

REVIEW ARTICLE

Small Cell Carcinoma of Bladder - A Rare Entity: Review of Literature

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Abstract

Introduction: Small cell carcinoma of the urinary bladder (SCCB) is an extremely rare malignancy, accounting for < 1% of all bladder tumors with poor prognosis due to its highly aggressive behaviour and high metastatic potential.

Aim: This study aimed to update the management and outcome of SCCB by searching the relevant literature.

Methods: Relevant studies were identified by searching PUBMED, MEDLINE using a combination of terms such as small cell carcinoma, bladder cancer, radical cystectomy, radiation therapy and chemotherapy.

Results: Studies have shown that SCCB has a significant male predominance, occurs mainly during the 7th and 8th decade of life and macroscopic hematuria is the most common presenting symptom. Patients with surgically resectable disease should be managed with multimodal therapy including chemotherapy, surgery and/or radiotherapy. Patients with unresectable disease (> or = cT4bN+M+) should be managed with palliative chemotherapy.

Conclusion: Poor prognosis and rarity render disease management complicated. Patients with surgically resectable disease should be managed with multimodal therapy associating chemotherapy, surgery and/or radiotherapy.

Keywords: Small Cell Cancer Bladder; Neuroendocrine Tumor; Chemotherapy; Radiotherapy; Poor Prognosis; Aggressive

Introduction

Bladder cancer is the ninth most common cancer in the world, with urothelial (previously known as transitional cell) carcinoma being the predominant histologic type. Urothelial cancer of bladder remains the second most common genitourinary malignancy after prostate cancer in men worldwide, with 430,000 new cases diagnosed in 2012 [1].

Primary small cell carcinoma of the bladder (SCCB) is a rare poorly differentiated neuroendocrine tumor accounting for less than 1% of all bladder tumors. The first case was described by Cramer, *et al.* in 1981 [2]. Small cell carcinomas of the urinary bladder are frequently found combined with other histological forms of bladder cancer such as urothelial, adenocarcinoma and squamous cell carcinoma. The pathogenesis of primary small cell carcinoma of bladder (SCCB) is unknown. Many hypotheses have been proposed till date but the most important hypothesis was the origin of SCCB may be a multipotential common stem cell [2]. Because of the rarity of small cell carcinoma, there is no standard treatment of the disease. This comprehensive review would provide a real insight into the epidemiology, pathogenesis, diagnosis, staging, treatment, and prognosis of SCCB.

A database search was conducted on Google scholar, PubMed and Medline using phrase words, small cell carcinoma, bladder cancer, in combination with terms such as "treatment," "features," "diagnosis" and "prognosis." References of all publication were also searched. All relevant publications were collected, reviewed and were analyzed in detail to summarized in this paper.

Epidemiology

Small cell carcinoma of the bladder is a rare entity with a mean frequency of 0.7% range between 0.35% and 1.8% [2-8]. Urothelial cancer of bladder is three times more common in men than in women [2]. On the other hand, majority of the patients are male, with male: female ratio of 5:1 range between 0.8:1 to 16:1 [9-15]. It is found in sixth to seventh decade of life. In urothelial bladder cancer the median age at diagnosis is 69 years old for males and 71 years old for females [2]. Whereas for small cell bladder cancer mean age at time of first diagnosis is 67 years; ranging between 29 to 91 year [10-14]. Like transitional cell carcinoma (TCC), SCCB is often associated with a smoking history in 65-79% of the cases [10-12]. It is associated with a more aggressive behaviour and poorer outcome than bladder TCC [16-19] (Table 1).

