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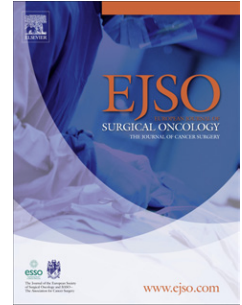
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## Multidisciplinary Approach in the Treatment of Patients with Small Cell Bladder Carcinoma

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**Abstract**

Small cell carcinoma of the urinary bladder (SCCUB) is considered to be a tumor with a neuroendocrine phenotype characterised by aggressive behaviour and poor prognosis. Small cell carcinoma of the urinary bladder comprises 0,35 to 1% of all bladder cancers and is frequently observed in combination with other histological subtypes of carcinoma. Clinical presentation is characterized by advanced stage at diagnosis and rapidly progressive disease. In daily clinical practice there is no gold standard for the management of patients affected by this disease. Treatment of patients with limited disease combines neoadjuvant platinum-based chemotherapy followed by specific local treatment of the primary tumour. Cystectomy or radiotherapy should be proposed on an individual basis. In the metastatic setting, prognosis remains poor with a potential benefit from chemotherapy containing platinum compounds. Treatment of small cell carcinoma of the urinary bladder is based on evidence obtained from case reports and retrospective analyses. Due to low disease frequency there is a lack of randomized trials to provide guidance as to optimal therapy. Thus, systemic and local approaches are extrapolated from the literature available for the treatment of small cell carcinomas at other (non-urological) sites. We provide an overview of the currently available literature with it's main focus on the treatment of either locally advanced or metastatic small cell carcinoma of the urinary bladder.

Keywords: Small cell carcinoma; Urinary bladder neoplasm; Chemotherapy; Radiotherapy; Cystectomy.

## Introduction

Small Cell Carcinoma of the Urinary Bladder (SCCUB) is a rare pathological presentation within the group of extrapulmonary small cell carcinomas. It is usually characterized by an advanced stage at diagnosis and rapid clinical progression. The mean survival time for all stages is 19.6 months, and the percentage of patients alive at 5-years is 8.1%<sup>1</sup>. Patients with localized disease are prone to develop distant metastases after treatment with a short time to progression.

There is no standard approach in the management of SCCUB diagnosed at an early stage and the currently available evidence supports a multidisciplinary approach incorporating neoadjuvant chemotherapy followed by local therapy (radiotherapy or surgery) in order to optimize clinical outcomes. Chemotherapy is usually based on platinum regimens in both the localized and metastatic settings. The prognosis of this disease remains poor and multi-institutional trials are needed to better define the best treatment for this rare disease.

## Methods

Data were obtained by a search within PubMed using the following search term “bladder cancer” and “small cell” and “bladder small cell carcinoma”. There were no limits applied for language, methodological characteristics, or year of publication. Case reports and case series were also selected.

## Epidemiology

The incidence of SCCUB has been reported to be between 0,35 to 1% [1-4] of all bladder cancers. In several pathology based retrospective studies small cell histology usually coexists with tumour types such as transitional cell carcinoma<sup>1, 5</sup>. The coexistence of distinct tumours in the same pathological sample can be considered as supporting a pluripotent stem-cell origin<sup>5, 6</sup>. The risks factors most frequently associated with SCCUB are smoking (65-79% reported) [1, 7], age (median: 66 years) and sex (male: female ratio up to 4:1)<sup>1, 5</sup>. Some retrospective studies also describe other risk factors associated with chronic inflammation such as stone disease, and recurrent urinary infection present before diagnosis<sup>8, 9</sup>.

## Clinical Presentation

The clinical presentation of SCCB is similar to other bladder cancers. The most common presenting symptom reported in various series is hematuria (68% - 88%)<sup>1, 10</sup>. Other reported symptoms include dysuria, urinary frequency, flank pain or acute renal failure due to urethral obstruction, hematospermia or recurrent urinary tract infection [1].

Partanen et al.<sup>11</sup> reported paraneoplastic syndromes with ectopic adrenocorticotrophic hormone (ACTH) production leading to Cushing’s syndrome,

hypercalcemia and hyperphosphatemia, although they are less frequently described than in small cell carcinoma of the lung<sup>11, 12</sup>.

### **Staging**

Complete staging workup includes history, physical examination and imaging studies with chest, abdomen and pelvis computed tomography (CT) to rule out metastatic disease. Brain magnetic resonance imaging (MRI) or brain CT scan should also be performed. The use of 18F-Fluoro-deoxyglucose positron emission tomography (18F-FDG PET) has also been described as an aid to staging although it is not adequate for detecting brain metastases<sup>14</sup>.

The staging system for SCCUB used in clinical practice is that advocated by the 2010 American Joint Committee on Cancer (AJCC) - TNM staging system for urothelial carcinoma<sup>15</sup>.

Table 1 summarizes histology and stage at clinical presentation of 2 major retrospective analyses.

