



## Original Study

# Primary Surgery in Treatment of Stages II & III Wilms' Tumour: A Developing Countries' Experience

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## Abstract

### Background

Treatment options for Wilms' tumour (WT) are costly and it affects the country's health budget and resources if adopted and implemented at the national level especially in developing countries with low or resource-challenged settings.

### Aim

The objective of this study is to evaluate the role and effectiveness of primary surgery in the treatment of stage II and III pediatric WT following the schedule indicated in the National Wilms' Tumor Study (NWTs-4) in the institutes of two developing countries.

### Patients and Methods

The study enrolled 40 children who were primarily diagnosed as stage II and III WT. They were divided into 2 equal groups. Group I (n = 20) included those children who have undergone neoadjuvant chemotherapy followed by surgery and postoperative chemotherapy, while group II (n = 20) included those children who have undergone primary surgery as an initial management followed by chemotherapy. After a mean postoperative follow-up period of 20±5 months, clinical and radiological evaluation was performed for all patients.

### Results

In group I, 15 patients were preoperatively diagnosed as stage II and 5 patients as stage III while in group II,

16 patients were proved to be stage II and 4 patients were stage III. After a follow up period, clinical and radiological evaluation using CT was performed on all patients. In patients with stage II, evidence of recurrence was noted in 4 patients of group I whereas no patient showed any evidence of recurrence in group II. In patients with stage III, rebound increase in size was seen in 2 patients in group I and only one patient in group II.

### Conclusion

Primary surgery with appropriate adjuvant therapy improves the treatment results compared to the neoadjuvant chemotherapy and delayed surgery for children primarily diagnosed as stage II and III WT. It may be used as a safe and effective tool in treating WT patients with relatively no changes from the long administration schedules. This will have a highly positive impact in lowering treatment cost in developing countries.

### Keywords

Wilms' tumour, children, chemotherapy and surgery, cost-effectiveness, resource challenge settings

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## Introduction

Wilms' tumour is ranked first among childhood malignant renal neoplasms<sup>(1,2)</sup>. Therapeutic approach varies based on many factors including geographic distribution and cost effectiveness<sup>(3)</sup>. In Europe and other countries, patients are treated according to Société Internationale d'Oncologie Pédiatrique (SIOP)'s protocol advocating preoperative chemotherapy for 4–6 weeks relying on initial diagnostic imaging followed by surgery<sup>(4, 5)</sup>.

On the other hand, the National Wilms' Tumor Study Group (NWTSG) protocol is followed in the United States and Canada. This protocol mandates primary nephrectomy for all cases with the exception of the large unilateral or bilateral tumors, while further adjuvant therapy is given based on surgical and pathologic findings<sup>(6–8)</sup>. The fundamental differences between these two large cooperative multinational trials are primary surgery in NWTSG versus initial or neoadjuvant chemotherapy in SIOP<sup>(5)</sup>.

Whether chemotherapy should or should not be started before surgery is a controversial issue, yet, the clinical outcomes are mostly the same in both groups<sup>(9,10,11)</sup>. The productive debate is still ongoing on the advantages and merits of each approach<sup>(4)</sup>.

The question in point is: which approach should be followed as the treatment option especially in Stages II and III<sup>(12)</sup>. Currently the decision to follow either approach is subjective in centers that are not a part of these groups.

Moreover, the cost effectiveness is another factor that should be considered in choosing the treatment protocol specially in developing nations with medium and low resource settings.

The current study aimed to evaluate the role and effectiveness of primary surgery as a guide to determine an accurate stage and to tailor treatment for children who were primarily diagnosed as stage II and III WT. The short administration schedule for treatment and its effectiveness (NWTSG-4) is to be compared with the long administration schedule as in SIOP for lowering the total treatment cost in developing nations with resource challenged settings.

