Wilms' Tumor: Single Centre Retrospective Study from South India

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Abstract Wilms' tumor is the most common malignant renal tumor in paediatric age group, and is classically managed by multimodal treatment which involves surgery, radiotherapy and chemotherapy. The last few decades have seen a dramatic change in the prognosis of this disease, which once was a uniformly lethal malignancy. While there is plenty of data in world literature on the outcome of Wilms' tumor, there is paucity of data from India. Hence, we conducted the present study to analyze the outcome of Wilms' tumor at our institute. To study the clinicopathologic profile and outcome of Wilms' tumor with NWTS (National Wilms' Tumor Study Group) IV protocol. Sixty-one patients with histopathological proven diagnosis of Wilms' tumor and had received treatment at our institute from Jan 2003 through Dec 2010 were included for analysis. Patients received treatment based on NWTS IV protocol. Patients were analysed for overall survival and event free survival and these outcomes were correlated with age, sex, stage at presentation and histology. Favourable histology

which included focal anaplasia was found in 80.3 % while unfavourable histology was elicited in 19.7 % of the cases. The estimated 5 year event-free survival was 83.3 % and overall survival was 85.2 %. Tumour histology was the single most important factor predicting the survival. Patients with childhood Wilms' still present very late in our setting, this poses management challenges as large tumor are technically difficult to deliver at surgery. Histology has a crucial role in outcome of this disease. With multidisciplinary approach, similar survival rates to National Wilms' Tumor Study Group seems to be achievable even in Indian scenario.

Keywords Wilms' tumor · India · Chemotherapy · Survival

Introduction

Wilms' tumor is the most common renal malignancy in children and the fourth most common childhood cancer. Wilms' tumor is a paradigm for multimodal treatment of paediatric solid malignancy. With surgery alone the survival was 30 % in the early 1930 [1], improved to 47 % with use of surgery and radiotherapy in early 1950 [2] and further introduction of adjuvant chemotherapy has led to survival of about 90 % in the present era [3]. This was also the first solid tumor where the role of adjuvant chemotherapy was established. Wilms' tumor may occur as a part of a multiple malformation syndromes including WAGR, Denys-Drash, and Beckwith-Wiedemann syndrome. Wilms' tumor is associated with mutations of a number of tumor suppressor genes. These include WT1, p53 and mutations at the 11p15.5 loci [4].

There is paucity of data about the epidemiology, pathology, treatment and prognosis of this disease from India. Therefore,

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we conducted the present study to analyze the outcome of multimodality treatment of Wilms' tumor over 8 years.

Material and Methods

All patients with proven diagnosis of Wilms' tumor between the period of 2003 and 2010 were noted from the hospital's cancer registry. Clinical case records of all patients were analyzed in detail for demographic profile, clinical features, imaging studies, treatment and outcome.

The hospital protocol for workup of these patients included: a) Laboratory studies for renal function (serum creatinine, GFR, urinalysis), liver function, and a complete blood count. b) Imaging {Abdominal ultrasonography/Doppler ultrasonography/Contrast-enhanced computed tomography (CECT)}. Doppler ultrasonography was performed to detect tumor infiltration of the renal vein and inferior vena cava, and to assess patency of blood flow. Contrast-enhanced CT was used to further evaluate the nature and extent of the mass. Imaging of the chest (CT or chest radiography) was done to rule out lung metastases.

The line of treatment for this tumor at our institution was based on NWTs IV protocol. This regime included upfront surgery; postoperative histopathological confirmation of diagnosis, followed by radiotherapy and chemotherapy based on stage of the disease. The institute has a heavy workload for pediatric cases and hence the protocol was modified with dactinomycin single dose on day 1. The same is being followed in the NWTs5 protocol. Classic Wilms' tumor was diagnosed based on varying proportion of three cell types (blastemal, stromal and epithelial). After completion of treatment, the follow-up was 3-monthly for the initial 2 years and 6-monthly thereafter. Every follow-up visit consisted of clinical examination, abdominal ultrasound and chest radiograph. Relapse and disease progression (labelled as appearance of new metastatic lesions/increase in size of the primary lesion) were considered as events. The outcome was correlated with age (less than or more than 2 years), sex, stage at presentation and histology. The event-free survival and overall survival were evaluated for all patients using the Kaplan Meier curve (SPSS 19 - SPSS Inc, USA).

