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ORIGINAL ARTICLE

# Treatment of bilateral Wilms' tumor in children: how to improve the application of nephron-sparing surgery

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## Abstract

**Purpose** To summarize the experience of nephron-sparing surgery (NSS) for bilateral Wilms tumors (BWT) in children.

**Methods** This study included children with BWT admitted to our hospital between January 2008 and June 2022. The details of the treatments and outcomes were analyzed.

**Results** In all, 70 patients (39 males and 31 females) were enrolled, including 66 patients with synchronous tumors and 4 patients with metachronous tumors. The median age at diagnosis was 13 (3–75) months. Overall, 59 patients received preoperative chemotherapy and 45.8% (54/118) of the 118 sides of WT achieved a partial response (PR). Of the 70 patients, 48 (68.6%) underwent bilateral NSS and 22 (31.4%) underwent unilateral NSS and contralateral total nephrectomy. The proportion of bilateral NSS in the preoperative chemotherapy group was significantly higher than in the non-chemotherapy group (P = 0.031). Additionally, there were 26, 25, 14, and 5 cases of stage I, stage II, stage III, and stage IV, respectively. Among the 70 children, 16 had a recurrence, and 8 died. The 4 years EFS and OS were 67.9% and 89.3%, respectively.

**Conclusions** The long-term survival rates of patients with BWT improved. Hence, preoperative chemotherapy should be administered to enhance the use of NSS in BWT.

**Keywords** Nephron-sparing surgery · Bilateral Wilms' tumor · Pediatrics · Long-term survival rates

## Abbreviations

| | |
|---|---|
| BWT | Bilateral Wilms' tumor |
| COG | Children's oncology group |
| CR | Complete response |
| EFS | Event free survival |
| ESRD | End stage renal disease |
| NSS | Nephron-sparing surgery |
| NWTS | National Wilms tumor study |
| OS | Overall survival |
| PD | Progressive disease |
| PR | Partial response |
| PRM | Pathological resection margin |
| SD | Stable disease |
| SIOP | International society of pediatric oncology |
| SRM | Surgical resection margin |

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## Introduction

Bilateral Wilms' tumor (BWT) accounts for approximately 5–8% of Wilms' tumors (WT) [1]. However, the Children's Oncology Group (COG) reported that the 4 years event-free survival (EFS) and overall survival (OS) of patients with BWT in AREN0534 were 82.1% and 94.9%, respectively. Compared with the National Wilms Tumor Study-5 (NWTS-5) report, the 4 years EFS and OS of BWT were 56.0% and 80.8%, respectively, which were significantly improved [2]; however, the possibility of long-term end-stage renal disease (ESRD) in BWT remained much higher than that in unilateral WT. Preserving the renal parenchyma is essential in reducing the occurrence of renal failure. Further, nephron-sparing surgery (NSS) can remove tumors while preserving the normal renal parenchyma and reducing the incidence of ESRD. Hence, this article reviewed the clinical data of children with BWT admitted to our hospital between

January 2008 and June 2022. It summarized how to maximize nephron-sparing to ensure complete resection of the tumor and negative surgical margins, thus improving the prognosis of children with BWT.

## Methods

### Patients

All patients with bilateral renal tumors admitted to Beijing Children's Hospital between January 2008 and June 2022 were reviewed. Patients diagnosed with BWT were retrospectively analyzed. The medical records were retrospectively reviewed and obtained data included patients' clinical characteristics (age, sex, initial symptoms, associated anomalies, localized or metastatic status), treatment received (neoadjuvant and adjuvant chemotherapy, radiotherapy), surgery performed (total nephrectomy and/or NSS, side and timing of surgery), and pathological results (tumor stage and grade, tumor rupture, margins). Inclusion criteria: complete clinical data, surgical treatment (including bilateral NSS, unilateral NSS and contralateral tumor nephrectomy), postoperative pathology of WT. Exclusion criteria: Incomplete clinical data, no surgical treatment, postoperative pathology of non-wilms tumor and nephroblastomatosis. This study was approved by the Medical Ethics Committee of Beijing Children's Hospital ([2021]-E-154-R), and the requirement for informed patient consent was waived.

