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Clinical Investigation

Small Cell Carcinoma of the Urinary Bladder: A Retrospective, Multicenter Rare Cancer Network Study of 107 Patients

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Summary

Small cell carcinomas of the urinary bladder are rare tumors. The present series reports the outcomes of 107 patients and is 1 of the 4

Purpose: Small cell carcinomas of the bladder (SCCB) account for fewer than 1% of all urinary bladder tumors. There is no consensus regarding the optimal treatment for SCCB.

Methods and Materials: Fifteen academic Rare Cancer Network medical centers contributed SCCB cases. The eligibility criteria were as follows: pure or mixed SCC; local, locoregional, and metastatic stages; and age ≥18 years. The overall survival (OS) and disease-free survival (DFS) were calculated from the date of diagnosis

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largest series that have been published to date. Ninety of these patients presented with pelvic-limited disease. Among the patients treated with curative intent, the type of treatment (ie radical surgery with or without chemotherapy vs a bladder-sparing approach with chemoradiation) did not significantly influence the overall survival or disease-free survival.

according to the Kaplan-Meier method. The log-rank and Wilcoxon tests were used to analyze survival as functions of clinical and therapeutic factors.

Results: The study included 107 patients (mean [±standard deviation, SD] age, 69.6 [±10.6] years; mean follow-up time, 4.4 years) with primary bladder SCC, with 66% of these patients having pure SCC. Seventy-two percent and 12% of the patients presented with T2-4N0M0 and T2-4N1-3M0 stages, respectively, and 16% presented with synchronous metastases. The most frequent curative treatments were radical surgery and chemotherapy, sequential chemotherapy and radiation therapy, and radical surgery alone. The median (interquartile range, IQR) OS and DFS times were 12.9 months (IQR, 7-32 months) and 9 months (IQR, 5-23 months), respectively. The metastatic, T2-4N0M0, and T2-4N1-3M0 groups differed significantly ($P = .001$) in terms of median OS and DFS. In a multivariate analysis, impaired creatinine clearance (OS and DFS), clinical stage (OS and DFS), a Karnofsky performance status <80 (OS), and pure SCC histology (OS) were independent and significant adverse prognostic factors. In the patients with nonmetastatic disease, the type of treatment (ie radical surgery with or without adjuvant chemotherapy vs conservative treatment) did not significantly influence OS or DFS ($P = .7$).

Conclusions: The prognosis for SCCB remains poor. The finding that radical cystectomy did not influence DFS or OS in the patients with nonmetastatic disease suggests that conservative treatment is appropriate in this situation.

Introduction

Small cell carcinoma of the urinary bladder (SCCB) is a rare tumor that accounts for fewer than 1% of all bladder carcinomas. SCCB is associated with a prognosis that is worse than that to transitional cell carcinoma (TCC) of the bladder. Since its description in 1981 (1), SCCB has been described in small series, case reports, and a few prospective trials (2, 3). Very recently, the largest series based on the National Cancer Database and Medicare data were published (4-6). The optimal treatment for pelvic-limited disease remains controversial. Here, we report 1 of the largest series that has been published to date. One of our goals was to describe the outcomes across a large multicenter study and to determine whether conservative treatment, including transurethral resection of the bladder (TURB) and radiation therapy and chemotherapy, produced results similar to those of strategies that included radical cystectomy.

Methods and Materials

Fifteen Rare Cancer Network medical centers contributed cases of SCCB. The eligibility criteria were as follows: pure or mixed small cell carcinoma; local, locoregional, and metastatic stages; and age ≥18 years. All patient data were collected through retrospective chart reviews. The histologic slides were not centrally reviewed. Proportions were compared by the χ^2 test for values ≥5 and the Fisher exact test for values 5. Survival curves were estimated by the Kaplan-Meier method. Time to any event was measured from the date of diagnosis. If clinical or pathologic evidence of active, recurrent disease was present, deaths were attributed to small cell carcinoma of the bladder. The events were death (all causes) for overall survival (OS) and death (all causes) or clinical relapse, radiologic relapse, or both for disease-free survival (DFS). Confidence intervals (CI) were calculated from standard errors. In the univariate analyses, differences between groups were assessed by the log-rank and Wilcoxon tests. For the multivariate analyses, we screened for prognostic factors with a P value <.05 in the univariate analyses using the Cox regression analysis to define the independent contribution of each prognostic factor. A P value <.05 was considered to be statistically significant. Late toxicity was assessed by the Common Terminology Criterial for Adverse Events version 4.0 score. All data were examined using JMP version 10 (SAS Institute Inc, Cary, NC).

