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Original Article

The influence of immunocompromised status on recurrence and progression free survival among nonmuscle invasive bladder cancers (NMIBCs) undergoing transurethral resection of bladder tumor (TURBT) and adjuvant intravesical bacillus Calmette Guerin (BCG): Analysis of USA insurance claim data

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Abstract

Introduction: Transurethral resection of the bladder tumor (TURBT) followed by intravesical Bacillus Calmette-Guérin (BCG) immunotherapy is a standard treatment for high-risk non muscle-invasive bladder cancer (NMIBC). However, due to potential risk of dissemination, current guidelines recommend caution when proposing BCG treatment in immunocompromised patients. Our aim was to assess the efficacy and safety of BCG treatment in immunocompromised patients.

Materials and Methods: Patients aged ≥18 with a diagnosis of bladder cancer (BC) who underwent BCG therapy in 2007-2021, were identified in the Merative™ Marketscan® Research Commercial and Medicare databases. Multivariable Cox proportion hazard regressions adjusted by relevant confounders were performed to investigate the influence of immunosuppression on the events associated with progression and recurrence of BC, both in the unmatched cohort and after 1:2 propensity score matching (PSM). Also, subgroup analysis on progression in patients without cancer other than BC was conducted.

Results: Immunocompromised and immunocompetent patients had similar rates of disseminated BCG infection after intravesical immunotherapy. However, immunocompromised patients had shorter progression-free survival and higher probability of progression (aHR: 1.23, 95% CI: 1.11−1.38), as well as shorter recurrence-free survival and a higher probability of recurrence (aHR: 1.13, 95% CI: 1.05−1.20). Similar significant associations were observed in the PSM cohort. A subgroup analysis of patients without any additional oncological diagnoses beyond BC confirmed a higher likelihood of progression in the immunocompromised group (aHR: 1.34, 95% CI: 1.15−1.56).

Conclusions: BCG immunotherapy is safe in immunocompromised patients. Nevertheless, the efficacy of intravesical BCG in these patients might be suboptimal thus advocating the need for appropriate counselling and a possible lower threshold to consider radical treatment.

Keywords: Bladder cancer (BC); Bacillus Calmette-Guérin (BCG); Immunodepression; Transurethral resection of bladder tumor (TURBT)

1. Introduction

Bladder cancer (BC) ranks as the ninth most prevalent malignancy globally and ranks sixth in the United States, with a 5-year relative survival rate of 77.9% in 2023 [1]. BC is nearly 3 times more frequent in males, and its age-standardized incidence rate is 17.7 per 100,000 individuals [2]. 75% of BC diagnoses present as Non Muscle Invasive Bladder Cancer (NMIBC) [3]. Radical Cystectomy (RC) is the standard treatment for localized Muscle-Invasive Bladder Cancer (MIBC), while NMIBC is more frequently managed conservatively. TURBT alone or followed by intravesical chemotherapy is the standard of care for low risk NMIBC at first presentation [4,5]. Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy is recommended by current guidelines in the case of an intermediate or high-risk NMIBC, as it is superior to either TURBT alone or TURBT and intravesical chemotherapy in the prevention of NMIBC recurrence [4,6]. Induction BCG instillations are administered in a well established 6-week schedule introduced by Morales et al [7]. To achieve optimal therapeutic efficacy, BCG is delivered in a maintenance schedule, and at least 1 year of maintenance BCG is required to obtain superiority of BCG over Mitomycin C (MMC) for recurrence and progression prevention [8,9]. Although the exact mechanism of action of Bacillus Calmette-Guérin (BCG) is not fully understood, the intravesical injection of this mycobacterial-based treatment is thought to exert its antitumor effect by stimulating an immune response and inflammation [10]. Given the immune-dependent mechanism of action of BCG therapy, it is plausible that immunocompromised patients and patients under immunomodulating therapy might experience lower response rates than their immunocompetent counterparts. Although usually well tolerated, both local and systemic BCG-related complications may occur following treatment [11]. Disseminated BCG infection is the most serious complication associated with BCG treatment, but is generally rare with an incidence <1% [12]. It is well accepted that immunocompromised patients should not receive live vaccines as they are at a higher risk of severe systemic viremia or bacteremia [13]. Despite that, only a few case reports have reported a higher risk of disseminated BCG infection with either intravesical BCG or BCG-vaccine for tuberculosis prevention [14,15]. Current guidelines recommend caution with BCG treatment in immunocompromised patients and Human Immunodeficiency Virus (HIV) infection is a relative contraindication [16]. Nevertheless, available research indicates that BCG treatment is relatively effective and safe for patients with immunomodulatory conditions, but the level of the evidence is generally low [17−20]. We feel that additional data is required to better define the efficacy and safety profile of BCG in patients with immunomodulatory conditions.

