Long-Term Nephrotoxicity in Adult Survivors of Childhood Cancer

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Summary

Background and objectives Because little is known about long-term treatment-related nephrotoxicity, the aim was to determine risk factors for renal impairment long after childhood cancer treatment.

Design, setting, participants, & measurements Data from 763 adult childhood cancer survivors (414 men) were obtained during regular visits at the late-effects clinic between 2003 and 2009. Median follow-up time was 18.3 years (range=5.0–58.2). Glomerular function was assessed by estimated GFR (using the Modification of Diet in Renal Disease formula), urinary albumin creatinine ratio, and tubular function by urinary β_2-microglobulin creatinine ratio. The association with treatment factors was analyzed with covariance analysis for estimated GFR and logistic regression for urinary albumin and urinary β_2-microglobulin creatinine ratios.

Results Survivors treated with nephrectomy and abdominal irradiation had significantly lower estimated GFR than survivors not treated with nephrectomy/abdominal irradiation (estimated mean=90 ml/min per 1.73 m^2 versus 106, $P<0.001$). Estimated GFR was significantly lower in survivors after treatment with high-dose ifosfamide (88 versus 98, $P=0.02$) and high-dose cisplatin (83 versus 101, $P=0.004$) compared with survivors not treated with these regimen. Nephrectomy combined with abdominal radiotherapy (odds ratio=3.14, 95% confidence interval=1.02; 9.69) and high-dose cisplatin (odds ratio=5.19, 95% confidence interval=1.21; 22.21) was associated with albuminuria. High-dose ifosfamide (odds ratio=6.19, 95% confidence interval=2.45; 15.67) was associated with increased urinary β_2-microglobulin creatinine ratio. Hypertension was present in 23.4% of survivors and 31.4% of renal tumor survivors.

Conclusions Treatment with unilateral nephrectomy, abdominal radiotherapy, cisplatin, and ifosfamide was associated with lower estimated GFR. Persisting tubular damage was related to ifosfamide treatment.

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Introduction

Childhood cancer survival rates have improved substantially over the last decades, leading to a 5-year survival of 80% (1). To date, 1 of 570 young adults is a childhood cancer survivor (2). However, even a long time after cessation of treatment, mortality rates seem to be significantly higher than in the general population (3). Not only excess of mortality but also excess of morbidity, including second malignancies, endocrinopathies, and cardiovascular disease, are important issues (4). Impaired renal function is one of the known potential late-effects after childhood cancer treatment at either the glomerular or tubular level. Nephrotoxic chemotherapy, abdominal irradiation, and nephrectomy contribute to renal injury (5). Nephrotoxicity induced by chemotherapeutic drugs, including ifosfamide, cisplatin and carboplatin, can manifest as acute reversible renal failure at the glomeruli or proximal tubules (6–10). Cyclophosphamide, an isomer of ifosfamide, is not thought to cause nephrotoxicity, possibly because of different pharmacology, but clinical studies to confirm, especially at very long-term follow-up, are lacking. In general, AKI during childhood cancer treatment remains subclinical and reversible but may lead to CKD later in life. To date, studies on nephrotoxicity in large cohorts of childhood cancer survivors at long-term (>5 years) and very long-term (>20 years) follow-up are limited. Studies so far mainly focus on single therapies and short-term follow-up (6,7,9,10). Because reduced GFR and albuminuria are independent predictors of cardiovascular disease and all-cause mortality, studies focusing on long-term renal function to define risk groups, implement early interventions, and limit potentially nephrotoxic treatments are needed (11–16). In the present study, we determined risk factors for renal impairment many years after childhood cancer treatment.

Materials and Methods

Ethics Statement

The data described in the current retrospective study were obtained during regular visits at the late-effects clinic, and clinical investigations were

assessed using the standard guidelines for screening late effects after childhood cancer using Good Clinical Practice. An official written informed consent from every patient that visited the outpatient clinic was obtained according to standards of the Institutional Review Board.

