ORIGINAL ARTICLE

Patient Characteristics and Results of Wilms Tumour Treatment - A Prospective Cohort Study from Pakistan

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ABSTRACT

Background: Wilms tumour, also called nephroblastoma, is the most common renal malignancy in children, presenting, mostly as an abdominal mass. Chemotherapy and surgery are the mainstays of treatment depending upon the histopathology, risk group and stage of treatment. The aim of the study was to determine the treatment outcome of Wilms tumour in a tertiary care hospital in Pakistan.

Methods: A Prospective cohort study was carried out at the Department of Pediatric Oncology, CMH-Rawalpindi, Pakistan. A cohort of patients with Wilms tumour, less than 16 years was followed prospectively from January 2012-2019. Statistical data were analysed by Chi-squared test and *p*-value<0.05 was considered statistically significant.

Results: The study included 39(50.6%) males and 38(49.4%) females. Abdominal mass [70(90.9%)] was the most common problem, followed by abdominal pain, hematuria, and fever. In stage I, [34(44.2%)] patients were followed up for histopathology. n=64(83.1%) patients were divided into the intermediate-risk group and 13(16.9%) in the high-risk group. The patients [50(64.9%)] with the localized disease received vincristine and Actinomycin D for chemotherapy before the operative procedure, whereas, [10(13.0%)] for metastatic disease, received preoperative chemotherapy, including vincristine, actinomycin D, and doxorubicin. Furthermore, 3(3.9%) cases had treatment-related mortality, 15(19.5%) patients relapsed, and 11(14.3%) of them died later due to their advanced stage. Overall survival (OS) was 81.8% and event-free survival (EFS) was 76.6%.

Conclusion: Stage of disease considerably affects treatment outcomes and survival. We acknowledge that low-stage Wilms tumour can be treated by early referral to a paediatric oncologist and surgeon. This intervention could improve survival of children with Wilms tumour.

Keywords: Wilms Tumour; Treatment Outcome; Developing Country; Event Free Survival.

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INTRODUCTION

Wilms tumour (WT) is a common and curable embryonal renal cancer. WT is one of the tumours considered by the World Health Organization's (WHO) Global Initiative for Childhood Cancer for the overall improvement in outcomes[1]. It has surfaced as the most common primary renal malignancy that affects every 1 of 10,000 children[2]. Of these, 5% of all childhood malignancies are reported as WT. Survival rates have improved to 90% in developed countries[2]. Histologically it resembles a developing kidney and has three components, which are stromal, epithelial, and blastemal[3]. The mean age of children diagnosed by Wilms tumour is 30 months for girls and 28 months for boys[4]. The tumour typically surfaces in one of the kidneys, however, in almost 5-8% of patients, bilateral or multifocal tumours were also noted. A bilateral tumour is mostly hereditary and predicted to

appear early[5]. There is a racial predominance of WT more in African people than the Caucasian patients[6].

There are two largest collaborative groups of WT management, the International Society of Paediatric Oncology (SIOP) and the Children's Oncology Group (COG). The COG endorses primary surgery before starting any other treatment, but the SIOP recommends chemotherapy before surgery. In SIOP protocol, vincristine and actinomycin D is given for localized problem, while doxorubicin is added in case of metastatic disease. A combination of chemotherapy and surgery remains the gold standard. Radiotherapy is used as an adjunct in high-risk patients. In developed countries, 70% to 90% of patients survive, with best results (90%) in the localized non-anaplastic tumours[7]. On the other hand, in underdeveloped countries, survival rates range between 0% and 52.7% [7]. The main reasons for the poor outcomes in the resource-constrained countries are late presentation, lack of facilities for advanced genetic testing, inability to afford therapy, and unavailability of drugs[8].

The patients were classified into three major groups after nephrectomy based on histopathology results. 1) Low-risk tumour group includes completely necrotic ones. 2) Intermediate risk group comprises epithelial, stromal, mixed, regressive, and focal anaplasia type. 3) High-risk group contains tumours with diffuse anaplasia and blastemal type[9,10]. Treatment is followed according to stage and histopathology of the tumour. International collaboration is mandatory for finding successful treatment options for unfavourable WT, for example, refractory metastatic and relapsed high-risk WT[11]. The main objective of the study is to determine the characteristics of patients in the cohort and to evaluate the treatment outcomes. We aimed to assess the overall survival and event-free survival of WT patients treated per SIOP WT 2001 protocol in Pakistan.

