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Long-term renal function after treatment for unilateral, non-syndromic Wilms tumor. A report from the St. Jude Lifetime Cohort Study

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Abstract

Background: The impact of specific treatment modalities on long-term renal function and blood pressure among adult survivors of Wilms tumor (WT) has not been well-documented.

Methods: Among 40 WT survivors and 35 non-cancer controls, we estimated the glomerular filtration rate (eGFR) using the Chronic Kidney Disease-Epidemiology (CKD-EPI) equations with and without cystatin C, obtained 24-hour ambulatory blood pressure readings, and, among survivors only, measured ^{99m}Tc diethylenetriamine pentaacetic acid (DTPA) plasma clearance. Survivors were treated with unilateral nephrectomy and non-nephrotoxic chemotherapy. Twenty received whole abdomen radiation therapy (WART) [median –16.5 Gray (Gy)], and 20 received no radiation therapy. Pairwise comparisons between survivors treated with and without WART, and each group to controls were performed using two-sample t-tests.

Results: Twenty-six (65%) WT survivors were female and 33 (83%) were non-Hispanic white. GFR estimated with creatinine or creatinine + cystatin C was decreased among irradiated survivors compared to controls. No irradiated or unirradiated participant had an eGFR (creatinine + cystatin C) < 60 ml/min/1.73m². The prevalence of hypertension was significantly increased among unirradiated (25%) and irradiated survivors (35%) compared to controls (0%). Of the 24-hour ambulatory blood pressure monitoring parameters evaluated, only mean sleep period diastolic blood pressure load of those who received WART was significantly different from that of controls.

Conclusions: Chronic kidney disease was infrequent in long-term survivors of unilateral non-syndromic WT, whether treated with WART or no radiation. The prevalence of hypertension was increased in both groups compared to controls, emphasizing the need for ongoing monitoring of renal and cardiovascular health.

Keywords

Wilms tumor; renal function; whole abdomen radiation therapy; nephrectomy; hypertension

Introduction

The survival rate of children with unilateral, non-syndromic, favorable histology Wilms tumor (WT) has improved dramatically as a result of randomized clinical trials (1). Less than one percent of children with these features treated on the National Wilms Tumor Study Group protocols developed end-stage renal disease (2), in contrast to 36 to 90 percent among those who presented with bilateral renal tumors or had syndromic WT [Denys-Drash syndrome or WT, aniridia, genitourinary malformation, mental retardation (WAGR) syndrome] (3, 4). Some have suggested that the risk of late renal failure may be significant following unilateral nephrectomy for WT (5). The experimental work conducted by Hostetter et al., which involved unilateral nephrectomy and infarction of five-sixths of the contralateral kidney in an animal model, produced an increase in the single nephron glomerular filtration rate, significant morphological changes, and hypertension, providing theoretical support for a clinically relevant “hyperfiltration injury” (6). However, the prevalence of hyperfiltration and adverse renal function outcomes in children with non-syndromic, favorable histology WT has not been well studied.

We undertook the current pilot study to compare renal function outcomes and blood pressure measurements among survivors of unilateral, non-syndromic WT who underwent nephrectomy and received non-nephrotoxic chemotherapy, with or without whole abdominal radiation therapy, to those of a matched control population.

Patients and Methods

The current analysis uses the St. Jude Lifetime Cohort Study (SJLIFE), a retrospective cohort study with prospective clinical follow-up and ongoing enrollment of survivors of childhood cancer treated at St. Jude Children’s Research Hospital (SJCRH). Participants in SJLIFE were randomly selected from the eligible population in groups of 50, described above (7). The detailed methods for ascertainment, recruitment, and evaluation of the members of this cohort have been reported previously (7–9). Eligibility for this pilot study included: 1) diagnosis of unilateral non-syndromic WT treated at SJCRH with nephrectomy, non-nephrotoxic chemotherapy, with or without whole abdomen radiation; 2) survival 10 years from diagnosis; and 3) current age 18 years.

