Original Article

Clinical features and prognosis of small cell carcinoma of the bladder: a single center retrospective analysis

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Background: Small cell carcinoma of the bladder (SCCB) is a rare and aggressive subtype, usually diagnosed at advanced stages. Due to its rarity, the clinical features, prognostic factors, and treatment strategies are not well defined, and data on long-term outcomes are limited. This study aims to analyze the clinical characteristics, treatment options, and prognostic factors of SCCB to enhance clinical understanding and guide practice.

Methods: A retrospective analysis of 41 SCCB cases treated at Changhai Hospital between 2006 and 2023 was conducted. Clinical, pathological, and treatment data were collected. The median follow-up duration was calculated as 41.0 months [95% confidence interval (CI): 31.3–50.7] using the reverse Kaplan-Meier method. Overall survival (OS) rates were estimated using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were used to identify prognostic factors.

Results: The median age was 71 years (range, 41–89 years). Pure SCCB accounted for 56.1% of cases, and 48.78% of tumors were located on the lateral bladder wall. Tumors ≥4 cm were found in 56.10% of cases. According to the tumor-node-metastasis (TNM) classification, 63.41% of patients underwent radical cystectomy, and 34.14% had lymph node or distant metastasis. None of the patients received neoadjuvant chemotherapy (NACT), while 41.03% underwent adjuvant chemotherapy post-surgery. The median OS was 30 months, with 1- and 3-year OS rates of 74.8% and 41.4%, respectively. Univariate analysis showed that T stage (P=0.002), lymph node metastasis (P<0.001), and distant metastasis (P<0.001) were associated with poor prognosis. Multivariate analysis confirmed T stage (P=0.04) and distant metastasis (P<0.001) as independent prognostic factors.

Conclusions: SCCB is often diagnosed at a late stage with gross hematuria as the most common symptom, Neoadjuvant therapy and immunotherapy can extend OS. T stage and distant metastasis are critical prognostic factors. Early diagnosis and intervention are crucial for improving outcomes.

Keywords: Small cell carcinoma of the bladder (SCCB); neuroendocrine carcinoma of the bladder; clinical characteristics; treatment; prognosis

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Introduction

Small cell carcinoma of the bladder (SCCB) is a poorly differentiated and rapidly progressing neuroendocrine malignant tumor, with an incidence rate of less than 1% among bladder malignancies (1,2). SCCB predominantly affects males and is characterized by high malignancy. It is often diagnosed at an advanced stage, leading to a poor prognosis. The current knowledge of this rare disease is limited, and most studies are case reports or case series (3,4), with few studies focusing on prognostic factors. This paper retrospectively analyzes the clinical data of 41 patients with SCCB, exploring their clinical characteristics and prognostic factors. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-2024-645/rc).

Methods

Study population and design

A retrospective analysis was performed on the case data of 41 patients with SCCB treated at Changhai Hospital, Navy Medical University, from November 2006 to November 2023, with all cases confirmed by pathological diagnosis. Clinical and pathological data encompassed age, gender, body mass index (BMI), histopathological classification, tumor location, tumor diameter, tumor count, clinical presentation, and surgical methods. Histopathological classification followed the 2016 World Health Organization (WHO) classification of urinary tract tumors (5), and tumor-node-metastasis (TNM) staging adhered to the 8th edition by the Union for International Cancer Control (UICC) in 2017 (6). Pathological diagnoses were verified by two pathologists. Follow-up was conducted through outpatient visits or telephone calls, from the initial pathological confirmation of SCCB to May 1, 2024. The primary endpoint was overall survival (OS), defined as the duration from surgery to death from any cause or the last follow-up. To minimize selection bias, all cases diagnosed as SCCB were included, and data collection was standardized across all patients. Missing data were handled through listwise deletion to ensure consistency in statistical analyses.

In the analysis, quantitative variables were handled based on clinical relevance and statistical considerations. Continuous variables, such as age, BMI, and maximum tumor diameter, were categorized into groups to facilitate analysis and interpretation: age was grouped into <70 and ≥70 years to reflect clinically relevant age thresholds for prognosis. BMI was categorized into <24 and ≥24 kg/m^2 to assess the impact of nutritional status on survival. Maximum tumor diameter was divided into <4 and ≥4 cm based on clinical guidelines suggesting tumor size as a prognostic factor. Other variables, such as smoking history (yes/no) and tumor staging (T, N, M), were grouped according to standard clinical classifications. These groupings were chosen to simplify interpretation, highlight clinically meaningful differences, and align with established prognostic factors.

