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ORIGINAL ARTICLES

PATTERN, CLINICAL PRESENTATION AND MANAGEMENT OF WILMS' TUMOR IN MOSHI, TANZANIA

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Objective: The aim of this study was to audit the treatment outcome of children with Wilms' tumor in East Africa, at a Urology referral center with limited access to imaging modalities and chemotherapeutic drugs, and no radiation facility.

Patients and Methods: This is a retrospective analysis of the hospital records of children with a diagnosis of Wilms' tumor treated from June 1996 to May 2005 at the Association of Surgeons of East Africa (ASEA) Institute of Urology, Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania.

Results: In total, 50 patients were diagnosed with Wilms' tumor in the 9 years study period, but only 39 files contained sufficient information for analysis. The average age at presentation was 44.7 months (median 36, range 8 to 120 months). 25.6% of the children were >60 months old. The male:female ratio was 1.4:1. All of the children presented with an abdominal mass detected by the parents. The hemoglobin was <100 gm/L in 21 (53.8%) and the platelet count was >450,000/ml in 8 (20.5%) cases. Ultrasound imaging was obtained in all cases, but CT imaging was not taken. Intravenous urography was done in 38 children and showed non-visualization of the involved kidney in 16 (42.1%). Fine needle aspiration cytology (FNAC) was performed in 25 cases and was diagnostic in 23 (92%). Preoperative vincristine and dactinomycin was given to 23 patients (59%) with marked tumor shrinkage in 20 (87%), while 3 (13%) showed no response. Radical nephrectomy was performed in all patients, and 3 patients (7.7%) died within 24 hours of surgery. Pathologic analysis showed favorable histology in 35 (89.7%) and unfavorable histology in 4 (10.3%) patients. Based on the pre- and intra-operative findings, NWTS stage 1, 2, 3, 4 and 5 was present in 25.6%, 17.9%, 15.4%, 38.5% and 2.6%, respectively. Postoperative dactinomycin and vincristine was given monthly for one year in all patients, while doxorubicin and cyclophosphamide were reserved for those with no response to the first-line drugs, or recurrent tumor. Radiotherapy was not available. At 12 months' follow-up the overall disease-free survival was 35.9%, recurrence had occurred in 38.6%, death in 15.4%, and 10.3% were lost to follow-up.

Conclusion: Children with Wilms' tumor in East Africa still have a dismal prognosis, with treatment outcomes at levels where it was before the advent of chemotherapy and radiation therapy in more advanced centers.

Key Words: Wilms' tumor, Africa, chemotherapy.

INTRODUCTION

Cancer in children and adolescents is rare. Wilms' tumor is the most common primary malignant renal tumor in children, constituting 7-8% of childhood cancer[1-3]. The majority of cases are sporadic, with only 1-2% having a positive family history[3-6]. The majority are unilateral,

with 4-5% being synchronous bilateral disease. Around 10-15% of children with Wilms' tumor are found to have associated anomalies[7-12].

The etiology of Wilms' tumor is not known. It appears to result from changes in one or more of several genes. Before the introduction of multimodality therapy the survival rate of Wilms' tumor patients with surgical excision alone was 25%. Cooperative multi-center studies (e.g. National Wilms' Tumor Study - NWTS in the USA, the International Society of Pediatric Oncology (SIOP) trial in Europe, and the United Kingdom Wilms' tumor study) brought about the evolution of modern multimodality treatment, which has made Wilms' tumor a highly curable disease, with >90% of children surviving 4 years after the diagnosis[13,14].

Despite an appreciable improvement in the survival rate of patients with Wilms' tumor in developed countries over the past few decades, children in East Africa may not have benefited from these advances, for a variety of reasons. We present our experience in a center in East Africa where no radiation facility and only limited access to chemotherapeutic agents are available.

PATIENTS AND METHODS

This is a retrospective study conducted at the Association of Surgeons of East Africa (ASEA) Institute of Urology, Kilimanjaro Christian Medical Center (KCMC), Moshi, Tanzania. The ASEA Institute of Urology is the only center solely dedicated to Urologic service and training of general surgeons in East and Central Africa over the past 10 years.

