DOI: 10.4081/aiua.2023.11380

ORIGINAL PAPER

History of infantile BCG immunization did not predict lamina propria invasion and/or high-grade in patients with non-muscle invasive bladder cancer

Anastasia MacDonald [1], Vahid Mehrnoush [1], Asmaa Ismail [1], Livio Di Matteo [2], Ahmed Zakaria [1], Waleed Shabana [1], Ashraf Shaban [1], Mohammed Bassuony [1], Hazem Elmansy [1], Walid Shahrour [1], Owen Prowse [1], Ahmed Kotb [1]

[1] Northern Ontario School of Medicine, Thunder Bay, ON, Canada;
[2] Department of Economics, Lakehead University, Thunder Bay, ON, Canada.

Summary ***Objective: To evaluate the utility of infantile BCG vaccination history in predicting stage and grade of tumours in non-muscle invasive bladder cancer (NMIBC).***

Materials and methods: We retrospectively analyzed data from patients from a single center who were diagnosed with new NMIBC and underwent transurethral resection of bladder tumour (TURBT) between 2017 and 2022. We assessed BCG immunization status with various demographics and comorbidities, as well as tumour recurrence, progression, stage, and grade.

Results: A total of 188 patients met the inclusion criteria for our study. The mean age of patients at the time of diagnosis was significantly lower in those that had been immunized with BCG (71 ± 9) than those who had not (77 ± 10) (p < 0.0001). History of BCG immunization did not correlate with sex, history of diabetes mellitus (DM), prior history of intravesical BCG treatment, and tumour recurrence, progression, stage, and grade.

Conclusions: History of infantile BCG vaccination did not correlate with the depth of invasion and/or the grade in patients with non-muscle invasive bladder cancer. Patients that received infantile BCG vaccination were significantly younger at the time of diagnosis of NMIBC.

KEY WORDS: BCG; Non-muscle invasive bladder cancer (NMIBT); Bladder cancer.

Submitted 11 April 2023; Accepted 26 May 2023

INTRODUCTION

Bladder cancer is the tenth most common malignancy worldwide, with increasing incidence, particularly in developed nations (1). Approximately 80% of bladder cancers arise in individuals aged 65 or older with the mean age being 73 years old (2, 3). This is thought to reflect a disease process requiring many decades of development following exposure to risk factors, such as tobacco (2). *Urothelial carcinoma* (UC) accounts for 90% of bladder cancers (4).

At the time of presentation, approximately 70% of UC cases are *non-muscle invasive* (NMIBC), while 30% are *muscle invasive* (MIBC) (4). Initial management of NMIBC is *transurethral resection of bladder tumor* (TURBT) (4). For those with NMIBC who are deemed to be at high risk for progression, intravesical *Bacillus Calmette-Guérin* (BCG) is the gold standard adjuvant therapy (4).

The use of intravesical instillation of BCG for high risk NMIBC demonstrates a role for immunotherapy in UC. BCG, originally used as a vaccine against *tuberculosis* (TB), contains live-attenuated *Mycobacterium bovis* (4).

The specific mechanism of BCG in NMIBC treatment continues to be studied, however, its role is attributed to both local immunological efforts and systemic immune responses (5). Some work has suggested that BCG vaccination may be associated with a lower rate of bladder cancer incidence (6). Despite this relationship, research on BCG immunization as a possible predictive factor in NMIBC has been limited. In the present study, we evaluated the relationship between history of infantile BCG vaccination with the depth of invasion and the grade in patients with NMIBC.

METHODS

Data were retrospectively collected between 2017 and 2022. Inclusion criteria included all patients with a new diagnosis of NMIBC at the *Thunder Bay Regional Health Sciences Centre* (TBRHSC), for whom complete clinical, lab, and pathological data could be retrieved. Data collected included the history of infantile BCG as well as the patients' age, sex, comorbid status, CBC, vaccination, history of intravesical BCG instillation, pathological data, recurrence, and progression. Vaccination status was correlated with these variables. Institutional ethical approval was obtained from the TBRHSC research ethics board (RP-741). Correlations between continuous variables were done using Student's t-test. Categorical variables were compared using Fisher Exact test. A p-value of < 0.05 was used to define significance.

RESULTS

A total of 188 patients met the inclusion criteria for our study. No patients were lost to follow up. The mean follow-up time was 26 ± 7 months. Of the 188 individuals meeting the eligibility criteria, 113 individuals had received the infantile BCG immunization and 75 did not.

A statistically significant difference was identified between the age of individuals who had received the immunization and those who did not ($p < 0.0001$). The mean age at the time of diagnosis for those immunized was 71 ± 9 years, and 77 ± 10 in the non-immunized group. There was no statistically significant difference found between immunization status and other patient characteristics including sex, history of *diabetes mellitus* (DM), or history of intravesical BCG treatment. History of immunization did not correspond with tumour recurrence, progression, stage, or grade in this population.
The results are summarized in Table 1.

Table 1.
Correlation of clinical and tumour data with history of infantile BCG immunization.

		No infantile BCG	Infantile BCG	P value
Age (mean + SD)		77 + 10	71 + 9	0.0001
Sex	Males	60	77	0.09
	Females	15	36	
Recurrence	No	34	57	0.5
	Yes	41	56	
Progression	No	72	108	1
	Yes	3	5	
Intravesical BCG	No	44	68	0.9
	Yes	31	45	
DM	No	61	86	0.5
	Yes	14	27	
Stage	Ta	58	86	1
	T1	17	27	
Grade	Low	54	81	1
	High	21	32	

SD: standard deviation.
BCG: Bacillus Calmette-Guérin.
DM: Diabetes Mellitus.

