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Ureteral Extension In Wilms Tumor: A Report from the National Wilms Tumor Study Group (NWTSG)

Michael Ritchey¹, Shane Daley¹, Robert C. Shamberger², Peter Ehrlich³, Thomas Hamilton², Gerald Haase⁴, and Robert Sawin⁵

¹Department of Urology, Mayo Clinic Arizona

²Department of Surgery, Children's Hospital Boston and Harvard Medical School

³Department of Surgery, University of Michigan

⁴Department of Surgery, University of Colorado

⁵Department of Surgery, University of Washington

Abstract

Background—Extension of Wilms tumor into the ureter is a rare event. We reviewed the National Wilms Tumor Study Group (NWTSG) database to define the clinical presentation, associated pathologic features and clinical outcome of these patients.

Methods—Records of children identified to have ureteral extension of Wilms tumor enrolled in NWTSG-3, -4, and -5 were reviewed. Presenting symptoms, diagnostic studies, histopathology, operation performed, and outcome were recorded. The NWTSG-5 data was prospectively collected.

Results—45 children were identified with ureteral extension. For NWTSG-5, the incidence of ureteral extension was 2%. Clinical presentations were gross hematuria in 22 patients, two had passage of tissue per urethra and one child had a urethral mass. The remainder had nonspecific presentations. Ureteral extension was seen on preoperative imaging in 14 patients, intraoperatively in 22, and on pathologic examination in nine patients. Hydronephrosis was noted in 12 patients and there was non function of the kidney in another 8. Laterality of the tumor was right side in 26 and left in 19. Cystoscopy was performed in 12 children. Findings included tumor seen at the ureteral orifice in six patients and bleeding from the orifice in one child. All patients had radical nephrectomy including partial ureterectomy. The ureteral margin was positive in three patients, including two of the seven with separate removal of the ureteral extension. The clinical stage was: stage I – 10, stage II – 18, stage III – 14, and stage IV – 3. The tumor extended into the proximal ureter in 23 patients, distal ureter in 13, seven had extension into the bladder, and one had urethral involvement. The level of ureteral extension was not clearly noted in the 45th child. The median follow-up was 96 months. Overall, 41 of 45 patients were alive at last contact. There were three deaths due to tumor in patients with unfavorable histology tumors, and one due to treatment toxicity in a child with favorable histology.

Conclusions—Ureteral extension occurs in approximately 2% of patients with Wilms tumor. The diagnosis should be suspected in patients with gross hematuria, hydronephrosis or nonfunctioning kidney. Cystoscopy with retrograde ureterogram may aid in preoperative diagnosis in these patients. Preoperative diagnosis is important since complete resection of the involved portion of ureter at the time of nephrectomy can avoid residual disease and the need for second surgery or radiation therapy.

INTRODUCTION

Wilms tumor (nephroblastoma) is the most common renal tumor of childhood. Although invasion of the renal collecting system is common [1], extension down into the ureter is not [2–17]. The staging system employed by the National Wilms Tumor Study Group (NWTSG) defines disease that extends beyond the kidney as Stage II. Patients with tumors of favorable histology and Stage II disease are usually effectively treated by complete nephrectomy and partial ureterectomy, followed by adjuvant chemotherapy employing vincristine and dactinomycin. Such treatment results in excellent long-term disease free survival. Some reports in the literature have suggested that tumors with ureteral extension are more resistant to therapy [9,10,16]. Others have suggested the need for cystoscopic surveillance postoperatively to detect tumor recurrence [16]. This review of a large series of children with ureteral extension enrolled in the NWTSG studies was performed to determine the clinical presentation, imaging findings, surgical management and outcome of these patients.

METHODS

Ureteral extensions of Wilms tumor was identified in 45 children enrolled in NWTSG-3, -4 and -5 from 1979 to 2003. Patients with ureteral extension in NWTSG-3, -4 were identified during several surgical reviews of patients from these studies and did not include all patients enrolled in these two studies. There were 26 NWTSG-5 patients identified prospectively during the quality assurance review conducted by the surgical committee. The incidence of ureteral extension for NWTSG-5 was 2%. The records of each patient maintained at the NWTSG Data and Statistical Center in Seattle were reviewed. This included operative and pathology reports, imaging reports and flow sheets detailing the patients' treatment and outcome. Data collected included: presenting signs and symptoms, age at diagnosis, gender, laterality of tumor, method of diagnosis, level of ureteral extension, cystoscopic findings, diagnostic imaging findings, size of the primary tumor, operative procedures performed, histopathology, and the development of recurrent or metastatic disease.

RESULTS

The median age at diagnosis was 33 months. The mean weight of the kidney and tumor was 417 grams. There were 20 females and 25 males. The stage that was assigned to the patients for treatment on study was as follows: 10 patients had stage I disease; 18 stage II, 14 stage III, and 3 stage IV. The laterality of the tumor was right-sided in 26 cases and left-sided in 19.