This is a retrospective study in which patient information was anonymized, and the study did not impact treatment or prognosis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Changhai Hospital, Navy Medical University (approval No. CHEC2022-147). The requirement for written patient consent was waived due to the retrospective nature of the study.

Treatment methods

Among the 41 patients, 26 (63.41%) underwent radical

Highlight box

Key findings

- This study analyzed 41 cases of small cell carcinoma of the bladder (SCCB) and identified key clinical and prognostic factors. The median age of patients was 71 years, and the most common presentation was gross hematuria. The median overall survival (OS) was 30 months, with 1- and 3-year OS rates of 74.8% and 41.4%, respectively. T stage and distant metastasis were identified as independent prognostic factors for survival.

What is known and what is new?

- SCCB is a rare and aggressive malignancy with limited treatment options. Most cases are diagnosed at an advanced stage, leading to poor prognosis.
- This study provides important insights into the clinical characteristics of SCCB, highlighting the significance of T stage and distant metastasis as key prognostic indicators. The findings also show that radical cystectomy improves survival, and chemotherapy or immunotherapy may have additional benefits for survival.

What is the implication, and what should change now?

- The study underscores the importance of early diagnosis and intervention in SCCB to improve patient outcomes. Clinicians should consider T stage and distant metastasis when assessing prognosis. Additionally, the findings support the potential role of chemotherapy and immunotherapy in improving survival, though further research is needed to establish standardized treatment protocols for SCCB.

Table 1 Correlation between basic characteristics and overall survival

Characteristics	n	%	Median survival time (months)	P value*
Gender				0.30
Male	38	92.68	30	
Female	3	7.32	11	
Age (years)				0.45
<70	16	39.02	NA	
≥70	25	60.98	30	
BMI (kg/m^2)				0.88
<24	18	43.9	30	
≥24	23	56.1	30	
Smoking history				0.49
Yes	23	56.10	NA	
No	18	43.90	30	

*, P value: log-rank test was conducted to determine the effect of each single factor on overall survival. BMI, body mass index; NA, not available.

cystectomy with urinary diversion, including 17 via laparoscopic surgery, 4 via robot-assisted laparoscopic surgery, and 5 via open surgery. Urinary diversion techniques included ureterocutaneostomy in 14 patients, ileal bladder in 8 patients, and neobladder reconstruction in 4 patients. Partial cystectomy was performed in 6 patients (14.63%), of whom 4 underwent laparoscopic partial cystectomy with ureteral reimplantation, and 2 underwent open partial cystectomy. Additionally, 6 patients (14.63%) received transurethral resection of bladder tumor (TURBT), 2 underwent debulking TURBT, and 1 underwent cystoscopic biopsy.

Postoperatively, 16 patients (39.02%) received chemotherapy (10 received cisplatin + etoposide and 6 received gemcitabine + cisplatin), while 9 patients (21.95%) received intravesical therapy [4 with gemcitabine, 4 with pirarubicin, and 1 with Bacillus Calmette-Guérin (BCG)]. Immunotherapy (toripalimab) and radiotherapy were administered to 3 patients each (7.31%).

Statistical analysis

Data sorting and statistical analysis were performed using R version 4.4.0 and GraphPad Prism 10.2.3 software. Missing data were addressed using listwise deletion, where cases with any missing values were excluded from the analysis. Differences between groups were deemed statistically significant at $P<0.05$. The Kaplan-Meier method was employed to generate survival curves and calculate survival rates, with group comparisons conducted using the log-rank test. Univariate Cox regression analysis was utilized to explore disease risk factors, and significant variables ($P<0.05$) were included in multivariate Cox regression to adjust for confounders and identify independent prognostic factors for SCCB, with results presented in a forest plot.

