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A California Cancer Registry Analysis of Urothelial and Non-urothelial Bladder Cancer Subtypes: Epidemiology, Treatment, and Survival

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Abstract

Bladder cancer outcome data are limited. We evaluated survival trends for bladder cancer subtypes using the California Cancer Registry (n [72,452). On multivariate analysis, non-urothelial histology was independently associated with poorer disease-specific and overall survival. These data characterize the epidemiologic trends of the common bladder cancer subtypes and indicate that small-cell and squamous cell subtypes carry the poorest prognosis.

Introduction: We evaluated epidemiologic trends and survival for bladder cancer histologic subtypes in California patients by comparing urothelial carcinoma of the bladder (UCB) and non-urothelial subtypes including squamous cell carcinoma (SCC), adenocarcinoma (ADC), and small-cell carcinoma (SmCC).

Materials and Methods: The California Cancer Registry (CCR) was queried for incident bladder cancer cases from 1988 to 2012. Epidemiologic trends basedon tumor histology were described. The primary outcome was disease-specific survival (DSS). Kaplan-Meier and multivariable Cox regression survival analyses were performed.

Results: A total of 72,452 bladder cancer cases (66,260 UCB, 1390 SCC, 587 ADC, 370 SmCC, and 3845 other) were included. The median age was 72 years (range, 18-109 years). ADC was more common in younger patients. Male:female ratios varied among cancer types (3.1:1 in UCB, 2.9:1 in SmCC, 1.6:1 in ADC, and 0.9:1 in SCC). Most non-urothelial cases (> 60%) presented at advanced stages, whereas most UCB cases (80.6%) were localized. Kaplan-Meier analysis revealed the best 5-year DSS and overall survival (OS) in UCB, whereas the worst outcomes were seen with SCC and SmCC ($P < .0001$). Multivariable analysis controlling for age, gender, tumor stage, and grade demonstrated that non-urothelial histologic subtypes were associated with significantly worse DSS compared with UCB (SCC hazard ratio [HR], 2.612; SmCC HR, 1.641; and ADC HR, 1.459; $P < .0001$). Conclusions: Non-urothelial bladder cancers have worse oncologic outcomes than UCB in California patients. SCC and SmCC are associated with the worst DSS based on univariable and multivariable analyses.

Introduction

Bladder cancer comprises 81,190 cancer cases and 17,240 deaths per year in the United States.[1] Of the bladder cancer histopathologic subtypes, urothelial carcinoma (UCB) is responsible for greater than 90% of cases.[2] Non-urothelial types include squamous cell carcinoma (SCC) (2%), adenocarcinoma (ADC) (1%), and small-cell carcinoma (SmCC) (0.5%-1%).[3,4] In Western countries, the pathophysiology of SCC is related to chronic bladder inflammation and irritation, such as that associated with indwelling urinary catheters.[5] SCC was historically the leading form of bladder cancer in regions such as the Middle East and North Africa owing to endemic schistosomiasis, but the incidence has decreased owing to anti-bilharzial treatments and snail control.[6] ADC is also more common in regions with schistosomiasis, and it is particularly associated with patients with bladder exstrophy.[3] SmCC is an uncommon neuroendocrine tumor resembling small-cell carcinoma of the lung. It typically presents in older Caucasian males and is associated with dismal survival outcomes compared with UCB.[7]

The rarity of non-urothelial bladder cancer subtypes largely precludes large-scale epidemiologic analysis and clinical trials. Furthermore, conflicting results have been reported regarding survival between urothelial and non-urothelial types. Some studies have suggested that, in addition to presenting at more advanced stages and being more aggressive,[5,8,9] non-urothelial subtypes also have worse survival than urothelial carcinoma.[2,10] However, other studies have found comparable survival probability between urothelial and non-urothelial subtypes, including SCC and ADC.[11-13]

Given the paucity of consistent data addressing survival outcomes for non-urothelial bladder cancer variants, we sought to conduct a large, population-based analysis in order to compare the epidemiology and survival for bladder cancer subtypes. We obtained data through the California Cancer Registry (CCR) in order to evaluate the incidence, clinicopathologic features, and survival rates of the most common bladder cancer subtypes. To our knowledge, this is the first report comparing the tumor characteristics and survival for UCB, SCC, ADC, and SmCC in a large, population-based analysis of California patients.