### The response to treatment and follow-up

The response to neoadjuvant chemotherapy was evaluated as follows: complete response (CR), the disappearance of the tumor; partial response (PR), at least a 30% decrease in the longest diameter (LD) of the tumor; stable disease (SD), neither sufficient shrinkage to qualify for PR nor an adequate increase to be eligible for PD; progressive disease (PD), at least a 20% increase in the LD of the tumor or the appearance of one or more new tumors. Resections should be described as R0, R1 and R2 as in radical, microscopic, macroscopic residual.

The patients were followed up every 3 months from the first to second year postoperation, and in the third year postoperation, the patients were followed up every 4 months. However, in the fourth year postoperation, the patients were followed up every 6 months. Furthermore, the patients were followed up once a year in the fifth year postoperation. The follow-up included abdominal ultrasound, abdominal enhanced computed tomography (CT), chest radiography, and blood biochemical renal function to detect the survival outcomes (recurrence, death) and long-term renal function (blood pressure, proteinuria and serum creatinine levels, need for dialysis or renal transplant) of the children.

### Statistical analysis

Data sorting and analysis were performed using SPSS 23.0 statistical software, and GraphPad Prism 8 was used for drawing. Non-normal distribution measurement data were expressed as the median, and the count data were expressed as the number of cases (percentage). The comparison between groups was analyzed using the Chi-square test or Fisher's exact test. All P values were two-sided, and values $< 0.05$ were considered statistically significant. OS was defined as the time from the date of registration to death from any cause or to the date of the last follow-up, and EFS was defined as the time from the date of registration to death from any cause or to the first occurrence of tumor recurrence (local or metastasis) or progression. OS and EFS were calculated using the Kaplan–Meier method.

## Results

### Patient characteristics

A total of 70 patients (39 males and 31 females) with BWT were included in this study. The age at presentation ranged from 3 to 75 months (mean 18.6 months, median 13.0 months). There were 66 cases of synchronous WT and 4 cases of metachronous WT. Clinical manifestations included an abdominal mass in 49 cases, hematuria in 9 cases, ultrasound findings in 5 cases, abdominal distension in 3 cases, abdominal pain in 2 cases, and vomiting in 2 cases. There were 22 cases associated with malformations, including 12 with cryptorchidism, 8 with hypospadias, 1 with indirect inguinal hernia, 1 with hepatic hemangioma. One patient was diagnosed with Denys–Drash Syndrome (DDS),and three patients were diagnosed with WAGR syndrome. No patients exhibited Beckwith-Wiedemann syndrome.

All children underwent abdominal ultrasonography, abdominal enhanced CT, chest CT, and other imaging examinations at diagnosis and as preoperative planning. There were 5 cases of lung metastasis, 17 sides of unilateral multiple renal tumors, and 12 sides of renal tumors located in the interior of the kidney without a convex surface completely surrounded by the renal parenchyma. The preoperative renal tumor size ranged from 1.1·1.0·1.2 cm to 12.3·13.0·19.2 cm, the maximum diameter of the tumor ranged from 1.5 to 19.2 cm, the mean maximum diameter was 9.5 cm, and the median maximum diameter was 9.7 cm.

## Preoperative biopsy and neoadjuvant chemotherapy

Tumor biopsy was performed before chemotherapy in 11 patients. Preoperative chemotherapy was administered in 59 patients; however, 11 patients did not receive preoperative chemotherapy due to the tumor is small which can be removed completely.

Preoperative chemotherapy was based on the VA regimen (vincristine + actinomycin D) in 45 cases, the VAD regimen (vincristine + actinomycin D + doxorubicin) in 9 cases, and the chemotherapy regimen was unknown in 5 cases. The median duration of preoperative chemotherapy was 12 weeks (2–24 weeks). Overall, 59 patients with 118 sides of WT underwent preoperative chemotherapy, and the imaging studies revealed that the response to the initial chemotherapy was as follows: 54 sides (45.8%) achieved PR, 55 sides (46.6%) achieved SD, PD occurred in 9 sides (7.6%), and no CR was observed.

## Surgery

A total of 48 (68.6%) patients underwent bilateral NSS, while 22 (31.4%) patients underwent total nephrectomy for one kidney and NSS for the contralateral kidney. Finally, 118 of the 140 kidneys (84.3%) were subjected to NSS. Among the 17 sides of unilateral multiple renal tumors, 15 sides of renal tumors were resected as NSS. Among the 118 NSS, only one patient who underwent total nephrectomy for one kidney and NSS for the contralateral kidney had a gross residual tumor at the surgical resection margin (SRM) when NSS was performed for unilateral renal pelvic wall invasion. The remaining 117 had no gross tumor residues. The surgical methods used in the preoperative and non-preoperative chemotherapy groups are presented in Table 1. The proportion of bilateral NSS in the preoperative chemotherapy group was significantly higher than in the non-preoperative chemotherapy group (36.4 *vs*.74.6%, $P = 0.031$).