Wilms tumor survivors were not eligible for this study if they had surgery on the contralateral kidney, tumor progression or recurrence, exposure to nephrotoxic chemotherapy (cisplatin, carboplatin, or ifosfamide), radiation therapy to the lungs, known genetic renal disease (e.g., polycystic kidney disease), renal impairment due to structural or functional ureteral/bladder/urethral abnormalities, need for sedation or anesthesia for magnetic resonance imaging, implanted medical device (pacemaker, neurostimulation system, bone/joint replacement, etc.), radiographic contrast allergy, or history of asthma (Figure 1). The first 20 eligible consented Wilms tumor patients, in each of the two groups

(unirradiated or treated with whole abdomen radiation therapy), were enrolled in this pilot study.

A comparison group was recruited from non-first-degree relatives or friends of St. Jude patients and SJCRH employees who were not a member or related to a member of the SJLIFE study team or supervised by SJLIFE study team members. Age (± 5 years), sex, and race/ethnicity matched control subjects included those with no history of cancer (excluding basal cell carcinoma or carcinoma in situ of uterine cervix), no history of renal or other abdominal surgery, no known genetic renal disease (e.g., polycystic kidney disease), no renal impairment due to structural or functional ureteral/bladder/urethral abnormalities, no need for sedation or anesthesia for MRI imaging, no implanted medical device (pacemaker, neurostimulation system, bone/joint replacement, etc.), and who were not currently pregnant or lactating.

This investigation was approved by the Institutional Review Board at SJCRH and all participants or their guardians provided written informed consent.

Laboratory Measurements

Creatinine was measured using the Roche/Hitachi Cobas C system (Roche Diagnostics Indianapolis, Indiana) Creatinine Plus ver. 2 (CREP2) and a National Institute of Standards and Trademarks (NIST) traceable standard for creatinine (10). Results using the NIST traceable standard were reported to one decimal place until September 25, 2013. Thereafter they were reported to two decimal places (Upper Limit of Normal (ULN): males – 1.33 mg/dl; females – 1.01 mg/dl). Sodium and potassium were measured using the ISE module of the Cobas Integra system (Roche Diagnostics, Indianapolis, Indiana). Cystatin C was measured using the Cobas C system (CYSC2; Roche Diagnostics, Indianapolis, Indiana; ULN: 1.15 mg/l). Glucose was measured using the Cobas C system Glucose HK (GLUC3) (Roche Diagnostics, Indianapolis, Indiana; ULN fasting blood sugar: 99 mg/dl). Twenty-four-hour urine protein excretion was measured using the Total Protein Urine/CSF Gen.3 (TPUC3; Roche Diagnostics, Indianapolis, Indiana; ULN: 225 mg/24 hours). Twenty-four-hour urine protein collections were judged to be complete for women who excreted 11 to 20 mg/kg/24 hours and for males who excreted 14 to 26 mg/kg/24 hours. All assays were performed using the Cobas C501 system (Roche Diagnostics, Indianapolis, Indiana). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equations (11).

^{99m}Tc Diethylenetriamine Pentaacetic Acid (DTPA) Plasma Clearance

With peripheral intravenous (IV) access, 2 mCi/m² (total dose: 2 – 4 mCi) of ^{99m}Tc-DTPA were administered intravenously. Plasma samples were collected at 1, 2, and 4 hours after injection using the same IV site, after discarding 3 ml blood to prevent contamination. After these specimens were analyzed, a plasma DTPA clearance curve was calculated and the quantitative glomerular filtration rate was derived (12). The institutional normal range is 81 to 137 ml/min/1.73m² for adult females and 72 to 176 ml/min/1.73m² for adult males (13). Control participants did not undergo DTPA clearance measurement.

