Chapter 9

Chronic Kidney Disease in Wilms Tumour Survivors – What Do We Know Today?

Joanna Stefanowicz,1 Mateusz Kosiak,2 Wojciech Kosiak,1 Beata S. Lipska-Ziętkiewicz3

1Department of Paediatrics, Haematology and Oncology, Medical University of Gdansk, Gdansk, Poland; 2Department of Family Medicine, Medical University of Gdansk, Gdansk, Poland, Medical Centre, Puck, Poland; 3Department of Biology and Genetics, Medical University of Gdansk, Gdansk, Poland

Author for correspondence: Joanna Stefanowicz, MD, PhD, Department of Paediatrics, Haematology and Oncology, Medical University of Gdansk, 7 Debinki Street, 80-952 Gdansk, Poland. Email: jstefanowicz@gumed.edu.pl

Doi: http://dx.doi.org/10.15586/codon.wt.2016.ch9

Copyright: The Authors.

 Licence: This open access article is licensed under Creative Commons Attribution 4.0 International (CC BY 4.0). http://creativecommons.org/licenses/by/4.0/

Users are allowed to share (copy and redistribute the material in any medium or format) and adapt (remix, transform, and build upon the material for any purpose, even commercially), as long as the authors and the publisher are explicitly identified and properly acknowledged as the original source.

Abstract

Currently, the treatment of Wilms tumour (WT) is successful in approximately 90% of cases, and consists of chemotherapy, nephrectomy, and, in some cases, radiation therapy. All treatments have potential long-term influence on the function of solitary kidneys in WT survivors (WTS). Severe reduction in glomerular filtration rate occurs after nephrectomy. All patients who underwent surgical treatment for WT could be considered to have
the risk of chronic kidney disease (CKD) because they lack a kidney. End-stage renal disease is rare (1.8% of National Wilms Tumour Study patients). Recent studies have revealed that patients with CKD have a greater risk of cardiovascular events and death. Most of the WTS have lower stages or no CKD. Regular biochemical studies and ultrasound examination at follow-up visits should be considered as indispensible elements of long-term care in uninephrectomized WTS. The evaluation of a single kidney function should be frequent, consisting of the assessment of estimated glomerular filtration rate (eGFR), assessment of albumin urine excretion, urine sediment analysis to detect abnormalities, ultrasound examination and measurements of blood pressure. According to Kidney Disease Improving Global Outcomes (KDIGO) recommendation and suggestions, GFR should be assessed using GFR-estimating equations that include serum creatinine and cystatin C concentrations. Cystatin C can be a more sensitive marker of kidney filtration function than creatinine, especially in diseases characterized by a mild decrease in glomerular filtration. This will facilitate the detection of early kidney impairment and assessment of the progression of CKD in WTS.

Key words: Chronic kidney disease; Renal function; Solitary kidney; Wilms tumour survivors

Introduction

Currently, the treatment of Wilms tumour (WT) is successful in approximately 90% of cases after chemotherapy, nephrectomy and, in some cases, radiation therapy (1). The number of survivors who have completed this treatment is increasing. All treatments can have potential long-term influence on the renal function of WT survivors (WTS) (2–4). A wide range of defects in kidney structure and function, from end-stage renal disease (ESRD) to varying degrees of chronic kidney disease (CKD), have been reported. CKD is associated with an increased risk of cardiovascular events, hospitalization and higher mortality (4, 5). The incidence and causes of renal dysfunctions vary depending on distinct clinical situations: sporadic (nonsyndromic) unilateral WT (UWT), sporadic bilateral WT (BWT) and WT arising in patients with genetic predisposition syndromes. All WTS are also considered to be at increased risk of acute kidney injury. Even mild deficiencies in the renal function may be associated with an increased risk of hypertension and cardiovascular disease.

End-stage renal disease in WT

ESRD, simply defined as the need for kidney replacement therapy, is very rare in WTS. Although observed mostly among patients who present with or develop BWT, it is also more frequent among children with syndromic WT. The latter include patients with microdeletion 11p13 syndrome (i.e., WAGR syndrome, MIM#194072: WT, Aniridia, Genitourinary
malformation, mental Retardation) and Denys–Drash syndrome (DDS, MIM#194080) (7). The 20-year cumulative risk of ESRD among WAGR syndrome and DDS patients was 43.3% [95% confidence interval (CI), 20.8–59.5%] and 82.7% (95% CI, 60.5–92.4%), respectively (8–10).