In order to assess the efficacy and safety of BCG treatment in immunocompromised patients we seek to provide further evidence to aid physicians and bolster future guidelines to safely exclude or include this heterogeneous population in BCG treatment protocols.

2. Materials and methods

2.1. Data source

This study was based on administrative insurance claims data from the Merative™ Marketscan® Research

Commercial and Medicare databases [21]. They consist of individual-level, de-identified, demographic data, diagnoses, procedures, overall health-related costs, pharmacy billing claims, and treatments allowing for longitudinal tracking of patients. International Classification of Disease Ninth and Tenth Revisions, Clinical Modification and Procedure Coding System (ICD-9-CM, ICD-10-CM, ICD-10-PCS), Current Procedural Terminology (CPT), and Healthcare Procedure Coding System (HCPCS) codes were used to identify the cohort of interest, treatments, and comorbidities. This method has been used in other studies [22,23] and given the de-identified information, the study was deemed exempt from informed consent requirements by the Stanford University Medical Center Institutional Review Board. Data for this study was accessed using the Stanford Center for Population Health Sciences (PHS) Data Core. The PHS Data Core is supported by a National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1TR003142) and from Internal Stanford funding.

2.2. Patients

Using the ICD-9/10-CM, ICD-10-PCS, and CPT diagnosis/treatment codes for BC and TURBT, data of patients at least 18 years old who underwent TURBT followed by BCG immunotherapy (first exposure up to 3 months after TURBT) for BC between 2007 and 2021 was evaluated to create the cohort of interest. Patients selected for analysis were enrolled in the database for at least 3 months before and 3 months following primary TURBT. Time of the first TURBT was set as the index date for further assessment. Within this cohort, diagnostic and procedural codes associated with immunosuppression were identified and reviewed in order to ensure the appropriate selection of patients. Immunosuppression was designated in a patient cohort after solid organ transplantation (kidney, lung, heart, liver, or pancreas), HIV positive status, and in certain autoimmune diseases (Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis, sarcoidosis, systemic scleroderma, Sjogren syndrome, and systemic lupus erythematosus) that were present before the initial TURBT.

The study cohort was stratified into 2 groups based on the presence of immunosuppression ("immunocompromised" vs. "immunocompetent"). For each patient, sociodemographic data, including age at the index date, gender, US region, and insurance status, were initially recorded. Charlson Comorbidity Index (CCI) was calculated according to Charlson and colleagues [24] and adapted according to Deyo and colleagues [25]. Also, immunomodulatory conditions, BC-specific comorbidity prevalence, additional interventions, and the occurrence of disseminated BCG infection were recorded. Treatment characteristics included tumor size (Small: $\leq$ 2 cm; Medium: 2 - 5 cm; Large: > 5 cm), TURBT procedural data (number of TURBTs, type of TURBT) and the need for repeated treatment. Two types of TURBT procedures were distinguished: "minor" and "major". Minor TURBT included procedures limited to cystoscopy with biopsy and/or fulguration, while major procedures were more involved and required resection. A flow chart diagram summarizing the analytical steps for the data analysis and inclusion/exclusion criteria was shown in Supplementary Fig. 1 and a detailed list of implemented ICD-9/10, CPT, and HCPCS codes was presented in Supplementary Table 1.

2.3. Outcome ascertainment

Our primary aim was to compare the safety and efficacy of adjuvant BCG treatment in immunocompromised patients with a BC diagnosis. In order to achieve this objective, we assessed the rates of disseminated BCG infections and evaluated the risk of events suggesting progression and recurrence of BC in immunocompromised and immunocompetent groups. As the insurance claims data do not allow for direct extraction of survival outcomes, we established specific events and their timeframes that serve as surrogates for progression and recurrence of BC. Progression was designated in patients that underwent radical cystectomy (RC), systemic chemotherapy (SC), immune checkpoint inhibitor therapy (ICI), or pelvic radiotherapy (RT) at least 3 months after the initial TURBT. Recurrence was designated in patients without progression that underwent subsequent TURBT >90 days after the index date.

