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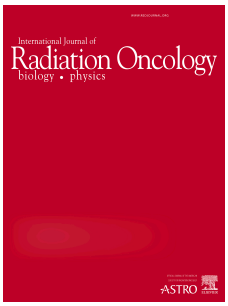

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Treatment outcomes for small cell carcinoma of the bladder: results from a UK patient retrospective cohort study

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Abstract

Background:

Small cell carcinoma of the bladder (SCCB) is rare, accounting for under 1% of all bladder carcinomas. It is aggressive and outcomes are poor due to early metastatic spread. Owing to its rarity, there are limitations on data to propose standardised management pathways.

Patients and methods:

We conducted a retrospective analysis of patients presenting with pure or predominant histology SCCB to 26 UK institutions between 2006 and 2016. Data cut-off date was 1/2/2018. We report on patient characteristics, treatment received and subsequent clinical outcomes.

Results:

409 eligible patients were included. 306 (74.8%) were male, median age was 71 years (range 35-96) and 189 (46.2%) had pure histology SCCB. At data cut-off, 301 patients (73.6%) have died. Median overall survival (OS) was 15.9 (95% confidence interval (CI) 13.2-18.7) months. 200 patients (48.9%), were confirmed to have bladder confined disease (N0 M0), with a median OS of 28.3 (95% CI 20.9-35.8) months, versus 12.7 (95% CI 10.9-14.6) months for 172 (42.1%) patients with confirmed N1-3 and/or M1 disease (hazard ratio 2.03, 95% CI 1.58-2.60, p=<0.001). 247 patients (61.5%) received primary chemotherapy, with a median OS of 21.6 (95% CI 15.5-27.6) months, versus 9.1 (95% CI 5.4-12.8) months in those who did not (HR 0.46, 95%CI 0.37-0.59, p=<0.001). Choice of chemotherapy agent did not alter outcomes. For those with bladder confined disease, 61 patients (30.5%) had cystectomy and 104/200 (52.0%) had radiotherapy. Survival outcomes were similar despite choice of

cystectomy or radiotherapy. Only 6 patients (1.5%) were identified to have brain metastases at any time point.

Conclusions:

This is the largest retrospective study of all stage SCCB to date. Patients have a poor prognosis overall but with improved survival in those able to receive chemotherapy and with organ confined disease. Brain metastases are rare.

Introduction

Bladder and urinary tract cancers account for approximately 10,200 new diagnoses and 5,400 deaths annually in the UK.[1] Approximately 90% are of transitional cell carcinoma (TCC) histology and treated with surgical resection, radiotherapy, platinum based chemotherapy and PD-1/PD-L1 checkpoint directed immunotherapy.[2] The remaining non-TCC histology urinary tract cancers include small cell and neuroendocrine carcinoma, squamous cell carcinoma, large cell carcinoma, adenocarcinomas (including urachal/mullerian cancers) and clear cell carcinoma.[3]

Small cell bladder carcinoma (SCCB) is rare, accounting for 0.5 to 1.0% of bladder cancers. Approximately half of cases comprise a mixed histology with small cell/neuroendocrine carcinoma and non-small cell carcinoma components present.[3] The disease is associated with aggressive clinical behaviour and high metastatic potential. Cramer et al first described this form of extra-pulmonary small cell cancer in 1981.[4] Established risk factors include male sex, advanced age and smoking.[5] The prognosis is poor with a 5-year survival rate of 16-25% for all stages combined.[6] Common metastatic sites include retroperitoneal and pelvic lymph nodes (28 – 53%), liver (23 – 47%), bone (23 – 33%), lung (9-13%) and brain (7.9%).[7]

Existing knowledge of this rare disease is limited and based mainly on retrospective review and case reports, leading to limitations for gaining consensus on relevant staging investigations and variability in therapeutic approach. Treatment paradigms have generally been pragmatic and adapted, with a somewhat hybrid approach, from those utilised for either small cell lung carcinoma (SCLC) or TCC. Patients with SCCB are typically disenfranchised

by explicit exclusion from TCC clinical trials, including within recent registration studies for immunotherapy.