WT1 gene expression has a crucial role in normal kidney development. The disruption of the activity of WT1 protein may lead to fewer functional nephrons at birth, and histological studies of patients with WAGR syndrome indicate a reduction in the size of glomeruli that is presumably related to the WT1 deletion. Reductions in nephron and podocyte number and mass could increase susceptibility to renal failure, particularly in patients with unilateral or partial bilateral nephrectomy. Reduced expression of WT1 in adult podocytes may reduce the GFR and eventually lead to glomerular sclerosis (9). Recently, Lipska et al. (11) evaluated genotype–phenotype associations in WT1 glomerulopathy. The authors reported that diffuse mesangial sclerosis is largely specific for WT1 disease, but focal segmental glomerulosclerosis was equally prevalent in WT1-positive and WT1-negative steroid-resistant nephrotic syndrome patients. According to the National Wilms Tumour Study (NWTS), the cumulative incidence of ESRD due to chronic renal failure (CRF) 20 years after WT diagnosis was 0.7% (9).

The low incidence of ESRD in WTS is also confirmed by European studies (12, 13). For ESRD due to progressive BWT, it was 4.0% at 3 years post-WT diagnosis in patients with synchronous BWT and 19.3% in patients with metachronous BWT. Lange et al. (9) concluded that metachronous BWT is associated with high rates of ESRD due to surgery for progressive WT. Carriers of germline WT1 mutation had markedly increased risk of ESRD due to CRF, despite a low risk in non-WT1 syndromic patients overall. Ritchey et al. (8) reported an incidence of renal failure of 0.25% among patients with UWT, with a median follow-up of 6 years from diagnosis (range: 2 months–22 years).

Analysis of NWTS trials performed by Grigoriev et al. (14) showed that ESRD was diagnosed in 173 patients among 9,162 individuals with WT treated between October 1969 and April 2002. The most common causes of ESRD were progressive BWT (55); DDS (27); WAGR syndrome (10); radiation nephritis (12); focal segmental glomerulosclerosis (18); CKD, aetiology unknown (16) and hypertension (7). Fifty-five patients whose ESRD resulted from progressive BWT experienced high early mortality from WT that limited their opportunity for transplant (47% at 5 years) and survival (44% at 10 years) compared with population controls. The remaining 118 patients, many of whom had WT1-associated congenital anomalies, had transplant (77% at 5 years) and survival (73% at 10 years) outcomes no worse than those for population controls. The risk of ESRD due to progressive BWT was largely confined to the first 3 years following the onset of bilateral disease, whereas the incidence rates of ESRD due to CKD continued to increase for 20–25 years from WT diagnosis (14).
It is known that patients with hereditary predisposition syndromes are at a higher risk of developing bilateral tumours (both synchronous and metachronous). Two main molecular subgroups are recognized: syndromes associated with germline WT1 mutation and overgrowth syndromes associated with epigenetic alterations in chromosome 11p15 (15, 16). Germline WT1 mutations are also associated with renal developmental abnormalities and are risk factors for renal dysfunction regardless of the occurrence of WT. The following syndromes are associated with WT1 mutation: DDS, WAGR syndrome, Frasier syndrome (MIM#136680) and isolated WT (MIM#194070). The 20-year cumulative incidence of ESRD in patients with DDS and WAGR syndrome treated for WT can be as high as 80% and 90%, respectively (9). In patients with overgrowth syndromes, the most common being Beckwith–Wiedemann syndrome (BWS, MIM#130650), there does not seem to be a higher risk for renal dysfunction. Nevertheless, almost 20% of WT are bilateral in individuals with BWS (16).

Romao et al. (15) suggests that patients with hereditary predisposition syndromes who develop UWT should be treated with preoperative chemotherapy followed by nephron-sparing surgery (NSS), with the goal of preserving normal kidney function. The issue remains, however, strongly controversial. For instance, data presented by Lipska et al. (11) support pre-emptive/elective bilateral nephrectomy in patients with exonic germline WT1 (i.e., Denys–Drash type) mutations (14). Using the international PodoNet cohort, Lipska et al. described the genotypic and phenotypic spectrum of WT1-associated kidney disease in 61 patients, the largest cohort of WT1 nephropathy analyzed to date. Eighty-two percent of DDS patients needed kidney replacement therapy within 10 years of diagnosis. Among patients with exonic mutations who initially presented proteinuria of various degrees, 67% eventually developed WT, including 23% BWT. A total of 27 patients (44%), including 4 with intronic (Frasier type) mutations, underwent bilateral nephrectomy. Half of them, all with exonic mutations, underwent the surgery before their fifth birthday. Nephrectomy was performed electively before transplantation (n=18) due to BWT (n=5) or suspicious sonographic findings (n = 4) (11).

