Kidney Outcomes and Hypertension in Survivors of Wilms Tumor: A Prospective Cohort Study

David I. Chu, MD, MSCE[1,2,*], Abdulla M. Ehlayel, MD[3,*], Jill P. Ginsberg, MD[4,5], Kevin E. Meyers, MBBCh[5,6], Maryjane Benton, RN, BSN[6], Melissa Thomas, BA[6], Claire Carlson, RN, BSN[4], Thomas F. Kolon, MD[5,7], Gregory E. Tasian, MD, MSCE, MSc[5,7], Jason H. Greenberg, MD, MHS[8], Susan L. Furth, MD, PhD[5,6], and Michelle R. Denburg, MD, MSCE[5,6]

Objective To assess the prevalence of therapy-related kidney outcomes in survivors of Wilms tumor (WT).

Study design This prospective cohort study included survivors of WT who were ≥5 years old and ≥1 year from completing therapy, excluding those with preexisting hypertension, prior dialysis, or kidney transplant. Participants completed 24-hour ambulatory blood pressure monitoring (ABPM). Abnormal blood pressure (BP) was defined as ≥90th percentile. Masked hypertension was defined as having normal office BP and abnormal ABPM findings. Urine was analyzed for kidney injury molecule-1, interleukin-18, epidermal growth factor, albumin, and creatinine. The estimated glomerular filtration rate (eGFR) was calculated using the bedside chronic kidney disease in children equation. Recent kidney ultrasound examinations and echocardiograms were reviewed for contralateral kidney size and left ventricular hypertrophy, respectively. Clinical follow-up data were collected for approximately 2 years after study enrollment.

Results Thirty-two participants (median age, 13.6 years [IQR, 10.5-16.3 years]; 75% stage 3 or higher WT) were evaluated at a median of 8.7 years (IQR, 6.5-10.8 years) after therapy; 29 participants underwent unilateral radical nephrectomy, 2 bilateral partial nephrectomy, and 1 radical and contralateral partial nephrectomy. In this cohort, 72% received kidney radiotherapy and 75% received doxorubicin. Recent median eGFR was 95.6 mL/min/1.73 m^2 (IQR, 84.6-114.0; 11 [34%] had an eGFR of <90 mL/min/1.73 m^2). Abnormal ABPM results were found in 22 of 29 participants (76%), masked hypertension in 10 of 29 (34%), and microalbuminuria in 2 of 32 (6%). Of the 32 participants, 22 (69%) had abnormal epidermal growth factor; few had abnormal kidney injury molecule-1 or interleukin-18. Seven participants with previous unilateral nephrectomy lacked compensatory contralateral kidney hypertrophy. None had left ventricular hypertrophy.

Conclusions In survivors of WT, adverse kidney outcomes were common and should be closely monitored. *(J Pediatr 2021;230:215-20)*.

Treatment of Wilms tumor (WT) often entails a combination of surgery, chemotherapy, and radiation therapy, depending on the stage and pathologic features of the tumor. Survival rates have steadily increased in the last few decades owing to advances in treatment and management. However, with more children surviving WT, the long-term risk of subsequent comorbidities has also increased.[1-3]

To date, there are limited data on the risk of adverse kidney outcomes, such as hypertension or chronic kidney disease (CKD), in patients after treatment for WT. Nephrotoxic chemotherapy, radiation, and nephrectomy are each associated with potential increased risk of CKD.[4-6] Because children with WT are still growing during the completion of their therapy, kidney outcomes may have substantial ramifications later in adulthood.[7-10]

Kidney function is typically quantified by estimating the glomerular filtration rate (GFR). However, various non-GFR-based characteristics, including overt and masked hypertension, microalbuminuria, and novel urinary biomarkers of kidney injury, have been associated with adverse outcomes.[11-15] Masked hypertension is defined as a normal in-office blood pressure (BP) but elevated BP measured with 24-hour ambulatory BP monitoring

ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
CKD	Chronic kidney disease
EGF	Epidermal growth factor
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
IL	Interleukin
KIM-1	Kidney injury molecule
LVH	Left ventricular hypertrophy
WT	Wilms tumor

From the [1]Division of Urology, Ann & Robert H. Lurie Children's Hospital of Chicago; [2]Feinberg School of Medicine at Northwestern University, Chicago, IL; [3]Division of Nephrology, Children's Hospital of New Orleans, New Orleans, LA; [4]Division of Oncology, Children's Hospital of Philadelphia; [5]Perelman School of Medicine at the University of Pennsylvania; [6]Division of Nephrology, Children's Hospital of Philadelphia; [7]Division of Urology, Children's Hospital of Philadelphia, Philadelphia, PA; and [8]Division of Nephrology, Yale New Haven Children's Hospital, New Haven, CT

*Contributed equally.

