

Primary small cell carcinoma of the urinary bladder: a 10-year retrospective review of treatment and survival at a single institution.

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Abstract

Objective: Primary small cell carcinoma of the urinary bladder (SCBC) is a rare condition. SCBC accounts for less than 1% of all urinary bladder tumors. The purpose of this study is to report the clinical experience, clinical features, treatment modalities and overall survival of patients diagnosed with SCBC.

Patients and methods: There were 12 patients who were diagnosed with SCBC between January 2002 and December 2012 at our institution. The features of the patients, including age, gender, smoking history, presenting symptoms, tumor size, tumor locations, treatment modalities, stages, pathology appearance, recurrence and overall survival, were retrospectively analyzed.

Results: Twelve patients were diagnosed with SCBC (male: female ratio, 3:1; mean age, 69.8 ± 7.1 y; mean follow-up, 18.3 ± 5.6 months). Nine of these patients had a history of smoking. Eleven patients presented with gross hematuria, and the other patient presented with urinary frequency. Only one patient had stage I disease; eight patients had stage III disease, and the other three patients had stage IV disease. The mean tumor size was 4.62 ± 1.33 cm in diameter. Nine patients were treated with surgery (six patients underwent radical cystectomy, and three patients underwent TUR-BT); the other three patients received sequential chemoradiotherapy because of the presence of lymph node or distant metastasis at the time of the initial diagnosis. Overall, eight patients were treated with chemotherapy. At the time of data analysis, only one patient was alive. The median survival time of all patients was 14 months. The median survival time was 19 months for patients receiving chemotherapy compared to 12.5 months for patients who did not receive chemotherapy.

Conclusion: Although many efforts have been made to treat SCBC, there is still no standard strategy for treatment. Despite the high response rate to chemotherapy, the overall prognosis is poor. SCBC is an aggressive disease with a propensity for early metastasis. Prospective multi-institutional randomized studies are needed to establish the best treatment modalities. New molecular markers for early diagnosis and novel targeted therapies may play important roles in the future.

Keywords: Small cell carcinoma, Bladder cancer, Treatment, Prognosis.

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Introduction

SCBC is very uncommon, accounting for less than 1% of all urinary bladder carcinomas [1]. This disease was first described in 1981 by Cramer et al. [2]. Since then, nearly 250 cases have been reported in the literature [3]. Although rare, SCBC is an aggressive malignant tumor with a poor prognosis, as many patients have progressed to advanced stages and exhibit early metastasis by the time that they are diagnosed. This disease affects mostly elderly male patients with a history of cigarette smoking. The most common symptom of SCBC is gross hematuria; a few patients present with urinary frequency, dysuria or pain. Paraneoplastic syndrome is uncommon. However, because of the relative rarity of SCBC, there is no established treatment strategy for managing this disease. In previously published studies, different treatments, including surgery, radiotherapy (RT), chemotherapy (CT) and

combinations of treatments were used. We reported our clinical experience of treating 12 patients with SCBC at our hospital between 2002 and 2012.

Patients and Methods

Each patient provided written informed consent, and our hospital ethical review board approved the study. We retrospectively analyzed data from all of the patients diagnosed with bladder carcinoma from January 2002 to December 2012 at our hospital. A total of 1963 patients with bladder tumors were reviewed, and there were 12 patients who had been diagnosed with SCBC (excluding tumors from other sites with metastasis to the bladder). SCBC accounted for approximately 0.61% of all bladder tumors at our institution. We focused on age, smoking history, gender, presented symptoms, tumor size, tumor locations, treatment modalities, stages, pathology

appearance, recurrence and overall survival. Radical cystectomy (RC) was performed in six patients. The RC surgical procedure was complex and consisted of several steps, including pelvic lymph node dissection (PLND), the RC itself, and urinary diversion. In our study, there were eight patients who received cisplatin-based chemotherapy; all patients signed consent to receive chemotherapy preoperatively. Chemotherapy regimens varied according to the components of the tumor. SCBC patients with non-small-cell carcinomatous components received four cycles of alternating chemotherapy. Ifosfamide 2,000 mg/m² was infused over 3 h daily on days 1 through 4. Doxorubicin 25 mg/m² was infused daily on days 1 through 3. Patients received the EP regimen (etoposide plus cisplatin) at 3-week intervals. Etoposide 100 mg/m² was infused over 2 h daily on days 1 through 5; cisplatin 40 mg/d was infused in 1 L of normal saline with mannitol 20 g daily on days 1 through 3. Each regimen was repeated every 6 weeks. Pure SCBC patients received the EP regimen, which was repeated every 3 weeks. All of the patients received four cycles unless serious adverse reactions occurred. Two-phase radiotherapy was used; the dose was 45 Gy to the pelvis followed by a boost of 15 Gy to the bladder (total tumor dose 60 Gy).