### **Treatment**

#### ***Limited disease***

There is no standard treatment for SCCUB due to a lack of prospective randomized clinical trials to provide definitive recommendations. The suggested treatment approach is mainly based on retrospective studies from single centers. The standard of care may include surgery, surgery plus chemotherapy either in the adjuvant or neoadjuvant setting and radiation therapy plus chemotherapy.

## Surgery

Despite the absence of clinical evidence surgical resection has been considered for many years to be the main standard for the treatment of limited-stage SCCUB. Cystectomy alone is, however, characterized by a relatively poor prognosis. In a retrospective study from the MD Anderson Cancer Center (MDACC) 25 patients were treated with cystectomy only<sup>16</sup>. The 5-year cancer-specific survival was 36%. Cheng et al. reported a case series of 64 patients; they observed no difference in survival between the cystectomy vs no cystectomy groups<sup>1</sup>.

Another retrospective analysis by Choong et al. found that patients with localized disease may have long term survival after cystectomy alone with 41% (7 of 17) of patients being disease-free<sup>10</sup>.

## Neoadjuvant chemotherapy

Neoadjuvant chemotherapy followed by local treatment, when disease response is documented, can be considered an optimal strategy for patients with limited SCCUB. The chemotherapy regimens typically used are platinum based as these have known activity against neuroendocrine or small cell tumours. The rationale behind this approach relies on the frequent observation of upstaging and rapid growth rates after initial surgery. When considering local treatment after chemotherapy there is insufficient data to recommend whether this should be cystectomy or radiation therapy.



- *Neoadjuvant chemotherapy plus cystectomy*

The potential efficacy of neoadjuvant chemotherapy was demonstrated in the MDACC phase II trial. Investigators included 18 patients with SCCUB staged ad cT2 or cT3b N0 disease. Patients underwent four cycles of chemotherapy, with a regimen including ifosfamide plus doxorubicin alternating with the combination of etoposide plus cisplatin<sup>17</sup>. The pathological downstaging to stage pT1N0M0 occurred in 14 (78%) out of 18 patients with a mean overall survival (OS) of 58 months. A retrospective analysis from MDACC, observed a 5-year disease specific survival rate of 78% in 21 patients treated with preoperative chemotherapy, compared to 36% in 25 patients treated with initial cystectomy (regardless of adjuvant chemotherapy)<sup>16</sup>. In another retrospective analysis Walther noted that five of seven patients were alive and cancer free at 36 months mostly attributed to the use of preoperative chemotherapy<sup>18</sup>.

- *Neoadjuvant chemotherapy plus radiotherapy*

Radiation therapy (RT) has been used as an alternative to cystectomy in many centers. The largest retrospective study to report on chemo-radiotherapy in SCCUB reviewed 17 patients with limited disease treated at The Netherlands Cancer Institute between 1993-2007<sup>19</sup>. All patients received platinum based chemotherapy prior to local radiotherapy with 56-70 Gy. A complete response was achieved in 15 patients (88%) and the median OS was 32,5 months and (?). Four patients had local recurrence with 3 requiring a cystectomy. In another retrospective analysis 10 patients were treated with multidrug chemotherapy combined with local irradiation. The overall survival rate was 70% at 2-year and 44% at 5-year<sup>3</sup>. Bastus et al. treated 5 consecutive patients with

systemic chemotherapy followed by external radiotherapy in those achieving a complete response<sup>20</sup>. Patients were alive and free of disease 60, 48 and 27 months after diagnosis.

All these data suggest that a bladder sparing approach with neoadjuvant systemic chemotherapy followed by radiotherapy should be considered as primary option in limited disease and should be further investigated in this disease.

### ***Metastatic or recurrent disease***

Patients with pure small cell metastatic carcinoma of the bladder are supposed to have a poor prognosis and worse survival compared to those with mixed subtypes or transitional cell carcinomas<sup>17</sup>.

In the metastatic setting optimal chemotherapy should be platinum-based mostly combining cisplatin with etoposide<sup>1,12,21</sup>.

A recently published phase II trial from Siefker-Radtke et al. treated 30 patients, of whom 12 had metastatic disease, with alternating doublet chemotherapy using ifosfamide/doxorubicin and etoposide/cisplatin<sup>17</sup>. In the metastatic arm the response rate was 100%, with 72% complete (eight patients) and 28% partial responses; one patient was excluded from the analysis due to refusal for continuing treatment after the first cycle. Despite the response rate, the median OS was only 13.3 months<sup>17</sup>.

Another prospective study, from Bex et al., included 25 patients of whom 8 were considered to have extensive disease<sup>19</sup>. They received cisplatin and etoposide. The median OS was 5 months.

Although SCCUB, like pulmonary small cell carcinoma, is considered highly chemosensitive the progression free survival obtained is still poor and relapse is observed in the vast majority of cases.

Treatment for relapsed disease after first line chemotherapy is rarely described. A report of three cases using weekly vinorelbine as second line therapy showed one complete response and two partial responses with no safety concerns<sup>22</sup>.

