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Yield of Urinalysis Screening in Pediatric Cancer Survivors

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Abstract

Background—The Children's Oncology Group (COG) publishes consensus guidelines with screening recommendations for early identification of treatment related morbidities among childhood cancer survivors. We sought to estimate the yield of recommended yearly urinalysis screening for genitourinary complications per Version 3.0 of the COG Long-Term Follow-Up Guidelines and identify possible risk factors for abnormal screening in a survivor population.

Procedure—A database of pediatric cancer survivors evaluated between January 2008 and March 2012 at Children's Healthcare of Atlanta was queried for survivors at risk for genitourinary late effects. The frequency of abnormal urinalyses (protein 1+ and/or presence of glucose and/or 5 red blood cells per high power field) was estimated. Risk factors associated with abnormal screening were identified.

Results—Chart review identified 773 survivors (57% male; 67% Caucasian; 60% leukemia/lymphoma survivors; mean age at diagnosis, 5.7 years [range, birth to 17.7 years]; time from diagnosis to initial screening, 7.6 years [range, 2.3 to 21.5 years]) who underwent urinalysis. Abnormal results were found in 78 (5.3%) of 1484 total urinalyses. Multivariable analysis revealed higher dose ifosfamide (OR=6.8, 95% CI 2.9-16.0) and total body irradiation (OR=3.0, 95% CI 1.0-8.4) as significant risk factors for abnormal initial urinalysis screening.

Conclusions—Pediatric cancer survivors exposed to higher dose ifosfamide or total body irradiation may be at higher risk of abnormal findings on urinalysis screening. Targeted screening of these higher risk patients should be considered.

Keywords

genitourinary; adverse effect; childhood cancer; ifosfamide; whole body irradiation

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Introduction

The population of pediatric cancer survivors in the United States is projected to approach half a million individuals by the year 2020.[1] Patients with childhood cancer benefit from decades of research and advancements in treatment strategies which incorporate surgery, radiation and combination chemotherapies to improve outcomes.[2] These multifaceted and often intense cancer therapies can predispose patients to acute, delayed and chronic treatment-related complications.[3,4] Disease or treatment-related morbidities occurring after cancer therapy, termed “late effects”, are common among pediatric cancer survivors. [5-7] For over a decade, standardized surveillance for late effects utilizing evidence based guidelines has been made possible through publication of the *Long-Term Follow-up (LTFU) Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers* by the Children's Oncology Group (COG).

In 2003, the initial version of the COG LTFU Guidelines was released. Version 3.0 (October 2008-2014) of the COG LTFU guidelines,[8] included recommendations for annual hematuria screening for bladder malignancy or hemorrhagic cystitis, as well as annual proteinuria and blood pressure screening for nephrotoxicity in at risk survivors (Supplemental Table I). In addition to urinalysis screening, recommendations for baseline laboratory screening blood tests (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, phosphorus, blood urea nitrogen, and creatinine) for those at risk for nephrotoxicity were also included. Genitourinary late effects have been attributed to several common treatment modalities utilized in current pediatric cancer therapy including alkylator, heavy metal and antimetabolite chemotherapies; genitourinary radiation and nephrectomy.[9,10] The authors of the LTFU Guidelines anticipated urinalysis screening would identify treatment related renal insufficiency, hemorrhagic cystitis and bladder cancer in at risk survivors; however, two recent studies (Landier *et al.*, [11] Hudson *et al.*[12]) have called into question the utility and necessity of this screening recommendation. As the survivor population continues to expand, it is imperative that research be undertaken to identify survivors or subgroups of survivors who might most benefit from urinalysis screening. This study will address the yield of the COG LTFU Guidelines' recommended urinalysis screening in pediatric aged survivors, as well as attempt to identify specific exposures or demographic variables which may make urinalysis screening in this population more effective.

Methods

Cancer Survivor Program

This study utilized the clinical database maintained through the Cancer Survivor Program (CSP) of the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta (CHOA). Patients who are at least two years from completion of cancer therapies are followed in a multidisciplinary (oncology, endocrinology, psychology, and social work) cancer survivor clinic. At the time of referral to the survivor program, each survivor's medical record is reviewed and key treatment data and medical diagnoses are entered into the CSP clinical database, from which a survivor healthcare plan is prepared. Annual survivor clinic follow-up is recommended for a majority of survivors. Recommended

surveillance for late effects, based on individual exposures per the COG LTFU Guidelines, is incorporated into the survivor healthcare plan and addressed at each CSP clinic visit.

