Treatment Paradigm Shift May Improve Survival of Patients With High Risk Superficial Bladder Cancer

Ganesh V. Raj,* Harry Herr, Angel M. Serio, Sherri M. Donat, Bernard H. Bochner, Andrew J. Vickers and Guido Dalbagni†

From the Departments of Urology (GVR, HH, AMS, SMD, BHB, GD) and Biostatistics (AJV), Memorial Sloan-Kettering Cancer Center, New York, New York

Purpose: Historically patients with recurrent T1 bladder tumors after bacillus Calmette-Guerin have been treated with bladder sparing approaches. Recently a paradigm shift has occurred since patients are increasingly offered radical cystectomy before disease progression to muscle invasion. In this study we explored the effect of this paradigm shift on progression rates and disease specific survival.

Materials and Methods: The historical cohort consisted of 307 patients from 3 prospective intravesical bacillus Calmette-Guerin protocols from 1980 to 1989. An institutional review board approved review identified 589 patients treated with bacillus Calmette-Guerin in a contemporary cohort from 1992 to 2004.

Results: In the historical cohort the 85 patients with documented T1 recurrence were initially treated with repeat transurethral resection and intravesical bacillus Calmette-Guerin. Of these 85 patients 60 had progression to muscle invasive disease. At 5 years after T1 recurrence, the cumulative incidence of progression to T2 disease was 71% (95% CI 61%, 81%) and the cumulative incidence of death from disease was 48% (95% CI 39%, 60%). In the contemporary cohort 129 patients had documented T1 recurrence. In this cohort 65 of the 129 patients with recurrent T1 underwent immediate radical cystectomy. At 5 years after T1 recurrence, the cumulative incidence of progression to muscle invasive disease was 28% (95% CI 20%, 38%) and the cumulative incidence of death from disease was 31% (95% CI 22%, 42%).

Conclusions: Preemptive radical cystectomy performed for recurrent T1 disease following intravesical bacillus Calmette-Guerin therapy may be associated with better disease specific survival.

Key Words: mycobacterium bovis, cystectomy, disease progression, treatment outcome

A significant number of patients with high risk superficial bladder tumors treated with intravesical BCG and TUR will have progression to invasive disease.[1–6] Progression to muscle invasion (T2) mandates immediate radical cystectomy. However, no consensus exists regarding the treatment of patients with recurrent bladder tumors that invade the lamina propria (T1).[6–12] Bladder sparing strategies, including repeat intravesical BCG therapy until T2 disease or combination chemotherapy and radiation, may mitigate the benefits of RC at an earlier stage.[6,9,10,13,14] To our knowledge no prospective randomized trial has evaluated the optimal timing of RC in such patients.[9,15–18] In this study we examined the effect of the paradigm shift toward earlier RC in a contemporary cohort in which most patients with T1 tumors after intravesical BCG undergo immediate RC. We contrast this cohort and the disease specific survival outcomes to those seen in historical cohorts from the 1980s, when RC was delayed until T2 disease.

Submitted for publication July 18, 2006.
Study received institutional review board approval.
* Current address: Department of Urology, UT Southwestern Medical Center at Dallas, Dallas, Texas 75390.
† Correspondence: Department of Urology, Memorial Sloan-Kettering Cancer Center, 353 E. 68th St., New York, New York 10021 (telephone: 646-422-4394; FAX: 212-988-0760; e-mail: dalbagng@mskcc.org).

MATERIALS AND METHODS

Patients

The historical cohort consists of 307 patients from 3 prospective protocols from 1980 to 1989 who underwent intravesical BCG therapy for documented bladder cancer at MSKCC.[16] In our review we include an evaluation of maintenance BCG therapy. All cases were included in our study since our prior multivariate analyses have shown that the BCG regimen used did not impact tumor progression.

An institutional review board approved retrospective review identified patients in the contemporary cohort who underwent intravesical BCG therapy for bladder cancer at MSKCC from 1992 to 2004. Patients who received intravesical BCG elsewhere were excluded from analysis. Outcomes for all patients were updated until June 2005. Medical records were diligently reviewed for pathological variables from preoperative and RC specimens. Patients with recurrent T1 tumors after intravesical BCG are the focus of this report.

More than 90% of patients in the historical and contemporary cohorts received the complete 6-week course of intravesical BCG. There was no difference in the number of intravesical therapy cycles between the historical and contemporary cohorts. All patients in both cohorts underwent a re-staging TUR at MSKCC. Marker lesions were generally not left behind and the bladder was cleared of gross tumor before initiation of intravesical BCG. Virtually all patients

DOI:10.1016/j.juro.2006.11.090

Clinical patient characteristics

	Historical Cohort	Contemporary Cohort
Median age (IQR)	61 (55, 69)	68 (62, 75)
No. gender (%):		
Male	72 (85)	107 (83)
Female	13 (15)	22 (17)
No. pre-BCG clinical stage (%):		
Ta	36 (42)	43 (33)
T1	49 (58)	73 (57)
T2	0 (0)	13 (10)
No. Ca in situ (%):		
No	1 (1)	36 (28)
Yes	84 (99)	93 (72)

had either a high grade lesion or carcinoma in situ. Due to the retrospective nature of the study additional variables including tumor location, multiplicity or size could not be accurately ascertained for all patients.

