

Patient Characteristics, Treatment Patterns and Prognostic Factors in Squamous Cell Bladder Cancer

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Abstract

Bladder squamous cell carcinoma (SCC) is rare with limited data on prognosis and treatment patterns. Herein we present a retrospective review of patients with bladder SCC treated at our institution. Radical cystectomy was the main treatment for resectable disease. The identified prognostic factors might help prognostication, treatment decision, and trial eligibility/stratification.

Background: Squamous cell carcinoma (SCC) is an uncommon histologic subtype of bladder cancer with limited data on treatment patterns, outcomes, and prognostic factors. “Real world” information might inform decision-making, prognostic estimates, and clinical trial designs. **Patients and Methods:** A retrospective review of patients with tissue-confirmed bladder SCC treated at Cleveland Clinic from 2007 to 2016 was performed. Data on patient characteristics, treatment patterns, and clinical follow-up were extracted. Univariate analysis was used to identify predictors of overall survival (OS), recurrence-free survival (RFS) and time to recurrence. **Results:** Of 58 identified patients, 42 had complete data available. Median age at diagnosis was 67 years (range, 37-90). Hematuria was the most common (71%) presenting symptom; 32 patients had pure SCC and 10 predominant/extensive squamous differentiation without major differences noted in clinicopathologic variables or outcomes among those 2 groups. Overall, 35 patients underwent cystectomy with 5 receiving neoadjuvant and 1 adjuvant chemotherapy, whereas 3 had chemotherapy for recurrent disease. Of patients with cystectomy, most had locally advanced disease (75% pT3/4, 35% pN+). Overall, 10 patients progressed and 14 died; median OS was not reached. The 2-year estimated OS, RFS, and cumulative incidence of recurrence were 61% ± 9%, 50% ± 9%, and 32% ± 9%, respectively. Hydronephrosis, older age (70 years or older), lymphovascular invasion, nodal metastases, and advanced T stage were associated with 1 or more poor outcomes. **Conclusion:** In patients with resectable bladder SCC, radical cystectomy remains the main treatment modality. The role of perioperative chemotherapy remains unclear. The identified prognostic factors might be helpful for prognostication, treatment discussion, and trial eligibility/stratification.

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Introduction

Bladder cancer is the fifth most common cancer and one of the leading causes of cancer deaths in the United States, causing significant morbidity and mortality as well as burden on health care systems.¹ Bladder cancer has multiple histologic types but urothelial (“transitional cell”) is the most common with approximate 90% prevalence, whereas only approximately 3% of bladder cancers are pure squamous cell carcinoma (SCC).² There are multiple risk factors for development of bladder SCC, such as chronic inflammation/irritation, long-term catheterization, neurogenic bladder, urinary tract calculi, and chronic infection with *Schistosoma haematobium*, especially in endemic areas.³⁻⁵ Also, certain histologic

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changes like keratinizing squamous metaplasia and SCC in situ, tend to increase the risk of bladder SCC, whereas their presence can help diagnosis.^{6,7}

Because of its rarity, there is a paucity of data on pure bladder SCC.⁸ Available data are mostly derived from single-institution or population-based studies with their own inherent limitations. A number of studies concluded that pure SCC has poorer prognosis compared with urothelial carcinoma, whereas other studies reported that the outcomes are similar regardless of the histology.⁸ It is also unclear whether urothelial carcinoma with predominant/extensive squamous differentiation and pure SCC are derived from the same cell type and exhibit similar clinical behavior. Notably, one study has shown that clinical behavior and outcomes after radical cystectomy are comparable between urothelial carcinoma with squamous differentiation and pure bladder SCC.³ To further address these issues, we retrospectively reviewed our experience to determine patient characteristics, treatment patterns, and clinical outcomes in patients with SCC of the bladder. To address the clinical significance of extensive SCC as a variant of urothelial carcinoma we included pure SCC as well as bladder tumors with predominant/extensive squamous differentiation.