Subjects

Survivors included in this study were evaluated at least once by the CSP between January 1, 2008-March 31, 2012 and had received cancer treatments placing them at risk for kidney or bladder complications per the COG LTFU Guidelines.[8] Survivors evaluated through the CSP older than 21 years of age at their clinic visit, with a known renal diagnosis prior to screening or not at risk for genitourinary late effects per the COG LTFU Guidelines (Version 3.0) were excluded. Demographic data and treatment exposure information were abstracted from the CSP clinical database. Exposure variables collected matched those identified by the COG LTFU Guidelines as placing survivors at risk for genitourinary toxicity (Supplemental Table I). Chemotherapy doses documented in mg/kg within the medical record were converted for analysis to equivalent mg/m² dosing.[8] Incomplete exposure information was estimated by a pediatric oncologist (KWM) or pediatric radiation oncologist (NE) where applicable, based on the recorded treatment protocol when more detailed documentation was lacking. Information relating to laboratory screening and evaluations, nephrology consultation, work-up, and final diagnosis was obtained through review of each consulting physician's medical records. This study was approved by the Institutional Review Board of Children's Healthcare of Atlanta.

Urinalysis Screening

The presence of hematuria, glucosuria or proteinuria on at least one occasion constituted an abnormal urinalysis finding. Proteinuria was defined as greater than one plus (1+) protein via urine dipstick or automated analysis. Hematuria was defined as greater than five red blood cells per microscopic high power field. Glucosuria was defined as the presence of glucose via urine dipstick or automated analysis. All urinalyses results were considered evaluable for screening purposes by the CSP with the exception of contaminated specimens from menstruating females which were excluded.

Data Analysis

Demographic data were compared for significant differences using Fisher's exact test or two sample t-test, where applicable. A Monte Carlo estimation of the exact *p*-value was calculated for the diagnosis variable due to the large contingency table. The effects of various demographic and treatment variables on the estimated odds of abnormal initial urinalysis findings was determined using both univariable and multivariable logistic regression models. Predictor exposure variables were reviewed for collinearity. Collinear variables included total body irradiation (TBI) and bladder radiation exposure, TBI and hematopoietic stem cell transplant (HSCT) exposure, as well as methotrexate and high dose methotrexate exposures. Only one variable from each collinear pair was tested in a logistic regression model at one time. Predictors included in the final regression model were identified by comparing alternative models using the likelihood ratio test. Lastly, interaction terms created among each pair-wise combination of the final predictor variables in the model were tested for significance. Age at diagnosis less than five years was adjusted for in

the final multivariable regression model due to previous reports relating young age at cancer diagnosis/treatment exposure to increased risk of renal damage.[13-16] All two-sided tests included in this study were conducted using SAS version 9.4 (Cary, NC) with a definition of statistical significance set at $\alpha = 0.05$.

Results

Query of the CHOA CSP clinic database identified 821 at risk pediatric cancer survivors who met study criteria and therefore constituted the cohort for this study (Figure 1). Among the 821 survivors at risk, 773 (95.1%) underwent at least one urinalysis screening per the COG LTFU Guidelines' recommendation, 40 subjects did not have a screening urinalysis, and 8 subjects were missing urinalysis screening documented in the medical record. Demographic characteristics and treatment exposures for survivors who had normal and abnormal initial screening tests were compared (Table I). The majority of screened survivors were Caucasian non-Hispanic (67.0%), of male gender (56.9%), and were treated for a leukemia or lymphoma diagnosis (59.5%). No statistically significant difference in demographic or cancer diagnosis was noted between screened survivors. Among treatment exposures, survivors treated with higher doses of ifosfamide ($\geq 30\text{g/m}^2$) and TBI had the largest percentage of abnormal urinalyses screens, 18.8% and 9.4%, respectively. Those exposed to genitourinary surgeries, excluding nephrectomy, had no abnormal urinalyses.