Statistical analysis

All statistical analyses were conducted by using SPSS version 20.0 statistical software; all data were expressed as $\bar{x} \pm s$. Survival curves were plotted using the Kaplan-Meier method.

Results

The general features of the patients are listed in Table 1. Patients with SCBC were predominantly male (male: female ratio 3:1), and the mean age at diagnosis was 69.8 ± 7.1 y old. Nine patients (75%) had a history of cigarette smoking. Eleven patients presented with gross hematuria, and the other patient presented with urinary frequency. According to the 2002 TNM classification of urinary bladder cancer, patients were staged based on computed tomography (CT), chest x-ray, bone scan and postoperative pathological results [4]. Only one patient was diagnosed with stage I disease, eight patients had stage III disease, and the other three had stage IV disease (Table 1).

Table 1. Features of the patients with SCBC (n=12).

Features	N (%)
Age (y)	
<60	1 (8.33)
60-70	7 (58.33)
>70	4 (33.33)
Smoking history	
Smoker	9 (75)
Non-smoker	3 (25)
Gender	

Male	9 (75)
Female	3 (25)
Present symptoms	
Gross hematuria	11 (91.67)
Urinary frequency	1 (8.33)
Stage	
I	1 (8.33)
II	0 (0)
III	8 (66.67)
IV	3 (25)

Treatments of SCBC are shown in Table 2. Six patients underwent radical cystectomy, two of whom received neoadjuvant chemotherapy and two received adjuvant chemotherapy. Three patients were treated with transurethral resection of the bladder tumor (TUR-BT), and one of them received adjuvant chemotherapy. Three patients received sequential chemoradiotherapy because of the presence of lymph node metastasis or distant metastasis at the time of diagnosis. In all, 8 patients were treated with chemotherapy, and two of them received cisplatin-based regimens as described before. Prophylactic cranial irradiation (PCI) was not performed on these patients.

Table 2. The details and outcomes of the patients with SCBC.

Patient	Stage	Treatment	Relapse/death	Outcomes (m)
1	I	TUR-BT	Lung	Dead (11)
2	III	TUR-BT+CT		Alive (12)
3	III	TUR-BT	Liver	Dead (9)
4	III	Neoadjuvant+RC	Lung	Dead (30)
5	III	Neoadjuvant+RC	Bone	Dead (41)
6	III	RC+adjuvant	Brain	Dead (26)
7	III	RC+adjuvant	Pelvis	Dead (19)
8	III	RC	Lung	Dead (16)
9	III	RC	Bone	Dead (14)
10	IV	Chemoradiotherapy	Lung infection	Dead (10)
11	IV	Chemoradiotherapy	Neutropenia	Dead (12)
12	IV	Chemoradiotherapy	Respiratory failure	Dead (7)

Abbreviations: TUR-BT: Transurethral Resection of the Bladder Tumor; CT: Chemotherapy; RC: Radical Cystectomy.

The tumor characteristics are shown in Table 3. The mean tumor size was 4.62 ± 1.33 cm in diameter. Eight tumors were located on the lateral wall; two tumors were located in the fundus, one in the trigone, and one in the dome of the bladder.

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Our study identified five patients with pure SCBC, which accounted for 41.6% of the total patient population.

Table 3. The tumor characteristics of the patients with SCBC.

Tumor characteristics	N (%)
Tumor size (diameter)	
<4 cm	5 (41.67)
4-6 cm	3 (25)
>6 cm	4 (33.33)
Main tumor location	
Dome	1 (8.33)
Left lateral	4 (33.33)
Right lateral	4 (33.33)
Trigone	1 (8.33)
Fundus	2 (16.67)
Tumor components	
Pure SCC	5 (41.67)
SCC with non-small-cell carcinomatous components	7 (58.33)

The average follow-up time was 18.3 ± 5.6 months; at the time of this analysis, only one patient was alive. The overall median survival time was 14 months (Figure 1).

Regardless of the clinical stage, the median survival time was 19 months for patients receiving chemotherapy, *versus* 12.5 months for patients who had not received chemotherapy (Figure 2).

