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Pediatric genitourinary tumors: Distribution, demographics, and outcomes

Azadeh Nazemi[1] | Siamak Daneshmand[2] | Andy Chang[3]

[1]Department of Urology, NYU Langone Medical Center, New York, USA
[2]Norris Comprehensive Cancer Center Institute of Urology, Keck School of Medicine of the University of Southern California, Los Angeles, California, USA
[3]Division of Urology, Children's Hospital Los Angeles, Los Angeles, California, USA

Correspondence
Azadeh Nazemi, NYU Langone Medical Center, 550 1st Avenue, New York, NY 10016, USA.
Email: azadeh.nazemi@nyulangone.org

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ABSTRACT

Importance: The diversity of pediatric genitourinary malignancies requires a timely resource detailing tumor characteristics and survival.

Objective: To determine the incidence, demographics, and outcomes of all pediatric genitourinary tumors within the United States.

Methods: A population-based search for patients diagnosed with genitourinary cancers under age 15 was performed using the National Cancer Institute's Surveillance, Epidemiology, and End Results 18 registry. Information on primary tumor location, histologic type, patient age, sex, year of diagnosis, race, treatment, cause of death, and survival months was extracted. Descriptive epidemiological and survival statistics were calculated for all variables.

Results: A total of 4576 cases from 1973 through 2015 were identified. The most common primary tumor sites were the kidney (80.3%), testis (12.3%), bladder (2.8%), and vagina (1.5%). Nephroblastoma (87.9%) and sarcoma (3.4%) were the most common renal malignancies. Rhabdomyosarcoma was common in the vagina, bladder, and testis at rates of 66.2%, 61.2%, and 24.6%, respectively. Germ cell tumors (71.0%) were the most common primary tumor of the testis. Ten-year overall survival (OS) for renal nephroblastoma and sarcoma was 88% and 82%, respectively. Ten-year OS for RMS of the testis was 91%, the bladder was 79%, the vagina was 79%, and the prostate was 56%. Germ cell tumor 10-year OS were 96% in the testis and 100% in the vagina.

Interpretation: A better understanding of the overall distribution and outcomes associated with pediatric genitourinary cancers allows physicians to best understand the patient's disease in the context of current frequency in a genitourinary setting and reported outcomes.

KEYWORDS

Bladder cancer, Epidemiology, Genitourinary cancers, Kidney cancer, Pediatrics, Prostate cancer, Testis cancer, Vaginal cancer

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INTRODUCTION

Childhood urologic cancers are rare entities: with kidney cancers accounting for 7% of all new cases of pediatric cancer in the United States, primary testicular tumors constituting 1% of all pediatric solid tumors, and urothelial carcinoma of the bladder having a reported incidence of 0.03% in those aged under 15 years.[1–3] The historically poor outcomes of these rare cancers have dramatically improved over the course of the past 50 years. Advances in treatment outcomes of pediatric urologic malignancies can be largely attributed to the creation of multi-institutional collaborations and clinical trials.[4,5]

Current studies focus on pediatric genitourinary cancers on an individual basis, assessing renal, testicular, and urothelial malignancies separately. These studies provide insight into tumor biology, current standards of care, and prognosis.[1–3,6–10] While there is an abundance of literature focusing on each tumor type, there is a dearth of resources providing comprehensive information on all pediatric urologic tumors. Two papers that assessed multiple pediatric urologic tumors were based on a literature review and focused on risk factors, clinical presentation, staging, and treatments options.[4,11] Other literature reviews focus on therapeutic strategies driven by developments in molecular diagnostics.[12–14] To our knowledge, there is no comprehensive large-scale study on the incidence, distribution, and outcomes of all genitourinary cancers in the pediatric population within the United States.

In this study, we use the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) registry to evaluate demographic characteristics, clinical features, and oncologic outcomes of all genitourinary cancers in a cohort of pediatric patients.

METHODS

Data source and study population

A population-based search for patients diagnosed with genitourinary cancers was performed using the NCI's SEER 18 database (www.seer.cancer.gov). The 18 registries represent 28% of the US population, and catchment areas are highly representative of the US population.[15] No internal review board approval was required for this publicly available database that provides information with no personal identifiers.

