

## Original Article

# Adverse events following intravesical *Bacillus Calmette-Guérin* therapy in Mater Dei Hospital, Malta

Gerald Busuttil, Luke Zammit, Christine Debattista

**Abstract**

**Introduction:** Intravesical administration of *Bacillus Calmette-Guérin* (BCG), following transurethral resection of bladder tumour, has been shown to reduce recurrence and progression in appropriately selected patients with non-muscle invasive bladder cancer. The aim of the study was to report the local incidence and range of adverse events experienced by patients managed with intravesical BCG.

**Methods:** All patients who received at least one dose of intravesical BCG treatment at Mater Dei Hospital in 2014 were included in the study. A database including demographic, histological and chronological data, together with complication type, degree and treatment required was created. Patient medical files were reviewed and the patients were invited to take part in this audit via a telephone survey

**Results:** 55 patients satisfied inclusion criteria and were included in the study. 54 patients were documented to have had induction BCG, with maintenance BCG in 32 patients. 22 of these experienced at least 1 adverse event with BCG, whilst 33 had no complications. 1 patient had 3 adverse events, 7 patients had 2 adverse events and 14 patients had 1 complication. Most adverse events were considered to be mild or moderate in severity. Storage bladder symptoms accounted for most of these adverse events. No death as a consequence of intravesical BCG therapy was recorded.

**Conclusion:** Intravesical BCG therapy remains one of the mainstay therapies in the management of bladder cancer. The majority of adverse effects recorded were self-limiting or easily treatable with oral analgesics or antibiotics.

**Keywords**

Bladder cancer, Intravesical *Bacillus Calmette Guérin*, Morbidity.

**Introduction**

Transitional cell cancer of the urinary bladder remains a common disease in the western world despite reduction in smoking habits and legislation which has banned carcinogenic industrial substances associated with bladder cancer causation. Urothelial bladder cancer is the 7<sup>th</sup> most common cancer diagnosis in males and 17<sup>th</sup> in females world-wide, with a higher incidence in the developed world.<sup>1</sup>

At initial presentation, three fourths of bladder tumours are non-muscle invasive, this group of bladder cancers represent a diverse group of tumours with a wide spectrum in their potential for recurrence, progression and eventual adverse outcomes.<sup>2</sup> The wide variation in the one-year recurrence rate quoted in the literature after initial trans-urethral resection, ranging from 15 to 61% attests to the heterogeneous character of non-muscle

**Gerald Busuttil** FEBU, FRCSEd\*Urology Unit,  
Department of Surgery  
Mater Dei Hospital  
geraldbusu@gmail.com**Luke Zammit****Christine Debattista** MD

\*Corresponding Author

invasive bladder cancer (NMIBC).<sup>3</sup>

The European Organisation for Research and Treatment of Cancer (EORTC) has developed tables which stratify NMIBC cases into risk categories based on number of tumours, tumour size, T stage, grade, recurrence history and presence of carcinoma in situ. These tables have been externally validated, and are extensively used to guide treatment and follow up.<sup>4-5</sup>

The mainstay of treatment in NMIBC remains a good quality endoscopic resection, with second re-staging resection in selected cases and various regimens of intravesical chemotherapy or immunotherapy.<sup>6</sup> Intravesical immunotherapy is also the primary treatment for isolated carcinoma in situ of the urinary tract.

Maintenance immunotherapy with Bacillus Calmette Guerin (BCG) is the only intravesical therapy which has been shown to reduce both recurrence and progression rates in NMIBC, however its use is reserved to EORTC intermediate and high risk categories in view of its higher morbidity compared to intravesical chemotherapy regimens.<sup>7-8</sup>

## Method

A retrospective list of patients who received at least one dose of intravesical BCG for the treatment of non-muscle invasive bladder cancer at Mater Dei Hospital in 2014 where included. Index patient list was compiled using clinical departmental database which is used to register and follow up all patients undergoing intravesical BCG therapy.

All the patients in our cohort received BCG OncoTice® strain (MSD Sharp & Dohme GMBH). Intravesical BCG instillation follows the Evidence-based Guidelines for Best Practice in Urological Health Care published by the European Association of Urology Nurses.<sup>9</sup>

One phial 12.5mg per vial containing 2-8 x 10<sup>8</sup> CFU Tice BCG is diluted in 60 mls of sterile 0.9% saline solution and instilled in the bladder via a 10 or 12F bladder catheter using aseptic technique and strict infection control measures.