METHODS

This was a prospective cohort study and was conducted at the Paediatric Oncology department of Combined Military Hospital (CMH). The Ethical Committee/Institutional Review Board (IRB) of CMH gave their consent for the study (Registration Serial Number 32). Informed consent was taken from the parents/guardian. SIOP WT – 2001 protocol was followed. This is a standard management regimen to treat WT.

We included all children younger than 16 years of age with a naive diagnosis of WT treated per SIOP protocol during January 2012-2019.We excluded patients with other renal tumours, relapsed WT, or those who left during treatment. Medical history and complete examination were performed on each patient. The following variables were recorded at the time of the first admission of each patient: age, date of diagnosis, sex, time to reach the oncologist, symptoms, and history of nephrectomy. The diagnostic modalities included ultrasound, CT scan, MRI, X-rays, bone scan, and lab tests (blood and urine). We also looked for all associated congenital anomalies such as aniridia, hemihypertrophy, etc. Blood Pressure was also checked to identify hypertensive cases. Biopsy was used as a confirmatory test.

International Society of Paediatric Oncology (SIOP) protocol includes percutaneous biopsy followed by preoperative chemotherapy for localized and metastatic disease. It includes nephrectomy and postoperative histopathological confirmation of the primary diagnosis and staging of the tumour. Postoperative chemotherapy and radiotherapy were administered based on the stage of WT.

Preoperative chemotherapy for the localized disease was given for four weeks. Preoperative chemotherapy for metastatic disease was administered for 6 weeks. The period between the last preoperative chemotherapy and the first postoperative chemotherapy was 3 weeks at the most. Intermediately, nephrectomy was performed, and specimens were sent to a histopathologist. The percentage of necrosis was assessed and classified as <66% (blastemal, mixed, epithelial, and stromal type), 66-99% (regressive type), and 100% (completely necrotic type). Those patients that came after upfront nephrectomy had risk assessment on the histopathology report, and postoperative chemotherapy started according to the risk stratification of SIOP, including stages and histology of the tumour tissue. Postoperative chemotherapy for stage I of the intermediate-risk group was given for 4 weeks. The duration of treatment for low and intermediate-risk stage II / III, high-risk stage I, and high-risk stage IV with absent metastasis or completely resected tumour were 27 weeks. The duration of treatment for high-risk stage II/III and high-risk stage IV with multiple inoperable metastases or incompletely resected tumour was 34 weeks. Details of chemotherapy drugs and weeks of drug administration were maintained according to the stage of the disease.

Postoperative flank radiotherapy was given to stage III of intermediate-risk, which includes nodes positive disease, tumour rupture, and residual disease left after surgery. Postoperative flank radiotherapy was also given to stage II of the high-risk group (excluding blastemal type), stage III, IV, and V of the high-risk group according to the local stage. Pulmonary radiotherapy was given to patients with residual tumour tissue through an X-ray

and CT scan of the chest. Re-assessment, according to SIOP guidelines at periodical intervals, was done according to the protocol. After treatment, periodic follow-ups were done at three months for the first two years and every 6 months later on. Each visit included abdominal ultrasound and chest X-rays. The selected cohort of seventy-seven patients was followed for seven years (January 2012-2019). Data were analysed using SPSS 23.0 and Microsoft Excel. Chi Square test was used for analysis of variables. The *p*-value of less than the alpha value of 0.05 was considered along with a 95% confidence level.

RESULTS

Wilm's Tumour presented on right side in 39 (50.62%) patients and on left side in 38 (49.4%) patients. We had 34 (44.2%) patients in stage I, 18 (23.4%), 12 (15.6%) and 13 (16.9%) in stage II, III, IV, respectively. Preoperative chemotherapy for localized disease and metastatic disease was given to 50 (64.9%) and 10 (13%) patients, respectively. Preoperative chemotherapy was not given to 17 (22.1%) cases. Some of the patients' characteristics are presented in Table 1.

Table 1: Characteristics of patients of the study.

Description		Frequency (n=77)	Percentage (%)
Age (Median)	2.67 ± 2.34 years		
	Less than 4 years	56	72.7
	4-16 years	21	27.3
Gender	Male	39	50.6
	Female	38	49.4
Symptom Duration (Mean)	42.26±60.65 days		
Presentation	Abdominal mass	70	90.9
	Abdominal pain	15	19.5
	Hematuria	13	16.9
	Fever	9	11.7
	Hematuria documented on urine routine examination (RE)	12	15.6
Histopathology	Epithelial type	2	2.6
	Stromal type	4	5.2
	Mixed type	47	61.0
	Regressive type	10	13.0
	Non-anaplastic type	1	1.3
	Blastemal type	8	10.4
	Diffuse anaplasia	2	2.6
	Rhabdoid tumour	3	3.9
Local Stage	I	33	42.9
	II	24	31.2
	III	19	24.7
	IV	1	1.3
Postoperative Chemotherapy	Stage I (IR)	25	32.9
	Stage I (HR)	4	5.2
	Stage II (IR)	21	27.3
	Stage II (HR)	2	2.6
	Stage III (IR)	9	11.7
	Stage III (HR)	1	1.3

IR: intermediate risk, HR: high risk, AVDm: actinomycin D vincristine and doxorubicin for metastatic disease, HRm: High-Risk Regimen HRm, Metastatic Disease, VOD: Veno-occlusive disease.

