

Clinical Outcomes of Small Cell Carcinoma of Bladder: A Single Institutional Experience

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Received: 02 June 2019; Accepted: 25 June 2019

Citation: Rasha Mohamed Abdel Latif. Clinical Outcomes of Small Cell Carcinoma of Bladder: A Single Institutional Experience. Cancer Sci Res. 2019; 2(2); 1-6.

ABSTRACT

Background: Small cell carcinoma (SCC) is a rare disease, lung is the commonest site. In the urinary bladder SCC represent less than 1% of tumors affecting bladder.

Objectives: In this study we tried to evaluate clinic-pathological data of cases with small cell carcinoma of bladder (SCCB), highlight the different lines of treatment used in our department and calculate overall survival (OS) and disease-free survival (DFS).

Patients and Methods: This are a retrospective study included patients diagnosed with SCC of bladder (SCCB), data collected from files and computer based of patients attended to Clinical Oncology & Nuclear Medicine department in the period from January 2006 to December 2016.

Results: The study included 19 patients with mean age 64.5 ± 7.2 , male: female ratio 3.75:1. Gross hematuria presented in 89.5%, mean size was 4.7 ± 1.6 and tumor located on 47.4% on lateral wall. Stage III was the commonest in 52.6%. Pure small cell diagnosed in only 5 patients (26.3%). Seven patients (36.8%) treated with radical cystectomy, fourteen (73.7%) received chemotherapy, vepsid-platinol was the commonest regimen used (36.8%). Radiotherapy used in 9 patients (47.4%). The median OS and DFS were 23 and 12 months respectively. Radical cystectomy associated with better survival, while chemotherapy did not show benefit.

Conclusion: The SCCB is a rare disease, presented in advanced stage, so require radical treatment because it is associated with early metastasis. However, as reported surgery associated with better survival specially with combined modality. More advanced researches are needed with more analysis of different lines of treatment and its combination for improvement of survival.

Keywords

Small cell carcinoma, Bladder tumors, Radiation therapy, Cystectomy, Chemotherapy.

Introduction

Small cell carcinoma is a rare disease, lung is commonest organ diagnosed with small cell carcinoma [1]. In 1981, was 1st time small cell carcinoma in urinary bladder (SCCB) diagnosed [2], it representing less than 1% of carcinoma affecting urinary bladder [3]. It is associated with aggressive biology and so with distant metastasis [4]. Usually, it is associated with other histological

types like urothelial carcinoma, squamous, or adenocarcinoma [5,6].

Because of rarity of the disease, no enough available literature confirm the best line and sequence of treatment. Transitional cell carcinoma (TCC) of urinary bladder is the commonest histopathology, so many articles reported lines of treatment as either surgery (radical cystectomy) or bladder preservation in the form of transurethral resection of bladder (TURB), chemotherapy and radiation therapy either in concurrent or sequential pattern [7-10].

Small cell carcinoma of bladder (SCCB) is often presented in advanced stage, with high rate of distant metastases, so systemic therapy is an important component of the treatment [11].

The optimal line of treatment of SCCB was unknown, as few literatures reviewed the outcomes of patients with different lines. However, retrospective studies reported that neo-adjuvant chemotherapy with platinum-based regimens followed by radical cystectomy or concurrent chemotherapy with radiation therapy and considered acceptable treatment options [12-15]. So, in this study we try to evaluate the clinic-pathological characters and outcomes of these cases.

Patients and Methods

After approval by Institutional Review Board of Mansoura faculty of Medicine (IRB-MFM), this is a retrospective study performed in department of Clinical Oncology & Nuclear Medicine, Mansoura University hospital, on patients diagnosed with small cell carcinoma of urinary bladder (SCBC) from January 2006 to December 2016.

Total number of cancer bladder was 1790, we analyzed 19 cases diagnosed with SCBC. The data collected from files and computer-based data. We reviewed clinicopathological characteristics as age, sex, smoking history, associated medical diseases, symptoms, tumor site, tumor size, stage and pathology.