The hospital records of all patients with a diagnosis of Wilms' tumor treated between June 1996 and May 2005 were retrieved.

Apart from the history and physical examination, all children had basic investigations (full blood count, urine analysis, renal function tests). Ultrasound imaging and chest X-ray were obtained in all cases. CT scanning was not performed because it was unaffordable.

During the study period there was no rigidly applied protocol for the treatment of Wilms' tumor, but in most cases the management consisted of:

- Preoperative chemotherapy with two drugs (vincristine and dactinomycin) if the tumor was regarded as surgically unresectable,
- Fine needle aspiration cytology (FNAC) prior to pre-operative chemotherapy,
- Postoperative chemotherapy with dactinomycin and vincristine monthly for one year in all patients (although this is not the standard NWTS protocol, the reason for choosing these two drugs was their consistent availability in our center),
- Due to the limited availability of doxorubicin and cyclophosphamide, these drugs were reserved for selected patients with recurrent tumors or non-response to dactinomycin and vincristine.

Follow-up consisted of monthly clinical examination and three-monthly ultrasonography and chest X-ray. The results of our management were evaluated at one year of follow-up when the children came for chemotherapy.

RESULTS

From June 1996 to May 2005, a total of 50 patients were diagnosed with Wilms' tumor. The files of 44 were retrieved, 5 were excluded due to incomplete information, and 39 (78%) were analyzed.

The male: female ratio was 1.4:1 The average age at presentation was 44.7 months with a median age of 36 months (range 8 to 120 months). 25.6% of the children were >60 months old (Table1).

All the children presented initially because of a visible or palpable abdominal mass, while a few complained of fever, hematuria or vomiting. On examination an abdominal mass reaching to the umbilicus or beyond

Table 1: Frequency distribution of age and sex in children with Wilms' tumor treated at ASEA Institute of Urology, 1996-2005.

Age (months)	Male		Female		Total	
	No.	%	No.	%	No.	%
1-12	3	13.0%	2	12.5%	5	12.8%
13-24	4	17.4%	3	18.8%	7	17.9%
25-36	7	30.4%	2	12.5%	9	23.1%
37-48	1	4.3%	4	25.0%	5	12.8%
49-60	1	4.3%	2	12.5%	3	7.7%
>60	7	30.4%	3	18.8%	10	25.6%
Total	**23**	**100.0%**	**16**	**100.0%**	**39**	**100.0%**

was identified in all children. An associated anomaly (hypospadias and undescended testis) was documented in 1 patient (2.6%).

The hemoglobin level was below 100 gm/L (normal value 100-140 gm/L) in 21 of 39 (53.8%) children and the platelet count was greater than 450,000/ml (normal value 150,000-450,000) in 8 (20.5%) cases. Liver function tests (i.e. SGOT, SGPT and ALP) were normal in all patients.

On ultrasound imaging it was possible to demonstrate the mass, and impossible to identify a normal kidney on the affected side in all cases (as indirect evidence of the tumor originating from the kidney rather than from the adrenal gland). Intravenous urography was obtained in 38 cases (97.4%) and showed non-visualization of the involved kidney in 16 (42.1%). Chest X-ray was obtained in all cases and none demonstrated evidence of pulmonary metastases at presentation. FNAC was performed in 25 cases (64.1%) and in 23 (92%) it was diagnostic, while in 2 it was inconclusive.

Preoperative chemotherapy (vincristine and dactinomycin) was given to 23 patients (59%), with marked tumor shrinkage in 20 (87%), while 3 (13%) cases showed no response. All patients underwent surgery through a chevron transverse abdominal incision. Radical nephrectomy was performed in all patients, with en bloc resection of the spleen, tail of the pancreas, colon or part of the liver in 6 patients (15.4%). Routine lymphadenectomy was not done, only suspicious lymph nodes were removed for histopathological examination. Surgical exploration of the contralateral kidney was not routinely performed.

The mean tumor diameter was 16.4 cm (range 12 to 24 cm). Pathologic analysis showed favorable histology in 35 (89.7%) and unfavorable histology in 4 (10.3%).

