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Non-Metastatic Small Cell Carcinoma of the Urinary Bladder – Clinical Outcomes from a Single Institution

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Abstract

Objective: This study aims to ascertain the oncological outcomes of histologically proven non-metastatic primary small cell carcinoma of the urinary bladder in a single institution.

Materials and Methods: All suitable patients were identified from a prospectively maintained cancer registry. The outcomes analysed included demographics, treatment received and survival outcomes of Overall Survival (OS) and Disease Specific Survival (DSS).The study cohort was also dichotomised to pure small cell carcinoma and mixed small cell carcinoma for an exploratory analysis to evaluate the influence of pathological subtypes on DSS and OS.

Results: Thirteen patients were identified to have organ-confined small cell carcinoma of the urinary bladder. The mean age of these patients was 60 years old at diagnosis. Treatment modalities included radical cystectomy (n=3), partial cystectomy (n=2), combined chemotherapy and radiotherapy (n=4), radiotherapy alone (n=2), and no immediate treatment (n=2). At diagnosis, clinical staging consisted of organ-confined disease cT2 or better (n=11) and cT3/4 disease (n=2). The Overall Survival (OS) and Disease Specific Survival (DSS) rate of the entire cohort were 13 months and 69.2% at 1 year, 69.2% at 2 years and 61.5% at 5 years respectively.

Out of the 13 patients, 5 had pure small cell carcinoma of the bladder, and 8 had mixed small cell carcinoma of the bladder. The OS was 10 months for the pure small cell carcinoma group and 97 months for the mixed small cell carcinoma group. The DSS rate was 40% at 1 year and 0% at 2 years for the pure SCCB group. The DSS rate was 75% at 1 year, 62.5% at 2 years and 37.5% at 5 years for the mixed SCCB group.

Conclusion: Small cell carcinoma of the urinary bladder has a poor prognosis with aggressive progression. The presence of conventional urothelial carcinoma in SCCB appears to confer a better prognosis. This needs validation in prospective studies, and the exact mechanism requires elucidation.

Keywords: Carcinoma; Small cell; Urinary bladder; Chemotherapy; Surgery; Radiation

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Introduction

Extrapulmonary small cell carcinoma is an uncommon neoplasm of the genitourinary tract, of which the urinary bladder is the most common site [1-4].

Small cell carcinoma of the urinary bladder (SCCB) has many features similar to small cell carcinoma of the lung, including an aggressive biological behaviour associated with early metastasis, and variable response to systemic chemotherapy [5]. It is also associated with an advanced stage at clinical presentation [6] and dismal 5 year survival rates of 8.1% to 16% [7,8].

SCCB accounts for less than 1% of all primary bladder malignancies [9-13], and this condition has no established best treatment strategy [14].

There have been less than 15 case series, to date, in the English literature, with case numbers in these reports ranging between 18 to 64 patients per series, with the largest multi-centre series

Table 1: Demographics of study cohort.

Demographics	
Mean Age At Diagnosis, Years (Median, Range)	60 (66; 50-85)
Gender, n (%)	
Male	10 (77%)
Female	3 (23%)
Smoking History, n (%)	
Yes	9 (69%)
No	4 (31%)
Presenting Symptoms, n (%)	
Haematuria	13 (100%)
Charlson Comorbidity Index, n (%)	
0-2	12 (92%)
3-4	1 (8%)

Table 2: Clinical staging and upfront treatment modalities of study cohort by histological subtype.

	Histological Subtype	
	PURE SCCB (N)	**MIXED SCCB (N)**
Charlson Comorbidity Index		
0-2	5	7
3-4	0	1
Clinical Tnm Stage		
cT2N0M0	5	6
cT3-4N0M0	0	2
Treatment Modality		
Surgery		
Radical cystectomy	0	3
Partial cystectomy	1	1
Chemoradiotherapy	2	2
Radiotherapy	1	1
Delayed treatment	1	1

consisting of 625 patients [15]. These case series comprise a heterogeneous mix of organ confined disease, locally advanced disease and metastatic disease, and do not always discriminate outcomes between the various stages of disease.