Tumor infiltrating the renal pelvis and/or ureteral wall and tumor growing into the renal pelvis or ureter were found in 30 patients: 38 kidneys (38/140, 27.1%), including 24 kidneys (24/38, 63.2%) with tumor invasion of the right renal pelvis or right renal pelvis wall. Among the 38 renal pelvic tumors, 24 infiltrated the renal pelvis wall and/or ureteral wall, and 14 grew into the renal pelvis or ureter. NSS was performed on 33 kidneys; 3 of 24 kidneys with renal pelvic wall infiltration underwent total nephrectomy, and 2 of 14 kidneys with tumors growing into the renal pelvis or ureter underwent total nephrectomy.

The clamping time of the renal pedicle was 4–30 min (median 20 min) in the 118 NSS. Thereafter, the surgeon estimated the percentage of residual renal parenchyma in each kidney and reported it in operative records. The residual renal parenchyma of the reserved kidney was greater than that of the unilateral kidney in 31 cases (44.3%), less than that of the unilateral kidney in 32 cases (45.7%), and uncertain in 7 cases.

**Table 1** Effect of preoperative chemotherapy on surgical choice and prognosis

| | Non-preoperative chemotherapy group ($n = 11$) | Preoperative chemotherapy group ($n = 59$) | $P$ |
|---|---|---|---|
| Bilateral NSS ($n$) | 4 | 44 | 0.031 |
| Postoperative event-free survival ($n$) | 8 | 41 | 1.000 |

## Pathology, adjuvant chemotherapy, and radiotherapy

According to the SIOP pathological classification system, 59 patients (118 kidneys) with preoperative chemotherapy had the following postoperative pathologies: 52 kidneys of stromal type, 8 kidneys of epithelial type, 5 kidneys of blastemal type, 27 kidneys of mixed type, nephroblatoma completely necrotic in 18 kidneys, fetal rhabdomyomatous nephroblastoma in 6 kidneys, cystic partially differentiated nephroblastoma in 2 kidneys, and no anaplastic type. The postoperative pathology of the 11 patients in the non-preoperative chemotherapy group was one kidney of stromal predominant, two kidneys of epithelial predominant, five kidneys of blastema predominant, nine kidneys of mixed predominant, two kidneys of fetal rhabdomyomatous nephroblastoma, cystic partially differentiated nephroblastoma in two kidneys, cystic WT in one kidney, and no anaplasia type. Of the 70 patients, 57.1% (40/70) had the same pathological type of bilateral WT. The histological risk assessment of 70 cases of bilateral WT and the corresponding surgical methods are shown in Table 2.

Intraoperative lymph node biopsy was performed routinely, the mean number of lymph nodes sampled at every operation was three. And only one nephroblastoma kidney was positive for the renal hilar lymph node. The pathological resection margin (PRM) was positive in 3 of the 117 NSS cases. Above all, in our study, 113 sides of R0, 3 sides of R1, 1 side of R2. (One patient with R2 was treated with postoperative radiotherapy and chemotherapy and survived without the disease. Three patients with R1 did not receive regular radiotherapy that showed recurrence, and one died.)

No preoperative chemotherapy staging was performed using the COG criteria based on unilateral staging. Preoperative chemotherapy staging was performed according to the SIOP criteria as follows: stage I, 26 cases; stage II, 25

