Small Cell Carcinoma of Bladder; Still A Diagnostic and Therapeutic Challenge: Seven Years of Experience and Follow-up in A Referral Center

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Purpose: To report clinical, histopathological, and treatment features of small cell carcinoma of (SmccB) bladder during 7 years in a referral center.

Methods: The clinical, histopathological features, treatment modalities, and outcome of all patients with bladder SmccB treated between 2009 and 2016 who were managed in Hasheminejad Kidney Center (HKC) were retrospectively collected.

Results: Thirteen patients were diagnosed and managed with SmccB. The average age of patients was 64.92 years. For each patient, 8 markers were used for IHC staining on average. Neuroendocrine markers such as CD 56, Neuron Specific Enolase, Synaptophysin, and Chromogranin were found in a significant percentage of patients (69%, 38%, 54%, and 31% respectively). Patients were managed with TURBT alone (N=3), chemotherapy after TURBT (N=4), chemotherapy plus radical surgery (N=4) and radical surgery alone (N=2). The best clinical result was seen in chemotherapy received patients with or without radical surgery. The mean(SE) of survival rate in patients who received only chemotherapy alone was 42.4 (10.0) months, while in those who were managed with chemotherapy plus radical surgery it was 47.7 (10.1) months.

Conclusion: In our center immunohistochemistry was needed for definitive diagnosis in 17/19 samples. Misdiagnosis happened in two samples without IHC request. We think that use of immunohistochemistry should be mandatory for diagnosis of SmccB to exclude misdiagnosis. Chemotherapy is the most important part of treatment and the addition of radical surgery can slightly improve patients' survival.

Keywords: bladder neoplasms; immunohistochemistry; small cell carcinoma; urinary bladder

INTRODUCTION

Primary Small cell carcinoma of the bladder (SmccB) is a highly invasive and rare tumor of the urinary system[(1)]. Although the lung is the most common organ involved by small cell carcinoma, this type of tumor can also affect many extra-pulmonary organs[(1,2)]. As many as 2-9% of cases of small cell carcinoma (Smcc) are extra-pulmonary, and following gastrointestinal tract, the bladder is the third most common site of involvement[(3)]. SmccB accounts for 0.5 to 0.7% of all bladder tumors [(4,5)]. Although this tumor is rare, it is not insignificant in any way[(6)]. This tumor has been considered by many scholars due to its difficulties in diagnosis, aggressive behavior, poor prognosis, rapid progression, and systemic nature[(1)]. The rarity of SmccB has limited our knowledge of the biological progression of this malignancy and thus prevented the ability to plan randomized prospective studies[(1,7)]. In the literature, a few papers have been published on the optimal clinical guidelines for SmccB[(6)]. There is still no therapeutic approach which is universally accepted and because of the rarity of the disease, the treatment modalities are not standard. The behavior of SmccB is far more invasive than that of urothelial cell carcinoma (UCC). Despite similar clinical and demographic risk factors, and diagnostic methods, the prognosis of SmccB is much worse than UCC [(7)], and therefore, its definitive diagnosis is very important. Pathologic diagnosis according to WHO criteria is performed through light microscopy, but some pathologists recommend immunohistochemical (IHC) staining for diagnosis and some others consider it mandatory.
In this study, we present the clinical as well as histopathological characteristics, therapeutic options, and outcomes of the SmccB patients managed in our center during a seven-year period, and emphasize the use of IHC staining for confirmation of pathologic diagnosis.

MATERIALS AND METHODS

From March 2009 until March 2016, 2763 patients with suspicious diagnosis of bladder tumors underwent transurethral resection of bladder tumor (TURB) in our center. A total of 301 cases later underwent radical cystectomy with urinary diversion. Hospital files of all patients with a final diagnosis of SmccB were reviewed.

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Table 1. Summary of demographic and clinical characteristics of 13 patients.

