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Survival analysis of small cell carcinomas of the genitourinary system

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ABSTRACT

Due to low incidence, there are no large prospective studies or clinical trials for small cell carcinoma (SCC) of the genitourinary system (GU), and most data are extrapolated from SCC of the lung. Using the SEER database, we analyzed incidence trends, overall survival, and cancer-specific survival using the log-rank test. Analysis of variables was performed using the Cox proportional hazards regression model. The analysis showed that SCC of the bladder and prostate were the most common types of GU SCC, with 1836 and 606 cases, respectively. In 2018, the incidence of SCC of the bladder and prostate was twice that of 2010 ($P < 0.001$). The overall survival and cancer-specific survival of patients with SCC of the bladder were significantly longer than those of patients with SCC of the prostate ($P < 0.0001$). SCC bladder patients with advanced age, more extensive growth, lymph node involvement, no surgical intervention, and the presence of the metastasis had worse survival outcomes ($P < 0.05$). The Asian/Pacific Islander race provided some survival benefits for patients with SCC of the bladder ($P < 0.05$). For patients with SCC of the prostate, only advanced age was a risk factor for poor outcomes ($P < 0.05$).

KEYWORDS Small cell carcinoma; small cell carcinoma of bladder; small cell carcinoma of prostate; survival analysis.

Small cell carcinoma (SCC) of the lung was first described in 1926.[1] However, extrapulmonary SCC was not described until more than half a century later when it was recognized in the bladder[2] and prostate.[3] SCC of the genitourinary (GU) system is rare, accounting for <2% of bladder and prostate cancers. GU SCC often presents at an advanced stage and has a poor prognosis. The survival of patients with SCC is significantly shorter than that of patients with conventional transitional cell carcinoma of the bladder and adenocarcinoma of the prostate.[4–10] Given the low incidence, there are no large retrospective studies or clinical trials to provide additional information about the demographics of these patients, survival data based on stage of the disease at the time of presentation, or racial and socioeconomic variables. In this study, we used the Surveillance, Epidemiology and End Result Program (SEER) database to examine the incidence, prevalence, and trends of GU SCC, as well as the effect of racial, geographic, and socioeconomic factors on treatment outcomes.

METHODS

All data for the present study were collected from the SEER database of the National Cancer Institute.[11] This database is a nationally representative longitudinal survey covering approximately 30% of the US population, with information on 9 million cancer cases and with more than 470,000 new cases added to the database each year.[12–14] For the current study, we retrieved the data from the SEER database, 18 registries, November 2020 submission (2000–2018). SEER data were de-identified, and data analysis for research purposes did not require the approval of the institutional review board or informed consent from the participants. Codes covering the GU system were initially used to query the database (C60.1–C68.9). The following tumor location sites were initially queried: penis, prostate gland, testis, epididymis, spermatic cord, scrotum, kidney, renal pelvis, ureter, urinary bladder, and not other specified tumors of the male genitals. Tumors arising from the female genital tract were excluded from this study. The histology codes ICD-O 8041–8043 were used to identify cases related to SCC. It is

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worth mentioning that neuroendocrine proliferation of adenocarcinoma with various levels of Ki-67 expression (as high as 50% or more) could very closely resemble pure SCC. This tumor usually develops as small foci of a neuroendocrine-expressing cell within adenocarcinoma primarily or secondary to androgen deprivation therapy, radiation therapy, abiraterone, or enzalutamide.[15–17] However, the SEER tracks a separate ICD-O code, 8574/3, to collect data about properly recognized cases. No age cut-off was used in this study. The goal of this study was to analyze tumors with an incidence of >100 cases recorded in the database.