Results

This retrospective study included a total of 81 patients diagnosed from 2003 to 2010. Of these, 61 patients received treatment and were followed up at our institute, while the others did not report for further management after their initial visit. The age of the patients ranged from 1 to 7 years (mean, 3.3 years). Majority of patients were aged more than 2 years, as shown in Table 1. Thirty four patients (56 %) were males. Majority of patients (92 %) had an abdominal mass noted by parents; other

Table 1 Clinical features

Clinical features		Number of cases (%)
Age	<2 years	24 (39 %)
	>2 years	37 (61 %)
Sex	Male	34 (56 %)
	Female	37 (44 %)
Stage at presentation	I	17 (27.8 %)
	II	10 (16.4 %)
	III	23 (37.7 %)
	IV	9 (14.8 %)
	V	2 (3.3 %)
Histology	Favourable histology	44 (72.1 %)
	Focal anaplasia	5 (8.2 %)
	Diffuse anaplasia	5 (8.2 %)
	Clear cell sarcoma	5 (8.2 %)
	Rhabdoid tumor	2 (3.3 %)
Metastasis at presentation	Lung	3
	Liver	2
	Bone	2
	Brain	2

symptoms and signs included abdominal pain in 18 patients (30 %), hematuria and hypertension in 5 patients each (8 %). Two patients had bilateral disease. Congenital anomalies were present in 10(16 %) patients as shown in Table 2, with some patients having more than one anomaly. Majority had classical Wilms' tumor of favourable histology. At diagnosis, majority of patients presented with stage III disease. Lung was the most common site of metastasis. Only eight patients had undergone surgery prior referral to our centre. The median follow-up was 48 months (range 6–84 months). The estimated 5 years event-free survival was 83.3 % and overall survival was 85.2 % (Fig. 1). The stage and histology wise event free survival is shown in Table 3. A total of 10 events occurred in follow up (seven had progressive disease, two relapsed and one had metachronous bilateral Wilms' tumor) with majority of them presenting with pulmonary metastases. Of these ten patients,

Table 2 Congenital anomalies

Associated anomalies in 10 patients with Wilms' tumor in our study	Number of cases
Hypospadias	4
Cryptorchidism	4
Aniridia	3
Cleft lip	2
Congenital cataract	2
Hemihypertrophy	1

Fig. 1 Estimated overall survival at 5 years was 85.2 %

seven patients abandoned treatment (lost to follow-up) and the remaining three were given treatment in the form of chemotherapy (NWTs-R protocol).

Discussion

To the best of our knowledge, this study is the largest data from India about the outcome of Wilms' tumor using NWTs 4 protocol.

The age and sex distribution was similar to other large series [5] and the most frequent presenting feature in our study was abdominal mass (92 %) compared to 74 % in United Kingdom Children's Cancer Study Group [6]. The

disparity may be due to higher number of patients presenting with advanced disease. Only 27.8 % presented with stage I disease in our study. This is in contrast to other larger studies which have bulk of their patients presenting with early stage disease [7]. The consequences of late presentation include very huge and advanced tumours which make operative intervention very difficult and prognosis correspondingly poor. Torrential bleeding may be a problem and because of very large size of tumor. To minimize this blood loss intra-operatively, the renal artery should be ligated first before the renal vein. This reduces vascularity of the tumor, though has the theoretical chance of increase tumor spread through the renal vein. Studies from the NWTs group have shown that ligating the vein later does not worsen the prognosis [8].