The treatment received also analyzed, options of lines whether surgery, chemotherapy and/or radiotherapy. Surgery was performed as radical cystectomy (RC) or transurethral resection of bladder tumor (TURBT), or no surgical interference. As regard chemotherapy, if received or not, regimens used which varied according to pathological components and sequence of chemotherapy as neo-adjuvant or adjuvant.

The radiation therapy used as radical treatment with concurrent chemotherapy as bladder preservation management or after TURBT. The total dose was 60 Gy in 2 phases, phase I whole pelvis with 45 Gy followed by phase II as boost of 15 Gy to the bladder, also, received as palliative treatment to bone or as hemostatic treatment.

Follow up of the patients performed clinically and radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) which available, chest x-ray or CT chest and bone scan if indicated. time of follow up calculated from surgery or end of chemo-radiotherapy till end of study, loss of follow up or death.

We analyzed overall (OA) and disease free survival (DFS). Overall survival calculated from diagnosis of the disease till end of study, loss of follow up or death. Disease free survival calculated from surgery or complete response of the tumor till recurrence, loss of follow up or death.

Statistical analysis

Data was analyzed using Statistical Package for Social Science

software computer program version 23 (SPSS, Inc., Chicago, IL, USA). Quantitative parametric data were presented in mean and standard deviation, while quantitative non parametric data were presented in median & range. Qualitative data were presented in frequency (Number-percent). Mann whitney was used for comparing two groups with quantitative non-parametric while Kruskal wallis followed by post-hoc Dunne's was used for comparing more than two groups with quantitative non-parametric. Chi-square " χ^2 " was used to compare the qualitative data. Kaplan–Meier curves were generated to compare disease free survival & overall survival of patient's method of treatment. P value less than 0.05 was considered statistically significant.

Results

This is a retrospective study done on 19 patients with small cell carcinoma of the bladder attended to Clinical Oncology & Nuclear Medicine department. Mansoura University Hospital from January 2006 to December 2016.

The small cell carcinoma of bladder represented about 1% of bladder tumors. The clinic-pathological characteristics are listed in table 1. The mean of age was 67.5 ± 7.2 , male was the predominant gender in 15 patients 78.9% and 4 (21.1%) were female with male to female ratio (3.75: 1). The history of smoking reported in 5 patients (26.3%), gross hematuria presented in 17 (89.5%) while frequency of micturition in 11 cases (57.9%). Only 4 patients had co-morbidities.

Characters		NO	%
Age		64.5 ± 7.2	
Sex	Male	15	78.9%
	Female	4	21.1%
Hemat	No	2	10.5%
	Yes	17	89.5%
Frequency	No	8	42.1%
	Yes	11	57.9%
Smoking	No	14	73.7%
	Yes	5	26.3%
Morbidity	No	15	78.9%
	Yes	4	21.1%
Site	ant	5	26.3%
	lat	9	47.4%
	orifice	1	5.3%
	post	4	21%
Path	S	5	26.3%
	S+ T	9	47.4%
	S+ad	2	10.5%
	S+Sq	3	15.8%
Stage	II	6	31.6%
	III	10	52.6%
	IV	3	15.8%

Table 1: Clinic-pathological characters of the patients. Hemat: Hematuria, Ant: Anterior, Lat: Lateral, Post: Posterior, Path:

Pathology, s: Small cell, t: Transitional, Ad: Adenocarcinoma, Sq: Squamous.

The mean of tumor size was 4.7 cm ± 1.6, as regards the location of the tumor lateral wall was the commonest site in 9 patients (47.4%) followed by anterior one in 5 patients (26.3%). Ten patients (52.6%) diagnosed with Stage III, 6 with stage II and only 3 patients with stage IV. The sites of distant metastases were liver in 2 cases and bone in one. Pathological analysis revealed 5 (26.3%) patients had pure small cell histology and 14 (73.7%) had associated histology with 9 (47.4%) urothelial, 3 (15.8%) squamous and 2 (10.5 %) adenocarcinoma.