Characteristics	
Gender; Male/Female	10/3
Age; mean, range	64.92 (41-83) years
Gross hematuria	12/13
Lower abdominal pain (large pelvic mass)	3/13
Uremia	6/13
Flank pain	1/13
Creatinine at diagnosis; mean, range	2.13 mg/dl (0.9 – 4.7)
Hemoglobin at diagnosis; mean, range	10.7 mg/dl (7.7 – 14.8)
Tumor size in imaging; mean, range	7.54 cm (2 – 12)
Bilateral hydronephrosis	6/13
Unilateral hydronephrosis	1/13

Abbreviation: SmccB, small cell carcinoma of bladder

Table 2. Pathologic and histologic details..

Stage	
At least T2	7/13
T3a N–	1/13
T3a N+	1/13
T3b N+	1/13
T4a N+	3/13
Pure SmccB	10/13
SmccB + UCC	1/13
SmccB + UCC + CIS	2/13

Abbreviations: SmccB, small cell carcinoma of bladder; UCC, urothelial cell carcinoma; CIS, carcinoma insitu

Demographic characteristics, clinical symptoms, and the most common cause of referral were extracted and recorded. The results of imaging studies including size and location of the mass, the presence or absence of hydronephrosis, local extension of tumor, and ultimately, lymph node involvement were recorded.

Serum hemoglobin and creatinine levels, preoperative urine cytology, therapeutic options including type of surgical procedure, chemotherapy regimen, and final pathological staging of tumor as well as multiple markers used in IHC staining of patients were recorded.

The patient's latest health status was obtained via phone call (at the end of October 2016)

Data was entered into SPSS software ver.19. Kaplan-Meier curves were employed to display survival and comparison of survivals across treatment groups was performed by logrank test. Statistical significance was set a *P*-value less than 0.05.

RESULTS

During this period, 13 patients with a mean age of 64.92 years (range; 41-83) were diagnosed with SmccB. Three patients were female and ten were male. The reasons for referral were gross hematuria (12/13), uremia due to bilateral hydroureteronephrosis (6/13), lower abdominal pain due to large bladder mass (3/13), and flank pain (1/13).

The mean (range) of presentation hemoglobin (Hb) was 10.7 (7.7-14.8) mg/dL. Renal functional impairment (Cr > 1.5 mg/dL) was observed in six patients. The mean (range) of presentation creatinine was 2.1 (0.9-4.7) mg/dL. The findings of imaging modalities were large bladder mass, which had often a size greater than 5 cm. Unilateral (N=1) or bilateral hydronephrosis (N=6) was observed in seven patients. In all patients, urinary cytology was positive for the presence of malignant cells. Demographic, clinical, and laboratory data on patients has been presented in **Table 1**.

All patients underwent TURBT. In 11 patients, histologic examination on primary TURB specimen was not diagnostic and only after IHC staining SmccB diagnosis was confirmed. In two patients in whom IHC was not performed, the initial histologic report of TURBT specimen was high grade poorly differentiated urothelial carcinoma (**Figure 1**). These two patients underwent radical cystectomy and the pathology report after radical cystectomy revealed SmccB of bladder. Details of pathological reports are presented in **Table 2**.

Treatment methods in our patients were TURBT alone (3/13), TURBT with chemotherapy (4/13), radical surgery combined with chemotherapy (4/13), and radical surgery alone (2/13) (**Figure 1**). The chemotherapy regimen included six courses of cisplatin and Gemcitabine.

