Chapter 9

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

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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

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a 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 ERSD 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.

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 non-syndromic 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 m^2. Increased excretion of albumin (ACR >30 mg/g creatinine) and B-2-microglobuin (BCR >0.04 g/mol) was observed in 22% and 13% of patients, respectively.

Table. 1 Renal function in Wilms tumour survivors based on publish data in recent years

	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 treat-ment
										BP	1/y	2-4/y
										ACR***	1/y	2-4/y
										SCr****/ eGFR	1/5y	2-4/y
Schiavetti 2015 [43]	35	25	20±5.43	I-IV	SIOP	midly decreased G2, (84.5, 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% 24 h SBP higher com-par to con-trol group ($p<0.05$)	Normal/0%	-	regular follow up should included BP monitoring, USG, ECHO, kidney function parameters		
Sanpakit 2013 [47]	30	-	4.8 (media)	I-IV	NWTS (ICE-9 patients)	119	30%	0%	-	necessary		

Dekkers 2013 [48]	85	27.9 (17.9-49.0)	24.4 (12.2-41.1)	I-IV	SIOP	60-90 51.8% 30-59 4,7% 15-29 0% <15 3.5%	31.4%	25%	-	necessary
Cozzi 2013 [34]	18	42.7±5.7	38.44±4.9	I-IV	VCR, ACTD, ADR	76.1±16.3 <90 – 78%	-	-	-	necessary
	42	15.8±8.0	11.38±7.8	I-IV	VCR, ACTD, ADR	95.1±18.5 <90 – 43%	-	-	-	
Stefanowicz 2011 [28]	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 [3]	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 [19]	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 the following: 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.

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 × (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.

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