Materials and Methods

The principles of the Declaration of Helsinki were followed. This was an institutional review board-exempt, retrospective study. We obtained data from the CCR, a large, population-based cancer surveillance system containing data reported to the Cancer Surveillance Section of the Department of Public Health from health care facilities. The CCR was queried for all incident bladder cancer cases from January 1, 1988 to December 31, 2012. The exclusion criteria were age < 18 years, 2 or more cancers, and diagnosis based solely on the death certificate or autopsy.

Entries were classified by histologic subtype according to their International Classification of Diseases for Oncology, Third Revision codes. The following International Classification of Diseases codes were used: UCB: 8120-8122, 8130, and 8131; SCC:8070-8072, 8075, 8083, 8084, and 8052; ADC: 8140-8147 and 8255-8490; SmCC: 8040-8049. Histologic subtypes accounting for less than 0.5% of bladder cancer cases were classified as ‘Other.’ Demographic and clinical information including age, gender, race, and treatment (surgical, chemotherapy, radiotherapy, and immunotherapy) were retrieved for each subtype.

Tumor stage was grouped according to 1 of 4 categories: localized, regional, distant, and unknown. The CCR's classification of tumor stage follows the TNM classification of bladder cancer.[14] Localized indicates that the cancer is confined to the primary site, regional indicates the spread of cancer to lymph nodes adjacent to the bladder within the true pelvis and/or along the common iliac artery, and distant indicates metastasis. Tumor grade was characterized in accordance with the CCR's 2-grade system for bladder cancer as low-grade (I and II), high-grade (III and IV), or unknown.

The primary outcome measure in this study was disease-specific survival (DSS), defined as the time interval from date of diagnosis to date of death from bladder cancer. The secondary outcome was overall survival (OS), defined as the interval from date of diagnosis to date of death by all causes.

Univariable Kaplan-Meier analysis was performed to evaluate OS and DSS based on tumor histology. Multivariable Cox proportional hazards regression analyses were performed to evaluate survival based on histology and to elucidate independent prognostic factors for each subtype. After controlling for age, gender, stage, and grade, the prognostic significance of SCC, ADC, SmCC, and other nonurothelial histologic types was assessed.

All statistical output was generated using SAS Version 9.4 (SAS Institute, Cary, NC). All statistical tests were 2-tailed, and $P < .05$ was considered statistically significant for all tests.

Results

A total of 72,452 bladder cancer cases from the CCR were included in this analysis. Demographic data, tumor pathologic characteristics, and treatment modalities are described in Table 1. UCB histology accounted for 66,260 (91.4%) cases, whereas 1390 (1.9%) presented with SCC, 587 (0.8%) with ADC, and 370 (0.5%) with SmCC.

The median patient age was 72 years (range, 18-109 years). Age and gender differed significantly among the histologic subtypes ($P < .0001$). ADC histology was less common in patients 70 years and older (37.1%), whereas 38% of patients with ADC were less than 60 years of age at diagnosis. Among all cases, 53,957 (74.5%) were male and 18,495 (25.5%) were female. Males made up a higher proportion of cases for all subtypes except for SCC, of which 728 (52.4%) patients were female compared with 662 (47.6%) males. ADC was the most common non-urothelial subtype among non-white races (31%).

Clinical and pathologic features also differed significantly according to histologic subtype. Most UCB cases were localized (81%), whereas SCC, ADC, and SmCC cases more frequently presented with regional or remote spread. The highest proportion of regional spread was seen in cases of SCC (32.4%) and ADC (32%). The proportion of cases with distant metastasis was highest in SmCC (25%). High-grade tumors were more common than low-grade across all subtypes. All cases of SmCC were high-grade.

Extirpative surgery was performed in 92.9% of all cases (95% of UCB, 85.3% of SCC, 91.8% of ADC, and 88.4% of SmCC). Non-urothelial subtypes had higher utilization of chemotherapy and radiation. Chemotherapy was utilized in 49.2% of SmCC, 26.9% of ADC, 19.6% of SCC, and 13.2% of UCB cases. Radiation, which was primarily given postoperatively for all subtypes, was utilized in 21.9% of SmCC, 16.3% of SCC, 13.5% of ADC, and 5.9% of UCB cases.

