The Timing of Radical Cystectomy for bacillus Calmette-Guérin Failure: Comparison of Outcomes and Risk Factors for Prognosis

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CSS = cancer specific survival
HG = high grade
IFN = interferon
IVT = intravesical therapy
LVI = lymphovascular invasion
NMIBC = nonmuscle invasive bladder cancer
OS = overall survival
RC = radical cystectomy
TUR = transurethral resection

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Purpose: We compared the pathological and survival outcomes of patients who underwent radical cystectomy soon after bacillus Calmette-Guérin failure with those of patients who received additional salvage intravesical chemotherapy before cystectomy for nonmuscle invasive bladder cancer. We also identified predictors of prognosis in the entire cohort.

Materials and Methods: We retrospectively analyzed the records of 117 patients who underwent radical cystectomy for recurrent nonmuscle invasive bladder cancer at our institution from 1990 to 2012. The cohort was divided into group 1 of 61 patients treated only with bacillus Calmette-Guérin with or without interferon-α and group 2 of 56 who received at least 1 additional salvage intravesical chemotherapy after bacillus Calmette-Guérin.

Results: Final pathology and survival outcomes did not differ significantly between the groups. Five-year overall and cancer specific survival was similar in groups 1 and 2 at 80% and 85%, respectively, at approximately equivalent followups. Median bladder retention was 1.7 years longer in group 2 ($p < 0.001$). On multivariate Cox regression analysis delayed cystectomy in group 2 did not convey a significant hazard for all cause mortality after cystectomy (HR 1.08, $p = 0.808$). Only up-staging to cT1 (HR 1.88, $p = 0.045$), lymph node invasion (HR 2.58, $p = 0.023$) and prostatic urethra involvement (HR 1.95, $p = 0.029$) achieved significance.

Conclusions: With appropriate selection for salvage intravesical chemotherapy patients who elect bladder sparing treatment instead of earlier radical cystectomy after bacillus Calmette-Guérin fails do not sacrifice positive pathological or oncologic outcomes while retaining bladder function for a significantly longer duration.

Key Words: urinary bladder neoplasms, BCG vaccine, treatment failure, cystectomy, mortality

ADJUVANT intravesical BCG is the first line treatment recommended for high risk NMIBC by the EAU (European Association of Urology)[1] and AUA (American Urological Association)[2] following TUR[2] as well as a treatment option for intermediate risk NMIBC.[3] Despite the proven efficacy of BCG 30% to 50% of patients experience disease recurrence and/or progression, and BCG is deemed to have failed.[4–6] Most clinicians and

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guidelines agree that patients in whom BCG fails should be offered RC as the gold standard oncologic treatment since they are at significant risk for disease progression, which entails a dramatically worsened prognosis.[7–10] At our institution many referrals are received for patients who understand the risk but are unwilling or unable to sustain the morbidity of RC and, therefore, seek investigational bladder preserving treatments.

Many studies have suggested that an oncologic benefit is associated with immediate RC in patients with HG cT1 or a subset with high risk NMIBC.[11–14] However, as a consequence of the primarily investigational nature of salvage IVT there is a scarcity of data that compares outcomes in patients who receive early RC after BCG fails to outcomes in those who undergo delayed RC after salvage IVT fails.

Accordingly, this study aimed to compare pathological and survival outcomes between early and delayed RC. We hypothesized that patients who underwent delayed RC after salvage IVT failed would have worse outcomes than those treated with earlier RC after BCG failure. Furthermore, to help guide clinical decisions in this challenging patient population we also sought to elucidate risk factors for poor prognosis to inform clinicians when RC should be more strongly favored over additional bladder preserving treatments.