This study aims to establish the oncological outcomes following treatment of histologically proven non-metastatic primary SCCB in a single institution.

Materials and Methods

With approval from the institutional ethics review board, all patients with histologically diagnosed non-metastatic primary small cell carcinoma of the urinary bladder were identified. Clinical data was extracted from the Department of Urology, Singapore General Hospital Urological Cancer Registry, Business Intelligence Enterprise Edition (Oracle Business Intelligence Enterprise Edition), and comprised of data captured between 1st January 1990 and 31st December 2014. Those with existing small cell carcinoma of the lung or synchronous upper urinary tract tumours were excluded.

All cases were restaged, at data analysis, using the 7th edition American Joint Committee on Cancer (AJCC) 2010 TNM classification system for diagnostic uniformity in this study.

The outcomes analysed included baseline characteristics and demographics, presenting symptoms, clinical stage of disease at diagnosis, treatment modality received and outcomes of Disease Specific Survival (DSS) and Overall Survival (OS).

As an exploratory analysis to evaluate the effect of histological subtypes, we segregated the cohort into 2 sub-groups – those with pure SCCB and those with mixed SCCB. The cohort of pure SCCB included patients with only small cell carcinoma on histopathology, and the cohort with mixed SCCB were defined as those with conventional urothelial carcinoma admixed with small cell carcinoma on histopathology.

The statistical analysis comprised the Mann Whitney U test for continuous variables, and Kaplan Meier analysis for survival outcomes determination. Statistical significance was defined at $p < 0.05$ in this study.

Results

There were 14 patients identified with organ confined small cell bladder carcinoma from the database, and after excluding one patient with a synchronous upper tract tumour, the number of suitable patients available for analysis was 13.

The mean follow-up period was 45 months (median 13, range 3–211). There were a total of 10 male and 3 female patients, with a mean age of 60 years (median 66 years, range 50-85 years. All patients had macroscopic haematuria as their initial presenting symptom. There were 9 patients with a history of chronic tobacco usage.

The clinical stage at diagnosis comprised of T2 stage in n=11 and T3/4 disease in n=2. The treatment received consisted of radical cystectomy (n=3), partial cystectomy (n=2), chemoradiotherapy (n=4) and radiotherapy (as a single treatment modality) (n=2). There were two patients that declined immediate therapy (Table 2).

Of those who underwent radical cystectomy and pelvic lymph node dissection, the pathological stage consisted of pT2N0 (n=2) and pT4N0 (n=1). These patients declined neoadjuvant therapy and adjuvant treatment. For patients who underwent combined chemotherapy and radiotherapy, the chemotherapeutic agents comprised a combination of etoposide and cisplatin or etoposide and carboplatin (in those with existing renal impairment). The dosage of radical radiation administered to the bladder were between 55-66 Gy in divided fractions.

Of the 2 patients who did not receive immediate treatment, one patient agreed to receive palliative treatment when symptomatic from rapid disease progression over 3 months. The other underwent repeated transurethral resection for bladder outlet obstruction and bleeding. Both patients had refused initial treatment offered by their managing physicians.

The OS and DSS rate for this patient cohort was 13 months and 69.2% at 1 year, 69.2% at 2 years and 61.5% at 5 years respectively (Figure 1).

As an exploratory analysis to determine the effect of histopathological subtype on survival outcomes, we dichotomised the population into two sub-groups comprising those with mixed small cell carcinoma histology (n=8) and those with pure small cell carcinoma histology (n=5).