Table 1 Demographics and Clinical Characteristics (Percentages Organized by Column)

	UCB, n (%)	SCC, n (%)	ADC, n (%)	SmCC, n (%)	Other, n (%)	Total, n	*P* Value
Total	66,260 (91.4)	1390 (1.9)	587 (0.8)	370 (0.5)	3845 (5.3)	72,452	
Age, y							
18-49	3757 (5.7)	110 (7.9)	115 (19.6)	17 (4.6)	270 (7.0)	4269 (5.9)	<.0001
50-59	8091 (12.2)	155 (11.1)	110 (18.7)	45 (12.2)	399 (10.4)	8800 (12.1)	
60-69	16,817 (25.4)	301 (21.7)	144 (24.5)	82 (22.2)	747 (19.4)	18,091 (25.0)	
70+	37,595 (56.7)	824 (59.3)	218 (37.1)	226 (61.1)	2429 (63.2)	41,292 (57.0)	
Gender							
Female	16,084 (24.3)	728 (52.4)	226 (38.5)	96 (25.9)	1361 (35.4)	18,495 (25.5)	<.0001
Male	50,176 (75.7)	662 (47.6)	361 (61.5)	274 (74.1)	2484 (64.6)	53,957 (74.5)	
Race							
White	53,947 (81.4)	1057 (76.0)	405 (69.0)	294 (79.5)	2980 (77.5)	58,683 (81.0)	<.0001
Black	2371 (3.6)	110 (7.9)	51 (8.7)	19 (5.1)	188 (4.9)	2739 (3.8)	
Hispanic	5669 (8.6)	155 (11.1)	91 (15.5)	35 (9.5)	402 (10.5)	6352 (8.8)	
Asian/PI	3453 (5.2)	51 (3.7)	36 (6.1)	21 (5.7)	223 (5.8)	3784 (5.2)	
Others	820 (1.2)	17 (1.2)	4 (0.7)	1 (0.3)	52 (1.4)	894 (1.2)	
Stage							
Localized	53,405 (80.6)	575 (41.4)	240 (40.9)	158 (42.7)	1635 (42.5)	56,013 (77.3)	<.0001
Regional	7389 (11.2)	451 (32.4)	188 (32.0)	112 (30.3)	465 (12.1)	8605 (11.9)	
Remote	3113 (4.7)	287 (20.6)	146 (24.9)	87 (23.5)	565 (14.7)	4198 (5.8)	
Unknown	2353 (3.5)	77 (5.5)	13 (2.2)	13 (3.5)	1180 (30.7)	3636 (5.0)	
Grade							
I	6787 (10.2)	107 (7.7)	59 (10.1)	0	156 (4.1)	7109 (9.8)	<.0001
II	19,776 (29.8)	446 (32.1)	103 (17.5)	0	483 (12.6)	20,808 (28.7)	
III	20,750 (31.3)	544 (39.1)	235 (40.0)	102 (27.6)	826 (21.5)	22,457 (31.0)	
IV	14,683 (22.2)	122 (8.8)	84 (14.3)	176 (47.6)	483 (12.6)	15,548 (21.5)	
Unknown	4264 (6.4)	171 (12.3)	106 (18.1)	92 (24.9)	1897 (49.3)	6530 (9.0)	
Treatment — surgical							
Surgery performed	62,916 (95.0)	1186 (85.3)	539 (91.8)	327 (88.4)	2351 (61.1)	67,319 (92.9)	<.0001
No surgery	3344 (5.0)	204 (14.7)	48 (8.2)	43 (11.6)	1494 (38.9)	4499 (6.2)	
Surgery unknown/CI	366	23	4	2	239	634	
PLND performed	7204	353	203	88	392	8240	
Treatment — chemotherapy							
Chemotherapy	8754 (13.2)	272 (19.6)	158 (26.9)	182 (49.2)	489 (12.7)	9855 (13.6)	<.0001
No chemotherapy	56,734 (85.6)	1078 (77.6)	416 (70.9)	172 (46.5)	3188 (82.9)	61,588 (85.0)	
Chemotherapy unknown/CI	361	16	5	7	143	532	
Treatment — radiation							
Radiation-total	3900 (5.9)	227 (16.3)	79 (13.5)	81 (21.9)	286 (7.4)	4573 (6.3)	<.0001
No radiation	62,345 (94.1)	1163 (83.7)	507 (86.4)	289 (78.1)	3537 (92.0)	67,841 (93.6)	
Unknown	15	0	1	0	22	38	
Preoperative only	116	7	6	3	4	136	
Postoperative only	3399	184	58	71	207	3919	

Kaplan-Meier analysis comparing histologic subtypes is presented in Figure 1. UCB exhibited the best survival of all subtypes, with a 5-year DSS of 77.3% and OS of 57.2%. Non-urothelial subtypes were associated with significantly poorer DSS and OS compared with UCB ($P < .0001$). SCC and SmCC were associated with the worst 5-year DSS at 33.6% and 33.7%, respectively. ADC was associated with a 5-year DSS of 50.3%. The worst 5-year OS was again observed for SmCC (21.7%) and SCC (22.2%). The 5-year OS was 33.8% for ADC.