Staging was performed according to the NWTS system based on the intra-operative finding and pathology report. The majority of cases (38.5%) were stage 4 (Table 2), mostly with pulmonary or liver metastases palpable at surgical exploration.

At one year follow-up, 6 patients (15.4%) had died (3 of them within 24 hours of surgery), and 4 (10.3%) were lost to follow-up. Extensive recurrences occurred within 8 months after initial treatment in 15 (38.5%) children. The disease-free survival, recurrence and mortality rates for the different stages are shown in Table 3.

DISCUSSION

Our study group had a slightly higher male to female ratio (1.4:1 versus 1:1), a

Table 2: Frequency distribution of stage in children with Wilms' tumor.

Stage	No.	%
1	10	25.6%
2	7	17.9%
3	6	15.4%
4	15	38.5%
5	1	2.6%
Total	**39**	**100.0%**

Table 3: Frequency distribution of treatment outcome at one year according to stage of Wilms' tumor.

Stage	No.	Lost to Follow Up		Disease-free		Recurrence		Death	
		No.	%	No.	%	No.	%	No.	%
1	10	0	0.0%	6	60.0%	3	30.0%	1	10.0%
2	7	0	0.0%	5	71.4%	2	28.6%	0	0.0%
3	6	0	0.0%	2	33.3%	4	66.7%	0	0.0%
4	15	4	26.7%	1	6.7%	6	40.0%	4	26.7%
5	1	0	0.0%	0	0.0%	0	0.0%	1	100.0%
Total	**39**	**4**	**10.3%**	**14**	**35.9%**	**15**	**38.5%**	**6**	**15.4%**

lower rate of synchronous bilateral tumors (Stage 5) (2.6% versus 5%), and a lower rate of associated congenital anomalies (2.6% versus 10-15%) compared to the figures cited in the literature. Their average (44.7 versus 42 months) and median age at presentation (36 months versus 36 months) is similar to that reported in the literature[1,2,7,8]. The male preponderance in our study group may be due to the smaller number of cases compared to the large cooperative studies. The lower incidence of bi-laterality and associated congenital anomalies in our patient cohort may be the result of failure to routinely perform bilateral renal exploration and failure to record the associated congenital anomalies in the notes.

All the children in this study presented with an abdominal mass detected by the mother or father, which is similar to most studies where >80% of children presented with a mass detected by the parents or primary care physician[1,2]. The low hemoglobin in 54% of these children is most probably due to late presentation.

It has been stated that intravenous urography is sufficient for the diagnosis and initial management of children with Wilms' tumor. IVU showed non-visualization of the affected kidney in 42% of our cases, which is significantly higher than the figure of 10% cited in the literature. This is probably due to the late presentation with massive involvement of the affected kidney. In the literature FNAC is recommended if preoperative chemotherapy is indicated[15,16]. FNAC confirmed the diagnosis in 23 of 25 (92%) cases in our study, with 2 inconclusive results, confirming the usefulness of FNAC.

In the literature preoperative chemo-therapy is recommended in patients with massive, non-resectable unilateral tumors, in those with vena cava thrombus extending above the hepatic veins, and in bilateral tumors[17-21]. Preoperative chemotherapy (two

courses of vincristine and dactinomycin) was given to 23 patients in this study, with significant reduction in tumor size in 20.

Pathologic analysis of the specimen revealed favorable histology in 89.7% and unfavorable histology in 10.3% of our patients, which is similar to the 90% and 10% distribution reported in other studies[13,14,22]. The stage distribution in our patients was 25.6%, 17.9%, 15.4%, 38.5% and 2.6% for stages 1, 2,3,4 and 5, respectively, compared to the distribution of 43%, 23%, 23%, 10% and 5%, respectively, reported in Western countries[23,24]. The high proportion of stage-4 disease in our study group (38.5% compared to 10% in the literature) is most probably due to late presentation because of poor access to medical care.

The number of stage-5 tumors may have been underestimated in our study, because pre-operative CT imaging was not available and exploration of the contra-lateral kidney at surgery was not routinely performed. We did not have a specific management protocol for stage-5 disease, and the only such patient in our study did not survive beyond 8 months.