Urinalysis findings on initial and subsequent screening in at risk survivors were evaluated (Table II). Of the 1484 urinalyses obtained within the study period, 78 (5.3%) of these tests had at least one abnormal finding. Proteinuria ($\geq 1+$) was the most common abnormal urinalysis finding (3.2%), followed by hematuria (1.6%) and glucosuria (1.1%). Of note, 0.6% of survivors had $\geq 2+$ proteinuria identified. Of the 78 total abnormal findings, urinary tract infections were identified in 12 patients. The proportion of survivors who yielded an abnormal initial urinalysis screening was 4.8% (37/773). Of the originally screened cohort, 355 survivors did not undergo subsequent urinalysis screenings through the CSP. Of the 736 survivors with a negative baseline screening urinalysis, 22 (3.0%) subsequently had positive screening results on second screening. Similarly, 18 of the 37 survivors (48.6%) who initially had positive screening results had negative results on at their next screening.

A total of seven survivors were referred for nephrology consultation due to abnormal urinalysis screening during the study period (Table III). Clinic charts for six of these seven survivors were available for review. Three of the seven survivors were referred for persistent hematuria, three for persistent proteinuria and one due to proteinuria and concomitant elevated blood pressure. Two of the six survivors referred to nephrology had elevated blood pressures for age and height percentile;[50] however, none of the referred survivors who had renal function testing at the same time as their urinalysis had abnormal blood urea nitrogen or creatinine levels. Testing upon nephrology consultation included repeat urinalysis, urine protein to creatinine levels and renal ultrasound. Three survivors were formally diagnosed with renal conditions including benign isolated micro-hematuria, thin basement membrane disease and orthostatic proteinuria.

Risk factors for abnormal urinalysis

Univariable logistic regression analysis of demographic, diagnosis and treatment exposures among the screened study cohort identified significant associations between abnormal initial urinalysis findings and a sarcoma diagnosis (O.R. 3.4; 95% C.I. 1.5-7.8) or higher dose (≥ 30 g/m²) ifosfamide chemotherapy exposure (O.R. 5.8; 95% C.I. 2.5-13.2) (Table IV). Multivariable logistic regression analysis identified higher dose (≥ 30 g/m²) ifosfamide chemotherapy exposure (O.R. 6.8; 95% C.I. 2.9-16.0) and TBI exposure (O.R. 3.0; 95% C.I. 1.0-8.4) as placing survivors at increased risk of an initial abnormal screening urinalysis when adjusting for age at diagnosis less than five years. No significant pair wise interaction terms among the variables included in the final multivariable model were identified. The Hosmer-Lemeshow Goodness of Fit test statistic was 0.91.

Discussion

The genitourinary tract is among several organ systems identified within the COG LTFU Guidelines⁸ for late effect screening with well documented susceptibility to commonly used cancer treatment modalities.[9,10] Similar to previous reports,[11,12] urinalysis screening for proteinuria, hematuria and/or glucosuria in our study of pediatric cancer survivors, identified as at risk for genitourinary late effects, resulted in a modest (5.3%) yield of abnormal findings. Unique to this study, screening of this large survivor cohort failed to identify any renal pathology requiring long term nephrology care. In this cohort of pediatric cancer survivors, those exposed to higher doses of ifosfamide (≥ 30 g/m²) and TBI were at highest risk for abnormal initial urinalysis screening.

While the goal of this study was urinalysis screening yield, several other findings deserve mention. First, no significant differences were identified in screening results based on gender or age at urinalysis. These findings are in contrast to several legacy studies from the general pediatric literature which showed increased yield of abnormal urinalyses in females and older children screened in the general population.[17-20] Second, age at cancer diagnosis and time off therapy did not appear to influence initial screening urinalysis findings, nor increase a survivor's risk of abnormal screening. Previous reports have linked lower age at diagnosis, a surrogate variable for young age at cancer treatment exposure, with increasing risk or severity of renal damage in pediatric cancer survivors.[13-16] Lastly, for survivors with normal initial screening, 3% had abnormal findings on screening the following year whereas nearly half of patients with an initial abnormal screening urinalysis had normal findings on the following urinalysis.