We used overall survival (OS), defined as the time from diagnosis to death from any cause, and cancer-specific survival (CSS), defined as the time from diagnosis to death from cancer, as primary outcomes in our study. Descriptive statistics were performed for all variables. Incidence trends were assessed using linear regression. OS and CSS curves were created using the Kaplan-Meier method, and the log-rank test was used to detect statistical differences between the groups. Cox proportional hazards regression was used to assess the covariables, providing hazard ratios and 95% confidence intervals for OS and CSS. The following variables were assessed: sex, race, tumor stage, presence of lymph node invasion, presence of metastasis, income, tumor grade, and area of residence. Races were defined as coded in SEER: white, black, Asian/Pacific Islander, American Indian, Hispanic, and unknown race. Income was analyzed in $5000 increments from <$35,000 to >$75,000. The SEER database defines residential areas based on population as rural and metropolitan, with further subdivision of metropolitan areas based on population. Tumor stage was classified as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated. Information on tumor stage (recorded as T1, T2, T3, T4), presence of lymph node involvement, and metastasis was obtained from the American Joint Committee on Cancer data recorded in the SEER database and was uniform among all American Joint Committee on Cancer editions used by the SEER database within the defined period.

Statistical significance was set at $P < 0.05$. The statistical software GraphPad PRISM 9.3.1 (San Diego, CA) and SEER stat software was used for data analysis.

RESULTS

We first used the SEER database to analyze the most common locations of SCC in the GU system. SCC was most common in the bladder (SCCB) (C67.0–C67.9), with 1836 reported cases, followed by the prostate (SCCP), with 606 cases reported. Other less common locations included the kidneys (C64.9) with 79 cases, ureters (C66.9) with 53 cases, renal pelvis (C65.9) with 22 cases, and urethra (C68.0) with 18 cases. Male genital organs had seven cases combined (C60.9, C62.1, C63.2, and C63.9), and there were six cases of overlapping (C68.8) and nonspecified tumors (C68.9). Notably, no patients <20 years were found in the database. Given the relatively higher number of cases, we focused our analysis on SCCB and SCCP for further statistical analysis.

Table 1. Incidence of small cell carcinoma of the genitourinary tract

Year	All cases	Bladder	Prostate
2000	0.9	0.66 (73.33%)	0.24 (26.67%)
2001	1.02	0.73 (71.57%)	0.29 (28.43%)
2002	0.93	0.68 (73.12%)	0.24 (25.8%)
2003	0.99	0.68 (68.7%)	0.31 (31.3%)
2004	1.12	0.93 (83.03%)	0.19 (16.97%)
2005	1.19	0.9 (75.63%)	0.29 (24.37%)
2006	1.25	0.96 (76.8%)	0.29 (23.2%)
2007	1.4	1.04 (74.29%)	0.36 (25.61%)
2008	1.36	1.09 (80.15%)	0.27 (19.15%)
2009	1.57	1.24 (78.98%)	0.33 (21.02%)
2010	1.87	1.48 (79.14%)	0.39 (20.86%)
2011	1.56	1.19 (76.28%)	0.37 (23.72%)
2012	1.67	1.33 (79.64%)	0.34 (20.36%)
2013	1.54	1.16 (75.32%)	0.38 (24.68%)
2014	1.75	1.32 (75.43%)	0.43 (24.57%)
2015	1.86	1.28 (68.82%)	0.58 (31.18%)
2016	1.93	1.59 (82.38%)	0.34 (17.62%)
2017	1.98	1.42 (71.72%)	0.56 (28.28%)
2018	1.95	1.39 (71.28%)	0.56 (28.72%)

Throughout the reviewed period, the combined incidence of SCCB and SCCP was 15.1 cases per 1 million. The number of cases steadily increased over time at both locations. Thus, the incidence of SCCB increased from 0.66 in 2000 to 1.39 in 2018 ($P < 0.001$). SCCP growth was also statistically significant, increasing from 0.24 in 2000 to 0.56 in 2018 ($P < 0.001$) *(Table 1)*.

SCCB was predominantly found in white men. At the time of diagnosis, most patients had T2 disease, without lymph node involvement, and with metastasis. In SCCP, the distribution between racial groups was similar. Patients with SCCP were most likely to present in stage T4. Most patients had lymph node invasion and metastasis. Patients with SCCB and SCCP were likely to have poor or undifferentiated tumors. Compared with SCCB, fewer SCCP patients received surgical treatment. The patients' income and area of living were fairly similarly distributed between the two groups. The demographic results of the SCCB and SCCP groups are reported in detail in *Table 2*.