Tumors were consisted of small cells with a lack of cytoplasm, which also had uniform nucleus size, fine granular chromatin and insignificant nucleoli. Mitotic images were common (Figure 3).

Discussion

SCBC is a rare type of bladder cancer that only accounts for less than 1% of all urinary bladder cancers. SCBC is an aggressive malignant tumor that is detected in advanced stages and patients diagnosed with SCBC have a poor prognosis. Although rare, a dramatic increase in the incidence of SCBC in the past 15 y has been reported by Koay et al. [1].

The incidence has significantly increased from 0.05 cases to 0.14 cases per 100,000 people from 1991 to 2005, which might be associated with population aging [1].

SCBC normally affects older male patients with a history of cigarette smoking. According to previous studies, most patients were in their sixth to seventh decade of life [5-8].

The etiology of SCBC is still uncertain. Different theories have been postulated; the most widely accepted theory is that SCBC originates from a multi-potent stem cell that has the ability to differentiate into various cell types.

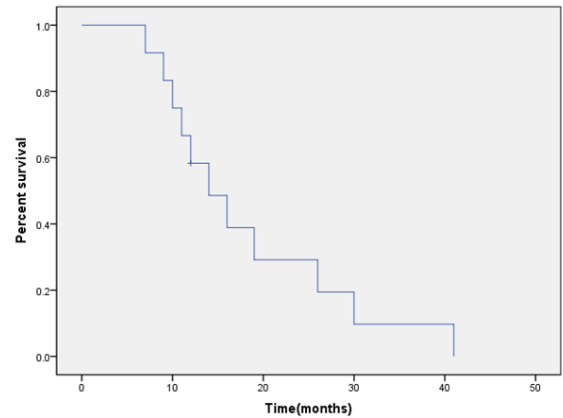


Figure 1. Kaplan-Meier survival rates for patients with SCBC.

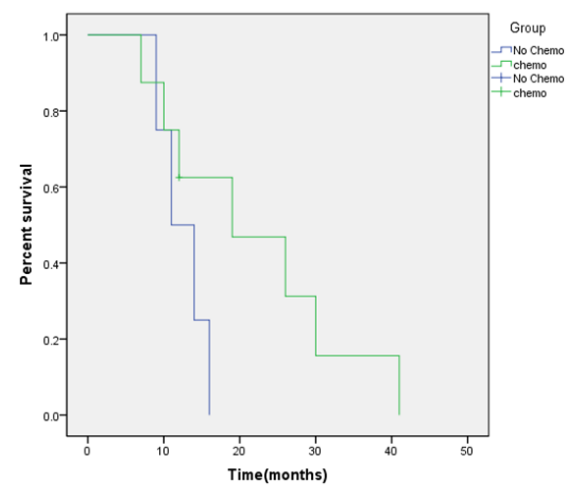


Figure 2. Kaplan-Meier survival curves for SCBC patients with or without chemotherapy.

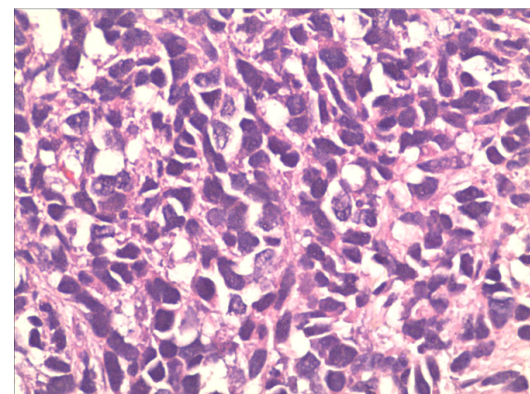


Figure 3. Pathologic characteristics: Tumors were consisted of small cells with a lack of cytoplasm, which also had uniform nucleus size, fine granular chromatin and insignificant nucleoli. Mitotic images were common (HE \times 400).

This theory was proposed due to the coexistence of SCBC with other types of bladder cancer such as urothelial carcinoma, adenocarcinoma, or squamous cell carcinoma within the same tumor [9-11]. Further support for this theory derives from the recent report by Cheng et al., which demonstrated an identical

pattern of allelic loss of coexistent urothelial and small cell counterparts, suggesting a common cell of origin [12]. Other hypotheses include the derivation of SCBC from the amine precursor uptake and decarboxylation system, and metaplasia from other high-grade malignancies [2,5].