Funding and disclosures information is available at www.jpeds.com.

Portions of this study were presented at the Pediatric Academic Society annual meeting, May 5-8, 2020, Toronto, Canada.

https://doi.org/10.1016/j.jpeds.2020.12.005

(ABPM). Both masked hypertension and microalbuminuria are independently associated with the development of CKD and left ventricular hypertrophy (LVH).[11,12] Novel urinary biomarkers such as interleukin (IL)-18, kidney injury molecule-1 (KIM-1), and epidermal growth factor (EGF) have shown promising results as candidate proteins indicative of kidney injury (IL-18 and KIM-1) or repair (EGF).[13-16] Collectively, these non-GFR-based biomarkers have not been well-studied in pediatric survivors of WT.

In this study, we prospectively enrolled survivors of WT and measured 24-hour ABPM and urinary albumin, IL-18, KIM-1, and EGF. We quantified the prevalence of masked hypertension, impaired estimated GFR (eGFR), and abnormal urine studies. We hypothesized that masked hypertension and CKD would be common among survivors of WT.

Methods

This was a prospective cohort study of survivors of WT. All participants were recruited from the cancer survivorship clinics at the Children's Hospital of Philadelphia from November 2016 through June 2018. Data were collected from the participants' charts retrospectively and prospectively up to 2 years after they completed the study visit. The Children's Hospital of Philadelphia Institutional Review Board approved this study (IRB #16-013208). Written informed consent was obtained from all legal guardians or participants ≥18 years, along with assent, when appropriate, from children <18 years of age.

Participants

Inclusion criteria were a history of WT, age ≥5 years, and ≥1 year since the completion of all therapy for WT. Potential participants were excluded if they had a history of bilateral radical nephrectomy.

Study Procedures

On the day of the study visit, participants collected a first morning voided urine specimen at home and brought the sample to the visit (kept refrigerated at home before the visit). Aliquots of the urine specimen were collected and stored at −80°C, and all assays were performed in batches. Urine microalbumin was processed using fluorescence commercial kits from Siemens. Urine creatinine was measured using isotope dilution mass spectrometry-calibrated enzymatic commercial kits from Roche. Urine IL-18 and KIM-1 were measured using electrochemiluminescence commercial kits from Meso Scale Discovery. Urine EGF was measured using ELISA commercial kits from R&D Systems.

Casual clinic BP readings obtained using an automated sphygmomanometer as part of standard of care for the clinical visit were recorded. ABPM was performed using the Spacelabs 90217 device according to manufacturers' instructions. Appropriate cuff size was determined according to the circumference of the nondominant upper arm. Instructions on operating the ABPM device were reviewed with participants and their guardians. Written instructions were also provided. Participants were given the option to start the 24-hour monitoring period at the research visit or another more convenient time.

Outcomes

Abnormal ABPM systolic and diastolic BPs were defined using the 90th percentile for age, sex, and height based on normative data from Wuhl et al.[17] At our institution, standard clinical practice is to use the 90th percentile BP as the cut-off for patients with underlying renal risk.[18,19] BP loads, defined as the percentage of BP readings ≥90th percentile, were categorized as: normal <25%, borderline 25%-50%, and elevated >50%. Nocturnal dipping of <10% was considered diminished. BP variability was quantified using average real variability, defined as the mean of the absolute difference of consecutive BP measurements during the ABPM period.[20] All ABPM reports were evaluated by a pediatric nephrologist on the study team and referred for further evaluation in nephrology clinic based on clinical judgement.

Casual clinic BP measurements were classified based on the 2017 American Academy of Pediatrics Clinical Practice Guideline and were defined as abnormal using the 90th percentile for age, sex, and height.[21] Masked hypertension was diagnosed if the casual clinic BP readings were normal but ABPM loads or nocturnal dipping were abnormal.