We next compared OS and CSS between SCCB and SCCP. The median OS for patients with SCCB was 11 months compared to 9 months for SCCP (hazard ratio 0.75, $P < 0.001$). Similarly, the median CSS for SCCB was 14 months compared to 10 months for SCCP (hazard ratio 0.68, $P < 0.0001$) *(Figure 1)*. There was no significant difference in OS or CSS of

Table 2. Characteristics of patients with small cell carcinoma of the genitourinary tract based on tumor site

Variable	All (N = 2469)	Bladder (*N* = 1863)	Prostate (*N* = 606)
Median age at diagnosis (years)	72.15 ± 0.4	72.58 ± 0.47	70.85 ± 0.83
Male	2084 (84.41%)	1478 (79.33%)	606 (100%)
Female	385 (15.59%)	385 (20.67%)	–
White	2016 (81.65%)	1568 (84.17%)	448 (73.93%)
Black	159 (6.44%)	104 (5.58%)	55 (9.08%)
America Indian/ Alaskan Native	11 (0.45%)	5 (0.27%)	6 (0.99%)
Asian/Pacific Islanders	102 (4.13%)	65 (3.49%)	37 (6.11%)
Hispanics	178 (7.21%)	120 (6.44%)	58 (9.57%)
Unknown	3 (0.12%)	1 (0.05%)	2 (0.33%)
T stage			
T is	5 (0.2%)	5 (0.27%)	0 (0%)
T1	335 (13.57%)	271 (14.55%)	64 (10.56%)
T2	996 (40.34%)	879 (40.34%)	117 (19.31%)
T3	347 (14.05%)	285 (15.3%)	62 (10.23%)
T4	381 (15.43%)	212 (11.38%)	169 (27.89%)
Unknown	405 (15.4%)	211 (11.33%)	194 (32.01%)
Lymph node disease			
No	1520 (61.56%)	1286 (69.03%)	234 (38.61%)
Yes	537 (21.75%)	339 (18.2%)	198 (32.67%)
Unknown	412 (16.69%)	238 (12.78%)	174 (28.71%)
Metastatic disease			
No	1537 (62.5%)	1357 (72.84%)	180 (29.7%)
Yes	820 (33.21%)	443 (23.78%)	377 (62.21%)
Unknown	112 (4.54%)	63 (3.38%)	49 (8.09%)
Grade			
Grade 1	1 (0.04%)	1 (0.05%)	0 (0%)
Grade 2	26 (1.05%)	7 (0.38%)	19 (3.14%)
Grade 3	559 (22.64%)	409 (21.95%)	150 (24.75%)
Grade 4	731 (29.61%)	661 (35.48%)	70 (11.55%)
Unknown	1152 (46.66%)	785 (42.14%)	367 (60.56%)
Surgical resection			
Yes	1810 (73.31%)	1647 (88.41%)	163 (26.9%)
No	648 (26.25%)	208 (11.16%)	440 (72.61%)
Unknown	11 (0.45%)	8 (0.43%)	3 (0.5%)
Location			
Metropolitan area >1m	1406 (56.95%)	1043 (55.98%)	363 (59.9%)
Metropolitan area 250k–1m	581 (23.53%)	456 (24.48%)	125 (20.63%)
Metropolitan <250k	181 (7.33%)	145 (7.78%)	36 (5.94%)
Non-metropolitan adjacent to metropolitan area	166 (6.72%)	124 (6.66%)	42 (6.93%)
Non-metropolitan-non-adjacent	135 (5.47%)	95 (5.1%)	40 (6.6%)
Income			
<$35,000	35 (1.42%)	23 (1.23%)	12 (1.98%)
$35,000–$39,999	49 (.98%)	35 (1.88%)	14 (2.31%)
$40,000–$44,999	85 (3.44%)	71 (3.81%)	14 (2.31%)
$45,000–$49,999	192 (7.78%)	146 (7.84%)	46 (7.59%)
$50,000–$54,999	232 (9.4%)	191 (10.25%)	41 (6.77%)
$55,000–$59,999	193 (7.82%)	150 (8.05%)	43 (7.1%)
$60,000–$64,999	335 (13.57%)	245 (13.15%)	90 (14.85%)
$65,000–$69,999	348 (14.09%)	259 (13.9%)	89 (14.69%)
$70,000–$74,999	213 (8.63%)	155 (8.32%)	58 (9.57%)
>$75,000	787 (31.88%)	588 (31.56%)	199 (32.84%)

patients diagnosed between 2000 and 2009 compared with those diagnosed between 2010 and 2018. The survival progressively worsened for more advanced stages for both SCCB and SCCP (Kaplan-Meier methods, $P < 0.05$; *Table 3*, *Figure 2*).