Blood Pressure Measurement

Resting blood pressure was measured in the SJLIFE Human Performance Laboratory after the participant had been sitting upright in a chair with both feet on the floor for five minutes. The right arm was supported at the level of the heart. A 12cm*26cm (most adults) or a 12cm*40cm sphygmomanometer was used, depending on the size of the participant's arm. Duplicate blood pressure readings were taken to ensure accuracy (14). Hypertension was graded using a modification of the Common Terminology Criteria for Adverse Events as: Grade 1 - systolic BP 120 – 139 mm Hg or diastolic BP 80 – 89 mm Hg; Grade 2 - systolic BP 140 – 159 mm Hg or diastolic BP 90 – 99 mm Hg; medical intervention indicated or initiated; recurrent or persistent (≥ 24 hours); symptomatic increase by >20 mm Hg (diastolic) or to $>140/90$ mm Hg if previously within normal limits monotherapy indicated or initiated; Grade 3 - systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or initiated; Grade 4 - Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated (9).

Ambulatory blood pressure monitoring was performed using the Suntech ambulatory BP monitor (Sun Tech Medical, Inc., Morrisville, NC). The monitors were programmed to measure blood pressure every 20 minutes. Mean systolic and diastolic blood pressure was obtained for the entire 24 hours (15, 16). The percentage of readings greater than normal (termed the blood pressure load) was calculated (17). The percent decline in both systolic and diastolic blood pressure at night was also calculated to indicate whether the nocturnal decline was normal ($>10\%$) or abnormal. Data from 12 individuals with hypertension or who were receiving anti-hypertensive medications were excluded from the analysis.

Radiation Therapy

Irradiated patients were diagnosed between 6/30/1973 and 9/30/1996 with the median patient diagnosed 3/24/1980, and received treatment to the whole abdomen, with or without a “boost” to the operative bed. Whole abdomen irradiation was prescribed as outlined in Supplementary Table 1 (18–20). Renal radiotherapy dose was quantified by reconstructing each patient's individual radiation treatment on a computed tomography (CT) based phantom with an organ library for calculation of normal organ radiation doses. For each patient's reconstructed radiation treatment plan, the volumetric dose to each kidney was calculated by recreating the treatment ports and actual beam energies in a modern radiation therapy planning software system (Eclipse, Varian Medical Systems, Milpitas, CA). The unirradiated patients were diagnosed between 1/25/1978 and 5/1/1996 with the median patient diagnosed 10/7/1982.

Statistical Analysis

Descriptive statistics were used to summarize demographic and treatment variables for WT survivors with and without WART, and non-cancer controls. The Fisher's exact test was used to compare categorical variables and the t-test was used to compare continuous variables among these three groups. Wilcoxon rank sum test was used to compare the sleep period

diastolic blood pressure load for its distribution was highly skewed among these three groups. These analyses were conducted using SAS software (SAS 9.4, Cary NC).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Forty-five patients were enrolled. Three of 23 unirradiated patients and two of 22 irradiated patients withdrew from the study due to inability to complete the magnetic resonance imaging. Among the 40 WT survivors who did not withdraw, 20 (50%) received WART and 20 (50%) did not receive radiation therapy. Thirty-five non-cancer control subjects were enrolled in this study (Figure 1). Table 1 shows the clinical features of the different treatment groups and comparisons between them for each feature. There were no significant differences in gender, race, or ethnicity between the two patient groups and non-cancer controls. Unirradiated patients were an average of 28.8 years of age and 26.9 years post-diagnosis, compared to 33.7 years of age and 30.1 years post-diagnosis among irradiated survivors. WT survivors who had received WART had significantly lower body mass index than either unirradiated survivors or controls ($p = 0.027$). The prevalence of diabetes mellitus did not differ among WT patients who did and did not receive WART ($p = 1.000$). The median radiation therapy dose to 100% of the remaining kidney was 11.0 Gy (interquartile range (IQR), 10.0 Gy, 11.5 Gy) (Supplementary Table 2).