The perioperative mortality in 3 (7.7%) of our patients presumably resulted from an over-courageous attempt at en bloc resection of the tumor rather than doing FNAC and giving preoperative chemotherapy. In our view, the recommendation in the literature to take an initial biopsy and use preoperative chemo- and even radiotherapy prior to attempted resection of a massive tumor should be followed[25].

The one-year recurrence-free survival of 35.9% in our study group is much less than the 4-year disease-free survival reported by large co-operative study groups (around 80%). This is probably due to the advanced stage at presentation of our patients, unavailability of a third chemotherapy drug, and the lack of facilities such as radiation therapy. The one-year recurrence-free survival of 60% and 71.4% for stages 1 and 2, respectively, in our study group is significantly less than the 4-year recurrence-free survival of 92% and 85% reported in other studies[23,24,26-29]. This may be due to understaging of our patients, because CT imaging was not available and lymphadenectomy was not routinely performed at surgery. Recurrence occurred less than 8 months from the time of primary treatment in 38.5% of our patients. One of the well known factors indicating a poor prognosis is recurrence within the first six months[29-31].

In conclusion, this study provides baseline data on the current reality of Wilms' tumor treatment in Africa. Children with Wilms' tumor in this part of the world still have a dismal prognosis, with treatment outcomes at levels where it was before the advent of chemotherapy and radiation therapy in more advanced centers. We recommend the establishment of a cooperative regional study and management protocol for the treatment of Wilms' tumor in African children.

REFERENCES

1. Young JL, Heise HW, Silverberg E, Myers MH. Cancer incidence, survival and mortality for children under 15 years of age. *Professional Education* Publication: American Cancer Society, Atlanta, GA,.1978 .
2. Duffy PG: Genitourinary malignancy. In: Thomas D, Rickwood AMK, Duffy PG. Essentials of Paediatric Urology.1st ed. chapt. 22, London.:Martin Dunitz; 2002, pp. 225-232.
3. Michael Ritchey: Paediatrics. Urologic oncology. In: *Walsh PC, Retik AB, Vaughan ED, Wein AJ,* Kavoussi LR, Novick AC, et al. Campbell's Urology, 8th ed., chapt.70, Philadelphia: W.B. *Saunders*, 2002, pp. 2481-2494 .
4. Breslow N, Beckwith JB, Ciol M, Sharples K. Age distribution of Wilms' tumor: Report from the National Wilms' Tumor Study.Cancer Res.1988 Mar 15;48(6):1653-7.
5. Bonaiti Pellie C, Chompret A, Tournade MF, Hochez J, Moutou C, Zucker JM, et al. Genetics and epidemiology of Wilms' tumor: The French Wilms' tumor study.Med.Pediatr.Oncol.1992;20(4):284-91.
6. Breslow NE, Beckwith JB. Epidemiological features of Wilms' tumor: Results of the National Wilms' Tumor Study.J.Natl.Cancer Inst.1982 Mar; 68(3):429-36.
7. Miller RW. Relation between cancer and congenital defects: An epidemiologic evaluation.J.Natl.Cancer Inst.1968 May;40(5):1079-85.

8. Miller RW, Fraumeni JF, Manning MD. Association of Wilms's tumor with aniridia, hemihypertrophy and other congenital malformations.N.Engl.J.Med.1964 Apr 30;270:922-7.

9. Green DM, Breslow NE, Beckwith JB, Norkool P. Screening of children with hemihypertrophy, aniridia, and Beckwith-Wiedemann syndrome in patients with Wilms' tumor: A report from the National Wilms' Tumor Study.Med.Pediatr.Oncol.1993; 21(3):188-92.

10. DeBaun MR, Siegel MJ, Choyke PL. Nephromegaly in infancy and early childhood: A risk factor for Wilms' tumor in Beckwith-Wiedemann syndrome. J.Pediatr.1998 Mar;132(3 Pt 1):401-4.

11. DeBaun MR,Tucker MA. Risk of cancer during the first four years of life in children from the Beckwith-Wiedemann Syndrome Registry.J.Pediatr.1998 Mar; 132(3 Pt 1):398-400.