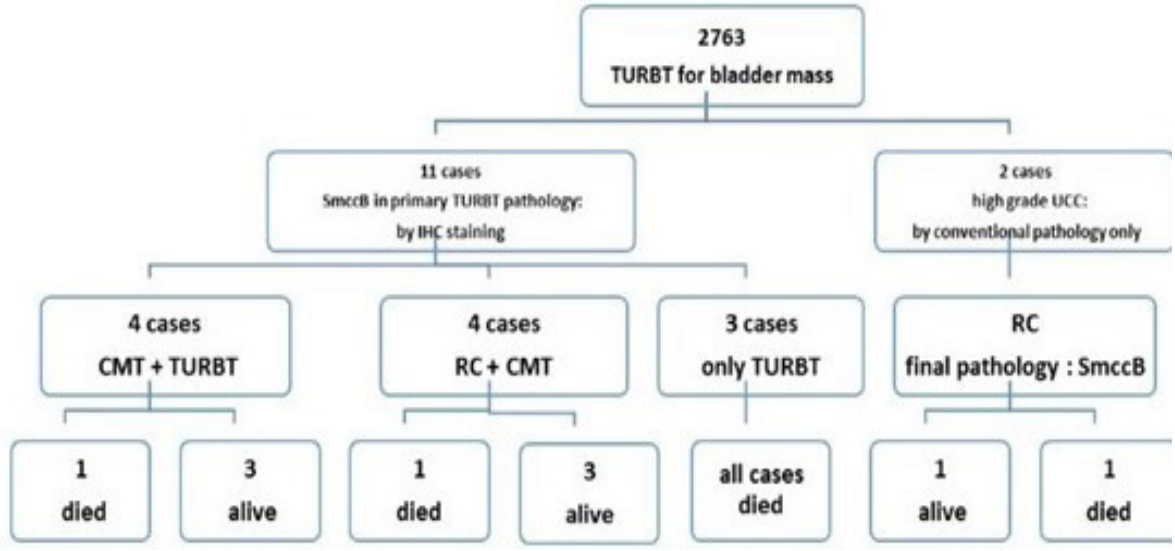

Figure 1. Summary of Treatments and Survival.
Abbreviations: TURBT, transurethral resection of bladder tumor; CMT, chemotherapy; RC, radical cystectomy

Table 3. Summary of all patients' data.

N	Age	Gender	Serum Cr	C stage*	RC	CMT	P Stage	Survival	Follow up (months)
1	77	male	1.63	T2	ND	D	T2*	Alive	54
2	41	male	3.3		D	D	T3b N+	Alive	52.8
3	75	female	1.0	T3	ND	ND	T2*	Deceased	6.2
4	59	male	1.4		D	D	T4a N+	Alive	50.5
5	47	male	1.3	T2	ND	D	T2*	Alive	40.7
6	75	male	4.7	T2	ND	ND	T2*	Deceased	2.6
7	62	male	1.9	T4 N+	ND	ND	T2*	Deceased	6
8	62	male	2.8		D	D	T4a N+	Alive	60.3
9	62	female	1.3		D	D	T3a N+	Deceased	10
10	61	female	2.2		D	ND	T4a N+	Deceased	8
11	66	male	4.1	T4	ND	D	T2*	Deceased	7.6
12	74	male	1.2		D	ND	T3a N-	Alive	9.6
13	83	male	0.9	T2	ND	D	T2*	Alive	9.4

Abbreviations: RC, radical cystectomy; CMT, chemotherapy; p Stage, pathological stage; D, done; ND, not done; Cr, creatinine
T2*: least pathological stage because patient only underwent TURBT
C stage*: clinical stage according to imaging in patients only underwent TURBT

The reasons for the differences in the treatment modalities were clinical judgment, patient's health, serum creatinine, performance status as well as his/her desire. The summary of treatment and survival has been shown in **Table 3** and **Figures 2** through 5. The mean (standard error (SE)) of survival in patients who received and did not receive chemotherapy were 36.4 (8.5) vs. 6.5 (1.0) months (P = .009; **Figure 2**) while the difference based on receiving surgery was not statistically significant (**Figure 3**). The mean (SE) survival of patients in clinical / pathological stages of T2, T3, and T4 independently of their treatment strategy were 41.1 (11.1), 25.1 (12.6), and 28.4 (11.6) months respectively (P = .73; Figure 4) The mean (SE) of survival in patients without any treatment, only surgery, only chemotherapy, and chemotherapy with radical surgery were 4.9 (1.2), 8.8 (0.6), 42.4 (10.0), and 47.7 (10.9) months respectively (P = .001; **Figure 5**)

In macroscopic pathologic examination, all cases showed a large tumor, filling most of the bladder cavity. Gross areas of necrosis were also evident. In all cases, areas of invasion into muscularis propria were noted. Diagnosis of SmccB, however, was suggested in simple microscopic examination of tissues but for definitive diagnosis, IHC staining was recommended for 17 pathology samples (11 TURBT and 6 radical surgery cases; Figure 6). As previously stated the pathology diagnosis in the only two samples which were reported without IHC staining was inaccurate (**Figure 1**).