Patients diagnosed with genitourinary cancer under the age of 15 were reviewed. This age range was chosen to adequately represent a prepubertal pediatric cohort while minimizing the number of patients within the adolescent age range who may have already entered or completed puberty.[4–6,8] Site-specific codes were used to identify primary tumors by location (International Classification of Disease for Oncology, third Edition [ICD-O-3] site codes). Primary tumors that originated in the following sites were searched by ICD-O-3 codes: penis (C60.0–C60.2 and C60.8–C60.9), prostate gland (C61.9), testis (C62.0–C62.1 and C62.9), epididymis (C63.0), spermatic cord (C63.1), scrotum (C63.2), male genital organs not otherwise specified (NOS) (C63.7–C63.9), vagina NOS (C52.9), cervix (C53.0–C53.9), uterus (C54.0–C55.9), kidney (C64.9), renal pelvis (C65.9), ureter (C66.9), urinary bladder (C67.0–C67.9), and other urinary organs (C68.0–C68.1 and C68.8–C68.9). These were grouped into the following primary sites: kidney, testis, bladder, vagina, prostate, cervix and uterus, scrotum, urinary system NOS, and male genital organs NOS. Histologic ICD-O-3 codes were then reviewed for all cases and grouped into the following histologic types based on prior literature: nephroblastoma (Wilms tumor), renal cell carcinoma (RCC), transition cell carcinoma (TCC), adenocarcinoma, germ cell tumor (GCT), rhabdomyosarcoma (RMS), sarcoma, fibrosarcoma, myosarcoma/liposarcoma, malignant rhabdoid tumor, lymphoma, leukemia, neural based tumors, other renal masses, unspecified tumors, and other tumors.[5]

Study variables

The following primary data were extracted for analysis: patient age, sex, year of diagnosis, race (white, black, Hispanic, American Indian or Alaska Native, Asian or Pacific Islander, or unknown), treatment with surgery, cause of death, and survival months. Patient age was grouped into 0–4, 5–9, and 10–14 years old. Year of diagnosis was grouped by decade, into 1973–1979, 1980–1989, 1990–1999, 2000–2009, and 2010–2015. Tumor stage and grade were not analyzed, as these data were largely unavailable.

Statistical analysis

Survival analysis was performed on the most common tumor histologies within each primary tumor site, with the exception of tumor histologies with too few cases for analysis. The primary outcome was defined as a time in months from diagnosis to death from any cause for overall survival. Descriptive epidemiological and survival statistics were calculated for all variables. All statistical analyses were performed using SPSS version 21 software (IBM Corp., Armonk, NY).

RESULTS

The search identified 4756 patients under the age of 15 with genitourinary cancer from 1973 to 2015. Baseline demographic features of the five most common tumor sites are reported in Table 1. Information on age at diagnosis for each tumor histology, stratified by primary tumor location,

TABLE 1 Demographic features of the five most common tumor locations, including kidney, testis, bladder, vagina, and prostate

