Outcome and renal function following salvage surgery for bilateral Wilms tumor: a single-institution experience

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Objective **The aim of this study was to determine the surgical outcomes and renal function following salvage surgery for bilateral Wilms tumor (BWT).**

Summary background data **The challenge for the surgeon treating BWT lies in striking a fine balance between renal preservation and oncological clearance.**

Methods **This is a retrospective review of medical records in a tertiary care hospital in India. Nine children with BWT who presented between 2005 and 2015 were reviewed and followed up through telephone. Survival rates were calculated using the Kaplan–Meier method. A *P* value of less than 0.05 was considered statistically significant.**

Results **Seven (78%) of nine children were boys and two (22%) were syndromic. Six (67%) children presented at less than 1 year of age. Eight (89%) children presented with an abdominal mass. There were no metastases at presentation. All children underwent trucut biopsy and neoadjuvant chemotherapy. Six children underwent surgery: four underwent bilateral nephron sparing surgery (NSS) and two underwent unilateral nephrectomy with contralateral NSS. Tumor recurred in two children. The mean follow-up was 38 months (range: 5–108 months). Creatinine clearance (CrCl) improved postoperatively in all children. Postoperative hypertension was transient and resolved with improvement in CrCl.**

Conclusion **Children with BWT in the Indian subcontinent may be younger than those in the rest of the world. NSS yields good outcomes even for recurrences. Postoperative hypertension is transient in the majority of patients and correlated with improvement in CrCl. Prognosis is related to operability and syndromic association. *Ann Pediatr Surg* 13:145–149 © 2017 Annals of Pediatric Surgery.**

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Introduction

Wilms tumor is the most common renal malignancy during childhood, with an incidence of 0.8 per 100 000 population. Approximately 5% of children have bilateral synchronous involvement. These children are usually younger than the unilaterally affected children and may have syndromic associations with compromised baseline renal functions.

Chemotherapy followed by nephron-sparing surgery (NSS) has become the standard of care for children with bilateral Wilms tumor (BWT). The oncosurgeon walks a tight rope between organ preservation and tumor clearance. Minimizing nephron loss is desirable in a young child requiring chemotherapy, thus avoiding hypertension and renal insufficiency. Renal parenchymal preservation, however, may pose an increased risk for recurrent disease. Here, we describe six children who were operated for BWT.

Bradley *et al.* [1] first described the association of hypertension with Wilms tumor in 1938. The incidence of hypertension in children with Wilms tumor is estimated to be between 50 and 90% [2]. The causal relationship of hypertension with Wilms tumor is supported by the reversal of hypertension after removal of the tumor in 91% children [2]. The present study examines renal outcomes and hypertension in children with BWT following salvage surgery and discusses the predicament faced by the surgical team treating these children in a resource-limited environment.

Methods

A 10-year retrospective chart review was conducted of children diagnosed with BWT between 2006 and 2015 at Christian Medical College, Vellore. Patients were identified through an electronic search of hospital databases. Nine children were identified, of whom six underwent surgery. The demographic data, imaging, surgical procedure, and related complications of the six children who underwent surgery were analyzed. Families were contacted through telephone to enquire about the child's current status.

All management decisions were made at a multidisciplinary tumor board consisting of pediatric surgeons, pediatric oncologists, and radiation oncologists. Chemotherapy was given according to the SIOP (International Society of Paediatric Oncology) protocol. NSS included heminephrectomy, partial nephrectomy, and enucleation. NSS was performed when a consensual decision was made that at least one-third of renal tissue could be spared. Renal function was estimated through serial monitoring of creatinine clearance (CrCl) and mean arterial pressure (MAP). Renal failure was defined by the

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need for dialysis or renal transplantation. CrCl was calculated using the Schwartz formula: [$k \times$ height (cm)/creatinine (mg/dl)], where k is 0.55 and 0.45 for children older and younger than 18 months, respectively [3]. Postoperative treatment, consisting of adjuvant chemotherapy with or without radiation, was given.

Cumulative survival analysis was performed using Kaplan–Meier estimate for disease-free survival (DFS) and overall survival rates. A P value of less than 0.05 was taken as statistically significant.

Results

Patient characteristics

Seven (78%) of nine children diagnosed with BWT during the study period were boys. Two (22%) children were syndromic: one child had Denys Drash syndrome and another had an unspecified syndrome consisting of squint, macrocephaly, hypotonia, and hypospadias. Six (67%) children presented at less than 1 year of age. Eight (89%) children presented with an abdominal mass with or without fever, vomiting, and failure to thrive. One child presented with pyonephrosis and his tumors were subsequently picked up on imaging following percutaneous drainage. The clinical features of the six operated children are summarized in Table 1. There were no metastases at presentation.

