

# Improvement of adherence to treatment in patients with non-muscle invasive bladder cancer (NMIBC) by spreading the 12 months maintenance Bacillus Calmette-Guerin (BCG) regimen over 18 months

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## ABSTRACT

**Purpose** - To evaluate what effect spreading the maintenance BCG regimen from 12 to 18 months has on the treatment completion rate.

**Patients and methods** - Retrospective data about patients diagnosed with intermediate or high risk non-muscle invasive bladder cancer were collected.

Suggested regimen started with 6 weekly induction intravesical full dose BCG instillations followed by 3 weekly instillations, 3 months after the 6th instillation. Thereafter, 3 weekly instillations were delivered 6 months after the 9th and the 12th instillation. In total, 15 BCG instillations were administered within 18 months. Cystoscopy and urine cytology were performed one month following the 6th, 9th, 12th and 15th instillations and then according to guidelines

**Results** - 195 patients met the inclusion criteria. 190 (97.4%) patients completed the induction instillations and 141 (72.3%) completed the treatment protocol. 39 patients discontinued treatment for medical reasons and 15 patients due to non-compliance. 162 patients completed follow up as recommended for a median of 46±20.1 months. Of those, 45 patients (27.8%) and 8 (4.9%) had disease recurrence and progression, respectively.

**Conclusion** - Spreading BCG instillations during maintenance protocol might achieve a better treatment completion rate, mainly due to improved patient compliance. No impacts on recurrence and progression rates have been observed in our cohort. Prospective randomized trials are warranted before suggesting clinical application.

**Keywords:** Non-muscle invasive bladder cancer; Maintenance BCG irrigations; Completion rate; Treatment spreading; Compliance

## INTRODUCTION

Following transurethral resection of bladder tumor (TURBT), most patients with high-risk (HR) and intermediate-risk (IR) non-muscle invasive bladder cancer (NMIBC) are commonly treated with intravesical bacillus Calmette-Guerin (BCG) bladder instillations in an attempt to reduce the risk of disease recurrence and eventual progression (Sylvester, van der Meijden & Lamm 2002; Han & Pan 2006; Babjuk et al. 2016). This treatment is usually started with 6 weekly induction instillations, commonly followed by scheduled maintenance instillations.

Many different maintenance protocols have been published. The optimal number, frequency and duration of instillations have yet to be determined. The European Association of Urology (EAU) recommend that standard induction should be followed by 3 weekly maintenance sessions of full dose BCG for 1 year (Figure 1a) for IR patients and 1-3 years for HR patients (induction plus 3 weekly instillations at 3, 6, 12, 18, 24, 30, 36 months) (Babjuk et al. 2016).

As demonstrated by The Southwest Oncology Group (SWOG) study, BCG bladder instillations are characterized by significant interruption and premature discontinuation rates: only 16% of patients completed all scheduled 3-years instillations. Among others, the most common reasons for treatment discontinuation are inefficacy, patient non-compliance and toxicity (Lamm et al. 2000)

Several attempts to reduce side effects were tested and reported, including anti-tuberculosis drugs (Vegt et al. 1997), antibiotics (Colombel et al. 2006), BCG dose reduction and shorter maintenance regimens (Oddens et al. 2013). In a recent leading trial, BCG related toxicity was reported in 70% of the patients and caused treatment discontinuation in almost 8% of them (Brausi et al. 2014).

Only a few trials focused on improving patient compliance, which is mainly impacted by mild underestimated toxicity and the frequent instillations followed by cystoscopies regimens that impair patients' quality of life (QOL) (Serretta et al. 2016).

The primary aim of our retrospective study was to determine if spreading the 12-month maintenance

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BCG regimen over 18 months, would achieve a better treatment completion rate compared to the regimen routinely practiced. Recurrence and progression rates have also been recorded.

**Patients and methods**

After institutional review board approval was obtained, data of consecutive patients treated from 2009 to 2016 with our protocol were retrospectively collected.

**Patients**

Study population included patients with IR or HR NMIBC (according to the European Organization for Research and Treatment of Cancer (EORTC) risk tables) (Bobinski & Lipinski 2009). These cases included any pathological (P) T1, high grade (HG) tumor and/or carcinoma in situ (CIS). Recurrent/multifocal PTa low grade (LG) tumors were also included. Patients with histopathology other than urothelial carcinoma and patients with upper tract involvement were excluded.

**Study design and endpoints**

A second TUR was scheduled 2-6 weeks after the first resection in cases where incomplete resection was reported or if any pT1 or HG (except CIS) tumors were found in the first resection. 3-6 weeks following the last TUR, patients were treated with 6 weekly induction BCG instillations followed by 9 maintenance instillations, designed as follows: 3 weekly instillations 3 months after last induction, then 3 weekly instillations 6 months after the 9th and the 12th instillation. In total, 15 BCG instillations were given within 18 months (Figure 1b).