2.4. Statistical analysis

Continuous variables were reported using means $\pm$ standard deviations (SDs) or medians and interquartile ranges (IQR). Categorical variables were presented as counts and percentages (%). The statistical analysis involved using the Chi-square test for comparison of categorical data, the Student's t-test for age, and the Wilcoxon rank-sum test for other continuous variables all stratified by immunosuppression status. Kaplan-Meier curves were used to explore the univariate effect of immunosuppression on the probability of progression and recurrence over time. Multivariable adjusted Cox proportional hazards regression models were implemented to ascertain the risk of progression and recurrence. Also, subgroup analyses for the risk of progression in patients without any additional oncological diagnoses beyond BC were performed as per sensitivity analyses. All regressions were adjusted by clinically relevant variables, such as age at the time of the index surgery (10 years increase), sex, CCI (2−4 vs. 0−1; ≥5 vs. 0−1), tumor size (large vs. small; medium vs. small; unknown vs. small), and BCG therapy duration (6−12 mo. vs. <6 mo.; >12 mo. vs. <6 mo.). All analyses were 2-sided with, $P < 0.05$ considered significant, and performed using statistical software SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study cohort

Baseline patient characteristics, as well as clinical, surgical, and tumor data of the entire cohort stratified into "immunocompromised" and "immunocompetent" groups are presented in Table 1. The present study included a total of 20,458 patients with a BC diagnosis, who underwent TURBT followed by BCG immunotherapy. Of these, 1,277 (6.2%) patients were associated with preoperative immunomodulating conditions. Male gender was largely predominant in both groups (73.0% immunocompromised, 80.6% immunocompetent). Of note, median age (71 y.o. immunocompromised vs. 68 y.o. immunocompetent) and follow-up period (2.0 years immunocompromised vs. 2.4 years immunocompetent) in both groups were similar. Importantly, immunocompromised patients had significantly higher median CCI scores (4 [IQR: 2−6]), when compared to the immunocompetent group (2 [IQR: 2−4]) ($P < 0.0001$). Additionally, the immunosuppressed had significantly higher rates of each specific comorbidities. Nevertheless, both groups presented similar rates of disseminated BCG infection after intravesical immunotherapy. In terms of conditions causing immunomodulation, autoimmune diseases accounted for 96.6% of the cases, while tumor, procedural, and BCG immunotherapy characteristics were comparable between the groups. To adjust for potential confounders, a 1:2 Propensity Score Matching (PSM) on age, gender, smoking, obesity and CCI group (0-1, 2-4, 5+) between the immunocompromised and immunocompetent cohorts was performed. Supplementary Table 2 presents baseline characteristics of the matched populations.

3.2. Outcomes

Descriptive statistics regarding the surrogates for recurrence and progression in "immunocompromised" and "immunocompetent" patient groups are shown in Table 2. 759 (59.4%) immunocompromised and 11,314 (59.0%) immunocompetent patients underwent TURBT over 90 days after the index date. We did not observe any evident differences between the groups in terms of repeated TURBT characteristics, nor in BCG failure parameters. Overall, events suggesting progression were significantly more common in the immunosuppressed group ($n = 357$, 28.0%), than in the immunocompetent group ($n = 4647$, 24.2%)($P = 0.0027$). SC was administered more frequently in the immunocompromised patients (22.9% vs. 18.6%, $P = 0.0002$), while there were no significant differences in the rates of RC, RT, and ICI implementation between the groups ($P > 0.05$). In the PSM cohorts, rates of SC were higher in immunocompromised patients (22.9% vs. 20.1%, $P = 0.044$), but when summed with other events suggesting progression, the difference did not reach the level of significance (28% vs. 25.2%, $P = 0.0657$) (Supplementary Table 3).

3.2.1. Risk of surrogate for disease progression

The Kaplan-Meier curve, used to evaluate the univariate probability of BC progression over time, demonstrated that immunocompromised patients experienced significantly shorter progression-free survival and a markedly higher probability of disease progression compared to immunocompetent patients (p<0.0001) (Fig. 1A). These findings were further supported by multivariate analysis, which accounted for potential confounders and demonstrated that immunocompromised individuals had a 23% higher risk of progression compared to their immunocompetent counterparts (aHR: 1.23, 95% CI: 1.11 - 1.38, p=0.0002).

When stratified by treatment type, the association between immunosuppression and increased progression risk persisted for patients treated with SC or ICI, with a 31% higher risk of progression in the immunocompromised group (aHR: 1.31, 95% CI: 1.16 - 1.47, p<0.0001) (Fig. 1B). Conversely, in patients who underwent RC or received RT, no statistically significant difference in progression probability was observed between the immunocompromised and immunocompetent groups in either univariate (p = 0.5246) or multivariate analyses (aHR: 1.05, 95% CI: 0.87 - 1.26, p=0.635) (Fig. 1C). Similar results were obtained from the PSM analysis, where immunocompromised patients demonstrated significantly higher risk of overall progression (aHR: 1.20, 95% CI: 1.05 - 1.36, p=0.0066) and progression to SC or ICI (aHR: 1.26, 95% CI: 1.09- 1.45, p=0.0015), but not to RC or RT (aHR: 1.06, 95% CI: 0.85- 1.32, p=0.5966) (Supplementary Fig. 2).