Results

Patients' characteristics

A total of 41 patients were included in the final analysis. Among them, 39 patients completed follow-up, while 2 were lost to follow-up (follow-up rate: 95.1%). The cohort comprised predominantly male patients (n=38, 92.68%), with a male-to-female ratio of 12:1. The median age was 71 years (range, 41–89 years), and the average BMI was 24.45±3.29 kg/m^2 (range, 19.03–32.00 kg/m^2). A total of 23 patients (56.10%) had a smoking history, all of whom were male, with 15 of the 23 smokers being heavy smokers (smoking index of 400). *Table 1* lists the basic clinical characteristics of the 41 patients and their relationship with OS.

Pathological characteristics

Among the 41 patients, pathological diagnoses included 23 cases (56.1%) of pure SCCB, 16 cases (39.02%) of SCCB combined with urothelial carcinoma, 1 case (2.43%) of SCCB combined with adenocarcinoma, 1 case (2.43%) of SCCB combined with both urothelial carcinoma and adenocarcinoma, and 4 cases (9.75%) of SCCB combined with prostatic adenocarcinoma. Immunohistochemistry (IHC) was performed on 37 patients (*Figure 1*), revealing neuron-specific enolase (NSE) positivity in 20 cases (80%), synaptophysin (SYN) positivity in 25 cases (80.65%), chromogranin A (CGA) positivity in 8 cases (21.62%), and cluster of differentiation 56 (CD56) positivity in 26 cases (70.27%). Postoperative pathological staging was stage III or above in 23 cases (56.10%). Fourteen cases had lymph node metastasis, with 4 confirmed by postoperative pathology and the remaining 10 suggested by postoperative follow-up imaging. Among the 14 patients with distant metastasis, 3 had metastasis at initial diagnosis, 2 underwent debulking TURBT, and 1 underwent cystoscopy with

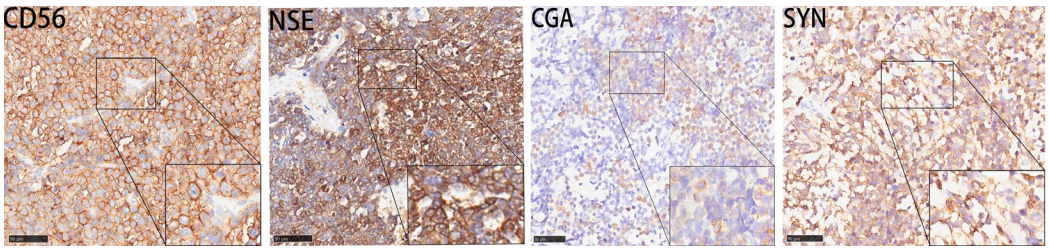

Figure 1 Immunohistochemical staining of CD56, NSE, CGA, and SYN in SCCB tissue. Tissue sections from different patients with SCCB, observed at 100× magnification. Each section is labeled with the corresponding immunohistochemical marker (CD56, NSE, CGA, or SYN) in the upper left corner, and the scale bar is located in the lower left corner, representing 50 μm. Each immunohistochemical section is magnified in a specific area, outlined in a box, to highlight the staining of the respective marker. These markers are used to identify specific cellular components, such as CD56, NSE, CGA, and SYN positive cells, in SCCB tissue. CD56, cluster of differentiation 56; NSE, neuron-specific enolase; CGA, chromogranin A; SYN, synaptophysin; SCCB, small cell carcinoma of the bladder.

biopsy, followed by chemotherapy. During follow-up, 11 patients developed distant metastasis. Postoperative metastasis sites primarily included the liver, bones, lungs, and pelvic and retroperitoneal lymph nodes. Subgroup analysis of prognostic factors for OS in M0 small cell bladder cancer patients undergoing radical surgery revealed a significant difference in OS based on T stage (P=0.005) (Table S1). The pathological characteristics of the patients and their relationship with OS are shown in *Table 2*. Treatment strategies and prognosis for patients with different pathological stages are shown in *Table 3*.

