Curr Oncol, Vol. 20, pp. 258-264; doi: http://dx.doi.org/10.3747/co.20.1338

ORIGINAL ARTICLE

Genitourinary small-cell carcinoma: a single-institution experience

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ABSTRACT

Background

Small-cell carcinomas (SCCS) of the genitourinary (GU) tract are rare systemic diseases, and there is no standard treatment strategy for patients with this malignancy. The objectives of the present study were to report the management and outcome of patients with SCC of the GU tract treated at a tertiary-care institution from 1982 to 2009.

Methods

In a chart review of all patients diagnosed with SCC of the GU tract between 1982 and 2009, data on demographics, clinical and pathologic characteristics, treatment, and patient outcomes were collected.

Results

The 58 patients identified had SCC in the following primary sites: urinary bladder ($n = 35$), prostate ($n = 17$), and upper urinary tract ($n = 6$). In 38 patients (66%), the SCC was of pure histology; in the remainder, histology was mixed. Overall, 28 patients had limited-stage disease; 24 had extensive-stage disease; and staging was unknown in 6 patients. Median survival for the entire cohort was 7.5 months, with extensive-stage disease being identified as a poor prognostic factor (survival was 22.0 months for limited-stage patients and 4.1 months for extensive-stage patients, $p < 0.001$). Based on site, prostate patients fared worst, with a median survival of only 5.1 months. Compared with best supportive care, treatment was associated with better outcomes (median survival: 12.3 months vs. 2.3 months, $p < 0.0001$).

Conclusions

Small-cell cancer of the GU tract is an aggressive cancer, with a poor prognosis overall. Although there is no standard of care, patients should be treated using a multimodality approach analogous to that used in the treatment of small-cell lung cancer.

KEY WORDS

Small-cell carcinoma, genitourinary tract, radiation, chemotherapy, surgery, retrospective review

1. INTRODUCTION

Extrapulmonary small-cell carcinomas (EPSCCS) are uncommon neoplasms that account for 2.5%–5.0% of all small-cell carcinomas (SCCS)[1]. Extrapulmonary SCC has been described in various organs, including these genitourinary (GU) tract sites[2–9]: the urinary bladder (UB), which is the most common site for GU SCC; the prostate; and the upper urinary tract (UUT), including the ureters and kidneys[5,6,9].

The cause of SCC is uncertain, and in general, this malignancy is more aggressive than conventional transitional-cell carcinomas of the GU tract. As with other EPSCCS, GU SCC has many features in common with small-cell lung carcinoma (SCLC), including aggressive behaviour (as manifested by the occurrence of metastases early in the course of the disease) and frequent but short-lasting responses to chemotherapy, except in limited-stage (LS) disease[10–13].

Currently, knowledge of GU SCC is limited, primarily because of the relative rarity of the tumour and the various organs of origin. Available knowledge is based mainly on small retrospective series and case reports[2–9]. Because no randomized trials have studied patients with GU SCC, there is no standard approach for managing the malignancy. Treatment algorithms are based on trials performed in patients with SCLC, a much more common site for this cancer, with a very similar pathology. Patients with LS disease are typically treated with surgery followed by chemotherapy or radiotherapy (or both); patients with extensive-stage (ES) are offered palliative

treatment using chemotherapy with or without radiotherapy, or supportive care. The present study is an outcome analysis of patients with GU SCC treated at our institution.

2. METHODS

2.1 Data Source

After approval was received from the Alberta Cancer Research Ethics Committee, we searched the Alberta Cancer Registry for patients with a diagnosis of primary SCC of the kidney, ureter, urinary bladder, or prostate who were seen at the Cross Cancer Institute, Edmonton, Alberta, Canada, between January 1982 and December 2009. Patients were included if they had a pathologically confirmed diagnosis of primary SCC of the GU tract and if there was no suggestion of a pulmonary primary on imaging studies. Histologic criteria for diagnosis were based on the World Health Organization (WHO) classification of SCLC[14]. Mixed SCC was defined as a tumour containing SCC and non-SCC components, regardless of the proportion of the latter.

