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The Outcomes of Patients Undergoing Radical Cystectomy for Small Cell Bladder Cancer (SCBC): A Single Centre Experience

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Abstract: *To review the literature of small cell bladder cancer (SCBC) and to compare those patients who had radical cystectomy with those having surgery for transitional cell carcinoma of the bladder.*

1. Introduction

SCBC is a rare (<1% of all bladder tumours) and aggressive form of bladder cancer. It shows similar behaviour to lung small cell cancer and is indistinguishable histologically. SCBC is from a family of neuroendocrine tumours, and is the most common epithelial subtype, that can affect the respiratory, gastrointestinal and genito-urinary tracts. Other neuroendocrine tumours include carcinoid and large cell carcinoma.

Untreated, it has a very poor prognosis with a 5 year survival less than 5% [1] due to high metastatic potential and lack of symptoms in early stage of the disease. There is usually a male predominance of 80%. Oncological surgery remains the most effective treatment. Systemic treatment can improve outcome.

The tumour is often mixed with urothelial cancer. Any component of SCBC drives the overall behaviour. Treatment usually involves a chemotherapeutic regime, which may be in addition to oncological surgery which should be offered to all non metastatic disease patients.

2. Methods

Papers were identified by searches of PubMed using the terms “small cell” “bladder” and “carcinoma”. Additional papers were identified from review of references of relevant articles.

3. Study Population

We reviewed retrospectively 258 patients having radical cystectomy from 1999 to 2013 and found 9 patients with neuroendocrine or small cell cancer (3%). Patients were considered to have SCBC if the histology showed any small cell component. We have emphasised stage, tumour volume, progression free survival (looking at local recurrence and metastasis) and compared these with patients having cystectomy for transitional cell carcinoma of the bladder. Our literature search has not shown any other study making this direct comparison.

4. Tumour Characteristics

Pathology was reviewed using TNM classification.

We compared the clinical and pathological outcomes of these patients to those with solely transitional cell cancer.

4.1. Statistical Tests

Graph pad Fishers exact test, Mann Whitney U tests, Kaplan Meier curves

5. Results

Table1: *Characteristics*

	SCBC	TCC	P Fishers, U test
Patients	9	215	
Male/female	4/5	170/43	0.02
Age years	Mean: 70.7 Median: 74 Mode: 82 First quartile: 63 Third quartile: 79	Mean (μ): 67 Median: 68 Modes: 67 71 75 76 First quartile: 61 Third quartile: 75	0.25

Grade High/intermediate	9/0	197/18	1
Tumour volume cc	Mean: 33.0 Median: 10 Interquartile range: 12 First quartile: 5 Third quartile: 17 Variance: 3328.4 Standard deviation: 57.6	Mean: 15.3 Median: 6.4 Interquartile range: 12 First quartile: 3 Third quartile: 15 Variance: 895.0 Standard deviation: 29.9	0.19
Positive surgical margins	2/9	21/215	0.23
Localised/locally advanced	3/6	133/82	0.15
Carcinoma in situ	4/9	97/215	1
Node positivity	3/9 33%	42/215 19%	0.39
Prostate cancer	3/4	74/98	0.32

Table2: *Survival curves*

	SCBC	TCC
5 years disease specific mortality	45%	29%
5 year all cause mortality	54%	39%
5 year progression free mortality	34%	24%

Incidence rate All cause mortality (ACM) SCBC = 0.02237 deaths/month

ACM TCC = 0.0095 deaths/month

Relative risk (ACM) = 2.344 (0.67-4.19)

Incidence rate DSM SCBC = 0.0178 deaths/month

DSM TCC = 0.00649

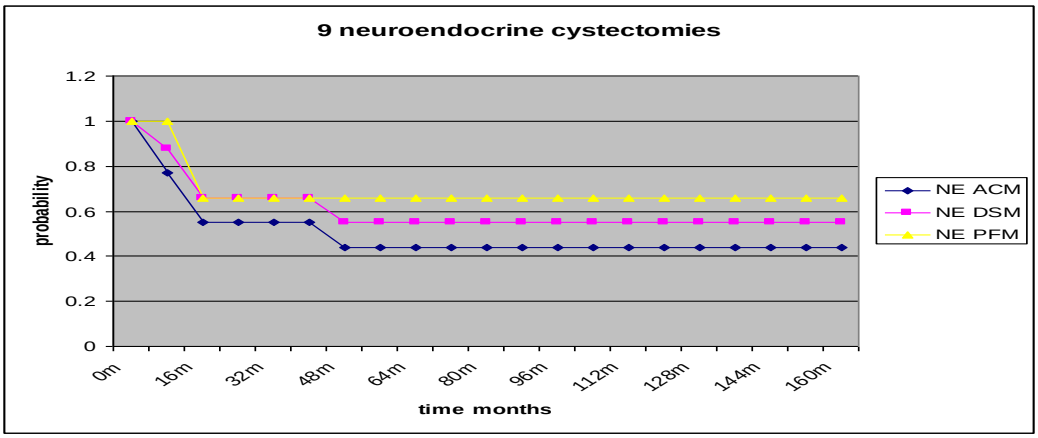
IRR (DSM) = 2.74 (0.979 – 7.666)