Urine microalbumin and EGF were indexed to urine creatinine. Microalbuminuria and macroalbuminuria were defined as a urine albumin-to-creatinine ratio of 30-300 mg/g and >300 mg/g, respectively. Cut-offs for urinary KIM-1, IL-18, and EGF were defined from previous studies, because these tests are not used clinically and do not have well-established normative ranges.[22,23]

Because most participants were children and not adults, the estimated GFR was calculated using the revised bedside chronic kidney disease in children equation with k = 0.413 using the most recent serum creatinine and height (before or after study visit).[24] Post-treatment imaging (ultrasound examination) and cardiac echocardiography data (if performed) were also collected from the most recent studies (before or after the study visit). Compensatory contralateral hypertrophy was documented based on kidney length on renal ultrasound using age-based reference data and was defined as >1 SD above the normal, mean, age-adjusted kidney length.[25]

We collected relevant follow-up data from subsequent survivorship clinic and nephrology clinic visits for approximately 2 years after the study visit. This included data on repeat ABPM and treatment with antihypertensive medications.

Covariates

Demographic information and clinical histories were obtained in person at the research visit and from chart review. Treatment histories for WT included details on past surgeries, chemotherapy, and radiotherapy.

Statistical Analyses

Descriptive statistics included median values and IQRs or frequencies and proportions as appropriate. ABPM results were analyzed by median BP loads and variability and proportions with abnormal loads or diminished nocturnal dipping. The Fisher exact test was used for categorical data analysis, and the Student *t* test or Wilcoxon rank-sum test was used for group comparisons of continuous data as appropriate. The Wilcoxon signed rank test was used to compare awake vs sleep period BP variability.

Given the limited sample size, we decided a priori not to perform multivariable regression analyses. The results are considered hypothesis-generating. All statistical analyses were performed with Stata (version 15, StataCorp, LLC).

Results

A total of 32 survivors of WT participated (50% female; median age, 13.6 years [IQR, 10.5-16.3 years]) at a median of 8.7 years (IQR, 6.5-10.8 years) after completion of treatment (Table I). None were diagnosed with genetic syndromes associated with WT. WT stage classification was 6%, 19%, 31%, 38%, and 6%, with stages 1, 2, 3, 4, and 5, respectively. Unilateral radical nephrectomy was performed in 29 patients (91%); 2 underwent bilateral partial nephrectomy, and 1 participant had a radical and contralateral partial nephrectomy. Radiotherapy to the kidney for either initial therapy or for recurrence was received by 72% of participants, with 48% of these further receiving radiotherapy to other organs (64% to the lung). Chemotherapy was received by all patients: 100% received vincristine/actinomycin-D; 75% received doxorubicin; 16% received cyclophosphamide, 16% received etoposide; 13% received carboplatin. The median most recent eGFR was 95.6 mL/min/1.73 m^2 (IQR, 84.6-114.0 mL/min/1.73 m^2), with 34% having an eGFR of <90 mL/min/1.73 m^2. No patients had an eGFR of <60 mL/min/1.73 m^2.

Table I. Characteristics of study participants

Characteristics	No. (%)*
Total patients (M/F)	32 (16/16)
Median age in years (IQR)	13.6 (10.5-16.3; range. 7.4-21.3)
Race	
White	25 (78)
Black	5 (16)
Other	2 (6)
WT stage	
1	2 (6)
2	6 (19)
3	10 (31)
4	12 (38)
5	2 (6)
Median years from completion of treatment (IQR)†	8.7 (6.5-10.8; range, 1.0-18.0)
Radiotherapy to the kidney	23/32 (72)
Radiotherapy to any other organ	11/23 (48)
Lung	7/11 (64)
Abdomen	2/11 (18)
Inferior vena cava	1/11 (9)
Whole body	1/11 (9)
Received chemotherapy	32/32 (100)
Type of chemotherapy	
Vincristine	32 (100)
Doxorubicin	24 (75)
Actinomycin-d	32 (100)
Cyclophosphamide	5 (16)
Etoposide	5 (16)
Carboplatin	4 (13)
Type of surgery	
Radical nephrectomy	29 (91)
Bilateral partial nephrectomy	2 (6)
Radical plus partial nephrectomy	1 (3)
eGFR median (IQR), mL/min/1.73 m^2	95.6 (84.6-114.0)
GFR <90 mL/min/1.73 m^2	11/32 (34)

*Unless otherwise specified.
†Median years from completion of treatment available only in 29 patients who completed ABPM.