Patients were staged using the Veterans Administration Lung Study Group staging for SCLC, in which a primary tumour volume with or without regional lymph node involvement was considered LS if it could be encompassed within a tolerable radiation port; all others were ES. Age, sex, smoking history, Eastern Cooperative Oncology Group performance status, primary tumour site, stage (LS vs. ES), histologic component, sites of metastasis, treatment modalities, and survival data were determined from patient records. Clinical response was recorded as complete, partial, stable disease, and progressive disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1[16].

2.2 Statistical Analysis

Descriptive statistics are presented for categorical and continuous variables. Mean and standard deviation are reported for continuous variables, and frequencies for categorical variables. Length of follow-up was based on data extracted from clinical records. Overall survival was defined as the period from pathologic diagnosis to death. Patients alive at the latest follow-up or the last investigation in the electronic medical record were censored at that time point. Overall survival was estimated using the Kaplan–Meier method, and median overall survival and the corresponding 95% confidence interval are reported. Log-rank tests were used to compare survival outcomes between patient groups. All statistical analyses were conducted using the SAS software application (version 9.2: SAS Institute, Cary, NC, U.S.A.), and a one-sided p value of 0.05 was considered to be statistically significant.

3. RESULTS

Table I summarizes characteristics and clinical findings for the 58 patients identified as meeting the criteria for inclusion in the analysis. Primary SCC of the GU had a male predominance (ratio of men to women: 3.8:1), and median age at diagnosis was 71 years (range: 45–91 years). The UB was the most common anatomic location ($n = 35$), followed by the prostate ($n = 17$), and then the UUT, including kidney, renal pelvis, and ureter ($n = 6$). Of the 35 UB SCCS, 22 were LS, and 8 were ES; staging details were unknown in 5 patients. Of the prostate SCCS, 12 were ES, 4 were LS, and 1 was of unknown stage. Among 40 patients with retrievable clinical histories, 36 (90%) were smokers. Of those patients, 23 had quit smoking for a median of 25 years (range: 4–50 years).

TABLE I Patient characteristics

Characteristic	*Value*
Patients (*n*)	58
Sex [*n* (%)]	
Men	46 (79)
Women	12 (21)
Age at diagnosis (years)	
Median	71
Range	45–91
Primary site [*n* (%)]	
Urinary bladder	35 (60)
Prostate	17 (29)
Ureter	1 (2)
Kidney	5 (9)
Presenting symptoms [*n* (%)]	
Hematuria	36 (62)
Urinary obstruction	20 (34)
Abdominal pain	7 (12)
Recurrent urinary tract infection	4 (7)
Smoking status [*n* (%)]	
Smoker	7 (12)
Ex-smoker	29 (50)
Non-smoker	4 (7)
Unknown	18 (31)
Performance status [*n* (%)]	
0–1	45 (78)
2–4	8 (14)
Unknown	5 (9)
Site of metastases (*n*)	
Liver	12
Bone	3
Lymph nodes[a]	9
Lung	3
Brain	1

[a] Pelvic and extrapelvic.

Hematuria was the most common presenting symptom, occurring in 62% of patients—especially those with UB SCC. Prostate SCC presented mainly with obstructive urinary symptoms (34%). Two patients had a paraneoplastic syndrome, one with hypercalcemia, and the other with syndrome of inappropriate antidiuretic hormone secretion.

A significant number of patients had another conventional GU malignant diagnosis in addition to their GU SCC. Of the 17 patients with prostate SCC, 7 (41%) had a history of adenocarcinoma of the prostate, and of the 35 patients who had UBSCC, 5 had a history of transitional-cell carcinoma of the bladder, and 2, prostate adenocarcinoma. We believe that these conventional cancers reported with GU SCC are not treatment-related and that the significance of these associations is unknown. The conventional malignancies were treated according to standard local guidelines.

Overall, 28 patients (48%) had LS disease at the time of diagnosis, and 24 (41%) had ES. In 6 patients (10%), stage could not be determined in the chart review. Based on the anatomic site of the primary, patients with UB SCC tended to present more commonly with LS disease (n = 22, 63%); those with a prostate primary were more likely to present with ES disease (n = 12, 71%, Table II).