Survival outcomes and prognostic factors

Among the 41 patients, 39 were followed up, and 2 were lost to follow-up, with a follow-up period of 5–131 months and a median follow-up time of 41 months. Twenty patients died, with a median OS of 30 months, and 1- and 3-year OS rates of 74.8% and 41.4%, respectively. The median OS for patients with T3–T4 stage was 15 months, and for patients with distant metastasis, it was 8 months. Univariate Cox regression analysis identified T stage (P=0.002), lymph node metastasis (P<0.001), and distant metastasis (P<0.001) as prognostic risk factors. Multivariate Cox regression analysis indicated that T stage [HR: 3.69, 95% confidence interval (CI): 1.06–12.82, P=0.04] and distant metastasis (HR: 11.12, 95% CI: 3.18–38.93, P<0.001) were independent prognostic factors for SCCB, as shown in *Figure 2*, with the survival curve depicted in *Figure 3*. The results of univariate and multivariate Cox regression analyses are presented in *Table 4*.

Discussion

Epidemiology, clinical presentation, and prognosis of SCCB

SCCB predominantly affects elderly males, with a male-to-female ratio of approximately 3:1. In this study, the median age was 71 years (38 males and 3 females), with the peak incidence observed in patients aged 70 to 80 years. Although survival rates in older patients (≥70 years) were lower than in younger patients, the difference was not statistically significant. SCCB typically occurs in the lateral walls and base of the bladder, with most tumors being solitary and around 50 mm in diameter (7). In our investigation, 48.78% of tumors were located in the lateral wall, with a median tumor size of 40 mm, and 65.85% of patients had solitary tumors. Survival analysis showed no significant correlation between tumor location, size, number, and prognosis.

Gross hematuria is the most common presenting symptom in SCCB, followed by dysuria, bladder irritation, and lower abdominal pain. In rare cases, patients may present with paraneoplastic syndromes such as ectopic adrenocorticotropic hormone (ACTH) secretion or hypercalcemia (8). In our study, 80.49% of patients presented with gross hematuria, and no cases of paraneoplastic syndrome were observed. Univariate analysis showed no significant association between presenting symptoms and prognosis. Most SCCB patients present at advanced stages (T3–T4) (8,9), as seen in 56.1% of our cases, and multivariate Cox regression confirmed T stage as an independent prognostic factor. In addition, our findings further demonstrate that T stage is a key prognostic factor influencing OS in M0 small cell bladder cancer patients

Table 2 Correlation between basic tumor characteristics and overall survival

Tumor characteristics	n	%	Median survival time (months)	P value*
Tumor location				0.008
Anterior/posterior wall	5	12.2	10	
Lateral wall	20	48.78	30	
Trigone	3	7.32	NA	
Dome	1	2.44	5	
Multiple locations	12	29.27	25	
Number of tumors				0.73
Single	27	65.85	30	
Multiple	14	34.15	30	
Maximum tumor diameter				0.045
<4 cm	18	43.90	NA	
≥4 cm	23	56.10	15	
Clinical presentation				0.81
No gross hematuria	8	19.51	30	
Gross hematuria	33	80.49	30	
Surgical method				0.15
No radical surgery	15	36.59	25	
Radical surgery	26	63.41	NA	
MIBC				0.53
Yes	34	82.92	30	
No	7	17.07	30	
T stage				<0.001
T1 + T2	18	43.9	NA	
T3 + T4	23	56.1	15	
N stage				<0.001
N–	26	65	NA	
N+	14	35	9.5	
M stage				<0.001
M0	26	65	NA	
M1	14	35	8	
NSE				0.86
Yes	20	80	25	
No	5	20	30	
SYN				0.93
Yes	25	80.65	30	
No	6	19.35	32	
CGA				0.93
Yes	14	51.85	30	
No	13	48.15	NA	
CD56				0.27
Yes	26	89.66	NA	
No	3	10.34	10	
Pure small cell carcinoma				0.71
Yes	23	56.1	30	
No	18	43.9	28	
Postoperative chemotherapy				0.24
Yes	16	41.03	NA	
No	23	58.97	25	
Radiotherapy				0.47
Yes	3	7.69	NA	
No	36	92.31	28	
Postoperative immunotherapy				0.71
Yes	3	7.69	10	
No	36	92.31	30	

The sum of the data in some categories may not equal the total number in each column due to missing data from patients who were lost to follow-up. *, P value: log-rank test was conducted to determine the effect of each single factor on overall survival. TNM, tumor-node-metastasis; MIBC, muscle-invasive bladder cancer; NSE, neuron-specific enolase; SYN, synaptophysin; CGA, chromogranin A; CD56, cluster of differentiation 56; NA, not available.

