



Long Term Follow-Up in Children Undergoing Nephron Sparing Surgery for Non-Syndromic Unilateral Wilms Tumor

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Abstract

Introduction: Wilms Tumor (WT) represents approximately six to seven percent of all pediatric cancers and accounts for more than 95 percent of all tumors of the kidney in the pediatric age group. Recently some centers have explored the role of nephron sparing procedures in children with unilateral wilms tumors because of the concern about late occurrence of renal dysfunction after unilateral nephrectomy. We assessed the long term renal functional outcome after parenchymal-sparing procedure for non-syndromic unilateral wilms tumor at our center.

Materials and Methods: We retrospectively reviewed the records of all children with unilateral Wilms tumor who had undergone nephron sparing surgery at our center. Patient's long-term renal function, tumor recurrence, and survival, were determined from a review of each patient's medical record.

Results: A total of eight patients underwent Partial Nephrectomy (PN) and the remaining three with polar tumors underwent Hemi-Nephrectomy (HN) following chemotherapy. Smaller tumor volumes were associated with not only preservation of renal function but also increase in eGFR during the follow-up period. The median preoperative eGFR was 106 ± 10.78 and median eGFR at the last follow-up was 131.0 ± 3.52 .

Conclusions: In properly selected children with non-syndromic unilateral Wilms tumor, nephron sparing surgery provides excellent renal function preservation.

Keywords: Wilms tumor; Nephron sparing surgery; Child; Nephrectomy

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Introduction

Wilms Tumor (WT) is the second most common intra-abdominal cancer of childhood and the fifth most common pediatric malignancy overall. It represents approximately six to seven percent of all pediatric cancers and accounts for more than 95 percent of all tumors of the kidney in the pediatric age group [1]. Survival of patients with Wilms tumor when considered as a whole, once <30%, is currently greater than 90%, making it one of the real successes of modern medicine [1,2].

Approximately 500 children are diagnosed with Wilms tumor in the U.S. each year; and five to seven percent of these children will have disease in both kidneys [3]. Several studies have demonstrated that patients with bilateral Wilms tumor are at risk for developing renal failure [4-7]. A review from the National Wilms Tumor Study Group (NWTSG) indicated that, among patients who had unilateral Wilms tumor without genitourinary abnormalities, Denys-Drash syndrome, or Wilms tumor-aniridia-genitourinary abnormality-mental retardation (WAGR) syndrome, the cumulative incidence of renal failure was only 0.6%. However, in patients who had bilateral disease, the incidence of renal failure was 11.5%, and patients with Denys-Drash and WAGR syndromes had an incidence >50% [7]. The exact etiology of renal failure is not always clear and is likely to be multifactorial, with contributing factors including intrinsic, progressive renal disease related to a genetic predisposition, inadequate renal parenchyma after one or more tumor resections, the nephrotoxic effects of chemotherapy and radiation, and the potential for hyperfiltration injury to the remaining renal parenchyma [5,7]. Due to an increased risk of renal failure in children with bilateral Wilms tumor, these children receive neoadjuvant chemotherapy in an effort to shrink the tumors prior to surgery and facilitate the preservation of renal parenchyma, thereby preserving renal

function. Also eligible for enrollment on this protocol are patients with Wilms tumor arising in a solitary kidney or those patients less than one year of age with a unilateral Wilms tumor who are at an increased risk for a metachronous tumor. Patients with a number of genetic syndromes, particularly those associated with abnormalities of the Wilms Tumor one (WT1) and Wilms Tumor two (WT 2) genes on the short arm of chromosome 11, carry this risk [1,2].

Several centers have explored the role of parenchymal-sparing procedures in children with unilateral Wilms tumors [1]. The primary motivation for this approach is concern about late occurrence of renal dysfunction after unilateral nephrectomy. However, the incidence of renal failure following nephrectomy for most children with unilateral Wilms tumor is low, 0.6% at 20 years post-treatment [7]. We took up this study to assess the long term outcome after parenchymal-sparing procedure for non-syndromic unilateral Wilms tumor.

Materials and Methods

We retrospectively reviewed the records of all children with unilateral Wilms tumor who had undergone nephron sparing surgery at our center. This study was approved by the Institutional Review Board of our Hospital. Patient demographics, including congenital anomalies, tumor histology, surgical procedure and outcomes (including surgical complications, long-term renal function, tumor recurrence, and survival), were determined from a review of each patient's medical record.

