Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Original Article

Oncological and Renal Function Outcome in Children with Unilateral Wilms' Tumors Treated with Nephron Sparing Surgery or Ablative Nephrectomy

R. B. Nerli[1]*, Manas Sharma[1], Shridhar C. Ghagane[2], Sreeharsha Nutalapati[1], Murigendra B. Hiremath[3], Neeraj S. Dixit[2]

[1]Department of Urology, JN Medical College, KLE Academy of Higher Education and Research (Deemed-to-be-University), JNMC Campus, Belagavi, Karnataka, India
[2]Department of Urology, KLES Kidney Foundation, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka, India
[3]Department of Biotechnology and Microbiology, Karnatak University, Dharwad, Karnataka, India

Abstract

Background: We prospectively evaluated the oncological and renal functional outcomes of children with unilateral Wilms' tumor (WT) undergoing nephron-sparing surgery (NSS) versus ablative nephrectomy. **Materials and Methods:** Children presenting with unilateral WT from January 2006 to December 2015 were prospectively randomized to undergo either ablative (simple/radical) nephrectomy or NSS. Treatment was administered according to the Societe Internationale d'Oncologie Pediatrique-2001 protocol. **Results:** During the 10-year study period, 13 children underwent ablative nephrectomy, and 15 underwent NSS (partial nephrectomy/wedge excision). The contralateral kidneys were found to be normal on ultrasonography and computed tomography imaging. The mean age at intervention was 44.8 ± 16.7 months. Eight children presented with Stage I disease and the remaining 20 had Stage II disease. The mean follow-up period was 53. 68 ± 23.82 months and all children were alive at the last follow-up without any clinical evidence of disease. The event-free survival rates were 100% and 92.3% in the children undergoing NSS and ablative nephrectomy, respectively. The children who underwent ablative nephrectomy presented with considerably higher mean systolic and diastolic blood pressures, as well as significantly elevated mean values of serum creatinine compared to their ablative nephrectomy counterparts. **Conclusion:** The oncological outcome of NSS was as good as ablative nephrectomy in children with unilateral WTs. NSS also minimized the loss of renal function.

Keywords: Blood pressure, creatinine, kidney failure, kidney neoplasms, Wilms' tumor

Introduction

Wilms' tumor (WT) is the most commonly occurring solid renal malignant neoplasm in children.[1] WT was formerly considered to be essentially a fatal disease despite aggressive

Address for correspondence: Dr. R. B. Nerli, Department of Urology, JN Medical College, KLE Academy of Higher Education and Research (Deemed-to-be-University), JNMC Campus, Belagavi - 590 010, Karnataka, India.
E-mail: rbnerli@gmail.com

Submitted: 09-Dec-2019 **Revised:** 14-May-2020
Accepted: 19-May-2020 **Published:** 01-Sep-2020

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/JCRP.JCRP_12_20

How to cite this article: Nerli RB, Sharma M, Ghagane SC, Nutalapati S, Hiremath MB, Dixit NS. Oncological and renal function outcome in children with unilateral wilms' tumors treated with nephron sparing surgery or ablative nephrectomy. J Cancer Res Pract 2020;7:116-20.

management. Several groups such as the National WT Study Group (NWTSG), Children's Oncology Group (COG), United Kingdom Children's Cancer Study Group, and Societe Internationale d'Oncologie Pediatrique (SIOP) have collaborated in the past several decades to study and improve the outcomes of children with renal tumors. These cooperative efforts have led to significantly improved outcomes despite the varying treatment protocols between the groups. Numerous studies have since reported an overall survival rate <90% for children suffering from WT.[2] Conventionally, children presenting with WT were treated with radical nephrectomy, whereas nephron-sparing surgery (NSS) was reserved for children either with bilateral tumors or tumors affecting a solitary kidney, as a means to avert immediate postoperative renal failure.[3] More recently, NSS has been used for children with WT in the absence of outright indications.[4,5] This change has been brought about due to several reasons, including the search for approaches to reduce the morbidity of WT treatment, the increasingly efficacious use of NSS in adults, increased understanding of NSS in a large number of urologists, and improvements in NSS technique over time that have further improved surgical success rates and minimized complications.[6] It is now recognized that NSS in adults offers substantial advantages in safeguarding the long-term renal and cardiovascular function in addition to overall survival benefits.[7,8] Wang *et al*.[6] retrospectively appraised the SEER database for children aged 18 years or younger diagnosed with WT. The authors analyzed data comprising of 876 boys and 956 girls with WT (mean ± SD age 3.3 ± 2.9 years) and found 114 (6.2%) children who underwent NSS (unilateral WT in 74 and bilateral in 37) with a median follow-up of 7.1 years. NSS was significantly related to unknown lymph node status (Nx vs. N0, $P < 0.001$) and smaller tumor size ($P < 0.001$). Despite lymph node under-staging, overall survival was comparable between patients undergoing NSS and radical nephrectomy. In the present study, we prospectively evaluated survival, local recurrence rates, and renal function outcomes in children with unilateral localized WT treated either with NSS or ablative nephrectomy.