Multivariate analysis showed that advanced age, advanced tumor spread, positive node status, presence of metastasis, and no surgical intervention were associated with worse outcomes *(Table 4)* in patients with SCCB. Those of Asian/Pacific Islander descent had better survival. Area of residence and income did not significantly impact survival. For patients with SCCP, only advanced age was associated with worse outcomes. Higher tumor stage, lymph node involvement, presence of metastasis, as well as absence of surgical intervention were not associated with worse OS or CSS. Area of residence was not associated with better or worse survival for either OS or CSS. For OS, Asian/Pacific Islander ethnicity and low income were associated with worse outcomes *(Table 4)*.

DISCUSSION

We reviewed multiple available database studies and retrospective analyses of SCCB. These studies included 20 to 409 patients and reported the most common age of onset in the 60s to 70s and a male predominance. Better survival among all studies was associated with younger age, lesser extent of the tumor, absence of lymph node involvement, and absence of

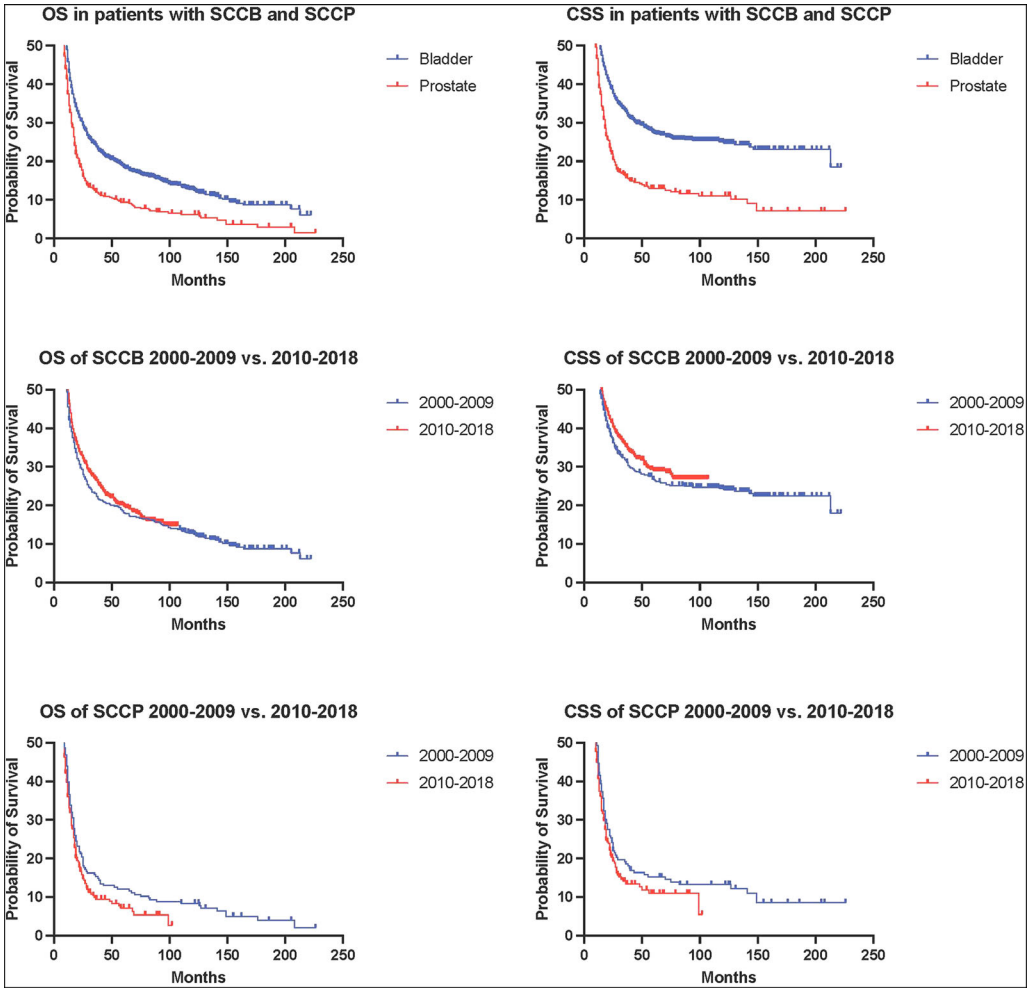

Figure 1. Overall survival (OS) and cancer-specific survival (CSS) in patients with small cell cancer of the bladder (CSSB) and small cell cancer of the prostate (SCCP), based on the time of initial diagnosis, either 2000 to 2009 or 2010 to 2018.

metastasis. OS ranged from to 10 to 15.7 months, which is consistent with the 11-month OS seen in our study. Survival improved with the administration of any treatment, as reported in our study. Most studies that assessed a combination of chemotherapy with surgery (cystectomy or transurethral resection of bladder tumor), radiotherapy, or both reported better prognosis than with chemotherapy alone.[5,8,18–26]