IHC staining was performed with an average of eight markers[6–16] for each patient.

We used a panel of neuroendocrine markers as CD 56, Neuron Specific Enolase (NSE), Synaptophysin, and Chromogranin to confirm the diagnosis (**Figure 6**). At least two of these markers were positive in each patient (**Table 4**). We also performed a combination of IHC staining for CK 7, CK 20, P63, CD 45, PSA, CD 99, Desmin, and Myogenin to rule out urothelial carcinoma, lymphoma, prostatic adenocarcinoma, Ewing sarcoma, and rhabdomyosarcoma.

DISCUSSION

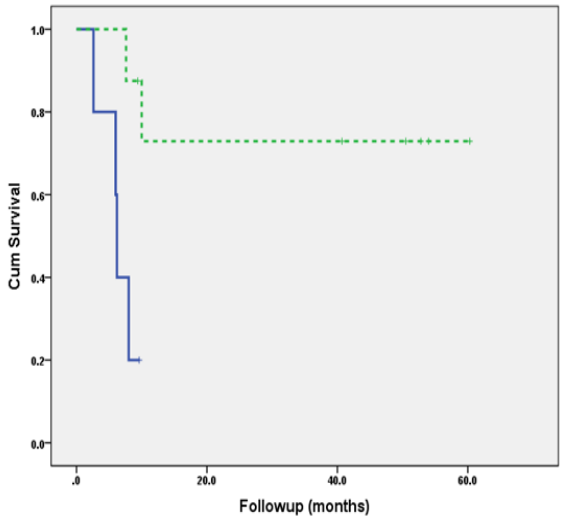

Figure 2. Kaplan-Meier curves to compare survival across survival based on receiving chemotherapy (dotted line denoted patients who received chemotherapy and solid line indicates patients who did not receive chemotherapy)

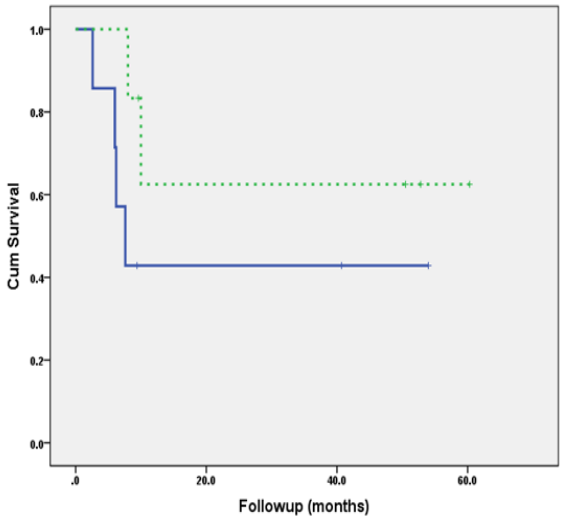

Figure 3. Kaplan-Meier curves to compare survival across survival based on receiving surgery or not (dotted line denoted patients who received surgery and solid line indicates patients who did not receive surgery)

Table 4. Positivity of markers of neuroendocrine differentiation in patients

IHC marker	Positive	Negative	Not performed
CD56 9 (69%)	1 (8%)	3 (23%)	
NSE 5 (38%)	1 (8%)	7 (54%)	
Synaptophysin	7 (54%)	3 (23%0	3 (23%)
Chromogranin	4 (31%)	6 (46%)	3 (23%)