Historically, urinalysis screening for genitourinary disease in all children was endorsed by the American Academy of Pediatrics; however, several large scale population studies described a low incidence rate of chronic kidney disease in asymptomatic children. [17,19-21] Moreover, a particularly strong criticism against urinalysis screening in asymptomatic children was the high rate of false positive test results or identification of only transient abnormalities.[22,23] While pediatric cancer survivors screened according to the COG LTFU Guidelines have been exposed to renal and bladder toxic therapies,[24-47] it remains unclear if repeated urinalysis screening is sensitive enough to separate late effects of cancer therapy from the underlying transient abnormalities seen in the non-exposed pediatric

population. Prospective research comparing exposed and unexposed children is needed. In addition the inconsistent results seen in some patients with normal baseline studies and subsequent abnormal studies and vice versa suggests the need to prospectively study alternative testing such as urine calcium/creatinine ratio and urine protein/creatinine ratio to identify a screening test with higher sensitivity/specificity for treatment related renal and bladder effects.

In the recent literature, two studies have reported on the yield of Version 3.0 of the COG LTFU Guidelines' urinalysis screening recommendation.[11,12] The most comparable study by Landier *et al.*, reported the yield of 370 pediatric cancer survivors undergoing screening in an outpatient setting. Their study identified 2 of 933 total urinalyses (0.2%) with proteinuria and 31 of 845 total urinalyses (3.7 %) with hematuria. Compared to the current study, Landier *et al.* analyzed a cohort that was predominantly Hispanic, and represented an older population (age at urinalysis screening 5-57 years, time from diagnosis to screening 5-55.8 years). Their analysis utilized a different criterion for proteinuria (2+ protein on urinalysis) than the current study, and they did not attempt multivariable analysis to identify high risk subgroups. Given their findings, Landier *et al.*, concluded that elimination of screening urinalysis of survivors should be considered. Of note, comparison of proteinuria screening yield between the current research and that of Landier *et al.*, utilizing the 2+ proteinuria criterion, yielded comparable findings.

Hudson *et al.* indirectly addressed the yield of urinalysis screening by reporting prevalence rates of kidney dysfunction and hemorrhagic cystitis in a survivor population per the COG LTFU Guidelines.[12] Their study enrolled 1713 predominately Caucasian, female pediatric cancer survivors who had survived at least 10 years from their original diagnosis and followed them prospectively for 5 years in an outpatient clinical setting. All participants in that study, including those not at risk for genitourinary late effects per the COG LTFU Guidelines underwent baseline urinalysis screening. Hudson *et al.* report a 2.3% (33/1410) rate of kidney dysfunction and a 0.4% (4/1130) rate for hemorrhagic cystitis diagnosed in survivors at risk for genitourinary late effects during clinic follow-up. Multivariable analysis to determine risk of abnormal screening was not performed. Several differences between the study by Hudson *et al.* and the current analysis make it difficult to compare findings. Similar to the Landier *et al.* study, the Hudson *et al.* cohort was older than the current study. Mean age at study recruitment was 33.1 (range 18-60) years old, and participants were on average 25.6 (range 10.9-47.9) years from diagnosis at study entry. Older age has been described as a risk factor which increases ones susceptibility to chronic kidney disease.[48] The Hudson *et al.* study also utilized different screening methods and definitions than the current analysis. Screening for "kidney dysfunction" utilized both blood and urinalysis tests; therefore, a subject could be diagnosed with kidney dysfunction with normal urinalysis findings. No details on the number of red blood cells which constituted a positive urinalysis test for hemorrhagic cystitis were given; consequently, one might assume that any number of red blood cells would constitute a positive screen. Specifics regarding the results of urinalysis screening for kidney dysfunction or hemorrhagic cystitis are likewise not available for direct comparison. Of interest, 7 of the 11 survivors diagnosed with hemorrhagic cystitis and 4 of the 37 survivors diagnosed with kidney dysfunction in the

Hudson *et al.* study were reported as having no identifiable cancer treatment related risk factors for these diagnoses.