Log Rank All Cause Mortality

Kaplan-Meier estimate	
Median survival time (1)	89.965
Median survival time (2)	15.7188
p-value	0.1989
Cox proportional hazards regression	
Hazard ratio	1.7829
Confidence interval	0.7242 - 4.3892
Log likelihood	-500.8272

Log Rank Disease Specific Mortality

Kaplan-Meier estimate	
Median survival time (1)	> 50% survival
Median survival time (2)	20.6875
p-value	0.185
Cox proportional hazards regression	
Hazard ratio	1.9484
Confidence interval	0.7095 - 5.3504
Log likelihood	-352.5892



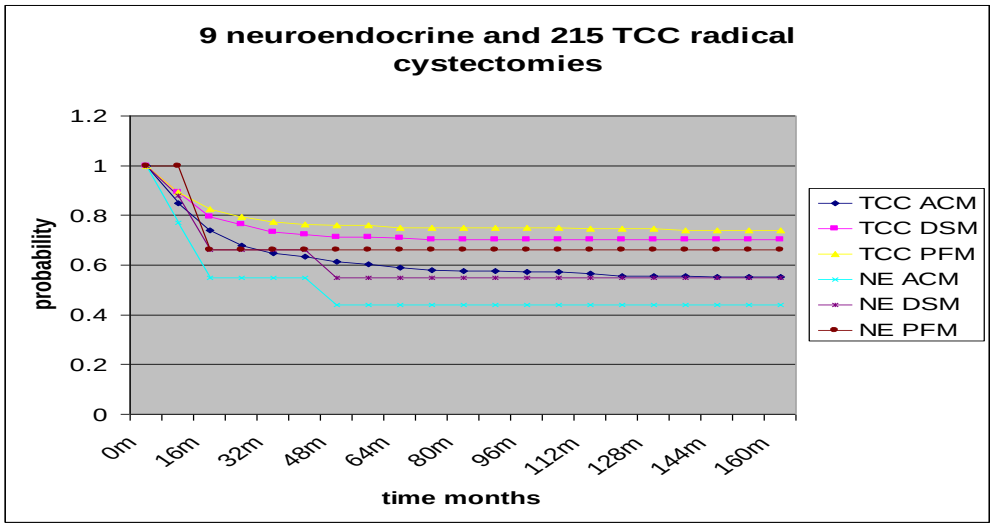


Table3: *Histological and immunological features*

Patient	Neuroendocrine Features	Other Histology
1	Neuroendocrine differentiation Neurone specific enolase positive Chromogranin A negative CD56 (neural cell adhesion molecule) negative	High grade urothelial with glandular components
2	Neuroendocrine cells 80% Hyperchromatic nuclei Chromogranin A positive CD56 positive	High grade urothelial carcinoma 20%
3	Synaptophysin positive Chromogranin A negative	High grade undifferentiated prostatic adenocarcinoma PSA, PSAP, BerEP4 positive
4	Small cell foci Neuroendocrine markers negative	High grade urothelial cancer
5	Neuroendocrine differentiation Chrmogranin A positive CD56 positive	Poorly differentiated papillary and solid carcinoma with glandular differentiation
6	Neuroendocrine differentiation CD56 positive Synaptophysin positive Ki67 70%	High grade papillary and solid urothelial carcinoma with squamous component
7	Neuroendocrine with small cell differentiation Scanty cytoplasm Vesicular nuclei with dotted chromatin Chromogranin A positive Neurone specific enolase positive	Poorly differentiated transitional cell carcinoma
8	Neuroendocrine differentiation	Grade 2 transitional carcinoma with glandular and squamous components
9	Sheets of oval/round hyperchromatic nuclei High mitotic rate CD56 positive Chromogranin A positive	Solid high grade carcinoma

Immuno stains were done in addition to histology in 8/9 cases

Chromogranin A (6 cases) sensitivity = 67%

Neural cell adhesion molecule CD56 (5 cases) sensitivity = 80%

Synapatophysin (2 cases)

Neurone specific enolase (1 case)

Neuroendocrine markers not specified (1 case)

All had coexisting tumour types

Comparison of Small Cell Lung Carcinoma

Small cell lung cancer stages and survival rates	
Stage	**Survival rate with treatment**
Limited	2-year: About 40%
Extensive	2-year: Less than 5%

6. DISCUSSION

This is a rare tumour forming less than 1% of all urological malignancies. The tumours are large necrotic masses with extensive local infiltration. The small cell component felt to drive the overall aggressive behaviour of the tumour. It is one of the most common sites of extrapulmonary small cell cancer [2]. Given this a rare disease, there have been no standard treatment regimes and extrapolation has been implemented from bronchogenic small cell cancer. Often a chemotherapeutic regime using a platinum based agent is involved, as an adjuvant treatment after oncological surgery. It seems that this improves outcomes especially for localised disease.