Subjects

We performed a retrospective cross-sectional single-center study. Follow-up at the late-effects outpatient clinic for long-term childhood cancer survivors starts 5 years after cessation of treatment and is individualized based on cancer diagnosis, treatment protocol, and current clinical condition. Patients younger than 18 years or without serum creatinine data available were excluded.

Data Collection

Data concerning disease and treatment protocol were retrieved from our local database and completed from the medical records. Follow-up time was defined as time since cessation of treatment until most recent renal function measurement. Follow-up data included height, weight, BP, glomerular function defined as estimated GFR (eGFR), glomerular damage defined as albuminuria, and tubular injury defined as elevated β_2-microglobulinuria. BP was electronically measured and defined as hypertensive if systolic BP was ≥140 mmHg, diastolic BP was ≥90 mmHg, or any antihypertensive medication was used (17). Body mass index (BMI) was calculated as weight in kilograms divided by the squared height in meters.

Laboratory Measurements

Serum creatinine, assessed using the Roche enzymatic assay, urinary creatinine, urinary β_2-microglobulin, and urinary albumin were analyzed in a fully automated computerized laboratory system with a Hitachi 917 chemistry analyzer (Roche Diagnostics, Almere, The Netherlands).

Evaluation of Renal Function

Serum creatinine (Cr) concentration was used to calculate the eGFR by using the abbreviated Modification of Diet in Renal Disease equation (18–20). Kidney disease was categorized according to the Kidney Disease Outcomes Quality Initiative guidelines: stage 3 eGFR=30–59 ml/min per 1.73 m^2, stage 4 eGFR=15–29 ml/min per 1.73 m^2, and stage 5 eGFR<15 ml/min per 1.73 m^2 with or without renal replacement therapy (19). Age-specific SD scores were calculated to compare eGFR data with data from healthy Dutch references retrieved from the Nijmegen Biomedical study (n=3732, aged 18–85 years) (21). Urinary albumin creatinine ratio (U-ACR) was calculated to determine the presence of microalbuminuria, which was defined as U-ACR≥3.5 mg/mmol Cr (women) and ≥2.5 mg/mmol Cr (men). Macroalbuminuria was defined as U-ACR>35 mg/mmol Cr (women) and >25 mg/mmol Cr (men) (19,22). Urinary β_2-microglobulin creatinine ratio (U-β_2MCR) was measured at the same time point as U-ACR and expressed in the same units (normal value<0.04 mg/mmol Cr). If urinary pH<6, measurements of U-β_2MCR were unreliable and excluded from the analysis.

Statistical Analyses

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS 18.0, Chicago, IL). Results are reported as median (range) for baseline characteristics and non-normative outcome variables and mean (95% confidence interval [95% CI]) for SD scores. For univariate analysis, the one-sample t test was used for SDS, and the Mann–Whitney U test was used for group comparisons. The chi-squared test was used for nominal variables. The associations between eGFR and baseline and treatment characteristics were analyzed using covariance analysis and are expressed as adjusted means. The associations between albuminuria and high U-β_2MCR (≥0.04 mg/mmol Cr) and baseline and treatment characteristics were analyzed with logistic regression and are expressed as odds ratios (ORs). Models were corrected for age, sex (except for eGFR), age at diagnosis, and BMI. Dummy variables for subjects treated with nephrectomy without abdominal irradiation, nephrectomy with abdominal irradiation, and abdominal irradiation without nephrectomy were added to the models. Total cumulative dosages of chemotherapeutics were divided into two groups using the median as the cutoff limit. Because only 16 survivors had been treated with carboplatin, this group was analyzed as a whole. For all chemotherapeutics, the group of survivors not treated with the subsequent chemotherapy was used as the reference category. Because the total cumulative dosages of methotrexate (MTX) were missing for 235 survivors, we added being treated with MTX as a dichotomous variable. To assess the influence of hypertension, this variable was added to all models. P values<0.05 (two-tailed) were considered statistically significant.