The National Cancer Care Network (NCCN) includes small cell bladder cancer recommendations within its bladder cancer guideline. It recommends considering bladder cancer patients with small cell histology for brain MRI as part of staging, and neoadjuvant chemotherapy for localised non-metastatic disease, regardless of stage, followed by either radiotherapy or cystectomy. The Canadian Association of Genitourinary Medical Oncologists (CAGMO) published a consensus statement on the management of SCCB in 2013.[8] This includes recommendation for pathology review in specialist centres, adoption of a limited versus extensive disease staging approach analogous to SCLC, and the use of platinum/etoposide based chemotherapy where this is indicated. The level of evidence for these recommendations is consistently assessed as being low.

In the UK, the National Institute for Health and Care Excellence (NICE) guideline, published in 2015, excluded discussion of SCCB. We have undertaken a national retrospective cohort study of UK experience for this rare disease to facilitate development of a standardised approach for staging and treatment.

Methods

Patients diagnosed with SCCB, where this histology was either the predominant component or pure, between January 2006 and January 2016, were eligible for inclusion. Data collection was through retrospective case note and database review. Data was collected using a common central spreadsheet designed for this study with specific data fields and guidance rules for completion sent out to participating institutions. Data collection was overseen at each institution by a Consultant Oncologist who specialised in cancers of the urinary tract. Data was then returned and collated within a central database. Patient and tumour characteristics, treatment received and clinical outcomes were recorded. The data cut-off was February 1st 2018. Treatments and managements decisions were consistent with local institutional guidelines. Consistent with mandated practice throughout the UK, every patient diagnosed with SCCB is assessed within a regional urological cancer multidisciplinary team meeting with core membership including oncologists, urologists and pathologists with a specialist interest in systemic therapy for urinary tract cancers. This research had UK National Research Ethics Service committee approval (10/H0405/99).

Statistical methods

Descriptive data are presented as percentages and frequency. Statistical analysis was performed using SPSS software version 20.0. Overall survival (OS) was calculated from the date of diagnosis until death, censoring at last known follow-up for patients who remained alive. Survival curves were plotted using the Kaplan-Meier method and statistical significance was determined using the log-rank test. P values were two-sided and considered statistically significant if <0.05.

Results

26 UK hospitals participated in this study (Supplementary Table 1) and 409 patients were eligible for inclusion.

Patient demographics, tumour characteristics and staging are summarised in Table 1. Patients were predominantly male (n=306, 74.8%), with a median age at diagnosis of 71 years (range 35 – 96). 331 (80.9%) patients were over the age of 60 and 7 patients (1.7%) were over 90. The median duration of follow up was 15.4 months and the median overall survival (OS) was 15.9 months (95% confidence interval (CI) 13.2 – 18.7, range 0 – 141 months; Figure 1).

Tumour histology was of pure SCCB in 189 patients (46.2%) with the remainder having mixed, but predominant SCCB, histology. Coexisting non-small cell carcinomatous components included urothelial carcinoma in over 90% with squamous cell carcinoma and adenocarcinoma seen in the remainder. The median OS for patients with pure versus mixed SCCB was not different at 14.2 (95% CI 11.6-16.8) and 17.2 (95% CI 12.8-21.6) months respectively (HR 0.85, 95% CI 0.68-1.08, p=0.18; Figure 2).

372 patients had available staging data from which 200 (53.8%) had organ confined (N0, M0) disease. 172 patients (46.2%) had either regional lymph node involvement (N1-3, M0) or metastatic disease (M1) at the time of diagnosis. Patients with organ confined disease had significantly better median OS than those with regionally or distant metastatic disease at 28.3 (95% CI 20.9-35.8) months and 12.7 (95% CI 10.9-14.6) months respectively (HR 2.03, 95% CI 1.58-2.60, p=<0.001) corresponding with 5 year survival rates of 37.1% and 13.4% respectively (Figure 3). For patients without organ confined disease, 62 had confirmed N1-3

M0 staging and 98 had Nany M0 disease (status unclear for a further 12 patients) with median OS respectively of 21.7 (95% CI 12.0-30.5) months and 12.9 (95% CI 10.2-15.6).

