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How to reduce bacillus Calmette-Guérin discontinuation in patients with severe functional impairment

Luca Di Gianfrancesco*, Mauro Ragonese, Massimiliano Foti, Giuseppe Palermo, Emilio Sacco, PierFrancesco Bassi, Marco Racioppi

Clinica Urologica, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS–Università Cattolica del Sacro Cuore di Roma, Rome, Italy

Abstract

Background: Severe functional impairment is often considered a contraindication to intravesical therapy for nonmuscle-invasive bladder cancer (NMIBC). A tailored intravesical bacillus Calmette-Guérin (BCG) procedure was evaluated in high-risk (HR)-NMIBC patients with severe functional impairment.

Materials and methods: Patients with a Katz Index score of 2 or less and an initial diagnosis of HR-NMIBC with atraumatic insertion of a Foley-type indwelling catheter, bladder emptying, and BCG instillation were prospectively treated; after 2 hours, the bladder was emptied and the catheter was removed (group A).

After propensity score matching, 52 patients in group A were compared with that of 52 consecutive patients in group B using a retrospective database, with similar baseline/oncological characteristics and treated with standard intermittent catheterization. Moreover, groups A and B were compared with that of 130 consecutive patients (group C) retrospectively evaluated, with similar oncological characteristics but with a Katz Index score of 3 or greater and treated with standard intermittent catheterization.

Results: The discontinuation rates were 11.5%, 35%, and 9% in groups A, B, and C, respectively (A vs. B, log-rank score 42.52 [$p < 0.05$]; B vs. C, 107.6 [$p < 0.05$]; A vs. C, 3.45 [$p > 0.05$]). The overall adverse event rates were 38.5%, 57.7%, and 39.2%, respectively (A vs. B, $p = 0.04$; B vs. C, 0.03; A vs. C, 0.92). The rates of severe adverse events were 1.9%, 1.9%, and 1.5%, respectively, without statistically significant differences. The cumulative HR disease-free survival rates were 63.4%, 48%, and 69.2%, respectively (A vs. B, log-rank score 154.9 [$p < 0.05$]; B vs. C, 415 [$p < 0.05$]; A vs. C, 244 [$p < 0.05$]).

Conclusions: A tailored intravesical instillation procedure may reduce BCG discontinuation and adverse effects.

Keywords: Intravesical bacillus Calmette-Guérin; Discontinuation rate; Adverse event; Tailored procedure; Severe functional impairment

1. Introduction

High-risk nonmuscle-invasive bladder cancer (HR-NMIBC) is an aggressive disease with high rates of recurrence and progression[1] that may require major surgery for optimal oncological control; therefore, treatment is warranted.

Intravesical bacillus Calmette-Guérin (BCG) therapy after transurethral resection of the bladdertumor (TURBT) reduces the recurrence risk, and in patients with HR-NMIBC, it is more effective than that of TURBT alone or TURBT and intravesical chemotherapy (level of evidence [LE], 1a, according to the European Association of Urology guidelines).[1] Moreover, BCG therapy delays and potentially reduces the progression risk of NMIBC (LE: 1a).[1]

However, this therapy is not free from adverse events, becoming even severe. The reasons why BCG causes adverse events are not well-known because it is not easy to precisely identify patients who experience adverse effects related to intravesical immunotherapy.[2] Adverse effects may be reduced in several different ways, for example, administration of the antituberculosis drug isoniazid or the antibiotic ofloxacin or reducing the BCG dose.[3] However, in urological guidelines, no standard of care has been defined for the reduction of adverse effects in frail patients.

Clinical experience shows that it is possible to identify patients most at risk for such events. Normal aging changes, and health problems frequently lead to a general decline in the functional status of patients. These may place the patient on a spiral of iatrogenesis leading to further health problems and increasing the risk of adverse events after any kind of therapy. One of the best ways to evaluate the health status in frail patients is through functional assessment, which provides objective data that may indicate changes in health status, allowing for appropriate intervention.