Serum and urine chemistry

No differences in mean serum sodium, potassium, or creatinine were identified among either unirradiated patients or irradiated patients compared to controls (Supplementary Table 3; Figure 2A). Creatinine values were less than the ULN for all unirradiated survivors and all but one irradiated survivor.

Serum cystatin C was significantly higher among those who received WART compared to control subjects ($p = 0.024$) (Supplementary Table 3; Figure 2A). However, cystatin C was greater than the ULN in only two irradiated and one unirradiated patient.

Twenty-four-hour urine protein excretion did not differ between either unirradiated or irradiated WT survivors, compared to control subjects (Supplementary Table 3; Figure 2B). Only two unirradiated and no irradiated patients had 24-hour urine protein excretion that was greater than the ULN (Figure 2B).

Glomerular filtration rate

The eGFR, using creatinine only or creatinine + cystatin C, was lower among those WT survivors who had received WART compared to controls. There was no difference in mean eGFR between unirradiated WT survivors and control subjects. Plasma ^{99m}Tc clearance was significantly lower among those WT survivors who had received WART compared to unirradiated WT survivors (Table 2 and Figure 2C).

Plasma ^{99m}Tc clearance did not correlate with eGFR using the creatinine only equations for either unirradiated (Figure 3A) (Pearson's $r = 0.323$; $p = 0.177$) or irradiated (Figure 3A) (Pearson's $r = 0.284$; $p = 0.254$) patients, but did correlate well with the eGFR using the creatinine + cystatin C equations among unirradiated (Pearson's $r = 0.488$; $p = 0.034$) (Figure 3B) and irradiated (Pearson's $r = 0.558$; $p = 0.020$) survivors (Figure 3B). 24-hour urine creatinine clearance did not correlate with plasma ^{99m}Tc clearance among either the unirradiated (Pearson's $r = 0.120$; $p = 0.625$) or the irradiated (Pearson's $r = 0.252$; $p = 0.314$) Wilms tumor participants (Figure 3C).

No participant had an eGFR < 60 ml/min/1.73m² using the CKD-EPI estimating equation with serum creatinine only, or with serum creatinine + cystatin C (Supplementary Table 4). Using the CKD-EPI estimating equation for creatinine only, two (10%) unirradiated, two (10%) irradiated and no control participants had an eGFR < 60 ml/min/1.73m² (Supplementary Table 4). Of these, only one of the unirradiated patients had 24-hour urine protein excretion exceeding the ULN.

eGFR for controls, using either creatinine only or creatinine + cystatin C, did not correlate well with 24-hour urine creatinine clearance (Figures 4A and 4B). By contrast, the 24-hour urine creatinine clearance for the unirradiated patients correlated well with the creatinine only eGFR (Pearson's $r = 0.501$; $p = 0.024$), whereas the 24-hour urine creatinine clearance for the irradiated patients correlated well with the creatinine + cystatin C eGFR (Person's $r = 0.553$; $p = 0.014$) (Figures 4A and 4B). When these analyses were restricted to those participants who had complete 24-hour urine collections based on the 24-hour urine creatinine excretion (mg/kg/24 hours), the only significant correlation was between the 24-hour creatinine clearance and the eGFR using creatinine + cystatin C (Person's $r = 0.553$; $p = 0.021$) (Supplementary Figures 1A, 1B, and 1C).

Hypertension

Grade 2 to 4 (mild, severe/disabling, life-threatening) hypertension was identified in 25% (5/20) of unirradiated survivors and 35% (7/20) of irradiated WT survivors compared to 0% (0/35) of controls ($p = 0.005$, $p < 0.001$) (Table 1). Twenty-four-hour ambulatory blood pressure monitoring was obtained from all participants in this study. The only statistically significant comparison was that of sleep period diastolic blood pressure load among those WT survivors who received WART compared to the same parameter among the control population ($p = 0.023$) (Supplementary Table 5; Supplementary Figures 2A and 2B).