Variables	Overall (n = 4670)	Kidney (n = 3817)	Testis (n = 586)	Bladder (n = 134)	Vagina (n = 71)	Prostate (n = 62)
Age (years)						
0–4	3322 (71.1)	2778 (72.8)	369 (63.0)	73 (54.5)	62 (87.3)	40 (64.5)
5–9	937 (20.1)	827 (21.7)	67 (11.4)	28 (20.9)	3 (4.2)	12 (19.4)
10–14	411 (8.8)	212 (5.5)	150 (25.6)	33 (24.6)	6 (8.5)	10 (16.1)
Sex						
Male	2547 (54.1)	1817 (47.6)	586 (100.0)	82 (61.2)	0	62 (100.0)
Female	2123 (45.9)	2000 (52.4)	0	52 (38.8)	71 (100.0)	0
Race						
Non-Hispanic white	2634 (56.4)	2145 (56.2)	278 (47.5)	127 (94.8)	43 (60.6)	41 (66.1)
Non-Hispanic black	703 (15.1)	628 (16.4)	54 (9.2)	2 (1.5)	13 (18.3)	6 (9.7)
American Indian/Alaska Native	51 (1.1)	41 (1.1)	6 (1.0)	1 (0.7)	1 (1.4)	2 (3.2)
Asian/Pacific Islander	229 (4.9)	168 (4.4)	56 (9.6)	0	3 (4.2)	2 (3.2)
Hispanic	1020 (21.8)	808 (21.2)	186 (31.7)	4 (3.0)	11 (15.5)	11 (17.8)
Unknown	33 (0.7)	27 (0.7)	6 (1.0)	0	0	0
Year of diagnosis						
1973–1979	341 (7.3)	268 (7.0)	45 (7.7)	19 (14.2)	4 (5.6)	5 (8.1)
1980–1989	559 (12.0)	468 (12.3)	64 (10.9)	13 (9.7)	4 (5.6)	10 (16.1)
1990–1999	826 (17.7)	679 (17.8)	101 (17.2)	23 (17.1)	14 (19.7)	9 (14.5)
2000–2009	1812 (38.8)	1461 (38.3)	244 (41.7)	49 (36.6)	32 (45.1)	26 (41.9)
2010–2015	1132 (24.2)	941 (24.6)	132 (22.5)	30 (22.4)	17 (24.0)	12 (19.4)
Surgery						
Yes	4305 (92.2)	3582 (93.8)	574 (98.0)	96 (71.6)	29 (40.9)	24 (38.7)
No	327 (7.0)	205 (5.4)	12 (2.0)	34 (25.4)	39 (54.9)	37 (59.7)
Unknown	38 (0.8)	30 (0.8)	0	4 (3.0)	3 (4.2)	1 (1.6)

is reported in Table S1. The most common primary tumor site was the kidney (3817, 80.3%), followed by the testis (586, 12.3%), bladder (134, 2.8%), vagina (71, 1.5%), prostate (62, 1.3%), cervix and uterus (40, 0.8%), scrotum (25, 0.5%), male genital organs NOS (14, 0.3%), and urinary system NOS (7, 0.1%). The most common tumors in both males and females were renal nephroblastomas, while the remaining common tumors differed based on gender (Table 2).

The most common tumor histologies by primary tumor site are reported in Table 3. Of renal malignancies, nephroblastoma (87.9%), sarcoma (3.4%), RCC (2.1%), and nervous system (NS) tumors (2.0%) were the most common histologies. The NS tumors comprised of peripheral primitive neuroectodermal tumors, neuroblastomas, and ganglioneuroblastomas. The remaining tumor histologies included malignant rhabdoid tumor (1.9%), adenocarcinoma (0.8%), lymphoma (0.7%), other renal masses (including papillary carcinoma, collecting duct carcinoma, medullar

TABLE 2 Top five most common genitourinary tumors in females and males

Most common tumors	Number of cases, n (%)
Female	2165
Renal nephroblastoma	1797 (83.0)
Vaginal RMS	47 (2.2)
Renal cell carcinoma	42 (1.9)
Renal nervous system tumors	41 (1.9)
Renal sarcoma	38 (1.8)
Male	2591
Renal nephroblastoma	1559 (60.2)
Testicular GCT	416 (16.1)
Testicular RMS	144 (5.6)
Renal sarcoma	90 (3.5)
Prostate RMS	59 (2.3)

Abbreviations: RMS, rhabdomyosarcoma; GCT, germ cell tumor.

