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Does Squamous Differentiation Portend Worse Outcomes in Urothelial Bladder Cancer?

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Abstract

Introduction: Interest on the impact of variant histology in bladder cancer prognosis is increasing. Although squamous differentiation is the most well characterized, only recently have less common variants gained increased recognition. We assessed whether squamous differentiation conferred a worse prognosis than nonvariant urothelial bladder cancer in a contemporary cohort of patients treated with radical cystectomy given the increased awareness of other less common variants.

Methods: We identified patients with squamous differentiation or nonvariant histology on transurethral resection of bladder tumor and/or cystectomy pathology during a 10-year period. Disease specific and overall survival were evaluated using Kaplan-Meier methodology. Cox regression was used to assess variables associated with mortality.

Results: Between 2003 and 2013, 934 patients underwent cystectomy for urothelial bladder cancer. Overall 617 nonvariant and 118 squamous differentiation cases were identified, and the remainder was nonsquamous differentiation variant histology. Overall 75% of patients with squamous differentiation had muscle invasive disease at diagnosis compared with 59% of those with nonvariant histology (p=0.002). Nonorgan confined disease at cystectomy was more common in patients with squamous differentiation (57% vs 44%, p=0.009). Among cases on neoadjuvant chemotherapy 20% (9 of 45) of nonvariant and 13% (1 of 8) of squamous differentiation were pT0N0 (p=0.527). Median followup was 52 months. Adjusted for demographics, pathological stage and chemotherapy, squamous differentiation was not associated with an increased risk of disease specific (HR 1.35, 95% CI 0.90−2.04, p=0.150) or all cause mortality (HR 0.90, 95% CI 0.60−1.25, p=0.515).

Conclusions: In a contemporary cohort of urothelial bladder cancer with recognition and characterization of less commonly described variants, squamous differentiation is not associated with a worse disease specific and all cause mortality when compared to a pure nonvariant cohort.

Abbreviations and Acronyms

CIS = carcinoma in situ

DSS = disease specific survival

LN = lymph node

LVI = lymphovascular invasion

NV = nonvariant

OS = overall survival

SQD = squamous differentiation

TURBT = transurethral resection of bladder tumor

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While variant histology in urothelial bladder cancer has been documented for decades, the WHO did not include variant histology in bladder cancer classifications until 2004 and the clinical significance of variant bladder cancer has yet to be fully determined.[1,2] Collectively, variant histology is often associated with more advanced disease and worse survival.[3−6] Nonetheless the heterogeneity of urothelial bladder cancer and the ability to display clinicopathological characteristics of single or multiple variant subtypes have further complicated the understanding of variant tumor biology.

As one of the first classified variants, squamous differentiation has consistently been described as the most common variant subtype, comprising anywhere between 30% and 80% of variant bladder cancers.[2,3,6−10] Although SQD was previously shown to be associated with higher pathological staging and increased risk of local recurrence, when accounting for stage, SQD does not alter overall or disease specific survival.[7,8,11−13] Furthermore, there is evidence suggesting that SQD may be equally sensitive to chemotherapy as nonvariant urothelial bladder cancer.[10,12,14−17]

Although SQD and NV seem to act similarly, many of the previous studies on SQD derive from older cohorts of patients, before the 2004 WHO classifications.[1] Since the use of systemic chemotherapy has increased, perioperative care and surgical techniques have improved, and the awareness of less commonly described variants has increased, we assessed whether SQD confers a worse prognosis than NV urothelial cancer in a contemporary series of patients undergoing radical cystectomy.

Materials and Methods

Population

Institutional review board approval was granted for the conduct of this study. We conducted a retrospective cohort analysis of our institutional bladder cancer database to identify all patients with urothelial carcinoma who underwent radical cystectomy with curative intent between 2003 and 2013 (934). Patients with nonurothelial cancer on TURBT or cystectomy pathology were not included in this cohort. As the primary focus of this project was comparison of SQD with NV, patients with other variant histology on TURBT or cystectomy (199) were excluded from analysis. SQD variant status was assigned by central pathological review. A single dedicated genitourinary pathologist reviewed all cases. All outside TURBT specimens were also rereviewed by the genitourinary pathologist. In the setting of unclear pathology, slides were reviewed with other dedicated genitourinary pathologists in the department to determine appropriate assignment of variant status. Any component of SQD variant histology with primary urothelial bladder cancer was considered sufficient to be identified as SQD for the purposes of this study.

Outcomes and Variables

The primary outcomes of interest in this study were nonorgan confined disease at radical cystectomy, disease specific survival and overall survival, and represented short and long-term oncologic outcomes. Nonorgan confined disease was defined as pT3 or greater, or lymph node involvement. OS and DSS were assessed using our institutional cancer registry and electronic medical records.

Variables included in the analyses were demographic, TURBT related, cystectomy related and therapy related. Demographic variables were age, gender and race. TURBT related variables included LVI, CIS, and TURBT stage and grade. Cystectomy related variables included pathological stage, grade, surgical margin status, CIS, and LN positivity and density. LN density was calculated as the number of positive LNs divided by the total number of LNs removed in patients with positive LN disease. Therapy related variables included neoadjuvant chemotherapy and postoperative chemotherapy.

Statistical Analyses

Descriptive analysis was performed using Pearson's chi-square test, Student's t-test, Fisher's exact test and the Mann-Whitney U test as appropriate to the data. In the setting of nonnormally distributed data median (IQR) is presented. Kaplan-Meier methodology with the log-rank test was used to evaluate DSS and OS for patients with SQD and NV histology. Univariate (table 1) and Cox proportional hazards regression models were generated to evaluate the relationship between SQD and disease specific and all cause mortality. These models were adjusted for age, gender, systemic chemotherapy, pathological stage and LN status. Variables chosen for inclusion in the models were decided a priori as variables considered to have the potential to