The development of renal dysfunction in survivors of BWT is a well-known complication. The philosophy of initial treatment with neoadjuvant chemotherapy for BWT is to avoid renal failure by maximal preservation of renal parenchyma (17). Bishop et al. (17) first reported a significant difference in the incidence of renal failure in NWTS patients with BWT (9% synchronous, 18% metachronous) versus unilateral involvement (1%). The primary cause of renal failure was bilateral nephrectomy for persistent or recurrent tumour. Within the NWTS 4, 23 out of 188 (12%) patients with bilateral disease followed from 1986 to 1994 developed ESRD (18). According to Lange et al. (9) who studied ESRD in non-WT1-syndromic patients treated by NWTS, the incidence of ESRD increased dramatically 20 years after diagnosis, reaching 3.1% for BWT. Non-WT1-syndromic BWTs have six times the risk of ESRD compared with unilateral ones.
Chronic kidney disease in WT survivors

The function of solitary kidney in WTS

The function of solitary kidney in WTS has been analyzed in several studies. Some investigators consider post-nephrectomy renal dysfunction as clinically insignificant (19, 20). In contrast, other investigators consider this renal dysfunction to be a harbinger of long-term consequences (21, 22). Romao et al. (15) were the first to draw attention to the need to develop risk stratification for renal dysfunction for unilateral nonsyndromic WT patients. Early detection of patients at risk may help tailor treatment (e.g., nephrectomy or NSS) and create focused monitoring protocols. As molecular biomarkers for both biological aggressiveness and multifocality are being discovered and incorporated into clinical practice, targeted interventions may be devised to improve the balance between cure and long-term morbidity.

Recently, Interiano et al. (23) evaluated the prevalence of hypertension and impaired renal function in a group of 75 long-term survivors of non-syndromic UWT (median length of follow-up, 19.6 years; range: 10.0–32.8 years) who were treated without nephrotoxic chemotherapy or ionizing radiation. Renal function was assessed by urinalysis and eGFR. Sixteen patients (21.3%) only had eGFR<90 ml/min/1.73 m2, no patient had an eGFR <60 ml/min/1.73 m2 and five patients (6.7%) had hypertension. At the time of last follow-up, no patient developed ESRD. The authors concluded that patients with UWT who were treated with unilateral radical nephrectomy without nephrotoxic chemotherapy or ionizing radiation appear to be at low risk of developing significant long-term renal dysfunction, but monitoring and counselling are important for early detection of subtle abnormalities. This group of WTS might be at an increased risk of adverse cardiovascular sequelae.

Hypertension is one of the components of the metabolic syndrome, which is indicated to be an important risk factor for developing cardiovascular diseases and type II diabetes mellitus. Van Waas et al. (24) reported that long-term adult survivors of childhood cancer are at increased risk of developing components of the metabolic syndrome. Their analysis of 500 adult survivors of childhood cancer provides information on the occurrence of components of the metabolic syndrome in long-term survivors of 11 types of childhood cancer. Systolic blood pressure was increased after the treatment of all types of malignancies, except for Langerhans cell histiocytosis and include WTS. It is unknown what determines the elevated blood pressure in survivors. Dysfunction of the endothelium has been hypothesized to be the initial step in the development of cardiovascular diseases. Chemotherapy agents like anthracyclines are known to damage the vascular endothelium. Additionally, radiotherapy could have a damaging effect on the endothelium.

Chronic kidney disease in WTS

According to the definition of the National Kidney Foundation (NKF), CKD is defined as abnormalities of kidney structure or function present for >3 months with implications for...
health. CKD is either a kidney damage or an eGFR below 60 ml/min/1.73 m$^2$ for over 3 months (6). Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (6, 25,). Signs of kidney damage may indicate the risk of deterioration of kidney function in the future. Long-term monitoring of renal function in WTS will facilitate the identification of those with treatment-related impairment of function. WTS are at risk of deterioration of renal function and CKD because of the following: decreased number of nephrons – after nephrectomy, nephrotoxic side effects of chemotherapy (carboplatin, cisplatin, ifosfamide, cyclophosphamide) or radiation therapy – if solitary kidney was in the field of radiation (3, 4, 26, 27). According to Daw et al. (3), the most severe reduction in GFR, measured by 99Tc-DTPA (technetium-99m-diethylenetriamine pentaacetic acid) clearance, occurs after nephrectomy. Decreasing the number of nephrons causes a compensatory increase in the filtration of the remaining nephrons to maintain excretory demands. Subsequent glomerular hyperfiltration in the remaining kidney leads to further deterioration of viable nephrons. Over time, the number of viable nephrons may become insufficient, resulting in a further reduction in kidney function (28-30).