Additionally, a subgroup analysis focused on patients without any additional oncological diagnoses beyond BC reaffirmed the higher progression probability among immunocompromised individuals (p < 0.0001). In this subgroup, the multivariate analysis revealed an even greater risk, with immunosuppressed patients experiencing a 34% increased likelihood of progression compared to their immunocompetent peers (aHR: 1.34, 95% CI: 1.15 - 1.56, p=0.0002) (Supplementary Fig. 3).

3.2.2. Risk of surrogate interventions for disease recurrence

Analysis of the likelihood of recurrence over time revealed that patients in the immunocompromised group experienced significantly shorter durations without recurrence and a higher probability of disease recurrence compared to the immunocompetent individuals. This association was evident in the Kaplan-Meier survival analysis ($P = 0.0106$) and was further confirmed in multivariate analyses, which demonstrated a 13% higher risk of recurrence in the immunocompromised group after adjusting for potential confounders (aHR: 1.13, 95% CI, 1.05−1.20, $P = 0.0005$) (Fig. 2A).

Table 1
Baseline patient demographic, clinical and hospital characteristics of the final cohort of the study according to the immunosuppression status (immunocompromised vs. immunocompetent).

	Immunocompromised	Immunocompetent	*P*-value
Number, *n* (%)	1,277 (6.2)	19,181 (93.8)	
Age, median (IQR)	71 (63−79)	68 (60−78)	< 0.0001
Age, quartiles (Q), *n* (%)			< 0.0001
Q1	246 (19.3)	4,807 (25.1)	
Q2	299 (23.4)	5,001 (26.1)	
Q3	346 (27.1)	4,457 (23.2)	
Q4	386 (30.2)	4,916 (25.6)	
Follow-up, years, median (IQR)	2.0 (0.9−4.0)	2.4 (1.1−4.5)	< 0.0001
Gender, *n* (%)			< 0.0001
Male	932 (73.0)	15,457 (80.6)	
Female	345 (27.0)	3,724 (19.4)	
US region, *n* (%)			0.0001
Northeast	353 (27.6)	4,423 (23.1)	
North central	363 (28.4)	5,225 (27.2)	
South	385 (30.2)	6,360 (33.2)	
West	165 (12.9)	2,829 (14.8)	
Unknown	11 (0.9)	344 (1.8)	
Insurance type, *n* (%)			< 0.0001
Comprehensive	348 (27.3)	4,525 (23.6)	
HMO	111 (8.7)	2,087 (10.9)	
PPO	664 (52)	9,615 (50.1)	
Other	154 (12.1)	2,954 (15.4)	
CCI score, median (IQR)	4 (2−6)	2 (2−4)	< 0.0001
CCI score, *n* (%)			< 0.0001
0−1	167 (13.1)	4,335 (22.6)	
2−4	585 (45.8)	10,999 (57.3)	
5+	525 (41.1)	3,847 (20.1)	
Prevalent comorbidities, *n* (%)			
Obesity	199 (15.6)	1,812 (9.5)	< 0.0001
Diabetes	455 (35.6)	5,399 (28.2)	< 0.0001
Hypertension	995 (77.9)	12,283 (64.0)	< 0.0001
Chronic kidney disease ≥3	289 (22.6)	2,411 (12.6)	< 0.0001
Smoking	278 (21.8)	2,947 (15.4)	< 0.0001
Infection	642 (50.3)	5,089 (26.5)	< 0.0001
Disseminated BCG infection, *n* (%)	<11	83 (0.4)	
Condition causing immunomodulation, *n* (%)			NA
Organ transplant	28 (2.2)	NA	
Autoimmune disease	1233 (96.6)	NA	
HIV	22 (1.7)	NA	
Tumor size, *n* (%)			0.32
Small (≤ 2 cm)	147 (11.5)	2,458 (12.8)	
Medium (2−5 cm)	495 (38.8)	7,055 (36.8)	
Large (> 5 cm)	506 (39.6)	7,815 (40.7)	
Minor TURBT, *n* (%)	848 (66.4)	12,465 (65)	0.30
Re-TURBT (<90 days from TURBT), *n* (%)	428 (33.5)	5,916 (30.8)	0.0455
Time from TURBT to re-TURBT, weeks, median (IQR)	4.3 (2.3−6.1)	4.1 (2.1−6.1)	0.17
Time from TURBT to intravesical BCG, months, median (IQR)	5.2 (3.7−7.6)	5.1 (3.7−7.5)	0.09
Duration of BCG exposure, months, median (IQR)	3.2 (1.2−12.0)	3.0 (1.2−12.5)	0.42
Duration of BCG exposure, months, n (%)			0.78
<6 months	772 (60.5)	11503 (60)	
6−12 months	185 (14.5)	2708 (14.1)	
>12 months	320 (25.1)	4970 (25.9)	
Concomitant UTUC, *n* (%)	26 (2.0)	386 (2.0)	0.95
RNU before TURBT, *n* (%)	33 (2.6)	242 (1.3)	< 0.0001
Time to RNU before TURBT, months, median (IQR)	7.4 (5.1−10.0)	7.0 (4.4−13.5)	0.93
RNU after TURBT, *n* (%)	17 (1.3)	352 (1.8)	0.19
Time to RNU after TURBT, months, median (IQR)	8.0 (1.9−28.4)	15.3 (5.9−35.1)	0.15