The full dose of OncoTice strain instillation containing 5x10<sup>8</sup> colony forming units (CFU) (81mg in 50 ml of saline) with indwelling time between 1-2 hours, was administered in all cases by one experienced

nurse (N.H). Urine cultures were obtained before each instillation and antibiotics were administered whenever bacteruria was detected.

Patients suffering from significant side effects were offered a one-week hiatus.

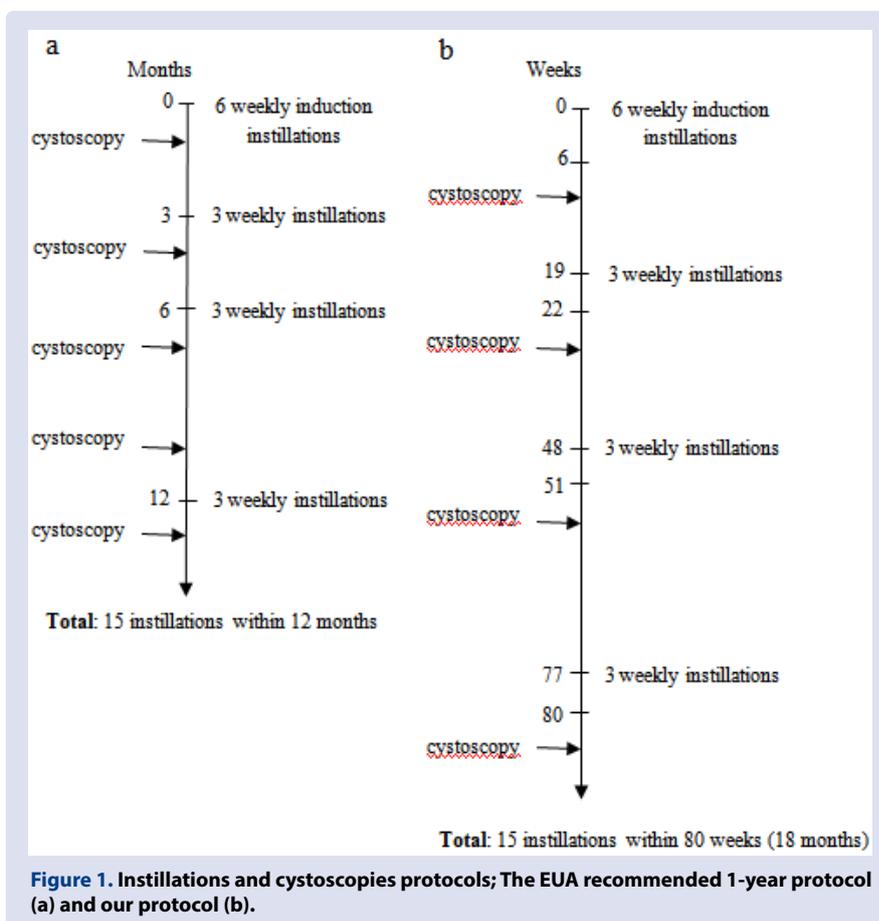
Cystoscopy and urine cytology were performed one month after the 6th, 9th, 12th and 15th instillation for all risk groups. Thereafter, IR patients were assessed annually, while HR patients were followed more closely (every 6 months for 3-5 years and then annually). For CIS patients the first follow up cystoscopy was accompanied by random bladder biopsies.

In the case of recurrence during treatment, TUR was performed. Where a LG tumor was detected, maintenance schedules were continued as planned; HG recurrence, upper tract involvement, second LG recurrence, distant metastasis or disease progression (an increase in tumor stage and/or grade) were considered a reason for stopping the protocol and offering alternative treatment options.

The length of follow-up was defined as the time from TURBT to the last control cystoscopy. Recurrence of disease was determined by lesions detected at cystoscopy and pathologically confirmed after TURBT during the follow-up period. Time to first recurrence or progression was defined as the time from TURBT to the day of cystoscopy in which the first recurrence or progression was found.

Data including: age, gender, pathology, recurrences, progressions, instillations postponement, reasons for treatment cessation and follow up were recorded.

The primary aim of this study was to evaluate the treatment completion rate.



## RESULTS

Of the 200 patients treated with our protocol, 195 met the inclusion criteria and were considered our study population. The median age was 70±11.3 (range 29-97) years; 156 males (80%), the rest females. Five patients were excluded due to concomitant upper tract urothelial tumor.