Results

Fifteen medical centers contributed 107 patients who received their diagnoses from 1984 to 2012. Eighty-five percent of the patients were treated in the 2000s. The male-to-female ratio was 2.3. The mean age (±standard deviation, SD) was 69.6 (±10.6) years, and the mean follow-up time (±SD) was 4.4 (±3.6) years (Table 1). The Karnofsky performance status was less than 80 and at least 80 in 23 and 69 patients, respectively (range, 40-100; missing data in 15 patients) (Table 1).

Hematuria was the most common presenting symptom (86% of the patients). Twenty-nine percent of the patients experienced dysuria and increased urinary frequency at diagnosis. Thirteen percent of the patients presented with

Table 1 Demographic and pathologic characteristics of 107 patients with SCCB

Characteristic	No. of patients	%
Male	75	70
Female	32	30
Mean age at diagnosis, y (±SD)	69.6 (±10.6)	
Karnofsky performance status		
<50	7	6.5
50-79	16	15
80-100	69	64.5
Missing data	15	14
Presenting symptoms		
Hematuria	92	87
Dysuria and frequency	31	29
Ureteral obstruction and acute renal failure	14	13
Follow-up surveillance cystoscopy after TURB for TCC	7	6.5
Location		
Lateral wall and fundus	95	89
Trigone	11	10
Bladder diverticulum	1	1
Histologic findings		
SCC only	71	66.4
SCC and TCC	29	27.2
SCC and adenocarcinoma	3	2.8
SCC and TCC and adenocarcinoma	2	1.8
SCC and squamous cell carcinoma	1	0.9
SCC and TCC and squamous cell carcinoma	1	0.9
Stage		
T2-4 N0 M0	77	72
T2-4 N1-3 M0	13	12
T2-4 N1-3 M1	17	16
Mean follow-up time, y (±SD)	4.4 (±3.6)	

Abbreviations: SCC = small cell carcinoma; SCCB = small cell carcinoma of the bladder; SD = standard deviation; TCC = transitional cell carcinoma; TURB = trans-urethral resection of the bladder.

Table 2 Treatments according to stage: pelvic limited disease (n=90) and metastatic disease (n=17)

Stage and treatment	No. of patients	%
Pelvic limited disease	90	100
Cystectomy and primary or adjuvant chemotherapy	26	29
Sequential or concomitant chemotherapy and radiation therapy	23	25
Cystectomy alone	21	23
Cystectomy and radiation therapy ± chemotherapy	7	8
Chemotherapy alone	7	8
Best supportive care	6	7
Metastatic disease	17	-
Chemotherapy	10	-
Best supportive care	7	-

ureteral obstructions and acute renal failure. In 7% of the patients, SCCB was found on follow-up surveillance cystoscopy after TURB for TCC (Table 1). Seventy-one percent (73/102) of the patients had a history of cigarette smoking.

The majority of the SCCB arose in the lateral bladder wall and fundus (95 patients), although the SCC involved the trigone and a bladder diverticulum in 11 patients and 1 patient, respectively. Histologic findings indicated that the majority of the patients (66%) had pure SCCB, 27% had mixed SCC-TCC, and the remaining patients presented with mixed tumors (Table 1).

The patients received adequate staging that included computed tomography (CT) or magnetic resonance imaging of the pelvis, chest CT or radiography, and abdominal CT or ultrasonography. Five percent and 31% of the patients underwent positron emission tomography and bone scan scintigraphy, respectively. The 2002 tumor, lymph node, and metastasis (TNM) classification system for bladder cancer was used for pathologic staging (7). Sixteen percent of the patients presented with synchronous extrapelvic metastases, and 72% and 12% were staged at T2-4N0M0 and T2-4N1-3M0, respectively (Table 1). The distant metastasis sites were the abdominal and/or mediastinal lymph nodes, liver, bone, and lung in 8%, 8%, 5%, and 3% of the patients, respectively. In the 17 patients who presented with a metastatic disease, 9 and 8 were treated with chemotherapy and best supportive care.