Discussion

We comprehensively assessed renal function among adult survivors of unilateral non-syndromic, favorable histology WT who were not exposed to nephrotoxic chemotherapy to address knowledge deficits regarding the long-term impact of nephrectomy and WART on renal function and blood pressure. Renal function, as evaluated by glomerular filtration rate estimating equations, did not differ between those treated with WART and those treated without such irradiation. ^{99m}Tc DTPA plasma clearance was lower among those treated with WART compared to those not so treated, but the mean for both groups was more than 60

ml/min/1.73 m², suggesting that renal function was not significantly impaired in either group.

Creatinine clearance, evaluated using 24-hour urine collections, correlated poorly with ^{99m}Tc DTPA clearance, whether data were analyzed using the entire study cohort, or excluding those with apparent incomplete 24-hour urine collections. However the assessment of a collection as incomplete may be confounded in this population by sarcopenia, which is present in 54.4% of female and 4.1% of male adult survivors of childhood cancer (21). Concurrent dual x-ray absorptiometry was not obtained on the participants in the present study, precluding an evaluation of the contribution of sarcopenia to decreased creatinine excretion.

We identified chronic kidney disease, characterized by decreased eGFR, with or without proteinuria, in only one (5%) unirradiated WT survivor and none of those who received WART. Some historical series (reviewed in (22)) demonstrated a greater prevalence of less serious renal dysfunction among survivors of WT. The measured GFR was < 80 mL/min/1.73 m² in 0% to 41.7% of WT survivors whose treatment included abdominal irradiation with an overall prevalence of 14.3% (23/161) and in 6.9% to 30.8% of those whose treatment for WT did not include abdominal irradiation, with an overall prevalence of 13.8% (11/80). Seven different methods for measuring the GFR, none of which included the use of a NIST traceable standard, were utilized in the studies reviewed above. Most series did not report the presence or absence of anomalies, such as hypospadias, cryptorchidism or aniridia, associated with the occurrence of renal failure in WT patients.

No patient in the current series had end-stage renal disease (need for chronic dialysis or renal transplantation) (23). The risk of end-stage renal disease in children with unilateral, non-syndromic WT treated on the National Wilms Tumor Study Group protocols was only 0.7 %, compared to 11.5% among those with non-syndromic, bilateral WT, 36% among patients with unilateral WT and WAGR syndrome, and 74% among patients with unilateral WT and Denys-Drash syndrome (2).

We observed that hypertension was more prevalent among survivors of non-syndromic, unilateral Wilms tumor treated with nephrectomy, regardless of radiation status, suggesting that nephrectomy contributes to its pathogenesis. Post treatment hypertension has been reported previously following abdominal irradiation for WT (24), including among patients found to have post-irradiation renal artery stenosis (25–27). One large series identified diastolic hypertension at the fifth anniversary after diagnosis of WT among 7% (39/561) of males and 7% (44/610) of females (28). The hazard ratio for hypertension was 8.2 (95% confidence interval (CI), 6.4 to 10.5) among survivors of WT enrolled on the Childhood Cancer Survivor Study (29). Hypertension was present in 14.8% (196/1328) of five-year Dutch childhood cancer survivors with a history of abdominal irradiation, but not nephrectomy, representing an independent treatment-related risk factor (30).

Twenty-four-hour ambulatory blood pressure monitoring identifies diurnal blood pressure rhythm, dipping status, morning surge, and blood pressure variability, parameters that are captured questionably or not at all using clinic or home blood pressure monitoring. Our

study is the first to utilize 24-hour ambulatory blood pressure monitoring to evaluate adult survivors of WT with extended follow-up after nephrectomy. Most parameters measured in un-medicated, normotensive, post-nephrectomy survivors did not differ between those treated with WART or no abdomen radiation therapy, compared either to each other or to the control population. The single statistically significant comparison was of sleep period diastolic blood pressure load between those treated with WART compared to controls. The significance of this isolated finding is unclear at present.