Results

Survivors

Of 885 adult survivors of childhood cancer diagnosed and treated between 1964 and 2005, 763 survivors met the inclusion criteria, of which 85 survivors survived a renal tumor. One patient was excluded because of bilateral nephrectomy, and one patient was excluded because of nephrophtosis before cancer diagnosis. Baseline and treatment characteristics are presented in Tables 1 and 2. Median follow-up time was 18.3 years (range=5.0–58.2), and median age was 26.9 years (17.8–65.8). Cisplatin, carboplatin, and/or ifosfamide had been administered in 51 (7%), 16 (2%), and 75 (10%) survivors, respectively. Cyclophosphamide and MTX had been administered in 305 (39.9%) and 319 (41.8%) survivors, respectively. The group of survivors who had received abdominal radiotherapy (n=47) consisted mainly of renal tumor survivors (n=29) and neuroblastoma survivors (n=8). None of the survivors had received renal shielding during abdominal or total body irradiation. Unilateral nephrectomy was performed in all 85 renal tumor survivors (11.1%) (Table 2). Data of U-ACR and U-β_2MCR were not available in survivors that had visited the outpatient clinic before 2006 (n=266, 35%). Survivors with available data were significantly younger than survivors with missing data (25.9 versus 29.3, P<0.001). Also, a higher percentage of survivors had been treated with nephrotoxic chemotherapy (19% versus 9%, P<0.001). However, the cohort was comparable with

Table 1. Baseline and treatment characteristics of adult childhood cancer survivors

Baseline Characteristics and Treatment Factors	Total Cohort *N* (%)/Median (Range; *n*=763 [100])		Renal Tumor Survivors *N* (%)/Median (Range; *n*=85 [100])	
Sex (men)	414 (54.3)		45 (52.9)	
Age at diagnosis (yr)	7.3 (0.0–18.0)		2.8 (0.0–15.0)	
Age at follow-up (yr)	26.9 (17.8–65.8)		27.9 (17.9–49.0)	
Follow-up time (yr)	18.3 (5.0–58.2)		24.4 (12.2–41.1)	
Long-term survivors (>5 yr)	438 (57.4)		—	
Very long-term survivors (>20 yr)	325 (42.6)		—	
Diagnosis *N* (%)				
Acute lymphoblastic leukemia/T-NHL	216 (28.3)		—	
Acute myeloid leukemia	26 (3.4)		—	
B cell non-Hodgkin's lymphoma	68 (8.9)		—	
Hodgkin's lymphoma	80 (10.5)		—	
Bone tumor	35 (4.6)		—	
Renal tumor	85 (11.1)		—	
Neuroblastoma	50 (6.6)		—	
Langerhans cell histiocytosis	14 (1.8)		—	
Germ cell tumor	18 (2.4)		—	
Malignant mesenchymal tumor	67 (8.8)		—	
Brain tumor	76 (9.9)		—	
Other tumors	28 (3.7)		—	
Recurrence (≥1)	91 (11.9)		8 (9)	
Treatment	*N* (%)	Median (Range)	*N* (%)	Median (Range)
Chemotherapy		TCD (mg/m^2)		TCD (mg/m^2)
Cisplatin	51 (6.7)	450 (18–900)	1 (1.2)	450
Carboplatin	16 (2.1)	2050 (500–7150)	0	NA
Ifosfamide	75 (9.8)	18,000 (4–96,000)	4 (4.7)	36000 (30,000–36,000)
Cyclophosphamide	305 (40.0)	3500 (45–45,990)	5 (5.9)	5250 (250–7400)
Methotrexate	319 (41.8)		1 (1.2)	Unknown
Intrathecal	277 (36.3	108 (1–420)		—
Intravenous	236 (30.9)	10,000 (45–198,000)		—
Oral	250 (32.7)	Unknown		—
Radiotherapy		TCD (Gray)		TCD (Gray)
Abdominal radiotherapy	47 (6.2)	23 (10–40)	29 (34)	21 (15–30)
Total body irradiation	26 (3.4)	10 (6–20)		—
Spinal irradiation	23 (3.0)	40 (21–44)		—
Nephrectomy		85 (11.3)		
Renal replacement therapy[a]		3 (0.5)		

T-NHL, T cell non-Hodgkin's lymphoma; TCD, total cumulative dose.
[a]Renal replacement therapy includes dialysis and renal transplantation.

regard to sex, diagnosis, and treatment with nephrectomy, abdominal radiotherapy, and total body irradiation.