Discussion

Studies assessing the relationship between NMIBC and BCG immunization have been limited. One scoping literature review identified a 35-37% lower age-standardized rate of bladder cancer incidence in individuals with BCG immunizations, suggesting an association between the two (6).
We demonstrated that BCG immunization did not correlate with tumour characteristics in NMIBC, including stage, grade, and risk stratification. This may be explained by the routes of administration and subsequent immune responses elicited. The anti-tumour activity of intravesical BCG therapy is attributed to non-specific immune mechanisms related to the direct interaction with urothelial cells, as well as a contribution of systemic immune response, though specific mechanisms have yet to be fully elucidated (7). BCG immunization is also associated with non-specific immune mechanisms that provide protection against tuberculosis, however, given the nature of vaccinations, this response is exclusively systemic (8). Interestingly, this generalized immune response from immunization has been shown to confer protection against other respiratory infections through a mechanism referred to as *trained immunity* (TI) (8, 9). It was demonstrated that BCG immunotherapy in NMIBC patients induced TI and provided protection against respiratory infections (9). This suggests that intravesical BCG therapy can produce similar systemic immune responses as the BCG vaccination. Given that our data demonstrated that immunization status did not impact the tumour progression characteristics and risk stratification, this may suggest increased importance in the role of the local immune response in intravesical BCG in preventing the progression of NMIBC.
Our findings may also be explained by the waning protection from immunization over time. While bladder cancer incidence increases in the elderly (10), individuals immunized with BCG are typically immunized as infants. It has been well documented that protection from this immunization against TB infections wanes over time (7). Studies have identified that a positive *purified protein derivative* (PPD) skin test, an indication of BCG immunity, was associated with a better response to intravesical BCG therapy than those with a negative reaction (11, 12). *Niwa et al.* (2017) demonstrated that the *recurrence-free survival* (RFS) in patients with a slightly positive or negative PPD skin test reaction was significantly diminished compared to the RFS in those with a strongly positive response. This may suggest that a reduced immune response from BCG immunization does not generate the same benefit in BCG treatment. Given that the mean age of those vaccinated with BCG in our study was 71 years, and our study specifically looked at infantile BCG immunization, this may also explain why individuals with waning immunity from remote immunization did not influence tumour characteristics or risk stratification in patients with NMIBC.
In our study, the mean age of patients diagnosed with new NMIBC was significantly lower in individuals who received the infantile BCG vaccination (71 ± 9) compared to those who did not (77 ± 10) ($p < 0.0001$). Increased age is a risk factor for developing UC, largely attributed to a disease course that develops decades after exposure to risk factors (2). Countries with the lowest incidence of bladder cancer are typically those found to be below average on the *human development index* (HDI), which may be attributable to less industrial chemical exposure and access to tobacco, major risk factors for UC (1).
Interestingly, such countries tend to have a higher incidence of tuberculosis and subsequently higher rates of infantile BCG immunization (13). This may imply that non-immunized individuals were likely raised in countries with low TB incidence, yet above-average HDI. Such individuals would likely have had a higher risk of exposure to industrial chemicals and tobacco, leading to the slow development of bladder cancer and presentation at a later age. Those immunized and likely raised in countries with less exposure to common risk factors may have developed UC earlier on due to other reasons, such as genetics, diets, or other lifestyle factors.
Older age at presentation has been shown to be a poor prognostic factor in NMIBC (4). Consequently, the older age of presentation with NMIBC in non-immunized individuals poses a significant healthcare concern. The incidence of bladder cancer has been steadily increasing, particularly in developed countries (1). Such countries do not tend to implement routine immunization against TB

given the low incidence. Consequently, there is a growing population of non-immunized individuals presenting with NMIBC and potentially at older ages. This may result in overall more complicated patients with poorer prognostics. Further research in this area would be of utility given the growing aging population and potentially increased demands on healthcare systems.
There are several limitations to our study. First, it is a retrospective study completed at a single center. Therefore, selection bias was inevitable, and our study represents a relatively small sample size of patients. This study also limited by the relatively short follow up period (26 + 7 months) for assessing recurrence and progression.
Additionally, we did not account for the various demographic factors that may influence the risk factors for developing NMIBC.

Conclusions

Infantile BCG immunization was not associated with higher risk stratification in patients with NMIBT. The mean age of patients diagnosed with NMIBC was significantly lower in patients who received the infantile BCG vaccination.

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Correspondence

Anastasia MacDonald, MD
anamacdonald@nosm.ca
Vahid Mehrnoush, MD
vahidmehrnoush7@gmail.com
Asmaa Ismail, MD
asmaaismail0782@gmail.com
Ahmed Zakaria, MD
aszakaria81@yahoo.com
Waleed Shabana, MD
waleed.shabana@gmail.com
Ashraf Shaban, MD
ashraf.shaban@tbh.net
Mohammed Bassuony, MD
mohammed.bassuony@tbh.net
Hazem Elmansy, MD
hazem.elmansy@tbh.net
Walid Shahrour, MD
walid.shahrour@tbh.net
Owen Prowse, MD
owen.prowse@tbh.net
Ahmed Kotb, MD, PhD, FRCSC, FRCS Urol, FEBU (Corresponding Author)
Associate Professor
drahmedfali@gmail.com
Northern Ontario School of Medicine (NOSM) and Thunder Bay Regional Health Research Institute (TBRHRI)
Thunder Bay, ON, Canada

Livio Di Matteo, MD
ldimatte@lakeheadu.ca
Department of Economics, Lakehead University, Thunder Bay, ON

Conflict of interest: The authors declare no potential conflict of interest.