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ORIGINAL ARTICLE

Retrospective analysis to determine outcomes of patients with bilateral Wilms tumor undergoing nephron sparing surgery: 15-year tertiary single-institution experience

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Abstract

Purpose To describe our clinical experience with nephron sparing surgery (NSS) for bilateral Wilms tumor and evaluate the outcomes of patients treated at one of the largest pediatric medical centers in China.

Methods Medical records of children with bilateral Wilms tumor undergoing NSS in the Children's Hospital of Chongqing Medical University during a 15-year period were retrospectively analyzed. Data collected were composed of age at surgery, tumor response, tumor rupture during resection, final pathologic margins, use of radiation therapy, pathology reports, renal function, and patient survival.

Results A total of 18 eligible patients (10 males, 8 females) with bilateral Wilms tumor at a mean age of 2.28 ± 1.12 years were identified. The administration of preoperative chemotherapy did not result in universally successful outcomes. All children underwent successfully unilateral or bilateral NSS, of which one had positive pathologic margins and five received radiation therapy postoperatively. The rates of tumor rupture and positive lymph nodes involvement were 11.1 and 19.4%, respectively. The pathological study showed favorable histology and unfavorable histology in 32 and 4 kidneys, respectively. The 4-year event-free survival and overall survival rates were 68.18 and 85.56%. In univariable analysis, tumor histology ($p = 0.0028$) and disease stage ($p = 0.0303$) appeared significantly associated with overall survival. After a median follow-up period of 41.5 months (range 10–89), three of the surviving patients were diagnosed with hypertension and one had renal insufficiency.

Conclusions Our experience suggests that NSS has become a feasible and effective option with good oncologic outcomes. Further research, ideally in a multicenter randomized manner, is warranted to better assess the role of NSS in this challenging clinical scenario.

Keywords Nephron sparing surgery · Retrospective · Survival · Wilms tumor

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Abbreviations

WT	Wilms tumor
NSS	Nephron sparing surgery
PN	Partial nephrectomy
RN	Radical nephrectomy
NWTSG	National Wilms Tumor Study Group
COG	Children's Oncology Group
SIOP	Société Internationale d'Oncologie Pédiatrique
eGFR	Estimated glomerular filtration rate
VAD	Vincristine, actinomycin D, and doxorubicin
OS	Overall survival
EFS	Event-free survival

Introduction

Wilms tumor (WT) is the most common solid renal cancer in children under 15 years of age, representing approximately 6% of all cancer diagnoses in this age group, with an incidence of 7.1 cases per million [1]. Of these individuals with WT, 5–10% have a bilateral disease with a clinical synchronous or metachronous occurrence. Generally, the prevalence of bilateral involvement is higher in individuals with genetic predisposition syndromes than in those without predisposition syndromes [2]. Multidisciplinary collaboration and multimodality therapies have dramatically improved survival for this malignancy. As multiple successive randomized clinical trials have been conducted by several multi-institutional study groups such as the European Société Internationale d'Oncologie Pédiatrique (SIOP) and the National Wilms Tumor Study Group (NWTSG) which was supplanted by the Children's Oncology Group (COG) in 2002, 5-year observed overall survival (OS) rates in developed countries have been approximately 90% at present as opposed to 75% in the 1970s [1, 3].

Although remarkable progress has been achieved in the therapeutic clinical trials for children with renal tumors, several issues remain to be addressed, ranging from high rates of morbidities associated with nephron sparing surgery (NSS) to the role of preoperative chemotherapy. Of note, partial nephrectomy (PN) has recently been gaining increasing attention after its introduction in the treatment of adult patients with localized kidney cancer, due to its acceptable surgical morbidity, equivalent cancer control, and better preservation of renal parenchyma versus radical nephrectomy (RN) [4–6]. The potential for a similar experience in children with WT would integrate consistently with the interest in reducing late effects of treatment [7, 8]. As such, the SIOP WT-2001 protocol has allowed NSS for polar or peripherally non-infiltrating tumors [9]. Moreover, COG recently opened protocol AREN0534, recommending NSS in children with bilateral WT or those genetically predisposed to developing bilateral tumors to facilitate this technical strategy after neoadjuvant 3-drug chemotherapy with vincristine, actinomycin D, and doxorubicin (VAD) for 6 or 12 weeks based on histologic response and tumor stage [10]. However, there are no standard evidence-based recommendations and appropriate criteria for NSS in the management of unilateral WT, especially the identification of which patients will have a lower incidence of chronic kidney disease in the long term [8, 11, 12]. Meanwhile, bilateral NSS is still not widely performed in some medically underserved regions, which could be attributed to a lack of experience and an increased risk of local relapse or incomplete resection. In this setting, we analyzed patients with bilateral WT who underwent NSS at our institution, with a special focus on the renal function as well as surgical and oncologic outcomes.