BCG = Bacillus Calmette-Guerin; CCI = Charlson comorbidity index; HMO = health maintanance organization; HIV = human immunodeficency virus; IQR = interquartile range; PPO = preferred provider organization; RNU = radical nephroureterectomy; TURBT = trasuretrhal resection of bladder tumor; UTUC = upper tract urothelial carcinoma; US = United States

Table 2
Descriptive statistics regarding the surrogates for recurrence and progression in "immunocompromised" and "immunocompetent" groups.

	Immunocompromised	Immunocompetent	*P*-value
Patients who underwent TURBT >90 days from index date, *n* (%)	759 (59.4)	11,314 (59)	0.75
Additional TURBT after index TURBT (>90 days), *n* (%)			0.33
0	518 (40.6)	7,867 (41)	
1	336 (26.3)	5,187 (27)	
2	203 (15.9)	2,675 (14)	
3	84 (6.6)	1,304 (6.8)	
4	58 (4.5)	790 (4.1)	
5+	78 (6.1)	1,358 (7.1)	
Time from index TURBT (>90 days) to first new TURBT, months, (IQR)	5.3 (4.2−8.5) (*n* = 759)	5.4 (4.2 - 9.1) (*n* = 11,314)	0.75
Time from index TURBT (>90 days) to second new TURBT, months, (IQR)	11.1 (7.5−19.0) (*n* = 423)	11.3 (7.9 - 19.8) (*n* = 6,127)	0.27
Time from first BCG exposure to first new TURBT (i.e., time to first rec.), classes, *n* (%)			0.23
<3 months (BCG refractory)	287 (37.0)	4,359 (37.8)	
3−12 months (BCG unresponsive)	385 (49.7)	5,431 (47.0)	
>12 months (BCG relapsing)	103 (13.3)	1,757 (15.2)	
RC after index TURBT (>90 days), *n* (%)	67 (5.3)	1,097 (5.7)	0.48
Time from index TURBT to RC, months, median (IQR)	11.5 (7.4−18.7)	11.7 (7.0 - 22.7)	0.48
SC after index TURBT (>90 days), *n* (%)	292 (22.9)	3576 (18.6)	0.0002
Time from index TURBT to SC, months, median (IQR)	7.4 (1.6−20.8)	8.8 (1.9−26.2)	0.07
ICI after index TURBT (>90 days), *n* (%)	43 (3.4)	511 (2.7)	0.13
Time from index TURBT to ICI, months, median (IQR)	3.0 (1.4−23.4)	6.4 (1.5−25.5)	0.47
RT after index TURBT (>90 days), *n* (%)	64 (5.0)	873 (4.6)	0.45
Time from index TURBT to ICI, months, median (IQR)	17.1 (10.5−29.2)	22.1 (11.0−42.0)	0.03
Total Progression (RC+SC+ICI+RT), *n* (%)	357 (28.0)	4647 (24.2)	0.0027
Time from index TURBT to progression, months, median (IQR)	6.9 (1.6−17.6)	8.4 (2.2−23.3)	0.01

BCG = Bacillus Calmette-Guerin; ICI = immune checkpoint inhibitor; IQR = interquartile range; RC = radical cystectomy; RT = radiotherapy; SC = systemic chemotherapy; TURBT = transurethral resection of bladder tumor.