Similarly to the other GU malignancies, worse survival was seen in patients with SCCP who had advanced age.[8] However, our study did not find any benefit of surgical intervention in patients with SCCP. Other variables such as tumor extent, lymph node involvement, metastasis, race, or income did not seem to be predictors for poor prognosis. These results are partially supported by those of another SEER-based study performed by Wang et al, which did not support the benefits of surgical intervention in patients with SCCP. Also, the study performed by Wang et al analyzed the effect of chemotherapy, which has been shown to improve survival. However, factors such as extent of disease, lymph node involvement, and the presence of metastasis were associated with worse survival, which is not in line with our results. Notably, this study only reviewed patients with primary SCCP, which may account for some differences in the results.[27]

Table 3. Survival for small cell cancer of the bladder and prostate based on the extent of disease

	Overall survival		Cancer-specific survival	
SCC type	Months	Hazard ratio [95% CI]	Months	Hazard ratio [95% CI]
Bladder				
Localized	17	Reference	28	Reference
Regional	13	1.24 [1.075–1.432]	16	1.378 [1.65–1.63]
Distant	6	3.655 [3.122–4.279]	7	4.548 [3.809–5.432]
Prostate				
Localized	17	Reference	20	Reference
Regional	11	1.619 [1.151–2.278]	12	1.672 [1.148–2.436]
Distant	7	2.151 [1.682–2.75]	8	2.231 [1.715–2.902]

The SEER database does not collect laboratory values of the patients. However, it was noted that elevated lactate dehydrogenase is a factor associated with poor outcomes in SCC of the