Materials and methods

Patient population

After obtaining local institutional review board approval, we identified all the children diagnosed with WT in the Children's Hospital of Chongqing Medical University between January 2002 and August 2017. The medical records of patients who underwent NSS for malignancy were retrospectively reviewed in this cohort. Eligibility criteria included diagnosis of WT, no prior therapy before study enrollment, unilateral or bilateral NSS, and provision of informed consent by a parent or legal guardian. Patients were excluded if cancer-related history or necessary operative reports were not evaluable.

Study design

Data were retrieved on age at surgery, gender, administration of neoadjuvant chemotherapy, tumor response, tumor stage, intraoperative blood loss, tumor rupture during resection, final pathologic margins, use of radiation therapy, postoperative complications, length of follow-up, pathology information provided by one professional pathologist, and estimated renal function before and after surgery. A local tumor stage with a diagnostic biopsy was assigned using the NWTSG/COG surgical-pathologic staging system in which the highest one for each side was stage III [13]. Bilateral needle biopsies were recommended to provide accurate histology and biological information independent of the effect of chemotherapy. Patients known to be alive or lost to follow-up at the time of analysis were censored at their last follow-up.

All patients received regimen EE-4A or VAD, depending on tumor response and biopsy, for 2 cycles 3 weeks per cycle as the initial induction therapy with the purpose of performing NSS. Tumor volume was estimated with a weekly ultrasound examination and tumor response per kidney was separately assessed using a revised guideline [14]. If the tumors were not yet amenable to bilateral NSS, regimen VAD was continued for another 2 cycles. Definitive surgery, either bilateral NSS or RN/PN, was to be undertaken within 12 weeks after pre-nephrectomy chemotherapy if deemed feasible by the surgeons. Postoperative treatment strategy was based on the kidney with the highest stage and the risk stratification used by SIOP [13]. Patients with high-risk factors such as tumor rupture or involved abdominal lymph nodes would be given flank or abdominal irradiation, the

dose of which ranged from 10.8 to 19.8 Gy when taking histology and patient age into account.

The value of serum creatinine was determined with a colorimetric assay by autoanalyzer technique, with height and weight being measured simultaneously from diagnosis until the last follow-up. The estimated glomerular filtration rate (eGFR) was regarded as the best measure of renal function. In patients ≤ 17 years, eGFR was calculated with the modified Schwartz equation [15]. In patients aged 18 years or older, eGFR was calculated with the abbreviated Modification of Diet in Renal Disease study equation [16]. Patients were classified as hypertensive if they had repeated systolic or diastolic blood pressure measurements above or equal to the 95th percentile at each scheduled physical examination, or if any antihypertensive medication was prescribed.

Surgical approach

All NSS procedures were performed in a standard fashion through an open transperitoneal or chevron approach, with both kidneys being operated on in the same general anesthetic. After carefully releasing the colon and opening Gerota fascia, we freed the entire kidney from surrounding fatty tissue. The renal hilar vessels were identified, isolated, and could be manually compressed on occasion. The extent of the renal lesion to be completely excised was routinely identified via manual palpation and intraoperative ultrasound. If possible, resection of all masses was realized along with a small surrounding rim (< 1 cm) of normal renal parenchyma during the conduct of NSS. Intraoperative frozen section was used to ensure negative surgical margins and subsequent histologic analysis, with lymph nodes being sampled at the same time. After tumor resection, sufficient hemostasis was obtained with suture ligation and argon beam coagulation. If the collecting system was entered, it was closed using 4/0 absorbable sutures and a double-J ureteral stent was inserted only in cases with a large degree of disruption. The parenchymal defect was then approximated by interrupted absorbable sutures. A percutaneous Penrose drain was commonly placed, which would be generally removed before patient discharge. The ureteral stent was left in place until completion of chemotherapy, followed by its removal under cystoscopy from 3 to 6 months later.