Materials and Methods

Children presenting with unilateral WT during the study period (January 2006 to December 2015) comprised the study group. The study was carried out after obtaining clearance from KLESKF Institutional Ethics Committee (KLESKF/2014/013). Written informed consent was obtained from all of the patients before entering the study. All children with nonmetastatic WT underwent standard preoperative chemotherapy (4 weeks of pretreatment with Vincristine weekly and Actinomycin D biweekly) as per the SIOP-2001 protocol. Postchemotherapy computed tomography (CT) was done in all children, and the feasibility of NSS was assessed by the surgical team in consultation with radiologists. The feasibility criteria were based on postchemotherapy CT as follows: (a) ≥50% reduction in the size of the tumor; (b) feasibility to excise the tumor by clamping the main renal vessels; and (c) after resection, the residual renal parenchyma should be a minimum of 20% of the original volume. Only children in whom it was feasible to perform NSS were prospectively randomized to undergo either simple/radical nephrectomy or NSS using a random number table. The surgical procedure in this study was performed through a wide transverse transabdominal incision. Simple nephrectomy was defined as removal of the tumor-containing kidney after incision of Gerota's fascia [Figure 1a and b]. Only the fatty tissue placed directly on the surface of the tumor was removed along with the tumor.[9,10] Radical nephrectomy was defined as removal of the tumor-containing kidney together with perirenal fat tissue and Gerota's fascia. The choice to perform either simple or radical nephrectomy was based purely on the decision of the operating surgeon. In the case of NSS, the Gerota's fascia was opened and the perirenal fat was dissected off the renal surface excluding the fat attached to the mass [Figure 2a-c]. Stage I disease and favorable histology tumors were assessed using frozen sections. Following NSS, Gerota's fascia was approximated over the kidney remnant to maintain tissue plains. Lymph node sampling was performed in all patients. All children received standard (two-or three-drug) adjuvant chemotherapy as per the SIOP 2001 guidelines. On follow-up, all children underwent physical examinations which included height, weight, and blood pressure measurements in the supine position (average of two readings which were recorded using a mercury manometer by a single investigator). Blood biochemistry tests to assess kidney function were done, including urinalysis, serum creatinine, urinary creatinine, and urinary protein excretion. Serum and urinary creatinine and urinary proteins were determined using an auto-analyzer. The urinary protein-to-creatinine ratio was determined in early morning urine samples collected before the patients were ambulant (normal range <20 mg/mmol). The Blood Pressure Control in Children Task Force guidelines were used to categorize the children with hypertension as "severe" or "significant" arterial hypertension. Standard statistical descriptions of parameters (mean, median, and range) were used to characterize the data. Statistical analysis was carried out using SPSS version 22.0 (Armonk, NY, USA) and GraphPad Prism version 7.0 (GraphPad Software La Jolla, CA 92037 USA).

Results

During the 10-year study period we treated 33 children presenting with nonmetastatic WT. Preliminary ultrasonographic and CT imaging confirmed the diagnosis. After initial chemotherapy, 28 children (18 males and 10 females) were eligible for NSS. Using the random number table method, the children were divided into two groups: NSS and ablative nephrectomy. As per randomization, 15 children underwent NSS and the remaining 13 underwent ablative (simple/radical) nephrectomy. The mean age of the children at the time of surgery was 44.8 ± 16.7 months. There were no significant differences between the two groups with respect to mean values of