Of the 32 participants, 17 (53%) had elevated casual clinic BP readings. Of these patients, 9 had elevated BP, 6 met the criteria for stage 1 hypertension, and 2 had readings consistent with stage 2 hypertension. Twenty-nine participants returned completed and usable ABPM results (Table II). Of these participants, 31% and 14%, had either borderline or elevated systolic BP loads, respectively, while awake. While asleep, 34% and 14% of participants had borderline or elevated systolic BP loads, respectively. Systolic nocturnal dipping was abnormal in 52%, and 28% had abnormal diastolic nocturnal dipping. The median values of BP variability ranged from 7.0 to 7.4 mm Hg for nighttime BPs and from 8.4 to 8.8 mm Hg for daytime BPs. Daytime diastolic BP variability was significantly different from nighttime diastolic BP variability ($P = .008$). The Spearman correlations between respective BP load and BP variability were all statistically significant (rho range, 0.41-0.69; all $P < .03$) except for nighttime systolic BP. Any ABPM abnormality was found in 22 of 29 participants (76%). Stratification of ABPM results by casual clinic BPs showed that 10 of 29 participants (34%) had masked hypertension (Table III). Only 1 of these 10 with masked hypertension had an eGFR of <90 mL/min/1.73 m^2.

Thirty participants had routine post-treatment clinical imaging with kidney ultrasound examination and 25 had transthoracic echocardiography performed (Table IV). The most recent kidney ultrasound examination was performed a median of 4.6 years (IQR, 3.1-6.2 years) after treatment. Of the 29 patients who underwent radical nephrectomy, contralateral compensatory hypertrophy was noted in 22 participants, with 15 having contralateral kidney length of >2 SDs above the mean. The most recent cardiac echocardiography was performed a median of 9.4 years (IQR, 8.1-11.7 years) after treatment. The median left ventricular mass index was 31 g/$m^{2.7}$ (IQR, 29-37 g/$m^{2.7}$); no participants met the criteria for LVH.

Abnormal ABPM results were not significantly associated with an eGFR of <90 mL/min/1.73 m^2, WT stage, or contralateral kidney compensatory hypertrophy (data not shown).

Of the urinary biomarkers, 2 participants had microalbuminuria, both of whom had an eGFR of >90 mL/min/1.73 m^2. The median urinary albumin:creatinine ratio was 5.5 mg/g (IQR, 3.9-8.0 mg/g). Four and 3 participants had

Table II. ABPM results (n = 29)

BP characteristics	Median BP load (IQR), %	Median BP variability (IQR), mm Hg	Correlation between BP load and variability, rho (*P* value)	Patients with BP load ≥25%, n (%)	Patients with BP load >50%, n (%)
Systolic awake	11.4 (2.9-26.5)	8.4 (7.4-9.2)	0.41 (.03)	9 (31)	4 (14)
Diastolic awake	11.5 (6.5-20.0)	8.8 (7.5-9.5)	0.59 (<.001)	3 (10)	0 (0)
Systolic asleep	12.5 (5.9-26.7)	7.4 (6.2-9.4)	0.27 (.16)	10 (34)	4 (14)
Diastolic asleep	15.4 (10.0-30.0)	7.0 (5.6-8.2)	0.69 (<.001)	10 (34)	1 (3)
		Median decline (IQR), %		Patients with nocturnal dipping <10%, n (%)	
Systolic dipping		9.0 (6.0-13.3)		15 (52)	
Diastolic dipping		17.2 (9.4-21.5)		8 (28)	

abnormal levels of IL-18 and KIM-1, respectively. Twenty-two participants (69%) had an abnormal creatinine-indexed, age-adjusted EGF (Table V). When stratified by eGFR, the creatinine-indexed EGF was significantly lower (ie, more abnormal) in those with an eGFR of <90 mL/min/1.73 m^2 (14.6 ± 6.6 mL/min/1.73 m^2 vs 22.1 ± 7.4 mL/min/1.73 m^2; $P = .009$).

