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Repeat nephron-sparing surgery for children with bilateral Wilms tumor

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ABSTRACT

Background: Renal insufficiency is a significant complication of Wilms tumor treatment in the 5% with bilateral disease. Nephron-sparing surgery (NSS) is recommended after neoadjuvant chemotherapy initially. However, the role of NSS in recurrent disease is unknown. We reviewed our experience to assess the feasibility and oncologic and functional outcomes of repeat NSS for children with recurrent disease.
Methods: A retrospective review was performed of all children treated at our institution for bilateral, favorable histology (FH) Wilms tumor. Patients undergoing repeat NSS for locally recurrent disease were identified. The outcomes evaluated included tumor recurrence, renal function, and patient survival.
Results: Since 2001, 36 children with bilateral FH Wilms tumor have been treated at our institution. Eight patients (22%) underwent repeat NSS for locally recurrent disease. Two patients had a second local recurrence and underwent a third NSS. Six patients are alive without disease (75%) with an average follow-up of 4.5 years. Two patients have died, each with blastemal-predominant histology at repeat NSS. The surviving patients have normal renal function, although two patients require medical management of hypertension.
Conclusions: Our experience suggests that repeat NSS for local recurrence of FH bilateral Wilms tumor is feasible and affords acceptable oncologic outcome with preservation of renal function. However, more aggressive therapy may be required for patients whose recurrence has blastemal-predominant histology, given the poor outcome for these patients in our series.

Wilms tumor (WT) is the most common renal cancer in children, with about 600 cases in the United States each year. Approximately 5% of these children will have disease in both kidneys [1]. In these patients with bilateral Wilms tumor (BWT), successful treatment must achieve oncologic control while preserving maximal renal parenchyma to ensure sufficient renal function. Renal insufficiency may adversely affect both overall health outcomes as well as quality of life [2]; this impact may be especially pronounced in children with BWT, who are often younger than their counterparts with unilateral disease and may also be afflicted with syndromes associated with poor renal function at baseline [3,4].

Upfront chemotherapy and nephron-sparing surgery (NSS) provide a safe and effective means of providing oncologic control while optimizing renal function [5,6]. BWT is an independent risk factor for the development of renal insufficiency, due in large part to the loss of renal parenchyma, especially in children who had not undergone upfront chemotherapy or initial nephron-sparing surgery [7,8]. Overall, about 15% of children with BWT who were enrolled in National Wilms Tumor Studies 1–4 developed renal insufficiency in the two decades following diagnosis; children with metachronous disease and those with underlying syndromes such as WAGR or Denys–Drash had increased risks of renal failure, with up to 50% of children affected [9]. With the addition of upfront chemotherapy, children who have undergone NSS have similar rates of hypertension (52.9%) before and after surgery and a low risk of renal insufficiency (13.3%, excluding two patients rendered anephric by completion nephrectomies) [5,10]. These favorable outcomes, as well as the ability to successfully perform NSS on technically challenging tumors owing to size or location, have enabled many children with BWT to delay or avoid hemodialysis, renal transplantation, and other adverse sequelae of renal insufficiency.

One risk of renal parenchymal preservation is the development of recurrent disease; the estimated recurrence rate after treatment of WT is between 8.5% and 13.9% [11,12]. Although all patients with WT must be monitored closely for local tumor recurrence, the multifocality of BWT, the young age at which patients develop primary tumors, and the increased prevalence of syndromes associated with renal compromise make treatment of tumor recurrence in patients

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with BWT especially challenging. Recurrent disease is typically treated with a combination of chemotherapy and surgical excision; balancing oncologic control with parenchymal preservation may be technically difficult in kidneys that have previously undergone surgery. Further renal parenchymal loss may increase the risk of renal insufficiency, particularly in the setting of the need for additional chemotherapy and/or radiation. To date, neither oncologic outcomes nor renal functional assessments have been reported in patients who have undergone treatment for tumor recurrence after NSS for BWT. We undertook this study to determine whether repeat NSS in patients with recurrent disease was associated with an increased risk of renal insufficiency or changes in overall survival.

1. Methods

After obtaining Institutional Review Board approval, ICD-9 codes were utilized to identify all patients who had undergone NSS for BWT at St. Jude Children's Research Hospital between January 2001 and August 2012. Patients without at least 3 months of postsurgical follow-up were excluded, as were patients with focal or diffuse anaplasia on histopathologic analysis at initial NSS. Data were collected on demographics, tumor characteristics, histopathologic findings including margin status, neoadjuvant and adjuvant therapy, locoregional and distant recurrence, development of hypertension, renal functional assessments, and event-free and overall survival. Demographic variables were described using measures of central tendency. Renal function was assessed using glomerular filtration rates calculated in technetium-99m renal clearance studies. Patients were classified as hypertensive if the medical record specifically noted a diagnosis of hypertension or if daily antihypertensive medication was required to maintain blood pressure within the normal range for age.