TABLE 3 Most common histologic types by primary tumor site

Histologic type	Number of cases, *n* (%)
Kidney	3817
Nephroblastoma	3356 (87.9)
Sarcoma	128 (3.4)
Renal cell carcinoma	80 (2.1)
Nervous system tumors	76 (2.0)
Other	177 (4.6)
Testis	586
Germ cell tumor	416 (71.0)
Rhabdomyosarcoma	144 (24.6)
Lymphoma	17 (2.9)
Leukemia	2 (0.3)
Other	7 (1.2)
Bladder	134
Rhabdomyosarcoma	82 (61.2)
Transition cell carcinoma	32 (23.9)
Lymphoma	4 (3.0)
Myosarcoma/liposarcoma	3 (2.2)
Other	13 (9.7)
Vagina	71
Rhabdomyosarcoma	47 (66.2)
Germ cell tumor	19 (26.8)
Sarcoma	3 (4.2)
Other	2 (2.8)
Prostate	62
Rhabdomyosarcoma	59 (95.2)
Sarcoma	1 (1.6)
Adenocarcinoma	1 (1.6)
Germ cell tumor	1 (1.6)

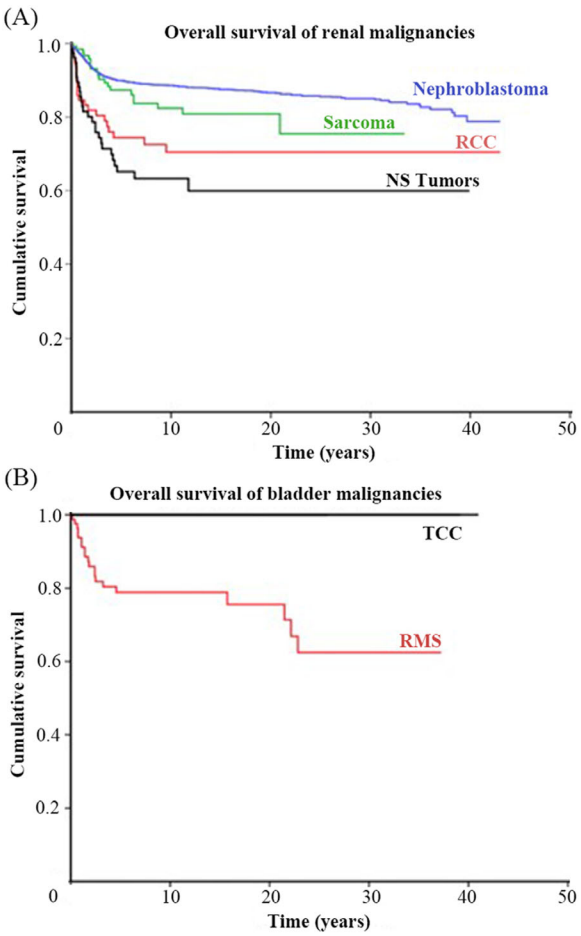

FIGURE 1 Survival analysis of patients with tumors of the (A) kidney and (B) bladder, stratified by the most common tumor histologic types. RCC, renal cell carcinoma; NS, nervous system; TCC, transition cell carcinoma; RMS, rhabdomyosarcoma.

carcinoma, granular carcinoma, and malignant cystic nephroma) (0.4%), unspecified neoplasm (0.3%), RMS (0.2%), and other tumor types (0.3%).

Of bladder malignancies, the most common histologic types included RMS (61.2%), TCC (23.9%), lymphoma (3.0%), and myosarcoma/liposarcoma (2.2%). These were followed in frequency by unspecified neoplasm (2.1%), sarcoma (1.5%), malignant rhabdoid tumor (1.5%), and other tumor types (4.6%). Testicular malignancies were predominantly GCT (71.0%), RMS (24.6%), lymphoma (2.9%), and leukemia (0.3%). The remaining tumor histologies included adenocarcinoma (0.2%), myosarcoma/liposarcoma (0.2%), unspecified neoplasm (0.2%), and other tumor types (0.6%). Vaginal malignancies were predominantly RMS (66.2%), followed by GCT (26.8%), sarcomas (4.2%) and other tumor types (2.8%). Of prostate malignancies, the most common tumor histologies were RMS (95.2%), sarcoma (1.6%), adenocarcinoma (1.6%), and GCT (1.6%).

Surgery was performed in 4393 (92.4%) patients and was not performed in 325 (6.8%) patients. The use of surgery was unknown in 38 (0.8%) of patients. When analyzed by tumor location, surgery was performed in 93.8% of kidney tumors, 98.0% of testis tumors, 71.6% of bladder tumors, and 38.7% of prostate tumors.