On clinical follow-up after the study visit, 14 and 23 of the 32 participants were seen in nephrology and survivorship clinics, respectively. Six participants underwent a total of 7 repeat ABPM studies. One participant was started on antihypertensive therapy with an angiotensin-converting enzyme inhibitor. All urinalyses obtained for clinical care had negative or trace protein.

Discussion

In this prospective study of pediatric survivors of WT, a substantial proportion of children screened for hypertension by ABPM had abnormal BP loads, especially during sleep. Diminished nocturnal dipping was the most frequent abnormality. One participant was started on antihypertensive therapy on clinical follow-up. Our findings suggest that long-term ABPM studies should be considered for routine post-treatment surveillance of CKD in survivors of WT.

Although the differential effect of the type of surgical approach (ie, unilateral radical nephrectomy vs unilateral partial nephrectomy) on kidney outcomes is inconclusive, the detrimental effects of radiotherapy to the kidney[6] are well-known. In our study, we found that 34% of participants had an eGFR of <90 mL/min/1.73 m^2, presumably because of the additional nephrotoxic therapies received, including radiotherapy to the kidney in 72% of our participants. To date, multiple studies have assessed the prevalence of kidney injury as defined by eGFR in survivors of WT, but with heterogenous cohorts and results.[4,5,26,27] One retrospective study of 75 patients who underwent a unilateral radical nephrectomy for WT without radiotherapy or nephrotoxic chemotherapy reported that at a median follow-up of 20 years, 21% and 0% had an eGFR of <90 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, respectively.[4] The authors concluded that survivors of WT are at low risk of developing significant long-term kidney dysfunction.[4] However, another study of longitudinal GFR measurements using technetium 99m-DTPA scans in 12 patients during therapy for WT found the greatest decrease in the GFR to occur after nephrectomy (38% decline), compared with chemotherapy or radiotherapy.[5]

In addition to GFR-based assessments of kidney injury, hypertension is a well-established risk factor for complication of CKD. In our study, we found that 53% of our participants had abnormal casual clinic BPs, 31%-34% had borderline BP loads on ABPM, and >50% had abnormal nocturnal dipping. On repeat ABPM performed clinically for 6 patients, only 1 had an ambulatory hypertension requiring antihypertensive therapy. BP variability has been shown to add prognostic value to ABPM results.[20] Although our participants had low variability, BP variability did correlate significantly with corresponding BP load. In a similar recent study of 37 survivors of WT evaluated at a median of 22.5 years after diagnosis, 40.5% were diagnosed with prehypertension or hypertension based on in-office BP measurements.[28] Similarly, a retrospective study of 30 survivors of WT at a median follow-up of 10 years found hypertension (BP ≥ 90th percentile) in 33% of participants.[29] Among 40 adult survivors who underwent treatment for unilateral, nonsyndromic WT, 12 (30%) had hypertension.[27] The role of ABPM has been increasingly recognized as a useful adjunctive tool in managing pediatric CKD. One retrospective study compared ABPM results in 44 children with a solitary kidney and 25 age-matched controls and found no differences.[30] However, their group of children with solitary kidney constituted a

Table III. Casual clinic BP measurements compared with ABPM measurements (n = 29)

BP characteristics	Normal clinic BP	Abnormal clinic BP
No.	13	16
Systolic awake load ≥25%	4 (31)	5 (31)
Diastolic awake load ≥25%	1 (8)	2 (13)
Systolic sleep load ≥25%	4 (31)	6 (38)
Diastolic sleep load ≥25%	4 (31)	6 (38)
Systolic dip <10%	8 (62)	7 (44)
Diastolic dip <10%	4 (31)	4 (25)
Any abnormality on ABPM	10 (77)	12 (75)

Values are number (%).

Table IV. Kidney and cardiac imaging at most recent evaluation

Variables	No. (%) or median (IQR)
Kidney imaging after treatment	30 (94)
Median duration for ultrasound examination after treatment in years	4.6 (3.1-6.2)
Median kidney percentile, %	98.1 (87.2-99.8)
Median kidney size, SD	2.1 (1.1-2.8)
Compensatory hypertrophy >1 SD above normal	22 (of 29 with unilateral radical nephrectomy, 76)
Compensatory hypertrophy >2 SD above normal	15 (of 29 with unilateral radical nephrectomy, 52)
Echo report available	25 (78)
Median time for echo after treatment, years	9.4 (8.1-11.7)
Median time for echo post-ABPM in years	1.0 (0.0-1.1)
Median LVMI in $g/m^{2.7}$	31.0 (29.0-37.0)

