Time Interval from Transurethral Resection of Bladder Tumor to Onset of BCG Induction Does Not Impact Therapeutic Response: Implications During Times of Impaired Access to Healthcare

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Introduction

Intravesical immunotherapy with BCG after TUR is the mainstay of treatment for patients with NMIBC. According to the AUA and EAU Guidelines, patients with intermediate- or high-risk tumors should undergo a complete induction course of intravesical BCG [1,2].

Exhaustive efforts have investigated the impact of a number of variables on BCG response and tolerability, including BCG strain [3], dosing [4], administration schedule [4,5], and combination treatments [6,7]. The first dose of induction BCG is traditionally administered after a 14-28 day period of recovery to allow for bladder TUR defect re-epithelialization and prevent adverse effects associated with systemic BCG absorption. The timing of induction BCG administration after TUR has never been formally studied, and available guidelines do not inform this decision. **Herein, the timing of induction BCG administration after TUR is investigated with regards to efficacy and tolerability.**

Methods

Patients diagnosed with NMIBC treated with complete induction BCG at our institution between 2000-2018 were included. Patients were stratified if they received 'adequate' BCG therapy according to the definition proposed by the US FDA [8,9].

Patients were stratified based on time from most recent TUR (index TUR or reTUR, if applicable) to first dose of induction BCG based on three time cutoff points:

(1) < or ≥ 3 weeks
(2) ≤ or > median
(3) Quartile
(4) Continuous variable

The primary outcome was RFS and PFS (any stage progression). Descriptive statistics were used to summarized the data by study group. Pearson's chi-squared, Wilcoxon's rank sum, and Kruskal-Wallis tests were used to compare the study groups and the KM product limit method was used to estimate median survival outcomes. Log-rank tests were used to determine differences in the survival outcomes between groups.

Results

Table 1. Descriptive statistics for patients treated with adequate BCG stratified by time from TUR to induction BCG <3 weeks vs. ≥3.

	<3 weeks (N=213)	≥3 weeks (N=329)	P-value
Age, median years (IQR)	69 (62-76)	68 (60-75)	0.229
Gender			
Male	165 (77.5%)	267 (81.2%)	0.297
Female	48 (22.5%)	62 (18.8%)	
Smoker			
Never	68 (31.9%)	102 (31.1%)	0.840
Current/Past	145 (68.1%)	226 (68.9%)	
Prior BCG	14 (6.6%)	31 (9.4%)	0.240
Underwent restaging TUR	129 (60.6%)	205 (62.7%)	0.619
Grade			
Low	24 (11.3%)	48 (14.7%)	0.254
High	189 (88.7%)	279 (85.3%)	
Primary stage			
CIS	14 (6.6%)	23 (7.0%)	0.180
Ta	90 (42.3%)	163 (49.9%)	
T1	109 (51.2%)	141 (43.1%)	
Tumor Size (cm), median (IQR)	3.0 (2.0-4.0)	3.0 (2.0-3.0)	0.489
Focality			
Solitary	83 (39.2%)	149 (45.3%)	0.159
Multifocal	129 (60.9%)	180 (54.7%)	
LVI	3 (1.4%)	4 (1.2%)	0.999
Variant histology	8 (3.9%)	13 (4.0%)	0.927
Concomitant CIS	76 (35.7%)	99 (30.1%)	0.174
Prostatic urethral involvement	14 (6.8%)	12 (3.8%)	0.129
Perioperative Chemotherapy	35 (16.9%)	38 (11.8%)	0.094
AUA Risk Category			
Low	10 (4.7%)	10 (3.0%)	0.018
Intermediate	29 (13.6%)	76 (23.1%)	
High	174 (81.7%)	243 (73.9%)	
BCG intolerance	20 (10.2%)	26 (8.4%)	0.507
Recurrence, any grade	87 (40.9%)	114 (34.7%)	0.145
Recurrence			
All	87 (40.9%)	114 (34.7%)	0.145
pTis	4/14 (28.6%)	8/23 (34.8%)	1.000
pTa	34/90 (37.8%)	58/165 (35.2%)	0.676
pT1	49/109 (45.0%)	48/141 (34.0%)	0.079
pTa-1 (+) CIS	29/62 (46.8%)	28/76 (36.7%)	0.239
pTa-1 (-) CIS	55/137 (40.1%)	78/230 (33.9%)	0.230
Low Grade	8/24 (33.3%)	20/50 (40.0%)	0.580
High Grade	79/189 (41.8%)	94/279 (33.7%)	0.075
BCG unresponsive	44 (20.9%)	53 (16.2%)	0.171
Progression, any stage	31 (14.6%)	32 (9.7%)	0.087
Progression to MIBC or distant metastasis	20 (9.4%)	23 (7.0%)	0.315
Radical Cystectomy	31 (14.6%)	38 (11.6%)	0.302