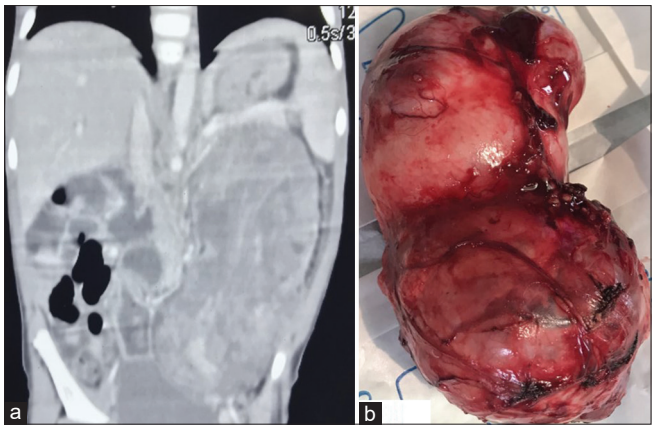

Figure 1: (a) Preoperative computed demography scan of a 4-year-old male child presenting with left sided huge renal mass. (b) Postoperative specimen of simple nephrectomy showing the normal upper pole with a huge renal mass in the lower pole

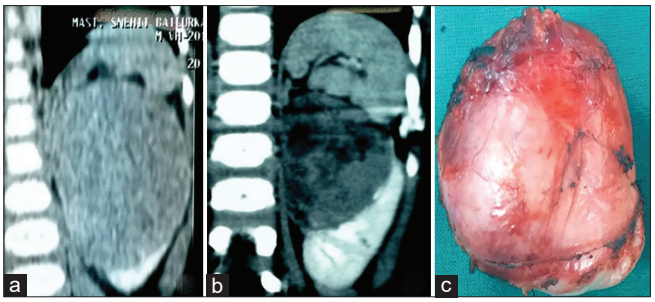

Figure 2: (a) Preoperative, Prechemotherapy computed demography scan of a 2-year-old male child showing a huge renal mass involving the left kidney. (b) Postchemotherapy computed demography scan showing massive reduction (>50%), in the size of the renal mass. (c) Operative specimen of partial nephrectomy

Table 1: Patient's clinical characteristics

Clinical characteristics	NSS	SN/RN
Age	46.4±15.79	42.4±18.59
Preoperative hypertension	-	-
Preoperative maximum diameter (cm)	12.01±0.11	11.32±0.32
Preoperative hemoglobin (g/dl)	13.21±0.22	12.81±0.32

NSS: Nephron-sparing surgery, SN: Simple nephrectomy, RN: Radical nephrectomy

Table 2: Preoperative and Intraoperative parameters of the children with Wilms tumor

Number	Parameters	NSS (15)	SN/RN (13)	*P*
1	Age	46.4±15.79	42.4±18.59	0.5701
2	Serum creatinine (mg %)	0.48±0.16	0.42±0.11	0.2482
3	Systolic blood pressure (mmHg)	102.6±9.57	104.0±6.47	0.6685
4	Diastolic blood pressure (mmHg)	65.3±6.18	64.3±6.04	0.6734
5	Mean operating time (min)	89.47±1.60	77.07±14.31	0.0024
6	Blood loss (cc)	34.73±1.90	34.55±2.84	0.8618
7	Percentage preservation of kidney in NSS	42.22±1.21	-	-
8	Lymph node sampled	3.04±0.22		
9	Comorbidity (%)	12	15	

NSS: Nephron-sparing surgery, SN: Simple nephrectomy, RN: Radical nephrectomy

age, gender, serum creatinine, systolic and diastolic blood pressure in the preoperative period [Tables 1 and 2]. None of the children were hypertensive in the preoperative period. The mean follow-up period was 53.68 ± 23.82 months. Only one child undergoing ablative (simple) nephrectomy had recurrence of the disease on the same side and was treated with radiotherapy and chemotherapy. The event-free survival rate was 100% in the children undergoing NSS and 92.3% in the children undergoing ablative nephrectomy. All of the children were alive with no clinical evidence of residual disease at the last follow-up. The children who underwent ablative (simple/radical) nephrectomy presented with greater mean systolic and diastolic blood pressure values, as well as considerably elevated mean serum creatinine compared to the children in the NSS group [Table 3] at 12 months postoperative follow-up [Figure 3a and b]. There was no significant difference between the two groups in mean urinary protein to creatinine ratio, however, two children in the simple/radical nephrectomy group had a urinary protein to creatinine ratio of >20 mg/mmol. A longitudinal study of the mean glomerular filtration rate (GFR) of all children undergoing simple/radical nephrectomy revealed a significant decrease with increasing postoperative follow-up period ($P < 0.0001$). The slope was indicative of a persistent and steep decline in GFR values in the ablative nephrectomy group [Figure 4].