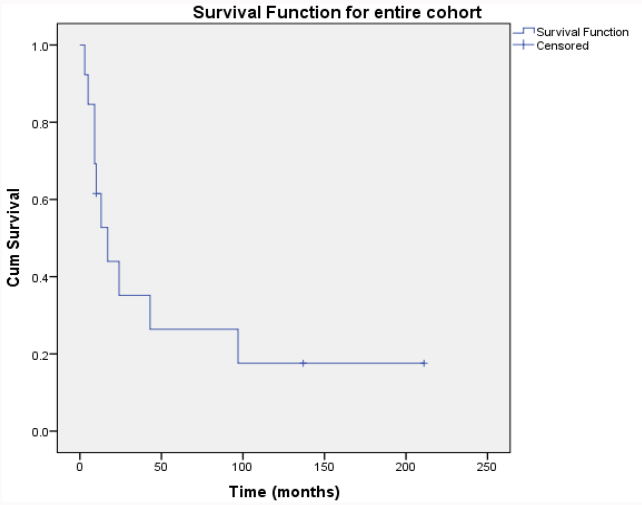

Figure 1: Kaplan-Meier overall survival (OS) curves for study cohort.

The mixed SCCB sub-group were younger (median age 60 years, mean 64, range 50-85) compared to the pure SCCB sub-group (median age 71 years, mean 69, range 50-83) (Table 1). The mixed sub-group SCCB comprised 20 percent (2 out of 8) with locally advanced disease (T3-4), while the pure SCCB sub-group all comprised of organ confined cancer. There were no major differences in the modality of treatment received across these 2 sub-groups (Table 2). Despite the disparity of clinical staging, the overall survival of the mixed SCCB group was higher than that of the pure SCCB group (Table 1). The OS for the pure and mixed SCCB group was 10 months and 97 months respectively. The DSS rate was 75% at 1 year, 62.5% at 2 years and 37.5% at 5 years for the mixed SCCB group, while corresponding figures for the pure SCCB group were 40%, 0% and 0% respectively. The corresponding Kaplan Meier survival curves are shown in Figure 2. The median follow-up period was 97 months (range 5-211 months) for the mixed SCCB group, while that of the pure SCCB group was 10 months (range 3-24 months) (Figure 3). The difference in follow-up duration was largely influenced by early occurrence of mortality events in the pure SCCB group.

The recurrence rate and median time to recurrence are

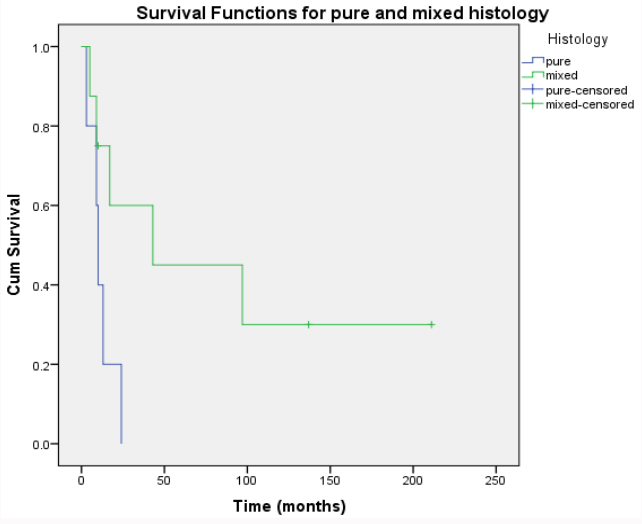

Figure 2: Kaplan-Meier overall survival curves (OS) for patients with pure SCCB versus mixed SCCB.