**Table 2** Histological risk assessment, corresponding surgical approach, and prognosis of 70 bilateral Wilms' tumors

| | Risk assessment | Surgery | | Follow-up | | |
|---|---|---|---|---|---|---|
| | | Bilateral NSS (*n*) | Total nephrectomy for one kidney, NSS for the contralateral kidney (*n*) | Tumor-free survival (*n*) | Recurrence (*n*) | Died (*n*) |
| Stage I[a] | Low risk (*n* = 1) | 1 | | 1 | | |
| | Intermediate risk (*n* = 24) | 15 | 9 | 22 | 2 | |
| | High risk (*n* = 1) | 1 | | 1 | | |
| Stage II[a] | Low risk (*n* = 2) | 2 | | 1 | | 1 |
| | Intermediate risk (*n* = 22) | 15 | 7 | 14 | 7 | 2 |
| | High risk (*n* = 1) | 1 | | 1 | | |
| Stage III[a] | Low risk (*n* = 2) | 1 | 1 | 1 | | 1 |
| | Intermediate risk (*n* = 12) | 8 | 4 | 6 | 6 | 2 |
| | High risk (*n* = 0) | | | | | |
| Stage IV[a] | Low risk (*n* = 0) | | | | | |
| | Intermediate risk (*n* = 2) | 1 | 1 | 1 | | 1 |
| | High risk (*n* = 3) | 2 | 1 | 1 | 1 | 1 |

[a]By the highest stage (either favorable histology focal or diffuse anaplasia present)

cases; stage III, 14 cases (3 cases of PRM positive, 1 case of SRM positive, 1 case of renal hilar lymph node positive, 5 cases of the tumor were found in the peritoneum, 4 cases of cancer has grown into nearby vital structures); and stage IV, 5 cases (5 cases of lung metastasis). Instead, preoperative chemotherapy group received postoperative chemotherapy or radiotherapy according to SIOP pathological risk stratification combined with staging. EE-4A and DD-4A were the main chemotherapy regimens in the group without preoperative chemotherapy according to NWTS-5.And 14 patients were treated with radiotherapy (including 1 case with a positive surgical margin and 3 cases with a positive pathological margin).

## Outcome

All children were followed up with a median follow-up duration of 39 months (range 2–162 months). The median age at follow-up was 62 months (range 11–181 months). Among the 70 children, 16 had a recurrence, and 8 died, of whom 3 died after recurrence.

Among the sixteen children with recurrence, two had stage I, seven had stage II, six had stage III, and one had stage IV tumors. There were 12 cases of local recurrence and 4 cases of retroperitoneal recurrence. The median recurrence time was 11 months (range 1–38 months). Two patients, recurrent tumors disappeared after intensive chemotherapy. Fourteen patients underwent surgical resection of the recurrent lesions; additionally, intensified chemotherapy with etoposide, carboplatin, and cyclophosphamide was administered post-operation. Among the 16 patients, 3 died, 2 were alive with tumors, and 11 were alive without tumors.

Among the eight children who died, three, three, and two had stage II, stage III, and stage IV tumors, respectively. Four patients underwent bilateral NSS, and four underwent total nephrectomy for one kidney and NSS for the contralateral kidney. The specific causes of death were cerebral hernia in 9 years without tumor in one case, pulmonary metastasis in two cases, renal failure caused by ESRD in two cases (including one case of DDS), and tumor recurrence in three cases after ineffective surgical treatment. There was no significant difference in postoperative EFS between the preoperative chemotherapy and non-chemotherapy groups (72.7 vs.69.5%, $P = 1.000$) (Table 1). However, the differences in the prognoses of the different tumor stages were statistically significant (92.3 *vs.* 64% *vs.* 50 *vs.* 40%, $P = 0.005$) (Table 3).

**Table 3** Effect of tumor stage on prognosis

| | Total (*n*) | Postoperative event-free survival (*n*) | Postoperative recurrence, death (*n*) |
|---|---|---|---|
| Stage I[a] | 26 | 24 | 2 |
| Stage II[a] | 25 | 16 | 9 |
| Stage III[a] | 14 | 7 | 7 |
| Stage IV[a] | 5 | 2 | 3 |

[a]By the highest stage (either favorable histology focal or diffuse anaplasia present)

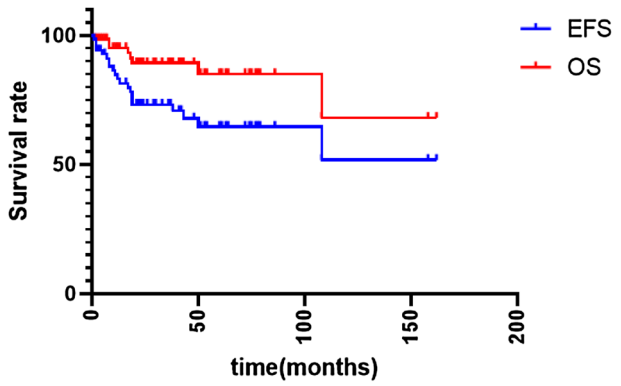


**Fig. 1** EFS and OS survival curves of 70 children with bilateral Wilms tumor

In summary, the 4 years EFS of the 70 children was 67.9%, and the 4 years OS was 89.3%, as shown in Fig. 1.