Statistical analysis

All quantitative variables are reported as the median value and the range (min–max) or the mean ± standard deviation. OS was defined as the time from the date of diagnosis to the date of death from any cause or last follow-up. Event-free survival (EFS) was defined as the length of time after diagnosis until following complications or events, namely (1) late effects after treatment, (2) occurrence of cancer progression, and (3) loss to long-term follow-up. Statistical analyses were performed using SAS® software package, version 9.2 (SAS Institute, Cary, NC, USA). Both survival rates were estimated using the Kaplan–Meier method. *p* values were two-sided, and values < 0.05 were considered statistically significant.

Results

A total of 301 consecutive children were diagnosed with WT at our institution in the 15-year period, where 18 (6.0%) met the inclusion criteria and were enrolled in the study with available pathological specimens for review (Table 1). 10 patients (55.6%) were male and the mean age at surgery was 2.28 ± 1.12 years. The administration of preoperative chemotherapy resulted in a variety of outcomes, consisting of complete response (8.3%), partial response (44.4%), stable disease (36.2%), and progressive disease (11.1%). Of these 18 patients, two underwent unilateral NSS with contralateral nephrectomy and bilateral NSS was effectively accomplished in the others. RN was employed as a rational approach to manage the kidney with larger tumor and ipsilateral thrombus rising into the inferior vena cava or the ureter. The rates of tumor rupture and positive lymph nodes involvement were 11.1% (4/36) and 19.4% (7/36), respectively, resulting in stage III designation in six patients.

Table 1 Demographics and characteristics of patients with Wilms tumor

Characteristics	No. Patients (%)	
Gender		
Male	10	55.6
Female	8	44.4
Age at surgery (years)		
0–1	7	38.9
2–3	8	44.4
> 4	3	16.7
Associated conditions		
Cryptorchidism	3	16.7
Hypospadias	2	11.1
Local tumor stage by kidney		
Stage I	8	22.2
Stage II	17	47.2
Stage III	11	30.6
Tumor histology at initial surgery		
Bilateral favorable histology	15	83.3
Unilateral favorable histology, contralateral unfavorable histology	2	11.1
Bilateral unfavorable histology	1	5.6

As mentioned above, the surgeons held a thorough consultation with experienced oncologists to implement unilateral PN with contralateral RN for one-ninth patients who had a tumor extension into the inferior vena cava or even into the right atrium. Cardiopulmonary bypass and hypothermia were used for an hour in the patient with a right atrial tumor extension. The median length of surgery was 165 min (range, 128–320) with a mean estimated blood loss of 173.79 ± 74.71 ml, and 14 patients required intraoperative packed erythrocyte transfusions.

15 patients (83.3%) had bilateral favorable histology with negative margins. The remaining pathology findings were bilateral focal anaplasia, unilateral diffuse anaplasia with contralateral favorable, and unilateral favorable with contralateral focal anaplasia, respectively. The mean length of stay was 24.29 ± 4.51 days, during which postoperative chemotherapy was initiated following the definitive surgical intervention. The postoperative chemotherapy regimens were correspondingly provided to all patients at our department, while the radiotherapy was given at the referring hospital. 5 (27.8%) patients received radiation therapy postoperatively to the abdomen for anaplasia or positive lymph nodes, including a boy who had positive pathologic margins. The total doses of radiation, given as 150 cGy daily fractions, were limited to 12 Gy for favorable histology and 19.8 Gy for anaplastic histology, respectively. 6 patients (33.3%) received the histology-tailored chemotherapy regimen including additional cyclophosphamide, carboplatin, or etoposide. Unfortunately, two children with unfavorable histology developed recurrent disease, even treated with consolidation chemotherapy plus irradiation, and ultimately both died of the disease.

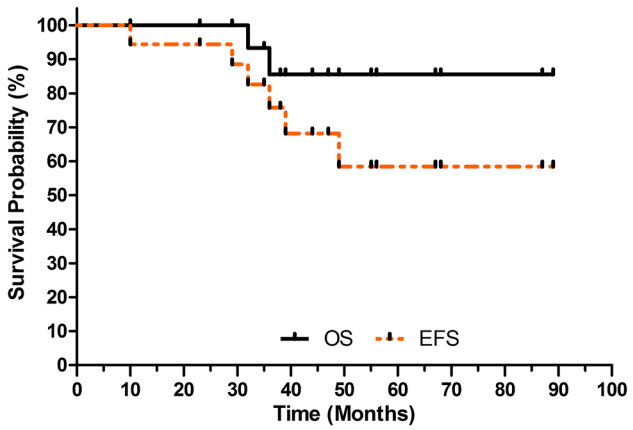

Fig. 1 Overall survival and event-free survival. *OS* overall survival, *EFS* event-free survival