Importantly, these findings were consistent across subgroups of patients stratified by recurrence patterns. In patients who experienced only a single recurrence, the immunocompromised group showed a similar 13% increased risk of recurrence compared to the immunocompetent group (aHR: 1.13, 95% CI: 1.01−1.25, $P = 0.0275$) (Fig. 2B). Similarly, among patients with multiple recurrences, the immunocompromised cohort exhibited an even higher risk, with a 16% increased likelihood of recurrence (aHR: 1.16, 95% CI: 1.06−1.27, $P = 0.0008$) (Fig. 2C). Results from the PSM analyses confirmed the increased risk of overall recurrence (aHR: 1.12, 95% CI: 1.04−1.22, $P = 0.0044$), single recurrence (aHR: 1.16, 95% CI: 1.02−1.31, $P = 0.0205$) and multiple recurrences (aHR: 1.15, 95% CI: 1.03−1.27, $P = 0.0093$) of the immunocompromised cohort (Supplementary Fig. 4).

4. Discussion

A precise characterization of the safety and effectiveness profiles of BCG treatment for NMIBC in immunomodulated patients remains difficult. Immunosuppression comprises a wide spectrum of conditions, with different underlying pathophysiological mechanisms and varying degrees of severity. Theoretically, patients with a weaker immune system should be at a higher risk of complications caused by potential systemic dissemination of the mycobacterium, as well as treatment failure given the hypothesized mechanism of action of BCG treatment. Although data from previous research has clearly shown a higher risk of complications after intradermal injection of the BCG vaccine for Tuberculosis (TB) prevention in immunocompromised hosts [26−29], research exploring safety and feasibility of intravesical BCG for BC recurrence prevention has failed to reach the same conclusions [17−19,30,31]. In addition, due to small sample sizes, no available study is currently able to effectively compare subgroups of immunocompromised patients. In this scenario, while current guidelines do not contraindicate BCG use in immunocompromised populations, the strength of the evidence supporting its feasibility remains low. A recent retrospective study on a total of 4277 patients with a diagnosis of NMIBC (606, 14.2% immunocompromised) addressed this issue [32]. In a Surveillance, Epidemiology, and End Results (SEER) − Medicare analysis, any solid-organ transplantation, HIV, and autoimmune conditions defined their immunomodulated population. They found no differences regarding progression to systemic therapy or radical cystectomy, cancer-specific death (p = 0.18), and 5-year total bladder cancer progression (p = 0.30) between the groups. The rates of disseminated BCG infection were low, comparable between the 2 groups and similar to that of the available literature. The authors concluded that BCG treatment can be offered to immunocompromised patients with the