Of the 70 children in this study, 2 cases had secondary hypertension and 3 cases (4.3%) had elevated serum creatinine and urea nitrogen during a mean follow-up of 47 months. Among these three cases, two underwent unilateral NSS + contralateral total nephrectomy, and one patient with DDS syndrome underwent bilateral NSS.

## Discussion

BWT accounts for approximately 5–8% of children with WT, divided into synchronous and metachronous BWT, accounting for 6.3% and 0.85% of WT, respectively [1]. BWT is characterized by a young age of onset and is often combined with other urinary system malformations such as cryptorchidism and hypospadias [3]. Our study results agreed with those of previous studies on bilateral WT. In our study, the median age of the 70 children who underwent BWT was 13.0 months. Metachronous BWT accounted for only 5.7% (4/70) of the BWT cases.

In children with BWT, NSS is essential for preserving renal tissue and reducing the incidence of renal failure. Therefore, the application of the NSS should be improved to reduce the incidence of ESRD. In 2006, Shamberger et al. reported that the 10 years OS for BWT patients treated with NWTS-4 was 82.1% [4]. Follow-up was conducted for 28 children with BWT by Japan Wilms Tumor Study Group (JWiTS) for a median of 8 years (1.3–13.1 years). The 5 years EFS and OS rates were 85.5% and 92.6%, respectively. However, for renal preservation, the percentage of NSS was only 56% of the 56 kidneys [5]. Sudour et al. reviewed the clinical data of 49 children with BWT treated according to SIOP 93 guidelines in France from 1993 to 2001: 3 months of preoperative chemotherapy, 67% of the kidneys underwent NSS, and the 5 years EFS and 5 years OS rates were 85.5% and 92.6%, respectively[6]. The 4 years EFS and OS of BWT in AREN0534 reported by COG were 82.1% and 94.9%, respectively, which were significantly higher than those of BWT reported by NWTS-5 56.0% and 80.8% [2]. It benefits from adding doxorubicin to initial chemotherapy, and subsequent chemotherapy was tailored according to the post-chemotherapy histologic response. In AREN0534, 87% of the patients had at least one NSS; nonetheless, only 35% had bilateral NSS. In our study, 48 patients (68.6%) underwent bilateral NSS, 22 (31.4%) underwent unilateral NSS + contralateral total nephrectomy, the 4 years EFS was 67.9%, and the 4 years OS was 89.3%. The proportion of children with bilateral NSS was higher than that reported in the literature, while the OS was consistent with that reported in the literature [2, 4, 5]. The EFS was similar to most reports in the literature but lower than that of AREN0534, which was considered to be related to preoperative chemotherapy with only vincristine and actinomycin D, and most of them without doxorubicin.

At present, neither COG nor SIOP recommends routine preoperative biopsy for BWT, and the preoperative diagnosis of BWT is more dependent on imaging examination. The main reasons for performing a biopsy for preoperative chemotherapy in unilateral WT are to avoid misdiagnosis and confirm the presence of anaplasia. However, the misdiagnosis rate of WT in the SIOP study was very low, ranging from 1.6 to 5.5% for unilateral renal tumors. Although rare cases of bilateral renal malignant rhabdoid tumors and bilateral renal carcinomas have been reported, the misdiagnosis rate of bilateral renal tumors remains extremely low. Hamilton et al. reviewed NWTS-4 data and failed to detect anaplastic WT by needle biopsy, whereas its detection rate by open biopsy was only 33.3% [7]. In the NWTS-5 review of 25 patients with bilateral anaplastic WT for whom preoperative biopsy and postoperative tumor specimens were available, only 2 patients (8%) had anaplastic types detected by preoperative biopsy [8]. In the JWiTS series, the pathological review revealed that all cases were favorable type nephroblastomas with no anaplastic cases [5]. Therefore, they considered a tumor biopsy unnecessary prior to chemotherapy. In our study, preoperative biopsy was performed in 11 cases,

including 1 case of atypical WT, which was considered to be clear cell sarcoma or lymphosarcoma. The other 10 cases underwent routine biopsy before chemotherapy. The biopsy pathology in these 11 patients was WT. No anaplastic WT was found in the postoperative pathology of the 70 patients. The incidence of anaplastic BWT in Asian children is significantly lower than that in European and American children though the reason is unclear [5]. Our study found that the higher the tumor stage, the worse the prognosis (P = 0.005). In conclusion, we believe that routine biopsy is not necessary for preoperative chemotherapy in BWT, so as not to increase tumor staging and reduce the prognosis of children.