Overall survival (OS) for the most common tumor histologies with a primary tumor site within the urinary tract is shown in Figure 1. OS of genital tumors, stratified by the most common histologic types, is presented in Figure 2. The 5 and 10-year OS for the most common tumor histologies, stratified by primary tumor site, are reported in Table 4. From 1973 through 2015, there was an improvement in OS for renal nephroblastomas ($P < 0.001$), renal NS tumors ($P = 0.001$), testicular lymphomas ($P = 0.001$),

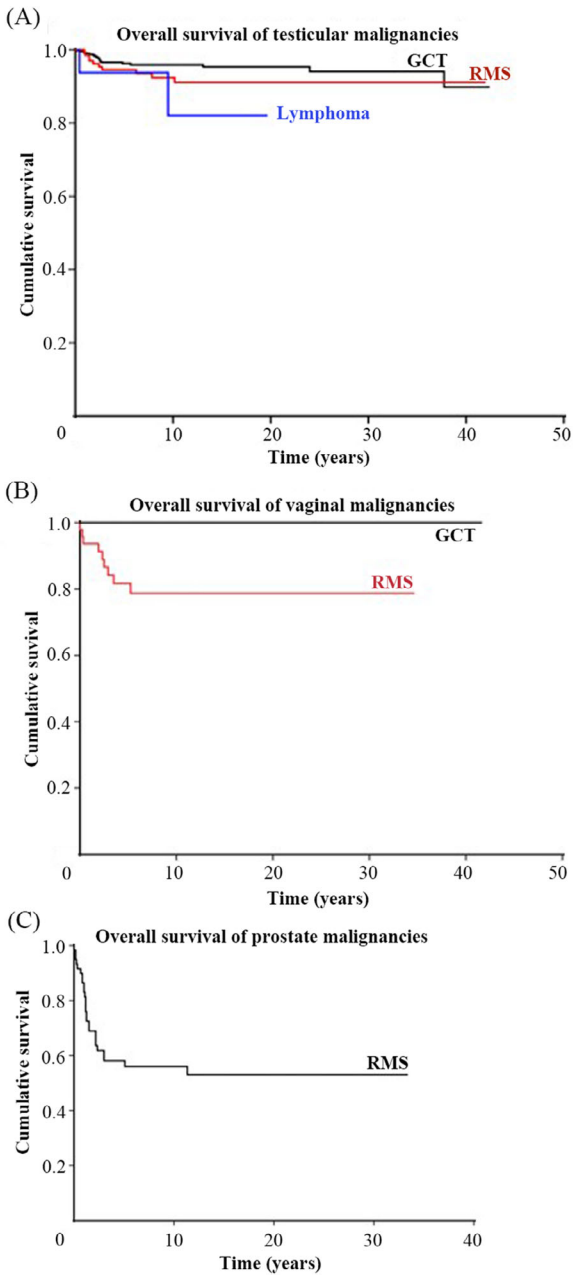

FIGURE 2 Kaplan-Meier survival analysis of patients with genital malignancies of the (A) testis, (B) vagina, and (C) prostate, stratified by the most common tumor histologic types. GCT, germ cell tumor; RMS, rhabdomyosarcoma.

testicular GCT ($P = 0.007$), and prostate RMS ($P = 0.021$). There was no difference in OS across generations for RCC, renal sarcomas, testicular RMS, or any bladder or vaginal malignancies.

DISCUSSION

Childhood urologic cancers are overall rare. The current literature assessing all pediatric genitourinary cancers is extremely limited, as most studies focus on each malignancy individually. A better understanding of the overall distribution and outcomes associated with genitourinary cancers in the pediatric population is important because it allows physicians to best understand the patient's disease in the context of current frequency and reported outcomes. Our study is the first to analyze population-level data on demographics, tumor distribution, histologic type, and oncologic outcomes within a pediatric population. In doing so, we provide comprehensive information on genitourinary tumors within the United States.