Ref	Pt No.	Age	Sex (M:F)	Clinical features	Frequency of SCC	addiction	Treatment	Results
Blomjous (1989)	18	69(50-81)	2.6:1	Hematuria, dysuria	0.48%	NR	CT (5pts) No CT (13pts)	2 year OS in two groups is 60% vs 15.5%
Holmang (1995)	25	71.2(54-87)	2.5:1	NR	0.7%	NR	RC→RT (18pts) CT (2pts) None (5pts)	5 years survival in the whole group is 20% vs radical cystectomy group (28%)
Lohrisch (1999)	14		1:1	Hematuria (100%), local pain (36%)	0.35%	79%	CT-RT (8pts) CT →RC (1pt) RT (2pts) None (2pts)	Survival at 5 years is 70% in the CT group vs. 0% in the non CT group
Iczkowski(1999)	46	67(32-91)	6.7:1	NR	NR	NR	NR	NR
Siefker-Radtke 2004 (MD Anderson) (2004)	88	68 (31-87)	3.3:1	Hematuria	NR	NR	NACT-RT (21pts) RC(25pts)	5 year OS in chemoradiotherapy arm vs Radical Cystectomy arm is 78% vs 36%
Cheng(2004)	64	66(36-83)	3.3:1	Hematuria (88%)	NR	65%	RC(38) RT(10) CT(23)	No significant survival difference was found between patients who did and did not undergo cystectomy (P = 0.65). 1-year, 18-month, 3-year, and 5-year disease-specific survival rates were 56%, 41%, 23%, and 16%, respectively.
Mangar(2004)	14	74 (54-91)	6:1	Hematuria (93%)	NR	NR	RC→CT→RT(1) RC→RT(3) RC(2) PRT(5) None(3)	The overall median survival was 5 months. Patients receiving radical treatment had a median overall survival of 21 months
Choong(2005)	44	67(47-88)	3:1	Hematuria (68.2%); Incidental finding (18%); Urinary obstruction (6.8%)	0.5%	NR	RC(17pts) PC (5pts) RC→CT (12pts) CT (5pts)	The overall median survival was 1.7 years. The 1-year survival rates for patients with Stage II, Stage III, and Stage IV disease were 100.0%, 76.9%, and 36.8%, respectively
Abrahams(2005)	51	67(39-87)	4:1	Haematuria (63%); Dysuria (12%)	NR	NR	RC (12pts) CT (9pts) NACT→RC (9pts)	5 Yr OS in cystectomy group is 40% and was NR in other arms
Bex(2005)	25	64(40-90)	11.5:1	NR	NR	NR	CT (13pts) No CT (12pts)	OS in CT arm vs no CT arm was 15 vs 4 months respectively (p = 0.003)
Quek(2005)	25	68(40-82)	3:1	NR	1%	NR	RC→ACT(13) NACT→RC(1) RC(11)	Five-year OS and RFS was 10% and 13%, respectively. Patients receiving multimodality therapy had significantly better OS (p = 0.051) and RFS (p = 0.003) than those treated with cystectomy alone.
Mukesh(2008)	20	68	3:1	NR	NR	NR	CT (13pts) No CT (7pts)	Outcome in CT group vs outcome in non-CT (OS = 33 months vs. 3 months, respectively)
Ismaili(2008)	14	60.5(45-78)	16:1	NR	1.8%	78.5%	RC→CT(4) RC(5) CT→RC(2) CT(1) CTRRT(1) None(1)	Mean overall survival was 27.2 months for all patients and 38.6 months for patients treated with cystectomy and adjuvant chemotherapy.
Bex(2009)	17	62(44-78)	16:1	NR	NR	NR	CT→RT (17pts)	OS was 32.5 months 2, 3, and 5 years survival was 56%, 47%, and 36% respectively