Glomerular Function

eGFR of the total group was not significantly different from healthy controls (mean SDS=0.03, 95% CI=−0.05; 0.11, *P*=0.47). An eGFR between 60 and 90 ml/min per 1.73 m^2 was found in 241 (31.5%) cases, an eGFR between 30 and 60 ml/min per 1.73 m^2 was found in 16 (2.1%) cases, an eGFR between 15 and 30 ml/min per 1.73 m^2 was found in 2 (0.3%) cases, and an eGFR below 15 ml/min per 1.73 m^2 was found in 3 (0.4%) cases (Table 2). Of the latter three cases (all renal tumor survivors), two cases had a functioning renal transplant: one case since childhood (cause by Denys Drash syndrome and nephroblastomatosis of the contra lateral kidney) and one case was treated with dialysis since 2009. Prevalence of ESRD was 10 times higher than in the normal Dutch population (<0.04%) (23). Survivors treated with unilateral nephrectomy (all 85 renal tumor survivors, SDS=−0.59, 95% CI=−0.85; −0.33, *P*<0.001), abdominal radiotherapy (*n*=47, SDS=−0.42, 95% CI=−0.83; −0.01, *P*=0.04), or the combination of both (*n*=29, SDS=−0.49, 95% CI=−0.98; −0.01, *P*=0.05) had significantly lower eGFR compared with healthy references (Supplemental Table 1). After adjustment for age at diagnosis and BMI, survivors treated with nephrectomy alone (91 ml/min per 1.73 m^2, 95% CI=76; 106, *P*<0.001) or combined with abdominal irradiation (90 ml/min per 1.73 m^2, 95% CI=74; 106, *P*<0.001) had significantly lower eGFR than survivors not treated with nephrectomy or abdominal radiotherapy (106 ml/min per 1.73 m^2, 95% CI=95; 119) (Table 3). Additionally, eGFR was significantly lower after treatment with high-dose ifosfamide (88 ml/min per 1.73 m^2, 95% CI=73; 103 versus 98 ml/min per 1.73 m^2, 95% CI=85; 112, *P*=0.02) and high-dose cisplatin (83 ml/min per 1.73 m^2, 95% CI=66; 100 versus 101, 95% CI=89; 113, *P*=0.004) compared with survivors who had not been treated with these regimen.

Table 2. Frequency, median, and range for estimated GFR, albumin-to-creatinine ratio, and urinary β_2-microglobulin creatinine ratio

Renal Function Parameters	Complete Group of Adult Childhood Cancer Survivors *N* (%)	Adult Renal Tumor Survivors *N* (%)
Glomerular function (estimated GFR; ml/min per 1.73 m^2)		
>90	501 (65.7)	34 (40.0)
60–90	241 (31.6)	44 (51.8)
30–59	16 (2.1)	4 (4.7)
15–29	2 (0.3)	0
<15	3 (0.4)	3 (3.5)
Albumin to creatinine ratio (mg/mmol Cr)		
Measurements/total group	496/763	61/85
<2.5 (if man) or <3.5 (if woman)	430 (86.7)	46 (75.4)
≥2.5–25 (if man) or ≥2.5–25 (if woman)	56 (11.3)	11 (18.0)
>25 (if man) or >35 (if woman)	10 (2.0)	4 (6.6)
Urinary β_2-microglobulin creatinine ratio (mg/mmol Cr)		
Measurements/total group	478/763	59/85
<0.04	348 (73)	41 (69)
≥0.04	130 (27)	18 (31)

Treatment with carboplatin, cyclophosphamide, and MTX was not significant associated with eGFR (Table 3).