Table 3 Treatment strategies and prognosis for patients with different stages

Stage and treatment strategy	Total (N=41)		Progression, recurrence or metastasis		Death	
	Cases	%	Cases	%	Cases	%
T1	6		4	66.66	3	50.0
RC	1	16.66	1		0	
RC + CT	1	16.66	0		0	
TURBT + CT + IVT	1	16.66	0		0	
TURBT + IVT	3	50.0	3		3	
T2	10		4	40.0	1	10.0
RC	4	40.0	1		1	
RC + CT	4	40.0	2		0	
RC + RT	1	10.0	1		0	
TURBT + CT + IVT	1	10.0	0		0	
T3	18		11	61.11	11	61.11
RC	8	44.44	5		5	
RC + CT	3	16.66	3		3	
RC + RT	1	5.55	1		1	
PC + CT	3	16.66	1		1	
PC	1	5.55	1		1	
PC + IT	1	5.55	0		0	
TURBT + RT + CT	1	5.55	0		0	
T4 or N1–3 or M1	7		5	71.4	5	71.4
RC + CT	2	28.5	1		1	
RC + IT	1	14.2	0		0	
PC + IT	1	14.2	1		1	
TURBT + CT	1	14.2	1		1	
TURBT	1	14.2	1		1	
BX + CT	1	14.2	1		1	

RC, radical cystectomy; RC + CT, radical cystectomy + chemotherapy; TURBT + CT + IVT, TURBT + chemotherapy + intravesical therapy; TURBT + IVT, TURBT + intravesical therapy; RC + RT, radical cystectomy + radiotherapy; PC + CT, partial cystectomy + chemotherapy; PC, partial cystectomy; PC + IT, partial cystectomy + immunotherapy; TURBT + RT + CT, TURBT + radiotherapy + chemotherapy; RC + IT, radical cystectomy + immunotherapy; TURBT + CT, TURBT + chemotherapy; Bx + CT, biopsy + chemotherapy.

undergoing radical surgery.

The prognosis of SCCB is generally poor, with previous studies reporting a median survival time of 4–23 months and 5-year survival rates ranging from 10% to 40% (10). In our study, the 1- and 3-year survival rates were 74.8% and 41.4%, respectively, with a median survival of 30 months, which is higher than that reported in the literature. This may be due to the small sample size and potential selection bias. SCCB primarily metastasizes via lymph nodes, and metastasis occurs earlier and more aggressively than in urothelial carcinoma (11). Studies have shown that SCCB patients with distant metastasis have a significantly worse prognosis compared to those without metastasis (12-14). In our cohort, 34.14% of patients had lymph node metastasis, and 34.14% had distant metastasis. Multivariate analysis confirmed distant metastasis as an independent prognostic

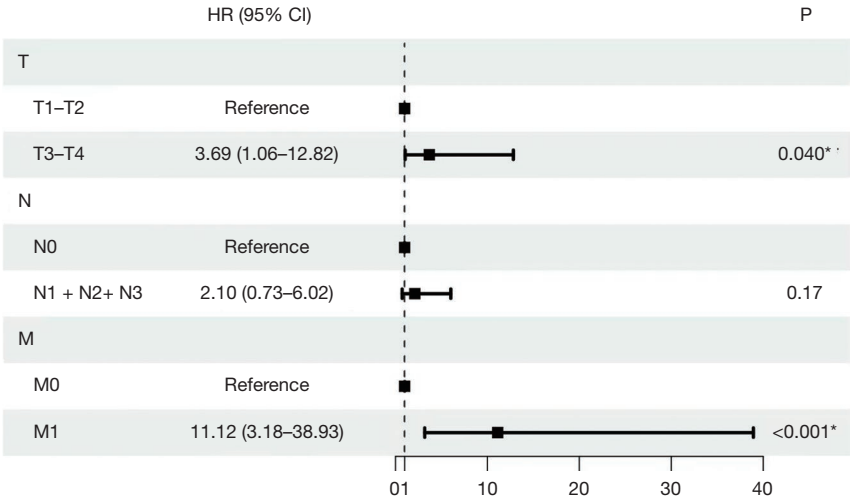

Figure 2 Cox multivariate regression analysis. *, significant difference. HR, hazard ratio; CI, confidence interval; T, tumor; N, node; M, metastasis.