Table 2 shows treatment characters. Radical cystectomy performed in 7 (36.8%) patients, six patients (31.6%) operated with TURB and no surgical treatment in 6 (31.6%) patients. Fourteen patients (73.7%) received chemotherapy, 2 (10.5%) of which were neoadjuvant, 7 (36.8%) as adjuvant, 3 (15.8%) as concurrent chemo-radiotherapy and 2 (10.5%) received chemotherapy for palliative aim. The regimen formed of vepside and platinol was most one used in 7 patients (36.8%), followed by gemzar plus carboplatin in 4 patients (21.1%).

Treatment		No	%
Op	None	6	31.6%
	RC	7	36.8%
	TURB	6	31.6%
Chemoth	No	5	26.3%
	Yes	14	73.7%
Ttype	Gem+carb	4	21.1%
	Gem+cispl	2	10.5%
	MVAC	1	5.3%
	VP	7	36.8%
Seq	adj	7	36.8%
	conc	3	15.8%1
	neoad	2	10.5%
	palliative	2	10.5%
RTH	No	10	52.6%
	Yes	9	47.4%

Table 2: Treatment characters of the patients.

Op: Operation, RC: Radical cystectomy, TURB: Transurethral resection of bladder, Chemoth.: Chemotherapy, Gem: Gemzar, Carb: Carboplatin, Cispl: Cisplatin, MVAC: Methotrexate-vinblastin-adriamycin-cisplatin, VP: Vepside-platinol, Seq: Sequence, Adj: Adjuvant, Conc: Concurrent, Neoad: Neoadjuvant, RTH: Radiotherapy.

The radiation therapy used in 9 (47.4%) patients included 3 (15.8%) as concurrent chemo-radiotherapy, received as adjuvant treatment with chemotherapy after TURB in 4 (21%) and used as palliative to hematuria in 1 (5.3%) and to metastatic bones in 1 (5.3%).

The median of follow up was 21 months (range 3-62 months). The median of overall survival of all patients was 23 months (range

3-64 months). For the patients treated with surgical resection DFS median was 12 months (range 10-49 months). At the end of the study there was 4 (21.1%) alive and 15 (78.9%) patients died, 1 free of disease, 3 alive with lesion. Recurrence diagnosed in 13 patients (68.4%), was local in only 1 case (5.3%), and bone was commonest of distant metastasis (31.6%) followed by lung (26.3%) (Table 3).

Treatment		NO	%
Relapse	No	6	31.6%
	Yes	13	68.4%
Site of relapse	Bone	6	31.6%
	Brain	2	10.5%
	Liver	2	10.5%
	Local	1	5.3%
	Lung	5	26.3%
Fate	Alive	4	21.1%
	Dead	15	78.9%
DFS		12.0 (10-49.0)	
OAS		23.0 (3.0-64.0)	
FU		21.0 (3.0-62.0)	

Table 3: Outcomes of the treatment.

DFS: Disease free survival, OAS: Overall survival, FU: Follow up.

On analysis of effect of surgery on OA, mean of survival in patients treated with RC was 44.304 (95%CI 30.168-58.439) was better in comparison to TURB (mean 17.333, 95% CI 11.339 - 23.327) or no surgery (mean 19.333, 95% CI 6.484 -32.183) , with significant difference (P = 0.025) (Figure 1). Also, DFS showed statistically significant difference (P=0.001) for radical cystectomy (RC) (mean 30.143, 95% CI 20.285 - 40.000) over TURB and no surgical interference (mean 12.500 95% CI 6.216 - 18.784 and 7.083 95% CI 2.811 - 11.35, respectively) (Figure 2).