LVMI, left ventricular mass index.

heterogenous cohort, with 34% having acquired solitary kidney owing to nephrectomy (only 4 owing to WT). Another study compared ABPM in 15 survivors of WT with 20 age-, weight-, and height-matched healthy children and found that 24-hour, daytime, and night-time systolic BPs and night-time diastolic BPs were significantly higher in the WT group compared with controls.[1] Based on the high prevalence of abnormal ABPM findings in our study and others, we advocate for consideration of ABPM as part of routine post-treatment surveillance among survivors of WT.

Masked hypertension specifically is associated with LVH in children with CKD.[12] We found that 34% of our participants had masked hypertension. We did not find any participants with LVH on transthoracic echocardiography. This finding is unexplained, but might be because of the opposing effects of anthracycline chemotherapy and systemic hypertension on left ventricular mass. Chemotherapy-related cardiotoxicity decreases the left ventricular mass and causes heart failure, but systemic hypertension increases left ventricular mass.[12,31,32] Our abnormal BP findings may also not have reached the threshold to cause LVH.

Urinary biomarkers provide additional, promising non-GFR-based indices of structural kidney injury and repair. Among children with CKD without diabetes, microalbuminuria is significantly associated with CKD progression.[11] We found 2 children with microalbuminuria. In our study, we also tested novel urinary biomarkers including IL-18, KIM-1, and EGF. We found that most of the participants had normal IL-18 and KIM-1, but 69% had abnormal creatinine-indexed EGF values, which were significantly lower in those with an eGFR of <90 mL/min/1.73 m^2. EGF is a pro-proliferative protein that is expressed by the ascending loop of Henle and distal convoluted tubule. EGF can mediate tubule cell regeneration and is a marker of functional tubular cell mass. Urine EGF has been found to be significantly lower in children with CKD compared with healthy controls and is directly correlated with eGFR, as confirmed in our study.[15,16] In a study of 80 children with congenital anomalies of the kidney and urinary tract, children with a nephrectomy were found to have the lowest urine EGF and creatinine levels as compared with other children with congenital anomalies or healthy controls.[33] In our study, the low urine EGF and creatinine concentrations may reflect the decrease in functional tubular mass after nephrectomy. A plausible but hypothetical reason for the mostly normal findings for IL-18 and KIM-1 is that, overall, our cohort has mostly preserved eGFR (median 96 mL/min/1.73 m^2), few comorbidities, and limited ongoing tubular injury.

Our study does have limitations. Our sample size is small, which limits the statistical power and prevents stratifying analyses by surgical approach or specific therapies, especially with a wide range of follow-up duration. However, our study is prospective in nature with robust, comprehensive, and granular assessment of non-GFR-based kidney injury, including ABPM and urine biomarkers. Our study was conducted in a single center, but because participants were treated with standard Children's Oncology Group protocols, these results may be generalizable to other survivors of WT. Last, most of our participants had advanced stage WT, so our findings may not reflect the risk in patients with earlier stage WT. However, because all survivors of WT come to our survivorship clinic regardless of stage or risks for late effects, and we did not include those with known CKD or hypertension because those were the outcomes of interest, selection bias is mitigated.

Table V. Urinary albumin, IL-18, KIM-1, and EGF levels (indexed to creatinine when indicated; n = 32)

Urine biomarkers	Cut-off used to define abnormal	Median (IQR)	No. (%) abnormal
Albumin/creatinine (mg/g)	≥30	5.5 (3.9-8.0)	2 (6)
IL-18 (pg/mL)	Ages 5-9 years: ≥54.3 Ages 10-14 years: ≥88.8 Ages 15-18 years*: ≥138.9	39.9 (21.2-67.6)	4 (12.5)
KIM-1 (pg/mL)	Ages 5-9 years: ≥1239.5 Ages 10-14 years: ≥1141.1 Ages 15-18 years*: ≥1876.2	618.3 (365.4-720.4)	3 (9)
EGF/creatinine (ng/mg)	Ages 7-12 years: ≤24 Ages 13-15 years: ≤26 Ages 16-18 years*: ≤23	19.2 (12.7-26.1)	22 (69)

*Cut-off applied to participants >18 years of age.