According to the previous study by Church et al., cigarette smoking was a risky factor of SCBC [13]. The most common presentation was gross hematuria, which was similar to transitional cell carcinoma (TCC) [5,9,14-16]. Dysuria, pelvic pain, local irritation, urinary obstruction and urinary infections were other common symptoms. Some patients may also present with systemic symptoms including anorexia, fatigue and weight loss. However, paraneoplastic syndromes including Cushing syndrome, hypercalcemia and hypophosphatemia were less commonly observed [9,15-19]. Most of the tumors were located on the lateral wall of the bladder and were less common in the fundus, trigone, anterior wall, and dome of the bladder [1,20].

The diagnosis of SCBC was based on the WHO classification system (2004), which was also used for the diagnosis of lung small cell carcinoma (SCLC) [21]. Under microscopic examination, the cancer cells stained with hematoxylin and eosin have scant cytoplasm with few organelles. Tumors are composed of small or intermediate-sized malignant cells in nests or sheets with marked hypercellularity, necrosis and mitosis. Individual cells have rounded to oval overlapping nuclei with evenly distributed salt-and-pepper-like chromatin [21]. The deposition of basophilic material around blood vessels (the Azzopardi phenomenon) is also observed in many cases. Immunohistochemistry plays an important role in the diagnosis of SCBC. Most of the SCBC express neural markers, of which neuron-specific enolase is the most common [22,23]. Chromogranin A and synaptophysin positive cells are detected in half of the cases. Cytokeratin (CAM 5.2) is expressed in 25% of SCBC, and the expression pattern in SCBC is different from the expression pattern in high grade urothelial tumors [24]. Immunocytochemical studies are useful for distinguishing SCBC from other tumors such as malignant lymphoma, lymphoepithelioma-like carcinoma, Merkel cell carcinoma and poorly differentiated TCC. Chromogranin A is detectable in 50% of SCBC samples and only 5% of urothelial carcinoma samples. CD44v6 is positive in only 7% of SCBC samples and 60% of urothelial tumors. Cytokeratin 20 expression is positive in 46-73% of urothelial tumors and is absent in SCBC [25].

In the majority of patients (38% to 70%), SCBC coexisted with non-small-cell carcinomatous components including urothelial carcinoma, adenocarcinoma, squamous cell carcinoma or sarcomatoid carcinoma [26]. Pure SCBC is uncommon [21]. According to a previous study by Hou et al., SCBC was most often present with UC; UC was detected in 61.11% of patients with SCBC [27]. Cramer et al. suggested that SCBC might originate from metaplastic urothelium [2]. Other studies proposed that SCBC originated from a multi-potential stem cell with the ability to differentiate into various cell types. These hypotheses might explain the coexistence of SCBC with UC [28].

Staging of SCBC is based on the TNM staging system, which is used for UC. Unlike urothelial cancers, when the diagnosis is confirmed, most patients with SCBC are diagnosed with an advanced stage of the disease, even though some patients are initially diagnosed with organ confined disease [29]. This disease progresses quickly and becomes metastatic [1,30]. A clinically relevant two-stage system of limited (T1-4N0-1M0) and extensive disease (TxNxM1 or TxN2-3M0) is widely used to determine prognosis and treatment. Limited disease (LD) is classified as a disease localized to an area that could be included in 1 radiation port or surgical field. Extensive disease (ED) refers to any disease beyond LD [1].

The optimum therapy for SCBC is difficult to define. Because it is a rare tumor, there are no standard guidelines for treatment and most of the treatment decisions are based on retrospective studies from a single center. The management of SCBC involves a multimodal approach including chemotherapy, chemo- radiotherapy, and surgery with or without chemotherapy. Chemotherapy is the mainstay of treatment and improves overall survival [31,32]. Clinical stage and performance status are the determining factors that guide treatment decisions in patients with SCBC. Surgeries, including radical cystectomy, partial cystectomy, and TUR-BT, are commonly performed for the LD form of SCBC. TUR-BT alone is probably inadequate for LD patients due to high recurrence rates and a short mean survival of only 3 to 6 months [23,33]. TUR-BT is only performed when the general condition of the patient is not suitable for other treatment modalities or when the patient requests bladder-sparing surgery.