Patients and Methods

After obtaining approval from the institutional review board of Cleveland Clinic, we performed a retrospective review of patients with pathology confirmed bladder SCC from 2007 to 2016. Data on patient characteristics, treatment patterns, and clinical follow-up was extracted from chart review. A total of 58 patients were identified from pathology review at our institution; 16 patients had inadequate clinical and/or pathological data and therefore were excluded. Patients were divided into 2 cohorts: one with pure SCC and another with urothelial carcinoma with extensive/predominant squamous cell differentiation/features, on the basis of the language of the pathology report (no specific percentage of squamous cell features was predefined).

Categorical clinicopathologic factors were summarized with frequency counts and percentages; continuous factors with medians and ranges. Fisher exact test and the Wilcoxon rank sum test were used to compare clinicopathologic factors between patients with pure SCC versus extensive/predominant squamous cell differentiation. Three outcomes were assessed; overall survival (OS) and recurrence-free survival (RFS), which were measured from diagnosis (or cystectomy), to death or the first of recurrence/death, respectively, and time to recurrence (TTR), which was defined similarly to RFS except death without recurrence was treated as a competing risk. OS and RFS were summarized using the Kaplan–Meier method and TTR was summarized using the cumulative incidence. Cox proportional hazards models were used for comparisons between factors with the Fine and Gray test being used with TTR. A P value $\leq .10$ was regarded as indicating a potentially important prognostic factor. Because of the small number of observed events multivariate modeling was not performed. All data analyses were carried out using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Baseline patient demographic and characteristics are shown in Table 1; 32 patients had pure SCC and 10 had tumors with

Table 1 Overall Patient Characteristics

Characteristic	Pure SCC (n = 32)	Predominant/Extensive Squamous Differentiation (n = 10)	P
Sex			1.0
Male	17 (53)	5 (50)	
Female	15 (47)	5 (50)	
Median Age (Range)	68 (37-89)	66 (39-90)	.81
<70	18 (56)	7 (70)	
≥70	14 (44)	3 (30)	
Hematuria as Presenting Symptom	22 (69)	8 (80)	.70
Hydronephrosis^a	10 (43)	2 (33)	1.0
Charlson Comorbidity Score^a			.9
0-1	5 (16)	1 (11)	
2-3	16 (52)	4 (44)	
4-5	6 (19)	4 (44)	
6-7	4 (13)	0	
Smoking History			.09
Never	16 (50)	8 (80)	
Former	14 (44)	2 (20)	
Current	2 (6)	0	

Data are presented as n (%), except where otherwise noted.

^aMissing data: hydronephrosis (n = 13), Charlson Comorbidity score (n = 2).

predominant/extensive squamous differentiation. Median age was 67 years and 22 patients (52%) were men. Hematuria was the most common presenting symptom followed by dysuria; hydronephrosis was noted in 12 out of 29 patients (41%) with available data. We evaluated several risk factors associated with bladder SCC; 3 patients (7%) had documented neurogenic bladder, 2 patients (5%) urinary tract calculi, 5 patients (12%) chronic/recurrent urinary tract infections, 3 patients (7%) chronic urinary catheterization, and 3 patients had known *Schistosoma* infection. When we compared pure SCC with tumors with predominant/extensive squamous differentiation, we did not observe major differences in demographic or baseline features, treatment (most had cystectomy), outcomes and laboratory, or clinicopathologic parameters, except that never-smokers appeared more common in the latter group (80% vs. 50%; $P = .09$). Only 2 patients had documented previous intravesical Bacille Calmette Guerin (BCG) treatment for nonmuscle-invasive bladder cancer.

Thirty-five patients (83%) underwent cystectomy (Table 2). Known reasons for not performing radical cystectomy were poor surgical candidacy and selection of alternative surgery (partial cystectomy). Five patients received neoadjuvant chemotherapy followed by cystectomy; 4 had cisplatin-based chemotherapy (1 unknown regimen) without pathologic response. All 5 patients had pure SCC at cystectomy pathology. The documented reasons for administering neoadjuvant chemotherapy varied. For example, 1 patient was referred to our institution after he had already received neoadjuvant chemotherapy with disease progression. Another

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