Albuminuria

Albuminuria was significantly more often present in survivors after nephrectomy (25% versus 12% if no nephrectomy, P=0.01) and after abdominal radiotherapy (39% versus 11% if no abdominal radiotherapy, P<0.001) (Supplemental Table 1). Macroalbuminuria was rare (n=10, 2.0%) and was present in four renal tumor survivors (Table 2). After adjustment for age, sex, age at diagnosis, and BMI, this risk of albuminuria was significantly higher after combination treatment with nephrectomy and abdominal radiotherapy (OR=3.14, 95% CI=1.02; 9.69, P=0.05) compared with no treatment with this combination treatment. Furthermore, being treated with high-dose cisplatin (OR=5.19, 95% CI=1.21; 22.21, P=0.03) was significantly and independently associated with albuminuria, whereas treatment with ifosfamide and/or carboplatin was not (Table 3).

Tubular Function

Median U-β_2MCR was 0.02 mg/mmol Cr and significantly higher in patients treated with ifosfamide (0.03 versus 0.02 if no ifosfamide treatment, P=0.01) and spinal irradiation (0.07 versus 0.02 if no spinal irradiation, P=0.02) (Supplemental Table 1). After adjustment for age, sex, age at diagnosis, and BMI, survivors treated with high-dose ifosfamide (OR=6.19, 95% CI =2.45; 15.67, P<0.001) and spinal irradiation (OR=12.40, 95% CI=2.06; 78.99, P=0.006) had a higher risk of having tubular dysfunction represented by U-β_2MCR≥0.04 mg/mmol Cr.

Blood Pressure

Arterial hypertension was present in 142 (23.4%) survivors. In renal tumor survivors treated with nephrectomy, 22 subjects were hypertensive (31.4%). In survivors treated with abdominal irradiation, 18 subjects were hypertensive (43% versus 22% in survivors not treated with abdominal irradiation, P=0.003) (Supplemental Table 1).

Discussion

In the current study among nearly 800 survivors of childhood cancer, we investigated a broad spectrum of parameters of chronic kidney impairment after a median follow-up of 18 years (range=5–58 years). Nephrectomy, abdominal irradiation, high-dose cisplatin, and high-dose ifosfamide were found to be independent risk factors for renal impairment, whereas former treatment with cyclophosphamide or MTX was not.

High-dosed abdominal radiotherapy, total body irradiation, ifosfamide, cisplatin, and carboplatin have been described as risk factors for renal impairment in several studies (24–27). However, in these studies, follow-up time was relatively short, and patient numbers were small. A recent study in a large cohort of childhood cancer survivors 12 years after diagnosis described nephrectomy and the combination of nephrectomy with abdominal radiotherapy as risk factors for renal damage, represented by hypertension, proteinuria, and reduced glomerular function (28). In the present study, with a median follow-up of 18 years, we showed that nephrectomy and the combination of nephrectomy with abdominal radiotherapy were associated with a decreased glomerular function and albuminuria but not tubular dysfunction.

Albuminuria, however, has been described to be associated with both glomerular and tubular dysfunction, because it is the result of the balance between glomerular filtration and tubular reabsorption (29,30). In case of tubular dysfunction, reabsorption of filtered albumin is decreased, causing albuminuria. Based on *in vitro* studies, Birn and Christensen (29) hypothesized that excess albumin in the tubular lumen, caused by glomerular dysfunction, may lead to interstitial inflammation and fibrosis, causing tubular damage (29,31,32). These findings illustrate that both glomerular and tubular dysfunction play a role in the existence of albuminuria.