Brain metastases

42 patients (10.3%) had a CT or MRI head scan as a part of initial staging investigations. Only 6 of 409 patients (1.5%) were found, at any time during their disease, to have brain metastases. Within this number, one patient had brain metastases diagnosed after radical chemo-radiotherapy treatment and one patient was diagnosed 5 years after his initial diagnosis but neither had brain imaging at diagnosis. Only 2 patients, both from the same institution, received prophylactic cranial irradiation.

Treatment and prognosis

Treatments administered to this patient cohort are summarised in Table 2. 247 patients (61.5%) received primary systemic cytotoxic chemotherapy. Reasons given for patients not receiving chemotherapy were poor fitness level, significant co-morbidities and patient decision. Performance status was more likely to be favourable (ECOG 0 or 1) in those who received chemotherapy (167 of 247 patients, 67.6%) than those who did not (35 of 155 pateints, 22.6%). Median OS of patients was longer at 21.6 (95% CI 15.5-27.6) months in patients who received chemotherapy versus 9.1 (95% CI 5.4-12.8) months in those who did not (HR 0.46, 95%CI 0.37-0.59, p=<0.001; Figure 4) with 33.1% and 13.7% respectively alive at 5 years. One patient received platinum-based adjuvant chemotherapy, but this was stopped after one cycle due to toxicity. Two thirds of patients with regional (N1-3) or

metastatic (M1) disease received chemotherapy and patients who did not have chemotherapy were mostly deemed to be unfit to do so.

The most commonly used chemotherapy regimen was carboplatin and etoposide (135 of 247 patients; 54.6%). 148 patients received a carboplatin based combination regime compared to 68 patients who received a cisplatin based combination. Etoposide was the most common agent used to pair with platinum (n=164) followed by gemcitabine (n=41). For those having chemotherapy combinations, we found no statistically significant difference in OS by choice of platinum agent. Median OS was 30.0 (95% CI 21.6-38.4) months for cisplatin combinations versus 19.2 (95% CI 14.7-23.7) months for carboplatin combinations (HR 0.83, 95% CI 0.58-1.19, p=0.31; Supplementary Figure 1). Similarly, there was no difference seen between gemcitabine versus etoposide as a 'paired' agent with median OS of 19.8 (95% CI 14.4-25.2) months versus 25.1 (95% CI 17.1-33.1) months respectively (HR 0.75, 95% CI 0.50-1.11; p=0.15; Supplementary Figure 2).

Median time from diagnosis to commencement of the first cycle of chemotherapy was 47 days (range 5 – 124 days). We found no OS advantage in patients who commenced chemotherapy earlier using a cut point of 47 days from diagnosis with median OS of 20.3 (95% CI 13.2-27.3) months if ≤47 days versus 34.9 (95% CI 15.2-54.6) months if >47 days (HR 0.87, 95% CI 0.61-1.23, p= 0.42; Supplementary Figure 3).

In patients with organ confined disease (n=200), 61 patients (30.5%) subsequently underwent radical cystectomy and 104 patients (52.0%) had radiotherapy. The most commonly used radiation dose schedules were 55Gy in 20 fractions and 64 Gy in 32 fractions. Other dose schedules used were palliative radiotherapy regimens, which included 36Gy in 6 fractions, 30

Gy in 10 fractions, 50 Gy in 20 fractions, 21 Gy in 3 fractions, 40 Gy in 15 fractions, 50.4 Gy in 28 fractions, 41/25 Gy in 15 fractions. No difference was observed in the median OS between patients who had radical cystectomy versus radiotherapy at 26.7 (95% CI 17.1-36.3) months versus 30.0 (95% CI 16.8-43.2) months respectively (HR 0.94, 95% CI 0.66-1.33, p= 0.726; Figure 5).

Discussion

This is, to our knowledge, the largest reported study of all stage small cell bladder cancer management practice and outcomes. We confirm the poor prognosis of the disease overall with a median survival of only 15.9 months. This patient cohort represents management in the modern era, confirming the significant unmet need that persists for such patients.