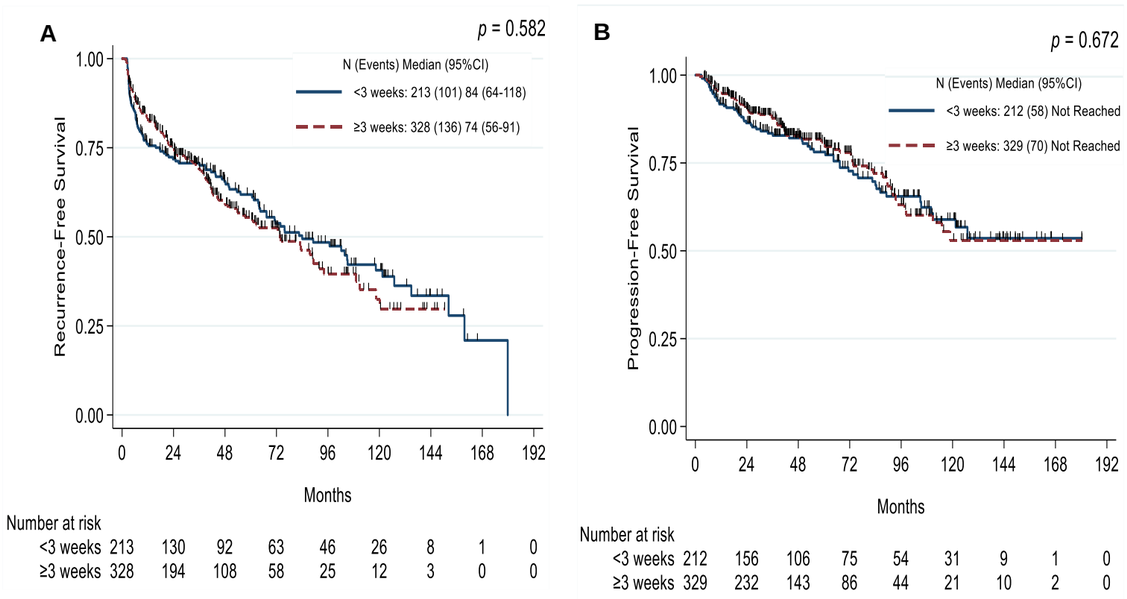

Figure 1. Kaplan-Meier survival curves for recurrence-free (A) and progression-free (B) survival in patients who received adequate BCG. Progression defined as any pT stage migration. Patients are stratified by time to BCG <3 weeks vs. ≥3 weeks.