The results of this study must be interpreted taking into consideration the limitations related to the small sample size and the study design, which was a non-randomized sample of the eligible unirradiated and irradiated patients. In addition, the small sample size limited our ability to conduct sophisticated multivariable analyses to evaluate the impact of older age at evaluation, male sex and non-Hispanic, black race/ethnicity on the prevalence of hypertension (31). These factors may limit the generalizability of the study findings. Study strengths include the use of a NIST traceable standard for measurement of creatinine. Prior studies have not employed this standard, a practice associated with substantial intra- and inter-institutional variation in serum creatinine measurements (18), and thus erroneous calculations of eGFR.

In conclusion, comprehensive renal function assessment of unilateral, non-syndromic WT survivors at a median of 27.6 to 30.9 years from diagnosis failed to identify evidence of impaired renal function, as evaluated using serum and urine chemistry measurements, traceable, when appropriate, to a NIST standard. However, we identified hypertension without decreased eGFR or proteinuria in a significant proportion of unirradiated (25%) and irradiated (35%) survivors. Additional research is needed to describe the evolution of renal function abnormalities in these survivors and to elucidate the mechanism of hypertension with regard to abnormal or autonomous function of the renin-angiotensin-aldosterone system. These data underscore the importance of ongoing health surveillance to identify modifiable risk factors and comorbidities for both renal and cardiovascular disease, and continued follow-up of survivors of unilateral, non-syndromic, favorable histology Wilms tumor to determine the impact, if any, of hypertension on the prevalence of subsequent cardiac disease or stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CKD-EPI	Chronic Kidney Disease-Epidemiology
DTPA	^{99m} Tc diethylenetriamine pentaacetic acid

eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
Gy	Gray
IQR	Interquartile range
NIST	National Institute of Standards and Trademarks
SJCRH	St. Jude Children's Research Hospital
SJLIFE	St. Jude Lifetime Cohort Study
ULN	Upper limit of normal
WAGR	Wilms tumor, Aniridia, Genitourinary malformation, mental Retardation syndrome
WART	Whole abdomen radiation therapy
WT	Wilms tumor

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Figure 1 -
Flow diagram

Figure 2 –.

Box plots of: A - serum creatinine and cystatin C by group; B - 24-hour urine protein by group; C - eGFR and ^{99m}Tc plasma clearance by group.

Figure 3 –.

Scatterplots with regression line for correlation of: A - ^{99m}Tc plasma clearance GFR versus CKD-EPI creatinine only eGFR in unirradiated survivors (solid line) and ^{99m}Tc plasma clearance GFR versus CKD-EPI creatinine only eGFR in irradiated survivors (dashed line); B - ^{99m}Tc plasma clearance GFR versus CKD-EPI creatinine + cystatin C eGFR in unirradiated survivors (solid line) and; C - ^{99m}Tc plasma clearance GFR versus 24-hour urine measured creatinine clearance in unirradiated survivors (solid line) and ^{99m}Tc plasma clearance GFR versus 24-hour urine measured creatinine clearance in irradiated survivors (dashed line).

Figure 4 –.

Scatterplots with regression line for correlation of: A - CKD-EPI creatinine only eGFR versus 24-hour urine measured creatinine clearance in unirradiated survivors (solid line), irradiated survivors (short dashed line), and controls (alternating dashed line); B - CKD-EPI creatinine + cystatin C eGFR versus 24-hour urine measured creatinine clearance in unirradiated survivors (solid line), irradiated survivors (short dashed line), and controls (alternating dashed line).