## Patients and Methods

The study involved 40 children who were primarily diagnosed of stage II and III WT over a period of 9 years (2004–2013). The initial assessment entailed clinical examination as well as laboratory investigations including complete blood count, urine analysis particularly urine catecholamines to rule out neuroblastoma, serum urea and creatinine levels. Abdominal ultrasonography and Computed tomography (CT) were done to all patients in order to verify diagnosis excluding other abdominal masses not originating from the kidney. Lung metastasis were detected with the aid of radiograph and chest.

All children with CT proved unilateral WT (stage II and III) were included. On the other hand, those children presenting with other abdominal malignancies and/or other renal lesions such as hydronephrosis or cystic disease were excluded as well as those with hematogenous metastasis.

Patients were divided into two equal groups. In group I (n=20); preoperative chemotherapy was decided according to CT diagnosis, whereas the stage was assigned after surgery. In group II (n=20); surgical intervention was done as an initial management followed by chemotherapy. Commonly employed chemotherapeutic agents included dactinomycin, vincristine, doxorubicin, cyclophosphamide, etoposide, and carboplatin.

Drug name	Pediatric dose
Dactinomycin	0.015 mg/kg IV push qd for 5 days
Vincristine	1.5 mg/m <sup>2</sup> IV q1–3 weeks; not to exceed 2 mg/dose
Cyclophosphamide	1.2–2.2 g/m <sup>2</sup> IV qd for 1–3 days
Etoposide	100 mg/m <sup>2</sup> IV qd for 5 days
Doxorubicin (adriamycin)	45 mg/m <sup>2</sup> IV

**Table 1: Chemotherapeutic agents used for WT treatment**

Stage	Chemotherapeutic regimen
Stage II (FH), stage III (FH)	DD-4A (AMD, VCR, and DOX; 24 weeks
Stage II or stage III (focal or diffuse anaplasia)	I (VCR + CPM + E; 24 weeks)

**Table 2: Chemotherapeutic regimens in relation to the stage of WT**

Acronyms: FH = favorable histology; AMD = Dactinomycin; VCR = Vincristine; DOX = Doxorubicin; CPM = cyclophosphamide; E = Etoposide

Chemotherapy dosage depends on the particular stage of the disease and the child (Tables 1, 2) <sup>(13,14)</sup>. In group I, surgery was initiated when the child's health was optimized, usually within 6 weeks after the primary diagnosis.

Surgery entailed radical excision of the tumour whenever amenable. A transverse abdominal incision was done to provide adequate exposure, from the tip of the 12<sup>th</sup> rib on the involved side to the lateral rectus border on the opposite side. Exploration of the contralateral kidney with biopsy as needed was carried out first; reflection of colon and complete mobilization of kidney are required for adequate visualization and manual inspection of front and back surfaces of the kidney. Radical nephrectomy was done whenever possible. Metal clips were left to identify residual masses in stage III patients.

Histopathological examination was performed for all surgically removed specimens. CT follow-up and clinical evaluation were applied aiming to detect recurrence in stage II and follow-up of the size of the residual mass in stage III. For statistical analysis, SPSS 20 was used. Collected data were tabulated and analyzed statistically using  $\chi^2$  analysis. Continuous variable was analyzed using the independent sample t-test. P values less than 0.5 were considered statistically significant.

## Results

Forty patients were studied. There were 22 males and 18 females with the ratio of 1.3: 1. The age

of the studied patients in group I ranged from 1.3 years up to 16.5 years (mean =  $7.2 \pm 1.4$ , mean  $\pm$  S.D.), while in group II, age ranged from 1.2 years to 15 years (mean =  $7.8 \pm 1.4$ ) with no statistical significant difference between the two groups. Palpable abdominal mass was the first presentation in 25 patients (62.5%), recurrent abdominal pain in 7 patients (17.5%) and hypertension in 8 patients (20%).