Renal function was assessed by estimating the glomerular filtration rate using the Schwartz formula: Creatinine clearance = $(k \times \text{height in cm})/\text{serum Creatinine}$, in which $k = 0.55$ for children aged >18 months, and $k = 0.45$ for children aged <18 months. Other measures of long-term renal function included blood pressure evaluation and the need for antihypertensive medications, and the presence of proteinuria.

Results

During the study period Jan 2000 through Jan 2014, 38 children underwent treatment for Wilms tumor at our center, of these children 11 (seven males and four females) diagnosed as non-syndromic unilateral Wilms tumor received preoperative chemotherapy with two drugs (vincristine, and dactinomycin) following confirmation of diagnosis on needle biopsy. The mean age of the children was 19.63 ± 14.49 months at diagnosis. This approach was within the scope of the recommended SIOP guidelines. After an initial treatment with preoperative chemotherapy for four to six weeks, patients were reassessed with CT imaging. Following pre-operative chemotherapy, all the tumors showed massive shrinkage of the tumor ($>50\%$) (Table 1). There were no serious complications noted during the pre-operative chemotherapy period.

A total of eight patients underwent Partial Nephrectomy (PN) and the remaining three with polar tumors underwent Hemi-Nephrectomy (HN) following chemotherapy. In all eleven children, the renal plane of resection showed a tumor-free margin. No major intra/post-operative complications were noted. Three children received intra-operative blood transfusions, whereas four other children received post-operative blood transfusions. Histopathological examinations of the operated specimen confirmed the diagnosis of Wilms tumor and were of low risk/favorable histology. Six (54.54%) of the children had stage I and five (45.45%) others had stage II disease. Post-operatively all children received chemotherapy as per the protocol and underwent

Table 1: Study characteristics of children and oncologic outcomes.

Median age at diagnosis (months)	19.63 ± 14.49	9-56
Gender n(%)		
Male	7 (63.63%)	
Female	4 (36.36%)	
Median size of tumor at diagnosis mL	60.0 ± 36.16	32-142
Median size of tumor at the time of surgery mL	29.0 ± 19.89	12-78
Stage n(%)		
I	6 (54.54%)	
II	5 (45.45%)	
Postsurgical therapy n (%)		
Adjuvant chemotherapy	11 (100%)	
Adjuvant radiotherapy	-	
Salvage chemotherapy	1 (9.09%)	
Overall survival	100%	
Recurrence free survival %	90.90%	
Median follow-up months	108.09 ± 38.41	45 - 167

Table 2: Renal Function of the study patients.

estimated glomerular filtration rate	median eGFR (range)
eGFR at diagnosis	106.0 ± 10.78 (87 – 121)
eGFR at 36 months Follow-up	130.0 ± 3.78 (124 – 135)
eGFR at last follow-up	131.09 ± 3.52 (124 – 135)

eGFR: Estimated Glomerular Filtration Rate

evaluation and imaging as needed. The overall survival was 100% and recurrence free survival was 90.90%. One child initially diagnosed to have stage II disease developed recurrence in the lung 23 months postoperatively. This child was put on salvage chemotherapy and at last follow-up was clinically/radiologically disease free.

Renal function outcomes were as shown in Table 2. None of the patients presented with CKD (Chronic kidney disease) in the follow-up period. We noted an inverse relation between the size of the tumor and renal function at diagnosis. Smaller tumor volumes were associated with not only preservation of renal function but also increase in eGFR during the follow-up period. In the follow-up period all children were assessed for blood pressure and none of the children have been advised use of anti hypertensive medications.

Discussion

The Wilms Tumor (WT) is a major success story for cancer treatment, with modern rates of cure approaching 90% [8]. Today there has been increasing interest focused on the lifelong health prospects for the growing number of survivors, who may be at risk of second malignancies. Development of End Stage Renal Disease (ESRD) is of particular concern due to the possibility of progression of bilateral WT, irradiation of the opposite kidney in those with unilateral disease or hyperfiltration of the remaining nephron following loss of a major portion of renal tissue [5,7]. Breslow et al. [7], accurately assessed the full spectrum of End Stage Renal Disease (ESRD) in Wilms tumor survivors by combining the unique resources of the National Wilms Tumor Study Group (NWTSG) and the U.S. Renal Data System (USRDS). Cumulative incidence of ESRD at 20 years from diagnosis of unilateral WT was 74% for 17 patients with Denys-Drash syndrome (DDS), 36% for 37 patients with WAGR syndrome. The authors concluded that the risk of ESRD was



Figure 1: Intraoperative photograph revealing tumour and normal parenchyma.