MATERIALS AND METHODS

The institutional review board approved, prospective Columbia Urologic Oncology Database was queried for patients who underwent RC for recurrent NMIBC at our institution from 1990 to 2012 and were treated with at least 1 initial 6-week induction course of BCG. Excluding those with incomplete followup data, this query yielded 145 patients. Some patients were excluded from analysis, including 20 who progressed to muscle invasive disease prior to RC as they no longer presented a clinical dilemma, 6 who received an intravesical agent before undergoing 6-week induction of BCG and 2 in whom an unclear course of IVT was administered following BCG. With these exclusions a cohort of 117 patients was eligible for analysis. The cohort was divided into group 1 of 61 patients treated only with BCG with or without IFN-α and group 2 of 56 who received at least 1 additional salvage IVT after BCG.

Because most patients underwent 3 or more diagnostic TUR procedures, composite variables were created from common clinicopathological features to better assess the severity of disease. For example, the percent of positive specimens with cT1 was used to differentiate a patient with 3 instances of cT1 disease in 3 diagnostic TURs (100%) to that of a patient with 1 instance of

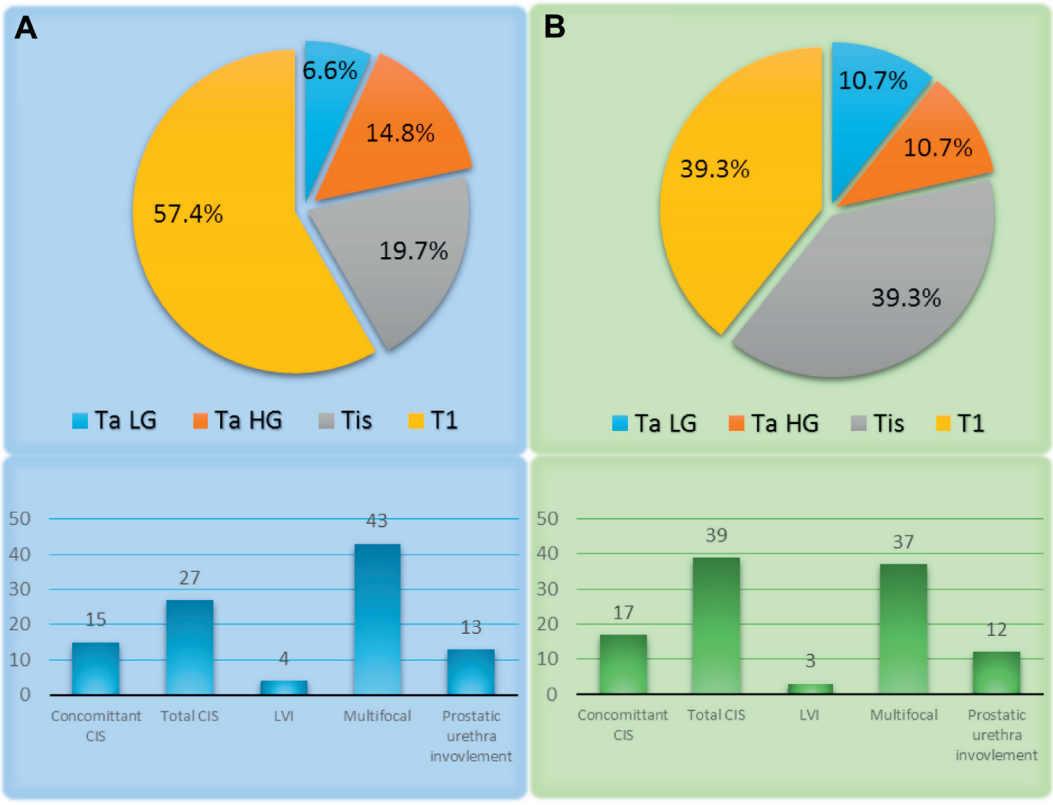

Figure 1. Clinicopathological features of NMIBC in 61 group 1 (*A*) and 56 group 2 (*B*) patients in last TUR specimen before RC. *LG*, low grade.

cT1 in 3 diagnostic TURs (33%). Binary variables that indicated whether an event occurred at least once throughout the clinical course were also created to better assess less frequently occurring features such as LVI.