Preoperative imaging confirmed ureteral extension in 14 cases. Ureteral extension was diagnosed intraoperatively in 22 patients and on pathologic exam in 9 patients. There was no difference by NWTSG study. Only 8 of the 26 children with ureteral extension noted in NWTSG-5 were detected on preoperative imaging. There were 10 patients in whom the preoperative CT scan demonstrated a mass in the ureter or bladder. Six of these patients also had an ultrasound performed that either showed a mass in the bladder or a mass in the collecting system. There was only one patient in whom only the ultrasound demonstrated the ureteral mass when the CT did not. Four patients had retrograde ureterograms performed during cystoscopy with filling defects noted. In two of these children, the other preoperative imaging failed to identify the ureteral extension. One child had a nephrostomy tube placed for hydronephrosis and the antegrade nephrostogram demonstrated the tumor extending into the collecting system. Eight children in whom the diagnosis was not made before surgery had the non-specific finding of non function of the involved kidney on either CT or IVP. Hydronephrosis was also a common finding on preoperative imaging seen in 7 children in whom the ureteral extension was not diagnosed preoperatively.

Clinical presentation was gross hematuria in 22 patients. One patient presented with flank pain, one had a urethral mass, and two passed tissue per urethra. Cystoscopy was performed in 12 patients. Six children were noted to have tumor protruding from the ureteral orifice, and bleeding from the ureteral orifice was seen in one child. Four children had retrograde ureterograms performed at the time of cystoscopy and this was diagnostic in all patients. Two of the latter patients had a presumptive diagnosis of ureteral extension from the preoperative imaging.

Nephrectomy and partial or complete resection of the ureter was performed in all 45 children. Tumor extended into the proximal ureter in 23 patients, distal ureter in 13, into the bladder in 7, and exited the urethra in one child. The level of ureteral extension was not clearly noted in one child. En bloc removal of the kidney and ureter was performed in 38 patients, and 7 patients had separate removal of the ureteral extensions. Six patients had removal of a bladder cuff to facilitate removal of the distal ureteral extension. Three of these patients had undergone cystoscopy prior to surgery, and a mass was seen at the ureteral orifice. Favorable histology Wilms tumor was identified in 38 patients. There were four patients with anaplasia, two had rhabdoid tumor of the kidney, and one had clear cell sarcoma of the kidney. Intralobar nephrogenic rests (ILNR) were identified in 20 patients and 3 patients were found likely to have ILNR. The location of the primary tumor was described as centrilobar in 31 patients and 3 children had midlobar tumors.

The histology of the tumor extension in the ureter was examined. The distal portion of the tumor extension showed necrosis in seven patients. Differentiated skeletal muscle was observed in 5 patients, epithelial papillary differentiation in one, and stromal differentiation in 4. There was no histologic evidence of tumor invasion through the wall of the ureter in any of the specimens.

There were four children reported by the surgeon to have tumor spill during the removal of the ureteral extension. All patients who had separate removal of the renal tumor and ureteral extension, would theoretically have had tumor spill from cutting across the ureter with tumor in the lumen. The resected ureteral margin was positive in three patients. All received postoperative irradiation of the renal bed. Two of these patients with positive ureteral margins had abdominal recurrences, and both had rhabdoid tumor of the kidney. There one other patient with unfavorable histology who developed an abdominal recurrence. The third child had a tumor with diffuse anaplasia and stage IV disease who received postoperative irradiation of the renal bed. All three of these patients with unfavorable histology and abdominal recurrence died of progressive disease. There was one recurrence in the renal bed in a patient with a favorable histology stage II tumor clear ureteral margins. Of note, this patient had undergone preoperative needle biopsy of the primary tumor. (Table 1)

Median follow-up time was 96 months. Forty-one of 45 patients were alive at the time of last contact. Three deaths occurred in patients with unfavorable histology; two had rhabdoid tumor of the kidney and one had diffuse anaplasia. One child with a favorable histology tumor died due to ARDS as a result of treatment toxicity. Eighteen patients underwent irradiation of the renal bed after surgery. All children were treated with a chemotherapy regimen appropriate for the assigned stage and histology for the enrolled NWTSG study.

DISCUSSION

Ureteral extension of Wilms tumor is uncommon with only 16 cases reported in the literature [2–16]. Of these reports, 11 were synchronous lesions seen at the time of presentation of Wilms tumor, and 5 were metachronous, occurring 3 months to 2 years after the primary renal tumor was removed [2,4–7]. It is unclear if the subsequent ureteral tumors were lesions missed at

initial exploration or represent recurrent disease due to seeding of the urothelium from tumor cells in the urine. In contrast, all of the cases in our review were synchronous. Although an uncommon finding, preoperative detection of ureteral extension may prevent the surgeon from cutting across tumor in the ureter producing local tumor spill and leaving residual tumor in the distal ureter.