Standardized preoperative chemotherapy is a prerequisite for improving the use of NSS in BWT. Currently, both COG and SIOP treatment principles for BWT aim to preserve renal tissue as much as possible through preoperative chemotherapy to improve the survival rate for long-term renal failure reduction. The selection of preoperative chemotherapy drugs differed slightly between the COG and SIOP groups. SIOP 2001 recommended vincristine + actinomycin D (VA) chemotherapy for 4 weeks to evaluate its efficacy. If the tumor volume was reduced by > 50%, chemotherapy was continued for 4 weeks before surgery. If the tumor was stable or progressive, doxorubicin was added for 4 weeks until the tumor was reduced to a feasible NSS. If the tumor size did not change further after the addition of doxorubicin, and the examination and evaluation of the tumor were difficult to perform NSS, an expert consultation was organized to discuss intensive chemotherapy and surgery. The UMBRELLA SIOP2016 protocol recommends limiting preoperative chemotherapy to no more than 12 weeks, with a 6 weeks interval between assessments [9]. In AREN0534, bilateral NSS was evaluated 6 weeks after the preoperative VAD regimen. If the tumor was reduced and bilateral NSS could not be performed, chemotherapy was continued for 12 weeks. If the tumor was stable or progressive, the chemotherapy regimen was adjusted to 12 weeks after bilateral biopsy before surgery [2]. In our study, 11 patients did not receive preoperative chemotherapy, and only 4 (36.4%) underwent bilateral NSS. Among the 118 kidneys of 59 patients receiving preoperative chemotherapy, 54 (45.8%) achieved PR, and 55 (46.6%) achieved SD. Among these, 44 (44/59, 74.5%) underwent bilateral NSS. The rate of NSS in the preoperative chemotherapy group was higher than that in the non-preoperative chemotherapy group, and the difference was statistically significant (36.4% *vs.*74.6%, $P = 0.031$); however, there was no statistically significant difference in the prognosis between the two groups. Therefore, we believe that PR can be achieved in approximately 45% of WT patients undergoing preoperative chemotherapy, reducing the tumor volume and increasing the chance of NSS.

Understanding the indications for NSS is the key to improving the application of NSS in BWT. The systematic review reported by Tricard et al. concluded that small tumors (< 4 cm) distant from the renal hilum (ideally on the upper pole) that respect at least 50% of the renal parenchyma (ideally superficial with exophytic development) seem to be the perfect indication for NSS in unilateral WT [10]. Cost et al. reviewed the pathological sections of 78 patients with unilateral WT who underwent radical resection and were considered ideal candidates for NSS according to the following criteria: (i) unifocal mass located outside of the renal hilum (therefore, polar and amenable to NSS) sparing a third or more of the normal kidney, (ii) favorable histology, (iii) absence of renal sinus or segmental vascular tumor invasion, (iv) no metastatic LNs, intraoperative tumor spill or gross regional disease at surgery, and (v) distinct interface between the tumor and renal parenchyma [11]. Although BWT often has the characteristics of large and multicentric tumors, the surgical indications for NSS in unilateral WT are often inapplicable to BWT because long-term ESRD must be considered. However, factors affecting NSS, such as tumor size, location, collecting system invasion, and proportion of residual kidney, should also be considered in bilateral NSS.

However, for BWT, tumor size should not be used as an absolute index to limit NSS. In our study, the mean maximum diameter of the renal tumors was 9.5 cm (range 1.5–19.2 cm), and about 50% of the tumors were larger than 9.7 cm. Attention should be paid to NSS for large renal tumors. It is necessary for surgeons to accurately identify the boundary between the tumor and normal renal parenchyma during the resection process. Large tumors have a large tumor bed area and a large wound after tumor resection, which increases the probability of damage to important renal branches and blood vessels or collecting systems, making wound suture and reconstruction more complicated, resulting in prolonged warm ischemia time. The surgeon can predict the intraoperative wound condition by imaging before surgery and reduce the damage to important blood vessels and collecting systems without affecting the tumor resection margin. In our study, the clamping time of the renal pedicle during surgery was 4–30 min, with a median of 20 min.