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There were no patients in the low-risk group after histopathology. However, 64 (83.1%) had the intermediate-risk group. In addition, 13 (16.9%) patients had the high-risk group. We had 8/77 (10.4%) of the patients who suffered complications of the surgery, including intestinal obstruction in 5 (6.5%) cases, tumour rupture in 2 (2.6%) cases, and one death. The chemotherapy details of the patients were given in Table 2.

Table 2: Chemotherapy details of the patients.

Chemotherapy Before Surgery			
Phase	**Drugs**	**Dosage**	**Weekly Administration**
Localised disease	Vincristine	1.5 mg/m2 IV bolus (max 2mg)	1-4
	Actinomycin D	45 mcg/Kg IV bolus (max 2mg)	1, 3
Metastatic disease	Vincristine	1.5 mg/m2 intravenous bolus (max 2mg)	1-6
	Actinomycin D	45 microgram/Kg IV bolus (max 2mg)	1, 3, 5
	Doxorubicin	50 mg/m2 IV infiltration (4-6 hrs)	1, 5
Chemotherapy After Surgery			
Low Risk (Stage I)	No chemotherapy		
Intermediate Risk (Stage I)	Vincristine	1.5 mg/m2 IV bolus (max 2mg)	1-4
	Actinomycin D	45 mcg/Kg IV bolus (max 2mg)	2
High Risk (Stage I)	Vincristine	1.5 mg/m2	8 weeks and then on the first day of week (total 20 doses)
	Actinomycin D	45 mcg/Kg IV bolus (max 2mg)	2, 5, 8, 11, 14, 17, 20, 23, 26 (total 9 doses)
	Doxorubicin	50 mg/m2 IV infiltration (4-6 hrs)	2, 8, 14, 20, 26 (total 5 doses)
Low and Intermediate Risk (Stage II / III)	Vincristine	1.5 mg/m2	8 weeks and then on the first day of the week (total 20 doses)
	Actinomycin D	45 mcg/Kg IV bolus (max 2mg)	2, 5, 8, 11, 14, 17, 20, 23, 26 (total 9 doses)
High Risk (Stage II/III)	Cyclophosphamide	450 mg/m2	Consecutive three days along with Doxorubicin on day one (total of 6 courses)
	Doxorubicin	50 mg/m2	
	Etoposide (VP16)	150 mg/m2	For consecutive three days along with Carboplatin, every 6 weeks from week 4 onwards (total of 6 courses)
	Carboplatin	200 mg/m2	
High Risk (Stage IV) Metastases absent or completely resected	Vincristine	1.5 mg/m2	1-8 and then in weeks 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27 (total 20 doses)
	Actinomycin D	45 µg/kg	2, 5, 8, 11, 14, 17, 20, 23, 26 total 9 doses)
	Doxorubicin,	50 mg/m2	2, 8, 14, 20 (total 4 doses)
High Risk (Stage IV) Multiple inoperable metastases or incompletely resected/high -risk primary tumour	Etoposide (VP16)	150 mg/m2	Consecutively for three days in week 4, 10, 13, 16, 22, 25, 28, and 34 (total 24 doses)
	Carboplatin	200 mg/m2	
	Cyclophosphamide	450 mg/m2	For consecutive three days in weeks 1, 7, 19, and 31 (total 12 doses)
	Doxorubicin	50 mg/m2	1, 7, 19, 31 (total 4 doses)

**Two-third of above the doses were administered for children <12 Kg, and for children below 6 months dose was reduced to half.*

The majority of the patients did not metastasize, that is 61 (79.2%). However, 12 (15.6%), 2(2.6%), and 2 (2.6%) had pulmonary, liver, and both pulmonary and liver metastasis, respectively. Radiotherapy was given to 21 (27.3%) cases, while 56 (72.7%) did not receive it. Therefore, the association between overall survival and event free survival in Wilms tumour' patients is shown in Table 3 while patients' outcomes have been presented in Figure 1.

Table 3: Results of difference in survival times between the groups studied at all time points.