Short-term glomerular and/or tubular dysfunction after treatment with cisplatin, carboplatin, or ifosfamide has been thoroughly described before, although studies investigating multiple treatment effects after very long-term follow-up are not available (24,26,33). Our data show that

Table 3. Multivariate analysis illustrating the association of hypertension and treatment factors with estimated GFR (eGFR), albuminuria, and urinary β_2-microglobulin creatinine ratio (U-β_2MCR)

Independent Variables	eGFR (ml/min per 1.73 m^2)			Albuminuria			U-β_2MCR≥0.04 mg/mmol Cr		
	Adjusted Mean	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Hypertension no	96	83.00; 110.00		1.00			1.00		
Hypertension yes	96	82.00; 109.00	0.82	1.71	0.86; 3.40	0.13	2.05	1.17; 3.61	0.01
No cisplatin	101	89.00; 113.00		1.00			1.00		
Cisplatin≤450	104	88.00; 120.00	0.54	1.73	0.44; 6.85	0.44	0.58	0.15; 2.26	0.43
Cisplatin>450	83	66.00; 100.00	0.004	5.19	1.21; 22.21	0.03	0.52	0.08; 3.29	0.49
No ifosfamide	98	85.00; 112.00		1.00			1.00		
Ifosfamide≤16,000	102	86.00; 117.00	0.42	1.35	0.34; 5.33	0.67	1.34	0.48; 3.76	0.58
Ifosfamide>16,000	88	73.00; 103.00	0.02	1.49	0.49; 4.54	0.48	6.19	2.45; 15.67	<0.001
No carboplatin	94	81.00; 106.00		1.00			1.00		
Carboplatin treatment	98	81.00; 115.00	0.50	2.18	0.45; 10.54	0.33	2.93	0.68; 12.64	0.15
No cyclophosphamide	96	82.00; 110.00		1.00			1.00		
Cyclophosphamide≤3500	96	83.00; 110.00	0.98	0.54	0.21; 1.39	0.20	1.09	0.56; 2.15	0.80
Cyclophosphamide>3500	95	81.00; 109.00	0.74	0.84	0.35; 2.00	0.69	1.61	0.81; 3.20	0.18
No methotrexate	97	84.00; 110.00		1.00			1.00		
Methotrexate treatment	95	81.00; 109.00	0.36	0.94	0.49; 2.16	0.94	1.07	0.59; 1.92	0.83
No total body irradiation	93	81.00; 106.00		1.00			1.00		
Total body irradiation	99	83.00; 115.00	0.29	3.28	0.88; 12.22	0.08	0.48	0.12; 1.96	0.30
No spinal irradiation	90	80.00; 101.00		1.00			1.00		
Spinal irradiation	102	82.00; 120.00	0.14	2.12	0.21; 21.21	0.52	12.40	2.06; 78.99	0.006
No nephrectomy/abd RT	106	95.00; 119.00		1.00			1.00		
Nephrectomy, no abd RT	91	76.00; 106.00	<0.001	1.83	0.66; 5.17	0.25	1.69	0.67; 4.31	0.27
abd RT, no nephrectomy	96	78.00; 113.00	0.09	3.29	0.69; 15.67	0.14	1.12	0.23; 5.55	0.89
Nephrectomy and abd RT	90	74.00; 106.00	<0.001	3.14	1.02; 9.69	0.05	1.31	0.43; 3.99	0.63

Models were adjusted for age and sex (except for eGFR), age at diagnosis, and body mass index. CR, creatinine; 95% CI, 95% confidence interval; OR, odds ratio; abd RT, abdominal radiotherapy.

tubular and glomerular impairment caused by former treatments with high-dose ifosfamide and high-dose cisplatin is still present at very long-term follow-up.

Some studies suggested that cyclophosphamide is not nephrotoxic in children with cancer, but up until now, long-term follow-up studies in large cohorts that confirmed this finding are not available. We show for the first time that cyclophosphamide on the long term is not nephrotoxic. The difference between the nephrotoxic effect of cyclophosphamide and its isomer ifosfamide may be explained by the differences in pharmacokinetics and pharmacodynamics (34). A recent study using murine and human proximal tubule cells showed that specific renal uptake of the metabolites of ifosfamide and not cyclophosphamide is the basis for the differential effect in nephrotoxicity between ifosfamide and cyclophosphamide (35). Our finding that ifosfamide and not cyclophosphamide is persistently nephrotoxic, even after almost 20 years of follow-up, may be useful for the ongoing discussion on the role of ifosfamide in current treatment protocols for pediatric sarcomas (36). However, in the design of upfront protocols, not only nephrotoxicity but also other late sequelae, such as gonadal damage, should be taken into account (37,38).