It is a smoking related cancer with a male predominance ordinarily, however our group showed a female predominance (P 0.02). Usually patients present in the sixth or seventh decade. The mean age here was 71 years.

The origin of the tumour is unclear. Perhaps a transformation from a bladder neuroendocrine cell or from a stem cell element [3]. There are a variety of chromosomal deletions seen in SCBC that are also seen in small cell cancer of the lung [4] suggesting a commonality in aetiology. There is also hypermethylation of tumour suppressor genes and amplification of oncogenes.

6.1. Pathology

The tumour is composed of sheets of round and spindle cells with little cytoplasm. The nuclei are hyperchromatic with a high mitotic rate and a “salt and pepper” chromatin [5]. The tumour is usually mixed with other urological tumours seen, urothelail, squamous and adenocarcinoma.

Immunohistochemcial stains are used to support the diagnosis of SCBC such as chromogranin A, synaptophysin, serotonin and neurone specific enolase. Perinuclear dot like immunoreactivity may be identified for cytokeratins [6]. The finding of numerous positive markers supports the diagnosis although light microscopy remains the gold standard. Given the stains are not specific for site of tumour origin, metastatic spread from other sites must always be excluded.

6.2. Prognosis

Untreated the 5 survival is less than 10% [1]. Limited stage shows a better prognosis than extensive stage [7]. Surgery, even for limited disease, may be inadequate [8] [9]. It has been reported that cis platin based chemotherapy is the only factor predicting survival [10] although others have not found this to be the case [11] yet neoadjuvant regimes were effective. There is no standardised regime, etoposide, cyclophosphamide, doxorubicin, gemcitabine and vincristine all have been employed.

Nevertheless oncological surgery is almost certainly the principal treatment for successful eradication of this disease [12]. Lymph node disease is common despite neoadjuvant treatment [13].

Multimodal TURBT, chemotherapy and radiation noted a higher relapse rate [14]. Chemotherapy alone gives a clearly inferior result [15] as does radiotherapy alone.

The treatment and survival varies among groups. A 15 year review of the Anglia Cancer Network revealed only 20 patients and only 3 had surgery. The median survival overall was 33 months for those receiving chemotherapy and 3 months for those not receiving chemotherapy [16]. The median survival for the Mayo group, who had 44 patients, was 1.7 years. They had a cure rate of 6/8 for stage 2 SCBC illustrating further that long term survival can be achieved with localised disease. Other institutions report small case series with a poor median survival of 7 months [17] or 34 months [18]. The MD Anderson cancer centre with 25 patients treated with cystectomy only yielded a 5 year survival of 36% [11], those 21 patients who had neoadjuvant chemotherapy had a 78% cancer specific survival.

We had a majority of 5 female patients in our SCBC population which is unusual for this bladder tumour (P=0.02) which represented 3.4% of all the 258 radical cystectomies

performed at our institution from 1999 to may 2013. The patients were not significantly older from the bulk of patients with transitional cell cancers of the bladder. All the tumours were high grade and larger than the TCC although not reaching statistical significance. All patients had muscle invasive disease and the majority, 6/9 cases, had locally advanced disease. There was no difference in the positive surgical margin rate. There was no significant difference in the carcinoma in situ or coincidental prostate cancer rates. Only 3 cases had nodal involvement but this was not significantly different from the TCC rate. Only 2 patients received adjuvant chemotherapy in the SCBC group compared to 36 in the TCC group (P = 0.6). Both patients who had adjuvant chemotherapy with gemcitabine and carboplatin have died. A total of 5 of 9 pts have died.

Three developed distant metastasis rather than local recurrence. The sites were in the bone and lung. All three showed progression at about a year with death occurring 3 months later in 2 cases. The patient with lung metastasis survived 32 months after progression was detected. Regarding metastasis, 1 bone metastasis at 10 months and died at 15 months, 2 bone and node metastasis at 13 months died at 16 months and 3 lung metastasis 10 months and died at 42 months.

Outcomes for SCBC may be improving with the use of neoadjuvant chemotherapy, although in our series none received this and the two patients who received adjuvant chemotherapy both died. Four of our patients are alive and two have shown long term survival at 75 and 58 months post surgery, neither of whom received chemotherapy of any modality.

The tumour seems to confer a worse prognosis. It does have recognisable features when using immunohistochemistry.

At least one marker is usually positive for these tumours (19). It also has a tendency for the tumour volume to be larger perhaps contributing to this worse prognosis. We detected a mean tumour volume of 33cc compared to 15cc for transitional cell tumour although the numbers were too small to be significant (P = 0.19). It has been shown to be significant with sarcomatoid tumours (20).

7. Conclusion

This is a small group of patients with this variant histology. Our survival figures are worse when compared to transitional cell outcomes; however they are not statistically significant. There is no established standard of care for this subtype of bladder cancer as it is rare entity and hence a unified approach will remain problematic. This study does contribute to the impression of a worse prognosis.

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