

Prognosis of early stage small cell bladder cancer is not always dismal

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ABSTRACT

Background Small cell carcinoma of the urinary bladder (SCCB) is an extremely rare malignancy which is often associated with poor survival outcome. Literature reporting such disease is scarce. There is no standardised management. This retrospective audit examines a UK Cancer Centre's SCCB management and survival outcomes.

Methods Histopathology database at Nottingham University Hospitals, UK, was used to identify patients diagnosed with SCCB from January 2008 to January 2016.

Results 27 patients had confirmed diagnosis of SCCB. Mean age at diagnosis was 68.7 (range 37–90). 30% of the cases had pure small cell histology, while the rest were mixed histological subtype. Of the 12 patients with early stage disease (stage I and II), three had radical cystectomy and chemotherapy, six had both radiotherapy and chemotherapy, two had either radiotherapy or chemotherapy alone, and one declined active treatment. Of the 12 patients with advanced disease (stage III and IV), four had chemotherapy alone, four had both radiotherapy and chemotherapy and four was for best supportive care. 13 out of 16 patients who had chemotherapy received combination of carboplatin and etoposide. Patients with advanced stage disease had median survival of 9 months (95% CI 3.9 to 14.1 months). The median survival for patients with early disease was not reached. There is significant difference in survival between early and late stage disease (p value 0.008, Log rank test).

Conclusions Our results demonstrated a reasonable survival outcome in early stage SCCB patients. Radical multimodality treatment options should not be precluded in patients with early stage SCCB.

INTRODUCTION

Small cell carcinoma of the urinary bladder (SCCB) is an extremely rare histological subtype of bladder cancer. Similar to the bronchogenic counterpart, this ultra-high grade neuroendocrine cancer is often very aggressive and has the propensity to metastasise. Patients often present with advanced disease and long-term survival outcome is poor. Literature reporting on such disease entity is scarce, and there is no consensus in the management of this cancer due to the lack of level I and II evidence on effective treatment strategies. Generally, treatment of small cell bladder cancer is extrapolated and modified from the management of small cell lung cancer and transitional cell bladder

Key questions

What is already known about this subject?

- ▶ Small cell carcinoma bladder cancer is extremely rare and often associated with poor prognosis.
- ▶ There is no randomised study investigating the optimum management of the disease.
- ▶ Treatment strategy to date is extrapolated from management of small cell lung cancer and bladder transitional cell carcinoma.

What does this study add?

- ▶ Prognosis of small cell bladder cancer is not as dismal if early stage disease is treated aggressively.
- ▶ Multimodality aggressive treatments include transurethral resection of bladder tumour, chemotherapy and radiotherapy.
- ▶ Salvage surgery should not be discounted if there is local recurrence of disease.

How might this impact on clinical practice?

- ▶ Multimodality treatments to be considered for early stage T1 small cell bladder tumours.
- ▶ Salvage surgery to be contemplated for local recurrence of small cell bladder cancer.

carcinoma.^{1 2} Bladder preserving radical treatment with chemotherapy, radiotherapy or combined modality of both is often the preferred option rather than radical cystectomy to avoid the morbidity risk of surgery in a disease with relatively low cure rate.^{1 2}

This retrospective study examines the clinical experience of a UK Cancer Centre in the management of a series of patients with small cell bladder cancer, with particular focus on radical treatment strategies and survival outcomes.

METHOD

Histological database at the Nottingham University Hospitals NHS Trust, UK, was used to identify patients diagnosed with small cell bladder cancer from 1 January 2008 to 1 January 2016. Patient demographics and clinical details were extracted from the local hospital clinical database NOTIS, MOSAIC and Chemocare. Data collection cut-off date was set at February 2018. Microsoft Excel and

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IBM SPSS Versions 22.0 Statistics software were used for data and statistical analysis. Kaplan-Meier method was used to plot survival curves.

RESULTS

A total of 27 patients were identified who were diagnosed with small cell bladder cancer. Mean age at diagnosis was 68.7 (range 37–90). The predominant gender was male, with male to female ratio of 4:1. 30% of the cases had pure small cell histology, while the rest were of mixed histological subtype, predominantly transitional cell carcinoma (48%). All patients' staging was modified and adapted to fit TNM eighth edition criteria. 45% (n=12) had early stage disease (stage I–II), and 45% (n=12) were advanced stage (stage III–IV) at diagnosis. Three patients did not complete staging scans hence final staging was unknown. Only three patients had CT imaging of the brain from the outset, and none of them had brain metastasis.

Patient characteristics, histology subtype and staging were summarised in [table 1](#).