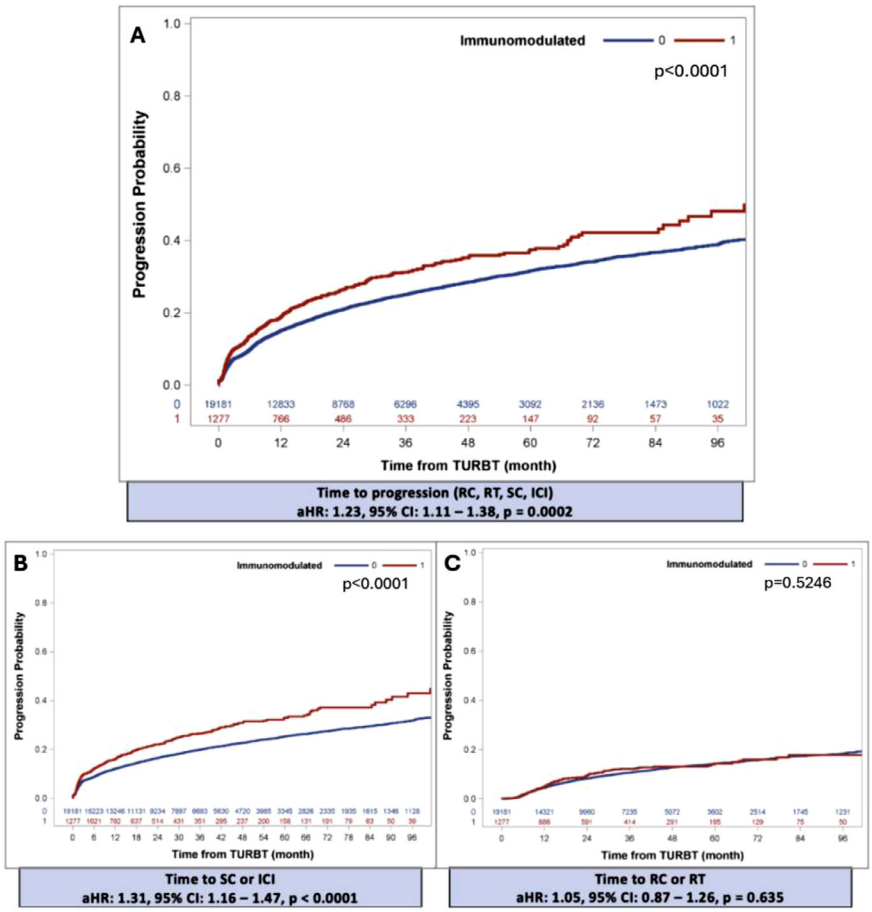

Fig. 1. Kaplan-Meier Curves and adjusted Hazard Ratios depicting the risk of BC progression in immunomodulated and immunocompetent patients. RC, RT, SC, and ICI (**A**), SC or ICI (**B**) and RC or RT (**C**) at least 3 months after the initial TURBT defined progression. **TURBT**: Transurethral Resection of Bladder Tumor; **RC**: Radical Cystectomy; **RT**: Radiotherapy; **SC**: Systemic Chemotherapy; **ICI**: Immune Checkpoint Inhibitor; **aHR**: adjusted Hazard Ratio; **95%CI**: 95% Confidence Interval.

same safety and efficacy profile as the general population [32].

Our present study to our knowledge, is the largest analysis available exploring the impact of immunomodulation on BCG treatment safety and efficacy. Our large sample size is a strength of our study and has allowed us to reach findings not previously highlighted by smaller cohorts with shorter follow up. We find that patients in the immunocompromised group had a shorter 1 to 5 years overall PFS, with a significantly lower median progression time (116 vs. 153 months, $P < 0.001$). Chemotherapy utilization, ICI administration, RT, and RC were used as surrogates for progression. After stratification on the secondary treatment received, immunocompromised patients were found to be more likely to receive chemotherapy or ICI, but there was no difference in RC or RT rates. In the case of progression, immunocompromised patients were more likely to be managed conservatively than their immunocompetent counterparts. The higher median CCI (including higher rates if diabetes, hypertension, IRC, and obesity) and age could partially explain the higher chemotherapy and ICI rates, as they likely influenced decision making, but cannot explain the lower overall PFS. Regarding ICI, it is important to mention that, despite there not being an absolut contraindication for their use in transplanted patients and patients under immunomodulating therapies, extreme caution is advised is these populations. It is safe to presume that, in the case of distant progression, these patients were more likely to be managed with SC alone and the fact that a portion of the immunocompromised group recived ICI is a reflection of the heterogeinity of the population. Moreover, we found shorter 1 to 5 years RFS ($P = 0.01$) with a lower median time to recurrence in the immunocompromised group (4.6 vs. 5.3 months, respectively for immunocompromised and immunocompetent patients). Finally, we found no significant difference in terms of serious complication rates between the 2 groups (both <1%), and the reported rates of disseminated BCG infection in the immunocompromised group are comparable to those described in the available literature for the general population. As described, we found significant differences in terms of recurrence and progression rates, PFS, and RFS.

Our series demonstrates that primary NMIBC patients affected by immunomodulating conditions and who