In the 90 patients who presented with intrapelvic disease, the most frequent treatments were cystectomy and primary or adjuvant chemotherapy (29%), sequential or concomitant chemotherapy and radiation therapy (25%), and cystectomy alone (23%). The remaining patients were treated with a combination of radiation therapy and radical surgery with or without chemotherapy (8%), chemotherapy alone (8%), and best supportive care (7%) (Table 2). The primary and adjuvant chemotherapy regimens were based on cisplatin or carboplatin in nearly all of the patients who were treated with chemotherapy (99%). Etoposide was combined with cisplatin or carboplatin in 77% of these patients. In the patients who were treated with cystectomy, radical and partial surgical procedures were used in 94% and 6%, respectively. Pathologic lymph nodes were found in 42% of the patients, and the mean number (±SD) of involved lymph nodes was 3.4 (±3). The conformal technique with or without intensity modulation was used in 80% of the patients who were treated with pelvic radiation therapy with curative intent. Target volumes encompassed the pelvic lymph nodes in half of these patients. The median (±SD) total dose was 61 (±7) Gy, and the median dose per fraction was 2 Gy (minimum, 1.8; maximum, 2.75). Two patients were treated with prophylactic cranial irradiation. In the 17 patients who presented with metastatic disease, 10 were treated with chemotherapy and 7 were treated with best supportive care (Table 2).

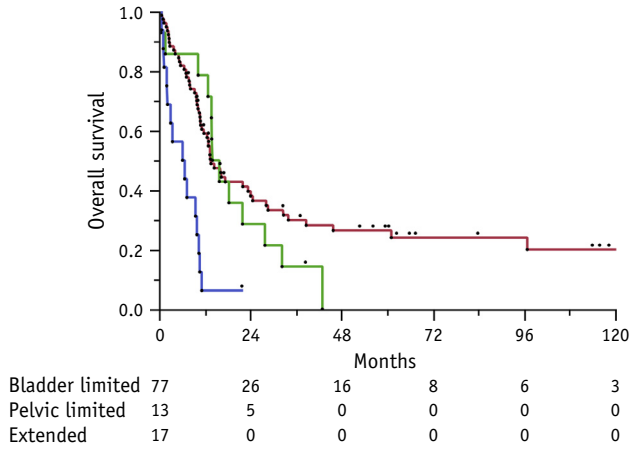

Fig. 1. Overall survival according to disease stage in patients with primary small cell carcinoma of the urinary bladder. Red line, bladder-limited group; green line, pelvic-limited group; blue line, extended disease group (log-rank, $P<.0001$; Wilcoxon, $P<.0001$). A color version of this figure is available at www.redjournal.org.

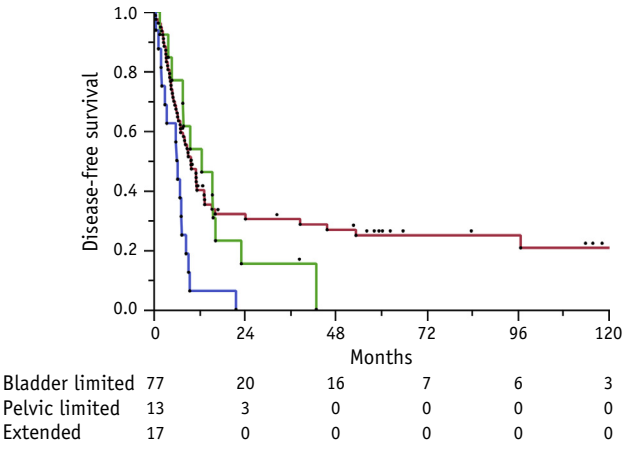

Fig. 2. Disease-free survival according to disease stage in patients with primary small cell carcinoma of the urinary bladder. Red line, bladder-limited group; green line, pelvic-limited group; blue line, extended disease group (log-rank, $P=.001$; Wilcoxon, $P=.008$). A color version of this figure is available at www.redjournal.org.