According to the Brenner theory, the reduced filtration surface area of the kidney resulting from an acquired deficit of glomeruli impairs the normal adjustment of blood pressure by pressure natriuresis (31). Therefore, patients with a solitary kidney reveal an increased risk of albuminuria, hypertension and CKD. CKD can be diagnosed in all WTS subjected to nephrectomy. According to Interiano et al. (23), the current guidelines do not recognize solitary kidney or unilateral nephrectomy as a structural abnormality, but further studies are needed to determine whether a lack of one kidney is a marker for CKD development. In our opinion, from the viewpoint of renal function and long-term survival among uninephrectomized WT patients, the above statement is neither certain nor obvious. There are few long-term studies that evaluate the renal function in adult WTS, and we do not have sufficient scientific evidence that confirms the validity of this thesis (4, 32-34). Certainly, solitary kidney is a risk factor for the progression of CKD.

Little is known about the renal function in adult WTS who underwent nephrectomy a long time ago. Patients with WT are mostly very young children, and the prevalence of severe renal dysfunction owing to multifactorial causes is likely to increase with longer follow-up and survival. Kern et al. (35) assessed the renal function in a group of 55 patients with nonsyndromic UWT and reported that increasing time between surgery and the last known GFR follow-up was associated with decreased GFR. They concluded that longer follow-up may reveal that a clinically significant decline in the renal function occurs in the years following nephrectomy. Because of the potential for long-term renal insufficiency in children who undergo unilateral nephrectomy, some groups have advocated for NSS in patients with UWT to preserve renal parenchyma and function (32, 33). The use of NSS was judged by
these investigators as essential to reduce post-nephrectomy renal morbidity. NSS is infrequently performed in patients with UWT because the majority of cooperative group protocols recommend a radical nephrectomy (36). Partial nephrectomy for patients with UWT is a more controversial topic, particularly in the case of excellent oncologic outcomes with unilateral radical nephrectomy. The risk of local recurrence, need for therapy intensification, and unclear long-term renal function benefits have been the basis for debate against NSS in the treatment of unilateral non-syndromic WT (15). NSS is necessary in patients with BWT for the preservation of nephrons and renal function (17, 18).

Cozzi et al. (33) also examined and compared the renal function of 20 WTS treated with NSS, 40 WTS aged 2–30 years treated with nephrectomy, and 18 WTS aged 33–51 years treated with nephrectomy. While only 8% of NSS and 42% of nephrectomized young WTS presented mild-to-moderate renal function, this was 78% in the oldest nephrectomized WTS. The authors demonstrated a significant reduction in eGFR in the fifth decade of life in a group of WTS who underwent nephrectomy compared with patients during the third decade after surgery. Currently, the role of NSS in the treatment of unilateral nonsyndromic WT patients is discussed in the context of ensuring adequate local control and protection of renal function. So far, the standard of UWT treatment according to the Societe International de Oncologie Pediatrique (SIOP) and Children’s Oncology Group protocols includes radical nephrectomy. Data from the SIOP 2001 study showed that NSS was only performed in 3% of patients with UWT. Wilde et al. (36) concluded that NSS as a new approach for UWT has now been shown to be safe in a small and highly selected group of patients, concordant with the intention of the SIOP 2001 protocol. The event-free and overall survival after NSS appeared to be as good as total nephrectomy with an equal local relapse rate as that of total nephrectomy. Despite excellent survival, the gain of nephrons needs to be weighed against the risk to induce stage III with intensified therapy. Studies on the renal function after NSS are based on relatively small patient groups. Larger prospective studies are needed to fully assess the gain of renal function and oncological outcome.