Patients were followed every 3 to 6 months with cystoscopy, urine cytology and repeat TUR, and intravesical BCG as necessary. Indications for RC in the historical cohort included muscle invasion of bladder or prostate. In the contemporary cohort indications for RC included extensive superficial noninvasive bladder tumors, recurrence with T1, or tumor invasion of the bladder or prostate. Generally repeat TUR was not performed to confirm the diagnosis of T1 after intravesical BCG. The decision of when to recommend RC was made by urologists on an individual basis.

Statistical Methods

Initial analysis revealed marked differences between cohorts in rates of death from other causes. This suggests important differences in case mix precluding a formal statistical comparison. Therefore, our approach was primarily descriptive. In the time-to-event analyses, events of interest were examined from the time of recurrent T1 disease. For progression to muscle invasive disease, RC and death without progression were accounted for as competing risks. For disease specific death, death from other causes was the competing risk. Cumulative incidence of muscle invasive disease and disease specific death were estimated separately for the historical and contemporary cohorts using the cmprsk package in R software (http://www.r-project.org).[19]

RESULTS

Progression to Muscle Invasion

In the historical cohort of 307 patients with superficial bladder cancer treated with intravesical BCG, 85 (28%) had documented T1 recurrence (see table). Median followup was 4.3 years. Since the prevailing philosophy was to reserve RC for T2 tumors, these patients were treated with repeat TUR and intravesical BCG. Consequently, 60 of these 85 patients had progression to muscle invasive (T2) disease following recurrence with T1. None of these patients underwent RC without evidence of progression to T2. Of these 60 patients 48 subsequently underwent RC. At 5 years after T1 recurrence the cumulative incidence of progression to T2 disease was 71% (95% CI 61%, 81%) (fig. 1, *A*).

In the contemporary cohort of 589 patients with superficial bladder cancer treated with intravesical BCG, 129 had documented T1 recurrence. Median followup was 2.2 years. In this cohort a more aggressive approach with RC was recommended upon identification of T1 disease. Thus, 65 of the 129 patients with recurrent T1 underwent immediate RC. Of these 65 patients 34 had disease pathologically up staged to T2 or higher, including 22 with pT3 or higher disease. Of these patients 17 subsequently died of disease and 14 died of other causes.

The remaining 64 patients who did not undergo immediate RC underwent additional TUR of bladder tumors and additional cycles of intravesical BCG as deemed necessary by the attending surgeon. Of these 64 patients 33 had progression to muscle invasive disease, with 13 subsequent deaths from disease. At 5 years after T1 recurrence the cumulative incidence of progression to muscle invasive disease was 28% (95% CI 20%, 38%) (fig. 1, *B*).

Disease Specific Survival

In the historical cohort the median followup for survivors was 13.3 years. A total of 42 patients died of disease while 9 died of other causes. Of the 48 patients treated with RC after

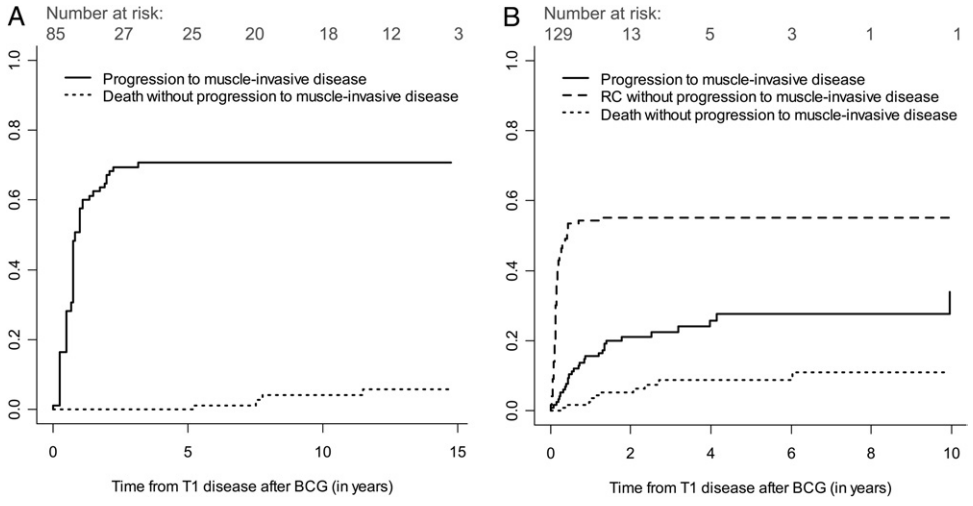

FIG. 1. Cumulative incidence of progression, accounting for radical cystectomy and death without progression as competing risks. *A*, historical cohort. *B*, contemporary cohort.