Primary study outcomes were progression to muscle invasive disease (pT2 or greater), OS and bladder CSS. Death from bladder cancer was explicit in the records or inferred when the patient had documented advanced metastatic disease at the time of death. The Social Security Death Index was queried for all cause mortality in patients who were lost to followup at our institution.

Differences in categorical variables between groups 1 and 2 were assessed using the Fisher exact test and differences in nonnormally distributed continuous variables were assessed with the Wilcoxon rank-sum test. Univariate and multivariable logistic regression analysis was performed to evaluate risk factors for up-staging to muscle invasion. Kaplan-Meier curves with the log-rank test were constructed to compare survival functions between the groups and multivariate Cox regression analysis was done to identify predictors of OS and CSS. All p values were the result of 2-sided tests with $p \leq 0.05$ considered significant throughout the study. Analyses were performed using SPSS®, version 21.

RESULTS

A total of 117 patients were identified who had RC after sustaining recurrent NMIBC and receiving treatment with at least 1 initial induction course of BCG. A total of 20 patients were excluded from study due to progression to cT2 before RC, of whom only 5 progressed after salvage IVT, including 1 who was noncompliant to followup and 1 who refused RC. Median cohort patient age at RC was 69.4 years (IQR 65–76) in group 1 and 70.1 years (IQR 65–74) in group 2 ($p = 0.967$). Supplementary table 1 (http://jurology.com/) lists the demographic and clinicopathological features of the initial patient disease that prompted BCG as well as composite disease variables. Notably, whereas group 1 had significantly more cT1 disease, group 2 had a heavier burden of CIS.

A mean of 1.4 (range 1 to 2) and 3.4 (range 2 to 6) induction courses of IVT were administered in groups 1 and 2, respectively. Supplementary table 2 (http://jurology.com/) lists the type and frequency of each IVT induction before RC. The majority of patients received a full 6-week induction course of IVT without maintenance IVT. Maintenance courses were noted in only 28 of 275 cases (10%). The 20 of 275 patients (7.2%) who received less than a 6-week course mostly did so as a result of poor tolerability of the drug. There were no significant differences in the number of weekly courses of IVT per induction course or of maintenance IVT between the groups when comparing the first 2 rounds of IVT. All patients had a final TUR diagnosis before RC with clinicopathological features (fig. 1). Group 1 had more cT1 than group 2 (57.4% vs 39.3%, $p = 0.065$) but group 2 had significantly more CIS on final cT staging (44% vs 70%, $p = 0.009$).

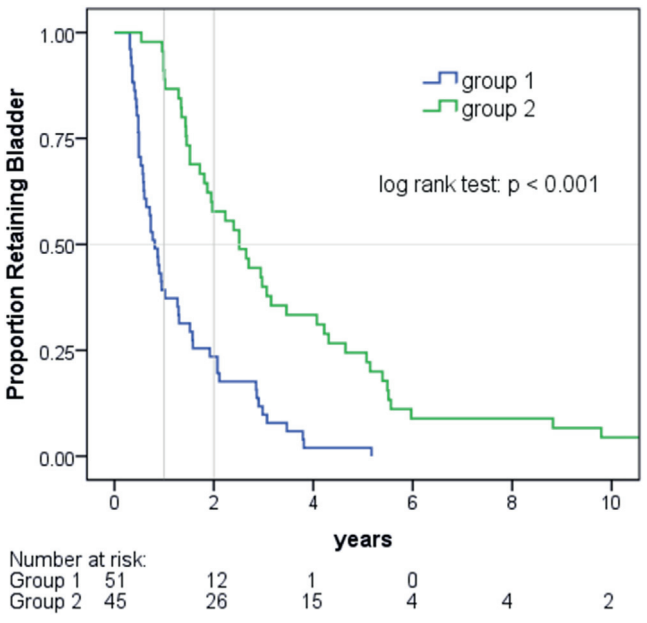

Figure 2. Kaplan-Meier curves of bladder retention in groups 1 and 2.