The majority of patients (86.2%) were defined as HR patients; only 27 patients (13.8%) had IR disease. In 44 (22.6%) patients, CIS component was present in their pathology specimen report. Table 1 summarizes patients' baseline variables.

Of 195 patients, 190 (97.4%) completed the 6 induction instillations, while 141 (72.3%) completed the treatment protocol. Table 2 shows the adherence to instillations schedules.

Of the 54 patients who discontinued treatment, 17 (8.7%) had disease recurrence requiring alternative treatment, 11 (5.6%) discontinued due to severe toxicity, 11 (5.6%) were lost to follow-up, 6 (3%) had serious concomitant disease, such as second primary and end stage heart failure, and were unable to complete the irrigation protocol. Five (2.6%) showed disease progression and 4 (2.1%) refused to continue treatment without a clear documented reason (Figure 2).

In 27 (13.8%) cases, instillations were delayed or temporarily stopped because of side effects.

162 patients (83.1%), completed follow up as recommended. Median follow-up time reached 46±20.1 months. 45 patients (27.8%) had documented disease recurrence and another 8 patients (4.9%) showed disease progression. Median time to first recurrence and progression was 23±17.7 and 9±11.1 months, respectively.

## DISCUSSION

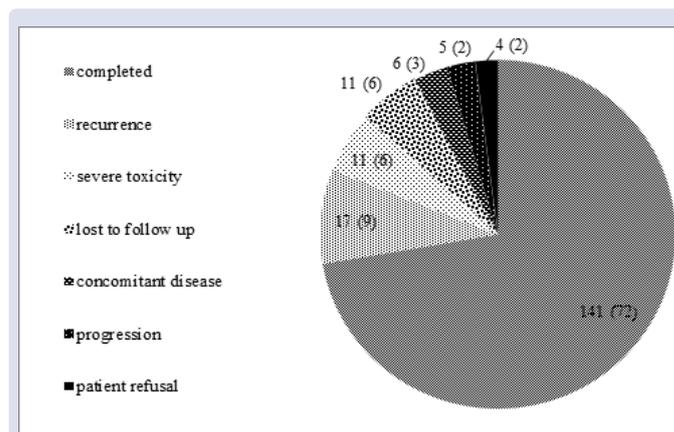
BCG maintenance is recommended by both the EAU [3] and the American Urological Association (AUA) (Chang et al. 2016) after a 6 week induction instillations, as the adjuvant treatment for patients with IR or HR NMIBC after TURBT.

**Table 1. Patients' baselines variables**

| Parameter                         | Result  |
|-----------------------------------|---------|
| Total number of eligible patients | 195     |
| Gender:                           |         |
| Male                              | 156     |
| Female                            | 39      |
| Age (Years):                      |         |
| Median                            | 70±11.3 |
| Range                             | 29-97   |
| Pathology (No.; %)                |         |
| Recurrent/multifocal TaLG         | 27;13.8 |
| Ta HG                             | 84;43.1 |
| T1 LG                             | 3;1.5   |
| T1 HG                             | 37;19   |
| CIS                               | 20;10.3 |
| Ta HG + CIS                       | 17;8.7  |
| T1 HG + CIS                       | 7;3.6   |

**Table 2. Number (n) and percentage of patients completing each cycle**

| Received instillations (n) | Patients completed (n) | Completion rate (%), n=195 |
|----------------------------|------------------------|----------------------------|
| 6                          | 190                    | 97.4                       |
| 9                          | 175                    | 89.7                       |
| 12                         | 161                    | 82.6                       |
| 15                         | 141                    | 72.3                       |



**Figure 2. Reasons for treatment discontinuation, numbers and rates (%)**

Many different maintenance schedules have been suggested, ranging from six induction instillations without maintenance (Martinez-Pineiro et al. 2015) to 27 instillations over three years (Lamm et al. 2000). The optimal frequency, number and duration of maintenance instillations are still to be determined. According to EAU guidelines a minimum of 1-year maintenance is needed.

The widely adopted SWOG protocol includes a course of 6-weekly induction instillations followed by 3 weekly instillations at 3 months and 6 months, and then every 6 months for 3 years (a total of 27 full-dose BCG instillations). This schedule resulted in significantly lower recurrence and progression rates of urothelial bladder tumor. Unfortunately, mainly due to BCG toxicity, most patients had their treatments interrupted or discontinued; only 16% of the maintenance cases completed all 8 scheduled courses. Other than for toxicity, treatment was also discontinued due to treatment inefficacy (recurrence or progression) or patients' non-compliance (Lamm et al. 2000).