Variable	Overall Survival (OS)		Event Free Survival (EFS)	
	Log Rank		Log Rank	
	Chi - square	*p* - V alue	Chi - square	*p* - V alue
Age Groups	8.489	0.004	11.220	0.001
Stage	8.315	0.04	11.926	0.008
Preoperative Chemotherapy	5.245	0.073	11.586	0.003
Local Stage	18.494	0.000	17.017	0.001
Radiotherapy	3.205	0.073	2.999	0.083
Risk Group	1.537	0.215	0.707	0.400

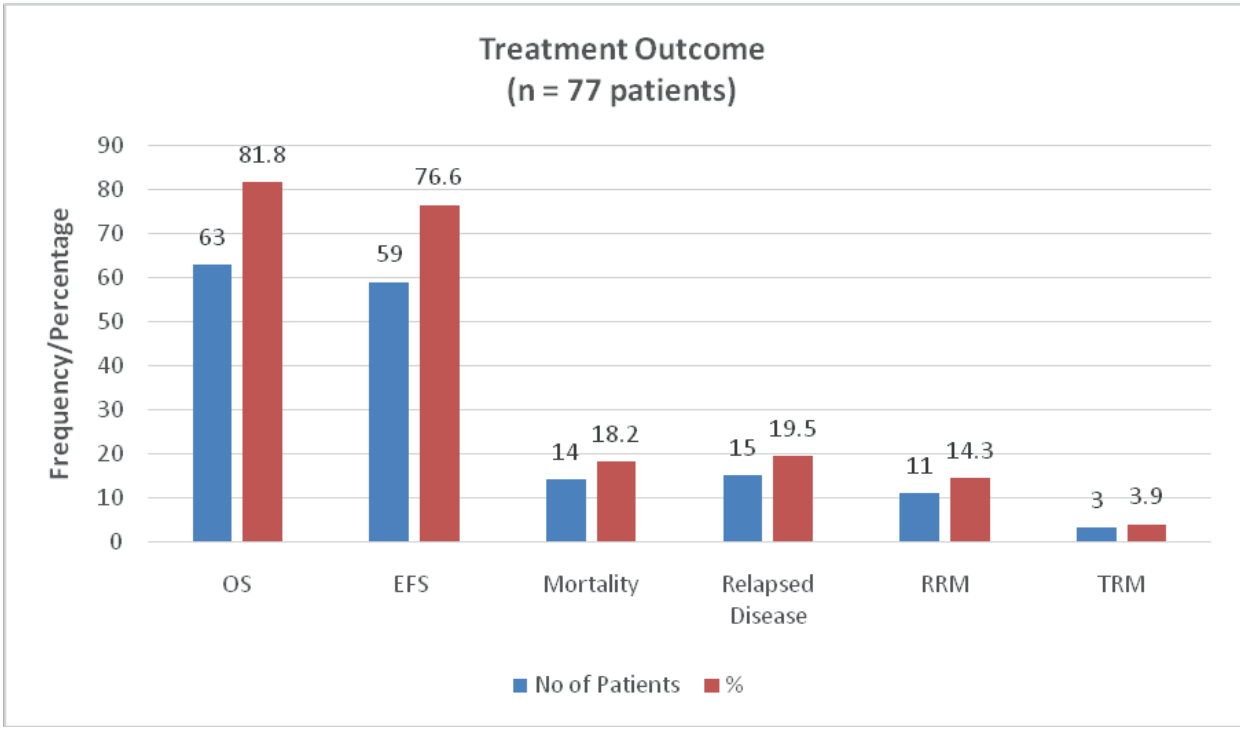

Figure 1: Wilms tumour treatment outcome.

TRM-Treatment Related Mortality, RRM- Relapse Related Mortality RD-Relapse Disease, OS- Overall Survival, EFS-Event Free Survival.

DISCUSSION

Based on the study results, we found out the majority of the patients who presented in stage 1 had a better outcome compared to those who presented late. We noticed only a few patients were diagnosed in stage 1V. The reasons could be either a delay in referral to the paediatric oncologist or early-undiagnosed deaths. The prolonged duration of symptoms also showed a lack of access to a tertiary care facility. We followed SIOP protocol, but a few patients had initial nephrectomy. We witnessed complications related to surgery in the form of tumour rupture and intestinal obstruction and one death. This data belongs to a tertiary care facility that receives a majority of the paediatric oncology patients. The strength of our study is that we had collected authentic data in the fullest possible detail. There is an enormous development in the outcome and survival of WT patients due to multidisciplinary management over time.

