologist. Identifying and tackling the causes of abandonment, improving resources together with creating awareness among parents, families and physicians are also essential to achieve this goal.

References

1. Bernstien L, Linet M, Smith MA. Renal Tumors. In: Ries LA, Smith MA, Gurney J, editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995, Bethesda, MD, 1999:79-90.
2. Varan A. Wilms' tumor in children: an overview. *Nephron* 2008;108(2):c83-90.
3. Arndt V, Lacour B, Steliarova-Foucher E, et al. Up-to-date monitoring of childhood cancer long-term survival in Europe: tumours of the sympathetic nervous system, retinoblastoma, renal and bone tumours, and soft tissue sarcomas. *Ann Oncol* 2007;18:1722-33.
4. D'Angio GJ. The National Wilms Tumor Study: a 40 year perspective. Lifetime data analysis. 2007;13:463-70.
5. Metzger ML, Dome JS. Current therapy for Wilms' tumor. *Oncologist* 2005;10:815-26.
6. Ekenze SO, Agugua-Obianyo NE, et al. The challenge of nephroblastoma in a developing country. *Ann Oncol* 2006;17:1598-600.
7. Sangkhathat S, Chotsampancharaen T, Kayasut K, et al. Outcomes of pediatric nephroblastoma in southern Thailand. *Asian Pac J Cancer Prev* 2008;9:643-7.
8. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. *Pediatr Blood Cancer* 2007;49:941-6.
9. D'Angio GJ. Management of children with Wilms' tumor. *Cancer* 1972;30:1528-33.
10. Neville HL, Ritchey ML. Wilms' tumor. Overview of National Wilms' Tumor Study Group results. *Urol Clin North Am* 2000;27:435-42.
11. Grabois MF, Mendonca GA. Prognosis for patients with unilateral Wilms' tumor in Rio de Janeiro, Brazil, 1990-2000. *Rev Saude Publica* 2005;39(5):731-7.
12. Seyed-Ahadi MM, Khaleghnejad-Tabari A, Mirshemirani A, et al. Wilms' tumor: a 10 year retrospective study. *Arch Iran Med* 2007;10(1):65-9.
13. Abuidris DO, Elimam ME, Nugud FM, et al. Wilms tumour in Sudan. *Pediatr Blood Cancer* 2008;50(6):1135-7.
14. Yildiz I, Yuksel L, Ozkan A, et al. Multidisciplinary approach to Wilms' tumor: 18 years of experience. *Jpn J Clin Oncol* 2000;30(1):17-20.
15. Nawaz A, Matta H, Jacobsz A, et al. Wilms' Tumor: The Tawam Hospital experience. *Ann Saudi Med* 1999;19(3):257-60.
16. Shah SH, Pervez S, Hassan SH. Frequency of malignant solid tumors in children. *J Pak Med Assoc* 2000;50(3):86-8.
17. Pritchard J, Imeson J, Barnes J, et al. Results of the United Kingdom Children's Cancer Study Group First Wilms' Tumor Study. *J Clin Oncol* 1995; 13(1):124-33.
18. Green DM, D'Angio GJ, Beckwith JB, et al. Wilms tumor. *CA Cancer J Clin* 1996;46(1):46-63.
19. Davidson A, Hartley P, Desai F, et al. Wilms tumour experience in a South African centre. *Pediatr Blood Cancer* 2006;46(4):465-71.
20. Kutluk T, Varan A, Buyukpamukcu N, et al. Improved survival of children with Wilms tumor. *J Pediatr Hematol Oncol* 2006;28(7):423-6.
21. Yeh CH, Lin CF, Tsai JL, et al. Determinants of parental decisions on 'drop out' from cancer treatment for childhood cancer patients. *J Adv Nurs* 1999;30(1):193-9.
22. Barr RD. The challenge of childhood cancer in the developing world. *East Afr Med J* 1994;71(4):223-5.
23. Grundy P, Breslow N, Green DM, et al. Prognostic factors for children with recurrent Wilms' tumor: results from the Second and Third National Wilms' Tumor Study. *J Clin Oncol* 1989;7(5):638-47.
24. Tournade MF, Com-Nougue C, Voute PA, et al. Results of the Sixth International Society of Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' Tumor. *J Clin Oncol* 1993;11:1014-23.
25. Pritchard-Jones K. Controversies and advances in the management of Wilms' tumor. *Arch Dis Child* 2002;87:241-4.
26. Argani P, Perlman EJ, Breslow NE, et al. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumor Study Group Pathology Center. *Am J Surg Pathol* 2000;24(1):4-18.
27. Tomlinson GE, Breslow NE, Dome J, et al. Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: age at diagnosis as a prognostic factor. *J Clin Oncol* 2005;23(30):7641-5.