Previously, we have analyzed the prevalence of CKD in nephrectomized WTS in a group of 32 patients (children and adolescents). All participants had undergone unilateral nephrectomy and had been treated according to the chemotherapy protocols SIOP 9, SIOP 1992, SIOP 2001 between the years 1987 and 2008. Kidney damage was established by the assessment of GFR using 99 Tc-DTPA clearance, the Schwartz formula, the new Schwartz equation, Filler formula, serum cystatin C concentration, β2-microglobulin and albumin urine excretion, urine sediment and ultrasound examination. Blood pressure was measured. The mean values of GFR assessed with different methods, 99Tc-DTPA clearance, eGFR Schwartz, eGFR new Schwartz equation for children with CKD and eGFR Filler, were all well above 60 ml/min/1.73 m². Increased excretion of albumin (ACR >30 mg/g creatinine) and B-2-microglobulin (BCR >0.04 g/mol) was observed in 22% and 13% of patients, respectively.
| Number of patients | Age at follow up mean±SD/ median (range) | Follow up duration [years] mean±SD/ median (range) | Stage | Treatment | eGFR * [ml/min/1.73 m^2] mean±SD/ median (range) | Hypertension | Albuminuria or proteinuria | BCR** | Recommendations of monitoring |
|-------------------|-----------------------------------------|---------------------------------------------------|-------|-----------|-----------------------------------------------|--------------|---------------------------|--------|-----------------------------|
| Mavinkurve- Groothuis 2015 [44] | 31 | 17.8±3.6 | 14.8±3.3 | I-IV | SIOP | 83±14 <60 - 4.2% | 26% | - | - | No renal injury | eGFR<60 and/or treatment |
| Schiavetti 2015 [43] | 35 | 25 | 20±5.43 | I-IV | SIOP | midly decreased G2, (64.5, 63-89), 22.9% CKD 8.6% | 2.9% | A2 (30-300 mg/L), 14% | - | necessary |
| Kern 2014 [36] | 55 | - | 6.3 (median) | - | - | ↓15% | - | - | - | necessary |
| Spreafico 2014 [45] | 15 | 18.3 (12.7-30.4) | 13.3 (10.2-19.3) | I, II | VCR, ACTD | 103.8 (89.2-166.7) | 24 h ABPM**** normal | 0.19 (0.02-13.2) | 0.57 (0.2-1.0) | at least every 5 years |
| Elli 2013 [46] | 15 | - | 9.9 (2-21) | I-IV | NWTS | 0% | 24 h ABPM 20% higher compared to control group (p<0.05) | Normal/0% | - | regular follow up should include BP monitoring, USG, ECHO, kidney function parameters |
| Sanpakit 2013 [47] | 30 | - | 4.8 (media) | I-IV | NWTS (ICE-9 patients) | 119 | 30% | 0% | - | necessary |
| Study             | Participants | Mean Age (Range) | # of Patients | Stage | SIOP | eGFR (Range) | Ultrafiltration | Proteinuria | Treatment | Follow-up | Outcome |
|------------------|--------------|------------------|---------------|-------|------|-------------|-----------------|-------------|-----------|-----------|----------|
| Dokkers 2013     | 85           | 27.9 (17.9-49.0) | 24.4 (12.2-41.1) | I-IV | SIOP | 60-90 | 51.8% | 31.4% | 25% | - | necessary |
| Cozzi 2013       | 18           | 42.7±5.7         | 38.4±4.9      | I-IV | VCR, ACTD, ADR | 76.1±6.3 | <90 - 78% | - | - | - | necessary |
| Stefanowicz 2011 | 32           | 12.2 (3.6-24.3)  | 7.75 (0.3-20.6) | I-IV | SIOP | 94.28 (10.24) | 6.3% | 21.9% | 12.5% | eGFR, ACR, BCR, urine sediment analyses, USG |
| Daw 2009         | 11           | 18.6 (12-25.6)   | 11.2 (7.3-12.8) | II-IV | ICE (Ifosfamide, carboplatin, etoposide), nephrectomy | 86 (10-169) | <90 - 54% | Renal transplantation 1 (with FSGS) | 18% | 18% | ↑ | necessary |
| Bailey 2002      | 40           | 14.31 (3.38-29.75) | 8.8 (0.06-27.5) | I-IV | VCR, ACTD, ADR | 100 (61-150) | 60-90 25% | 30-59 0% | 15-29 0% | <15 0% | 0% | 5% | - | necessary, not specified |

*eGFR – estimated glomerular filtration rate.
**BCR – β2microglobulin/urine creatinine.
***ACR-albumin/ urine creatinine.
****SCr – serum creatinine.
*****ABPM – ambulatory blood pressure monitoring.
Arterial hypertension, based on the mean values of systolic and diastolic blood pressures from three independent measurements, over the 95th centile was observed in 6.25% individuals (27).

Ultrasound examination of WTS provides an opportunity to detect signs of kidney damage. According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), sonographic features associated with CKD include: nephrocalcinosis, stones, hydronephrosis, cysts, increased echogenicity of kidney, small ‘hyperechoic kidney’, large kidneys, size disparities and scars, and venous thrombosis or renal stenosis (25). Thus, ultrasound examination can be used to identify WTS with CKD and risk of deterioration of eGFR. In our previous study, sonographic signs of kidney damage, including hyperechoic rings around renal pyramids (37.5%), renal scars (9%), increased echogenicity of renal cortex (15.5%) and cysts (3%), were observed in 43% of WTS (27).