Table 1. *Final pathology results at RC and cohort followup characteristics after RC*

	No. Group 1 (%)	No. Group 2 (%)	Total No. (%)
Overall	61	56	117
Stage:			
T0	7 (11)	2 (4)	9 (7.7)
Ta	10 (16)	10 (18)	20 (17.1)
Tis	15 (25)	26 (46)	41 (35.0)
T1	16 (28)	7 (13)	23 (19.7)
T2 or greater:	13 (21)	11 (20)	24 (20.5)
T2	5 (8)	4 (7)	9 (7.7)
T3	5 (8)	4 (7)	9 (7.7)
T4a	3 (5)	3 (5)	6 (5.1)
Lymph node status:			
Any	8 (13)	4 (7)	12 (10.3)
Nx	3 (5)	7 (13)	10 (8.5)
N0	50 (82)	45 (80)	95 (81.2)
N1	3 (5)	0 (0)	3 (2.6)
N2	5 (8)	3 (5)	8 (7.7)
N3	0	1 (2)	1 (0.09)
Present:			
CIS	45 (74)	51 (91)	96 (82.1)
LVI	10 (16)	11 (20)	21 (17.9)
Post-RC followup:			
Urinary tract urothelial cell Ca recurrence	7 (11)	11 (20)	18 (15.4)
Urothelial cell Ca metastasis	13 (21)	12 (21)	25 (21.3)
Local +/or metastatic recurrence	15 (24)	17 (30)	32 (27.3)
Alive	33 (54)	26 (46)	59 (50.4)
Dead of disease	13 (21)	12 (21)	25 (21.4)
Dead of other cause	15 (25)	18 (32)	33 (28.2)

Table 2. *Univariate and multivariate logistic regression analysis of up-staging to muscle invasion or greater on final pathology evaluation*

	Univariable		Multivariable	
	OR (95% CI)	p Value	OR (95% CI)	p Value
	Binary variables			
Group 2	0.82 (0.37–2.22)	0.823	3.02 (0.74–12.32)	0.124
Female gender	1.25 (0.46–3.40)	0.658	—	—
Initial:				
T1	2.44 (0.88–6.7)	0.084	—	—
CIS	4.23 (1.89–13.89)	0.017	—	—
T1 after 1st BCG	4.89 (1.55–15.42)	0.007	—	—
Ever:				
Ta low grade/ multifocal	0	0.998	—	—
Concomitant CIS	2.48 (0.94–6.54)	0.066	—	—
LVI	22.75 (4.42–117)	<0.001	20.9 (3.53–124.1)	0.001
Prostatic urethra	1.39 (0.55–3.56)	0.489	—	—
Up-staged to T1	1.93 (0.70–5.27)	0.203	—	—
	Continuous variables			
Age	1.05 (0.99–1.11)	0.128	1.09 (1.02–1.17)	0.015
Yrs from 1st BCG-RC	0.86 (0.65–1.14)	0.291	—	—
No. IVTs	0.82 (0.56–1.19)	0.294	—	—
% TUR:				
T1	1.02 (1.01–1.04)	0.003	1.040 (1.02–1.07)	0.001
CIS	1.01 (0.99–1.03)	0.203	1.026 (1.00–1.05)	0.034
Multifocal	0.99 (0.98–1.01)	0.335	—	—

Median time from diagnosis prompting BCG with or without IFN-α induction to RC was 0.81 and 2.51 years in groups 1 and 2, respectively. This 1.7-year difference was significant on Kaplan-Meier analysis (fig. 2). The difference in bladder retention may have been underestimated as 37 patients were not included in study who underwent salvage IVT and did not require cystectomy a median of 5.7 years after first receiving BCG. Median followup after RC was approximately equivalent in groups 1 and 2, including 4.69 (IQR 2.4–8.9) and 5.14 years (IQR 2.5–7.9), respectively (p = 0.45). Median followup in patients censored at last followup was 5.06 years (IQR 3.5–8.2).