Discussion

NSS (partial nephrectomy or wedge excision) for WT is conventionally indicated for children with synchronous disease in bilateral kidneys (accounting for approximately 5% of all patients with WT) and for those with syndromes that predispose to late renal failure such as Denys-Drash syndrome.[11] Several authors have suggested that NSS should not be considered as a standard treatment for unilateral disease due to the higher risk of positive surgical margins and local recurrence of tumors.[12,13] In addition, it is assumed that the risk of renal failure is a matter of concern in patients with bilateral WT only.[13] Currently, the incidence of end-stage renal disease is approximately 15% at 15 years postsurgery; however, this might vary according to the genetic etiology.[11] Nephrectomy is the central component of WT management, and attaining a high cure rate remains a priority. Largely due to collaborative efforts of various study groups such as NWTS, SIOP, COG and others, the overall survival of children with WT now exceeds 90%.[2] The treatment regime often comprises of radical nephrectomy and adjuvant chemotherapy. The improved prognosis of WT patients has allowed surgeons and oncologists to shift their focus towards reducing the morbidity of treatment. NSS or

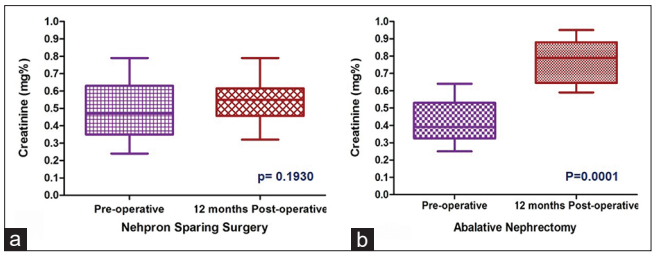

Figure 3: (a) Graphical representation of serum creatinine done preoperatively and 12 months postoperatively in children under going nephron sparing surgery. (b) Graphical representation of serum creatinine in children under going ablative nephrectomy: Preoperative versus 12 months Postoperative ($P = 0.0001$)

Table 3: Postoperative parameters at 12 months following surgery

Number	Parameters	NSS	SN/RN	*P*
1	Serum creatinine (mg %)	0.56±0.08	0.88±0.06	0.0001
2	Systolic blood pressure (mmHg)	109.4±5.57	110.6±7.63	0.0012
3	Diastolic blood pressure (mmHg)	74.5±5.19	82.1±8.78	0.0114

NSS: Nephron-sparing surgery, SN: Simple nephrectomy, RN: Radical nephrectomy

partial nephrectomy (removing just the tumor and the portion of the kidney that surrounds it) is used as a means to diminish the burden of therapy in children with WT. The NWTS group recently released the treatment protocol AREN0534, the first official protocol to endorse partial nephrectomy for WT. As per this protocol, neoadjuvant chemotherapy (chemotherapy given before nephrectomy) followed by partial nephrectomy is indicated only for patients in whom preserving renal tissue is essential. These patients include those with bilateral WT, tumor in a solitary kidney, or unilateral disease with predisposing syndromes that increase the risk of recurrence in the contralateral kidney.[14] Although partial nephrectomy in place of radical nephrectomy is gaining acceptance, partial nephrectomy for children with unilateral nonsyndromic WT is still deemed investigational. The fear of local tumor recurrence or positive surgical margins has been addressed adequately in several reports. Recently, Wilcox Vanden Berg *et al*.[15] examined the Cochrane controlled trials register and compared the efficacy of NSS to radical nephrectomy for the treatment of children with WT. They identified 694 relevant articles, of which 118 were selected for full-text review, and 66 were included in the final analysis. The data included 4,002 children, of whom 1,040 (26%) underwent NSS and 2,962 (74%) underwent radical nephrectomy. Intra-operative tumor rupture (spillage) rates were comparable between the radical nephrectomy and NSS groups (13 vs. 7%), as were recurrence rates (12 vs. 11%) and survival rates (85 vs. 88%). The authors concluded that most contemporary studies reported that the use of NSS in children with WT and the long-term oncological outcomes were similar to radical nephrectomy. We also found