The median (interquartile range, IQR) overall survival (OS) and disease-free survival (DFS) were 12.9 months (IQR, 7-32 months) and 9 months (IQR, 5-23 months), respectively. The bladder-limited, pelvic-limited, and extended disease groups differed significantly in terms of OS and DFS. At 2 years, the overall survivals were 36% (95% CI: 25%-47%), 24% (95% CI: 1%-46%), and 0% (95% CI: 0%-11%) according to the initial stage: bladder-limited, pelvic-limited, and extended disease, respectively ($P<.0001$) (Fig. 1). The 2-year DFS also differed significantly according to stage: 30% (95% CI: 19%-41%), 15% (95% CI: 0%-35%), and 0% (95% CI: 0%-12%) in the bladder-limited, pelvic-limited, and extended disease groups, respectively ($P=.008$) (Fig. 2). The 2-year OS rates were 45% (95% CI: 30%-60%) and 22% (95% CI: 12%-32%) in patients with mixed and pure SCC histology, respectively ($P=.017$) (Fig. 3).

In patients who were treated with curative intent, complete and partial responses, no change, and progression were observed in 65.5%, 3.3%, 2.2%, and 22%, respectively. Data were missing for 7% of these patients. In patients with pelvic-limited disease treated with curative intent who presented with relapse during the follow-up, the locations of the first relapse were pelvic, metastatic, or both in 24%, 44%, and 32%, respectively. Eight of the 107 patients presented with brain metastases at relapse. Five of them presented with pelvic-limited disease initially treated with curative intent.

In a multivariate analyses, impaired creatinine clearance (OS and DFS), clinical stage (OS and DFS), a Karnofsky performance status <80 (OS), and pure SCC histology (OS) were found to be significant independent adverse prognostic factors (Cox regression, $P<.05$ for all of these items) (Table 3). In the patients with nonmetastatic disease, the type of treatment (ie radical surgery with or without chemotherapy vs a bladder-sparing approach) did not significantly influence OS or DFS ($P=.7$) (Figs. 4 and 5). The type of chemotherapy regimen (platin salt ± etoposide) did not influence outcomes ($P=.4$).

Late toxicity occurred in 11 of 94 patients (missing data in 13 patients). One patient presented a lethal toxicity (sepsis after radical cystectomy). Ten patients presented with grade 1 to 3 late toxicity (no grade 4): urethral obstruction, nephrotoxicity, ototoxicity, cystitis, and proctitis.

Discussion

To the best of our knowledge, this series is 1 of the 4 largest series published to date (5, 6, 8). One of the

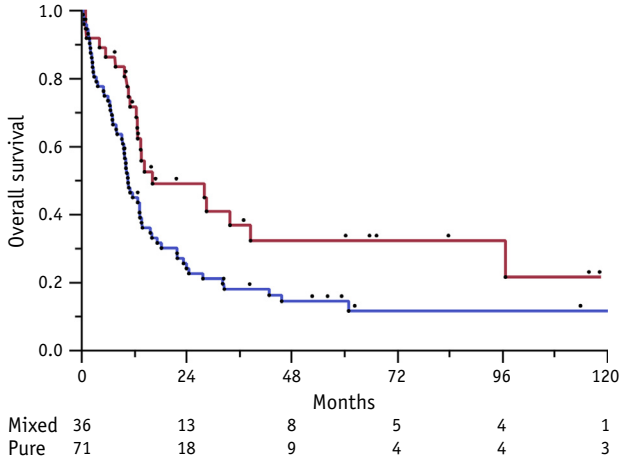

Fig. 3. Overall survival according to histology. Red line, mixed histology; blue line, pure small cell carcinoma histology (log-rank, $P=.017$; Wilcoxon, $P=.014$). A color version of this figure is available at www.redjournal.org.

Table 3 Multivariate Cox proportional hazard model by prognostic factors for overall survival and disease-free survival

Survival	Group	*P* value	HR	95% HR confidence limits
Overall survival				
Karnofsky performance status	>80 vs <80	.039	3.1	1.09-3.38
Impaired creatinine clearance	>60 mL/min vs <60 mL/min	.0097	3.1	1.13-4
Clinical stage	T2-4 N0 M0 vs T2-4 N1-3 M0	.0168	3.3	1.06-3.9
	T2-4 N1-3 M0 vs T2-4 N0 M1	.0168	2.5	1-3.38
Histology	Mixed vs pure small cell histology	.05	4.2	1.35-5.1
Disease-free survival				
Impaired creatinine clearance	>60 mL/min vs <60 mL/min	.0013	2.63	1.02-4.34
Clinical stage	T2-4 N0 M0 vs T2-4 N1-3 M0	.0117	3.34	2.22-4.9
	T2-4 N1-3 M0 vs T2-4 N0 M1	.0117	2.92	1-4.5

Abbreviation: HR = hazard ratio.