Tumor location also affects the choice of NSS. NSS should be performed as far as possible when the tumor is distant from the renal hilum. However, completely intrarenal kidney tumors present an additional challenge in that they are completely enclosed by renal parenchyma, and there are often no visual cues when resecting the tumor. Curtiss et al. showed that there was no significant difference in the rate of estimated blood loss, operative time, warm ischemia time, positive surgical margins, and complications between intrarenal lesions and the exophytic cohort [12]. Intraoperative ultrasonography is required to locate and excise the tumor [13]. NSS is safe and effective for completely intrarenal kidney tumors in BWT, despite technical difficulties.

The botryoid growth pattern is a polypoid mass growing into the renal pelvis, rarely seen in BWT, representing a surgical challenge [14]. Vujanić et al. concluded that intrapelvic botryoid growth should not be a reason for tumor upstaging. Even when the tumor extends into the ureter and reaches the bladder without infiltrating the wall, it should remain regarded as stage I if completely excised [15]. In our series, tumor infiltration of the renal pelvis and/or ureteral wall and tumor growth into the renal pelvis or ureter were found in 38 kidneys (38/140, 27.1%). Tumor invasion or growth into the right renal pelvis was observed in 26 cases (26/38, 68.4%). Among the 38 kidneys, the tumors infiltrated the renal pelvis and/or ureteral wall in 24 kidneys, and the tumors grew into the renal pelvis in 14 kidneys. Among them, 33 kidneys underwent NSS, and 5 underwent tumor nephrectomy. NSS was performed in 12 kidneys with intrapelvic tumors, and 2 kidneys with intrapelvic tumors underwent tumor nephrectomy. One patient was treated with NSS because of tumor invasion of the renal pelvic wall during the operation. During the operation, there was a residual tumor at the edge of the renal pelvis, and DD-4A chemotherapy and local radiotherapy were administered postoperatively. Therefore, we believe that BWT can be classified as stage I if the tumor growing into the renal pelvis is completely removed. When conditions permit, NSS can be performed, and the whole tumor and botryoid mass in the pelvis can be removed without any rupture during the operation. If the tumor infiltrates the renal pelvis, NSS remains feasible, and the renal pelvis wall invaded by the tumor must be removed to avoid a positive tumor margin.

The NSS surgical resection margin was positive, increasing the probability of tumor recurrence. Therefore, a positive resection margin should be avoided as much as possible during surgery. There is no significant difference in the risk of local recurrence between children with positive NSS margin and those with negative margin. However, it increases the risk of long-term postoperative hypertension [16, 17].In our study, the patient with R2 was treated with postoperative radiotherapy and chemotherapy and survived without the disease. Three patients with R1 did not receive regular radiotherapy that showed recurrence, and one died. Therefore, NSS is important for ensuring negative surgical margins. Regular radiotherapy is needed to reduce the possibility of tumor recurrence if there is residual tumor during surgery or positive surgical margins post-operation. Based on our experience, we believe that reducing the tumor volume and promoting the thickening of the tumor pseudocapsule by preoperative chemotherapy, paying attention to the weak part of the capsule, and favoring renal enucleation are the methods to prevent positive resection margins. Therefore, attention should be paid to the application of preoperative chemotherapy for the treatment of BWT.

The limitations of this study, including the limited sample size and retrospective study design, should be considered when extrapolating these results. The surgeon estimated the percentage of residual renal parenchyma in each kidney which needed a more objective approach. In addition, the average follow-up time was 47 months and the maximum follow-up time was 162 months. Therefore, further follow-up should be conducted to understand better the long-term renal function of children undergoing NSS.

In conclusion, the long-term survival rates of patients with BWT have improved. In this study, bilateral NSS accounted for 68.6% of patient cases, which was related to standardized preoperative treatment and reasonable indications for NSS. Therefore, the application of NSS in BWT in children should be improved by standardized preoperative chemotherapy; careful consideration of tumor size, location, residual kidney volume, and degree of invasion of the collecting system; and avoidance of positive surgical margins.

**Author contributions** All authors have read and approved the manuscript. Conception and design: YWF, HCS; Analysis and interpretation of data: YWF, ZWL; Drafting of the manuscript: YWF; ZWL; Critical revision of the manuscript for important intellectual content: NS,WPZ.

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## Declarations

**Conflict of interest** The authors declared that they have no conflict of interest.

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