Our analysis revealed several important findings. Firstly, we showed that the use of chemotherapy for patients was associated with improved overall survival irrespective of disease stage. Clearly, there will be bias inherent in this analysis due to the lack of randomisation to treatment. However, these data are supportive of a management approach that places emphasis on early systemic cytotoxic chemotherapy, for those suitable for treatment, irrespective of disease stage. Second, we did not detect a difference in outcomes on the basis of pure versus mixed SCCB histology. Potentially this may be influenced by the fact that we required, at least, predominant small cell histology for inclusion. Third, we saw a marked difference in prognosis between organ confined versus locally advanced or metasatic disease staging. This supports careful assessment of disease stage at initial diagnosis as patient management and outcomes are critically tied to initial disease staging assessment. Fourth, we did not detect a difference in outcome based on chemotherapy choice or, for patients with organ confined disease, choice of either cystectomy or radiotherapy. This allows us to support flexibility in choice for chemotherapy agent, providing a platinum doublet is utilised in those fit to receive it. Finally, we found that the incidence of brain metastases in SCCB was rare (1.5% at any point) in this cohort. This suggests that imaging specifically for this event, and prophylactic cranial irradiation may not be required in this disease, and in distinction with SCLC.

We undertook a MEDLINE database search and found less than 60 retrospective series and case reports on small cell bladder cancer, with a median number of patients per study of 27. There were only two, small, prospective studies. In a single-centre study of 25 patients, Bex et al investigated the efficacy and feasibility of adopting a SCLC therapeutic strategy in SCCB. It concluded that the use of chemotherapy improved overall survival regardless of disease stage, and supported the use of a bladder sparing approach for most patients, within the context of few long term remissions, in patients with small confined tumours and no deaths from locoregional disease progression.[9]

Siefker-Radtke et al conducted a phase II clinical trial over 5 years, and treated separate neoadjuvant and palliative patient cohorts with alternating doublet chemotherapy comprising ifosfamide plus doxorubicin (IA) and etoposide plus cisplatin. The surgically resectable cohort, of 18 patients, achieved a median overall survival of 58 months, with 13 remaining alive and cancer free, whereas the palliative cohort, of 12 patients, had a median overall survival of 13.3 months. They found eight patients with brain metastases (26.7%), with a strong positive association between more advanced stage disease (bulky tumour or metastatic disease) and development of brain metastases.[10]

The largest retrospective study of SCCB was reported by Geynisman et al in 2015. Unlike our data set, it was restricted to patients with either regional lymph node or distant metastatic disease involvement comprising 960 patients identified from 1998 to 2010.[11] The authors compared the clinical characteristics, treatment patterns and outcomes to patients with TCC. It concluded that advanced SCCB has a poor prognosis and palliative therapy is common. In

comparison to UC, the outcomes for advanced SCCB are worse in those with lymph node only involvement but similar in those with distant disease.

Our patient demographics are similar to those reported in the literature, with the majority of patients in the sixth to seventh decade and a male: female ratio of 3:1. Our study showed an apparent increase in incidence of SCCB from 2011, with two-thirds of our patients diagnosed between 2011 to 2016. This may relate to bias in obtaining data in older cases or a genuine rise in incidence. The Surveillance, Epidemiology, and End Results (SEER) database review of 642 SCCB patients in the United States from 1991 to 2005 also found an increase in incidence from 0.3% to 0.6% with approximately 500 new cases per year.[12]

As expected, patients with bladder only disease had a better prognosis than those with regional or distant metastatic spread (28.3 months versus 12.8 months, p=<0.001). In Geynisman's retrospective study with 960 advanced SCCB patients (N1-3 and/or M1), the reported median overall survival was 8.6 months; 13.0 months in N1-3M0 versus 5.3 months in Nany M1 patients (p<0.0001). The authors also found that the survival was similar between TxN1M0 and TxN2-3M0 patients (14.8 months versus 12.1 months, p=0.15).[11] In bladder only disease (T1-4aN0M0), Fisher-Valuck et al reported a median OS of 20.7 months and estimated 3 year and 5 year OS were 37.5% and 28.2% respectively. Our OS appears better in both N+/M+ disease and N0M0 disease, the exact reason is unknown but it could be due to earlier referral, more accurate staging, a better awareness of this rare subtype of cancer or aspects of selection of patients.[13]