Abbreviations: IHC, Immunohistochemical; NSE, neuron specific enolase

The results of this study reveals that for definitive diagnosis of SmccB, IHC is necessary as in all properly diagnosed pathology specimens, IHC was performed and in 2 improperly diagnosed samples, IHC was not requested. Furthermore, chemotherapy seems to be the mainstay of treatment, however adding surgery to chemotherapy may increase patient survival; however this benefit was not statistically significant in our series.
Smcc is a rare tumor with a very aggressive behavior, and accounts for less than 1% of bladder malignancies [2,8]. Despite the recognition of disease since 1981 by Cramer et al.[9], less than 1,000 cases of this disease have been reported so far, and most published studies are small case series[6]. This type of bladder cancer has many challenging aspects especially in diagnosis and treatment methods.
The histological diagnosis of the disease is not so easy and evidence suggests that diagnostic errors in the bladder Smcc may occur frequently. A large study by Linder and his colleagues reclassified SmccB in 9% of the cases with inconsistency in previous histopathological diagnosis[10]. In another study by Kaushik et al., a review by a uropathologist, the rate of SmccB detection increased[11]. Diagnosis of SmccB is based on the WHO criteria by light microscopic examination[12]. On microscopic examination, discrimination of SmccB from pulmonary type is impossible[13]. The tumor usually shows a patternless diffuse growth, composed of round small cells in nests or sheets with scant cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli. The nuclei show nuclear crowding and molding. Geographic necrosis, crush artifact, Azzopardi effect, and frequent mitotic figures are usually evident[14]. The microscopic features of hematoxylin and eosin staining (H&E) sections usually lead to diagnosis. Nevertheless, for further confirmation and ruling out major differential diagnoses including malignant lymphoma, poorly differentiated urothelial carcinoma and rhabdomyosarcoma, IHC studies are usually performed.
For the first time in 1986, Ordonez and colleagues used IHC staining to detect the differentiation of neuroendocrine cells, constituting the origin of this type of cancer [15]. SmccB exhibits both neuroendocrine and epithelial markers[6]. A recent study has reported that CD56 may be among the most sensitive neuroendocrine markers, staining 71.4% of bladder SmCC cases, followed by synaptophysin and chromogranin[16]. Neuron Specific Enolase (NSE) is positive in 25-100%, Chromogranin in 22-89%, and Synaptophysin in 67-76% of SmccB patients[14,17,18].
Several epithelial markers are also positive in this cancer. CK-7 and Epithelial Membrane Antigen (EMA) are positive in 60% and 80% of SmccB patients, respectively[4,19]. Tumors show a dot-like positivity for pancytokeratin. Markers of neuroendocrine differentiation including Synaptophysin, Chromogranin, CD 56, NSE are usually positive in tumoral cells. However, CD 45, Myogenin, and Desmin are negative[20]. IHC panel should include CD56, CD45, Synaptophysin, CAM-22, and CK8/18[6].
In our experience, the IHC staining was performed with the aim of demonstrating the neuroendocrine differentiation, presence of epithelial elements, and excluding other malignancies. For each patient, between 6 and 16 markers and on average 8 markers were used.
The use of IHC staining to diagnose SmccB routinely is still controversial. Some pathologists only use IHC staining for supplementation of morphological recognition, and believe that neuroendocrine markers are not required to make diagnosis[21]. On the other hand, a

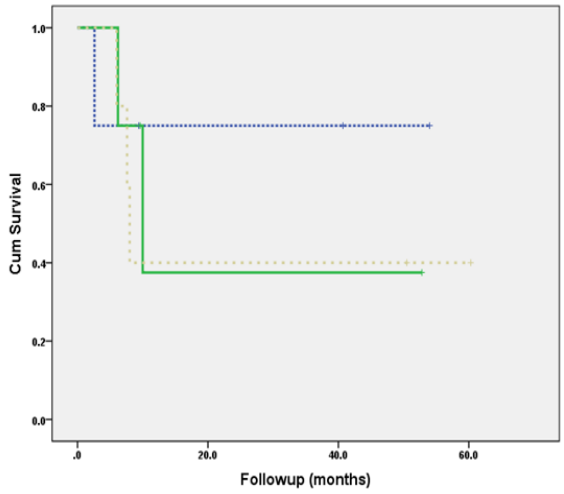

Figure 4. Kaplan-Meier curves to compare survival across survival based on pathological or clinical stage (narrow spaced dotted line indicates stage T2, wide dotted line indicates stage T4 and solid line indicates stage T3)