Preoperative status

All children underwent a bilateral trucut biopsy followed by neoadjuvant chemotherapy. All tumors were of a favorable histology; *WT1* gene was positive in six of seven patients tested. Of the 12 renal units operated, 10 showed a mean 24% decrease in tumor size following chemotherapy. Two renal units increased in size by an average of 16%. One of these lesions showed rhabdomyoblastic differentiation and the others had blastemal components.

A computed tomography (CT) was performed for all patients after initial chemotherapy to measure response by change in size and vascularity and plan surgery. A select group of patients underwent a two-dimensional color Doppler to look for vascular involvement or to confirm the presence of a tumor thrombus.

Both syndromic children died before surgery. The child with pyonephrosis failed to attend the outpatient department for chemotherapy after diagnosis; the other presented with septic shock and died before chemotherapy could be initiated. Another child with nephrotic syndrome failed to respond to second-line chemotherapy and was referred for a renal transplant. He was lost to follow-up.

Surgical management

Six children underwent surgery following chemotherapy. The median time from diagnosis to surgery was 63 days (range: 50–280 days). Both sides were operated at the same time. Surgery was decided based on preoperative imaging and intraoperative findings. Intraoperative ultrasound was used when NSS was planned. Bilateral NSS was possible in four children (cases 1–3, 5). Cases 4 and 6 underwent unilateral nephrectomy and contralateral NSS.

Surgical margins were negative in all patients. All tumors were of favorable histology. Five of six tumors were *WT1* positive.

Postoperative complications included urinomas requiring percutaneous drainage in patients 1 and 2 and a urinary tract infection in patient 3. The development of the urinoma did not have any bearing on the long-term function of the kidney.

Outcome

Functional outcome was monitored by serial CrCl and MAP evaluations. CrCl preoperatively ranged from 59 to 217 (mean: 129). Postoperatively, there was an initial fall in CrCl, followed by a steady rise in half of the children. The CrCl was within normal limits for age at 1-year follow-up with an average CrCl of 124 (range: 81–228). Figure 1a shows the comparison of CrCl values for the six children at various points in time.

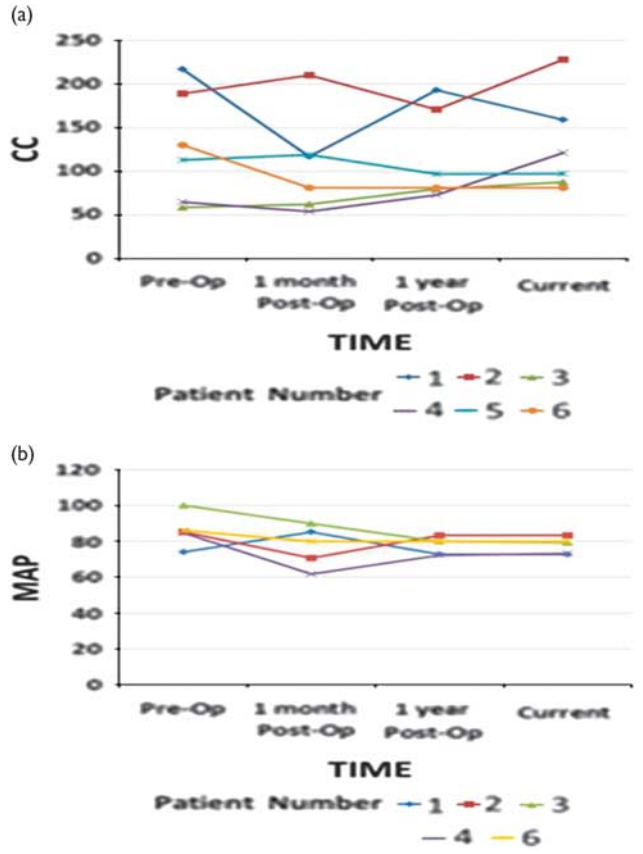
Four of six patients were hypertensive preoperatively and one additional child developed hypertension postoperatively. At 1-month follow-up, antihypertensive therapy was stopped for three children, and 1 year later for another child. One child required antihypertensives for 92 months. All surviving operated children are presently normotensive and off medication. The median time to resolution of hypertension postoperatively was 1 month (interquartile range: 1–12 months). Figure 1b shows the trend of MAPs in the six operated children. (For case 5, only the hypertensive status was known but no MAP value was available; therefore, he was not included in the graph). Resolution of hypertension seemed to be associated with improvement in CrCl.