Surgical aspects: Classically all patients underwent radical nephrectomy via transperitoneal approach. One patient had renal vein thrombosis extending to IVC and right atrium which was operated under cardiopulmonary bypass by a cardiothoracic surgeon and a surgical oncologist after neoadjuvant chemotherapy. This has been reported [14]. Two patients had bilateral wilms tumor who received neoadjuvant chemotherapy for 6 weeks and later underwent nephron sparing surgery on both sides in one patient and the other underwent radical nephrectomy on one side and nephron sparing surgery in the contralateral side. Both the patients were doing well after a follow up period of 28 months and 36 months. Two patients developed small bowel obstruction who had received adjuvant radiotherapy after radical nephrectomy after a period of 16 months and 24 months and both failed on conservative management. On exploration,

Table 3 Outcome

Outcome (EFS %)		Our study (%)	NWTs4 (%) [10]
Favourable histology	Stage I	92.3	94.9
	Stage II	83.3	85.9
	Stage III	94.4	91.1
	Stage IV	80	80.6
	Stage V	50	
Focal anaplasia	Stage I–IV	80	
Anaplastic histology	Stage I	–	87.5
	Stage II–IV	60	83.3
CSSK:	Stage I–IV	80	84.1
Rhabdoid:	Stage I–IV	50	

both patients had multiple adhesions with no evidence of recurrence and underwent adhesiolysis. Postoperative recovery was uneventful for both of them.

There was a higher incidence of associated anomalies (16.7 % in our study vs. 7.3 % in NWTs group [7]). There was lower incidence of hemihypertrophy noted in our study, which was commonest malformation in NWTs group. This difference in the associated anomalies may be due to the changes in the cytogenetics and molecular biology in Indian patients which need to be further studied.

Age, sex and stage of presentation did not have statistically significant impact on survival with only tumor histology being the significant ($p < 0.001$) prognostic marker in our study. Diffuse anaplasia as noted by the presence of irregular mitotic figures, large nuclear size, and hyperchromasia had a poor outcome. Focal anaplasia had similar outcome to favourable histology. Even Rhabdoid and clear cell subtype had poor prognosis. This has been shown in other studies including the first National Wilms' Tumor Study (NWTs-1) [9].

With single-dose regimen dactinomycin (45 $\mu\text{g/kg}$ IV) no case of severe hepatic toxicity was noted. This regimen further reduces the need for hospitalization when compared to divided-dose 5 day course. Studies have shown a similar outcome between the regimens [10]. This is more suitable in Indian scenario.

We had better survival when compared to an earlier study from India [11], and a similar event free survival in all stages, when compared to original NWTs IV protocol study group as shown in Table 3. Lower survival rate was seen noted from other historical studies from India; majority of patients in these studies had undergone surgery prior to referral to tertiary care and had a higher incidence of incomplete staging work up, inadequate surgery and tumor spillage [13]. Management of patients in India deserves special attention as we have a very diverse population. As is evident from our study, 20 out of a total of 81 patients did not choose to get any treatment at our institute. Even amongst the 10 patients having an event; seven patients abandoned treatment. While it is possible that some of these patients took treatment at other institutions, other causes like poor socioeconomic status, use of alternative therapies, and lack of knowledge about the excellent prognosis with this cancer cannot be neglected in the Indian scenario.

Short follow-up, small number of patients and the lack of cytogenetic assessment are the limitations of our study. A larger sample size would provide greater confidence with respect to the conclusions of this study highlighting the message that most Wilms' tumor has a good prognosis even in Indian scenario. We recommend a more comprehensive investigation with special attention to favourable histology with blastemal predominance, and loss of heterozygosity (LOH) at chromosomes 1p and 16q [12], and long term follow up of patients for studying the late effects of treatment and survival.

Conclusion

- Patients with childhood Wilms' still present very late in our setting, this poses management challenges as large tumor are technically difficult to deliver at surgery.
- Histology is crucial in outcome as focal anaplasia had similar outcome similar to favourable histology Wilms' tumor.
- Finally, further studies are needed to augment therapy for favourable histology with blastemal predominance subtype or for those associated with loss of heterozygosity (LOH) at chromosomes 1p and 16q aiming at improved survival

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