Nonprimary pT1 Nonmuscle Invasive Bladder Cancer Treated With Bacillus Calmette-Guerin is Associated With Higher Risk of Progression Compared to Primary T1 Tumors

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Purpose: Few studies have examined the prognostic significance of prior tumor resection(s) in cases of T1 nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette-Guerin. We examined this issue by comparing the prognosis of primary vs nonprimary T1 nonmuscle invasive bladder cancer treated with bacillus Calmette-Guerin.

Materials and Methods: Patients with pT1 nonmuscle invasive bladder cancer treated with bacillus Calmette-Guerin were identified and tumor pathology was reviewed. Patients were then stratified into primary vs nonprimary tumors, and outcomes were compared using univariate, multivariate and Kaplan-Meier survival analyses, and the Cox regression model adjusting for various clinical and pathological features including, age, gender, tumor size, multifocality, pathological grade and associated carcinoma in situ.

Results: The study included 191 patients, 95 (49.7%) with primary and 96 (50.3%) with nonprimary tumors. The clinical and pathological characteristics were comparable. For the primary vs the nonprimary group progression rates were 24.2% vs 39.6%, respectively (HR 2.07, 95% CI 0.98–3.71, multivariate $p = 0.03$) and the 5-year progression-free survival rates were 71.9% vs 51.5%, respectively (log rank $p < 0.001$). This difference remained significant on multivariate Cox regression analysis (HR 2.53, 95% CI 1.40–4.57, $p = 0.002$). There was no difference between the groups in recurrence or disease specific mortality.

Conclusions: Nonprimary T1 nonmuscle invasive bladder tumors treated with bacillus Calmette-Guerin carry a significantly higher risk of progression to muscle invasive disease compared to primary tumors. This information may be used in combination with other prognostic factors to identify those at high risk for progression when counseling patients.

Key Words: urinary bladder neoplasms, disease progression, recurrence, mortality, BCG vaccine

Abbreviations and Acronyms

BCG = bacillus Calmette-Guerin
CIS = carcinoma in situ
DSS = disease specific survival
NMI-BC = nonmuscle invasive bladder cancer
PFS = progression-free survival
RFS = recurrence-free survival

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THE management of nonmuscle invasive bladder cancer treated with intravesical BCG is challenging, especially since it is difficult to predict the response to this therapy on an individual basis. This is particularly true in high grade T1 disease as it has a higher risk of progression to potentially lethal bladder cancer. Various prognostic factors including clinical,

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pathological, molecular and immunological parameters have been described for NMI-BC treated with BCG.[1] The prognostic value of some of these factors has been established while the value remains controversial for others. T1 high grade tumors represent a mixed bag comprising tumors presenting for the first time as such but also tumors which originally presented as Ta or CIS and later progressed to high grade lamina propria invading tumors.

While several studies examined the prognostic significant of prior tumor resection(s) in NMI-BC, and showed a significant relation to recurrence,[2,3] progression,[4] and recurrence and progression,[5] others have failed to show such a correlation.[6–10] Moreover most of these studies included all pT stages of NMI-BC collectively and did not focus on T1 tumors only. However, we believe there are strong arguments to analyze T1 tumors as a separate entity due to their different behavior compared to Ta and Tis. We asked whether the response to BCG therapy and risk of recurrence and/or progression to muscle invasive disease is different in primary vs nonprimary high grade T1 bladder tumors.

MATERIALS AND METHODS

Patients and Followup

After obtaining approval from our local research and ethics board we retrospectively identified all patients with pT1 disease treated with intravesical BCG at our institution (University Health Network, University of Toronto) between 1990 and 2008. After excluding those patients who underwent upfront radical cystectomy we divided our cohort into 2 main groups of primary—those patients diagnosed with pT1 disease as the first presentation of bladder cancer, and nonprimary—those with a history of lower stage NMI-BC who had progression from pTa and/or CIS to pT1 disease during followup. Patients with a previous muscle invasive tumor were not considered in the analysis. We then recorded clinical and pathological variables including age at diagnosis of T1 disease, gender, tumor grade, size, multiplicity and associated CIS.

Repeat transurethral bladder tumor resection for patients with pT1 disease has been the standard of care at our institution since 2000. All patients were followed with a routine history, physical examination, cystoscopy, urine cytology every 3 months and upper tract imaging on an annual basis. Followup was calculated starting from the day of diagnosis of pT1 disease to the date of the last encounter with the patient or death. Intravesical BCG was given to all patients at a dose of 81 mg in 50 cc normal saline once weekly for 6 weeks as induction. Maintenance BCG was given at the discretion of the treating urologist.

Pathological Evaluation

All pathological specimens were processed and read by experienced genitourological pathologists. A standard reporting template, which includes reporting of secondary pattern of disease and whether detrusor muscle was sampled, is used at our pathology department, and we routinely send all slides from outside hospitals for review by our pathologists as well. We used the WHO 1973 grading system and a pathological review of tumor grade was performed for all patients.

Statistical Analysis

The clinical and pathological features as well as recurrence (defined as recurrence of at least pT1 disease), progression (defined as progression to muscle invasive disease, ie pT2 or higher) and disease specific mortality rates were compared between the groups using univariate and multivariate logistic regression analyses with $p \leq 0.05$ considered statistically significant. RFS, PFS and DSS were compared between the groups using Kaplan-Meier survival curves. The log rank test was used to compare strata with $p \leq 0.05$ considered statistically significant. A multivariate Cox regression analysis adjusting for all clinical and pathological variables, and primary vs nonprimary disease was used to identify factors associated with PFS, RFS and DSS. Statistical analysis was performed using SPSS® version 16.

RESULTS

A total of 191 patients were identified from our database, of which 148 (77.5%) were male and 43 (22.5%) were female. Mean age at diagnosis was 68.5 years and median followup was 48 months. Based on previous history of bladder tumor 95 (49.7%) patients were classified as having primary tumors and 96 (50.3%) as having nonprimary tumors. In the nonprimary group and before progression to pT1 disease 50 patients (52.1%) received at least 1 induction course of intravesical BCG, and of these 22 (22.9%) received at least 1 maintenance intravesical treatment for various indications including concomitant CIS, large tumors or multiple recurrences. Median number of BCG courses was 2. The time between receiving the last BCG therapy and progression to pT1 ranged from 2 to 225 months (median 19).

On univariate analysis both groups were comparable in terms of age, gender, median followup, tumor grade, multifocality and associated CIS, while the only difference was in the higher percentage of larger tumors (greater than 3 cm) in the primary group (53.7%) vs the nonprimary group (33.3%, $p = 0.006$, table 1). The rate of detrusor muscle sampling at pT1 diagnosis was 59% for nonprimary tumors vs 63% for primary tumors ($p = 0.7$).

There were 7 patients (7.3%) in the primary group vs 9 (9.4%) in the nonprimary group who underwent deferred cystectomy for BCG refractory pT1 disease ($p = 0.51$) with a mean time to cystectomy of 11.5 months (median 8). The percentage of patients lost to followup was 4.2% in the primary group vs 9.4%