The event free survival (EFS) of a study conducted in the United Kingdom by Pritchard-Jones et al. was

77.2%, which was close to our results[12]. Another study from China by Yao et al. had an OS of 81%, similar to our overall survival (OS) of 81.8% [13]. We have compared our results to some other countries as well. Li et al. from China reported EFS 92.7% and OS 94.5% [14]. Cafferata et al. from Argentina followed SIOP 01 protocol and had an EFS 85% and OS 91%[15]. The reason for good results can be a feasible treatment plan. A study from Lebanon by Rabeh et al. showed 85.7% EFS and 88.6% OS [16]. These good results can be attributable to a better multidisciplinary team, availability of supportive care, and financial coverage of health expenditures. In comparison to the studies conducted in Pakistan, our results show a better outcome. Anwar et al. and Fadoo et al. had an EFS of 67% and 56%, respectively[17,20]. The reason for the improvement in the outcome can be increasing awareness and referral to the right facility.

Gender wise prevalence was almost equal, and 56 (72.7%) patients were under four years of age. The median age was 2.67±2.34 years (5.5 Months - 11 years). This was in line with other studies done in Lebanon, Kenya, and other parts of Pakistan[17-20], and lower than Egypt and Tanzania[21,22]. In this study, Abdominal mass (90.9%) was the most frequent complaint followed by hematuria, abdominal pain, coinciding with the work of Abd El-Aal et al., in which abdominal mass was the most common presenting symptom (82.3%) [21].

The disease stage is of utmost importance in deciding further treatment. A study carried out by a Pakistani author, Anwar et al., had 5% of patients in stage I [17]. We received 44.2% of WT patients having stage I disease. This may indicate improved awareness for early screening and referral to the right hospital. Regarding the surrounding countries, Guruprasad et al. from India, who conducted a similar study, noticed a high incidence of stage III (37.7%) followed by Stage I (27.8%), stage II 1(6.4%), stage IV (14.8%,) and stage V (3.3%) disease[19]. It can be due to the late presentation of the patient to the paediatric oncologist. Taran et al. reported that in prognostic factors presented by SIOP, histology of the tumour is of more importance than the stage of WT [22,23]. Preoperative chemotherapy leads to some degree of regression and necrosis of the original tumour tissue, which is why the regressive subtype is added in the intermediate-risk group of WT. However, the persistence of blastemal component even after preoperative chemotherapy shows the non-responsive nature of tumour tissue to the drugs and is related to adverse outcomes. Even though the two large groups, Children's Oncology Group (COG) and SIOP, differ scientifically from each other but with or without preoperative chemotherapy, the treatment outcome of WT in developed countries is much better than the developing countries. We have compared the treatment outcomes of the current study with other studies conducted around the world.

Vincristine and actinomycin D have played their undisputed role since the 1950s in the successful treatment of WT, followed by the addition of doxorubicin in 1970s [24]. Cyclophosphamide, ifosfamide, carboplatin, and etoposide are the drugs used for more advanced and resistant cases. The presence of anaplasia in WT is a strong bad prognostic factor. In another study, stage 1 anaplastic WT was treated on COG AREN0321 protocol with vincristine, actinomycin D, doxorubicin, and flank radiation showed excellent survival results[25]. Survival rates in Pakistan have improved over the past ten years from 56% as reported by Fadoo et al. using National Wilms Tumour Study Group (NWTSG) guidelines to 76.6% in our study using SIOP WT 2001 protocol[20].

We have highly experienced paediatric oncologists, surgeons, histopathologists, radiologists, and tertiary care hospitals. However, most of the patients cannot get the best treatment because of a lack of financial resources to pay out of pocket for their health care expenditure. A centralized tumour data collection should be devised. It is expected that with improved awareness and availability of newer therapies, the outcomes will improve further. With a multidisciplinary approach, including a paediatric oncologists, paediatric surgeons, histopathologists, and radiation oncologists, good survival outcomes can be achieved, particularly for low-stage disease.

CONCLUSION

Accurate diagnosis by evaluating all characteristics of patients and well-timed initiation of therapy improves the outcome in children with Wilms Tumour. By using the SIOP WT 2001 protocol, we have achieved results comparable to western studies. The improvement in management and timely treatment (chemotherapy, surgery, and radiation therapy) can help the patients in recovery.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

The Ethical Committee/Institutional Review Board (IRB) of CMH approved the study with the registration serial number: 32.

PATIENT CONSENT

Informed consents were taken from the parents/guardian of the patients.

AUTHORS' CONTRIBUTION

FB collected the data and wrote the manuscript. TG analysed and interpreted the patients' data. SA helped in writing the first draft and assisted in data interpretation. TA facilitated the literature review search.

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