We approach all nephron-sparing surgeries similarly, whether or not the patient has previously undergone renal surgery. We have previously described our surgical technique in detail [5]. NSS is considered in all patients with WT involving all renal units, with the only absolute contraindications being venous involvement with tumor thrombus and anaplastic histology. All families are counseled that nephrectomy will be considered when the tumor precludes preservation of the renal hilar vessels or when less than 25% of the renal parenchyma can be salvaged; in our experience, this is the case in very few patients. Since renal parenchymal loss is the most common cause of end-stage renal disease in children with WT [9], patients who are not candidates for NSS are at increased risk of requiring dialysis and/or renal transplantation in the future.

We employ a transverse upper abdominal incision to maximize exposure to the peritoneal cavity, and each renal unit is approached sequentially. The colon is reflected medially and the renal hilar vessels as well as the ureter are identified and isolated. The renal hilum is compressed manually; we do not employ clamps in order to minimize the risk of crush injury to delicate pediatric vessels, nor do we employ topical ice slush or other cooling agents. With the aid of preoperative cross-sectional imaging as well as intraoperative ultrasound, we identify all intrarenal masses and excise them sequentially with a small surrounding rim (<1 cm) of normal renal parenchyma, when possible. Hemostasis is obtained with suture ligation of localized bleeding points and argon beam electrocautery of raw surfaces. Careful inspection determines if the collecting system has been entered; if so, the defect is oversewn with absorbable suture. A double J ureteral stent is placed antegrade to maximize drainage when a complex closure is required. Parenchymal defects are closed with a separate layer of mattress silk sutures, where feasible. A percutaneous Penrose drain may be placed on the side where the collecting system has been entered; a Foley catheter is placed to dependent drainage and left in place for at least 48 h or until the Penrose drain output is minimal. The drains are removed if the output does not increase following Foley catheter removal. Ureteral stents are left in place until completion of chemotherapy and are removed cystoscopically.

2. Results

Thirty-six patients with favorable histology BWT met the inclusion criteria, of whom 8 (22.2%) patients had a local recurrence. Of these eight patients, seven had initial bilateral NSS procedures after neoadjuvant chemotherapy while one patient (#6) underwent an initial unilateral nephrectomy with subsequent contralateral NSS for a metachronous Wilms tumor. Patient demographics and characteristics of the initial NSS are summarized in Table 1. Six (75%) patients were male and the mean age was 1.34 (range: 0.54–3.37) years at initial NSS. One patient (#8) had Beckwith–Wiedemann syndrome; the others had no known syndromes associated with the development of Wilms tumor, although patient #2 had bilateral undescended testes for which he underwent bilateral orchiopexies at the time of initial NSS. The 7 patients undergoing bilateral NSS were treated with upfront chemotherapy prior to initial NSS: all patients received three-drug chemotherapy consisting of vincristine, actinomycinD and doxorubicin; one patient (#3), initially treated at another institution, had etoposide and cyclophosphamide added due to poor initial tumor response. All patients had FH at initial NSS although patient #3 had blastemal-predominant histology in one of the tumors from the right kidney and positive margins in tumors from both kidneys, for which he received bilateral flank irradiation. All other patients had negative margins at initial resection.

Following initial NSS, 6 patients received histology-directed chemotherapy per the contemporaneous COG protocol; one patient (#7) did not receive any postoperative chemotherapy following initial NSS, and the aforementioned patient (#3) with an alternative chemotherapy regimen continued receiving those additional agents.

Seven of these patients initially recurred in one kidney; each patient underwent repeat NSS as part of local control for the recurrence. Six recurrences were on the right side and one on the left. One patient (#3) had bilateral disease at initial recurrence and underwent bilateral repeat NSS. Initial repeat NSS was performed a mean of 1.39 (range: 0.13–2.59) years after the initial surgery. Table 2 summarizes the treatment course of the recurrent tumors. Favorable histology tumor was found in all eight patients undergoing redo NSS; one patient (#4) had a cystic lesion obstructing the ureteropelvic junction which was suspicious for cystic WT and underwent a pyeloplasty and NSS with final pathology being equivocal for Wilms tumor. At redo NSS, two patients (#3, #8) had blastemal-predominant histology. Postoperatively, five patients again received chemotherapy with vincristine, doxorubicin, and actinomycinD. One patient (#3) subsequently received ifosfamide, carboplatin, and etoposide. After he developed progressive disease, he was transitioned to a topotecan-based chemotherapy regimen, but had continued disease progression. Patient #7 was treated with carboplatin/cyclophosphamide/etoposide postoperatively. Three patients (#1, #3, #7) underwent flank irradiation for positive margins at redo NSS. One patient (#4) received no further therapy.

Three patients had a second recurrence. One patient (#2) developed a retroperitoneal recurrence that was successfully excised and treated with adjuvant chemotherapy and radiotherapy. Two patients (#3, #8) underwent a third NSS for recurrent disease, a mean of 0.96 (range: 0.81–1.11) years after the first redo NSS (Table 3). Patient #3 developed a right renal mass for which he underwent right NSS; pathology showed diffuse anaplasia with negative margins. He underwent stem cell apheresis and was treated with high-dose consolidation chemotherapy with busulfan and melphalan. He continued to have disease progression with hepatic metastases and ultimately died of disease. Patient #8 developed a second recurrent tumor in the left kidney (the first recurrence had been in the right kidney) and underwent repeat left NSS; pathology showed diffuse