Radical cystectomy alone may not be curative in the majority of cases. It might be adequate for patients with early stage disease, as described in the studies from the Mayo clinic in which eight patients were diagnosed with stage II SCBC. In this study, six patients survived for at least 5 y, one patient had local recurrence and one patient developed metastatic disease less than one year after the surgery [5]. However, as most patients with SCBC present with advanced stage disease at the time of diagnosis, surgery without chemotherapy may be inadequate to treat SCBC. In a review by Cheng et al., there was no significant difference in survival between patients who underwent cystectomy and those who did not (5-y survival, 15% vs. 18%, $P=0.65$) [14]. According to a recent report from the MD Anderson Cancer Center, 52% of patients who underwent cystectomy had a better survival, and neoadjuvant chemotherapy administered before surgery played an important role in improving overall survival and in the pathologic downgrading of the tumor [8,34]. Half of our patients received radical cystectomy, and four received neoadjuvant or adjuvant chemotherapy (Table 2).

The most common regimen performed for SCBC is platinum-based chemotherapy (etoposide and cisplatin), which appears to improve overall survival. Mackey et al. reported that cisplatin-based chemotherapy was the only type of chemotherapy associated with better overall survival according to a multivariable analysis [31]. According to the study by Bex

et al., there is a significant difference in survival apparently between SCBC patients who received chemotherapy and those who did not, regardless of the tumor stage. The median duration of survival of patients who received chemotherapy was 15 months, while the length of survival of patients without chemotherapy was only 4 months ($P=0.003$) [8]. In another published study, patients who received neoadjuvant chemotherapy had a significantly better 5-y survival rate than those who had undergone cystectomy alone (78% vs. 36%, $P=0.026$) [35]. Quek et al. reported on a series of 20 patients who had undergone cystectomy. Patients treated with neoadjuvant or adjuvant chemotherapy had significantly better overall and tumor-free survival [7]. In our study, eight patients received cisplatin-based chemotherapy. All of the patients received four cycles unless serious adverse reactions occurred. The median survival time was 14 months, but the patients who had received chemotherapy had improved outcomes, with a median survival of 19 months compared with 12.5 months in the patients who had not received chemotherapy (Figures 1 and 2). Despite the rarity of this cancer and a lack of randomized controlled studies, the available data strongly suggests a significant survival advantage with chemotherapy.

Chemoradiotherapy has been shown to be effective in the treatment of SCLC and has been used in many studies for SCBC [36]. Oblon et al. first described chemotherapy combined with radiotherapy for SCBC [37]. In a retrospective study by Bex et al., 17 patients with LD received sequential chemo-radiotherapy followed by TUR-BT, 88% of patients had a complete response, and the median overall survival was 32.5 months [8]. Bastus et al. reported on 5 patients with SCBC treated with platinum-based chemotherapy and radiotherapy; four patients had a complete response and only one exhibited local relapse. The patients had a disease-free survival of between 10 to 60 months [38]. Lohrisch et al. described a retrospective analysis of 10 LD patients in whom the overall survival at 2 and 5 y was 70% and 44%, respectively. Chemoradiotherapy has been shown to improve survival, and when combined with transurethral resection, could be used as a trimodal approach for patients who wish to avoid or delay radical cystectomy [15]. However, these patients accepted that chemo- radiotherapy with bladder preservation may increase the risk for the development of urothelial cancers, although it is uncommon [15].

Patients with metastasis have a poor prognosis, with a median survival of approximately 7 to 13 months [34,39]. A cisplatin-based chemotherapy regimen is generally considered to be the best choice [5,15,36]. The incidence of brain metastases in patients with SCLC is approximately 50-60% over 2 y. Prophylactic cranial irradiation (PCI) is the established treatment for patients with SCLC who have a complete response to therapy; PCI has been shown to prolong disease-free survival and to improve overall survival [22]. Nevertheless, data on the use of PCI to prevent brain metastases in SCBC is limited, and the role of PCI is unclear.

SCBC is a rare and aggressive tumor; patients often present with an advanced stage of the disease and have a poor

prognosis. SCBC mostly affects older men with a history of smoking. Because SCBC is rare, there are no standard guidelines for the management of patients. Chemotherapy is the mainstay of treatment and has demonstrated survival benefits. Based on previous studies, we recommend a combined modality approach for SCBC. Patients with LD who are eligible for surgery may experience better outcomes with neoadjuvant chemotherapy followed by radical cystectomy. For patients not eligible for surgery, sequential chemoradiotherapy might improve overall survival. Palliative chemotherapy should be offered to patients with extensive disease.

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