Figure 2: Tumour beds in following Heminephrectomy.

remarkably low for the majority of WT patients however children with WAGR syndrome or associated GU anomalies were at higher risk and needed to be screened indefinitely to facilitate prospective management of impaired renal function.

Because of an increasing appreciation of the potential for renal failure in patients with bilateral tumors, the management of synchronous, bilateral Wilms tumors has evolved from primary kidney resection to renal-preserving surgical approaches facilitated by the use of preoperative chemotherapy. In 1979, the NWTSG formally recommended initial biopsy and chemotherapy before surgical resection of bilateral tumors [9]. Since then, several studies have confirmed the beneficial effects of preoperative chemotherapy followed by conservative surgical resection in patients with amenable, favorable histology, bilateral Wilms tumors [1,10,11].

As the overall survival of Wilms tumor increased to over 90% secondary to multidisciplinary therapy and multi-institutional cooperative group trials, several institutions have recently shifted their therapeutic focus to reduction in treatment morbidity and renal preservation while maintaining the high survival rates. Unilateral Wilms tumors associated with predisposing syndromes are usually treated with preoperative chemotherapy followed by surgical resection [12]. Romao et al. [12], described their experience with nephron sparing surgery for Wilms tumor in this population at risk for metachronous lesions. From 2000 to 2010, 13 of 75 (19%) patients treated for Wilms tumor were diagnosed with predisposing syndrome(s). Eight patients with unilateral tumors were treated and had a mean age at diagnosis of 27 months (range seven months to nine years). Beckwith-Wiedemann syndrome, isolated hemihyperplasia, WAGR (Wilms tumor, Aniridia, Genitourinary abnormalities, mental Retardation) syndrome and isolated 11p13 deletion were the



Figure 3: Approximation of Renal Capsule.



Figure 4: Operative specimen of Wilms Tumour.

underlying diagnoses in three, two, two and one patient, respectively. All but two patients were diagnosed by screening ultrasound and five underwent preoperative chemotherapy. Median tumor size at surgery was 2.5 cm (range 1 to 13). Nephron sparing surgery was performed in six of eight patients. Pathological study showed favorable histology Wilms tumor and nephrogenic rests in six and two patients, respectively. After a mean follow-up of 36 months (range 6 to 72) no recurrences were documented and all children had normal Creatinine levels. The authors concluded that nephron sparing surgery appeared safe for patients with unilateral Wilms tumor associated with predisposing syndrome(s), allowing for the preservation of renal function and good oncologic outcomes for the available follow-up time.

Most pediatric oncology cooperative groups, recommend radical nephrectomy as the surgical management for patients with non-syndromic Unilateral Wilms Tumor (uWT). However, data from adult renal malignancies demonstrate that when oncologically feasible, Nephron-Sparing Surgery (NSS) decreases long-term chronic renal disease and associated co-morbidities [1]. There are two reasons frequently cited to justify partial nephrectomy/nephron sparing surgery in children with unilateral non-syndromic Wilms tumor. One is the potential for renal insufficiency and the other is the risk of metachronous Wilms tumor development. Several authors have noted an increased risk of proteinuria and decreased Creatinine clearance in children undergoing nephrectomy [1]. Similarly several other studies have found no significant deterioration in renal function following unilateral nephrectomy [5,7]. A review of the NWTSG found that the rate of renal failure was 0.25% in this group of patients [7].

Cost et al. [13], retrospectively reviewed cases of children with non-syndromic uWT managed with attempted NSS. Thirteen children (5F:8M) diagnosed at a median age of 2.01yr (0.2-8.1) were followed for 8.7yr (0.24-31.8). All children had a solitary mass with a median Tumor Volume (TV) at diagnosis of 59.0mL (2.7-