The Katz Index (KI) of Independence in Activities of Daily Living (ADL), commonly referred to as the Katz ADL, is the most appropriate instrument to assess functional status as a measurement of the ability to independently perform ADLs. Clinicians typically use the tool to detect problems in performing ADLs and to plan care accordingly.[4]

Anyway, neither age[5] nor baseline immune status[6] is a contraindication to BCG therapy, but in some frail patients, adverse events

*Corresponding Author: Luca Di Gianfrancesco, Clinica Urologica, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS–Università Cattolica del Sacro Cuore di Roma, L.go A. Gemelli, Rome, 8 00168, Italy. E-mail address: luca.digian@libero.it (L. Di Gianfrancesco).

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may be more frequent. Because the precise immunological mechanism of BCG therapy is still unclear, the pathogeneses of adverse reactions after intravesical BCG instillation have been not fully elucidated. Controversy exists between the inflammatory hypersensitivity hypothesis, supported by histological findings of granulomas in the absence of microorganisms, and the bacteria invasion hypothesis based on reports about the positive findings of active bacilli in a variety of tissues.[7]

In patients with severe functional impairment, chronic urinary retention may potentially increase the contact time of the BCG with the bladder wall and thereby increase the drug-induced inflammatory state on an immunological basis.

In case of adverse events, generally, BCG therapy is interrupted, and the discontinuation of BCG therapy has been shown to have a significantly deleterious effect on the incidence of tumor recurrence.[8] Therefore, it is crucial to reduce predisposing factors to BCG-related adverse events to safely treat patients.

2. Materials and methods

2.1. Patients

From 2012 to 2017, 69 consecutive patients with severe functional impairment (KI ≤ 2) and an initial diagnosis of HR-NMIBC were treated with a tailored intravesical BCG procedure as follows: patients underwent atraumatic insertion of a 16 Fr Foley-type indwelling bladder catheter. After bladder emptying, one vial of BCG (Medac, Wedel, Germany) was introduced into the bladder. The patients were kept under clinical observation for 2 hours, and subsequently, the bladder was passively emptied and the catheter removed (group A).

2.2. Study design

Data of patients in group A were entered in a prospective database approved by the institutional review board. Inclusion criteria were as follows: initial diagnosis of proven HR nonmuscle-infiltrating urothelial neoplasm[1] (high grade, carcinoma in situ, papillary tumor T1 of any grade) and a KI score of 2 or less.

Exclusion criteria were the following: nonurothelial neoplasm, neoplasm in the urethra and/or upper urinary tract, absence of muscle in the histopathological report, and inability to sign consent.

After propensity score matching, patients in group A were compared with that in group B, comprising retrospectively evaluated patients, with an initial diagnosis of proven HR-NMIBC and a KI score of 2 or less and treated at our clinic with the same therapy schedule but with standard intermittent catheterization.

Moreover, patients in both groups A and B were compared with those in another group of retrospectively evaluated patients with an initial diagnosis of HR-NMIBC and a KI score of 3 or greater and treated with the same therapy schedule but with standard intermittent catheterization (group C).

2.3. Treatment

All examined patients underwent TURBT under general or locoregional anesthesia; patients with papillary neoplasia underwent complete TURBT and second TURB, if indicated, according to guidelines.[1] A computed tomography (CT) scan examination was performed in every patient to study the upper urinary tract.

Four weeks after TURBT, BCG therapy was initiated. The BCG was administered once a week for a total of 6 treatments (induction course). In case of therapy response, patients underwent a monthly BCG maintenance course for at least 1 year.

In case of traumatic catheterization, gross hematuria, and symptomatic urinary tract infection, treatment was postponed for at least 1 week, as recommended.[1]

2.4. Follow-up and clinical management

Forty-five days after BCG treatment and then every 6 months, patients underwent cystoscopy, systematic bladder biopsies, voiding and washing cytology, and radiological study of the upper urinary tract (UroCT or ultrasound of the abdomen, interspersed).

2.5. End points

The primary end point was assessment of the rate of therapy discontinuation, and the secondary end points were assessment of the rate of adverse events, high-risk disease-free survival (HR-DFS), overall survival (OS), cancer-specific survival (CSS), recurrence rate, and progression rate.

Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 5.0.

Regarding the HR-DFS curves, the presence of any histologically proven HR disease recurrence or progression was evaluated. For the OS, the interval from the treatment to death due to any reason, including cancer and all other causes, was examined. For the CSS curves, the interval from the treatment to death from the disease was assessed. Tumor recurrence was defined as the presence of an NMIBC on biopsy or positive urinary cytology during follow-up. Tumor progression was defined as the evidence of muscle-invasive disease during follow-up.