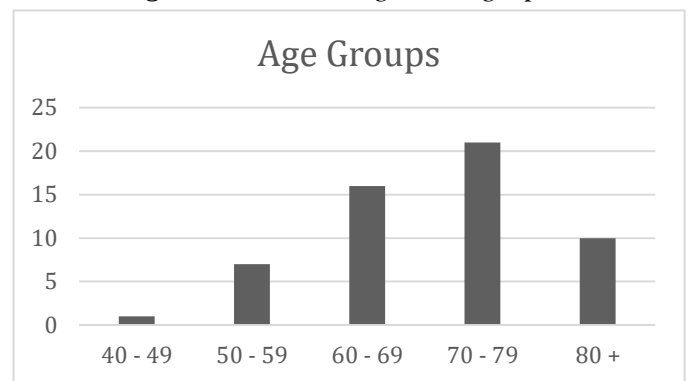
Induction intravesical BCG protocol involves six instillations one week apart, starting not less than two weeks after initial diagnostic TURBT, with a maintenance protocol consisting of three doses of intravesical BCG a week apart at three monthly intervals over three years in high risk cases of non-muscle invasive bladder cancer.

A custom designed database was written to include demographic, histological and chronological data, together with complication type, degree and treatment. Data sources included medical case notes, departmental intravesical treatment patient database and a standard telephone survey one week after each BCG dose.

## Results

55 patients were included in the study, all of which received at least one dose of intravesical BCG in 2014. 46 of these were male and only 9 being female. Most of these patients were elderly, as show in Figure 1.

**Figure 1: Patient age demographics**



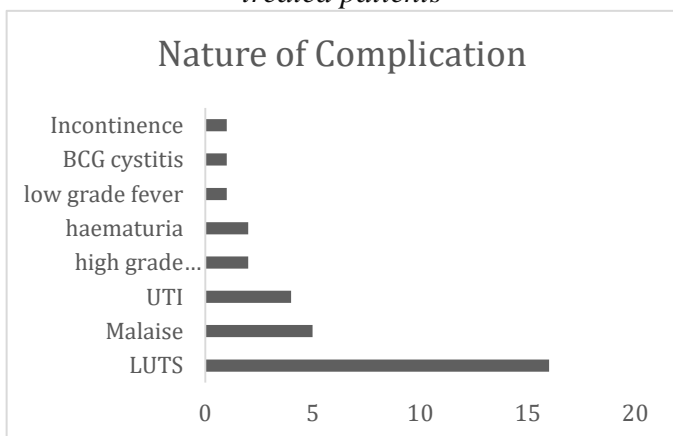
The indications for BCG treatment included various subgroups of high risk or recurrent non-muscle invasive bladder cancer, as showing in Table 1. The indication for BCG treatment was not documented in one patient. 54 patients received induction BCG, 32 of these went on to received maintenance BCG.

**Table 1: Tumour characteristics in patients undergoing BCG therapy**

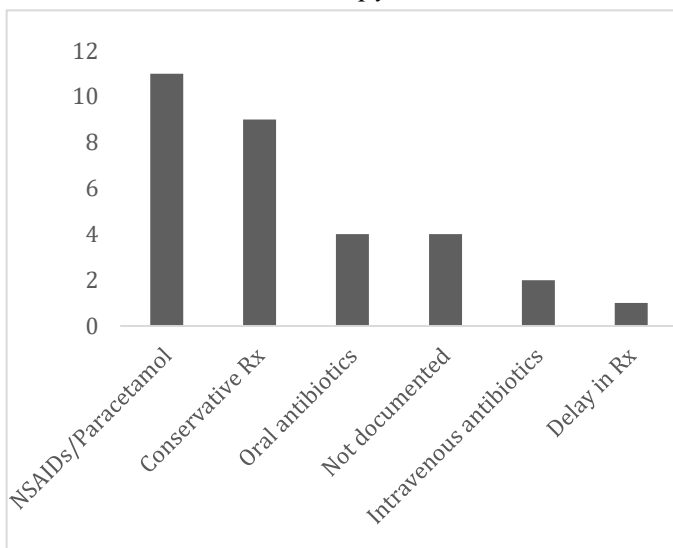
Indication	
recurrent T1G3 TCC	15
solitary T1 TCC	9
multifocal T1 TCC	9
recurrent T1 TCC	9
solitary T1 G3 TCC	4
multifocal G3 TCC	3
multifocal T1G3 TCC	3
recurrent CIS	1
Not available	1

22 patients out of 55 experienced at least one adverse event with BCG. One patient had three adverse events, seven patients had 2 adverse events, 14 patients had one complication. Most of these adverse events were considered to be of mild or moderate in severity, with two events qualifying as serious adverse event (SAE) by American Food and Drug Administration criteria (culture positive UTI requiring admission for intravenous antibiotics). All other adverse events were either managed conservatively or else with simple measures such as analgesics, oral antibiotics or delay in the next dose of BCG with a good outcome in all cases. No cases of mortality from intravesical BCG therapy were recorded. The full list of adverse events reported is given in Figure 2. Figure 3 outlines the treatment administered to manage these complications.