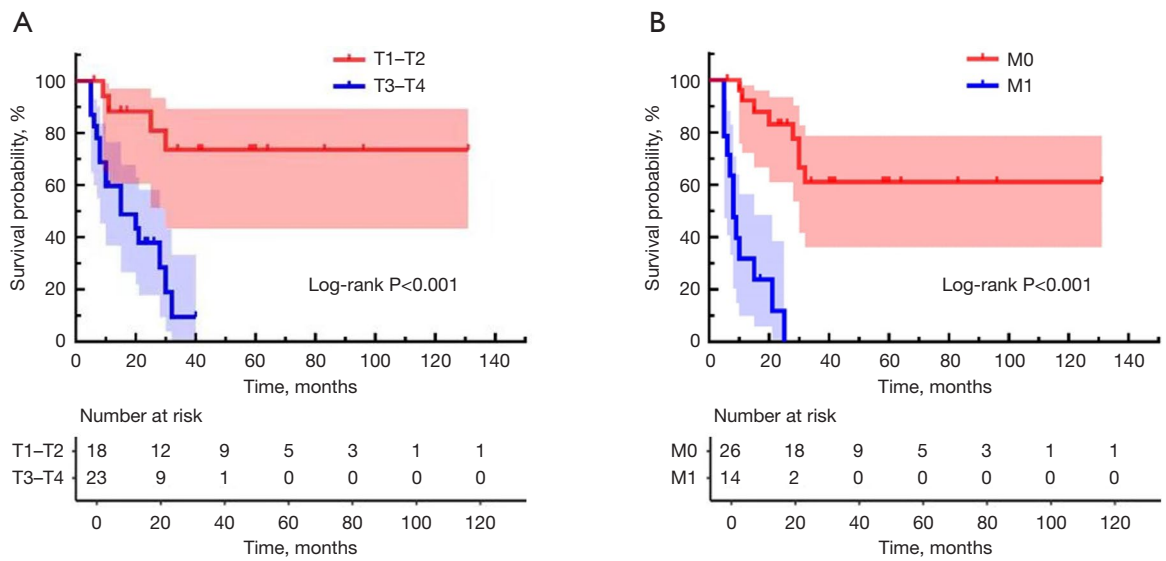

Figure 3 Kaplan-Meier survival curves for independent risk factor. (A) Patients with T1 or T2 tumors showed significantly better survival than patients with T3 or T4 tumors (P=0.001). (B) The presence of distant metastases significantly affected survival (P<0.001).

factor, supporting the observation that advanced-stage SCCB has a poor prognosis.

SCCB often coexists with other histological types of bladder cancer, such as urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma, which can complicate diagnosis. Therefore, pathological examination remains the "gold standard" for diagnosis (15). A study suggests that pure SCCB has a worse prognosis than mixed SCCB (13). However, in our study, pure SCCB accounted for 56.1% of cases and mixed SCCB for 43.9%, with no significant difference in survival rates between these two groups. IHC plays an important role in diagnosing SCCB, with common neuroendocrine markers including NSE, Syn, CgA, and CD56. The reported positive expression rates for NSE, CgA, and Syn range from 25–100%, 22–89%, and 67–76%, respectively (13). Elevated serum NSE levels (>25 ng/mL) have been associated with poor prognosis (16). In our study, 37 patients underwent IHC testing, and while the presence