2.6. Analysis plan

A post hoc retrospective, monocentric, nonrandomized cohort study was carried out in the department of urology in our institution.

The rationale for the study was based on clinical experience developed in our clinic with patients with severe functional impairment. Based on the good empirical results seen in these patients, we aimed to evaluate retrospective data to standardize this target treatment.

The target treatment in group A was offered on a prospective phase 2 trial basis; there was no prespecified protocol or enrollment of patients in groups B and C (retrospectively evaluated).

Patients in group A were compared with those in group B in a post hoc retrospective cohort study. In the nonrandomized setting and post hoc analysis, the statistical power of the study for the primary outcome (discontinuation rate) was 80.8%; sample sizes calculated according to both the Kelsey[9] and Fleiss methods[10] confirmed 52 cases (group A) and 52 controls (group B), respectively.

Moreover, patients in groups A and B were compared with those in group C. Patients in group C were retrospectively extracted from the same population base to be representative of the population from which cases were obtained. More than one control was enrolled for every case with a ratio of at least 1:2.

2.7. Katz Index

The KI allows for the evaluation of the independence in ADL. The index ranks adequacy of performance in the 6 functions of bathing, dressing, toileting, transferring, continence, and feeding. Patients' independence in each of the 6 functions was evaluated through their yes/no answers. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment. The instrument is most effectively used among older adults in a variety of care settings, when baseline measurements, taken when the patient is well, are compared with periodic or subsequent measures. In the 35 years since the index has been developed, it has been modified and simplified, and different approaches to scoring

Table 1

Baseline characteristics.

				p		
	Group A	**Group B**	**Group C**	**A vs. B**	**B vs. C**	**A vs. C**
Patients, n	52	52	130			
Age, median (range), yr†	73.5 (45–90)	76 (48–89)	70.7 (48–84)	0.10	0.05	0.05
Male/female, no. pts*	41/11	43/9	105/25	0.62	0.76	0.77
ASA, median ± SD†	3.1 ± 0.3	3.1 ± 0.4	2 ± 0.6	0.78	<0.01	<0.01
WHO, median ± SD†	2.6 ± 0.6	2.8 ± 0.6	0.3 ± 0.5	0.09	<0.01	<0.01
CCI, median ± SD†	4.3 ± 0.6	4.3 ± 0.5	2.6 ± 0.7	0.61	<0.01	<0.01
KI score, median ± SD†	1.9 ± 0.2	1.9 ± 0.3	5.2 ± 0.9	0.70	<0.01	<0.01
Pathological status, no. pts (%)*						
pTaHG	7 (13.5%)	6 (11.5%)	19 (14.6%)	0.77	0.58	0.84
pT1	20 (38.5%)	22 (42.3%)	56 (43.1%)	0.69	0.92	0.57
Solitary CIS	16 (30.8%)	18 (34.6%)	41 (31.5%)	0.68	0.69	0.91
Concurrent CIS	9 (17.3%)	6 (11.5%)	14 (10.8%)	0.40	0.88	0.23

*Categorical (χ^2).

†Continuous (*z* test).

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; CIS = carcinoma in situ; HG = high grade; KI = Katz Index; Pts = patients; WHO = World Health Organization.

have been used. However, it has consistently demonstrated its utility in evaluating functional status in the elderly population. Although no formal reliability and validity reports can be found in the literature, the tool is used extensively as a flag signaling functional capabilities of older adults in clinical and home environments. The Katz ADL assesses basic ADLs. It does not assess more advanced ADLs. Katz developed another scale for instrumental activities of daily living such as heavy housework, shopping, managing finances, and telephoning. Although the Katz ADL is sensitive to changes in declining health status, it is limited in its ability to measure small increments of change seen in the rehabilitation of older adults. A full comprehensive geriatric assessment should follow when appropriate. The Katz ADL is very useful in creating a common language about patient function for all practitioners involved in overall care planning and discharge planning.[11,12]