12. Hoyme HE, Seaver LH, Jones KL, Procopio F, Crooks W, Feingold M. Isolated hemihyperplasia (hemihypertrophy): Report of a prospective multicenter study of the incidence of neoplasia and review.Am.J.Med.Genet.1998 Oct 2;79(4):274-8.

13. Diller L, Ghahremani M, Morgan J, Grundy P, Reeves C, Breslow N, et al. Constitutional WT1 mutations in Wilms' tumor patients.J.Clin. Oncol.1998 Nov;16(11):3634-40.

14. Coppes MJ, Haber DA, Grundy PE. Genetic events in the development of Wilms' tumor.N.Engl. J.Med.1994 Sep 1;331(9):586-90.

15. Saarinen UM, Wikstrom S, Koskimies O, Sariola H. Percutaneous needle biopsy preceding preoperative chemotherapy in the management of massive renal tumors in children.J.Clin.Oncol.1991 Mar;9(3):406-15.

16. Dykes EH, Marwaha RK, Dicks-Mireaux C, Sams V, Risdon RA, Duffy PG, et al. Risks and benefits of percutaneous biopsy and primary chemotherapy in advanced Wilms' tumour.J.Pediatr.Surg.1991 May;26(5):610-2.

17. Ritchey ML. The role of preoperative chemotherapy for Wilms' tumor: The NWTSG perspective. National Wilms' Tumor Study Group.Semin.Urol.Oncol.1999 Feb;17(1):21-7.

18. Ritchey ML. Primary nephrectomy for Wilms' tumor: approach of the National Wilms' Tumor Study Group.Urology.1996 Jun;47(6):787-91.

19. Ritchey ML, Kelalis PP, Breslow N, Etzioni R, Evans I,Haase GM, et al. Surgical complications after nephrectomy for Wilms' tumor.Surg.Gynecol. Obstet.1992 Dec;175(6):507-14.

20. Tournade MF, Com Nougue C, Voute PA, Lemerle J, de Kraker J, Delemarre JF, 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 Jun;11(6):1014-23.

21. Oberholzer HF, Falkson G, De Jager LC. Successful management of inferior vena cava and right atrial nephroblastoma tumor thrombus with preoperative chemotherapy.Med.Pediatr.Oncol.1992;20(1):61-3.

22. Zuppan CW, Beckwith JB, Luckey DW. Anaplasia in unilateral Wilms' tumor: A report from the National Wilms' Tumor Study Pathology Center.Hum. Pathol.1988 Oct;19(10):1199-209.

23. Vujanic GM, Harms D, Sandstedt B, Weirich A, de Kraker J, Delemarre JF. New definitions of focal and diffuse anaplasia in Wilms tumor: The International Society of Paediatric Oncology (SIOP) experience. Med.Pediatr.Oncol.1999 May;32(5):317-23.

24. Faria P, Beckwith JB, Mishra K, Zuppan C, Weeks DA, Breslow N, et al. Focal versus diffuse anaplasia in Wilms tumor-new definitions with prognostic significance: A report from the National Wilms Tumor Study Group.Am.J.Surg.Pathol.1996 Aug;20(8):909-20.

25. Green DM, Breslow NE, Beckwith JB, Finklestein JZ, Grundy PE,Thomas PR, et al. Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: A report from the National Wilms' Tumor Study Group.J.Clin. Oncol.1998 Jan;16(1):237-45.

26. Green DM, Breslow NE, Beckwith JB, Finklestein JZ, Grundy P, Thomas PR, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: A report from the National Wilms' Tumor Study Group.J.Clin. Oncol.1998 Dec;16(12):3744-51.

27. D'Angio GJ, Breslow N, Beckwith JB, Evans A, Baum H, deLorimier A, et al. Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study.Cancer.1989 Jul 15;64(2):349-60.

28. Montgomery BT, Kelalis PP, Blute ML, Bergstralh EJ, Beckwith JB, Norkool P, et al. Extended followup of bilateral Wilms tumor: Results of the National Wilms Tumor Study.J.Urol.1991 Aug;146(2(Pt 2)):514-8.