The diagnosis of SCC was based on WHO[14] criteria, which are identical to the criteria for SCLC. The carcinomas comprised sheets of small cells, round to oval, with overlapping nuclei having evenly distributed chromatin, a lack of prominent nucleoli, and sparse cytoplasm. Mitotic figures were frequent in all tumours. In some tumours, the diagnosis of SCC was made solely on morphologic grounds even if neuroendocrine differentiation had not been assessed, a diagnostic process that is acceptable under the WHO criteria[14].

Immunohistochemical studies were not systematically performed, but at least 1 neuromarker was detected in 37 of the study patients (64%). Synaptophysin was the most common neuromarker, staining positive in 24 of the 37 patients (65%), followed by CD56 in 18 (49%), chromogranin in 11 (30%), and neurospecific enolase in 7 (19%).

Most patients (n = 38) had pure SCC; in the remaining patients, the SCC was associated with a carcinoma, mainly urothelial carcinoma in the UB (37%) and adenocarcinoma in the prostate (29%).

TABLE II Characteristics of small-cell carcinoma by anatomic location

Characteristic	*Location [*n *(%)]*			
	Overall	*Urinary bladder*	*Prostate*	*Upper urinary tract*
Stage				
Overall	58	35	17	6
Limited	28 (48)	22 (63)	4 (24)	2 (33)
Extensive	24 (41)	8 (23)	12 (71)	4 (67)
Unknown	6 (10)	5 (14)	1 (6)	0
Histology				
Pure	38 (66)	22 (63)	12 (71)	4 (67)
Mixed	20 (34)	13 (37)	5 (29)	2 (33)

3.1 Treatment of Patients with LS Disease

Among the 28 patients with LS disease, treatment varied, mainly because of the disease site. In UB SCC, 8 of 22 patients (36%) were treated with surgery followed by adjuvant chemoradiotherapy, 6 (27%) were treated with surgery alone, 4 (18%) were treated with surgery followed by adjuvant chemotherapy, 2 were treated with surgery followed by adjuvant radiotherapy, 1 was treated with chemoradiotherapy, and 1 was treated with chemotherapy alone. Among LS prostate SCCS, none were treated with surgery. Of 4 patients, 3 (75%) were treated with chemoradiotherapy, and 1 was treated with chemotherapy alone. Patients with disease of the renal pelvis and ureter (n = 2) were treated with surgery, with 1 patient also receiving adjuvant chemotherapy. The treatment regimen consisted of 4 cycles of platinum-based chemotherapy (cisplatin or carboplatin) with etoposide. The radiotherapy started at cycle 2, using a dose of 30–60 Gy in 15–30 fractions to the primary tumour and involved lymph nodes. Overall, 9 of 11 patients (82%) responded to chemoradiotherapy, with 8 (73%) experiencing a complete response; 1, a partial response; and 2, disease progression.

Even in patients with LS disease, the rate of failure was high, with 17 of 28 relapsing (61%). The most common sites of relapse were liver (42%), bone (18%), lymph nodes (17%), lung (17%), and peritoneum (17%). Notably, brain was the site of first distant relapse in only 1 patient in the entire cohort (2%), despite the fact that prophylactic cranial irradiation (PCI) was not routinely administered (only 1 patient received PCI).

3.2 Treatment of Patients with ES Disease

Most patients with ES GU SCC (14 of 24, 58%) received best supportive care (BSC). Palliative chemotherapy similar to the treatment in LS disease was administered to 7 patients (29%). In renal SCC, 2 patients received nephrectomy as primary treatment. In 1 patient treated with a primary radical cystectomy, locoregional disease was discovered at the time of surgery, and chemotherapy was subsequently given.

3.3 Survival and Prognostic Factors

For the entire cohort, overall survival was 41% and 21% at 1 and 3 years respectively. Median overall

survival was 7.5 months. Median survival in all patients with prostate SCC was 5.4 months, compared with 6.9 months for patients with UB SCC, and 12.7 months for patients with UUT SCC ($p = 0.433$, Figure 1).