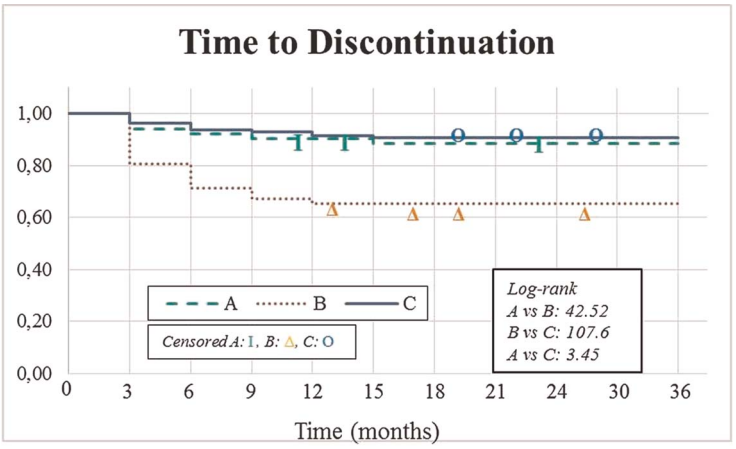
2.8. Informed consent

The study involved human participants after signing the consent form, with guarantee of confidentiality and permission to report anonymous individual data. All patients were informed of all details regarding their therapeutic choice; they were requested to provide a detailed surgical and medical history.

2.9. Statistics

We performed the χ^2, Fisher exact, and Student *t* tests for categorical and continuous variables, Kaplan-Meier and log-rank tests for survival curves, and logistic regression. *P* values less than 0.05 were considered statistically significant.

The study was approved by the local ethics committee (Fondazione Policlinico Universitario "A. Gemelli," IRCCS, Università Cattolica del



Patients at risk

A	52	49	48	47	46	44	44	44	43	43	43
B	52	42	37	35	34	33	32	32	31	30	30
C	130	125	123	122	120	119	119	118	117	116	116

Figure 1. Time to discontinuation.

Table 2

Discontinuation rates.

	Group A		Group B		Group C		*p*		
	Pts	%	Pts	%	Pts	%	A vs. B	B vs. C	A vs. C
Discontinuation rate	6	11.54%	18	35%	12	9%	0.01	<0.01	0.64
Grade ≤ 2 adverse events	4	7.69%	13	25%	7	5.38%	0.01	<0.01	0.55
Grade ≥ 3 adverse events	1	1.92%	2	4%	2	1.54%	0.56	0.38	0.85
Other reasons	1	1.92%	3	6%	3	2.31%	0.31	0.47	0.87

Pts = patients.

Sacro Cuore, Rome, Italy; approval no. 1112 [Tailored-BCG/2020. v1]) and the protocol project conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