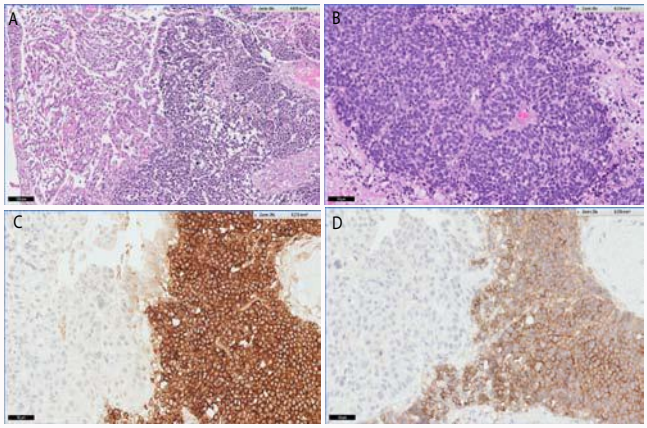

Figure 3: A: H&E staining for mixed SCCB. Urothelial carcinoma admixed with small cell carcinoma. **B**: H&E staining for pure SCCB. Solid sheets of cells, some in rosette formation. **C**: Synaptophysin staining for mixed SCCB. Only small cell carcinoma stained with synaptophysin. Urothelial carcinoma is not stained. **D**: CD 56 staining for mixed small cell carcinoma. Only small cell carcinoma staining positive for CD 56.

summarised in Table 3. All the recurrence were distant metastasis to brain and bone. Only 1 recurrence from the radiotherapy group had a local recurrence in the bladder detected together with distant metastasis.

Discussion

The optimal treatment strategy for this aggressive malignancy is not clear, although evidence from retrospective data suggests that neoadjuvant chemotherapy combined with radical surgery is associated with the most favourable OS [15]. The difference in 3-year OS is reported to range between 53% in the combination treatment arm, to 39% for those treated by radical cystectomy alone, and 14% for those who underwent radical cystectomy followed by adjuvant chemotherapy. Reported a retrospective series of patients with small cell carcinoma of the bladder who underwent radical cystectomy and found that those who underwent adjuvant chemotherapy had improved 5-year survival compared with those who did not (43% versus 20%, p=0.03). The patients who had adjuvant chemotherapy had a higher rate of nodal metastasis than those who did not (61.1% versus 27.7%, p=0.01). The need for multimodality therapy in SCCB comprising local and systemic therapy is also emphasized by other authors [7,9,10,13]. This principle of therapy is also mirrored in the management of small cell carcinoma in other extra-pulmonary sites,

Table 3: Recurrence rate by treatment modality.

	Histological Subtype	
Treatment Modality	**Pure Sccb (n)**	**Mixed Sccb (n)**
Surgery (n=5)		
Recurrence (time to recurrence)*	3 (8 months)	1 (17 months)
No recurrence	0	1
Chemoradiotherapy (n=4)		
Recurrence (time to recurrence)*	2 (11 months)	2 (54 months)
No recurrence	0	0
Radiotherapy (n=2)		
Recurrence (time to recurrence)*	1 (24 months)	0
No recurrence	0	1

* = Mean time to recurrence in months

where the need for combined local and systemic therapy confers superior survival outcomes [16].

The optimal regime for chemotherapy is not clear for SCCB. Mukesh et al. [4] reported their series of patients who underwent chemotherapy either using cyclophosphamide, doxorubicin and vincristine, or carboplatin with etoposide, or alternative platinum-based regimes. The chemotherapy regime used in our patients were etoposide and a platinum based agent, combined with radiotherapy.

Although there are larger reported case series in literature, these include patients with metastatic disease at presentation. To our knowledge, the largest reported series [15] was a retrospective analysis using the National Cancer Database comprising 625 patients. However, as the data was derived from an administrative dataset, detailed information about treatment rendered was not available for analysis. The patients from this existing series included only individuals with organ-confined disease, and largely comprised those with clinical stage T1 or T2 at presentation (85% of cohort). The overall survival was 13 months for the entire study group, however, suggests that SCCB is a highly aggressive disease, with a short time from diagnosis to metastasis or death. The treatment received by patients in this study cohort were varied, and largely reflected the retrospective nature of the study where patient selection predominated. In the patients without disease related mortality, the treatment received included radical cystectomy (n=1), chemoradiotherapy (n=1), and radical radiotherapy (n=1). The follow-up for the patient who had radical cystectomy was 211 months, radiotherapy alone 137 months, and chemoradiotherapy 10 months. There is a suggestion that neoadjuvant chemotherapy followed by radical surgery provides the best survival outcomes [15,17], these conclusions are limited by the retrospective nature of these reports. A multi-centre randomised controlled trial will help to validate our results, but we recognize that trial recruitment would be logistically challenging for such a rare condition.

