



Small-Cell Carcinoma of the Bladder: 20-Year Single-Institution Retrospective Review

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Abstract

We performed a retrospective survival analysis of 38 patients with small-cell carcinoma of the bladder treated at our institution. In multivariable adjusted analysis, we could not find any significant survival advantage associated with neoadjuvant chemotherapy, surgery, or radiation. Most of the long-term survivors received platinum-based neoadjuvant chemotherapy followed by radical cystectomy.

Introduction: Small-cell carcinoma of the bladder is a poorly differentiated neoplasm with aggressive behavior. We analyzed clinical outcomes of patients who were treated at our institution to identify an optimal treatment strategy.

Materials and Methods: Retrospective chart analysis was performed for patients who were treated for small-cell carcinoma of the bladder at Fox Chase Cancer Center between 1995 and 2015. Survival was compared between different treatment periods (before January 2010 vs. after January 2010) and different treatment modalities (surgery vs. neoadjuvant chemotherapy vs. radiation). **Results:** Thirty-eight patients were treated for small-cell carcinoma of the bladder at our institution during the 20-year study period. Median survival was 11.8 months and overall survival rates after 1, 3, and 5 years were 46.6%, 26.2%, and 14%, respectively. Survival analysis adjusted for age, histology, and stage showed that no single treatment strategy was significantly superior (95% confidence interval [CI], 0.26-3.03; $P = .860$ for surgery; 95% CI, 0.31-2.87; $P = .928$ for neoadjuvant chemotherapy; 95% CI, 0.65-5.49; $P = .238$ for radiation). In separate analyses of long-term survivors, we found that most received platinum-based neoadjuvant chemotherapy followed by radical cystectomy. Among the 20 patients who received neoadjuvant chemotherapy, downstaging occurred in 9 (45%). **Conclusion:** Although none of the treatment options were found to be significantly superior with respect to survival, neoadjuvant chemotherapy might halt the progression of the disease until cystectomy and lead to downstaging. At our institution, the best outcomes were observed in patients who received neoadjuvant platinum-based chemotherapy combined with radical cystectomy.

Clinical Genitourinary Cancer, Vol. 15, No. 3, e337-43 © 2016 Elsevier Inc. All rights reserved.

Keywords: Cystectomy, Neoadjuvant chemotherapy, Platinum-based chemotherapy, Retrospective chart review, Survival outcome

Introduction

Small-cell carcinoma of the bladder (SCCB) is a poorly differentiated and rapidly progressive neuroendocrine malignancy.

Despite evidence that SCCB has the same clonal origin as urothelial cancer,¹ clinical characteristics and treatment recommendations are significantly different between the two histologies.²

Small-cell carcinoma of the bladder is a rare disease, accounting for 0.5% to 0.7% of all bladder tumors.^{3,4} The survival rate of patients with SCCB reported in the literature has been poor. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the median survival of patients with a diagnosis of SCCB was 11 months and the survival rate was worse for patients with metastatic disease as would be expected.⁵ A retrospective review conducted at the Mayo Clinic showed that 5-year survival rates for patients with stage II, III, and IV SCCB were 63.6%, 15.4%, and

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Submitted: Aug 5, 2016; Revised: Sep 14, 2016; Accepted: Sep 16, 2016; Epub: Sep 30, 2016

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10.5%, respectively.⁶ Survival rates were also discouraging among the patients with localized and surgically resectable tumor, most of whom died of the disease within 1 year from the diagnosis, suggesting many of these patients are clinically understaged.⁷

Because of the aggressive behavior of the disease, multiple strategies that incorporate different treatment approaches have been evaluated. Surgical resection of SCCB even in the absence of muscle invasion is recommended² because of the propensity of the disease to metastasize even when the cancer appears to be clinically localized. Chemotherapy and/or radiotherapy are options for patients whose functional status is not suitable for invasive surgery.⁸ Although there have been no randomized clinical trials conducted so far, some retrospective analyses have provided insight into the treatment efficacy of neoadjuvant chemotherapy. In a study at the M.D. Anderson Cancer Center, the 5-year survival rate for patients who had preoperative chemotherapy was significantly longer than for the patients who had initial cystectomy without neoadjuvant chemotherapy (78% vs. 36%, $P = .026$).⁷ A recent study by Lynch and colleagues showed that neoadjuvant chemotherapy was associated with prolonged overall survival (OS) and progression-free survival (PFS) and resulted in pathologic downstaging to less than pT1N0 in 62% of tumors.⁹ A phase II clinical trial of neoadjuvant chemotherapy alternating between ifosfamide/doxorubicin and etoposide/cisplatin reported a promising result in 18 patients with surgically resectable disease, with median OS of 58 months.¹⁰