640). 5 children (38.5%) received pre-surgical chemotherapy and in those observed a median total and percent TV reduction of 26.7mL (2.13-70.2) and 62.6% (15-77), $p = 0.043$. After accounting for TV reduction, the median TV at surgery for the entire cohort was 21.0mL (2.7-640). All children underwent NSS. Staging was: 9 Stage I, 2 Stage II and 2 Stage III (1 case done as an enucleation and 1 with a positive lymph node). Final pathology showed negative surgical margins and favorable histology WT in all specimens. During follow up there was 1 local recurrence (7.7%) in a Stage II patient after 1.9yr which was salvaged with chemotherapy and radiation. There was one death from chemotherapy-related sepsis in a Stage III patient after 0.24yr. The median pre-operative Cr and Estimated Glomerular Filtration Rate (eGFR) were 0.5 (0.22-1.0) and 88.2 (39.4-151.4), respectively. The median Cr and eGFR at last follow-up were 0.6 (0.29-1.1) and 131.8 (57.5-180.0), respectively. During follow up, there was a statistically-significant change in eGFR with a median increase of 32.2 (0.9-83.0), $p = 0.002$. The authors observed that in a highly selected children population, NSS for non-syndromic uWT offered reasonable oncologic outcomes and outstanding long-term renal function preservation.

Linni et al. [14], retrospectively studied seven children with unilateral nephroblastoma (four stage I, one stage III and two stage IV) who had tumor resection by partial nephrectomy (five right side, two left side), following four to six weeks of chemotherapy and the tumor shrinking by at least 50%. The authors opined that partial nephrectomy in children with unilateral WT, carried out by an experienced surgeon, was a reasonable alternative to nephrectomy if strict guidelines such as excellent tumor response to preoperative chemotherapy and easy resectability far away from the tumor margins through healthy kidney tissue were followed. Nerli et al. [15], similarly explored the role of NSS in children with unilateral non-syndromic Wilms tumor. Nine children with a mean age of 19.66 \pm 14.37 months received preoperative chemotherapy, following which they underwent nephron sparing tumor resection. Post-operative serum Creatinine repeated at the end of three months following surgery revealed maintenance of good renal function.

Haecker et al. [16], evaluated long term outcome after Partial Nephrectomy (PN) for unilateral Wilms tumor performed as initial surgery or after induction chemotherapy. The data was collected from children who undergone PN in the German Study SIOP 93-01/GPOH. Thirty seven children underwent PN of which 15 were performed at primary surgery and 22 after chemotherapy. Tumor stage, overall survival of 93% and relapse free survival of 88% were equal after PN and total nephrectomy in analysis of the whole group. The authors concluded that NSS should be performed only for small, histologically low or intermediate risk tumors after good response to chemotherapy to secure a complete resection.

Cost et al. [17], compared a group of children with non-syndromic uWT treated with NSS with a stage matched cohort managed with Radical Nephrectomy (RN). Fifteen children (six females and nine males) at a mean age of 2.5yrs underwent NSS and fifteen (eight females and seven males) others stage matched cohort with a mean age of 3.7yrs underwent RN. The median preoperative (eGFR) was 91.7 and 149.9 for NSS and RN respectively. The median eGFR at last follow-up was 135.3 and 131 for NSS and RN respectively, $P = .95$. The median change in eGFR during the study period was a gain of 28.6 for the NSS cohort vs. a loss of 19.1 for the RN cohort, $P = .007$. In this study NSS provided excellent renal function preservation when compared with RN. The authors however felt that this data needed

further validation via prospective large scale studies.

Our study too shows that in carefully selected patients with non-syndromic uWT, the oncologic outcomes are not compromised by managing these children with NSS. Moreover our limited data supports the information that NSS does not negatively impact the long term renal function in these children. Similar to the experience published by Cost et al. [17], we too noted an increase in eGFR during the study period. Several authors have postulated that the low eGFR in children at presentation could be due to an effect of the tumor on the renal function via an unclear physiologic mechanism [17-19]. A higher eGFR has been noted in all children undergoing NSS during the follow-up period. This increase in eGFR is theorized to be the result of compensatory hyperfunction by the remaining nephrons [17]. Cost et al. [17], hypothesized that compensatory hyper function requires a sufficient number of remaining nephrons and by preserving enough nephrons with NSS the renal function is adequately compensated. The principal concern with advocating partial nephrectomy/nephron sparing surgery for children with unilateral Wilms tumor is risk of positive surgical margins. It is a matter of concern as children with local recurrence after surgical resection are clearly at a survival disadvantage. Shamberger et al. [18], reported a 43% survival 2 years after local relapse and the survivors required a much more intensive therapy with increased risk of late sequelae.

Conclusions

In properly selected children with non-syndromic unilateral Wilms tumor, nephron sparing surgery provides excellent renal function preservation.

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