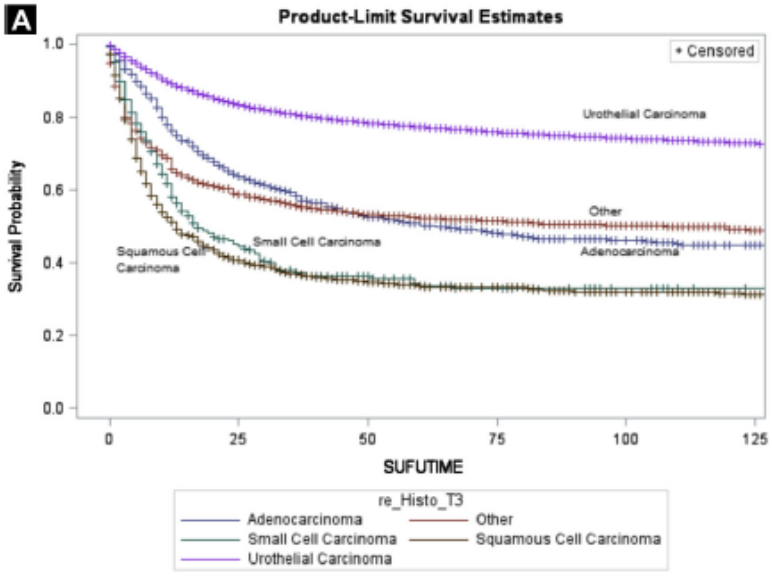
Multivariable Cox regression analysis is presented in Table 2. Older age, female gender, and regional and remote stages were associated with worse survival. Multivariable analysis controlling for tumor stage, grade, age, and gender revealed that non-urothelial histology was independently associated with poorer DSS and OS. Among non-urothelial tumors, SCC histology prognosticated the worst DSS, and both SmCC and ADC were also associated with significantly worse survival compared with UCB.

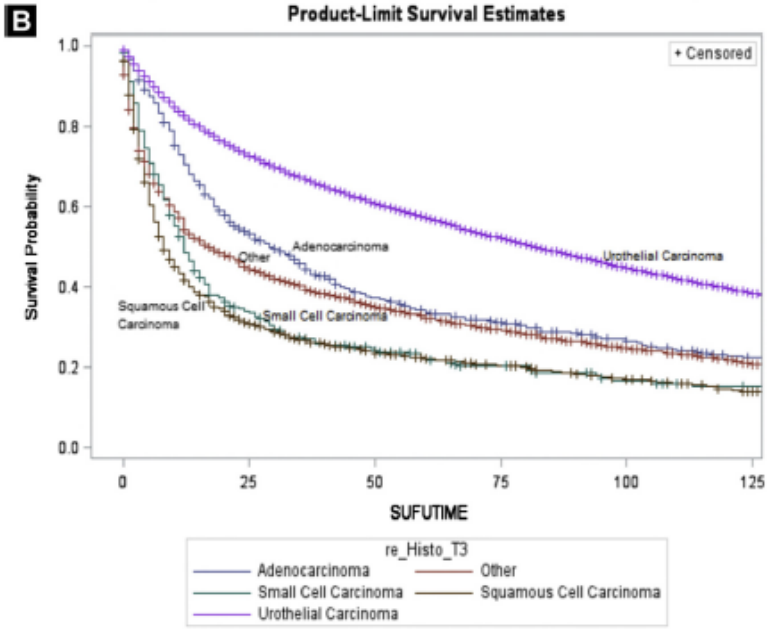
Discussion

Non-urothelial bladder carcinomas comprise a significant proportion of all bladder cancer cases. In the current study, we found that 8.6% of cases in the CCR were non-urothelial subtypes, which is consistent with the estimated national rate of 10%.[3,4] Our findings also suggest that non-urothelial cancer is associated with poorer oncologic outcomes in comparison with UCB, which is consistent with prior studies.[2,10] Generally, UCB is less aggressive than non-urothelial variants and presents at an earlier stage.[5,8,9] Indeed, we observed that UCB presents at lower stages more frequently, with a 2-fold higher rate of localized tumors compared with the non-urothelial subtypes. On multivariable analysis controlling for patient age, gender, and tumor stage and grade, nonurothelial histology prognosticated worse outcomes than UCB. We also found that UCB had the highest male:female ratio and affected the largest proportion of white patients. Previously, non-UCB bladder cancer has been found to be more common in female and black patients[2,15]; similarly, our data indicate that nonurothelial subtypes affect a larger proportion of these patients compared with white patients.