TABLE 1

Demographic and anthropometric characteristics of study participants

Variable	Category	No radiation therapy (N = 20)	Whole abdomen radiation therapy (WART) (N = 20)	Controls (N = 35)	p-value (No radiation therapy versus WART)	p-value (No radiation therapy versus Controls)	p-value (WART versus Controls)
Gender	Female – N(%)	13 (65)	13 (65)	22 (63)	1.000 [†]	1.000 [†]	1.000 [†]
	Male – N(%)	7 (35)	7 (35)	13 (37)			
Race	Black – N(%)	4 (20)	3 (15)	3 (9)	1.000 [†]	0.242 [†]	0.657 [†]
	White – N(%)	16 (80)	17 (85)	32 (91)			
Ethnicity	Spanish speaking, Hispanic N(%)	0 (0)	0 (0)	1 (3)		1.000 [†]	1.000 [†]
	Non Spanish speaking, Non-Hispanic – N(%)	20 (100)	20 (100)	34 (97)			
Laterality of renal tumor	Left – N(%)	8 (40)	10 (50)		0.751 [†]		
	Right – N(%)	12 (60)	10 (50)				
Age at diagnosis (years)	Mean (STD)	2.3 (1.6)	4 (2.5)		0.013		
	Median (IQR)	2.2 (0.7,3.6)	3.3 (2.6,4.4)				
Age at evaluation (years)	Mean (STD)	28.8 (4.0)	33.7 (5.2)	31.5 (5.6)	0.002	0.069	0.152
	Median (IQR)	29.5 (26.5,31.5)	33.5 (32.5,37.0)	31.0 (28.0,35.0)			
Elapsed time from diagnosis to evaluation (years)	Mean (STD)	26.9 (4.5)	30.1 (5.0)		0.040		
	Median (IQR)	27.6 (25.3,30.4)	30.9 (28.6,33.6)				
Diabetes mellitus	Missing – N(%)	0 (0)	0 (0)	1 (3)			
	CTCAE Grade 0 – N(%)	18 (90)	17 (85)	32 (91)	1.000 [†]	0.622 [†]	0.347 [†]
	CTCAE Grades 1 – 4 – N(%)	2 (10)	3 (15)	2 (6)			
Hypertension	CTCAE Grades 0 – 1 – N(%)	15 (75)	13 (65)	35 (100)	0.731 [†]	0.005 [†]	<0.001 [†]
	CTCAE Grades 2 – 4 – N(%)	5 (25)	7 (35)	0(0)			
Body mass index (kg/m ²)	Mean (STD)	28.2 (7.2)	24.6 (6.2)	27.8 (6.4)	0.099	0.829	0.077
	Median (IQR)	25.6 (23.5,32.6)	24.5 (20.3,27.8)	28 (22.4,32.8)			

CTCAE – Common Terminology Criteria for Adverse Events; N - number of patients; % - percentage of participants; STD – standard deviation; IQR – interquartile range

Fisher's exact test

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TABLE 2

Estimated glomerular filtration rate (eGFR) and ^{99m}Tc DTPA plasma clearance GFR

Variable	Category	No radiation therapy	Whole abdomen radiation therapy (WART)	Controls	p-value (No radiation therapy versus WART)	p-value (No radiation therapy versus Controls)	p-value (WART versus Controls)
eGFR (CKD-EPI) (creatinine only) (ml/min/1.73m ²)	Mean (STD)	103.9 (17.2)	94.9 (14.7)	107.1 (15.2)	0.084	0.482	0.006
	Median (Range)	101.3 (70.7, 133.5)	94.8 (72.2, 124.0)	110.1 (72.0, 136.7)			
eGFR (CKD-EPI) (creatinine and cystatin C) (ml/min/1.73m ²)	Mean (STD)	97.4 (14.8)	90.3 (15.3)	102.9 (13.8)	0.147	0.173	0.003
	Median (Range)	97.0 (65.0, 122.5)	87.6 (67.9, 124.9)	104.5 (76.7, 130.1)			
^{99m} Tc DTPA plasma clearance GFR (ml/min/1.73m ²)	Mean (STD)	91.2 (17.9)	75.6 (12.1)		0.004		
	Median (Range)	97.0 (42.0, 113.0)	78.5 (53.0, 97.0)				

eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; DTPA - diethylenetriamine pentaacetic acid; STD – standard deviation