Ref	Pt No.	Age	Sex (M:F)	Clinical features	Frequency of SCC	addiction	Treatment	Results
Siefker-Radtke (2009)	30	66.2(43-81)	14:2	NR	NR	NR	Resectable (18pts) Non resectable SCCB (12pts)	OS was 58 months vs 13.3 months, in operable vs non operable patients, respectively
Bex (2010)	51	65(57-74)	4.1:1	NR	NR	NR	CTRT PCT	Survival of patients with LD was 35 months (CTRT group) vs 6 months in patients with ED (palliative CT).
Bastus(1999)	5			NR	NR	NR	CT→RT(5)	2 year OS was 80%
Bhatt VR(2014)	14	77.5 years (range 36-89). C	.8:1	hematuria (61%)	2.4%	NR	cystectomy(72%), CT (50%) RT (22%).	Median overall survival was 18.5 months (95% confidence interval, 7-36 months). radical surgery with or without chemotherapy had a median overall survival of 26 months compared to 10 months with other treatment
Chen Z(2017)	9	56 (43 – 68)	3.5:1	Hematuria	NR	55%	RC (100%) ACT in 4 pts Adj RT in 1 pt	median survival time was 33 months.
Eswara JR(2015)	28	NR	NR	NR	NR	64%	TURB and/ or cystectomy, chemotherapy, and/or radiation	Patients with T1-2NoMo had a median survival of 22 months compared to 8 months for those with more advanced disease (p = 0.03).
Geynisman DM(2015)	960	69.2, (29–90)	3:1	NR	3.33%	NR	50% of subjects received palliative therapy local therapy (15%) surgical (21%) radiation-based (14%) multimodal therapy.	Median OS was 8.61 months;

Table 1: summarizing important case series with epidemiology, clinical characteristics, treatment and outcome

Pathogenesis

The pathogenesis of primary small cell carcinoma of bladder (SCCB) is unknown. However, several hypotheses were proposed to explain the origin of small cell carcinoma (SCC) in the bladder. The most important hypothesis were malignant transformation of bladder neuroendocrine cells gives rise to bladder SCC; SCCB arises from urothelial metaplastic changes and the most accepted theory suggests that the origin of SCCB may be a multipotential common stem cell that has the ability to differentiate into various cell types depending on the influence of specific transformation or progression-related gene: this may explain the coexistence of SCCB with TCC, and the heterogeneity of the immunohistochemical staining (cytokeratin [CK] and endocrine markers) [2,3].

Clinical presentation

Macroscopic hematuria was the most common presenting symptom at the time of diagnosis followed by dysuria and irritative symptoms [4,6,7,11,20-24]. Cushing's syndrome and hypercalcemia were also reported in rare cases [2,11,14].

Diagnosis

Diagnosis is obtained via histopathological examination of specimens obtained by cystoscopy and transurethral resection of bladder tumor.

The tumor usually has a pattern of diffuse growth, whereas occasionally and focally, nests and trabeculae are observed. The tumor cells have sparse cytoplasm and consequently exhibit nuclear crowding and molding. Nucleoli are often inconspicuous, and the chromatin is finely stippled (referred to as powdery or salt-and-pepper). Frequent mitoses, crush artifact, geographic necrosis, and Azzopardi effect are indicative of its high proliferation rate [2]. In most reports, the authors showed a higher incidence of mixed SCC [4-7,20,24]. In a study by Abraham, *et al*, mixtures of SCC with transitional cell carcinoma was present in 70% of the cases, while mixtures of SCC with adenocarcinoma and squamous carcinoma were present only in 8% and 10% of the cases respectively [20].

Immunohistochemistry was also very important for the diagnosis of SCC-BL, Neuroendocrine markers including NSE (neuron specific enolase), synaptophysin, serotonin, chromogranin are immunoreactive in 88.5%, 50%, and 72.4% cases respectively [4,10,20]. SCCB also stained with epithelial markers including cytokeratin, EMA, CK7 and CAM 5,2 [24-28]. Few studies have also demonstrated the expression of TTF-1, EGFR, C-KIT and PDGFRA [2-5].

A Comparative genomic hybridization (CGH) study has demonstrated chromosomal deletions at 10q, 4q, 5q and 13q [2,3].

Imaging

Pelvic and abdomen computed tomography can be used to determine bladder mass and the loco regional extension of the disease, outside the bladder wall and in the pelvic lymph nodes.

Small cell bladder cancer is sometimes difficult to identify by conventional imaging tools due to small tumour size and variable anatomical location. Computed tomography, ultrasound, and magnetic resonance imaging are sometimes unable to detect such tumors. Here comes the role of functional imaging in NETs [2].