SCC was the most common non-urothelial histology, accounting for 2% of CCR cases, and demonstrated the worst DSS. Conflicting data exist regarding survival outcomes between SCC and UCB.[2,10-12,16] Previous studies have also reported a worse prognosis for SCC compared with UCB.[10,16-18] Our data also indicate that SCC has the lowest rate of chemotherapy use and the second-lowest rate of radiation use among the subtypes. This was expected, as radical cystectomy and urinary diversion is the standard treatment for SCC, and SCC does not respond well to chemotherapy or radiation alone.[5] Although adjuvant radiotherapy and chemotherapy may potentially improve outcomes in bilharzial SCC,[19,20] further trials are needed to determine their efficacy in non-bilharzial SCC. Furthermore, a recent study of programmed death-ligand 1 expression in SCC suggested that immunotherapy may serve as a viable treatment option in the future.[21] Regarding demographic patterns, SCC affected the highest proportion of females in our cohort and was the only subtype with a female:male ratio > 1. This is likely owing to the fact that non-bilharzial SCC is associated with risk factors that both genders are exposedto, including chronic inflammation, recurrent UTI, and cigarette smoking.[5]

Figure 1 Kaplan-Meier Analysis (Survival Time in Months). A, Disease-specific Survival (P < .0001); B, Overall Survival (*P* < .0001)





Histology	5-year DSS	5-year OS	Median DSS	Median OS	Mean DSS	Mean OS
UCB	77.3%	57.2%	*	82	221.61	114.29
Other	52.4%	32.4%	108	17	125.74	67.05
ADC	50.3%	33.8%	65	29	106.26	80.24
SmCC	33.7%	21.7%	17	12	57.44	47.53
SCC	33.6%	22.2%	13	8	86.73	48.21

*Not available due to censoring

Abbreviations: ADC = adenocarcinoma; DSS ¼ disease-specific survival; OS = overall survival; SCC = squamous cell carcinoma; SmCC = small-cell carcinoma; UCB = urothelial carcinoma of the bladder.

Table 2 Multivariable Cox Proportional Hazards

Variables	DSS				OS			
	HR	95% HR Confidence Limits		*P* Value	HR	95% HR Confidence Limits		*P* Value
Age								
18-49	Reference				Reference			
50-59	1.146	1.053	1.247	.0016	1.678	1.575	1.788	<.0001
60-69	1.31	1.212	1.416	<.0001	2.707	2.554	2.869	<.0001
70+	2.215	2.058	2.385	<.0001	5.989	5.66	6.338	<.0001
Gender								
Male	Reference				Reference			
Female	1.234	1.195	1.273	<.0001	1.007	0.987	1.027	<.0001
Stage								
Localized	Reference				Reference			
Regional	2.902	2.795	3.013	<.0001	1.91	1.859	1.963	<.0001
Remote	9.435	9.028	9.859	<.0001	6.332	6.112	6.559	<.0001
Grade								
I	Reference				Reference			
II	2.231	2.003	2.484	<.0001	1.138	1.1	1.178	<.0001
III	6.337	5.714	7.027	<.0001	1.65	1.594	1.707	<.0001
IV	7.061	6.358	7.841	<.0001	1.734	1.671	1.8	<.0001
Histology								
UCB	Reference				Reference			
SCC	2.612	2.429	2.808	<.0001	1.855	1.749	1.967	<.0001
ADC	1.459	1.337	1.592	<.0001	1.327	1.241	1.418	<.0001
SmCC	1.641	1.429	1.885	<.0001	1.413	1.26	1.584	<.0001
Other	1.922	1.809	2.043	<.0001	1.596	1.53	1.665	<.0001

Abbreviations: ADC = adenocarcinoma; DSS = disease-specific survival (5-year); HR = hazard ratio; OS = overall survival (5-year); SCC = squamous cell carcinoma; SmCC = small-cell carcinoma; UCB = urothelial carcinoma of the bladder.