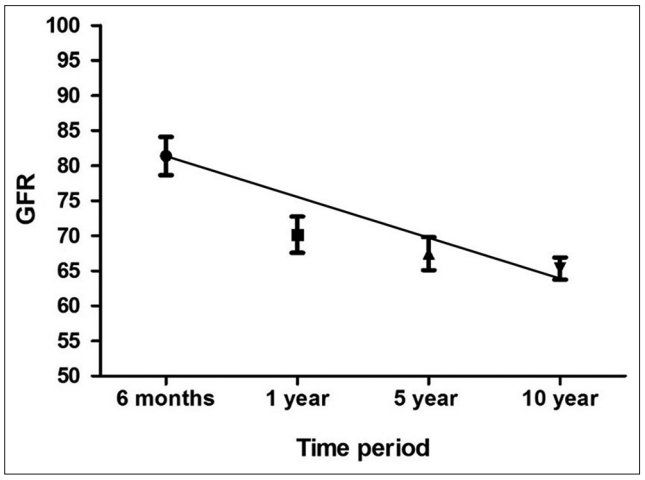

Figure 4: Longitudinal changes of Glomerular filtration rate in children under going ablative nephrectomy ($P = 0.0001$)

no increase in local recurrence rates following NSS and that the event-free survival was 100% in the children undergoing NSS. Many would question the role of NSS/partial nephrectomy in children with unilateral nonsyndromic WT, as the incidence of end-stage renal disease in WT patients is as low as 0.7%.[16] One of the main concerns following ablative (radical/simple) nephrectomy is the potential threat of renal failure secondary to surgical reduction of renal mass. The loss of functioning renal mass is followed by a rise in glomerular capillary pressure and flow leading to increased GFR and hypertrophy of the remaining nephrons. These hemodynamic changes serve to reduce the functional consequences of nephron loss. However, clinical and investigational data suggest that sustained hyper-filtration in the remaining nephrons leads to progressive glomerular injury, which increases in proportion to the amount of renal tissue resected and the period of exposure to hyper-filtration.[17] In 1932, Chanutin and Ferris described a syndrome of progressive uremia ensuing glomerulosclerosis after unilateral nephrectomy and contralateral partial nephrectomy in a rat model.[18] The benefits of NSS/partial nephrectomy in children with WT are of principal importance given the anticipated long survival of children, the young age at diagnosis, probable need for chemotherapy, and substantial risk of recurrence (2%–3%) in the contralateral kidney.[19,20] Children with bilateral WT often require surgical removal of more than half of functioning renal tissue which makes them susceptible to renal failure.[11] Accordingly, the NWTSG and SIOP cooperative group recommends NSS for children with bilateral disease. This raises the question of whether the risk of renal failure is increased only when more than 50% of the renal mass is removed. Due to several conflicting reports in the literature, further studies are necessary to investigate the natural history of renal function in a cohort of surviving children with unilateral primary renal tumors following nephrectomy or NSS. Our study conclusively showed a persistent and steep decline in GFR in the children undergoing ablative nephrectomy. Cozzi *et al*.[8] studied the natural history of renal function following the removal of different amounts

of renal mass in a cohort of 28 children with unilateral renal tumors. At a mean cross-sectional follow-up of 72 and 65 months, respectively, patients undergoing nephrectomy had elevated serum creatinine ± standard deviation (SD) compared to those undergoing NSS (1.27 ± 0.69 vs. 0.70 ± 0.49, $P = 0.02$), as well as higher systolic blood pressure SD score (0.72 ± 0.74 vs.-0.10 ± 0.92, $P = 0.01$) and higher diastolic blood pressure (± SD) (0.87 ± 0.77 vs. 0.19 ± 0.62, $P = 0.01$). Serum creatinine (± SD) and systolic blood pressure (± SD) were positively correlated ($r = 0.44$, $P = 0.02$). In addition, a postoperative longitudinal study indicated a progressive elevation in serum creatinine value with increasing follow-up (r2 = 0.49, $P = 0.02$).

Conclusion

In children with unilateral renal tumors, NSS curtails the decrease in renal function following ablative renal surgery and may benefit children prone to progressive renal dysfunction. Our results conclusively confirmed progressive renal dysfunction in the patients who underwent ablative nephrectomy for unilateral WT. In addition, the current study also showed that the children undergoing NSS had better renal function compared to those undergoing ablative nephrectomy. This advantage is clinically pertinent, as ablative nephrectomy led to a progressive deterioration in renal function on follow-up. A longitudinal study with a larger patient cohort is needed to confirm our findings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflict of interest.

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