Gross hematuria was a common finding in this series (49%). This symptom may be a significant clue of the tumor involvement of the collecting system. While 25–30% of all patients with Wilms tumor present with microscopic hematuria, gross hematuria is uncommon. Only 8 of the 22 children who presented with gross hematuria had a cystoscopy performed, but most of the cystoscopic exams were abnormal and identified either tumor or blood emanating from the ureteral orifice.

Preoperative imaging studies were able to detect the ureteral extension in 14 patients. CT scans were especially helpful, with 10 patients diagnosed by CT imaging alone. The ureteral extension was seen less often with ultrasound. The finding of hydronephrosis or non-function of the kidney should alert the surgeon to the possibility of ureteral extension. These non-specific findings were common in this cohort. Other causes of non-function could be extrinsic compression of the ureter by the tumor or intravascular extension of tumor [18].

If there is suspicion of ureteral extension due to gross hematuria or hydronephrosis or non-function on preoperative imaging, cystoscopy with retrograde ureterogram can establish the diagnosis. It is important to ascertain the extent of the tumor before transecting the ureter. It is recommended that the tumor and ureteral extension be removed en bloc to avoid cutting across tumor and causing tumor spill. The current Children's Oncology Group studies classify all tumor spills as stage III disease increasing the intensity of postoperative therapy. If the ureteral extension is entirely removed intact, the patient would be considered Stage II. Correct identification of ureteral extension is also important to avoid residual disease. One could speculate that prior published reports of asynchronous ureteral tumor were from missed ureteral extension at the initial surgical procedure.

Of the 16 previously reported patients with ureteral extension, there were 3 tumor related death [1,4,9]. Two of these children were treated in the era before multimodal therapy was standard treatment for Wilms tumor. The other death was in a child with metastatic disease. Several reports have suggested that these tumors are resistant to therapy [9,10,16]. In our review, there were three deaths from tumor in children with unfavorable histology, and this likely contributed more to the poor prognosis than the ureteral extension. One child with a favorable histology tumor died from ARDS as a result of treatment toxicity. Two patients with relapse were alive at last follow-up; one had relapse to the lung, and the other to the renal bed. Due to the small numbers of patients in this review, we cannot speculate on the impact of tumor spill from the ureter or positive ureteral margins on survival. In any event, increased awareness of ureteral extension and preoperative detection is important. This would allow for complete resection of the ureteral extension and minimize the risk of local recurrence.

One report suggested the need for cystoscopic surveillance postoperatively to detect tumor recurrence [16]. Our data does not support such a recommendation. No distal or bladder recurrences have been noted. It would appear that complete resection of the ureteral extension is the most important factor in preventing local recurrence.

ILNR was noted in nearly 50% of these children with ureteral extension. This finding may signify a relationship between ILNRs and the development of Wilms tumor involving the collecting system and ureter. Nephrogenic rests (NR) are precursor lesions found in the kidneys which usually undergo involution during development [19]. Rests are separated into two categories, perilobar and intralobar (PLNR and ILNR). PLNR are only found at the periphery,

whereas ILNR are found anywhere within the lobe as well as the renal sinus and even within the wall of the pelvicalyceal regions. Tumors that arise from ILNR are more likely to have a central location seen in the majority of our patients. Tumors that arise from ILNRs often appear more differentiated with heterologous tissues, e.g. skeletal muscle, commonly present. Fetal muscle histology has been reported in several of the previous reports of ureteral tumor extension [5,11,14]. Approximately one quarter of those separately analyzed ureteral tumors had these histologic features in the present series. The number of patients is too small to permit conclusions about the prognostic significance, but none of the tumors with this fetal muscular appearance developed recurrence or metastatic disease.

CONCLUSION

Tumor extension into the ureter is an unusual finding in nephroblastoma, but its recognition is important. Clues to the presence of ureteral involvement include presentation with gross hematuria and the finding of hydronephrosis or non function of the kidney on preoperative imaging studies. Cystoscopy should be considered in patients with these clinical presentations. Once identified, complete resection of the ureteral disease is important. This may include a cuff of bladder if necessary to obtain a negative microscopic margin for tumor extending out the ureteral orifice. The prognosis for these children with complete resection remains excellent and does not necessitate adjuvant radiation therapy or 3-drug chemotherapy.

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Table 1

Outcome of patients with tumor relapse.

Site of Relapse	Stage	Histology	Positive ureteral margin	Irradiation of renal bed	Outcome after treatment of relapse
Renal Bed	2	FH	No	No	No evidence of recurrence
Abdomen	3	RTK	Yes	Yes	Patient died of progressive tumor
Abdomen	4	DA	No	Yes	Patient died of progressive tumor
Abdomen, Pelvis, Lung	3	RTK	Yes	Yes	Patient died of progressive tumor
Lung	3	FH	No	No	No evidence of recurrence
Lung	3	FH	No	Yes	No evidence of recurrence