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ORIGINAL ARTICLE

Small cell carcinoma of the bladder: A search of the current literature

K. Gkirlemis, A. Miliadou, G. Koukourakis, A. Sotiropoulou-Lontou
Second Department of Radiation Oncology, 'Saint Savvas' Anticancer Institute of Athens, Athens, Greece

Summary

Purpose: Small cell carcinoma of the urinary bladder (SCC-BL) is an extremely rare malignancy, accounting for < 1% of all bladder tumors. Its prognosis is very poor because of its highly aggressive behavior and high metastatic potential. This study aimed to update the management and outcome of SCC-BL by searching the relevant international literature.

Methods: Relevant studies were identified by searching MEDLINE and the Cochrane Central Register of Controlled Trials using a combination of terms such as small cell carcinoma, bladder cancer, therapeutic approach, radical cystectomy, radiation therapy and chemotherapy. Additional papers were identified from reviewing references of relevant articles.

Results: Previously published series have shown that SCC-BL has a significant male predominance, occurs mainly during the 7th and 8th decade of life and macroscopic hematuria is the most common presenting symptom. According to the most important studies, cystectomy alone seems not to be efficient enough for the management of the disease. On the other hand, radiation therapy when combined with chemotherapy is highly effective with increased survival rates.

Conclusion: Poor prognosis and rarity render disease management complicated. A definitive treatment is not yet established but combined therapy with systemic platinum-based chemotherapy and adjuvant local radiotherapy seems to be the most effective therapeutic approach for limited-stage SCC-BL. Further research is required in order to clarify whether prophylactic cranial irradiation (PCI) should be performed on a regular basis.

Key words: bladder cancer, chemotherapy, radiation therapy, small cell carcinoma

Correspondence to: Konstantinos Gkirlemis, MD.
Second Department of Radiation Oncology, 'St Savvas' Anticancer Institute of Athens, 171 Alexandras Ave, GR11522 Athens, Greece.
Tel: +30 210 6409 420, E-mail: kostasgkirlemis@hotmail.com
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Introduction

Small cell carcinoma (SCC) comprises a fifth of lung cancers [1] but has also been described in extrapulmonary sites such as esophagus, breast, larynx and bladder. Reported extrapulmonary sites in the literature are summarized in Table 1.

SCC-BL, histologically identical to small cell lung carcinoma (SCLC), is an extremely rare malignancy that accounts for < 1% of all bladder tumors. Incidence rates of SCC-BL range from 0. 48 to 1% according to some important studies shown in Table 2.

The first case [14] was reported in 1981 and since then about 1000 cases have been published in small series and case reports. The prognosis is very poor as SCC-BL is associated with a highly aggressive behavior and high metastatic potential. he 5-year overall survival rates depend on the stage of disease at the time of the diagnosis [15] and the kind of treatment.

Herein, a search of the current literature on the management and outcome of SCC-BL was attempted and presented.

Methods

Identification of eligible studies

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (last search on May 2012) using combinations of terms, such as: small cell carcinoma, bladder carcinoma, therapeutic approach, radical cystectomy, radiation therapy and chemotherapy. We considered all English-written metaanalyses, randomized controlled trials and research trials providing evidence about the therapeutic interventions in SCC-BL and future directions of ongoing research.

Data extraction

Information was extracted from each eligible study. The data recorded included author's name, year of publication, number of patients included in the study, combination(s) of treatment(s) used, doses of radiation therapy, disease free survival, median time to progression, median and overall survival.

Results

Bladder cancer accounted for 5% of all newly diagnosed cancers and was the second most common urologic malignancy. The incidence rates in Western countries were the highest. Transitional cell carcinomas represented the majority (> 90%) of all bladder cancers. Pure squamous cell carcinomas accounted for 5 to 8%, pure adenocarcinomas for 1 to 2% and the rare extra pulmonary SCC-BL accounted for < 1% (Table 2).