Table 4 Analysis of prognostic factors for overall survival time in patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male)	2.16 (0.48–9.63)	0.31		
Age (<70 years)	1.41 (0.56–3.55)	0.46		
BMI (<24 kg/m^2)	1.07 (0.44–2.62)	0.88		
Smoking history (no)	0.74 (0.30–1.78)	0.50		
Tumor location				
Anterior/posterior wall	1.00 (Reference)			
Lateral wall	0.54 (0.15–1.97)	0.35		
Trigone	0.45 (0.05–4.39)	0.50		
Dome	11.68 (0.88–155.7)	0.06		
Multiple locations	0.52 (0.12–2.17)	0.37		
Maximum tumor diameter (<4 cm)	2.55 (0.97–6.66)	0.056		
Number of tumors (single)	0.85 (0.32–2.20)	0.73		
Clinical presentation (no gross hematuria)	0.87 (0.29–2.62)	0.81		
T stage (T1–T2)	6.17 (1.99–19.10)	0.002	3.69 (1.06–12.82)	0.04
Lymph node metastasis (N0)	4.66 (1.88–11.54)	<0.001	2.10 (0.73–6.02)	0.17
Distant metastasis (M0)	13.44 (4.17–43.32)	<0.001	11.12 (3.18–38.9)	<0.001
NSE (no)	1.12 (0.31–4.10)	0.87		
SYN (no)	0.94 (0.26–3.39)	0.93		
CGA (no)	1.06 (0.28–3.99)	0.93		
CD56 (no)	0.43 (0.09–2.03)	0.29		
Pure small cell carcinoma (yes)	0.84 (0.34–2.07)	0.71		
Postoperative chemotherapy (no)	0.57 (0.22–1.49)	0.25		
Postoperative radiotherapy (no)	0.48 (0.06–3.63)	0.48		
Postoperative immunotherapy (no)	1.47 (0.19–11.59)	0.72		

BMI, body mass index; CD56, cluster of differentiation 56; CGA, chromogranin A; CI, confidence interval; HR, hazard ratio; NSE, neuron-specific enolase; SYN, synaptophysin; TNM, tumor-node-metastasis.

of neuroendocrine markers confirmed the tumor's origin, there was no association between these markers and patient prognosis.

T staging and distant metastasis were identified as independent prognostic factors in our multivariate analysis, findings consistent with previous literature (17,18). Additionally, studies have also shown that lymph node positivity is associated with poor prognosis (19). While the significance of T staging and metastasis as prognostic factors is well-established in oncology, our study adds to the body of evidence specific to SCCB, which remains poorly understood due to its rarity. The diversity of treatment strategies observed in the study by Lu *et al.* (20) further reflects the lack of standardized protocols for SCCB, irrespective of whether the disease is localized or locally advanced. Our findings highlight the aggressive nature of advanced SCCB and reinforce the need for early and aggressive treatment strategies.

Treatment and prognosis of SCCB

Due to the rarity of SCCB, there is no established standard

treatment regimen. Given its histological and biological similarities to small cell lung cancer (SCLC), SCCB treatment often follows the protocols used for SCLC. Surgical interventions for SCCB include radical cystectomy, partial cystectomy, and TURBT, typically supplemented by chemotherapy, radiotherapy, or immunotherapy. Although radical cystectomy is the standard surgical approach for muscle-invasive SCCB and has been associated with better survival outcomes, patient-specific factors often necessitate alternative approaches. In our cohort, 63.41% (26/41) of patients underwent radical cystectomy, while the remaining patients underwent partial cystectomy or TURBT.

TURBT is commonly used for localized SCCB but has a high recurrence rate postoperatively (10). It has been reported that the median survival of just 11 months for patients who underwent TURBT or biopsy alone (21). More than half of SCCB patients undergo radical cystectomy, which has been shown to significantly improve survival (7,22,23). In our analysis, the use of partial cystectomy and TURBT in some cases reflects patient-specific considerations such as advanced age, significant comorbidities, or limited surgical tolerance, which made them unfit for radical surgery. Additionally, certain patients presented with localized disease or declined more extensive surgery due to personal preference. However, these limited surgical approaches may have contributed to poorer outcomes due to incomplete tumor resection. Survival analysis showed that patients who underwent radical cystectomy had higher survival rates than those with other surgical methods, but the difference was not statistically significant (P=0.15).