In group I, 15 patients were preoperatively diagnosed as stage II, while the remaining five patients were preoperatively diagnosed as stage III. After a mean postoperative follow-up period of  $20 \pm 5$  months (mean  $\pm$  S.D.), four patients with preoperatively diagnosed stage II showed CT evidenced recurrence. On the other hand, remission was noted in three patients with stage III whereas rebound increase in size was seen in the remaining two.

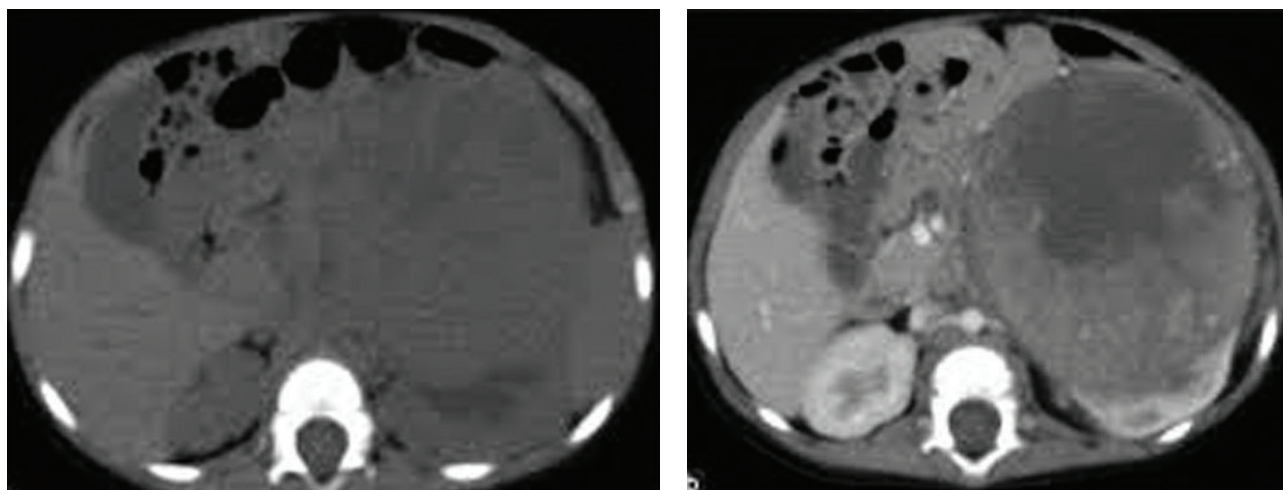
In group II, 16 patients were proved to be stage II, whereas four patients were stage III. The postoperative follow-up was identical to that of group I. Yet, no patients with stage II showed any evidence of recurrence. Nevertheless, only one patient with stage III showed relapse. In this group, chemotherapy regimens were modulated taking into

Relapse	Group I	Group II	P value
Stage II	4 (20%)	0	< 0.02
Stage III	3 (15%)	1	< 0.04

**Table 3: Relapse in both groups**

Complication	Number of patients
Bone marrow depression	9 (22.5%)
Bowel obstruction	4 (10%)
Hepatic dysfunction	6 (15%)
Interstitial pneumonitis	2 (5%)
Cardiomyopathy	1 (2.5%)

**Table 4: Complications of chemotherapy among the studied patients**



**Figure 1: CT image showing a left renal mass with enhancing renal parenchyma posteriorly. Lobulated tumor thrombus is present in the left renal vein and IVC.**

consideration the histopathological grade found at biopsy. Table 3 shows the relapses in both groups.

In group I, seven patients (35%) were found to be under staged at histopathological examination with CT accuracy of 68.7% ( $P < 0.03$ ) compared to surgical exploration and biopsy. This was due to unresectable tumour margins in spite of being stage II on CT (Figure 1). On the other hand, histopathological examination confirmed free margins in all patients stage II in-group II, ( $P < 0.01$ ).

The overall histopathological results revealed favorable histology (tubular predominance) in 35 patients (87.5%) whereas unfavorable histology (anaplasia, rhabdoid and clear cell sarcoma) in five patients (12.5%). The most commonly encountered complications among our patients after chemotherapy were tabulated (Table 4).