For all patients with LS GU SCC, median survival was 22 months; it was 4.1 months for patients with ES disease ($p < 0.001$, Figure 2). In subgroup analysis, the median survival for LS prostate SCC was only 11.2 months compared with 24.8 months for UB SCC and 36.2 months for the UUT SCC (p = nonsignificant). In general, ESSCC carries a poor prognosis, with median survivals of 3.8, 3.4, and 6.3 months for cancers arising in the prostate, the UB, and the UUT respectively.

Mixed histology was noted in 34% of the tumours (20 of 58, Table II), which is important, because patients with pure SCC showed a significantly longer overall survival (11.2 months vs. 6.4 months, $p = 0.02$).

Compared with BSC alone, active therapy was highly statistically significant for overall survival. Patients who received any form of treatment (surgery, chemotherapy, or radiotherapy alone or in combination) had a longer overall survival (12.3 months vs. 2.3 months, $p < 0.0001$, Figure 3). Adding systemic therapy meaningfully prolongs survival regardless of disease stage or anatomic location. Patients who received chemotherapy lived longer than those who received only surgery, radiotherapy, or BSC (observed overall survivals of 12.3 months, 6.9 months, and 2.3 months respectively, $p < 0.0001$).

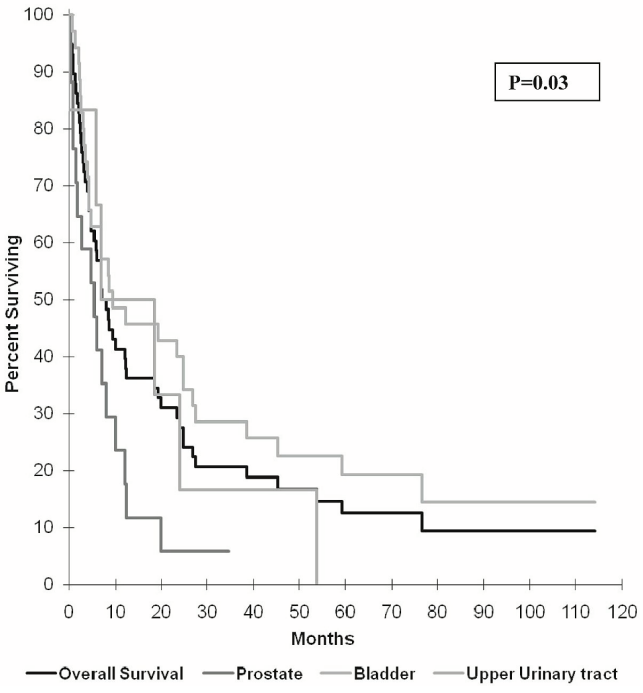

FIGURE 1 Overall survival in extrapulmonary small-cell carcinoma by anatomic location.

4. DISCUSSION

Our single-institution series confirms what has previously been reported in the literature: that the GU tract is one of the most common sites for EPSCC. Most of the data come from single-institution series. Table III

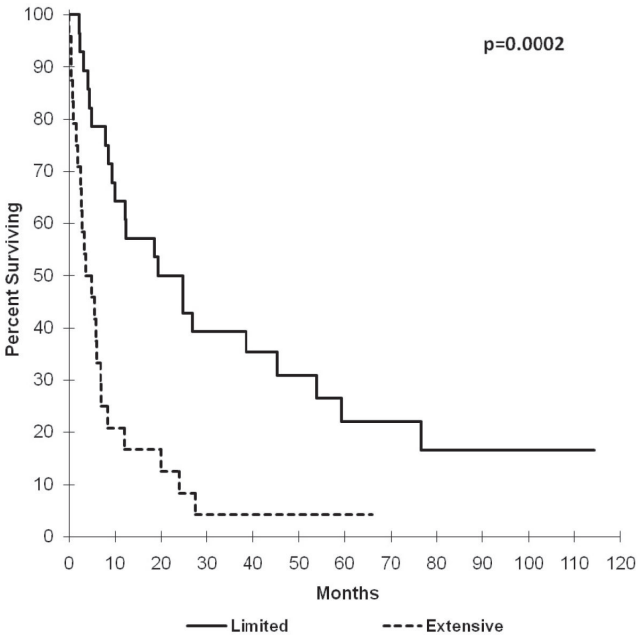

FIGURE 2 Overall survival in extrapulmonary small-cell carcinoma by stage.