Chemotherapy, particularly cisplatin-based regimens, has been demonstrated to significantly improve survival in SCCB patients (22,24,25). Neoadjuvant chemotherapy (NACT) not only reduces tumor stage but also improves long-term survival (26). Recent studies have demonstrated that T1 SCCB patients undergoing upfront surgery (i.e., without NACT) face a high risk of pathological upstaging to pT2+ (71%). This finding further underscores the importance of early systemic therapy, even in patients with seemingly low-stage disease (17). Another study of 203 patients with neuroendocrine carcinoma of the urinary tract (NEC-URO) found that NACT significantly improved downstaging rates compared with initial surgery alone (49.6% *vs.* 14.5%, P<0.0001), particularly when using an ifosfamide plus doxorubicin/etoposide plus cisplatin (IA/EP) regimen (65% downstaging) versus EP (39%), methotrexate, vinblastine, doxorubicin, and cisplatin/gemcitabine plus cisplatin (MVAC/GC) (27%), or other regimens (36%). Furthermore, patients treated with NACT followed by surgery had significantly better 5-year OS (57%) compared with surgery alone (22%) or surgery followed by adjuvant chemotherapy (30%) (27). These findings highlight the critical role of NACT, particularly NEC-specific regimens, in improving outcomes for NEC-URO and SCCB patients.

Radiotherapy, either alone or in combination with chemotherapy, is another treatment option for localized SCCB. A study by Chau *et al.* showed no significant difference in median OS between patients treated with surgery and those treated with radiotherapy (1). However, some studies have reported recurrence of urothelial carcinoma in patients undergoing bladder-preserving treatment for SCCB, which may necessitate salvage cystectomy (28). Immunotherapy, particularly immune checkpoint inhibitors, may offer a promising treatment for SCCB, especially in patients with programmed cell death 1 (PD-1) or programmed death-ligand 1 (PD-L1) positivity who have relapsed after surgery (3,29). A recent report described a patient with SCCB who progressed on cisplatin/etoposide and nivolumab/ipilimumab showed a prolonged response to lurbinectedin. Genomic analysis identified a TP53 mutation and amplifications in E2F3 and MYCL. Following lurbinectedin resistance, a repeat biopsy revealed an actionable ERBB2 alteration, suggesting a resistance mechanism and potential therapeutic target (30). These findings highlight the role of molecular profiling in guiding personalized treatment for SCCB.

In our study, none of the patients received NACT, reflecting the historical evolution of clinical practice. This is primarily due to the long study period, spanning nearly two decades, during which treatment protocols for SCCB were not standardized. NACT was not widely adopted as a standard approach in the earlier years, which may have influenced treatment outcomes and limits comparisons with contemporary treatment regimens that include NACT. Sixteen patients received adjuvant chemotherapy postoperatively, seven of whom died due to disease progression. Among the 26 patients who underwent radical cystectomy, 17 were classified as M0. Of these, 7 received adjuvant chemotherapy, while 10 did not. Subgroup analysis of these localized patients suggests that adjuvant chemotherapy may provide a survival benefit, though the small sample size limits statistical significance. Univariate analysis showed no statistically significant association between adjuvant chemotherapy and OS (P=0.57), possibly due to this limitation. Importantly, we found that 56% of cases that underwent upfront surgery were stage 3 or above,

underscoring the need for neoadjuvant therapy in muscle-invasive disease. This is consistent with the National Comprehensive Cancer Network (NCCN) guidelines, which recommend concurrent chemoradiotherapy or NACT followed by local treatment (cystectomy or radiotherapy) for SCCB patients with limited stage disease. Three patients received immunotherapy, all of whom were PD-1-positive. Two patients remained tumor-free during follow-up, while one patient relapsed and died of distant metastasis 4 months after starting immunotherapy. These findings suggest that immunotherapy may offer a new treatment avenue for patients who are unresponsive or intolerant to chemotherapy.

Study limitations

The primary limitation of this study is the small sample size, which is a consequence of the clinical rarity of SCCB. This may introduce selection bias and limit the statistical power of the analysis. Larger sample sizes or multicenter randomized controlled trials are needed to strengthen the reliability and generalizability of these findings.

Conclusions

SCCB is a highly malignant and aggressive urinary system tumor predominantly affecting males, commonly diagnosed at an advanced stage, and prone to metastasis. There is currently no standardized treatment protocol. Radical cystectomy is the preferred treatment for localized SCCB, and NACT and immunotherapy can extend OS. T stage and distant metastasis are independent prognostic factors for SCCB patients. Early diagnosis and treatment are crucial for improving prognosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-2024-645/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-2024-645/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Changhai Hospital, Navy Medical University (approval No. CHEC2022-147) and individual consent for this retrospective analysis was waived due to the retrospective nature.

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