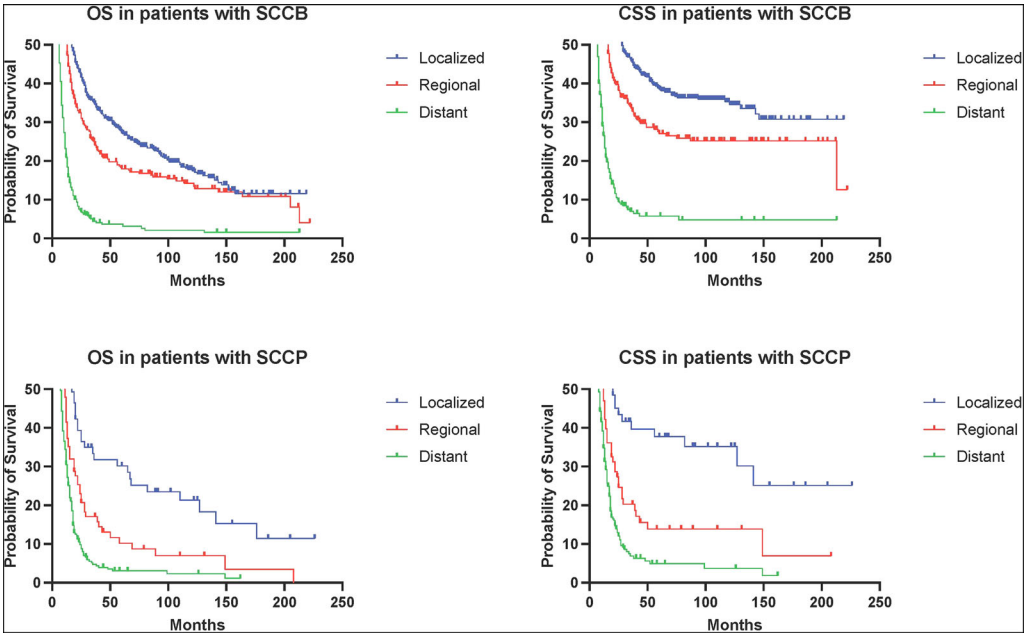

Figure 2. Overall survival (OS) and cancer-specific survival (CSS) in patients with different extent of disease at the time of diagnosis, for both small cell cancer of the bladder (SCCB) and small cell cancer of the prostate (SCCP).

Table 4. Cox regression analysis of overall and cancer-specific survival in patients with bladder and prostate small cell carcinoma

	Hazard ratio (95% confidence interval)			
	Overall survival		Cancer–specific survival	
Variable	**Bladder**	**Prostate**	**Bladder**	**Prostate**
Age	**1.037 (1.031–1.043)**	0.9980 (0.9753–1.022)	**1.03 (1.023–1.036)**	**1.03 (1.012–1.048)**
Sex (vs. female)	1.094 (0.9619–1.249)	–	1.008 (0.8721–1.171)	–
Race (vs. white)				
Black	1.192 (0.9484–1.48)	0.8519 (0.3287–1.975)	1.171 (0.9017–1.497)	1.315 (0.6989–2.353)
Hispanic	0.923 (0.7329–1.147)	0.9134 (0.424–1.814)	0.9257 (0.771–1.184)	0.808 (0.4556–1.359)
Asian/Pacific Islander	**0.6899 (0.4986–0.9285)**	**4.119 (1.784–8.671)**	**0.5721 (0.3785–0.8268)**	1.86 (0.9415–3.374)
American Indian/Alaskan Native	0.9234 (0.2837–2.188)	–	0.7824 (0.1926–2.073)	1.961 (0.1082–9.669)
Grade (vs. poorly differentiated)				
Undifferentiated	1.065 (0.9869–1.434)	1.151 (0.3487–3.269)	1.092 (0.9379–1.281)	0.9856 (0.4612–1.965)
Moderately differentiated	0.8427 (0.2984–1.852)	1.059 (0.3543–2.965)	0.4591 (0.07566–1.449)	0.4713 (0.1918–1.068)
T stage (vs. T1)				
T2	**1.264 (1.078–1.49)**	1.084 (0.4639–2.654)	**1.459 (1.204–1.78)**	1.014 (0.5497–1.92)
T3	**1.387 (1.142–1.685)**	1.726 (0.6887–4.441)	**1.574 (1.251–1.986)**	0.9072 (0.4368–1.863)

(*Continued on next page*)