In October 2013 a new version of the COG Long-Term Follow-Up Guidelines (Version 4.0) was released. In this newest version of the guidelines annual urinalysis was removed as a screening recommendation for hemorrhagic cystitis and bladder cancer in patients exposed to cyclophosphamide, ifosfamide, and radiation exposure to the bladder, and was instead suggested as a “consideration for further testing and intervention” in patients with a positive history.[49] The recommendation for annual urinalysis and blood pressure measurements as well as baseline blood work (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, phosphorus, blood urea nitrogen, and creatinine) remain as screening for renal toxicity in patients with exposure to radiation to the kidneys and nephrotoxic chemotherapy (ifosfamide; heavy metals; methotrexate).[49] In our analysis, while TBI was a risk factor for abnormal screening, bladder and renal radiation exposure were not. However, of the five abnormal screens in TBI exposed survivors, one was due to a urinary tract infection, and all five survivors had normal concurrent blood urea nitrogen/creatinine levels. In comparison, only two survivors out of 33 who underwent bladder radiation without TBI exposure had abnormal urinalyses. This discrepancy may be related to nephrotoxic insults (ex. calcineurin inhibitors, aminoglycoside antibiotics) commonly encountered in the transplant setting. While higher-dose ifosfamide (30 mg/m^2) was associated with abnormal urinalysis screening, other nephrotoxic chemotherapy agents including lower cumulative doses of ifosfamide yielded few abnormal results. These findings emphasize the need for ongoing assessment of the screening recommendations contained within the COG LTFU Guidelines.

An incidental finding during this study was identification of urinary tract infection (UTI) in 12 survivors who underwent urinalysis screening which accounted for approximately 15% of abnormal findings. While UTI was not a primary endpoint of the study, or a reason for screening, it does highlight that screening in this population may inevitably identify an incidental finding in a portion of individuals that may require intervention. Landier *et al.*, and Hudson *et al.* do not comment on urinary tract infections identified in their studies. Despite including survivors with UTI in our abnormal screening results, the overall yield remained comparable to those published by Landier *et al.* UTI screening should not be the focus of the COG LTFU Guidelines; however, we feel not reporting these abnormal results would exclude an important finding.

The findings of the current study must be appraised acknowledging some limitations. First, this study cohort may not adequately represent the overall CHOA pediatric cancer survivor population as the study cohort was limited to those survivors who presented for CSP evaluation. Past evaluations of our survivor population compared to newly diagnosed patients have shown white race, diagnosis of a liquid versus solid tumor, geographic location closer to the institution and private insurance are all positively associated with a CSP visit. [50] Therefore survivors with sarcomas and ifosfamide exposure are likely under-represented in this analysis. Second, the time from cancer treatment completion to first screening urinalysis varied among survivors. Third, providers differed in their clinical approach after abnormal urinalysis findings were identified, with work-up ranging from no further testing to repeat urinalysis with or without further blood or urine testing. Forth, the

large number of subjects who were lost to follow-up during the study period is another recognized weakness. This censorship limited the ability for extended analysis of abnormal findings on subsequent urinalysis screening tests. Fifth, the variables included in the final model identified in this study were limited by the low number of abnormal screens. Other models may better describe the interaction between treatment exposure and abnormal urinalysis screening. Lastly, several potentially renal toxic therapies (ex. aminoglycoside antibiotics) are utilized in pediatric cancer care and conceivably could contribute to abnormal urinalysis screening in the survivor population. The focus of this study was evaluating those risk factors identified in the COG LTFU Guidelines; a detailed analysis of all possible contributing treatment related factors is beyond the scope of this study.

This study represents a detailed and focused analysis of pediatric aged cancer survivors who underwent urinalysis screening per Version 3.0 of the COG LTFU Guidelines. Our analysis confirms previously published reports which found a low yield of abnormal urinalysis findings in screened at risk survivors. This study also documents that urinalysis screening in a large survivor cohort failed to identify serious renal pathology. Our results suggest improved yield may be obtained with urinalysis screening of survivors exposed to higher doses of ifosfamide, or total body irradiation. Further study is needed to investigate the utility of urinalysis screening to identify treatment related renal pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CHOA	Children's Healthcare of Atlanta
COG	Children's Oncology Group
CSP	Cancer Survivor Program
LTFU	Long-Term Follow-Up
TBI	total body irradiation
HSCT	hematopoietic stem cell transplant

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a) COG LTFU Guidelines (Version 3.0)

Figure 1.