Carboplatin is a cisplatin analog, but it is less nephrotoxic than cisplatin. Carboplatin treatment has been reported to be associated with tubular and to a lesser extent, glomerular dysfunction. In the current study, former treatment with carboplatin was not associated with tubular or glomerular dysfunction. However, because the number of survivors treated with carboplatin was relatively small in this study, results should be interpreted with caution.

The contribution of MTX to nephrotoxicity was reported during and shortly after treatment (5,39,40). For the first time, we show that MTX-related acute nephrotoxicity seems to be completely reversible, because after long-term follow-up, MTX-treated cancer survivors did not manifest glomerular or tubular dysfunction.

Renal tumor survivors treated with nephrectomy had a significantly lower glomerular function than survivors who kept both kidneys. Nephrectomy is known to result in compensatory hypertrophy and hyperfiltration of the remaining kidney because of loss of 50% of nephrons, leading to glomerulosclerosis, albuminuria, and high BP in the long run (41). A meta-analysis reported a decrease in eGFR of 10–20 ml/min per 1.73 m^2 after 5–10 years in healthy adult renal graft donors. Moreover, 12% of healthy donors reached an eGFR below 60 ml/min per 1.73 m^2 (42,43). Furthermore, unilateral nephrectomy for several renal diseases in childhood (including obstructive uropathy and reflux nephropathy) resulted in a reduced eGFR (median=85 ml/min per 1.73 m^2) after very long-term follow-up (44). It is remarkable that, in our group of renal tumor survivors treated with nephrectomy and additional nephrotoxic treatment, renal function was well maintained with a mean eGFR of 87.3 ml/min per 1.73 m^2, although eGFR was significantly lower than in the normal population (SDS=−0.6). Thus, renal function was relatively well preserved in our cohort of childhood cancer survivors 18 years after treatment with nephrectomy whether combined with abdominal irradiation or nephrotoxic agents.

Hypertension can be both a cause as well as a complication of renal disease, and it should therefore be monitored in childhood cancer survivors, because it can be a disguised symptom. Hypertension was present in 23%, which is relatively high compared with previous findings of 14% and 19% among childhood survivors; this finding could be explained by the fact that survivors were older and follow-up time was longer in the current study (28,45,46). This percentage was even higher (31%) in survivors treated with unilateral nephrectomy. Because renal impairment is highly associated with an increased risk of cardiovascular morbidity and death, renal tumor survivors should, therefore, be monitored with extra care (12). Based on our results, we recommend intensive renal screening (one time per 3 years) in high-risk groups (being treated with high-dose cisplatin [>450 mg/m^2] or high-dose ifosfamide [>16,000 mg/m^2] and nephrectomy with or without abdominal irradiation) by measurement of creatinine, eGFR, and albuminuria. Furthermore, treatment with angiotensin-converting enzyme inhibition is indicated not only for hypertension but also in case of isolated microalbuminuria, because it is described to reduce cardiovascular risk in nondiabetic patients (47).

Our study comprises nearly 90% of all adult survivors treated and diagnosed at the Erasmus Medical Center between 1964 and 2005, with a long and nearly complete follow-up. A limitation of this study is the fact that urine measurements were not part of the follow-up scheme of the late-effects clinic before 2006. Because the reason for selection was based on timing of follow-up rather than patients or treatment characteristics, the chance of selection bias is small, although it is not completely excluded.

In conclusion, lower eGFR in the long run is associated with former treatment with unilateral nephrectomy whether combined with abdominal irradiation, cisplatin, or ifosfamide. Albuminuria is related to combination treatment of nephrectomy and abdominal radiotherapy. Persisting tubular damage is particularly associated with treatment with ifosfamide. Treatment with cyclophosphamide and MTX is not related to very long-term nephrotoxic sequelae in childhood cancer survivors.

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Disclosures

None.

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