Hypertrophy of a solitary kidney [length or volume of kidney over 2SD (standard deviation of reference value)] in WTS was observed in 50–88% of individuals (9, 37, 38). Mean value of renal length was 128 ± 14% of the reference value. Mean value of renal volume was from 155±35% to 213% (39, 40). In one study, correlation between microalbuminuria and renal volume was observed (40). The parenchymal thickness/kidney length ratio correlated with the deterioration of renal function (cystatin C serum concentration) (38). Currently, in light of the definition of CKD for individuals with the risk of deterioration of kidney function, it is essential not only to assess GFR but also to establish the presence of structural and functional markers of kidney damage. A marker for CKD, which may be more sensitive to the detection of early renal impairment, is cystatin C. According to Kazama et al. (41), a cystatin C serum concentration greater than 0.98 mg/dl has a sensitivity of 88.5% and a specificity of 95.2% for detecting GFR below 80 ml/min/1.73 m2. Recently, Schiavetti et al. (42) evaluated the prevalence of and the possible risk factors for the renal impairment in 35 adult WTS by estimating GFR categories and CKD according to KDIGO guidelines from 2012 (6). Only eight (23%) survivors presented a mildly decreased eGFR, three survivors (9%) had CKD and one (3%) hypertension. Data on the renal function in WTS from recent reports are included in Table 1.

Conclusion

To conclude, in our opinion, the evaluation of a single kidney in WTS should be regular and consist of the assessment of eGFR using equations, albumin excretion, urine sediment analysis, ultrasound examination and blood pressure measurements. If we do not have progressive renal injury, this nephrological follow-up should be once per year. It is necessary to diagnose early renal impairment. According to KDIGO recommendations, CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health, and CKD is classified based on cause, GFR category and albuminuria category.
Chronic kidney disease in WT survivors

The assessment of eGFR and albumin excretion is necessary to determine the risk of CKD. For GFR evaluation, KDIGO recommends using serum creatinine and a GFR estimating equation for initial assessment and suggests using additional tests such as cystatin C for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. In children, GFR can be estimated using Schwartz formula \[41.3 \times \text{(height/serum creatinine)}\], where height is expressed in meters and serum creatinine in mg/dl (6).

Furthermore, according to Romao et al. (15), the discussion about renal dysfunction in WTS will evolve and receive more attention. At present, survival in patients with WT is very good. The number of survivors increases from year to year. It is necessary to agree on the standardized follow-up protocols and tools to measure renal dysfunction over time. A complete assessment of renal function in WTS should be simple, easy, generally available and, according to NKF recommendations, include estimated GFR, urine test with albuminuria, ultrasound examination and measurements of blood pressure. This will facilitate the assessment and detection of the progression of CKD in WTS.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

References

1. Tournade MF, Com-Nougué C, de Kraker J, Ludwig R, Rey A, Burgaers MB, et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms tumor in children older than 6 months: results of the ninth International Society of Pediatric Oncology Wilms Tumor Trial and Study. J Clin Oncol. 2001;19:488–500.
2. Barrera M, Roy PL, Stevens M. Long-term follow-up after unilateral nephrectomy and radiotherapy for Wilms’ tumour. Pediatr Nephrol. 1989;3:430–43.
3. Daw NC, Gregornik D, Rodman J, Marina N, Wu J, Kun EL, et al. Renal function after ifosfamide, carboplatin and etoposide (ICE) chemotherapy, nephrectomy and radiotherapy in children with Wilms tumor. Eur J Cancer. 2009;45:99–106. http://dx.doi.org/10.1016/j.ejca.2008.09.017
4. Mulder RL, Knijnenburg SL, Geskus RB, van Dalen E, van der Pal HJH, Koning CCE, et al. Glomerular function time trends in long-term survivors of childhood cancer: a longitudinal study. Cancer Epidemiol Biomarkers Prev. 2013;22:1736–46. http://dx.doi.org/10.1158/1055-9965.EPI-13-0036
5. Go AS, Chertow GM, Fan D, McCulloch CF, Hsu C. Chronic kidney disease and the risk of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;551:1296–305. http://dx.doi.org/10.1056/NEJMoa041031
6. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Accessed February 07, 2016.
7. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. Pediatrics. 2005;116:984–8.
   http://dx.doi.org/10.1542/peds.2004-0467
8. Ritchey ML, Green DM, Thomas PR, Smith GR, Haase G, Shochat S, et al. Renal failure in Wilms’ tumor patients: a report from the National Wilms Tumor Study Group. Med Pediatr Oncol. 1996;26:75–80.
   http://dx.doi.org/10.1002/(SICI)1096-911X(199602)26:2<75::AID-MPO1>3.0.CO;2-R
9. Lange J, Peterson SM, Takashima JR, Grigoriev Y, Ritchey ML, Shamberger RC, et al. Risk factors for end stage renal disease in non WT1-syndromic Wilms tumor. J Urol. 2011;186:378–86.
   http://dx.doi.org/10.1016/j.juro.2011.03.110
10. Breslow NE, Collins AJ, Ritchey ML, Grigoriev YA, Peterson SM, Green DM. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol. 2005;174:1972–75.
   http://dx.doi.org/10.1097/01.ju.0000176800.00994.3a
11. Lipska BS, Ranchin B, Iatropoulos P, Gellermann J, Melk A, Ozaltin F, al.; PodoNet Consortium. Genotype-phenotype associations in WT1 glomerulopathy. Kidney Int. 2014;85:1169–78.
   http://dx.doi.org/10.1038/ki.2013.519
12. Ardissino G, Dacco V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003;111:e382–7.
13. Knijnenburg SL, Mulder RL, Schouten-Van Meeteren AY, Bökenkamp A, Blupfand H, van Dulmen-den Broeder E, et al. Early and late renal adverse effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2013;8:10.
14. Grigoriev Y, Lange J, Peterson S, Takashima JR, Ritchey ML, Ko D, et al. Treatments and outcomes for end-stage renal disease following Wilms tumor. Pediatr Nephrol. 2012;27:1325–33.
   http://dx.doi.org/10.1007/s00467-012-2140-x
15. Romao RLP, Lorenzo AJ. Renal function in patients with Wilms tumor. Urol Oncol. 2016;34:33–41. http://dx.doi.org/10.1016/j.urolonc.2015.07.002
16. Dome JS, Huff V. Wilms tumor. In: Pagon RA, Bird TD, Dolan CR, et al. (eds). GeneReviews™ (Internet). Seattle, WA: University of Washington, 1993.
   http://www.ncbi.nlm.nih.gov/books/NBK1294/
Chronic kidney disease in WT survivors