The final RC pathology of all patients was reviewed (table 1). RC pathology evaluation revealed muscle invasion or deeper in 13 patients (21%) in group 1 and in 11 (19%) in group 2. Single and multivariable logistic regression analysis identified predictors of up-staging to muscle invasion or greater (table 2). No model assigned any significance to delayed RC after salvage IVT (group 2) compared to quicker RC after BCG failure (group 1). Four of the 5 predictor variables used in the model were statistically significant, including LVI ever, age, percent of TURs with cT1 pathology and percent of TURs with CIS. The presence of LVI most strongly predicted muscle invasion as 8 of 10 patients with at least 1 TUR specimen showing LVI had progressed to pT2 or greater at RC (OR 20.9, p = 0.001).

After RC bladder cancer recurred in 32 patients, including 15 in group 1 and 17 in group 2. Table 1 lists additional followup details. When comparing survival data with Kaplan-Meier curve analysis, there was no statistically significant difference between groups 1 and 2 in OS or CSS (log-rank test p = 0.58 and 0.70, respectively, fig. 3). Because the initial date of diagnosis prompting BCG induction was not accurately available for 21 patients referred from elsewhere, the total cohort size was decreased to 96 for this analysis. Five-year OS was 80% and 5-year CSS was 85% in both groups. When controlling for up-staging to cT1 before RC, older age, presence of LVI and prostatic urethra involvement in a Cox proportional hazards model, group 2 was not at significantly worse risk for death after RC (HR 1.08, p = 0.808). Only up-staging to cT1 (HR 1.88, p = 0.045), LVI (HR 2.58, p = 0.023) and prostatic

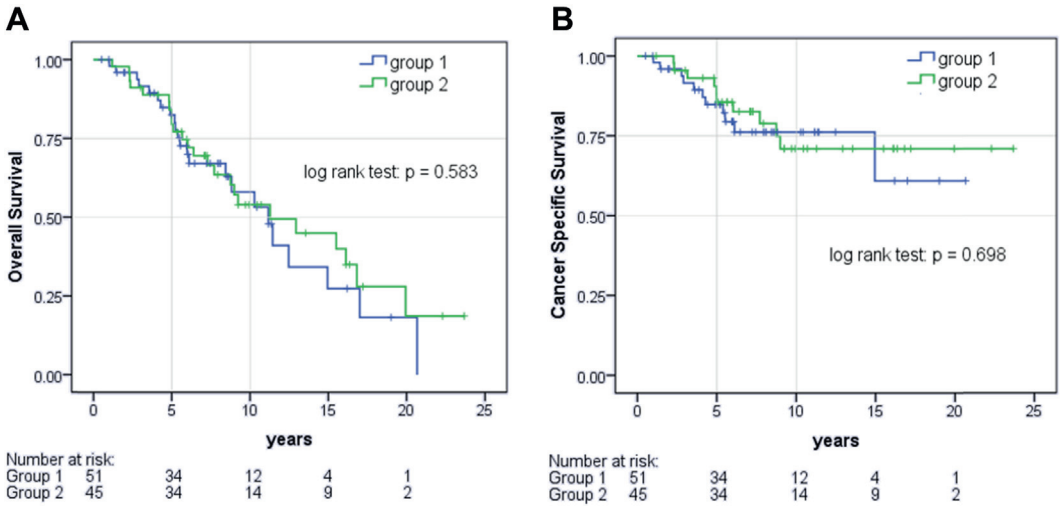

Figure 3. Kaplan-Meier analysis of OS (*A*) and CSS (*B*) in groups 1 and 2 with time from first diagnosis prompting BCG induction