Table 4. Continued

Variable	Hazard ratio (95% confidence interval)			
	Overall survival		Cancer–specific survival	
	Bladder	Prostate	Bladder	Prostate
T4	**1.474 (1.185–1.831)**	1.375 (0.5836–3.434)	**1.620 (1.256–2.89)**	1.044 (0.5768–1.955)
Node positive (vs. node negative)	**1.241 (1.071–1.434)**	1.759 (0.9795–3.225)	**1.323 (1.124–1.552)**	1.179 (0.7608–1.832)
Metastasis (vs. no metastasis)	**2.334 (2.026–2.684)**	1.207 (0.6832–2.159)	**2.728 (2.334–3.18)**	1.271 (0.8431–1.928)
No surgery (vs. surgery)	**1.38 (1.148–1.651)**	1.122 (0.6243–2.083)	**1.343 (1.031–1.664)**	0.7853 (0.5358–1.165)
Income (vs. <$35,000)				
$35,000–$39,999	0.6873 (0.3383–1.236)	**0.1050 (0.0051–0.765)**	**0.4722 (0.2442–0.9123)**	0.5171 (0.1196–2.101)
$40,000–$44,999	0.8146 (0.4969–1.387)	0.2413 (0.03036–1.344)	0.6998 (0.4095–1.241)	0.2651 (0.03564–1.352)
$45,000–$49,999	0.7600 (0.4734–1.275)	**0.1957 (0.03966–0.9339)**	0.6265 (0.3755–1.093)	0.4446 (0.1362–1.603)
$50,000–$54,999	0.6636 (0.4152–1.11)	**0.0789 (0.0138–0.415)**	**0.5085 (0.3055–0.8826)**	0.3803 (0.1130–1.385)
$55,000–$59,999	0.6076 (0.3771–1.022)	**0.2104 (0.0298–0.7996)**	**0.5134 (0.3063–0.8994)**	0.6315 (0.2–2.2225)
$60,000–$64,999	0.6539 (0.4081–1.096)	**0.08837 (0.01764–0.4397)**	**0.5605 (0.3369–0.9769)**	0.3606 (0.11–1.322)
$65,000–69,999	0.6793 (0.4214–1.145)	0.2338 (0.05189–1.065)	0.5880 (0.3508–1.032)	0.5718 (0.1795–2.050)
$70,000–74,999	0.6426 (0.3942–1.092)	**0.07735 (0.01352–0.4231)**	**0.5589 (0.329–0.991)**	0.3776 (0.1061–1.462)
>$75,000	0.6473 (0.4057–1.082)	**0.1672 (0.03785–0.7537)**	**0.5714 (0.3452–0.9925)**	0.5578 (0.1808–1.957)
Area of living (vs. counties not adjacent to metropolitan area)				
Metropolitan area >1m	0.9642 (0.7136–1.309)	0.8447 (0.2769–3.152)	1.032 (0.761–1.422)	0.7039 (0.3251–1.651)
Metropolitan area 250k–1m	0.9181 (0.6808–1.242)	1.343 (0.433–4.975)	1.069 (0.7853–1.479)	0.8367 (0.381–1.966)
Metropolitan <250k	0.9881 (0.7589–1.301)	0.9471 (0.2082–4.177)	1.049 (0.7371–1.504)	0.7149 (0.2651–1.891)
Non–metropolitan adjacent to metropolitan area	0.9871 (0.761–1.296)	1.033 (0.3034–3.69)	0.9823 (0.6948–1.396)	0.807 (0.3363–1.955)

lung and GU system.[4,8,28] Low albumin was discovered to be an additional poor prognostic factor in patients with SCCP.[28]

Despite the benefits that SEER provides for epidemiological research, there are several limitations to the results presented here. SEER database analysis is a retrospective process, and the risk of selection bias is present. Moreover, the database was created to include more ethnic or racial minorities, so the results of the analysis can be skewed toward those populations. Information on patient comorbidities was absent, and information could be missing within each variable. Detailed information on radiation therapy and surgical treatment is not available within the SEER database. If a patient had a procedure or treatment outside of the location that participated in the SEER data collection, this information may be missing as well.[12,29,30] Change of pathology classifications could potentially lead to a perceived increased incidence of GU SCC. Also, although the SEER database covers a huge population, the limited number of patients with SCCP might lead to an inability to reach statistical significance in variables other than age.

In conclusion, SCC is a rare cancer type that accounts for approximately 2% of all GU cancers. However, the incidence of the most common locations of GU SCC has steadily increased and nearly doubled within the last 18 years. The OS and CSS of patients with SCCB were significantly longer than those of patients with SCCP. SCCB patients with advanced age, more extensive growth, lymph node involvement, and no surgical intervention had worse survival outcomes. The Asian/Pacific Islander race is associated with some survival benefit for patients with SCCB. For patients with SCCP, only advanced age was a risk factor for poor CSS outcomes. For OS, Asian/Pacific Islander race and income of <$35,000 in addition to advanced age were associated with worse survival. The extent of tumor growth, lymph node involvement status, and the presence of metastasis did not affect OS and CSS for patients with SCCP. Despite recent advancements in medicine, the survival of patients with GU SCC has not changed in the second decade of the 21st century compared with the first.

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