In light of our findings, and consistent with the long-term follow-up guidelines from the Children's Oncology Group, we recommend annual outpatient visits with blood tests for kidney function and electrolytes, BP check, and urinalysis.[34] Prior recipients of anthracyclines should be evaluated by echocardiogram dependent on anthracycline dosage received. In addition, however, we recommend considering screening with ABPM after completion of all therapy.

Additional research and longer-term follow-up are needed to assess the overall hypertension and CKD risk facing survivors of WT. ■

Submitted for publication Sep 24, 2020; last revision received Nov 23, 2020; accepted Dec 2, 2020.

Reprint requests: Michelle R. Denburg, MD, MSCE, 3401 Civic Center Boulevard, Philadelphia, PA 19104. E-mail: denburgm@email.chop.edu

References

1. Elli M, Sungur M, Genc G, Ayyildiz P, Dagdemir A, Pinarli FG, et al. The late effects of anticancer therapy after childhood Wilm's tumor: the role of diastolic function and ambulatory blood pressure monitoring. Jpn J Clin Oncol 2013;43:1004-11.
2. Wong KF, Reulen RC, Winter DL, Guha J, Fidler MM, Kelly J, et al. Risk of adverse health and social outcomes up to 50 years after Wilms tumor: The British Childhood Cancer Survivor Study. J Clin Oncol 2016;34:1772-9.
3. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31:3673-80.
4. Interiano RB, Delos Santos N, Huang S, Srivastava DK, Robison LL, Hudson MM, et al. Renal function in survivors of nonsyndromic Wilms tumor treated with unilateral radical nephrectomy. Cancer 2015;121:2449-56.
5. Daw NC, Gregornik D, Rodman J, Marina N, Wu J, Kun LE, et al. Renal function after ifosfamide, carboplatin and etoposide (ICE) chemotherapy, nephrectomy and radiotherapy in children with Wilms tumour. Eur J Cancer 2009;45:99-106.
6. de Graaf SS, van Gent H, Reitsma-Bierens WC, van Luyk WH, Dolsma WV, Postma A. Renal function after unilateral nephrectomy for Wilms' tumour: the influence of radiation therapy. Eur J Cancer 1996;32A:465-9.
7. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
8. Denburg MR, Jemielita TO, Tasian GE, Haynes K, Mucksavage P, Shults J, et al. Assessing the risk of incident hypertension and chronic kidney disease after exposure to shock wave lithotripsy and ureteroscopy. Kidney Int 2016;89:185-92.
9. Hooper SR, Gerson AC, Butler RW, Gipson DS, Mendley SR, Lande MB, et al. Neurocognitive functioning of children and adolescents with mild-to-moderate chronic kidney disease. Clin J Am Soc Nephrol 2011;6:1824-30.
10. Fine RN. Etiology and treatment of growth retardation in children with chronic kidney disease and end-stage renal disease: a historical perspective. Pediatr Nephrol 2010;25:725-32.
11. Fuhrman DY, Schneider MF, Dell KM, Blydt-Hansen TD, Mak R, Saland JM, et al. Albuminuria, proteinuria, and renal disease progression in children with CKD. Clin J Am Soc Nephrol 2017;12:912-20.
12. Mitsnefes M, Flynn J, Cohn S, Samuels J, Blydt-Hansen T, Saland J, et al. Masked hypertension associates with left ventricular hypertrophy in children with CKD. J Am Soc Nephrol 2010;21:137-44.
13. Zubowska M, Wyka K, Fendler W, Mlynarski W, Zalewska-Szewczyk B. Interleukin 18 as a marker of chronic nephropathy in children after anticancer treatment. Dis Markers 2013;35:811-8.
14. Bienias B, Zajaczkowska M, Borzecka H, Sikora P, Wieczorkiewicz-Plaza A, Wilczynska B. Early markers of tubulointerstitial fibrosis in children with idiopathic nephrotic syndrome: preliminary report. Medicine (Baltimore) 2015;94:e1746.
15. Ju W, Nair V, Smith S, Zhu L, Shedden K, Song PXK, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Sci Transl Med 2015;7:316ra193.
16. Tsau Y, Chen C. Urinary epidermal growth factor excretion in children with chronic renal failure. Am J Nephrol 1999;19:400-4.