All cases of SCCB in this study were confirmed through specialist Uro-Pathologist review of specimens obtained by cystoscopy and transurethral resection of the bladder tumour

(TURBT) at individual institutions but no central pathology review was undertaken. Immunohistochemistry staining played an important role in confirming the diagnosis. Our results showed a similar proportion of pure and mixed small cell bladder cancer (46.2% versus 52.1% respectively). Published data showed the percentage of mixed SCCB ranges between 30% to as high as 88%.[14] Interestingly, we found no statistically significant difference in OS between pure and mixed SCCB, this is in contrast to other series which have shown a 2 – 3 times shorter median OS in pure compared to mixed SCCB.

Chemotherapy is recognised to be an important treatment modality for SCCB. A number of retrospective studies, case reports as well as one phase II prospective clinical trial have demonstrated the advantage of chemotherapy in the neoadjuvant setting.[15] Our results support this, showing a median OS of 21.6 months in patients who had chemotherapy compared to 9.1 months in those who did not receive chemotherapy. Clearly a major driver is likely to be an association between aggressive disease phenotype, advanced stage and poor performance status with non-receipt of chemotherapy.

We looked at the choice of chemotherapy agents used. Nearly all (>95%) were platinum based combination regimens, with carboplatin and etoposide being the most common. Carboplatin was also the preferred platinum choice, with 138 patients compared to only 68 patients who had cisplatin combination. We found no statistically significant difference in median OS between the two groups. More patients received etoposide as the second cytotoxic agent compared to gemcitabine (164 patients versus 41 patients respectively). Again, we did not find a difference in outcome between these two groups. The choice of chemotherapy regimens in the UK is in keeping with other reported series. No toxicity data for the different chemotherapy regimens were collected. We acknowledge that this is a

limitation as information as such could help guide the choice of systemic therapy. In one retrospective study of 106 patients, Mackey et al also demonstrated, on multivariate analysis, that cisplatin chemotherapy is the only predictive factor for survival of SCCB patients ($p < 0.0001$).[16] However, there has been no prospective trial to determine the optimum chemotherapy regimen.

In our cohort, only 30.5% of patients with organ confined disease had radical cystectomy with radiotherapy the more common definitive treatment modality. Many different radiotherapy dosing schedules were used across the 26 UK institutions, reflecting the lack of prospective data to support treatment decisions. The most commonly used schedules were radical regimens of 64Gy in 32 fractions and 55Gy in 20 fractions. Limitations exist in our data set in relation to recording of radical versus palliative intent for use of radiotherapy. As such it is difficult to draw definitive conclusions on choice of radical local intervention (cystectomy versus radiotheapy). Twelve other radiotherapy dosing schedules were also used. This highlights the need to standardise radiotherapy regimen choice in SCCB. Different retrospective studies have published data supporting both approaches. A population based study published in 2019 using SEER database (n=384) showed that surgery was associated with better outcome compared with radiotherapy in patients with T2 disease ($p<0.001$).[17] However, a large American observational study with 856 patients (with early stage disease only) found no significant difference in survival between chemoradiotherapy and surgery with chemotherapy (34.1 months and 32.4 month respectively, $p=0.42$).[13] In our own cohort of 200 patients with organ confined disease, we also found no difference in median OS between patients who had surgery and those who had radiotherapy (26.7 months versus 30.0 months respectively, $p=0.726$). 28 patients had complications following their radical treatment. 16 patients had complications following cystectomy with 4 patients requiring ITU

admission (paralytic ileus, bowel obstruction. Pneumonia, pulmonary oedema). Other complications include wound infection and fluid collection requiring drainage. Complications following radiotherapy include cystitis, LUTs and rectal bleeding. There has been no successfully completed randomised study comparing the clinical outcome between cystectomy and bladder sparing therapy as a means of definitive local treatment. SPARE, a multicentre randomised controlled trial attempted to address this question in bladder TCC, but the trial was closed due to poor accrual.[18]