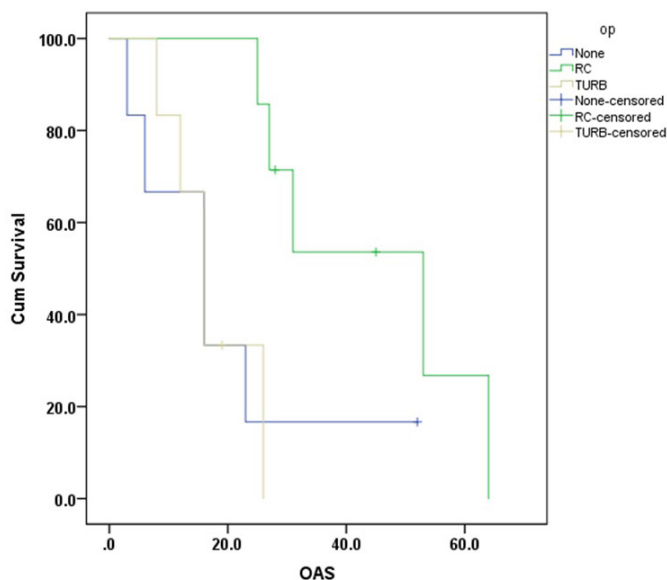


Figure 1: Kaplan-Meier overall survival (OS) curves for SCCB patients with different surgeries.

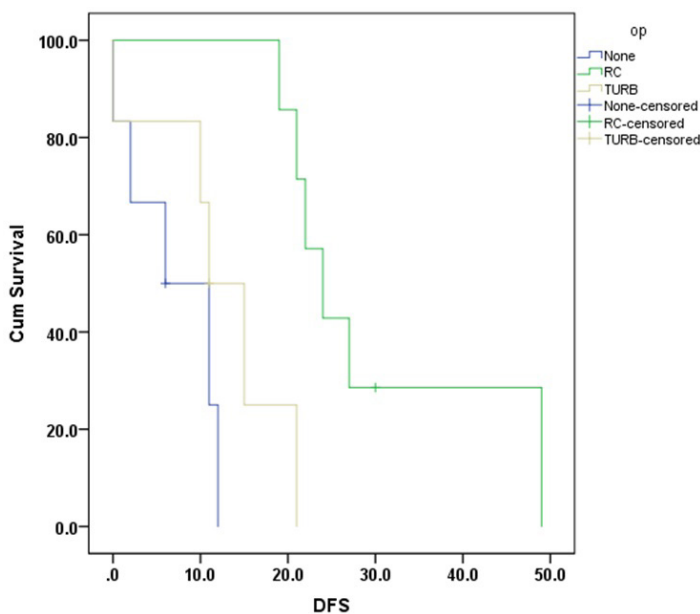


Figure 2: Kaplan-Meier disease survival (DFS) curves for SCCB patients with different surgeries.

Chemotherapy treatment had better mean of OS (32 months, 95%CI 9.696- 54.304) over who did not receive chemotherapy (26.255, 95% CI 17.732- 34.778), but not reach statistical significance (P=0.79), the same obtained with DFS (p=0.13).

Discussion

Epithelial tumors account for 95% of bladder tumors [11], while, non-epithelial are rare as small cell carcinoma of bladder (SCCB) (which occurs mainly in lung and oesophagus) represent only 1% of primary bladder tumors [3]. In our department SCCB also represented about 1%.

Because of this rarity few studies mainly retrospective performed to review clinic-pathological data and treatment lines used in SCCB. So we performed this retrospective study on patients diagnosed with SCCB attended to Clinical Oncology & Nuclear Medicine department of Mansoura University Hospital in the period from January 2006 to December 2016, to evaluate clinic-pathological data and treatment lines used.

The mean age was 67.5 ± 7.2 , with predominance of male gender with male: female ratio 3.75:1, gross hematuria was the most presenting symptom in 89.5%. This result coincides with other literatures reported average age of 67 years, male: female 5:1 and hematuria was main complain in 90% of patients [4,11,16].

Small cell carcinoma of bladder (SCCB) is characterized by poor prognosis and associated with aggressive behavior with early metastasis [15], stage IV presented 65% at diagnosis and stage II & III 35% [17], however, there is a literature reported 75% of patients were diagnosed as limited stage and 25% with extensive disease [18]. In our review stage III was 57.6%, stage II 31.6 %, IV 15.8 % and no case with stage I which resemble literatures where stage III was more frequent (40% - 65%) than stage IV [19,20].

Different theories suggested the etiology of SCCB and the most accepted one that the tumor originates from a multi-potent stem cell which in turn differentiate into different cells and consequently explain the coexistence of SCCB with other histologies as urothelial carcinoma, squamous cell carcinoma and adenocarcinoma [5,21,22].