The 4-year EFS and OS rates were 68.18 and 85.56%, as shown in Fig. 1. On the whole, only tumor histology ($p = 0.0028$) and disease stage ($p = 0.0303$) appeared significantly associated with OS in univariable analysis. A moderate number of complications were observed in the patient cohort, including hypertension (16.6%), urinary tract infections (11.1%), and transient renal insufficiency (5.6%). After a median follow-up period of 41.5 months (range 10–89), three of the surviving patients had persistently elevated blood pressure, requiring oral antihypertensive medication at their last visit (Table 2). Finally, all but one had an eGFR more than 75 ml/min/1.73 m^2 without clinically significant proteinuria.

Discussion

Current therapeutic regimens for children with WT have been developed through a number of large multi-institutional cooperative group trials, resulting in an excellent OS more than 90% [3, 17, 18]. Nonetheless, patients with bilateral WT have poorer EFS and are at a higher risk of renal failure than those with unilateral disease. In spite of the differences in treatment approach and their implications for unilateral WT, the bilateral disease is treated similarly in the COG and SIOP protocols. In either system, patients with bilateral, favorable histology WT should receive more intensive treatment composed of preoperative chemotherapy and NSS, which merits the combination of optimizing survival potential and preserving as much normal renal tissue as possible. Therefore, NSS has been supported in the management of bilateral renal tumors in children. In this study, we have analyzed a series of 18 children with bilateral WT who underwent NSS at one comprehensive center for pediatric health care in China, providing our practical experience to support these clinical strategies.

Table 2 Characteristics of patients with hypertension

Patient	Age at diagnosis, years	Surgical procedure	Histology	Stage	Pathologic margins	Radiation therapy
1	3.4	PN/RN	FH/uFH	III	Negative	Received
2	4.2	B NSS	FH/FH	III	Negative	Received
3	5.6	B NSS	FH/FH	II	Negative	Not received

B bilateral, *RN* radical nephrectomy, *PN* partial nephrectomy, *NSS* nephron sparing surgery, *FH* favorable histology Wilms tumor, *uFH* unfavorable histology Wilms tumor

The role of preoperative chemotherapy with regard to bilateral WT has been progressively defined. For example, the most significant issues are the duration of preoperative chemotherapy and the initial chemotherapy regimen. Sudour et al. [19] indicated that 80 days of preoperative chemotherapy allowed them to perform NSS in 68% of the kidneys according to the SIOP 93 protocol but did not specify the maximum duration. By comparison, the AREN0543 study preferred to decrease the time from diagnosis to surgical resection, with 84% patients being operated within 12 weeks [10]. It has been thought that the use of three-drug chemotherapy before surgery has been more effective in shrinking tumor volume than two drugs, raising the possibility to perform NSS [13]. In general, unfavorable histology and inadequate response to preoperative chemotherapy may lead to a more intensive chemotherapy regimen with the addition of doxorubicin or other drugs such as cyclophosphamide and carboplatin. In our study, both regimen EE-4A and VAD achieved a complete or partial response in the majority of kidneys. Despite our results are not as encouraging as those reported from COG and SIOP studies, the attempt to complete NSS, in our opinion, could be compensated by outstanding surgical techniques.

The information of initial needle biopsy was routinely collected before therapeutic interventions in our patient cohort, and yet the majority on AREN0534 only underwent the real-time central review of imaging, increasing misdiagnosis rates to some extent [10]. To date, NSS has been primarily employed in patients with bilateral WT, which is traditionally performed through an open transperitoneal approach. More recently, retroperitoneal PN has been studied in a single-institution analysis suggesting enhanced recovery and slightly fewer complications with equivalent outcomes, but this approach has not been widely adopted [20]. Fuchs et al. [21] described their technique to perform longitudinal PN as a single-stage procedure for central tumors with good outcomes. Along with our experience, all bilateral surgeries could be successfully carried out in one step during the patient's stay, if treating surgeons have sufficient expertise with such conditions. Minimally invasive surgery has revolutionized the management of renal tumors in adults and been successfully performed in selected patients with WT, demonstrating a promising accomplishment [22]. However, it is important to realize that NSS poses more significant challenges than RN, particularly laparoscopic PN. Technical concerns are composed of rigorous selection criteria, an increased risk of tumor rupture, longer warm ischemia time, and possible positive surgical margins.