#### *Patients with Brain Metastasis or Relapse*

In metastatic SCCUB the presence of brain metastasis is less frequently reported, even though described in 16% of patients<sup>10, 23, 24</sup>.

Two studies performed prophylactic cranial irradiation in few selected patients<sup>3, 25</sup>, but prospective and randomized studies confirming the benefit from such an approach are still awaited.

#### **Prognostic Factors**

Patients with SCCUB are most likely to have advanced or metastatic disease at first presentation. The proportion of patients with advanced disease at diagnosis ranges from 32% to 56% in most retrospective analyses<sup>12, 19, 24</sup>. Early metastatic spread is usually observed in small cell urinary carcinoma explaining the high relapse rate and the short disease free survival<sup>3, 4, 19, 25, 26</sup>.

The main prognostic factor observed is stage with a median OS from 7,3 to 59,2 months for limited disease and from 5 to 8,1 months for advanced disease<sup>4, 17, 19, 27</sup>. Other

possible prognostic factors associated with SCCUB include performance status prior to therapy<sup>19</sup> and tumour histology as pure SCCUB histology has been described as having a lower survival than mixed tumour subtypes<sup>17</sup>.

## Conclusions

Small cell carcinoma of the urinary bladder is a rare condition. Tumours are chemoresponsive although short times to progression are usually described. The management of limited disease remains a challenge and the integration of a neoadjuvant chemotherapy (with a cisplatin based regimen) followed by a local approach (surgery or radiotherapy) should be considered optimal. The choice between cystectomy or radiotherapy as local treatment should be decided on an individual basis. Cystectomy alone or cystectomy followed by adjuvant chemotherapy resulted in inferior long-term disease free-survival and OS. Prospective, multi-institutional, randomized studies are required to assess the role of neoadjuvant chemotherapy followed either by surgery or radiotherapy. The rarity of this disease is a major limitation to patient accrual in such hypothetical trials. In metastatic disease prognosis remains poor but with a trend of benefit from platinum-based chemotherapy. Another dilemma that remains to be answered is whether mixed small cell carcinoma should be managed with the same therapeutic approach as pure small cell carcinoma since these histological subtypes have been reported to have different prognoses.

In conclusion, a multidisciplinary approach involving urologist, radiation therapist and medical oncologist, should drive clinical decision making in patients with small cell carcinoma of the urinary bladder.

ACCEPTED MANUSCRIPT

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#### Table legends

Table1: Histopathological characteristics of two major retrospective studies.

Table 2: Multidisciplinary approach and clinical outcome according to stage in prospective and retrospective studies.

Table1: Histopathological characteristics of two major retrospective studies.

	Abrahams, 2005 <sup>5</sup>	Cheng, 2004 <sup>4</sup>
<b>N</b>	51	64
<b>Stage frequency</b>		
-I	5%	2% (T1)
-II	44%	47%(T2)
-III	24%	45%(T3)
-IV	27%	6%(T4)
<b>Histological characteristics</b>		
-Pure SCC	12%	32%
-Mixed:		
--Urothelial carcinoma	70%	55%
--Adenocarcinoma	8%	6%
--Urothelial and Adenocarcinoma	-	5%
--Sarcomatoid	-	3%
--Squamous	10%	-

Table 2: Multidisciplinary approach and clinical outcome according to stage in prospective and retrospective studies.

Author/Year	Type of Study	Number of Patients	Treatment	Results
<i>Localized</i>				
Siefker-Ratdke 2009	Prospective	18	Ifosfamide+Doxorubicin and Etoposide+Cisplatin alternated plus cystectomy	OS: 58 months RR*:78%
Siefker-Ratdke 2004	retrospective	46	Upfront cystectomy VS Preoperative chemotherapy	DFS 5 years: 36% vs 78%
Bex 2009	retrospective	17	TUR + Platinum –based chemotherapy + local RTx(56-70 Gy)	OS: 32.5 months RR: 100%
Lorisch 1999	retrospective	10	Cisplatin+Etoposide followed by local RTx	OS 2-y: 70% OS 5-y: 44% DFS 2y/ 5y: 70%
<i>Metastatic</i>				
Siefker-Ratdke 2009	prospective	12	Ifosfamide+Doxorubicin and Etoposide+Cisplatin alternated	Response: 72% CR, 28% PR; OS: 13.3 months
Bex 2005	prospective	8	Cisplatin+Etoposide (3 patients)	OS: 6, 16 and 17 months
Mukesh 2009	retrospective	9	-Cyclophosphamide+ doxorubicin+vincristine, -carboplatin+etoposide (3), -platinum-based chemotherapy.	Response: 50% CR,25% PR ; OS> 33 months vs 3 months with no chemo
Asmis 2006	retrospective	4	Platinum+etoposide;	Response not stated; OS: from 3.7 to 20 months
Choong 2005	retrospective	5	Platinum+etoposide	100% response for carbo+etoposide

\* Response rate – considered pathologic downstaging to &lt; pT1N0M0.