Table 1 Clinical features of the six operated patients

		Surgery		Histology			Creatinine clearance			Hypertension				
Patient no.	Age (months)	Right	Left	Right	Left	*WT1*	Preoperative	1 year	Current	Preoperative	Postoperative	Maximum follow-up (months)	Recurrence	Outcome
1	17	NSS	NSS	FH	FH	Positive	217	193	159	–	TH	28	Nil	Alive
2	10	NSS	NSS	FH	FH	Positive	189	171	228	+	TH	29	Nil	Alive
3	12	NSS	NSS	FH	FH	Positive	59	80	88	+	+	108	Bilateral	Alive
4	10	NSS	Nephrectomy	FH	FH	Negative	65	73	121	+	TH	41	Nil	Alive
5	48	NSS	NSS	FH	FH	FP	113	97	97.2	+	–	10	Unilateral	Died
6	6	NSS	Nephrectomy	FH	FH	P	130	NA	81	–	–	5	Nil	Died

Current refers to the value/status at last follow-up.
FH, favorable histology; FP, focally positive; NA, not applicable; NSS, nephron-sparing surgery; TH, transient hypertension.

Fig. 1



(a) Creatinine clearance (CC) trends over time. (b) Mean arterial pressure (MAP) trends over time.

Two children had renal scintigrams on follow-up in view of postoperative urinomas (cases 1 and 2). Despite the formation of urinomas postoperatively both renograms showed good uptake, outline, and drainage at 1-year follow-up.

The tumor recurred in two children. Case 3 (Fig. 2a) developed recurrence on the right side 4 months after bilateral NSS (Fig. 2b) and subsequently underwent a right nephrectomy. Two years later he was found to have a nodule in the left kidney (Fig. 2c), which was enucleated. He is well at 108 months' follow-up (Fig. 2d). Case 5 developed a skin nodule at the biopsy site 7 months after surgery, which on evaluation revealed a widespread recurrence in the right renal bed. His family opted for alternative medicine and he died 3 months later.

The mean follow-up was 38 months (range: 5–108 months). The DFS was 63% at 3 years, which corresponded to a mean DFS time of 28 months (95% confidence interval of 13–42 months) (Fig. 3). The overall survival at 3 years was 75%, which corresponded to a mean survival period of 30 months (95% confidence interval of 18–40 months).

Discussion

From a surgical perspective, BWT remains a challenge for more than one reason. These children present at an earlier age compared with those with unilateral Wilms tumor. The mean age at presentation in our study was 16 months, which is younger than that reported elsewhere [4–6]. Most children present with large abdominal masses [4–8]. These predispose to recurrent aspiration due to increased intra-abdominal pressure. Further, administering chemotherapy in younger children with renal impairment is not without risk. A high index of suspicion is necessary for unusual presentations, as highlighted in the child who presented with bilateral pyonephrosis.

Imaging plays a crucial role in the preoperative planning, especially for NSS. The use of-fluorine-18 fluorodeoxyglucose PET or quantitative MRI preoperatively to assess response and plan surgery are desirable [9]. We found a combination of ultrasound and computed tomography to be cost-effective and adequate. Intraoperative ultrasound is a useful adjunct to define the extent of dissection required.