29. Shamberger RC, Guthrie KA, Ritchey ML, Haase GM, Takashima J, Beckwith JB, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4.Ann.Surg.1999 Feb;229(2):292-7.

30. Abu Ghosh AM, Krailo MD, Goldman SC, Slack RS, Davenport V, Morris E, et al. Ifosfamide, carboplatin and etoposide in children with poor-risk relapsed Wilms' tumor: A Children's Cancer Group report. Ann.Oncol.2002 Mar;13(3):460-9.

31. Kung FH, Bernstein ML, Camitta BM, Harris MB, Vietti TJ, Sullivan J, Ifosfamide/Carboplatin/ Etoposide (ICE) in the treatment of advanced, recurrent Wilms' tumor. Proceedings of the American Society of Clinical Oncology;1999.18: A-2156,5899.

RESUME

Configuration, presentation clinique et prise en charge de la tumeur de Wilms à Moshi, Tanzanie

Objectif: Le but de cette étude était d'évaluer les résultats du traitement des enfants présentant une tumeur de Wilms en Afrique de l'Est, dans un centre de référence d'urologie avec un accès limité à l'imagerie médicale et aux drogues chimiothérapeutiques, et aucun service de radiothérapie.
Patients et méthodes: C'est une analyse rétrospective des dossiers médicaux d'enfants présentant une tumeur de Wilms traités de juin 1996 à mai 2005 à l'hôpital de l'association des chirurgiens de l'Afrique de l'Est, institut d'urologie (ASEA), le centre médical chrétien de Kilimanjaro (KCMC), Moshi , Tanzanie .
Résultats: Au total, 50 patients ont été diagnostiqués porteurs de tumeur de Wilms pendant les neuf ans d'étude, mais seulement 39 fichiers ont contenu l'information suffisante pour l'analyse. L'âge moyen à la présentation était de 44.7 mois (médiane 36, extrêmes 8 à 120 mois). 25.6% des enfants étaient >60 mois. Le sexe ratio était de 1.4/1. Tous les enfants se sont présentés avec une masse abdominale détectée par les parents. L'hémoglobine était <100 g/l chez 21 patients (53.8%) et le compte des plaquettes était >450,000/ml chez 8 patients (20.5%). Une échographie a été réalisée chez tous les patients, mais le CT scan n'était pas disponible. L'urographie intraveineuse a été faite chez 38 enfants et a montré un rein mué dans 16 cas (42.1%). La cytologie de l'aspiration à l'aiguille fine (FNAC) a été réalisée chez 25 cas et a confirmé le diagnostic dans 23 cas (92%). La vincristine et l'actinomycine préopératoire ont été administrés à 23 patients (59%) avec une diminution marquée de la tumeur dans 20 cas (87%), alors que 3 (13%) ne montraient aucune réponse. La néphrectomie radicale a été réalisée chez tous les patients, et 3 patients (7.7%) sont morts dans un délai de 24 heures de la chirurgie. L'analyse pathologique a montré une histologie favorable chez 35 (89.7%) et défavorable chez 4 patients (10.3%). Basé sur les résultats pré et per-opératoires, les stades de NWTS 1, 2, 3, 4 et 5 étaient présents chez, respectivement, 25.6%, 17.9%, 15.4%, 38.5% et 2.6%. L'actinomycine et le vincristine ont été administrés en postopératoire mensuellement pendant une année chez tous les patients, alors que la doxorubicine et le cyclophosphamide étaient réservés pour ceux sans réponse aux drogues principales, ou aux récidives de tumeur. La radiothérapie n'était pas disponible. Au suivi à 12 mois la survie sans récidive globale était de 35.9%, la récidive était diagnostiquée dans 38.6% des cas, décès dans 15.4%, et 10.3% ont été perdus de vue.
Conclusion: Les enfants présentant une tumeur de Wilms en Afrique de l'Est ont toujours un pronostic réservé, avec des résultats de traitement au même niveau où il était avant l'arrivée de la radiothérapie et de la chimiothérapie dans des centres plus avançés.

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