Some of the most known causes which seem to be associated to bladder cancer were cigarette smoking, exposure to industrial chemicals, obstructive uropathy, fertilizers, radiation exposure, genetic predisposition and probably coffee consumption [11,16].

Previously published series have shown that SCC-BL had a significant male predominance with a male to female ratio between 2:1 – 16:1 [8,12,15,22-26]. SCC-BL occurred mainly during the 7^{th} and 8^{th} decade of life [8-10,12,15,16,18-22,27-30]. Mean age at the time of diagnosis was usually 67 years. Macroscopic hematouria was the most common presenting symptom (>63%) at the time of diagnosis [8,9,11,12,15,16,18,19,21,22,24,31], followed by dysouria and irritative symptoms. Cushing's syndrome [12,32] and hypercalcemia [33] were also reported in rare cases.

SCC-BL was usually diagnosed as locally advanced disease, presented on MRI or CT scan as a locally invasive mass (Figure 1). Additionally, SCC-BL was characterized by a high metastatic potential involving parailiac and paraaortic lymph nodes, liver, vertebral and costal bones, abdominal cavity and brain [8,12,16].

Histologically SCC-BL was identical to SCLC, composed of small round tumor cells with sparse cytoplasm, round to oval nucleus and numerous mitotic figures (Figure 2). Specimens were obtained by cystoscopy and transurethral biopsy [8]. Immunohistochemistry was also very important for the diagnosis of SCC-BL, showing positive immunoreactivity to neuroendocrine markers including NSE (neuron specific enolase), synaptophysin, serotonin, chromogranin and epithelial markers including cytokeratin and CAM 5,2 [8] . Low incidence rates and aggressive clinical course of SCC-BL render disease management complicated. Cystectomy alone as treatment of SCC-BL seemed not to be efficient, especially for patients diagnosed with advanced disease stages [13,18,28,34].

Table 1. Reported small cell carcinoma in extra-pulmonary sites

First author	*Year of publication*	*Extrapulmonary sites reported*
Matsusaka [2]	1975	Stomach
Wade [3]	1983	Breast
Capella [4]	1984	Kidney
Galanis [5]	1997	GI: pancreas, esophagus, larynx, salivary glands; GU: penis, bladder, prostate; GYN: endometrium, ovary, cervix, lymph nodes; submandibular lymph nodes, inguinal lymph nodes, thymus
Ibrahim [6]	1984	Head/ neck, esophagus, stomach
Abbas [7]	1995	Pharynx, larynx, esophagus, pancreas, vagina, uterus, skin, breast, cervix, kidney, prostate, bladder

GI: gastrointestinal, GU: genitourinary, GYN: gynecological

Table 2. Incidence rates of small cell carcinoma of the bladder

First author	*Year of publication*	*Number of patients*	*Frequency of SCC-BL, %*
Blomjous [8]	1989	18	0.48
Lopez [9]	1994	6	1
Holmang [10]	1995	25	0.70
Lohrisch [11]	1999	14	0.35
Choong [12]	2005	44	0.5
Quek [13]	2005	25	1

SCC-BL: small cell carcinoma of the bladder

Cheng et al. [15] reported on 64 patients. The authors found that 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. Grignon et al. [18] reported on 22 patients; 5 of these 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). Surgery alone seems to be effective only for early disease stages, however diagnosis of SCC-BL is rarely performed at early stages [10]. Choong et al. [12] 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.

The most commonly used chemotherapy regimen was etoposide and cisplatin (EP). Holmang et al. [10] reported on 25 cases, concluding that limited stage SCC-BL can be cured by partial or radical cystectomy combined with radiotherapy. Total doses of 51 and 67 Gy had been delivered to long-term survivors in that series.