Five patients (26.3%) diagnosed with pure SCCB and 73.7% associated with other histologies (47.4%, 15.8% and 10.5 as urothelial, squamous and adenocarcinoma, respectively). This in agreement with other literatures as pure SCCB present 32% & 41.6% [17,20].

The tumors usually located on the lateral wall and less common in the fundus, trigon, anterior wall and the dome [23]. We reported lateral wall in 9 patients (47.4%) as commonest site.

As SCCB is uncommon tumors, no treatment guidelines recommended and all trials depend on retrospective studies or case reports. The treatment of SCCB is usually including multimodality with chemotherapy, chemo-radiotherapy and surgery with or without chemotherapy, but because of aggressiveness of the disease and high possibility of distant metastasis, chemotherapy is considered the cornerstone of the management [18,24].

Most of researchers believed that SCCB is a mixed carcinoma, so surgical treatment is preferred in the form of radical cystectomy, partial cystectomy or transurethral resection of bladder tumor (TURBT) [15]. But literatures found that surgery alone can be reserved to early stage of the tumor [3,25].

However, many studies concluded that combined treatment in the form of surgery plus chemotherapy is better than surgery alone even in early stage [6,25]. On the other hand, Cheng et al., reviewed cases with SCCB and found no survival benefit in patients operated with RC over who did not [11], this may be explained by comparing cystectomy alone with who received combined modality treatment (p=0.65).

As regards sequence of chemotherapy with surgery, neo-adjuvant chemotherapy (NAC) improved survival in comparison to adjuvant, Siefker-Radtke et al, registered 5-years survival rate of 78% for NAC then surgery versus 36% with surgery alone [26]. Similar improvement obtained by Lynch and colleagues, as reported OS of 159.5 months with NAC versus 18.3 months with adjuvant [27].

In our study 7 patients operated by RC (93.8%), 2 received neoadjuvant, 2 received adjuvant chemotherapy and 3 treated with surgery alone, this may be attributed to that 4 of patients were stage II.

The median of OS in the present study was 23 months and DFS was 12 months, these results coincide with most of literatures reported median survival from 12-24 months [6,15,28], but higher than reported in Ram et al, and Nabi et al, who reported survival 16.5 and 18.5, this may be related to smaller number of patients (11

patients) and shorter period of follow up (14.2 months) [19,29]. In the current study, on analysis of effect of surgery on OS there was improved survival (mean 44.304) for who operated with RC over who did not (mean 19.333) with significant difference ($P=0.025$).

Vepsid-platinol regimen was the commonest regimen used in the present study in (36.8%), followed by Gemzar- carboplatin in 21.1%, this confirm the results of other literatures that platinum-based regimens are more effective and improve survival [24,30]. Chemotherapy associated with improved survival and this, but not reach statistical significance, may be explained by not all patients treated with RC and TURB, carry better survival, received chemotherapy, beside that 13 cases of the fourteen received chemotherapy developed disease progression and small number of patients in each sequence which consider it not liable for more analysis.

An alternative option to RC and chemotherapy, for patients unfit for surgery or with advanced stage, is chemo-radiotherapy [31,32]. Lohrish et al., reported 70% overall survival rate at 2-years in patients treated with chemo-radiotherapy combined with TURB [33]. Also, Bex et al., evaluated 17 patients received chemo-radiotherapy followed by TURB and registered median survival of 15 months [34]. Concurrent chemo-radiotherapy has promising results more than radiation alone [30,35].

Six patients in the current study treated by TURB, four of them received chemo-radiotherapy, and one chemotherapy alone, with median of 16 months which resemble that obtained by Bex et al. [34].

Conclusion

Small cell carcinoma of bladder is rare disease (1%), carry poor prognosis as at diagnosis present in advanced stage. This rarity render treatment guidelines difficult. Surgery with combined treatment is better than one modality alone, especially with platinum-based chemotherapy. Transurethral resection of bladder tumor (TUR-BT) with chemo-radiotherapy is an effective alternative treatment. More prospective studies with larger numbers and more analysis of different factors with survival are needed to clarify treatment options.

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