Table 3. *Univariate and multivariate Cox regression analysis of OS and CSS*

	Univariate		Multivariate OS		Multivariate CSS	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Binary:						
Group 2	1.26 (0.75–2.12)	0.379	1.08 (0.60–1.92)	0.808	0.87 (0.36–2.09)	0.758
Female gender	0.62 (0.32–1.24)	0.117	–	–	–	–
Initial T1	0.70 (0.37–1.33)	0.277	–	–	–	–
T1 after 1st BCG	1.27 (0.75–2.16)	0.369	–	–	–	–
Ta low grade/multifocal ever	1.12 (0.57–2.24)	0.735	–	–	–	–
Concomitant CIS ever	1.33 (0.78–2.25)	0.297	–	–	–	–
Up-staged to cT1 after IVT	1.77 (0.96–3.21)	0.061	1.88 (1.01–3.50)	0.045	2.64 (1.09–6.39)	0.032
LVI ever	2.01 (0.94–4.31)	0.071	2.58 (1.14–5.84)	0.023	8.26 (3.11–21.9)	<0.001
Prostatic urethra ever	1.69 (0.99–2.87)	0.055	1.95 (1.07–3.54)	0.029	4.29 (1.78–10.3)	0.001
Continuous:						
Age	1.05 (1.01–1.08)	0.007	1.03 (0.99–1.07)	0.119	1.00 (0.96–1.04)	0.962
Yrs from 1st BCG-RC	1.00 (0.90–1.13)	0.919	–	–		
No. IVTs	1.04 (0.85–1.26)	0.723	–	–		
% TUR T1	1.00 (0.99–1.01)	0.685	–	–		
% TUR CIS	1.01 (0.99–1.02)	0.113	–	–		

urethra involvement (HR 1.95, $p = 0.029$) achieved significance. The same significant variables also had larger HRs when analysis was done for CSS (table 3).

DISCUSSION

Patients with recurrent NMIBC in whom initial BCG induction failed represent a challenging disease state to manage. Depending on markers of disease severity, and patient and clinician preference, options include repeating BCG with or without an IFN induction course, changing to an alternative salvage intravesical chemotherapy or proceeding with RC. We aimed to isolate the effect on outcomes due to delayed RC after receiving at least 1 and as many as 4 additional courses of salvage IVT. On direct Kaplan-Meier analysis and multivariate Cox regression analysis controlling for markers of aggressive disease we found no significant difference in OS or CSS between early and delayed RC. Similar rates of up-staging to muscle invasion, bladder cancer recurrence after RC, and CSS and OS were observed in groups 1 and 2.

To control for differences in disease severity between the 2 groups we used a novel approach with composite variables that combined all data on the numerous TURs, in addition to controlling for other previously described risk factors such as female gender,[15] older age,[16] multifocality,[15] prostatic urethra involvement[17] and LVI.[18] Of these variables the percent of positive TUR specimens with cT1, the percent of positive TUR specimens with CIS, older age and LVI were significant predictors of up-staging to muscle invasion or deeper. Significant predictors of death included up-staging to cT1 from cTa or cTis, prostatic urethra involvement and LVI. LVI on any TUR specimen was an especially poor predictor of prognosis as 8 of 10 patients had muscle invasive disease at RC and 7 of 10 died of bladder cancer.

Caution is advised when making any overarching conclusions regarding the noninferiority of electing salvage intravesical therapy over earlier RC for BCG failure. Without randomization in a prospective trial this retrospective study captures selection bias whereby patients with higher risk, recurrent cT1 disease tended to undergo earlier cystectomy. This flaw could not fully be corrected for on regression analyses. A randomized trial in which patients are randomized to salvage IVT or RC after BCG failure, should they meet certain criteria, would be most valuable to determine the true efficacy of salvage IVT. However, this trial is likely never to be done.

Because this study includes only a subset of patients who underwent salvage IVT, future studies should look at the entire cohort of patients who receive salvage IVT, from those who progress to cT2 to those who never require RC. Including these salvage IVT successes and failures would provide a more accurate comparison to the currently recommended guideline of cystectomy after BCG failure, and would better elucidate the candidates best suited for salvage IVT.

CONCLUSIONS

With appropriate selection for salvage intravesical chemotherapy patients in whom BCG fails and who then elect salvage IVT over earlier RC do not make significant oncologic sacrifices while retaining bladder function for a longer duration. Risk factors of poor prognosis in this heavily treated population include repetitive instances of cT1 and CIS, LVI, up-staging to cT1 and prostatic urethra involvement. LVI, or 2 or more of these risk factors should prompt serious consideration of abandoning further IVT in favor of RC.

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