The most important studies are summarized in Table 3. Based on their results, one can conclude that chemotherapy is crucial for the treatment of SCC-BL. Neoadjuvant chemotherapy followed by surgery is proven to improve the 5-year disease-free survival. Siefker-Radtke et al. [29] 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. Moreover, the majority of the studies showed that adjuvant chemotherapy is associated with increased 5-year overall survival. Blomjous et al. [8] reported on 18 cases. Five patients who received chemotherapy

Table 3. Eligible studies for small cell carcinoma of the bladder

First author [Ref]	*Year of publication*	*Number of patients*	*Treatment*	*2- year overall survival %*	*5- year overall survival %*	*Overall survival (months)*
Blomjous [8]	1989	18	Chemotherapy (5pts)	60	NR	NR
			No chemotherapy (13pts)	15.5	NR	NR
Lopez [9]	1994	6	Cystectomy alone (4pts)	NR	NR	NR
			Cystectomy-radiotherapy (1pt)	NR	NR	5-25
			TURB – radiotherapy (1pt)	NR	NR	NR
Holmang [10]	1995	25	Radical cystectomy-radiotherapy (18pts)	28	28	0
			Chemotherapy (2pts)	0	0	7.15
			No therapy (5pts)	0	0	-
Lohrisch [11]	1999	14	Chemotherapy-radiotherapy (8pts)	88	NR	NR
			Chemotherapy-radical cystectomy (1pt)	70	44	
			Radiotherapy (2pts)	0	0	15.11
			No therapy (2pts)	0	NR	8.2
Siefker- Radke [29]	2004	46	Neoadjuvant chemotherapy – radiotherapy (21pts)	NR	78	NR
			Radical cystectomy alone (25pts)	NR	36	NR
Abrahams [16]	2005	51	Cystectomy (12pts)	NR	40	23
			Chemotherapy (9pts)	NR	NR	NR
			Neoadjuvant chemotherapy-radical cystectomy (9pts)	NR	NR	NR
Choong [12]	2005	44	Radical cystectomy (17pts)	NR	NR	NR
			Partial cystectomy (5pts)	NR	NR	NR
			Radical cystectomy-chemotherapy (12pts)	NR	NR	NR
			Chemotherapy (5pts)	NR	NR	NR
Bex [27]	2005	25	Chemotherapy (13pts)	NR	NR	15
			No chemotherapy (12pts)	NR	NR	4
Mukesh [36]	2008	20	Chemotherapy (13pts)	NR	NR	33
			No chemotherapy (7pts)	NR	NR	3
Siefker- Radke [25]	2009	30	Resectable SCC-BL (18pts)	NR	NR	58
			Non resectable SCC-BL (12pts)	NR	NR	13.3
Bex [17]	2009	17	Sequential chemoradiotherapy (17pts)	56	36	NR
Bex [26]	2010	51	Limited disease	NR	NR	35
			Extensive disease	NR	NR	6

Pts: patients, NR: not reported

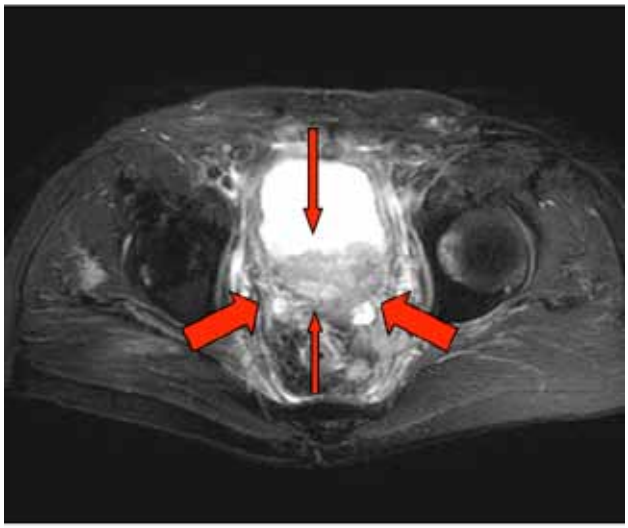

Figure 1. MRI of abdomen and pelvis showing small cell carcinoma of the bladder as a locally invasive mass (arrows).