strengths of our series is its recent nature; 85% of the patients were treated after 2000 and received adequate staging and platinum-based chemotherapy. Some series include patients examined over longer time periods, during which histologic classification and staging methods might vary. Another strength of our series was our ability to directly access the medical charts to determine the strategies according to stages, which cannot be done accurately in large series based on national or health insurance data. Patel et al (6) used the National Cancer Database to publish the largest series to date, but this series included no information about chemotherapy type or performance status. Another strength of our series is the substantial number of patients who were treated with curative intent. In a series based on the Surveillance, Epidemiology and End Results Medicare database (5), fewer than 20% of the 533 patients received potentially curative therapies (ie a bladder-sparing approach [transurethral resection combined with chemotherapy and radiation] or cystectomy with chemotherapy). In our series, 72% of the 107 patients were treated with these different combinations. We recognize that a weakness of our study lies in its retrospective character and in the associated inherent bias and difficulty of assessing toxicity-related treatment; this weakness is, however, present in all of the series published to date with the exception of 2 small prospective trials including 25 and 30 patients, respectively (2, 3).

The sex ratio and median age were similar to those reported in other series (5, 6, 8-11). In most of the patients, tumors arose in the lateral bladder wall and fundus; this is different from TCC, which usually involves the trigone. In our series, the majority of patients (63%) presented with pure SCCB, which is similar to the 27 of 44 patients reported by Choong et al (10). Cheng et al (9) observed that in 68% of the patients, small cell carcinomas coexisted with another carcinoma component. Similarly, Lynch et al (8) observed that 38% of the patients were characterized as having pure small cell histology. This information was not available in the largest series (5, 6). In our series, pure SCCB was associated with a worse prognosis in the multivariate analysis, which is similar to the results of univariate analyses that have been performed in smaller

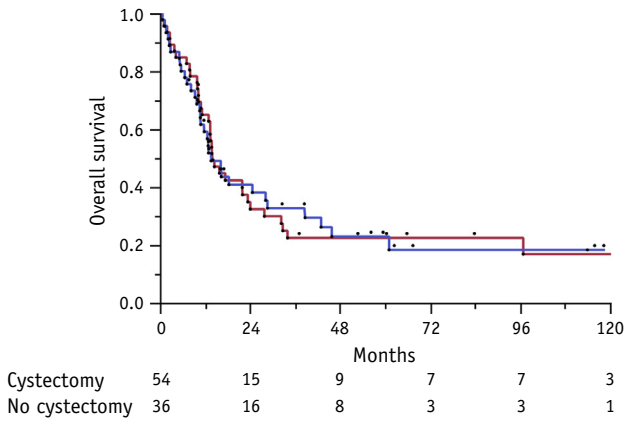

Fig. 4. Overall survival curves for patients with small cell carcinoma of the urinary bladder stratified according to treatment with cystectomy. Blue line, treatment without cystectomy; red line, treatment with cystectomy (log-rank, $P = .3$; Wilcoxon, $P = .1$). A color version of this figure is available at www.redjournal.org.

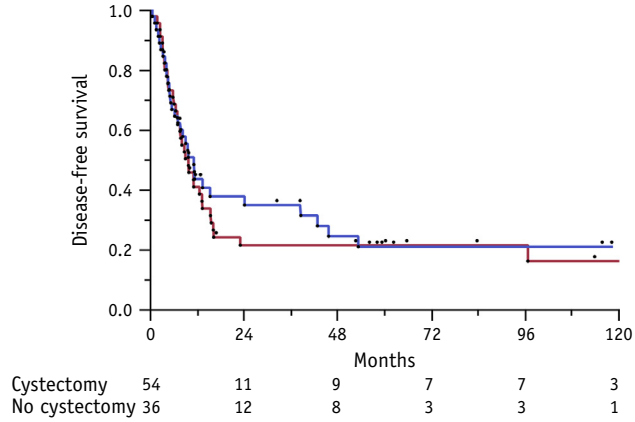

Fig. 5. Disease-free survival curves for patients with small cell carcinoma of the urinary bladder stratified according to treatment with cystectomy. Blue line, treatment without cystectomy; red line, treatment with cystectomy (log-rank, $P = .7$; Wilcoxon, $P = .5$). A color version of this figure is available at www.redjournal.org.

studies (10-12). By contrast, a pure or mixed histology has not been found to be a prognostic factor in other series (9). The prognoses reported in our series were poor and depended on the initial stage and performance status, similar to the results of other studies in the literature (5, 6, 8-11). In our series, the incidence of brain metastasis (8/107) was similar to that reported in the literature and seems lower than that for small cell lung cancer (13, 14). This type of retrospective study cannot make conclusions regarding the use of prophylactic cranial irradiation. Late toxicity is difficult to assess in a retrospective manner and cannot be accurately compared with data in the literature.