17. Wuhl E, Witte K, Soergel M, Mehls O, Schaefer F, German Working Group on Pediatric Hypertension. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. J Hypertens 2002;20:1995-2007.
18. Urbina EM, Mendizabal B, Becker RC, Daniels SR, Falkner BE, Hamdani G, et al. Association of blood pressure level with left ventricular mass in adolescents. Hypertension 2019;74:590-6.
19. Hamdani G, Flynn JT, Becker RC, Daniels SR, Falkner B, Hanevold CD, et al. Prediction of ambulatory hypertension based on clinic blood pressure percentile in adolescents. Hypertension 2018;72:955-61.
20. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Sulbaran T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens 2005;23:505-11.
21. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140:e20171904.
22. Bennett MR, Nehus E, Haffner C, Ma Q, Devarajan P. Pediatric reference ranges for acute kidney injury biomarkers. Pediatr Nephrol 2015;30:677-85.
23. Meybosch S, De Monie A, Anne C, Bruyndonckx L, Jurgens A, De Winter BY, et al. Epidermal growth factor and its influencing variables in healthy children and adults. PLoS One 2019;14:e0211212.
24. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int 2012;82:445-53.
25. Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. AJR Am J Roentgenol 1984;142:467-9.
26. Interiano RB, McCarville MB, Santos ND, Mao S, Wu J, Dome JS, et al. Comprehensive renal function evaluation in patients treated for synchronous bilateral Wilms tumor. J Pediatr Surg 2017;52:98-103.
27. Green DM, Wang M, Krasin MJ, Davidoff AM, Srivastava D, Jay DW, et al. Long-term renal function after treatment for unilateral, nonsyndromic Wilms tumor. A report from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer 2020;67:e28271.
28. Neu MA, Russo A, Wingerter A, Alt F, Theruvath J, El Malki K, et al. Prospective analysis of long-term renal function in survivors of childhood Wilms tumor. Pediatr Nephrol 2017;32:1915-25.
29. Stefanowicz J, Owczuk R, Kaluzynska B, Aleksandrowicz E, Owczarzak A, Adamkiewicz-Drozynska E, et al. Renal function and solitary kidney disease: Wilms tumour survivors versus patients with unilateral renal agenesis. Kidney Blood Press Res 2012;35:174-81.
30. Shirzai A, Yildiz N, Biyikli N, Ustunsoy S, Benzer M, Alpay H. Is microalbuminuria a risk factor for hypertension in children with solitary kidney? Pediatr Nephrol 2014;29:283-8.
31. Jordan JH, Castellino SM, Melendez GC, Klepin HD, Ellis LR, Lamar Z, et al. Left ventricular mass change after anthracycline chemotherapy. Circ Heart Fail 2018;11:e004560.
32. Bates JE, Howell RM, Liu Q, Yasui Y, Mulrooney DA, Dhakal S, et al. Therapy-related cardiac risk in childhood cancer survivors: an analysis of the Childhood Cancer Survivor Study. J Clin Oncol 2019;37:1090-101.
33. Bartoli F, Pastore V, Cale I, Aceto G, Campanella V, Lasalandra C, et al. Prospective study on several urinary biomarkers as indicators of renal damage in children with CAKUT. Eur J Pediatr Surg 2019;29:215-22.
34. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, version 5.0. www.survivorshipguidelines.org. Accessed November 1, 2020.

Funding and Conflicts of Interest Disclosure

Supported by a Pilot Grant from the Children's Hospital of Philadelphia Center for Pediatric Clinical Effectiveness (to D.C.). D.C. is also supported by the NIH/NIDDK (K23 DK125670). G.T. was supported by the NIH/NIDDK (K23 DK106428). Ja.G. was supported by NIH/NIDDK (K08 DK110536). M.D. was supported by the NIH/NIDDK (K23 DK093556). The NIH and NIDDK had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the official view of the NIDDK nor NIH. G.T. serves on the scientific advisory boards for Allena Pharmaceuticals, Novome Biotechnology, and Dicerna Pharmaceuticals and serves as a consultant for Alnylam Pharmaceuticals, all of which are unrelated to this work. M.D. receives research funding from Mallinckrodt unrelated to this work. The other authors declare no conflicts of interest.