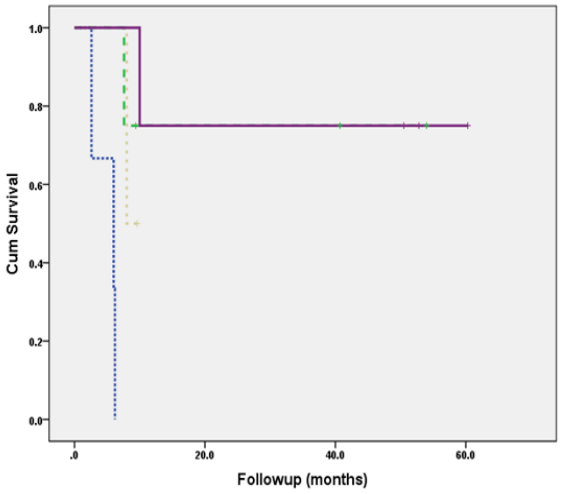

Figure 5. Kaplan-Meier curves to compare survival across survival based on treatment strategy (solid line indicates chemotherapy plus surgery, dashed line indicates only chemotherapy, wide spaced dotted line indicates only surgery, and narrow spaced dotted line indicates no treatment)

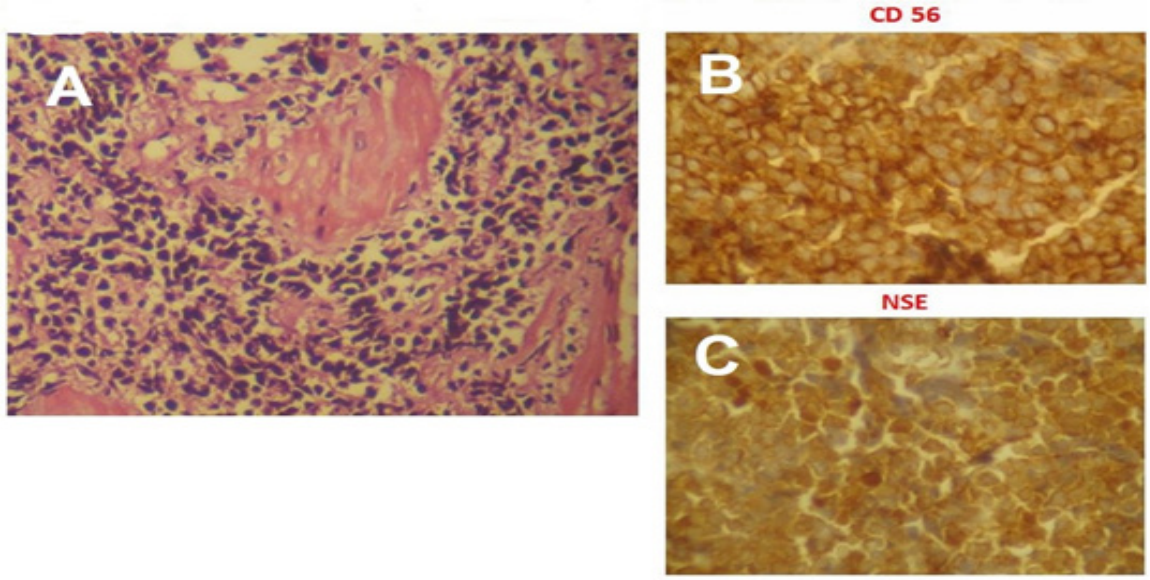

Figure 6. A) Microscopic examination of tumor shows patternless growth of discohesive small neoplastic cells with scant cytoplasms and hyperchromatic nuclei. The picture shows invasion of tumoral cells into muscularis propria; **B)** Immunohistochemical staining reveals diffuse positive immunoreactions for CD 56 and NSE in tumoral cells in one case (x20). **C)** Immunohistochemical staining reveals diffuse positive immunoreactions for CD 56 and NSE in tumoral cells in one case (x20).

significant number of uropathologists also perform IHC staining to help and support SmccB diagnosis[13].