ADC was the second-most common non-urothelial histology, presenting in 0.8% of CCR cases; this is similar to other reports in the United States, which range from 0.5% to 2%.[4,9] The 5-year DSS for ADC in our cohort was 50.3%, which is similar to other reported figures.[4,22] On multivariable analysis, ADC prognosticated the best DSS among the non-urothelial subtypes. Based on data from the Surveillance, Epidemiology, and End Results (SEER) database, Patel and colleagues also reported that ADC has the best survival outcomes for non-urothelial bladder cancer, though their cohort revealed a more comparable OS and DSS between ADC and UCB.[10] Survival appears to be dependent on the specific variant of ADC as well as the treatment method, as outcomes are worse for non-urachal ADC and better for groups that undergo postoperative radiotherapy.[23,24] Urachal ADC makes up 10% of ADC cases and has a better prognosis than non-urachal ADC,[22] with the standard treatment consisting of partial cystectomy and resection of the urachal ligaments and umbilicus. Non-urachal cancer is often diagnosed at a later age and is treated with radical cystectomy.[24] Of all the histologic subtypes in our cohort, ADC had the highest proportion of cases in younger people, which is explained by its association with bladder exstrophy.[25] ADC was also seen at rates almost twice that of UCB in black and Hispanic individuals; although this association has been reported previously, its cause is unknown.[10,26]

SmCC was the third most common non-urothelial histology and showed one of the poorest survival outcomes along with SCC. SmCC had the lowest 5-year OS of all the bladder

cancer types, which is consistent with previous reports.[10] SmCC is known as an aggressive entity, with 95% of cases diagnosed at stage T2 or higher.[27] Indeed, all SmCC tumors in our study were high grade (grade III and IV). Owing to its poor prognosis, aggressive, multimodality treatment is used more frequently than with other bladder cancer variants.[4] Accordingly, in this study, SmCC had the highest rates of chemotherapy and radiation use. SmCC also had the highest male:female ratio (3:1) among the non-urothelial subtypes, which was similar to that for UCB. This coincides with other ranging from 3:1 to 3.3:1.[28,29]

Our analysis is limited by the population-based nature of the study. This study lacked a central pathology review. Other potential limitations include our inability to control for other UCB and SCC prognostic factors including lymphovascular invasion and lymph node metastases, as these were not consistently reported in the CCR. Also, bladder cancer treatment approaches have advanced over time, which may impact survival outcomes and confound our analysis, as we did not control for treatment strategy. We also did not account for changes over time in known risk factors such as the use of indwelling catheters. Our findings are also difficult to generalize to other populations, as the data in this study are collected from California patients only. This may lessen their relevance to other regions of the United States or to regions where bilharziasis is endemic; however, our data were consistent with previously reported trends from United States databases. Despite these limitations, our findings provide information regarding the outcomes of both urothelial and non-urothelial variants of bladder cancer, which is of value given the difficult nature of studying non-urothelial subtypes owing to their relative infrequency in the United States. To our knowledge, this report is the largest for bladder cancer outcomes specific to California. The current study corroborates other reports showing poorer DSS and OS for non-urothelial bladder cancer subtypes compared with UCB, particularly SmCC and SCC. However, the need remains for well-designed prospective studies in order to obtain more detailed treatment and outcome data for bladder cancer subtypes.

Conclusions

Based on data from the CCR, non-urothelial subtypes of bladder cancer are associated with worse oncologic outcomes compared with UCB. Overall, SCC and SmCC have the most unfavorable survival outcomes. Non-urothelial subtypes present more frequently at an advanced stage and exhibit a different age and gender predilection compared with UCB.

Clinical Practice Points

- In the current study, we found that 8.6% of bladder cancer cases in the CCR were non-urothelial subtypes, which is consistent with the estimated national rate of 10%. Our findings suggest that non-urothelial bladder cancer is associated with poorer oncologic outcomes in comparison to UCB, which is also consistent with prior studies.
- Although conflicting data exist regarding survival outcomes between SCC and urothelial subtypes, this large population-based study indicates that SCC and SmCC of the bladder are associated with the lowest 5-year DSS and OS, respectively.
- Relatively more black and Hispanic patients presented with adenocarcinoma histology compared with white patients; the cause of this phenomenon remains unknown. Importantly, the female:male ratio for the prevalence of SCC was greater than 1, reinforcing the need for vigilance in evaluating at-risk female patients.

- To our knowledge, this is the only population-based study of California patients that characterizes the epidemiologic and survival trends of the most common bladder cancer subtypes.

Disclosure

The authors have stated that they have no conflicts of interest.

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