In recent series, the importance of combined treatment with chemotherapy was emphasized for patients with pelvic-limited disease. In a phase II trial, 18 patients with surgically resectable SCCBs received primary systemic treatment consisting of alternating doublet chemotherapy, and they experienced a median OS of 58 months; 13 of these patients are currently alive and cancer free. Pathologic downstaging occurred in 14 of 18 patients. For the patients with T2N0M0 stage, the 5-year OS rate is 80%, whereas only 1 of 4 patients with stage T3b-4N0M0 remains alive (median OS, 37.8 months) (3). In Lynch et al (8), primary systemic treatment was found to be associated with improved OS and DFS compared with initial cystectomy among 95 patients who were surgical candidates (median OS, 159.5 vs 18.3 months, $P<.001$; 5-year DFS, 79% vs 20%, $P<.001$). In another retrospective study (n = 46) conducted by the MD Anderson Cancer Center, the patients who received primary chemotherapy experienced significantly better survival than those who did not (15). The data in the literature highlight the role of systemic therapy in this disease, and primary chemotherapy is advised before local treatment in cases of limited disease (16, 17).

The optimal local treatment of pelvic limited disease (ie combined chemotherapy and radical surgery or a bladder-sparing approach with chemotherapy and radiation therapy) remains controversial. To date, data are available only from retrospective studies with inherent biases. The reported bladder-sparing approach data might include patients who were not surgical candidates and were likely to have worse outcomes because of their comorbid medical conditions. The 2 recent and largest series published to date seem to be contradictory in terms of the role of radical surgery (5, 6). In Patel et al (6), the subgroup with the most favorable survival was the primary chemotherapy plus radical cystectomy group with a 3-year rate of 53%. Nevertheless, OS was not significantly different between the bladder preservation therapy + multimodality treatment (BPT + MMT) and radical cystectomy + multimodality treatment (RC + MMT) groups. In the multivariate OS analysis, BPT + MMT and RC + MMT showed similar hazard ratios (0.52, 95% CI: 0.39-0.68; and 0.52, 95% CI: 0.33-0.83, respectively) compared with BPT alone. Other studies are in favor of surgery as local treatment (10, 11). Koay et al (5) described 533 patients from the Surveillance, Epidemiology and End Results Medicare database who were treated from 1991 to 2005. As in our series, a bladder-sparing approach involving TURB combined with chemotherapy and radiation yielded no significant difference in overall survival compared with the survival of the patients who underwent at least a cystectomy with chemotherapy ($P>.05$). Furthermore, in our series, no difference in DFS was found between these 2 strategies. Other studies are in favor of conservative treatment (9, 18-21). Meijer et al (21) described the results in 27 patients treated with primary chemotherapy and radiation therapy. For the complete responders to primary chemotherapy (n = 19), the median cancer-specific survival was 52 months, with a 5-year cancer-specific survival of 45.9%, versus a median cancer-specific survival of 22 months and a 5-year cancer-specific survival of 0.0% for the incomplete responders (n = 8; $P = .034$).

Although limited by their retrospective character, our data are in agreement with the guidelines for SCCB management. The National Comprehensive Cancer Network guidelines state that patients with SCCB are best treated with initial chemotherapy followed by either radiation therapy or cystectomy as consolidation if there is no systemic disease (16). In the Canadian guidelines, these 2 strategies are classified with the same level of evidence (level 3, grade C) (17). The response after primary chemotherapy might aid the selection of local treatment, although we lack prospective data to confirm this hypothesis.

It is concluded that SCCB is a rare and severe disease. The only available data, apart from 2 small series, are from retrospective studies. Here, we report 1 of the 4 largest series to date and confirm the demographic findings and the severe prognosis. The most important finding in our series is that radical cystectomy did not influence DFS or OS in cases of limited disease. The selection of patients for a bladder-sparing approach or radical surgery requires clarification.

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