17. Bishop HC, Teft M, Evans A, D’Angio GJ. Survival in bilateral Wilms’ tumor – Review of 30 National Wilms’ Tumor Study Cases. J Pediatr Surg. 1977;12:631–63.
18. Hamilton TE, Ritchey ML, Haase GM, Argani P, Peterson SM, Anderson JR, et al. The management of synchronous bilateral Wilms tumor: a report from the Wilms Tumor Study Group. Ann Surg. 2011;253:1004–10. http://dx.doi.org/10.1097/SLA.0b013e31821266a0
19. Bailey S, Roberts A, Brock C, Price L, Craft AW, Kilkarni R, et al. Nephrotoxicity in survivors of Wilms’ tumours in the North of England. Br J Cancer. 2002;87:1092–98. http://dx.doi.org/10.1038/sj.bjc.6600608
20. Schell M, Cochat P, Hadj-Aissa A, Bouffet E, Dubourl L, Brunat-Mentigny M. Renal function following unilateral nephrectomy for neuroblastoma and Wilms’ tumor. Pediatr Nephrol. 1995;9:579–82.
21. Argueso LR, Ritchey ML, Boyle ET Jr, Milliner DS, Bergstralh EJ, Kramer SA. Prognosis of children with solitary kidney after unilateral nephrectomy. J Urol. 1992;148:747–51.
22. Levitt GA, Yeomans E, Dicks Mireaux C, Breatnach F, Kingston J, Pritchard J. Renal size and function after cure of Wilms’ tumour. Br J Cancer. 1992;66:877–82.
23. Interiano RB, Santos ND, Huang S, Srivastava DK, Robinson LL, Hudson MM, et al. Renal function in survivors of nonsyndromic Wilms tumor treated with unilateral radical nephrectomy. Cancer. 2015;121:2449–56. http://dx.doi.org/10.1002/cncr.29373
24. van Waas M, Neggers SJCM, Pieters R, van den Heuvel-Elbrink MM. Components of the metabolic syndrome in 500 adult long-term survivors of childhood cancer. Ann Oncol. 2010;21:1121–26. http://dx.doi.org/10.1093/annonc/mdp414
25. National Kidney Foundation KDOQI GUIDELINES. http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm. Accessed November 20, 2011.
26. Green DM. Evaluation of renal function after successful treatment for unilateral, non-syndromic Wilms tumor. Pediatr Blood Cancer. 2013;60:1929–35. http://dx.doi.org/10.1002/pbc.24738
27. Stefanowicz J, Kosiak M, Romanowicz G, Owczuk R, Adamkiewicz-Drożyńska E, Balcerska A. Glomerular filtration rate and prevalence of chronic kidney disease in Wilms’ tumour survivors. Pediatr Nephrol. 2011;26:759–66. http://dx.doi.org/10.1007/s00467-011-1759-3
28. Thorner P, Arbus G, Celermajer D, Baumal R. Focal segmental glomerulosclerosis and progressive renal failure associated with a unilateral kidney. Pediatrics. 1984;73:806–10.
29. Fotino S. The solitary kidney: a model of chronic hyperfiltration in humans. Am J Kidney Dis. 1989;13:88–98.
30. Zucchelli P, Cagnoli L, Casanova S, Donini U, Pasquali S. Focal glomerulosclerosis in patients with unilateral nephrectomy. Kidney Int. 1983;24:649–55.
31. Brenner B, Mackenzie H. Nephrons mass as a risk factor for the progression of renal disease. Kidney Int. 1997;52:124–27.
32. Cozzi DA, Ceccanti S, Frediani S, Schiavetti A, Cozzi F. Chronic kidney disease in children with unilateral renal tumor. J Urol. 2012;187:1800–05. http://dx.doi.org/10.1016/j.juro.2011.12.109
33. Cozzi DA, Ceccanti S, Frediani S, Mele E, Cozzi F. Renal function adaption up to fifth decade after treatment of children with unilateral renal tumor: a cross sectional and longitudinal study. Pediatr Blood Cancer. 2013;60:1534–8. http://dx.doi.org/10.1002/pbc.24545
34. Knijnenburg SL, Mulder RL, Schouten-Van Meeteren AY, Bökenkamp A, Blufpand H, van Dulmen-den Broeder E, et al. Early and late renal adverse effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2013;8:10
35. Kern AJ, Inouve B, Ko JS, Gorin MA, Allaf ME, Goldstein S, et al. Impact of nephrectomy on long-term renal function in non-syndromic children treated for unifocal Wilms tumor. J Pediatr Urol. 2014;10:662–6. http://dx.doi.org/10.1016/j.jpurol.2014.06.017
36. Wilde JCH, Aronson DC, Sznajder B, Van Tinteren H, Powis M, Okoye B, et al. Nephron sparing surgery (NSS) for unilateral Wilms tumor (UWT): the SIOP 2001 experience. Pediatr Blood Cancer. 2014;61:2175–9. http://dx.doi.org/10.1002/pbc.25185
37. Zerin JM, Haliloglu M, Cohen MD. Growth of the solitary kidney after nephrectomy in children with unilateral Wilms’ tumor. Pediatr Radiol. 1996;26(8):547–52.
38. Stefanowicz J, Kosiak M, Kosiak W, Korbus-Kosiak A, Sierota D, Owczuk R. Cystatin C and parenchymal thickness/kidney length ratio in Wilms tumor survivors. Pediatr Blood Cancer. 2010;54:41–6. http://dx.doi.org/10.1002/pbc.22249
39. Krawczuk-Rybak M, Kuźmicz M, Kitszel A, Wysocka J, Zalewska B, Olszewska M. Renal function and size after complex treatment of Wilms’ tumour. Med Wieku Rozwoj. 2003;7:359–67.
40. Di Tullio MT, Casale F, Indolfi P, Polito C, Giuliano M, Martini A, et al. Compensatory hypertrophy and progressive renal damage in children nephrectomized for Wilms’ Tumor. Med Pediatr Oncol. 1996;26:325–8. http://dx.doi.org/10.1002/(SICI)1096-911X(199605)26:5<325::AID-MPO4>3.0.CO;2-K
41. Kazama JJ, Kutsuwada K, Ataka K, Maruyama H, Gejyo F. Serum cystatin C reliably detects renal dysfunction in patients with various renal diseases. Nephron. 2002;91:13–20. http://dx.doi.org/10.1159/000057599