Many studies that followed the SWOG publication, deal with methods to reduce treatment toxicity. Recent studies show that these methods in addition to the improved experience of the medical teams dealing with BCG administration and its side effects, achieved better treatment completion rates (Brausi et al. 2014). Fewer studies however, focused on improving other aspects of patient's compliance, which is a major dropout cause.

A recent EORTC trial (30962) compared administration of a third versus full dose of intravesical BCG and a 1-year versus a 3-years maintenance protocol (4 treatment groups). This study included 1355 HR and IR NMIBC patients. The results showed improved effectiveness of full dose treatment which was translated to a slight benefit on recurrence rate but not on progression rate or overall survival. This effect was shown for the 3-year maintenance protocol and only in HR patients (Oddens et al. 2013). The mythical impression of lower toxicity experienced by reduced dose or shortened protocol has not been proven, as almost 70% of the patients reported side effects and 7-8% discontinued treatment, among the 4 groups. In 15.7% of patients, instillations were delayed or temporarily stopped due to side effects (Brausi et al. 2014). Only 36.1% completed the 3-year-protocol and 62.8% completed the 1-year full dose maintenance protocol.

Sarita et al. retrospectively studied the reasons for stopping treatments in their HR NMIBC patients who were scheduled for 1-year full-dose BCG maintenance protocol, stopped treatment (Figure 1a). They found that patient compliance played a major role: 13.3% discontinued treatment due to slight but persistent local discomfort that reduced their QOL and thus their compliance to treatment. 8.5% refused to continue treatment and 5.8% were lost to follow up. Only a total of 52% completed the entire protocol and for 18.8% , 1-2 instillations needed

to be postponed (Serretta et al. 2016). Other reasons to stop treatment included toxicity (6%), systemic disease (6.3%) and disease recurrence or progression (7.5%) that necessitated other interventions.

In our practice, patients had a quite significant dropout rate and complaints about the high intensity of the classical schedule (unpublished data). The most highly reported side effects of the BCG instillations appeared in the first year of maintenance (Brausi et al. 2014), where the burden of undergoing the induction instillations and an additional 3 maintenance sessions along with the quite intense follow-up cystoscopies protocol, may have been the reason for impaired patient compliance.

In an attempt to improve patients' compliance for BCG treatment, we set up the spreaded protocol described above. The patients were followed for 46±20.1 months. Although, unfortunately, not compared in a prospective manner to the classical protocol, a greater percentage of patients completed this treatment plan.

To the best of our knowledge, this is the first report of a spreaded BCG maintenance treatment protocol. Our theory is that spreading the instillations over 18 months as well as slightly spacing the follow-up cystoscopies during treatment might be the reason to improved adherence to the treatment protocol. We achieved a 72.3% treatment completion rate even though patients underwent a longer total instillations period.

We compared our results for patient non-compliance to those in the literature and found that only 7.7% of our patients refused treatment or were lost to follow-up as compared to 27.6% in other studies. While, similar rates (20% versus 19.8% in the literature) were found when comparing treatment cessation not related to patient compliance (toxicity, concomitant disease, recurrence or progressions). Rates of instillations deferral were also comparable.

We assumed that spreading out the instillation and cystoscopy schedules during BCG maintenance treatment caused less local discomfort - maybe due to better bladder recovery- and less QOL impairment. This may have contributed to better compliance and completion rates. Delivery of the treatments by the same highly experienced nurse may also have played an important role.

This study was not designed to evaluate recurrence and progression rates. Complete follow up was reported for 83.1% of patients for a median time of 46±20.1 months. Rates of recurrence and progression are comparable with recently published data.

We recognize the limitations of this study: The data are based on retrospective reports; therefore attempts to inspect correlations between demographic and safety contributions for compliance regarding the instillations is limited. Comparing results with results of previous studies would be another limitation, as the cohorts of patients and the methods of management are difficult to compare.

Because we spread out both the irrigation regimen and the follow-up cystoscopies, it is not easy to determine exactly what caused the better completion rate.

Future studies should be based on prospective controlled cohorts which would probably result in more statistically significant and operative conclusions. Some data about side effects and previous instillations treatments are also lacking.

## CONCLUSIONS

Our modest retrospective inspection suggest that spreading BCG instillations during maintenance protocol might achieve better treatment completion rates, mainly due to improving patient compliance. We did not observe any impact on recurrence and progression rates in our cohort of patients.

A randomized controlled trial (RCT) comparing our suggested instillations protocol (with and without spreading the cystoscopy schedule) with the recommended 1-year protocol is mandatory to confirm our results.

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## ETHICAL APPROVAL

This study is a retrospective. For this type of study formal consent is not required.

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