There are inherent limitations to the interpretations of our data. Most importantly, the retrospective nature of the study, the potential for various forms of selection bias and the lack of randomisation between treatments received. Furthermore, there was no central pathologic review to confirm small cell histology. We acknowledge that this is a rare disease, the lack of central pathology review may have resulted in discrepancies in the histological diagnosis and tumour staging. Prospective study would be a means to address some of these potential sources of bias.

Conclusion

This is, to our knowledge, the largest reported cohort study of all stages small cell bladder cancer to date. Given its aggressive nature and poor prognosis, a multidisciplinary approach to each patient is crucial to help streamline appropriate and timely management for each patient. Our results support that the use of primary chemotherapy at any disease stage is associated with improved overall survival and that brain metastases in SCCB is rare. Our data support choice between different options for platinum based chemotherapy combinations, and between cystectomy or radiotherapy for organ confined disease. There is a need for

prospective trials to provide better quality information to guide management in this rare disease.

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Figure 1. Overall survival for the whole patient cohort

Figure 2. Overall survival with respect to pure (continuous line) versus mixed (broken line) SCCB histology

Figure 3. Overall survival with respect to localised (staged N0 M0; continuous line) versus locoregionally advanced or metastatic (staged N1-3 and/or M1; broken line) disease (B)

Figure 4. Overall survival with respect to the use of primary chemotherapy (continuous line) versus not (broken line) (A)

Figure 5. Overall survival with respect to the use of radical radiotherapy (continuous line) or radical cystectomy (broken line)

Table 1. Patient and Tumour characteristics

Data	**N (%)**
Age (years)	
Median (range)	71 (35-96)
≤60	78 (19.1)
>60	331 (80.9)
Year of diagnosis	
2006 - 2010	142 (34.7)
2011 - 2015	267 (65.3)
Gender	
Male	306 (74.8)
Female	103 (25.2)
Histology	
Pure small cell carcinoma	189 (46.2)
Mixed histology (small cell predominant)	213 (52.1)
Missing data	7 (1.7)
CIS present	
Yes	69 (16.9)
No	283 (69.2)
Missing data	57 (13.9)
Disease	
N0 M0	200 (48.9)
N+ or M+	172 (42.1)
Missing data	37 (9.0)
CT or MR head scan at diagnosis	
Yes	42 (10.3)
No	353 (86.3)
Missing data	14 (3.4)

CIS, carcinoma in situ

Table 2. Treatment details

Data	**N (%)**
Primary cytotoxic chemotherapy	
Yes	247 (61.5)
No	155 (37.9)
Missing data	7 (0.6)
Primary chemotherapy for stage N0 M0 patients (n=200)	
Yes	124 (62.0)
No/Unfit	74 (37.0)
Missing data	2 (1.0)
Primary chemotherapy in N1-3 and/or M1 patients (n=172)	
Yes	117 (68.0)
No/ Unfit	53 (30.8)
Missing data	2 (1.2)
Chemotherapy regimen as first line (n=247)	
Carboplatin and etoposide	135 (54.6)
Cisplatin and etoposide	42 (17.0)
Cisplatin and gemcitabine	35 (14.2)
Carboplatin and gemcitabine	13 (5.3)
Other *	9 (3.6)
Missing data	13 (5.3)
No. of cycles received (n=247)	
1 – 3 cycles	48 (19.4)
4 – 6	138 (55.9)
Missing data	61 (24.7)
Definitive treatment in N0 M0 disease (n=200)	
Radiotherapy	104 (52)
Cystectomy	61 (30.5)
Missing data	35 (17.5)

* 9 patients received other first line chemotherapy treatments including accelerated MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), CAV (cyclophosphamide, doxorubicin, vincristine) carboplatin only, gemcitabine only, ACE (doxorubicin, cyclophosphamide, etoposide) and carboplatin/methotrexate/vinblastine.