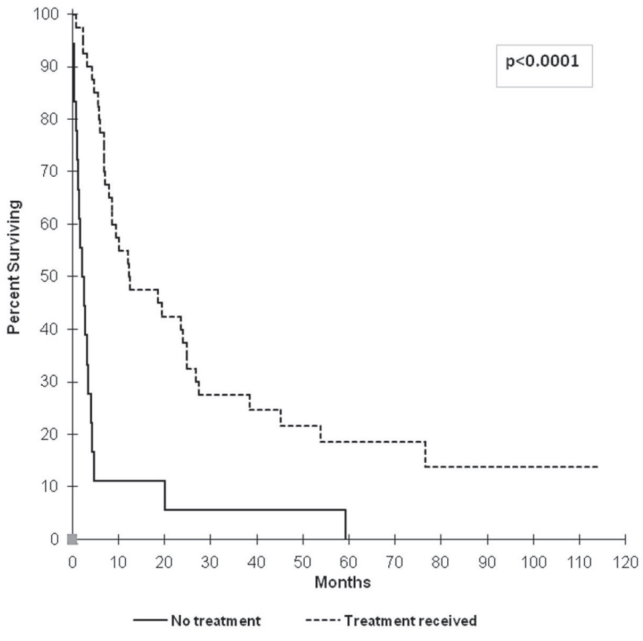

FIGURE 3 Overall survival in extrapulmonary small-cell carcinoma, any treatment compared with best supportive care.

TABLE III Published data on small-cell carcinoma of the genitourinary tract

Variable	*Reference*				
	Lo Re et al.[10]	*Holmäng* et al.[17]	*Mangar* et al.[18]	*Choong* et al.[8]	*Current study*
Patients (*n*)	24	25	14	44	58
Tumour site (*n*)					
Urinary bladder	5	25	14	44	35
Prostate	4				17
Kidney	2				
Upper urinary tract					6
Presentation (*n*)					
Limited-stage disease		18	10	39	28
Extensive-stage disease	>50%	7	4	5	24
Unknown					6
Median survival (months)					
Overall	13	7.3		1.7 Years	7.5
Limited-stage disease			21		22
Extensive-stage disease			5		4.1

compares published series of SCC and shows that the UB is the most frequently involved site[19]. Genitourinary SCC is a disease of the elderly: median age at diagnosis is 71 years, and this malignancy is more common in men[7,8,18]. Like SCLC, GU SCC is associated with cigarette smoking; 90% of the patients in our series with retrievable clinical histories were either smokers or past smokers, a finding seen in other studies[8,11,18,20,21].

The biology of GU SCC is complex, and like other EPSCCS, its origin is uncertain. In one proposal, SCC is suggest to arise from a multipotential stem cell with the ability to differentiate into various tissue types[2,17,22,23]. That view is supported by a recent report identifying an identical pattern of allelic loss in coexisting UB SCC and urothelial carcinoma, suggesting a common progenitor cell of origin[21]. Similarly, the high concordance rate of transcription factors from an *ERG* rearrangement between the small-cell and acinar components in a given patient supports a common origin for these two subtypes of prostate cancer[24]. Another theory suggests that GU SCC may originate from the transformation of a pre-existing malignancy, a hypothesis that is supported by a preclinical study demonstrating the ability of a human prostate cancer cell line to transform into neuroendocrine-like cells[25]. The observation that 29% of the patients with prostate SCC had adenocarcinoma and 37% of the patients with UB SCC had transitional-cell carcinoma is concordant with earlier findings (41% and 15% respectively) and with the latter hypothesis[18]. It would appear that, compared with having pure SCC, having a mixed-histology malignancy confers an adverse prognosis (6.4 months vs. 11.2 months, $p = 0.02$). That finding conflicts with those in other studies, which found that patients have a similar or better prognosis with mixed UB SCC than with pure UB SCC[8,15].