Treatment of small cell bladder cancer received by patients in this study is shown in [table 2](#). All patients who received radical radiotherapy had transurethral resection of the bladder tumour prior to treatment. In the early stage disease group, nine patients had multimodality treatments, of which three had radical cystectomy and six had radical radiotherapy as primary treatment. Chemotherapy was given either neoadjuvantly, concurrently or adjuvantly. Two patients had single modality treatment, either with radical radiotherapy or chemotherapy

Patient characteristics	Number (%)
Age	
<65	10 (37%)
65 or more	17 (63%)
Gender	
Male	20 (74%)
Female	7 (26%)
Histology	
Pure small cell (SC)	8 (30%)
SC+transitional cell	13 (48%)
SC+sarcomatoid	2 (7%)
SC+squamous	2 (7%)
SC+adenocarcinoma	1 (4%)
SC+large cell	1 (4%)
Stage (TNM8)	
I	3 (11%)
II	9 (34%)
III	6 (22%)
IV	6 (22%)
Unknown	3 (11%)

Table 2 Summary of treatments received by patients

Treatment	Number
Stage I–II patients (n=12)	
Neoadjuvant chemotherapy + radical cystectomy	1
Radical cystectomy + adjuvant chemotherapy	2
Induction chemotherapy + concurrent chemoradiotherapy	2
Induction chemotherapy + radical radiotherapy (RT)*	2
Induction chemotherapy + radical RT + adjuvant chemotherapy	1
Radical RT + adjuvant chemotherapy	1
RT alone (55 Gy in 20#)	1
Primary chemotherapy alone	1
Best supportive care	1
Stage III Patients (n=6)	
Induction chemotherapy + radical RT with nodal irradiation	3
Primary chemotherapy alone	2
Best supportive care	1
Stage IV patients (n=6)	
Primary chemotherapy alone	2
Palliative RT (21 Gy in 3#) then primary chemotherapy	1
Best supportive care	3

*Radical radiotherapy – 64 Gy in 32# over 6.5 weeks

alone. One patient declined all treatment and had best supportive care. The dose fractionation regime of the radical radiotherapy delivered was 64 Gy in 32# at 2 Gy per fraction over 6.5 weeks, using intensity modulated radiotherapy technique and image guidance.

In patients with stage III disease, three patients had induction chemotherapy followed by radical radiotherapy to bladder and nodes. Two had chemotherapy as primary treatment and one had best supportive care. In stage IV patients with distant metastatic disease, two had primary chemotherapy alone, one had palliative radiotherapy to the bladder to control local symptoms followed by primary chemotherapy, and three had best supportive care.

A total of 18 patients had chemotherapy. The predominant regime was carboplatin and etoposide, with carboplatin given at area under curve 5 (AUC5) and etoposide at 100 mg/m² intravenously on day 1, then further etoposide either intravenously or orally on day 2 and 3 every 3 weeks. This regime is based on the small cell lung cancer regime according to local guidance.³ Summary of other regimes can be seen in [table 3](#).

In this study, the median overall survival (OS) for all patients was 28 months (95% CI 8.7 to 47.3 months) as per [figure 1](#). The median survival for patients with early

Table 3 Chemotherapy regime received

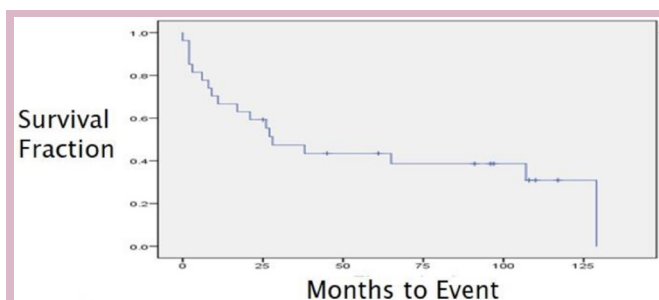
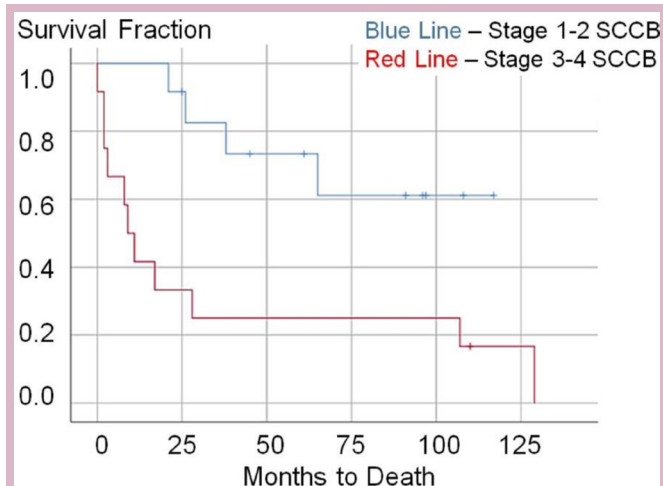
Chemotherapy	Number (%)
Cisplatin+etoposide	2 (11%)
Carboplatin+etoposide	13 (72%)
Cisplatin+gemcitabine	2 (11%)
Carboplatin+gemcitabine	1 (6%)

stage disease was not reached. Patients with advanced stage disease had median survival of 9 months (95% CI 3.9 to 14.1 months). **Figure 2** shows the Kaplan-Meier survival curves comparing the OS between patients with early stage and late stage small cell bladder cancer. There is significant difference in OS between early and late stage disease (p value 0.008, Log rank test).