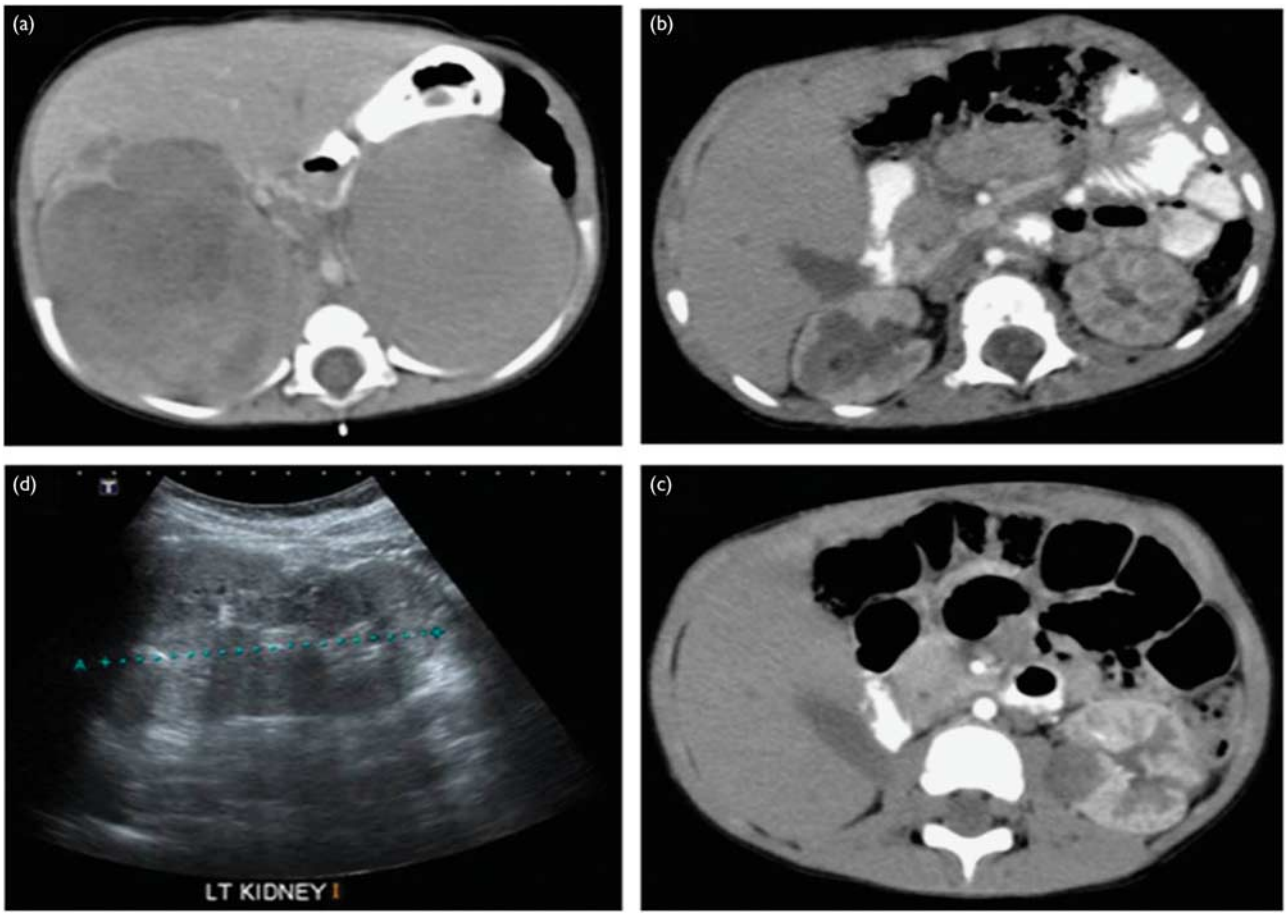
Preoperative chemotherapy is essential in NSS as the aim is to safely preserve as much functional renal tissue as possible. This has unified the SIOP and NWTS protocol for BWT. Renal failure rates in NWTS-1 and NWTS-2 dropped from 16.4 to 3.8% respectively in NWTS-4 [10]. When the response to first-line chemotherapy is not encouraging, second-line chemotherapy may be initiated. Persistent unresponsiveness should raise suspicions of non-Wilms renal tumors. These tumors may tend toward needing renal replacement therapy (RRT). One child in our study required second-line chemotherapy.

WT1 was positive in 86% tumors in this study. There was no statistically significant difference in outcome in relation to *WT1*. A long-term study on the clinical relevance of *WT1* mutations revealed no significant difference in the overall survival of patients with and those without *WT1* mutations [10]. Contrary to this, Oue *et al.* [5] reported higher rates of nephropathy in *WT1* tumors in the long term. They suggested a minimum of 10-year follow-up after treatment completion. Likewise, Royer-Pokora *et al.* [11] identified and increased risk for bilateral tumors and second tumor events in those with *WT1* germline mutations, thereby advocating surveillance until adulthood.

In the management of Wilms tumor, NSS is usually reserved for BWT [12]. We found that the type of surgical procedure used did not have a bearing on outcome. Several groups advocate favoring a more NSS over achieving negative surgical margins [4,10]. Positive surgical margins do not necessarily lead to local recurrence as adjuvant chemotherapy and radiation prevent the same [4,10]. Urine leak, pyelonephritis, and proteinuria are some of the expected complications with NSS. Although three patients developed complications, this did not affect their function or survival. This is in accordance with the 2001 SIOP report, which reported that, although the complications with NSS are higher, the difference is not statistically significant [13].