Somatostatin receptor scintigraphy (SRS) is an important tool for imaging of NETs and has been shown to be superior as compared to other morphological imaging modalities because the percentage of small cell carcinoma component in small cell bladder cancer is positively correlated with the percentage of SSTR-2A (somatostatin receptor 2A) expression while negatively correlated with patient age [2].

There is physiologic uptake of Ga-68 DOTATATE seen in the bladder which makes the possibility of using PET scan out of question [29-34].

CT scan thorax, Bone scan and brain CT scan are recommended in advanced stages.

Staging

As for bladder Transitional Cell Carcinoma (TCC), the TNM-staging system was commonly used for SCCB. In most cases, the diagnosis is made at advanced stages (T3-T4/N+/M+). More than 95% of SCCB cases are diagnosed at muscle invasive stage T2 or more [7-11,20,24].

The most frequent sites of metastasis were pelvic and retroperitoneal lymph nodes (28.6% - 53%), liver (23.8% - 47%), bone (23.8% - 33%), brain (7.9% - 16%) and lung (9.5% - 13%) [7,11].

Differential Diagnosis

1. Metastatic SCCB from other sites example lung: can be differentiated from bladder SCC due to presence of TCC component in bladder SCC
2. Primary lymphoma of bladder: positive for LCA and negative for neuroendocrine markers
3. Direct invasion of bladder by SCC of prostate which is negative for PSA.

Disease management

Because of the rarity of SCCB, there is no standard treatment of the disease. Many treatments have been tried, but the optimal management of these tumors has multimodality therapy, which includes surgery, chemotherapy, and radiation [2]. The treatment options include either the radical cystectomy followed by adjuvant treatment or the bladder preservation protocols.

Surgery

Small cell bladder carcinomas are often treated as small cell lung carcinomas with the exception that surgical therapies are often important part of management in small cell bladder carcinomas. In a study by Cheng, *et al.* there was no significant 5-year overall survival difference between the 38 patients who had undergone cystectomy alone and those who hadn't undergone cystectomy and received combined modality treatments ($p=0.65$). The exact 5-year disease-free survival rates were 16 and 18%, respectively in the two groups [24]. In another study out of 22 patients, 5 underwent radical cystectomy and received adjuvant chemotherapy. In these patients overall survival was higher but not statistically significant in comparison with the other patients who hadn't received adjuvant chemotherapy ($p>0.10$) [2]. Choong, *et al.* reported on 44 patients and the 5-year overall survival rates for patients with stage II, III, IV disease were 63.6, 15.4 and 10.5%, respectively. The authors proposed that all patients with limited disease should undergo radical cystectomy and adjuvant treatment should be considered for patients with stage III and IV disease [7].

Radiation Therapy

Due to the similarities of histological and clinical course of SCCB with SCLC, combined chemo radiotherapy is preferred as the main treatment for SCCB [2-4,6,35]. Lohrisch, *et al.* reported on 14 patients (71% underwent surgery) and observed 70% 2-year and 44% 5-year overall survival in 10 patients who were treated with chemotherapy and local radiotherapy [6]. Total radiotherapy doses ranged from 3500 to 6400 cGy. Studies have also shown that radiation therapy when combined with chemotherapy was

highly effective compared to radiation therapy alone [5,16]. Bex A, *et al.* reported on 17 patients, all treated with sequential chemo radiotherapy and concluded that the clinical results of this approach were comparable to a series of SCC-BL treated with cystectomy and adjuvant chemotherapy [16]. The 5-year survival of patients with SCCB treated with radiation ranges from 20% to 70% in various studies in literature [5,6,21]. However, most of these studies have utilized chemotherapy either in the Neoadjuvant setting or as an adjuvant to radiation therapy.

Chemotherapy

Chemotherapy is the major treatment modality for SCCB [1,2]. In surgically resectable disease chemotherapy is used as Neoadjuvant therapy to shrink the tumour prior to local therapy or as adjuvant treatment after surgical resection whereas in advanced disease palliative chemotherapy is used [7,11].