Within the early stage disease subgroup, 11 out of 12 patients had definitive treatments. Four patients developed relapse with mean time to relapse at 19.5 months. One patient had local recurrence after chemoradiotherapy and was treated with salvage cystectomy. Two patients had oligo-metastatic recurrence and one had distant recurrence. Half of these patients who relapsed were still alive at data cut-off date.

DISCUSSION

The heterogeneity of small cell bladder cancer treatment strategy in our study series reflects the lack of standardised approach in treating this disease. It appears that bladder preservation therapy, which is maximal transurethral resection of bladder tumour followed by radical chemoradiotherapy, is the preferred first line treatment option for early stage small cell bladder cancer compared with radical cystectomy in this study. The general perception of small cell histological subtype of any cancer was always associated with high tendency of metastasis and high mortality. Therefore, it was not surprising that the trend of small cell bladder cancer treatment leaned towards a more conservative approach, to spare patients from a highly morbid procedure in radical cystectomy and then to have rapid recurrence and death. This mirrored the consensus in small cell lung cancer treatment as surgery was not a recommended treatment due to poorer outcomes.^{4,5}


Figure 1 Kaplan-Meier survival curves for all patients with small cell carcinoma of the bladder (SCCB).

Figure 2 Kaplan-Meier survival curves for patients with small cell carcinoma of the bladder (SCCB) stratified according to their staging.

However, surgery should not be completely disregarded in small cell bladder cancer management.⁶ Chang *et al* suggested that small cell bladder cancer shared some genomic mutations with small cell lung cancer, but the pathogenesis of small cell bladder cancer resembles more of cells originating from urothelial bladder carcinoma.⁷ As shown in this study, small cell bladder tumour histology often had mixed cell types, mostly with transitional cell carcinomas. This could be an important factor in treatment decision making for such group of patients, as it had been shown that the survival outcome of localised bladder transitional cell carcinoma treated with bladder preservation therapy could only be as good as radical cystectomy if salvage surgery was performed should the cancer recur.⁸ Therefore, it was reasonable to treat small cell bladder cancer with bladder preservation approach, but to be considered for surgical resection if the cancer recurs locally with no distant metastasis.

Irrespective of radiotherapy or surgery as the definitive treatment of small cell bladder cancer, chemotherapy would remain an essential part of the treatment strategy in view of its metastatic potential.^{9,10} In a large retrospective series, neoadjuvant chemotherapy followed by surgery improved rates of pathological downstaging, and most importantly better OS, in patients with $\leq cT4aN0M0$ small cell bladder cancer, compared with surgery alone.^{11,12} It was not unreasonable to consider chemotherapy for early stage small cell bladder cancer including stage I (T1N0M0), as high grade T1 bladder tumours had shown to have higher risk of occult nodal metastasis.¹³ It provided a possible explanation for the good survival outcome of early stage small cell bladder cancer patients in our study, as they had been treated aggressively with multimodality treatments. Platinum based combination chemotherapy would be the preferred choice, with meta-analysis of nine randomised controlled trials showed improved survival in bladder cancer patients.^{14,15} Our platinum chemotherapy treatment regime favoured the combination with

etoposide, in view of its established benefit in the treatment of small cell lung cancer.¹⁶

The prognosis of our patients with stage III and IV small cell bladder cancer remained poor, with significant difference in survival outcome from the patients with early stage disease. Nodal involvement in small cell bladder cancer was found to be a poor prognostic feature with dismal survival outcome.^{17 18} Some patients with nodes positive small cell bladder cancer in our study received radical chemoradiotherapy to the bladder alongside nodal irradiation. A review suggested that treatment approach with patients with node positive or metastatic small cell bladder cancer should be conservative with palliative intent, such as monotherapy with chemotherapy.¹⁹ It raised doubts on the benefit of aggressive chemoradiotherapy treatment in such patient group, as these patients could have been spared from the toxicities of chemoradiotherapy.

CONCLUSION

Within the limitation of our small retrospective study, we showed that the survival outcome of early stage small cell bladder cancer was not dismal, if treated aggressively with multimodality treatment. Bladder preservation therapy was reasonable as primary treatment of localised small cell bladder cancer but salvage surgery should not be completely discounted. Further studies are required to establish an optimal treatment strategy in small cell bladder cancer.

Contributors JHL designed the data collection tools, collected data for the study, cleaned and analysed the data, and drafted and revised the paper. SS analysed the data, proofread manuscript and provided supervision throughout the conduct of this study.

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