42. Schiavetti A, Altavista P, De Luca L, Andreoli G, Megaro G, Versacci P. Long-term renal function in unilateral non-syndromic renal tumor survivors treated according to International Society of Pediatric Oncology Protocols. Pediatr Blood Cancer. 2015;62:1637–44. http://dx.doi.org/10.1002/pbc.25558

43. Mavinkurve-Groothuis AMC, van de Kract F, Westland R, van Wijk JAE, Loonen JJ, Schreuder MF. Long-term follow-up of blood pressure and glomerular filtration rate in patients with solitary functioning kidney: a comparison between Wilms tumor survivors and nephrectomy for other reasons. Pediatr Nephrol. 2015;Oct 19 [Epub ahead of print].

44. Spreafico F, Terenziani M, Testa S, Perotti D, Collini P, Piva L, et al. Long-term renal outcome in adolescent and young adult patients nephrectomized for unilateral Wilms tumor. Letter to the Editor. Pediatr Blood Cancer. 2014;61:1136–37. http://dx.doi.org/10.1002/pbc.24876

45. 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. http://dx.doi.org/10.1093/jjco/hyt105

46. Sanpakit K, Triwatanawong J, Sumboonnanonda A. Long-term outcome in pediatric renal tumor survivors: experience of a single center. J Pediatr Hematol Oncol. 2013;35:610–13. http://dx.doi.org/10.1097/MPH.0b013e3182a06265

47. Dekkers IA, Blijdorp K, Cransberg K, Pluijm SM, Pieters R, Negers SJ, et al. Long-term nephrotoxicity in adult survivors of childhood cancer. Clin J Am Soc Nephrol. 2013;8:922–9. http://dx.doi.org/10.2215/CJN.09980912