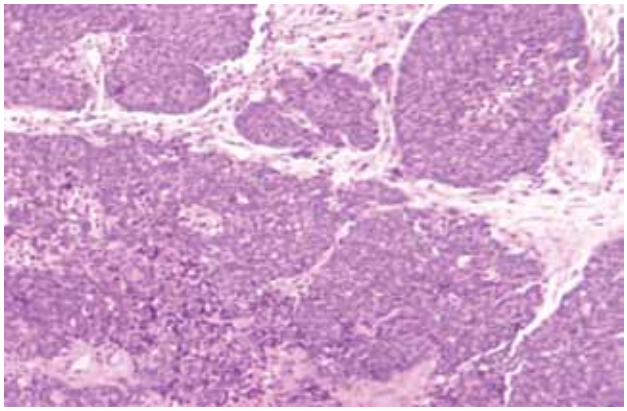

Figure 2. Immunohistochemistry of small cell carcinoma of the bladder showing small cells with sparse cytoplasm and hyperchromatic nuclei (hematoxylin and eosin x20).

(doxorubicin, cyclophosphamide and methotrexate-cisplatin) had prolonged overall survival periods (15-38 months). The authors suggested that chemotherapy may offer considerable benefit. Bex et al. [27] 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).

Due to the similarities of histological and clinical course of SCC-BL with SCLC, combined chemoradiotherapy is preferred as the main treatment for SCC-BL [8,11,18,34,35]. Lohrisch et al. [11] 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. Common chemotherapy regimens used were etoposide and cisplatin (EP) and cisplatin, doxorubicin, vincristine and etoposide (PAVE). 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 [10,17]. Bex A et al. [17] reported on 17 patients, all treated with sequential chemoradiotherapy and concluded that the clinical results of this approach were comparable to a series of SCC-BL treated with cystectomy and adjuvant chemotherapy. All patients received platinum-based chemotherapy and radiotherapy with mean total dose of 60 Gy.

Several studies have reported brain relapses in patients with SCC-BL [18,19,35]. However, the necessity of PCI performed regularly in patients with SCC-BL, like in patients with SCLC, is still a matter of debate.

Discussion

According to the most important studies summarized in Table 3, prognosis is very poor for patients with SCC-BL. Prognosis is strongly related to the stage of the disease at the time of diagnosis [15]. Overall survival was higher in patients diagnosed with limited disease [26]. Additionally performance status and the level of serum lactate dehydrogenase (LDH) are factors with prognostic significance [11].

Clinical course is very aggressive and renders disease management complicated. There is not yet a definitive treatment but is seems that systemic platinum-based chemotherapy, especially when combined with local radiotherapy, is highly effective. Overall survival was higher in patients who were treated with adjuvant systemic chemotherapy in comparison with patients who had undergone cystectomy alone as well as patients who had received chemotherapy or radiotherapy alone.

The most commonly used regimen was cisplatin and etoposide in analogy to SCLC. Etoposide was administered at 100mg/m intravenously for 3 consecutive days repeated every 3 weeks. Cisplatin was given

at 80-100mg/ m on day 1.

SCC-BL is a very rare malignancy. Pathogenesis of the disease remains still unclarified. Several hypothesis were proposed to explain the origin of SCC-BL. Cramer et al. [14] suggested that SCC-BL arises from metaplastic changes of urothelium. Neuroendocrine cells had been documented previously in the urinary bladder [22]. Ali et al. [22] proposed the most important hypothesis that SCC-BL arises from malignant transformation of bladder neuroendocrine cells.

Brain relapses in patients with SCC-BL are documented in the literature [18,29,35] although in lower rates compared to those of SCLC. Therefore there is not yet evidence that PCI should be performed regularly in patients with SCC-BL.

Conclusion

SCC-BL 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.

Further research is required in order to clarify whether PCI should be performed on a regular basis, as it is a common practice in the management of SCLC.

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