Another opinion emphasizes the use of IHC staining for diagnostic confirmation ruling out some malignancies including lymphoma[6]. In our experience, only IHC stained samples were correctly diagnosed at initial pathology examination of TURBT samples despite evaluation of pathology samples by an experiences uro-pathologist with more than 20 years of experience. Therefore, we strongly recommend the use of IHC for diagnosis of SmccB in TURBT samples.

The rarity of this cancer has created many difficulties in the design of appropriate prospective clinical trials with the aim of finding better treatment modalities[22,23]. For this reason, treatment modalities are not standard, and current therapeutic options are mainly based on limited retrospective small case series. The treatment requires a multiple and different clinical approach. The physician should be aware of the clinical stage of cancer in the initial presentation and the patient's status , as it may impose some restrictions on the use of certain therapies [8,22]. In this regard, in our experience, renal function impairment significantly affected proper chemotherapy and radical surgery in some patients.

In a study, Kouba et al. compared the results of 23 articles in the treatment of bladder small cell carcinoma [7]. Of these, only one paper was prospective and the rest were retrospective. The results of this study indicated that the highest average survival rate was observed in patients who underwent radical cystectomy with chemotherapy and/or radiotherapy, while the minimum survival was observed in the bladder sparing only without referring to the pathologic stage of the cancer.

The primary manifestation in more than one-third of patients is advanced disease and distant metastases, and the average survival rate for all patients is 10-21 months. On the other hand, distant metastases, the most common cause of death in these patients, occur in 70-80% of patients who do not respond to the treatment [24,25]. Therefore, chemotherapy plays an important role in the treatment of SmccB, which is indeed the mainstay of SmccB treatment[26].

Also, our patients' data revealed that the therapeutic results in the chemotherapy received group were far better than those who did not receive chemotherapy for any reason. Out of 8 chemotherapy receiving patients, six (75%) patients with an average survival of 46.377 months (range: 9.4 – 60.3) were alive at the last follow-up.

Interestingly, the percentages of patients undergoing radical surgery in stage T2, T3, and T4 were 0%,75%, and 60% respectively (**Table 3**). On the other hand, 75% of patients in stage T2, 50% in stage T3, and 60% in stage 4 received chemotherapy. Two patients with a pathological stage of T4a N+ with a mean 55.4-month follow up were alive at the last follow-up.

For local cancer control, we only used radical surgery, and none of our patients was managed with radiotherapy. The difference in survival in patients undergoing surgery with those who were not operated is not significant.

Our study indicated that the average survival rate in patients undergoing radical surgery plus chemotherapy (47.7 months) was slightly superior however not statistically significant to patients who received only chemotherapy (42.4 months).

According to these findings, we believe that the most effective treatment option for SmccB given the clinical or pathological stage is chemotherapy and addition of radical surgery may offer a better survival.

One of the clinical findings that attracted our attention was the relatively high prevalence of impaired renal function secondary to ureteral obstruction, of which six patients had serum creatinine levels above 1.5mg/dL. Average serum Cr levels in this group was 3.06 mg/dL (1.6-4.7). This finding, together with the high prev-

alence of hydronephrosis, is associated with advanced disease at presentation and is consistent with the pathologic stage of the patients.
In our patients, as mentioned above, the average size of the bladder mass in the first imaging was 7.54 cm. Hydronephrosis and impaired renal function were seen in more than half of the patients in the first manifestation of the disease. In addition, the mean total creatinine in all 13 patients also lied within the range of renal failure. This issue, in addition to the advanced stage of the disease, will be a barrier to optimal radiological diagnosis with contrast agents and effective chemotherapy which as we discussed earlier constitutes the mainstay of treatment.
The limitations of our study for clinical judgment are small number of cases, retrospective nature, different disease stage, different treatment modalities, and small cases in each stage.

CONSLUSIONS

Definitive diagnosis of SmccB requires the help Of IHC in most cases. Chemotherapy constitutes the mainstay of treatment with additional surgery offering a slightly better survival.

CONFLICTS OF INTEREST

All authors declare that there is no conflict of interest.

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