Even though NSS has been accepted as an option of therapy for bilateral WT, this technique remains controversial in unilateral disease and plays a limited role. A growing body of evidence suggests that PN in adults with primary renal tumors offers many benefits compared with RN in terms of long-term renal and cardiovascular function as well as overall mortality [5, 8, 23]. In earlier years, Linni et al. showed that NSS could be a reasonable alternative to nephrectomy for children with unilateral WT [24]. The surgical procedure has been performed for unilateral WT in small series with good results, and thus this approach could be considered to treat polar or peripherally non-infiltrating tumors after a good response to chemotherapy based on the SIOP 2001 experience [9]. Interestingly, a similar analysis in the United States also concluded that NSS was associated with smaller tumors and that survival outcomes were similar to RN [12]. Nevertheless, both reports acknowledged that a relatively small proportion of patients underwent NSS and that the benefits of NSS must be carefully weighed against the risks of local recurrence in the name of improved renal preservation for patients with unilateral WT in whom renal failure is quite rare [9, 12]. In a review of pathologic specimens from 78 radical nephrectomies performed for unilateral WT, as many as 24.4% children undergoing pre-chemotherapy surgery were found to have post-resection pathological tumor characteristics favorable for NSS [25]. Ferrer et al. [26] recently reported on the image-based feasibility of NSS in children with very low-risk unilateral WT, indicating that 8% of very low-risk unilateral WT would have been amenable to up-front PN. As advanced diagnostic imaging techniques and multimodality therapy are being widely used, it is tempting to extend the NSS to other children with renal tumors, specifically in SIOP protocols.

The loss of renal parenchyma and the nephrotoxic effects of chemotherapeutic agents are thought to be the most common pathogenic factors of end-stage renal disease in children with bilateral WT [27]. Patients who are not suitable for NSS are at increased risk of requiring dialysis and/or renal transplantation as anticipated by their longer life expectancy. It has been investigated that an eGFR below 75 ml/min/1.73 m^2 in children and adolescents is a sign of disease that needs further clinical assessment [28]. In the current study, one girl was diagnosed with renal insufficiency after NSS, for whom renal replacement therapy has yet to be required. Thus far, it has not been verified that her renal failure developed due to insufficient renal parenchyma rather than an intrinsic renal disease, because she had mildly decreased clearance before surgery. Three patients had hypertension requiring pharmacotherapy, which could impair the remnants of healthy renal tissue. In fact, Cozzi et al. [29] demonstrated a slight increase in eGFR up to the third decade of life in WT survivors who underwent NSS compared with RN. Furthermore, hypertension has been reported to be less frequent after bilateral NSS than RN/PN [30]. Notably, chronic kidney disease is more likely for patients with WT1-related syndromes such as Denys-Drash and WAGR (Wilms tumor, Aniridia, Genitourinary anomaly, mental Retardation). Therefore, it is imperative to closely

monitor renal function and blood pressure as deterioration can occur in years to come.

Our findings should be interpreted on the basis of some principal limitations, such as retrospective character, small series, lack of control group, and a short period of follow-up. In addition, the equations used to calculate eGFR are considered reasonably accurate, whereas these equations do not perform well at near normal level [15]. In the context of exploring the genetic landscape of pediatric renal cancers, the rapid development of tumor biology could enable us to establish appropriate treatment strategies that could be incorporated into the implications for NSS [17, 18]. Hopefully, risk stratification scheme would be precisely revised with more supplements through multidisciplinary collaboration among pediatric urologists and surgeons, pathologists, and oncologists.

Conclusions

In conclusion, NSS has been a feasible and effective option with good oncologic outcomes in our population of patients with bilateral WT, but the conclusion is somewhat limited by relatively low power. Above all, functional and survival advantage should be acquired in the clinical decision-making by the maximal preservation of normal renal parenchyma without sacrificing cancer control. Further research, ideally in a multicenter randomized manner, is warranted to better assess the role of NSS in this challenging clinical scenario.

Author contributions Xiao-Hui Tan conceived and designed the study, read and analyzed documents, and drafted the paper. De-Ying Zhang and Xing Liu conducted the document search, read and analyzed the documents, and revised the manuscript. Da-Wei He, Xu-Liang Li, Tao Lin, and Guang-Hui Wei conceived and designed the study, advised on the search, read and analyzed documents. All authors take equal responsibility for guaranteeing the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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