The observation that macroscopic hematuria is the most common presentation of SCC of the bladder[8,18,21] may explain why, compared with patients having prostate SCC, patients having UB SCC often present with earlier-stage disease (63% vs. 24% LS, $p = 0.008$).

Our data demonstrated a change in the staging approach for GU SCC over the decades. Staging investigations were limited in patients before the year 2000. Before 2000, most patients were staged by chest radiography and ultrasonography. All patients diagnosed after 2000 ($n = 41$, 70%) received diagnostic computed tomography of chest, abdomen, and pelvis for staging. Only 1 patient underwent magnetic resonance imaging, and 2 patients underwent a bone scan. No patients underwent positron-emission tomography. In 80% of patients, computed tomography was also used to assess treatment response during follow-up.

Our study demonstrates that, compared with BSC alone, active treatment is associated with superior outcomes in SCC patients (median survival: 12.3 months vs. 2.3 months, $p < 0.0001$). Potential explanations for that finding include the chemosensitive nature of SCC and the fact that patients fit for treatment usually have a better performance status and better-preserved organ function; they are also generally more able to tolerate therapy with surgery, radiation, or chemotherapy.

Data from LS SCLC patients indicate that surgery alone or in combination with chest radiotherapy provides no survival advantage compared with radiotherapy alone[26]. Meta-analyses indicate that chemotherapy combined with chest irradiation improves

survival in LS SCLC patients[27,28]. Integration of systemic chemotherapy is critical in LS SCLC, and in the present series, the need for such integration would appear to be true for GU SCC as well. Regardless of the local modality of therapy (surgery or radiotherapy), the addition of systemic chemotherapy improves outcomes and survival, and therefore chemotherapy should be given whenever possible.

Several studies have reported rapid systemic recurrence and an unfavourable outcome with local therapy alone for SCC of other sites[20,29–31]. In the present study of GU SCC, we found that, compared with patients treated with surgery or radiotherapy alone, patients who received systemic therapy showed a trend toward better survival (12.3 months vs. 6.9 months, $p = 0.22$) regardless of the primary location, site, and stage of the disease. That finding is likely a result of the high incidence of occult micrometastatic disease present in LS patients, an observation made by other groups[2,19,32–34].

Patients with ES GU SCC are generally treated with a platinum agent in combination with etoposide, analogous to treatment in the SCLC population[35,36]. In our series, we found that, compared with ES GU SCC patients receiving BSC, those receiving palliative chemotherapy experienced improved survival (6.25 months vs. 2.3 months). However, because of the small number of patients with ES GU SCC, a meaningful statistical analysis cannot be undertaken.

Our study is consistent with previous reports, in that the rate of metastasis to the brain as site of first relapse is lower in EPSCC than in SCLC[37–40]. Compared with the 20%–40% incidence rate of brain metastases in SCLC[41,42], only 1 patient (2%) in the present series developed brain metastasis. Although PCI is valuable in SCLC for both LS and ES patients, our data showed a low rate of central nervous system failure, and hence, PCI in GU SCC may not be routinely delivered.

5. CONCLUSIONS

Genitourinary SCC is a rare cancer, with an aggressive clinical course. As in SCLC, patients with LS GU SCC do better than those having ES GU SCC. Compared with patients having UB or upper GU tract tumours, those with prostate primaries tend to present with more advanced disease. Because no dedicated trials have been conducted in EPSCC, treatments are based on SCLC treatment protocols. Wherever possible, integration of chemotherapy into the treatment plan is critical in achieving the best outcomes, although survival is poor even with optimal therapy. Patients with LS disease should be treated with curative intent because approximately 20% will experience long-term survival. Our data showed that PCI may not be routinely required in GU SCC (as it is in SCLC) because of a low rate of central nervous system failure. Collaboration is required so that further research and randomized clinical trials can be undertaken to better understand this disease and to find more-effective treatment strategies.

6. ACKNOWLEDGMENTS

The authors thank Joseph Jones, medical student, USESOM, and Syed Hussain, science student, University of Alberta, for their help in the preparation of this manuscript.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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