TABLE 4 Survival data for tumors diagnosed from 1973–2015 by primary tumor location and histologic type

	Overall survival	
Histologic type	**5-year**	**10-year**
Kidney		
Nephroblastoma	89%	88%
Sarcoma	87%	82%
Renal cell carcinoma	74%	70%
Nervous system tumors	65%	63%
Testis		
Germ cell tumor	96%	96%
Rhabdomyosarcoma	95%	91%
Bladder		
Rhabdomyosarcoma	79%	79%
Transition cell carcinoma	100%	100%
Vagina		
Rhabdomyosarcoma	79%	79%
Germ cell tumor	100%	100%
Prostate		
Rhabdomyosarcoma	56%	56%

We found that the majority of pediatric genitourinary tumors presented in the kidney. The most common renal malignancy was nephroblastoma, and our reported incidence of 87.9% was within the previously reported rates of 95% and 75% for this malignancy.[1,4,8,14] RCC comprises 2% to 5% of all pediatric renal masses and sarcomas comprise approximately 3% of pediatric renal tumors.[4,8,16]

Nephroblastomas have a reported median age of onset of 3.5 years, with 80% of cases occurring in patients under 5 years of age.[4] A study using National Cancer Database data reported that 5% of RCC cases were presented in patients under 5 years of age.[8] Demographically, renal malignancies have been found to affect females at slightly higher rates than males and affect non-Hispanic whites and non-Hispanic blacks at disproportionately higher rates than Asians.[4,8]

We reported that over 90% of patients with renal malignancies received surgery. Standard therapy for nephroblastomas is surgery and chemotherapy, which is often vincristine, dactinomycin, and doxorubicin. In many cases, radiation therapy is also used based on tumor stage, histology, and molecular factors.[12] Sarcomas of the kidney also benefit from surgical resection with adjuvant therapy.[12] Complete resection has the largest impact on the outcome for RCC, as it is notoriously radiation and chemoresistant.[12]

The second most common primary tumor location was the testis. These tumors have a bimodal distribution with a peak in infancy and a second, substantially larger peak in adolescence and young adulthood.[2,4,6,14] Our finding of highest incidence between ages 0 and 4 falls within the first peak, as our analysis of a pediatric cohort, utilized a cutoff of 15 years of age to exclude postpubertal patients. Consistent with literature, our results found the majority of patients were white, Hispanic, Asian or Pacific Islander, and black.[2,10]

Germ cell tumors comprise the majority of testicular malignancies.[10] RMS of the testis/paratestis was the third most common site of RMS in our analysis, after RMS of the prostate and bladder which reportedly account for approximately 5% to 10% of all RMS.[4,17] Treatment of GCTs differs by primary location. Almost all patients with GCTs of the testis received surgical intervention, as the current standard of care for prepubertal patients is radical or partial orchiectomy.[6] Patients with vaginal GCTs benefit from partial vaginectomy, if possible, in conjunction with chemotherapy with etoposide, cisplatin, and bleomycin.[18]

The third most common primary tumor site was the bladder. About 60% of bladder tumors occurred in males, in concordance with another study that reported that 65% of patients under age 25 with bladder tumors were male.[19] RMS is the most common bladder tumor of childhood and has a bimodal age distribution and greater than half of the cases occur at a median of 2 years of age.[4] Urothelial carcinomas of the bladder are rare entities in pediatric patients, affecting 0.1% to 0.4% of the population in the first two decades of life, but there are no reports on its relative frequency compared to other bladder cancers.[20] Our findings provided further insight on this, as we reported that TCC comprised 23.9% of all bladder tumors.