Survivors evaluated at the Children's Healthcare of Atlanta Cancer Survivor Program during study period.

TABLE I

Demographic characteristics and treatment exposures for survivors at risk for genitourinary complications screened at the Cancer Survivor Program clinic ($n = 773$)

	Abnormal Urinalysis^a <i>n</i> (%)	Normal Urinalysis <i>n</i> (%)	<i>p</i>-value
Total Subjects	37 (4.8%)	736 (95.2%)	
Gender			0.18
Male	17 (3.9%)	423 (96.1%)	
Female	20 (6.0%)	313 (94.0%)	
Race			0.76
Caucasian non-Hispanic	23 (4.5%)	495 (95.6%)	
Black non-Hispanic	8 (5.3%)	143 (94.7%)	
Other	6 (5.8%)	98 (94.2%)	
Mean age at diagnosis, (range)	6.2 (< 1.0-15.8)	5.7 (< 1.0-17.7)	0.53
Mean age at urinalysis, (range)	13.3 (6.0-20.6)	13.3 (2.8-21.8)	0.96
Mean time from diagnosis to urinalysis, years (range)	7.2 (2.9-13.3)	7.6 (2.3-21.5)	0.50
Mean time off therapy at time of urinalysis, years (range)	5.8 (2.0-13.0)	6.1 (2.0-20.7)	0.68
Diagnosis			0.11 ^b
Leukemia/lymphoma	18 (3.9%)	442 (96.1%)	
Central nervous system	1 (2.1%)	47 (97.9%)	
Germ cell	1 (7.7%)	12 (92.3%)	
Neuroblastoma	2 (3.2%)	60 (96.8%)	
Other solid tumors	1 (4.8%)	20 (95.2%)	
Renal tumors	4 (4.8%)	79 (95.2%)	
Sarcomas	10 (11.6%)	76 (88.4%)	
Treatment Exposures			
Hematopoietic Stem Cell Transplant			0.61
No	31 (4.6%)	641 (95.4%)	
Yes	6 (5.9%)	95 (94.1%)	
Chemotherapy			
Carboplatin			0.30
No	35 (5.2%)	645 (94.8%)	
Yes	2 (2.2%)	91 (97.8%)	
Cisplatin			1.00
No	32 (4.8%)	633 (95.2%)	
Yes	5 (4.6%)	103 (95.4%)	
Cyclophosphamide			0.40
No	12 (5.3%)	215 (94.7%)	
< 3 g/m ²	6 (3.0%)	195 (97.0%)	
3 g/m ²	19 (5.5%)	326 (94.5%)	
Ifosfamide			< 0.01
No	27 (4.0%)	651 (96.0%)	

	Abnormal Urinalysis^a <i>n</i> (%)	Normal Urinalysis <i>n</i> (%)	<i>p</i>-value
< 30 g/m ²	1 (2.1%)	46 (97.9%)	
30 g/m ²	9 (18.8%)	39 (81.2%)	
Methotrexate			0.13
No	22 (6.0%)	342 (94.0%)	
Yes	15 (3.7%)	394 (96.3%)	
High Dose Methotrexate ^c			1.00
No	30 (4.8%)	593 (95.2%)	
Yes	7 (4.7%)	143 (95.3%)	
Surgery			
Nephrectomy			1.00
No	33 (4.8%)	653 (95.2%)	
Yes	4 (4.6%)	83 (95.4%)	
Other genitourinary			-
No	37 (4.9%)	724 (95.1%)	
Yes	0 (0.0%)	12 (100.0%)	
Radiation			
Total body irradiation			0.10
No	32 (4.4%)	688 (95.6%)	
Yes	5 (9.4%)	48 (90.6%)	
Bladder radiation			0.17
No	30 (4.4%)	657 (95.6%)	
Yes	7 (8.1%)	79 (91.9%)	
Renal radiation			0.58
No	32 (4.6%)	658 (95.4%)	
Yes	5 (6.0%)	78 (94.0%)	