This study is the first, as we are aware, to hypothesize a difference in biological behaviour between pure SCCB and mixed SCCB, where the presence of urothelial carcinoma in SCCB confers a more favourable prognosis. The small study size precludes univariate and multivariate analysis of histological subtype as an important prognostic factor in survival outcomes. Being aware of the limitations of a small study sample size, it would be useful to validate this hypothesis in larger studies. However, the predominant confounders in survival analysis, such as age, Charlson Comorbidity Index, and tumour stage at presentation are in favour of the pure SCCB sub-group, strongly suggesting that histological subtype is a significant contributor to DSS and OS.

There have been 3 theories regarding the histogenesis of small cell bladder carcinoma [21]. The first theory is that SCCB is derived from the Amine Precursor Uptake and Decarboxylation (APUD) system. APUD cells are neuroendocrine cells located next to the basal lamina of epithelial surfaces. Although a common cell of origin is suggested for tumours with mixed SCCB [22], divergent clonality during tumour progression is hypothesized to lead to different cell types within the same lesion. This hypothesis provides supporting evidence, but does not offer a mechanistic explanation for a less aggressive biological behaviour observed by mixed SCCB [17]. The second theory is that SCCB is derived from metaplasia of high grade malignancies, which may explain why SCCB is sometimes found with other bladder malignancies with a mixed histology [18]. The third theory is that SCCB stems from multipotential stem cells [18,19] and may explain why SCCB can exist as a mixed histology or as a pure histology.

In a study comprising 10 patients, Terraciano et al. [20] used Comparative Genomic Hybridization (CGH) to analyse copy number aberrations in the tumours. This study demonstrated that SCCB was characterised by frequent genomic alterations [23], such as DNA deletions at 10q, 4q, 5q and 13q, and DNA gains at 8q, 5p, 6p and 20q. In one case with coexistent urothelial carcinoma, both small cell carcinoma and urothelial carcinoma areas showed similar genotypic alterations and therefore, a similar clonality.

Therefore, we hypothesize that mixed SCCB may arise from different genomic alterations distinct from pure SCCB, resulting in their different clinical behaviour. The elucidation of the mechanistic pathways behind such a differential phenotype will likely yield insights into potential therapeutic pathways that may be used in novel treatment strategies. Although the comparison between pure SCCB and mixed SCCB was statistically not significant (p=0.09), this was most likely due to the small sample size of the cohort.

Over the decade from which the study patients were identified, we recognise that evolution of treatment strategies and patient selection would contribute biases to outcomes analysis, although its magnitude of influence is not easily quantifiable. At the same time, we recognise that limiting the duration of the study period would also lead to a smaller study population in this rare condition.

While attempts were made to restage all cases using a more contemporary staging system, the limitations inherent to refinement of diagnostic imaging modalities in the later part of the study duration may affect the accuracy of clinical staging. However, given that all patients underwent axial imaging at diagnosis, it is unlikely that these changes in imaging technique will affect staging to a large extent. The strengths of this study include central pathological review and clinical data obtained from a prospectively maintained cancer registry.

Conclusion

Small cell bladder carcinoma is an uncommon disease with an aggressive oncologic behaviour and poor prognosis. Although mixed small cell bladder carcinoma has a relatively better prognosis compared to pure small cell bladder carcinoma, further studies need to be done to prove this observation. Good outcomes are observed in different treatment modalities and large multicentre studies are required to better ascertain best treatment options in view of the rarity of this disease.

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