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy followed by surgery has shown improvement in the 5-year disease-free survival. Siefker-Radtke, *et al.* reported on 46 patients. Twenty-one patients received Neoadjuvant chemotherapy before radical cystectomy and 78% achieved a 5-year overall survival which was much higher compared to 36% 5-year overall survival of 25 patients who had undergone radical cystectomy alone [11].

Ahsaini, *et al.* reported a rare case of a 54-year-old Arab male native of Moroccan, diagnosed as small cell neuroendocrine carcinomas of the ureter and the bladder with stage T2N0M0. Neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin (EP) was given, and nephroureterectomy associated to a cystoprostatectomy was carried out. After 24 months of follow-up, no local or distant metastasis was detected. Based on these data, NACT should be considered as the treatment of choice for surgically resectable SCCB [2].

Adjuvant chemotherapy

Studies have demonstrated that adjuvant chemotherapy is associated with increased 5-year overall survival [4,9,21]. Blomjous, *et al.* reported on 18 cases. Five patients who received chemotherapy had prolonged overall survival periods (15-38 months). The authors suggested that chemotherapy may offer considerable benefit [4]. Bex, *et al.* reported on 25 patients, 13 of whom received platinum-based chemotherapy; 5 of these patients had undergone complete transurethral resection of the bladder (TURB) before chemotherapy. Overall survival was 15 months vs. 4 months of those without chemotherapy ($p=0.028$) [21].

Palliative chemotherapy

In case of stage IV disease or metastatic cancer, radical surgery alone does not result in good outcome. In one study, Neoadjuvant chemotherapy (alternating ifosfamid/doxorubicin and etoposide/cisplatin) with intent for surgical consolidation in responders resulted in 100% partial or complete response rate in patients with metastatic disease, however, most patients relapsed and the overall survival was 13.3 months [14].

There is a lack of data on the second-line chemotherapy options for patients who develop disease progression or recurrence. In a case series ($n=3$), single-agent weekly vinorelbine had shown promising safety and efficacy profile. In study by Bhatt, *et al.* one patient who had disease recurrence after neoadjuvant chemotherapy with cisplatin and etoposide followed by radical surgery was successfully treated with cisplatin and gemcitabine followed by paclitaxel (nanoparticle albumin bound), thus indicating the possible role of these agents [18].

Nervous system and Bone metastasis

Based on the high efficacy of chemotherapy against metastatic small cell carcinoma, palliative radiotherapy is rarely adopted. However, radiotherapy is reserved for treatment of symptomatic brain metastases, symptomatic bone metastases and cord compression.

The pooled analysis of available literature revealed a cumulative incidence of brain metastasis of approximately 11% among small cell bladder carcinomas. Based on this, some experts recommend against prophylactic cranial irradiation [15]. On another hand, the authors at MD Anderson, report in the phase II clinical trial a 50% incidence of brain metastases in patients with stage III-IV disease; this information suggests a possible group to consider for PCI [14].

Targeted therapy

Despite the use of multimodality treatment, the outcomes of treating bladder SCC remain poor. Novel targeted agents have been tried to improve survival. The majority of SCCB express vascular EGFR on endothelial cells, the EGFR, the c-KIT, the platelet-derived growth factor receptor, and the fibroblast growth factor receptor [31, 36-46]. Antiangiogenesis agents and tyrosine kinase inhibitors can be tried in metastatic setting. However, the beneficial effect of these agents in terms of survival has not been proven yet.

Conclusion

SCCB is a very rare and extremely aggressive malignancy. At the time of diagnosis the disease is usually at advanced stage (pelvic lymph nodes or distant metastasis). Poor prognosis and its rarity render management difficult. No definitive treatment is yet established, but combined therapy with systemic platinum-based chemotherapy and local radiotherapy with preservation of the bladder seems to be the most efficient therapeutic approach for patients with limited disease.

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