Predicting Nonmuscle Invasive Bladder Cancer Recurrence and Progression in Patients Treated With Bacillus Calmette-Guerin: The CUETO Scoring Model

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Purpose: Bacillus Calmette-Guerin is the most effective therapy for nonmuscle invasive bladder cancer. Recently to calculate the risks of recurrence and progression based on data from 7 European Organisation for Research and Treatment of Cancer trials a scoring system was reported. However, in that series only 171 patients were treated with bacillus Calmette-Guerin. We developed a risk stratification model to provide accurate estimates of recurrence and progression probability after bacillus Calmette-Guerin.

Materials and Methods: Data were analyzed on 1,062 patients treated with bacillus Calmette-Guerin and included in 4 Spanish Urological Club for Oncological Treatment trials. Stepwise multivariate Cox models were used to determine the effect of prognostic factors. In each patient the weight of all factors was summed to a total score. Patients were then divided into groups, and cumulative recurrence and progression rates were calculated.

Results: A scoring system was calculated with a score of 0 to 16 for recurrence and 0 to 14 for progression. Patients were categorized into 4 groups by score, and recurrence and progression probabilities were calculated in each group. For recurrence the variables were gender, age, grade, tumor status, multiplicity and associated Tis. For progression the variables were age, grade, tumor status, T category, multiplicity and associated Tis. For recurrence calculated risks using Spanish Urological Club for Oncological Treatment tables were lower than those obtained with Sylvester tables. For progression probabilities were lower in our model only in patients with high risk tumors.

Conclusions: We propose a scoring model to stratify the risk of recurrence and progression in patients treated with bacillus Calmette-Guerin.

Key Words: urinary bladder, urinary bladder neoplasms, Mycobacterium bovis, risk, prognosis

Abbreviations and Acronyms

AIC = Akaike's information criterion

BCG = bacillus Calmette-Guerin

CUETO = Spanish Urological Club for Oncological Treatment

EORTC = European Organisation for Research and Treatment of Cancer

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Study received institutional review board approval.

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BACILLUS Calmette-Guerin is currently the most effective intravesical therapy for nonmuscle invasive bladder cancer with a high and intermediate risk of recurrence and progression. Intravesical chemotherapy can decrease the

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recurrence risk in patients with intermediate risk tumors in the short term. However, in the long term it has only a modest effect on the recurrence risk without decreasing the progression risk. For highly recurrent tumors or multiple recurrences it was suggested to change to BCG therapy.[1] Moreover, BCG immunotherapy markedly improves the outcome of high risk nonmuscle invasive bladder cancer.[2] Nevertheless, a subgroup of patients fails to respond and is at risk for disease progression. In these patients a tool to predict the response to intravesical immunotherapy would be invaluable. Despite extensive research currently molecular markers for recurrence and progression have not gained usefulness in clinical practice.

Based on multivariate analysis of data on 2,596 patients with superficial bladder cancer in 7 EORTC trials Sylvester et al developed a simple scoring system that provides a powerful tool for the clinician to calculate the short-term and long-term risks of recurrence and progression based on available clinical and pathological data.[3] However, most of their patients were treated with chemotherapy and in 171 treated with BCG no maintenance was administered.

Recently we analyzed prognostic factors for recurrence and progression after intravesical adjuvant BCG immunotherapy with a similar maintenance schedule in 1,062 patients with nonmuscle invasive transitional cell carcinoma in 4 CUETO trials.[4] To our knowledge this is the largest multivariate prognostic factor analysis to date in patients treated with BCG. Like Sylvester et al,[3] we developed a risk stratification model to provide accurate estimates of recurrence and progression probability after intravesical adjuvant BCG therapy.

PATIENTS AND METHODS

Data on 1,062 patients treated with BCG (Connaught strain) from February 1990 to May 1999 were analyzed (table 1). All patients were included in 4 CUETO prospective, phase 3, randomized trials comparing different intravesical treatments in patients with noninvasive bladder cancer.

Protocols with identical treatment BCG regimens and followup schedules were used in all patients in the current series. Briefly, visible tumors underwent complete transurethral bladder resection and were staged according to the 1987 TNM classification and the 1973 WHO grading system. First instillation was given 7 to 14 days after transurethral bladder resection and repeated once weekly for 6 consecutive weeks. Thereafter 6 additional instillations were repeated at 2-week intervals. Each patient received a total of 12 instillations within 5 to 6 months after surgical intervention. By the study end 45 patients (4.2%) received fewer than 6 instillations, 239 (22.5%) received 6 to 9 and 778 (73.3%) received more than 10.

Table 1. *Patient and tumor characteristics*

	No. Pts (%)
Age:	
60 or Less	404 (31.2)
61–70	487 (37.6)
71–80	367 (28.3)
Greater than 80	38 (2.9)
Prior treatment:	
No	864 (66.7)
Yes	432 (33.3)
No. tumors:	
1	639 (49.3)
2–3	348 (26.9)
4–7	194 (15)
8 or Greater	115 (8.9)
Tumor size (cm):	
1 or Less	343 (26.5)
1–3	47 (26.8)
3 or Greater	593 (45.8)
No. instillations:	
Less than 6	66 (5.1)
6–9	421 (32.5)
10 or Greater	809 (62.4)
Doses (mg):	
13.5	137 (10.6)
27	447 (34.5)
81	519 (40)
81 + 30 mg Mitomycin C	193 (14.9)
T category:	
Ta	251 (19.4)
T1	1,001 (77.2)
Isolated Tis	44 (3.4)
Ca in situ:	
No	1,162 (89.7)
Yes[1]	134 (10.3)
Grade:	
G1	197 (15.2)
G2	750 (57.9)
G3	305 (23.5)
Isolated Tis	44 (3.4)
T1G3:	
No	1,030 (79.5)
Yes, Ca in situ	208 (16)
Yes, Ca in situ	58 (4.5)

* Isolated in 44 patients and associated with papillary noninvasive bladder carcinoma in 90.

Patients were evaluated every 3 months during the first 2 years and every 6 months thereafter. Evaluation included cytology, cystoscopy and biopsy of suspicious lesions. Excretory urography, done at bladder tumor diagnosis to rule out a synchronous upper urinary tract tumor, was repeated yearly during followup. When recurrence was detected, the tumor was resected. When recurrence was not detected but urinary cytology was positive, bladder and prostatic urethra biopsies were taken and the upper urinary tract was examined. Patients were withdrawn from study at the first relapse after the completion of treatment and those with Tis were withdrawn if positive cytology persisted or reappeared after 12 instillations, there was tumor in the upper urinary tract or prostatic urethra, or grade 3–4 toxicity was observed. Patients were followed until study end or death.