We analyzed the clinical outcomes of patients who underwent treatment for SCCB at Fox Chase Cancer Center (FCCC) on the basis of the hypothesis that patient survival would improve over time with the recent increase in the use of neoadjuvant chemotherapy and improvements in radiotherapy. We also compared the survival outcomes of each treatment option for SCCB to identify the optimal treatment strategy.

Materials and Methods

Study Population

Patients who had a pathologic diagnosis of small-cell carcinoma or mixed urothelial and SCCB were included in this analysis. Cases were identified from our institutional bladder cancer database, institutional tumor registry, and radiation oncology patient registry at FCCC. Primary tumor specimens for pathologic examination were obtained from either transurethral resection of bladder tumor (TURBT) or cystectomy during the period between January 1, 1995 and December 31, 2015. All pathologic diagnoses were confirmed by the Department of Pathology at FCCC. All pathologic reports were reviewed by the authors during data collection. There was no patient with concurrent small-cell carcinoma of the prostate or lung in our study population.

We estimated that 40 patients were treated at our institution during the 20-year period. Assuming a median survival of 11 months on the basis of previous reports, we planned to test the alternative hypothesis that the survival durations are 8 and 16 months when the patients are divided into 2 groups. With a sample size of 40, we would be able to distinguish the null from the alternative hypothesis with 80% power and 10% type I error. The study protocol was reviewed and approved by the institutional review board at FCCC.

Data Analysis

Information on patient demographic characteristics, smoking history, family history, comorbidities, disease stage, treatment received, and time of death or last contact was obtained. Stage was dichotomized into I/II/III and IV for analysis, on the basis of the 2-tier staging system of small-cell lung cancer.^{5,11}

Primary end points of this study were OS and PFS. OS was estimated as the time between diagnosis of SCCB and death from any cause. Patients who were alive were censored at the time of last contact. PFS was calculated from the date of diagnosis to the first documentation of disease progression, including death. Median survival and OS and PFS at 1, 3, and 5 years were estimated using the Kaplan–Meier method. Survival was compared between patients who were treated before January 2010 and after January 2010 using a log rank test. Using the cutoff date of December 31, 2010 equally divided the total number of patients. Changes in treatment strategy over time were compared using a t test. Survival was also compared in patients who received different treatment modalities—surgery, chemotherapy, or radiation as single or combination therapy. Proportional hazards regression model was used for comparison of survival in different treatment groups with adjustment for age, histology (pure small cell vs. mixed with urothelial cell), and stage. Statistical analyses were performed with R version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) and STATA version 11.2 (Stata-Corp, College Station, TX).

Results

Demographic and Clinical Features

From January 1995 to December 2015, a total of 38 patients with SCCB were treated at FCCC. The median age was 68 years and 28 of 38 patients (73.7%) were male. Twenty-two patients were current smokers (57.9%) and 6 patients (15.8%) were previous smokers. There was 1 patient of East Indian descent; all other patients were Caucasian. Staging computed tomography was performed in all cases. Thirty-three patients (86.8%) had localized disease at the time of diagnosis and 5 patients (13.2%) had metastatic disease. Fourteen patients (36.8%) had mixed small and urothelial carcinoma on the basis of the pathology report. The most common presenting symptom was hematuria (71.1%) and the most common sites of metastases were liver, bone, and lung. The patient demographic and disease characteristics are summarized in [Table 1](#).

Treatments

Treatments provided to the patients are summarized in [Table 2](#). The treatment strategy most commonly used for patients with localized disease was neoadjuvant chemotherapy followed by cystectomy. A total of 26 patients underwent surgery, of which 20 (73.1%) had received neoadjuvant chemotherapy. One patient with locally advanced disease (T3N1M0) underwent cystectomy after resolution of lymphadenopathy with neoadjuvant chemotherapy. Among the 6 patients who underwent initial cystectomy, 5 patients had adjuvant chemotherapy postoperatively. One patient could not receive chemotherapy because of poor renal function and rapid disease progression after surgery.

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