^a Hematuria, proteinuria or glucosuria present

^b Monte Carlo estimation for exact test

^c Any single dose 1g/m²

TABLE II

Results of urinalysis screening in at risk survivors evaluated at the CHOA CSP

Urinalysis Screening	Survivors Screened <i>n</i>	Normal Urinalysis <i>n</i> (%)	Abnormal Urinalysis ^a <i>n</i> (%)	Proteinuria <i>n</i>	Hematuria <i>n</i>	Glucosuria <i>n</i>
First	773	736 (95.2%)	37 (4.8%)	23	11	8
Second	418	391 (93.5%)	27 (6.5%)	17	9	4
Third	213	203 (95.3%)	10 (4.7%)	6	3	2
Forth	75	72 (96.0%)	3 (4.0%)	1	0	2

^a 1 abnormal finding possible

TABLE III

Work-up and final diagnosis for survivors referred for nephrology consultation

Age/Sex	Diagnosis	Treatment Exposure ^a	BUN/Cr ^b	BP ^c	Reason for Nephrology referral	Nephrology Work-Up	Nephrology Diagnosis
9/F	Wilms Tumor	CDDP, CTX, K-XRT, N	16/0.8	138/67 Elevated	Persistent Micro-Hematuria	Urinalysis Protein/Creatinine Ratio	Benign Isolated Micro-hematuria
10/F	T cell-Acute Lymphoblastic Leukemia	MTX	n/a	99/59 Normal	Persistent Micro-Hematuria	Urinalysis	Thin Basement Membrane Disease ^d
11/M	Myelodysplastic Syndromes	CTX, TBI	16/0.5	104/63 Normal	Persistent Micro-Hematuria	Urinalysis Calcium/Creatinine Ratio Renal Ultrasound	None (Normal Findings)
12/F	Neuroblastoma	CTX	12/0.6	119/72 Elevated	Persistent Proteinuria	No Records Available	
14/F	Wilms Tumor	N	19/0.9	113/73 Normal	Persistent Proteinuria Elevated Protein/Creatinine Ratio	Urinalysis 2-Protein/Creatinine Ratio	Orthostatic Proteinuria
16/F	Acute Lymphoblastic Leukemia	CTX, MTX	n/a	102/60 Normal	Persistent Proteinuria	Urinalysis 2-Protein/Creatinine Ratio	Initial visit completed without diagnosis
19/F	Acute Myeloid Leukemia	CTX, TBI	16/0.9	126/90 Elevated	Proteinuria Elevated Blood Pressure	Urinalysis Protein/Creatinine Ratio	Initial visit completed without diagnosis

^a (CDDP)carboplatin;(CTX)cyclophosphamide;(K-XRT)kidney radiation;(MTX)methotrexate;(N)nephrectomy;(TBI)total body irradiation

^b blood urea nitrogen level (mg/dL) / creatinine level (mg/dL) at survivor clinic visit immediately prior to nephrology referral

^c isolated blood pressure measurement (mmHg) at survivor clinic visit immediately prior to nephrology referral. "Elevated" blood pressure mmHg for age 18

90th percentile for age/height if age < 18, [51] and > 120/80

^d diagnosis made due to family history and laboratory findings

TABLE IV

Univariable and multivariable models predicting odds of abnormal initial screening urinalysis among pediatric cancer survivors ($n = 772$)^a