3. Results

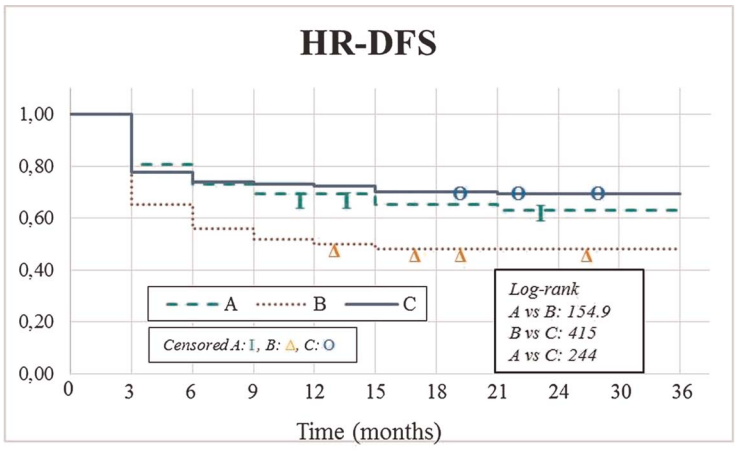
The patients' baseline and oncological characteristics are summarized in Table 1. Patients in groups A and B did not differ in terms of the American Society of Anesthesiologists, World Health Organization - Performance Status, Charlson Comorbidity Index, and Katz scores ($p > 0.05$), whereas both groups differed from those in group C for all items ($p < 0.01$). The cumulative discontinuation rates were 11.5%, 35%, and 9% in groups A, B, and C, respectively (A vs. B, log-rank score 42.52 [$p < 0.05$]; B vs. C, 107.6 [$p < 0.05$]; A vs. C, 3.45 [$p > 0.05$]; Fig. 1 and Table 2). The cumulative HR-DFS rates were 63.2%, 48.1%, and 69.2% in groups A, B, and C, respectively (A vs. B, log-rank score 154.9 [$p < 0.05$]; B vs. C, 415 [$p < 0.05$]; A vs. C, 244 [$p < 0.05$]; Fig. 2). The overall adverse event rates were 38.5%, 57.7%, and 39.2% in groups A, B, and C, respectively (A vs. B, $p = 0.04$; B vs. C, 0.03; A vs. C, 0.92), whereas the rates of severe adverse events were 1.9%, 1.9%, and 1.5% in groups A, B and C, respectively, without statistically significant differences ($p > 0.05$; Table 3). The cumulative OS rates were 94.2%, 92.3%, and 97.7% in groups A, B, and C, respectively (A vs. B: log-rank score 0.99 [$p > 0.05$]; B vs. C, 3.92 [$p < 0.05$]; A vs. C, 3.96 [$p < 0.05$]; Fig. 3). The cumulative CSS rates were 98%, 96.1%, and 98.4% in groups A, B, and C, respectively (A vs. B, log-rank score 4.99 [$p < 0.05$]; B vs. C, 3.97 [$p < 0.05$]; A vs. C, 5.46 [$p < 0.05$]; Fig. 4). The cumulative recurrence-free rates in groups A, B, and C were 73.8%, 61.9%, and 78%, respectively (A vs. B, log-rank score 59 [$p < 0.05$]; B vs. C, 180.6 [$p < 0.05$]; A vs. C, 98 [$p < 0.05$]; Fig. 5). The cumulative progression-free rates in groups A, B, and C were 86.6%, 80.8%, and 89.8%, respectively (A vs. B, log-rank score 3.1 [$p > 0.05$]; B vs. C, 17.55 [$p < 0.05$]; A vs. C, 7.06 [$p < 0.05$]). The mean follow-up was 41 months (range, 36–49 months; Fig. 6).

4. Discussion

It is important to treat all patients with HR-NMIBC, an aggressive disease with high rates of relapse and progression; according to the European Association of Urology guidelines, BCG must be given with a maintenance schedule for optimal efficacy (LE: 1a)[1]; therefore, it is crucial for patients to undergo a complete treatment schedule.

Several preventive strategies to improve BCG treatment compliance are available; among these are the sequential administration of hyaluronic acid[13] and administration of adjuvant ofloxacin (even with unknown effect on long-term efficacy),[14] the antituberculous drug isoniazid (with risk of transient disturbances on liver function, making it prophylactic, not recommended),[15] and oxybutynin (despite that it should not be used in the routine prophylaxis against urinary symptoms during BCG therapy according some authors).[16] Better results were seen with the reduction of the BCG dose[17,18] and the correct education of healthcare personnel and patients.

In particular cases (patients who do not completely empty the bladder, patients with neurological bladder, frail patients, patients with reduced autonomy in daily/semidependent activities), the literature lacks specific indications and clinical practice suggestions; in these cases, clinical experience may help overcome some difficulties and limitations, to treat patients who may be often excluded from therapy due to these problems.



Patients at risk

A	52	42	38	36	35	32	32	31	30	30	30
B	52	34	29	27	26	24	23	23	22	21	21
C	130	101	96	95	94	91	91	89	88	87	87

Figure 2. High-risk disease-free survival.

Table 3

Adverse events.