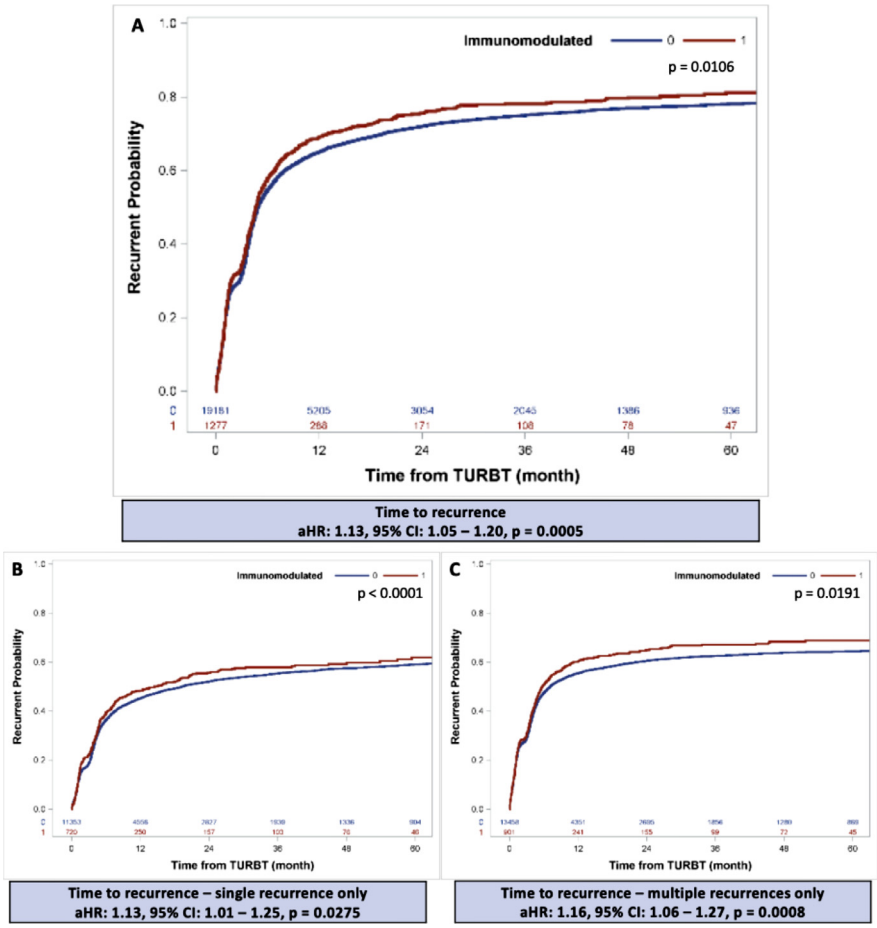

Fig. 2. Kaplan-Meier Curves and adjusted Hazard Ratios depicting the risk of BC recurrence in immunomodulated and immunocompetent patients. One or more TURBT at least 3 months after the initial TURBT defined recurrence. Data are stratified in any recurrence (**A**), only single recurrences (**B**), and only mulitple recurrences (**C**). aHR = adjusted hazard ratio; TURBT = transurethral resection of bladder tumor; 95% CI = 95% confidence interval.

undergo conservative BC interventions are associated with significantly higher recurrence and most importantly, inferior survival outcomes due to progression. While on 1 hand, we may assume that most of the immunocompromised patients still benefited from BCG administration, at the same time our findings highlight a necessity for adequate counselling and prompt offering of upfront radical surgery if appropriate. In this scenario, given also the comparable rates of complications, while our results do not provide reason to exclude patients with immunomodulatory conditions from BCG treatment protocols, a prioritization of upfront radical treatment seems to be the appropriate pathway for patients fit for undergoing RC.

We acknowledge several limitations of our research. As this is a retrospective study it is subject to the limitations of that research approach. Also, we extracted data from insurance claims using codes which could be subject to misclassification. Moreover, while the cohort includes only patients who underwent BCG treatment, thus mostly only intermediate and high risk cases, specific data on tumor stage and grade was not availble in our data sources. In addition, we acknowledge that immunomodulation is a condition with a wide spectrum of severity, which could confound our analysis.

5. Conclusions

Results from our large cohort suggest that intravesical BCG is a safe therapeutic option for immunocompromised patients, as the rate of serious adverse effects was similar to that of the immunocompetent population. Nonetheless, patients with immunomodulatory conditions experience a higher rate of recurrence and progression compared to their immunocompetent counterparts. In light of this, clinicians should consider having a lower threshold for the radical treatment options in this specific population.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Francesco Del Giudice: Writing − review & editing, Methodology, Conceptualization. **Valerio Santarelli:** Software, Methodology, Formal analysis. **Jan Łaszkiewicz:** Writing − original draft, Methodology, Formal analysis. **Shufeng Li:** Software, Resources, Project administration, Methodology, Formal analysis. **Wojciech Krajewski:** Data curation. **Łukasz Nowak:** Data curation. **Tomasz Szydełko:** Data curation. **Matteo Ferro:** Data curation. **Bernardo Rocco:** Writing − original draft, Project administration. **Felice Crocetto:** Writing − original draft. **Biagio Barone:** Writing − original draft. **Carlo Buonerba:** Visualization. **Roberto Contieri:** Visualization. **Renate Pichler:** Visualization. **José Daniel Subiela:** Investigation. **Benjamin Pradere:** Writing − review & editing. **Marco Moschini:** Validation. **Andrea Mari:** Supervision. **Keiichiro Mori:** Visualization. **Francesco Soria:** Writing − review & editing. **Roman Mayr:** Validation. **Jung Ki Jo:** Investigation. **Mohamed Gad:** Validation. **Ben Challacombe:** Investigation. **Yasmin Abu-Ghanem:** Writing − original draft. **Elsie Mensah:** Writing − original draft. **Rajesh Nair:** Supervision, Conceptualization. **Ramesh Thurairaja:** Supervision, Conceptualization. **Muhammad Shamim Khan:** Supervision, Conceptualization. **Benjamin I. Chung:** Writing − review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2025.07.005.

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