Tumors of the vagina were the next most common in incidence, presenting in a predominantly non-Hispanic white population. Our findings of only 47 cases of RMS in the vagina are consistent with reports that the vagina, cervix, and uterus are relatively rare sites for this tumor type.[4] Vaginal RMS has a bimodal age distribution with the first peak between age 1 and 4.[4] Administration of vincristine, dactinomycin, and cyclophosphamide is the current standard chemotherapy.[21] If microscopic residual disease is found, brachytherapy or external beam radiotherapy can be used.[11] Exenteration is rarely performed and is reserved for patients who have failed previous therapies.[11] GCTs of the vagina are treated with surgery followed by platinum-based chemotherapy, except in dysgerminomas and pure immature teratomas of lower grades for which surgery alone is generally curative.[21]

Prostatic tumors were the fifth most common incidence among all pediatric genitourinary tumors. The prostate is reported to be one of the most common sties of RMS, and we reported a 95.2% rate of these tumors.[4] In congruence with the age distribution of RMS, we reported that the majority of patients with prostatic malignancies presented before 5 years of age.

Our survival analysis of each tumor type by primary site was largely in agreement with previously reported survival data. OS for nephroblastoma are reported to exceed 90%.[1] For RCC, one review reported 5-year OS of 72% to 87%.[4,16] RCCs and sarcomas, though rare, account for a disproportionate number of relapses and deaths among renal malignancies.[12]

Testicular malignancies have survival rates above 90% with no difference between the different histologic types.[2] Specifically, among those with testicular/paratesticular RMS, 5-year OS reportedly exceed 80%.[7] In contrast, RMS in the bladder and prostate are considered unfavorable sites, while outcomes of vaginal RMS are more favorable.[4,21] Amongst bladder tumors, we found that all 5 and 10-year OS for TCC were 100%, which strongly supported the well-established finding of improved overall disease-free survival in the pediatric population compared to adult patients.[19]

The improved OS over time seen in renal nephroblastomas has been shown by the National Wilms' Tumor Study.[22] The improvement is primarily a result of available chemotherapy, improvements in radiation oncology, supportive care, and improved surgical and anesthetic techniques.[23] Over the last four decades, five clinical trials have shown improved survival using combination dactinomycin with vincristine as the building block of therapy, adding doxorubicin in patients with more advanced disease, and selective/targeted use of radiation therapy.[24]

The trend of improved OS in testicular GCT over time may be attributable to improved imaging, the International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification, treatment regimens tailored to risk group, and better adherence to the use of cisplatin-etoposide-based regimen as primary treatments. Improved salvage therapies also play a role.[25] Improved survival over time for prostate RMS, compared to other RMS, is likely a result of earlier detection with improved imaging techniques. It was interesting

to note that some tumor histologies did not exhibit a significant temporal trend in survival.

Cancer is a major cause of death in children, with pediatric solid tumors comprising almost half of these cases. Solid tumors in children have distinct clinical features and outcomes compared to those in adults.[26] Tumors originating in the genitourinary tract are among the most common of these, with nephroblastomas and genitourinary RMS being the second and third most common extracranial pediatric solid tumors, behind neuroblastomas.[4] The data presented in this paper highlights the importance of a focused evaluation of pediatric tumors by site and histology, and addresses the need for a greater understanding of pediatric tumors arising in the genitourinary system.

There are several limitations to address in this study, including an inherent risk of bias with a retrospective observational study. Specifically, relying on the SEER database presents its own set of limitations, including large amounts of missing information on tumor grade and stage, as well as a lack of information on treatments such as radiation and chemotherapy. Additionally, as with any large database across multiple institutions, the SEER database is subject to miscoding and may have data that is mislabeled and would not provide accurate results. Nevertheless, this is the first large-scale study to present a comprehensive review of the demographics, incidence, and survival outcomes of genitourinary malignancies in a pediatric population within the United States. Given the paucity of resources providing all-inclusive information on these rare malignancies, the information here adds to the current literature in a meaningful way.

In conclusion, pediatric genitourinary malignancies are a rare entity, and comprehensive studies on the prevalence of genitourinary tumors are lacking in the literature. We reported that tumors most commonly present in the kidney, testis, bladder, vagina, and prostate. Nephroblastomas were the most common renal malignancies, while RMS were most prevalent in the vagina, bladder, and prostate. Ten-year survival rates were most dismal for prostatic tumors and varied by histologic type among primary tumor sites. Our results provide a framework for clinicians to best counsel patients, by providing clinicians a better understanding of the disease prevalence and outcomes in the US population.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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