Adverse event, no. pts (%)	Group A		Group B		Group C		*p*		
	Pts	%	Pts	%	Pts	%	A vs. B	B vs. C	A vs. C
Hematuria									
Absent	34	65.4%	27	51.9%	87	66.9%	0.16	0.06	0.84
Present	18	34.6%	25	48.1%	43	33.1%			
Grade 1	15	28.8%	18	34.6%	36	27.7%			
Grade 2	3	5.8%	7	13.5%	6	4.6%			
Grade 3	0	0.0%	0	0.0%	1	0.8%			
Frequency/urgency									
Absent	33	63.5%	23	44.2%	85	65.4%	0.05	<0.01	0.81
Present	19	36.5%	29	55.8%	45	34.6%			
Grade 1	12	23.1%	20	38.5%	30	23.1%			
Grade 2	7	13.5%	9	17.3%	15	11.5%			
Grade 3	0	0.0%	0	0.0%	0	0.0%			
Dysuria									
Absent	35	67.3%	28	53.8%	87	66.9%	0.16	0.09	0.96
Present	17	32.7%	24	46.2%	43	33.1%			
Grade 1	11	21.2%	16	30.8%	26	20.0%			
Grade 2	6	11.5%	8	15.4%	17	13.1%			
Grade 3	0	0.0%	0	0.0%	0	0.0%			
Incontinence									
Absent	46	88.5%	39	75.0%	121	93.1%	0.07	<0.01	0.30
Present	6	11.5%	13	25.0%	9	6.9%			
Grade 1	4	7.7%	8	15.4%	6	4.6%			
Grade 2	2	3.8%	5	9.6%	3	2.3%			
Grade 3	0	0.0%	0	0.0%	0	0.0%			
Pain									
Absent	36	69.2%	31	59.6%	95	73.1%	0.31	0.07	0.60
Present	16	30.8%	21	40.4%	35	26.9%			
Grade 1	12	23.1%	16	30.8%	21	16.2%			
Grade 2	4	7.7%	5	9.6%	14	10.8%			
Grade 3	0	0.0%	0	0.0%	0	0.0%			
Cystitis									
Absent	36	69.2%	30	57.7%	92	70.8%	0.22	0.09	0.83
Present	16	30.8%	22	42.3%	38	29.2%			
Grade 1	12	23.1%	14	26.9%	28	21.5%			
Grade 2	3	5.8%	8	15.4%	10	7.7%			
Grade 3	1	1.9%	0	0.0%	0	0.0%			
Transitory fever									
Absent	43	82.7%	36	69.2%	116	89.2%	0.11	<0.01	0.23
Present	9	17.3%	16	30.8%	14	10.8%			
Grade 1	5	9.6%	8	15.4%	10	7.7%			
Grade 2	4	7.7%	8	15.4%	4	3.1%			
Grade 3	0	0.0%	0	0.0%	0	0.0%			
Sepsis									
Absent	52	100.0%	51	98.1%	129	99.2%	0.31	0.50	0.53
Present	0	0.0%	1	1.9%	1	0.8%			
Overall complication	20	38.5%	30	57.7%	51	39.2%	0.04	0.03	0.92
Severe complication	1	1.9%	1	1.9%	2	1.5%	1.00	0.85	0.85

Pts = patients.

Because of patients' condition, the discontinuation rate of BCG therapy may sometimes be higher than usual, to avoid the occurrence of adverse events. As previously reported by Thomas et al.,[19] the rate of patients not undergoing intravesical BCG is up to 38% (in the general population). Moreover, Sylvester et al.[20] reported that only 32.7% of patients completed the maintenance schedule, 19.7% stopped because of BCG toxicity, 16.4% stopped because of inefficacy, and 31.2% stopped treatment because of other reasons; however, the authors concluded that BCG adverse effects occurring within the first 6 months of treatment did not represent a prognostic factor for subsequent recurrence.

Differently, Takeda et al.[8] showed how discontinuing BCG instillation therapy for NMIBC negatively affects tumor recurrence. They demonstrated in a multivariate analysis that discontinuation of BCG therapy ($p = 0.02$) was an independent predictor of tumor recurrence, in addition to tumor multifocality ($p = 0.04$). However, the occurrence of adverse effects was not an independent predictor of tumor recurrence ($p = 0.93$). Multivariate analysis also demonstrated that neither discontinuation of BCG therapy ($p = 0.31$) nor the occurrence of adverse effects ($p = 0.33$) represented an independent predictor for tumor progression. The authors concluded that when major adverse effects occur, it may be preferable to attempt to mitigate the major adverse effects to keep BCG therapy on schedule.[8]

Conversely, Alhogbani et al.[21] evaluated the impact on long-term prognosis of bladder cancer patients after discontinuation of BCG instillations. The authors showed in a multivariate analysis that BCG discontinuation had a significantly deleterious effect (independent predictor) on tumor recurrence ($p < 0.001$) and progression rates ($p = 0.005$). The authors indicated BCG toxicity as a major cause of discontinuation, as well as BCG shortage as a potential and risky cause.[21]

Decaestecker et al.[22] evaluated the management of adverse events related to intravesical BCG therapy. The authors demonstrated that the 20% BCG discontinuation rate due to adverse effects could be decreased to less than 8% with appropriate counseling on adverse effect expectation.[22]

The KI is a useful tool as reported by Blackwood et al.,[23] who evaluated the Katz ADL disability in older cancer survivors by age, stage, and cancer type and showed that Katz ADL disability differs by cancer type, stage, and age with greater impairment on those with advanced age and stage.