Variables	Total Urinalysis <i>n</i>	Abnormal Urinalysis <i>n</i> (%)	Univariable Odds Ratio (95% CI)	<i>p</i> -value	Multivariable Odds Ratio (95% CI)	<i>p</i> -value
Sex						
Male	439	16 (3.6%)	1			
Female	333	20 (6.0%)	1.7 (0.9-3.3)	0.13		
Race						
Caucasian non Hispanic	517	22 (4.3%)	1			
Black non Hispanic	151	8 (5.3%)	1.3 (0.5-2.9)	0.59		
Other	104	6 (5.8%)	1.4 (0.5-3.5)	0.50		
Age (years) at Diagnosis						
< 5	444	22 (5.0%)	1		1	
5-9	182	6 (3.3%)	0.7 (0.3-1.6)	0.37		
10-14	98	6 (6.1%)	1.3 (0.5-3.2)	0.64	0.7 (0.3-1.4)	0.26
15-20	48	2 (4.2%)	0.8 (0.2-3.7)	0.81		
Age (years) at Urinalysis						
< 5	17	0 (0.0%)	<i>d</i>			
5-9	195	12 (6.2%)	1.5 (0.7-3.4)	0.33		
10-14	250	11 (4.4%)	1.1 (0.5-2.4)	0.90		
15-21	310	13 (4.2%)	1			
Years off Therapy						
2-5	380	19 (5.0%)	1			
5-9	268	15 (5.6%)	1.1 (0.6-2.3)	0.74		
10-14	104	2 (1.9%)	0.4 (0.1-1.6)	0.19		
15-20	20	0 (0.0%)	<i>d</i>			
Diagnosis						
Leukemia/lymphoma	459	17 (3.7%)	1			
Central nervous system	48	1 (2.1%)	0.6 (0.1-4.3)	0.57		
Germ cell	13	1 (7.7%)	2.2 (0.3-17.6)	0.47		
Neuroblastoma	62	2 (3.2%)	0.9 (0.2-3.8)	0.85		
Other solid tumors	21	1 (4.8%)	1.3 (0.2-10.3)	0.80		
Renal tumors	83	4 (4.8%)	1.3 (0.4-4.0)	0.63		
Sarcomas	86	10 (11.6%)	3.4 (1.5-7.8)	< 0.01		
<u>Treatment Exposures</u>						
HSCT ^b						
No	671	30 (4.5%)	1			
Yes	101	6 (5.9%)	1.4 (0.5-3.3)	0.51		
Carboplatin						
No	679	34 (5.0%)	1			

Variables	Total Urinalysis <i>n</i>	Abnormal Urinalysis <i>n</i> (%)	Univariable Odds Ratio (95% CI)	<i>p</i> -value	Multivariable Odds Ratio (95% CI)	<i>p</i> -value
Cisplatin						
Yes	93	2 (2.2%)	0.4 (0.1-1.8)	0.23		
No	664	31 (4.7%)	1			
Cyclophosphamide						
Yes	108	5 (4.6%)	1.0 (0.4-2.6)	0.99		
No	227	12 (5.3%)	1			
< 3 g/m ²	201	6 (3.0%)	0.6 (0.2-1.5)	0.24		
3 g/m ²	344	18 (5.2%)	1.0 (0.5-2.1)	0.98		
Ifosfamide Exposure						
No	677	26 (3.8%)	1		1	
Dose < 30 g/m ²	47	1 (2.1%)	0.5 (0.1-4.1)	0.56	0.4 (0.0-3.0)	0.35
Dose ≥ 30 g/m ²	48	9 (18.8%)	5.8 (2.5-13.2)	< 0.01	6.8 (2.9-16.0)	< 0.01
Methotrexate						
No	363	21 (5.8%)	1			
Yes	409	15 (3.7%)	0.6 (0.3-1.2)	0.17		
High Dose Methotrexate						
No	622	29 (4.7%)	1			
Yes	150	7 (4.7%)	1.0 (0.4-2.3)	0.99		
Nephrectomy						
No	685	32 (4.7%)	1			
Yes	87	4 (4.6%)	1.0 (0.3-2.9)	0.98		
Other GU ^c Surgery						
No	760	36 (4.7%)	1			
Yes	12	0 (0.0%)	<i>d</i>			
Total Body Irradiation						
No	719	31 (4.3%)	1		1	
Yes	53	5 (9.4%)	2.3 (0.9-6.2)	0.10	3.0 (1.0-8.4)	0.04
Bladder Radiation						
No	686	29(4.2%)	1			
Yes	86	7 (8.1%)	2.0 (0.9-4.7)	0.11		
Kidney Radiation						
No	689	31 (4.5%)	1			
Yes	83	5 (6.0%)	1.4 (0.5-3.6)	0.53		

^aDiabetic patient with glucosuria removed from analysis

^bHematopoietic stem cell transplant

^cGenitourinary

^dModel failed to converge. For multivariate model: -2 Log L = 271.69, Hosmer-Lemeshow Goodness of Fit: 0.91