## Discussion

Management of Wilms' tumor remains a paradigm for multimodal cancer therapy <sup>(5, 15)</sup>. The two main study groups are SIOP and NWTSG.

SIOP has advocated preoperative radiotherapy in the first two trials and then used chemotherapy in the following four trials for 4–6 weeks. The advantage of SIOP protocol is to reduce the incidence of tumour rupture, intra-peritoneal tumour spillage, obtain a more favorable stage distribution, and in turn, reduce the treatment burden. Besides that, this protocol gives the opportunity to judge responsiveness of the tumour to the standard regimen of chemotherapy so

that risk stratification and treatment adjustments are feasible in postoperative period.

However, the potential disadvantages of SIOP are not obtaining untreated tissue for proper histopathological study, treatment of a benign condition with chemotherapy and treatment of a different malignant disease with the wrong chemotherapy as well as the relative long time of administration schedule that may be more expensive and unfeasible for developing nations with challenged or low resource setting <sup>(9, 12–13)</sup>.

The NWTSG approach recommends up-front surgery with certain exceptions: bilateral tumours, tumours in a solitary or horseshoe kidney, extension of tumour thrombus in the supra-hepatic cava or heart, and extensive metastatic disease causing respiratory distress.

There are mainly two advantages of this approach; accurate and early staging and obtaining an untreated tumour specimen that can be subjected for tissue diagnosis and other biological prognostic studies as well as the short administration schedule that may decrease the cost of treatment (3). The disadvantage of this approach is higher rate of surgical complications like tumour rupture and intra-operative spillage <sup>(12–15)</sup>.

In our current study, we have applied the two protocols for children who were primary staged as stage II and III according to the CT findings. Neoadjuvant chemotherapy was adopted as the first line of management in group I children including a



period of preoperative chemotherapy followed by surgery and a period of postoperative chemotherapy<sup>(14,16–17)</sup>. In group II, we adopted the National Wilms' Tumour Society protocol (NWTs) with surgery as the first line of treatment followed by chemotherapeutic application<sup>(18–19)</sup>. This group has the advantage of histological confirmation of the disease as well as accurate staging during surgery. During the operation, the contralateral kidney was also explored to ensure that the disease was indeed unilateral and lymph node dissection was carried out<sup>(20)</sup>. We did not perform transcutaneous biopsy for any of our cases with the concept that it may complicate the treatment in accordance with the same concept in a previous studies<sup>(21, 22)</sup>.

The study results showed that patients in group I were having a significantly less success rate as compared to those in group II. Such results were contradictory to previous published results of SIOP protocols<sup>(21)</sup> which coincided with those of National Wilms' Tumor Study Group<sup>(23, 24)</sup>.

Tumor histology and stage are the two most significant prognostic factors for patients with Wilms' Tumor<sup>(25)</sup>. In group I, the preoperative chemotherapy alters the tumor's histological features<sup>(26)</sup>, thus making the pathologist's job to assign the subtype of histopathology and stage very difficult while in patients with group II, the pathologist could properly identify and stage the tumor.

Generally, children can tolerate the acute toxicities of chemotherapeutic drugs better than adults<sup>(27)</sup>. However, they are more susceptible for delayed side effects of chemotherapy like growth problems, infertility and neuropsychological dysfunction<sup>(28)</sup>. Our data showed that the most commonly encountered complication is bone marrow depression (30%) followed by bowel obstruction (13.3%). This is in agreement with other recent studies<sup>(29–30)</sup>.

In conclusion, primary surgical resection remains a crucial part for treatment of Wilms' tumour patients as a part of the short administration schedule that will decrease the cost–effectiveness of treatment especially in developing countries with resource challenged settings as in our case. It can provide a local primary tumour control, accurate staging, proper histological interpretation and possibly controlling the metastatic spread. However, patient

selection for surgery is an important determinant for successful outcome.

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