To our knowledge, this is the first study focusing on HR-NMIBC treatment in patients with severe functional impairment. We reported how the tailored intravesical drug procedure may lead to a statistically lower rate of overall adverse events (in group A, up to 20% less compared with that in group B), whereas in terms of severe adverse events, the rates seemed to be similar, which may be related to the nonmodifiable factors. The better results in the occurrence of adverse events were also linked to the discontinuation rate (<20% in group A compared with that in group B), allowing to optimally and completely treat more patients despite severe functional impairment.

Patients with severe functional impairment experienced a statistically significant lower rate of HR-DFS compared with those with a KI score of 3 or greater (63.2% in group A vs. 69.2% in group C), but the tailored procedure has increased this rate up to 15% (48.1% in group B). Similarly, the cumulative recurrence-free rate increased with statistical significance by greater than 10% (73.8% in group A vs. 61.9% in group B), unlike the cumulative progression-free rate that did not achieve the same statistical power.

This study has several limitations of small sample size, in comparison with retrospectively evaluated patients, and potential selection bias.

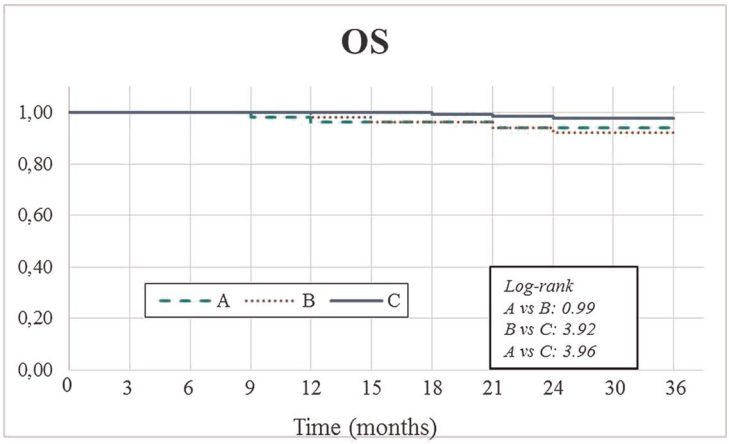
5. Conclusions

High-risk NMIBC is an aggressive disease, and patients with HR-NMIBC need to be treated to reduce the chances of recurrence and progression requiring major surgery. The need of a comprehensive evaluation of the patients' functional status, even in the outpatient setting, is mandatory to guarantee an optimal treatment for all patients.

The adoption of some precautions, essentially based on clinical experience, allows treatment of patients in whom BCG-related adverse events could be more likely. Further studies with longer follow-up and more cases are needed to confirm these findings.

Acknowledgments

None.



Patients at risk

A	52	42	38	36	36	33	33	32	32	32	32
B	52	34	29	27	25	24	24	23	23	23	23
C	130	101	96	95	94	91	91	90	89	88	88

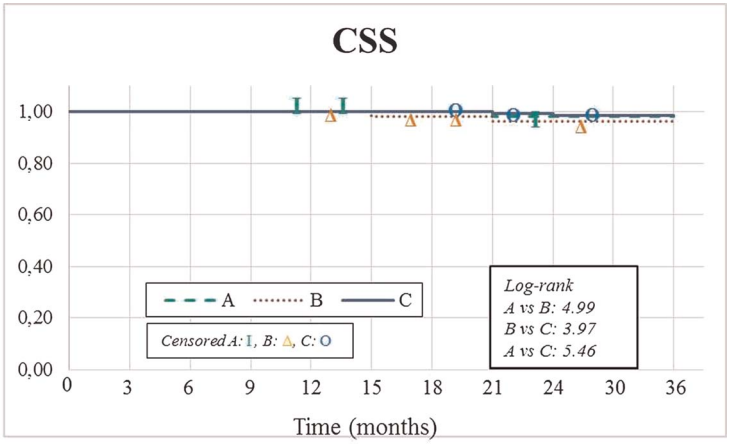
Figure 3. Overall survival.