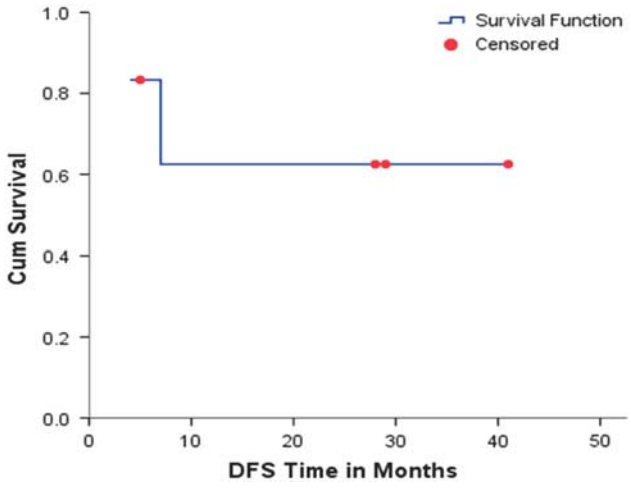
The development of hypertension has been a cause of concern following bilateral renal surgery. We found that two children required antihypertensives for more than a

Fig. 2



Radiological images of patient 3. (a) Preoperative computed tomographic (CT) image of patient 3 showing bilateral large renal masses. (b) CT image showing recurrence on the right side 4 months after bilateral nephron-sparing surgery. (c) Follow-up CT 2 years later showing the left renal recurrence. (d) Ultrasonographic image at last follow-up demonstrating good left residual kidney.

Fig. 3



Kaplan–Meier plot depicting disease-free survival (DFS).

month postoperatively (cases 1 and 3). The type of operation did not seem to correlate with the need for antihypertensives in our study as compared with the study by Herbetus *et al.* [14], who found higher rates of hypertension with unilateral NSS and contralateral nephrectomy. However, our cohort is small and further studies may be required to decide the best possible outcome for children with BWT with regard to hypertension.

Further, in the same series, there was a decrease in the prevalence of hypertension postoperatively (58.8–41.2%) [14]. Our results are similar, suggesting that hypertension is likely multifactorial and may reflect tumor activity, tumor location, and postoperative nephron preservation. The fact that an individual's hypertensive status is subject to change over time should also be considered when analyzing variability in results.

It is known that the Schwartz formula for CrCl calculation is not routinely applicable to children below 2 years and is further limited by its tendency to overestimate CrCl. This explains some spuriously high CrCl values in our study. However, as the comparison was within the same patients as regards preoperative and postoperative CrCl, the trend rather than the absolute value was considered to reflect improvement or deterioration in renal function.

The preoperative range in CrCl varied among children and there was no correlation between the actual value of CrCl and development of hypertension. However, we

found that, after the procedure, children with a low CrCl required antihypertensives for a longer duration. CrCl improved steadily (after an initial fall) in all patients postoperatively, and correspondingly the need for antihypertensive therapy decreased.

Lange *et al.* [15] reported that the incidence of end-stage renal disease among nonsyndromic patients was 4.0% at 3 years from diagnosis in patients with synchronous BWT and 19.3% in those with metachronous BWT. Recent reports from NWTS indicate that the incidence of renal failure in patients with BWT without associated anomalies is 11.5% at 20 years [10]. During the course of follow-up, none of our operated patients had renal failure or required renal replacement therapy.

Besides the child with the recurrence who refused further treatment, there was one other death in the study (patient 6). The child died following an episode of gastroenteritis 5 months after surgery. Opponents may argue that the gastroenteritis precipitated acute renal failure and that death was due to compromised renal reserves; however, the postoperative renal function was normal. As the cause of death was unrelated to the primary disease, the event was considered as a competing risk event. Competing risk events decrease the overall survival, and, although rare, it must be borne in mind that they can adversely affect survival rates.

Five-year DFS and overall survival rates are steadily improving worldwide. Renal failure and recurrence are the main factors affecting survival rates. NWTS-3 [16] and NWTS-4 [10] indicated a 10-year overall survival of 69 and 78%, respectively, in BWT. Oue *et al.* [5] had 5- and 10-year survival rates, with normal renal function being 85.1 and 52.8%, respectively. Our results are comparable but are limited by the small cohort.

Conclusion

The surgical treatment of BWT is troubled by renal insufficiency, hypertension, and the challenge of performing NSS. Our findings suggest that children with BWT in the Indian subcontinent may be younger than the rest of the world. NSS yields good outcomes even for recurrences. Postoperative hypertension is transient in the majority of patients and correlated with improvement in CrCl. Prognosis is related to operability and syndromic association.

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Conflicts of interest

There are no conflicts of interest.

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