Effect of African-American Race on Tumor Recurrence After Radical Cystectomy for Urothelial Carcinoma of the Bladder

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Abstract

African-American race was found to be independently associated with the recurrence of urothelial carcinoma of the bladder after controlling for established clinical and pathologic characteristics. These data corroborate emerging molecular data, suggesting differences in tumor biology according to race and the potential relevance of profiling both host and tumor to discover new therapeutic targets and individualize treatment strategies.

Background: African-American race appears to be associated with higher stages of urothelial carcinoma of the bladder (UCB) at presentation and poorer survival. However, the independent effect of African-American race on objective tumor recurrence after radical cystectomy (RC) after controlling for clinical and pathologic variables is unknown. **Patients and Methods:** The data from consecutive patients with UCB who underwent RC with curative intent at a single institution (University of Alabama, Birmingham) from 2001 to 2012 with or without perioperative chemotherapy or chemoradiation were reviewed. The patient demographics, risk factors, clinical course, pathologic characteristics, and long-term outcomes were collected. Descriptive statistics were performed. Cox regression analysis was performed for key clinical, demographic, and pathologic variables, including race, stratified as African American versus white. **Results:** A total of 215 patients, 163 men (76%) and 52 women (24%), with a mean age at RC of 65.6 years, were identified and reviewed. A total of 186 patients (87%) were white and 28 (13%) were African American. The median follow-up period after RC was 17.6 months. On conventional multivariate analysis, African-American race nearly attained statistical significance (hazard ratio [HR], 2.48; 95% confidence interval [CI], 0.98-6.29; $P = .055$). In a stepwise regression model, race was significantly associated with tumor recurrence (HR, 3.11; 95% CI, 1.2-7.4; $P < .011$). **Conclusion:** African-American race appears to be independently associated with a greater risk of tumor recurrence after RC for UCB. The effect of host genetics on tumor biology needs to be characterized at the genomic level to develop precision medicine.

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Introduction

Urothelial carcinoma of the bladder (UCB) accounts for an estimated 74,690 new cases and 15,580 cancer-related deaths in the United States in 2014.[1] Of the newly diagnosed patients, approximately 70% to 80% will present at an early non–muscle-invasive stage. However, 50% to 70% of these cases will recur and 10% to

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30% will progress to muscle-invasive or advanced disease. Patients with muscle-invasive disease require multidisciplinary strategies to target local disease by radical cystectomy (RC) with pelvic lymphadenectomy and perioperative chemotherapy.

Disparities in cancer diagnosis, more aggressive disease at presentation, and poorer outcomes in African Americans have been documented during the past 40 years.[2-6] In these patients, a more advanced stage at diagnosis suggested that suboptimal access to healthcare or more comorbidities might be the primary determinants of poorer survival in African-American patients. Variability in nonbiologic factors might also have contributed to these findings, such as the choice of therapy, education level, and access to healthcare, partly attributable to low socioeconomic status (SES).[7-11] However, survival might be a suboptimal endpoint in this population because of the multiple competing causes of non−cancer-related mortality, such as age, gender, race, ethnicity, SES, and comorbidities. Potential biologic differences might exist according to race, which might be reflected by an association of race with a more objective clinical endpoint, such as tumor recurrence. Also, the independent effect of African-American race on objective tumor recurrence after RC after controlling for clinical and pathologic variables is unknown.[12,13] We present a large consecutive series of patients from the University of Alabama at Birmingham (UAB), who underwent RC for UCB. We studied the potential association of African-American race and objective tumor recurrence, as a variable independent of the clinical and pathologic characteristics.

Patients and Methods

Study Cohort

The clinical records of 215 consecutive patients with UCB who had undergone RC with curative intent at UAB from 2001 to 2012 with or without perioperative chemotherapy and/or radiation were retrospectively reviewed. The patient demographics, cigarette smoking history, clinical variables, pathologic characteristics, and tumor recurrence were collected. The RC specimens were evaluated at a single institution (UAB) by different surgical pathologists. The Research Electronic Data Capture electronic database provided to Clinical and Translational Science Awards program institutions was used to record and manage the data. The institutional review board of UAB approved the study. Multiple internal data reviews were performed to ensure the accuracy and completeness of the data elements. Tobacco consumption was self-reported at the initial assessment.

Neoadjuvant and/or adjuvant radiation and/or chemotherapy were administered at the discretion of the treating physician. Tumor recurrence, the primary clinical outcome, was measured by the time to objective recurrence after RC. Bladder cancer recurrence was categorized as local when confined to the pelvis and distant when the tumor was metastatic outside the pelvis, including the lymph nodes and/or visceral organs. New tumors in the ureter or urethra were considered to be second primaries and not recurrences. Patients who died with another documented non-UCB cause of death before clinical recurrence were censored at the time of death.

Follow-up Period

The follow-up protocol of the patient population was performed according to the treating or referring physician. Surveillance was similar in the African-American and non−African-American cohorts. Most patients underwent follow-up examinations at the UAB (155 of 215 patients, 72%). When the follow-up examinations were performed by referring physicians outside the UAB, the data for recurrence and outcomes were obtained from these physicians. The patients were generally seen postoperatively every 3 to 4 months in the first year, every 6 months in the second year, and annually thereafter. Diagnostic imaging studies of the upper urinary tract, such as ultrasonography with or without excretory urography, were performed at the discretion of the treating physician or when clinically indicated.

Covariates

We examined various patient- and disease-related parameters in the present study, including age at RC, gender, race, pathologic stage, smoking history, Charlson comorbidity index, histologic type (pure transitional cell carcinoma [TCC], mixed TCC and other components, and other non-TCC histologic features), and RC pathologic margins. The TNM classification was used according to the specifications of the American Joint Committee on Cancer (AJCC), 7th edition, classification published in 2010.[14] The consensus pathologic stage at RC was determined by the postoperative pathologic stage. Lymphovascular invasion (LVI) was defined as the presence of tumor cells in an endothelium-lined space without underlying muscular walls.

Statistical Analysis

Descriptive statistics was used to summarize the patient and treatment characteristics and outcomes. Recurrence-free survival (RFS), the primary clinical endpoint, was calculated as the interval from RC to the date of objective clinical recurrence. Overall survival (OS), a secondary endpoint, was measured from RC to death of any cause. The Kaplan-Meier method was used to assess RFS and OS. The Student t test, χ^2 test, and Fisher exact test were used to evaluate unadjusted associations between race and other demographic and clinical characteristics. Cox proportional hazards regression models were used to examine the relationship between RFS and the demographic and clinical factors. Unadjusted (univariate) hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each covariate. Any variables that were statistically significant at $P < .05$ were then included in a multivariate regression analysis to calculate adjusted HRs. All P values were 2-sided, and $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Patient Demographic Characteristics

A total of 215 patients, 163 men (76%) and 52 women (24%), with a mean ± SD age at RC of 65.6 ± 10.6 years (range, 35-85 years) were identified and reviewed (Table 1). A total of 186 patients (87%) were white and 28 (13%) were African American. Only 1 patient had an unknown race, and that subject was removed from the analyses; thus, all evaluable patients were either African-American or white. No other race was identified in our cohort. In total, 69% of patients had a smoking history of ≥ 20 pack years, with 35% current smokers and 34% previous smokers at