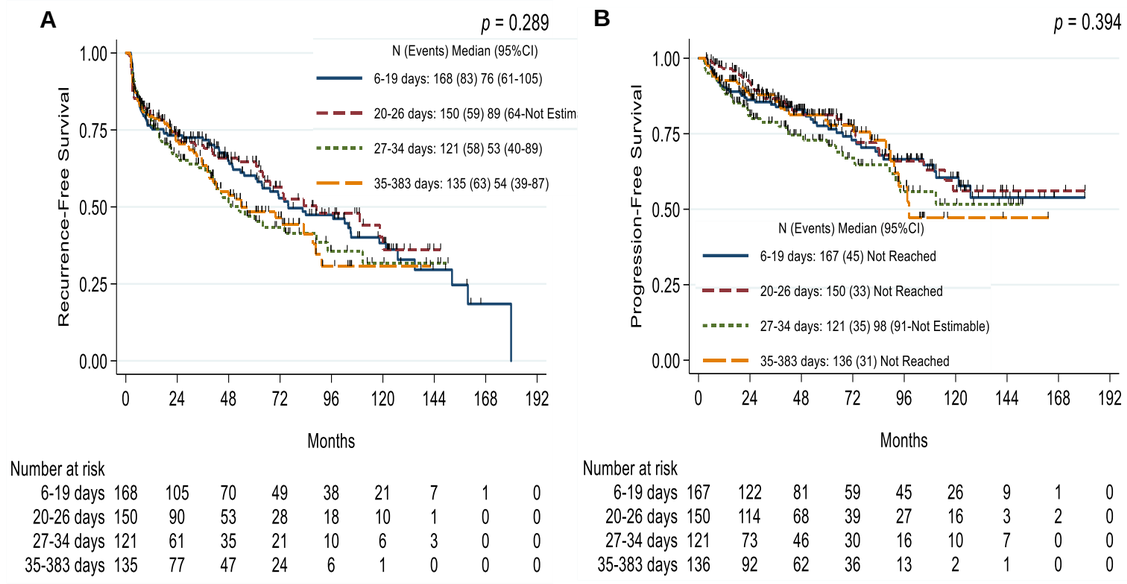

Figure 2. Kaplan-Meier survival curves for recurrence-free (A) and progression-free (B) survival in patients managed with at least induction BCG stratified by quartile.

Conclusions

- **In patients who received adequate BCG, there exists no significant difference in recurrence, BCG unresponsive disease, stage progression, or tolerability of BCG when administered in an early vs. delayed fashion after TUR, *stratified over multiple time cutoff points*.**
- **These data support the safety of early administration of BCG in appropriately selected patients, but also indicate that delays in induction therapy do not significantly affect therapeutic response.**
- **These data have implications during times of limited healthcare access, including the ongoing COVID-19 pandemic.**

References

[1] Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. Eur Urol. 2019;76:639-57.
[2] Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. 2016;196:1021-9.
[3] Boehm BE, Cornell JE, Wang H, Mukherjee N, Oppenheimer JS, Svatek RS. Efficacy of bacillus Calmette-Guérin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis. J Urol. 2017;198:503-10.
[4] Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. 2013;63:462-72.
[5] Martínez-Piñeiro L, Portillo JA, Fernández JM, Zabala JA, Cadierno I, Moyano JL, et al. Maintenance Therapy with 3-monthly Bacillus Calmette-Guérin for 3 Years is Not Superior to Standard Induction Therapy in High-risk Non-muscle-invasive Urothelial Bladder Carcinoma: Final Results of Randomised CUETO Study 98013. Eur Urol. 2015;68:256-62.
[6] Huang D, Jin YH, Weng H, Huang Q, Zeng XT, Wang XH. Combination of Intravesical Bacille Calmette-Guérin and Chemotherapy vs. Bacille Calmette-Guérin Alone in Non-muscle Invasive Bladder Cancer: A Meta-Analysis. Front Oncol. 2019;9:121.
[7] Shepherd AR, Shepherd E, Brook NR. Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer. Cochrane Database Syst Rev. 2017;3:Cd012112.
[8] Kamat AM, Sylvester RJ, Böhle A, Palou J, Lamm DL, Brausi M, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol. 2016;34:1935-44.
[9] BCG-Unresponsive Non-muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry. FDA Maryland. 2018.