**Figure 2:** List of adverse events reported in BCG treated patients



**Figure 3:** Treatment strategies adopted to manage adverse events secondary to intravesical BCG therapy



## Discussion

Intravesical Bacillus Calmette-Guérin, an attenuated form of the *Mycobacterium bovis*, has been used by urologists for many years following first reports of its potential anti-carcinogenic effects in 1929 by Pearl.<sup>10</sup> In an autopsy series he noticed that cancer occurred less frequently in individuals with active tuberculous lesions compared to healthy controls, and postulated that tuberculous infection may be protective in this respect. Morales *et al* were the first to describe intravesical BCG use for the treatment of bladder cancer in 1976, where they showed a significantly reduced recurrence rate in nine treated patients. The regimen used, consisting of six weekly intravesical instillations of BCG, is still the most popular induction protocol in most centres.<sup>11</sup>

Further investigation in the optimal BCG schedule, published by Lamm *et al* in 2000, which showed that progression rates can be reduced by an additional maintenance protocol has resulted in the widespread adoption of this combined induction-maintenance schedule for the treatment of high-risk non-muscle invasive bladder cancer following initial diagnosis at transurethral resection.<sup>12</sup>

Risk stratification in this patient group is essential for many reasons. Non-muscle invasive bladder cancer included a heterogeneous cohort of patients with very variable cancer specific mortality outcomes. Intravesical BCG therapy has a significant morbidity, with a potential for serious adverse events, treating low risk patients with intravesical BCG has the potential for overtreatment and unnecessary morbidity. In view of this the European Organization for the Treatment and Research of Cancer (EORTC) has published risk stratification nomograms which are used to guide patient selection after histopathological diagnosis of NMIBC.<sup>13</sup>

In this retrospective study the local morbidity from intravesical BCG therapy was assessed and compared to similar series. 40% of the patients included reported at least one adverse event, which is within the published rate of 10-50% in other series.<sup>14-16</sup>

Half of the adverse events were reported as irritative culture-negative lower urinary tract symptoms, this is not surprising and is in keeping with the inflammatory bladder reaction which invariably follows intravesical BCG instillation. Other common reactions included culture positive

UTI and haematuria. Uncommon effects were mostly systemic in nature, including malaise and fever. This highlights the fact that the adverse effect profile of intravesical BCG extends beyond the confines of the lower urinary tract, and should be considered as a therapeutic modality with potential for severe systemic side effects, including potentially life threatening BCG sepsis.

This study has some strengths and numerous limitations. The index case list captures all the patients treated with intravesical BCG for the given study period at a national level as this therapy is administered by one urology unit and a clinical database is in place to register and follow up all patients receiving BCG treatment. This also allows for standardisation of the BCG strain, dose and method of administration across the patient cohort.

The limitations of this study are mostly related to its retrospective nature, which may have resulted in incomplete data capture and underestimation of adverse events rates. In addition, patients may have presented to their private general practitioner or government health centre with minor BCG-therapy related complaints, and these events may have gone unnoticed and unreported by the investigators. In an attempt to limit these unreported adverse events all patients were contacted by phone a week after their BCG dose and the severity of any events were also assessed at this time. Moreover, in the absence of strict definitions of drug related adverse events severity, the classification of adverse events into mild or moderate is somewhat arbitrary. The FDA definition of a serious event was used to identify serious morbidity according to established criteria.

The relatively low number of patients on maintenance intravesical BCG may also have had an impact on morbidity rates. This is a matter of debate in the urological community as maintenance BCG treatment has not been shown to increase morbidity in published literature. However, this does highlight the clinical concern that maintenance BCG might be underutilised in our unit, especially given that most of the patients in this patient cohort classify as EORTC high-risk patients.

## Conclusions

Morbidity secondary to intravesical BCG therapy in the local population of high-risk non-muscle invasive bladder cancer patients compares favourably to published series. Adverse events are

mostly low grade and are managed successfully with simple measures in the majority of cases.

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