Statement of ethics

The study was approved by the local ethics committee (Fondazione Policlinico Universitario "A. Gemelli," IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy), and the protocol project conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). This study was registered in the publicly accessible International Committee of Medical Journal Editors-accepted registry (https://eudract.ema.europa.eu/) with EudraCT number 2021-000221-27 issued for our protocol number Tailored-BCG/2020.v1 (retrospectively registered on January 14, 2021). The study involved human participants after signing the consent form, with guarantee of confidentiality and permission to report anonymous individual data. All patients were informed of all details regarding their therapeutic choice; they were requested to provide a detailed surgical and medical history.

Conflict of interest statement

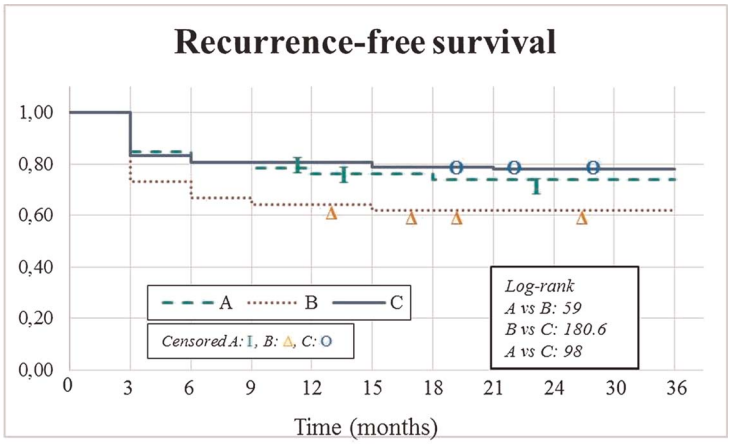
No conflict of interest has been declared by the authors.



Patients at risk

A	52	42	38	36	35	32	32	31	30	30	30
B	52	34	29	27	26	24	23	23	22	21	21
C	130	101	96	95	94	91	91	89	88	87	87

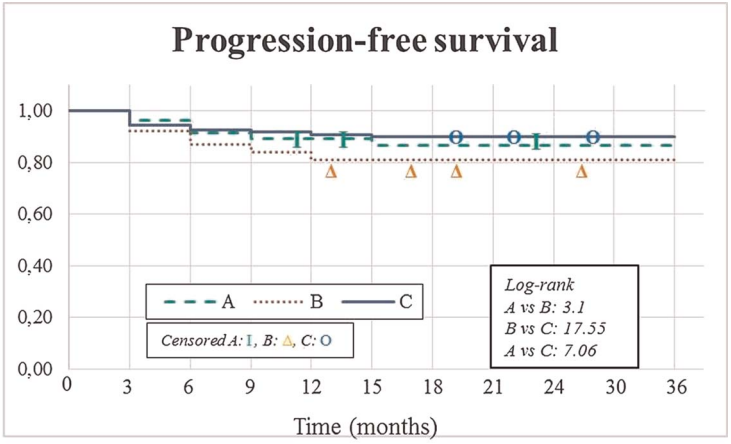
Figure 4. Cancer-specific survival.



Patients at risk

A	52	42	38	36	35	32	32	31	30	30	30
B	52	34	29	27	26	24	23	23	22	21	21
C	130	101	96	95	94	91	91	89	88	87	87

Figure 5. Recurrence-free survival.



Patients at risk

A	52	42	38	36	35	32	32	31	30	30	30
B	52	34	29	27	26	24	23	23	22	21	21
C	130	101	96	95	94	91	91	89	88	87	87

Figure 6. Progression-free survival.

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Author contributions

LDG: Conceptualization, data curation, writing, investigation;
MR: Writing of the methodology and visualization;
MF and GP: Data curation;
ES: Review, editing;
PFB: Supervision;
MR: Validation, supervision;
LDG, MR, MF, GP, ES, PFB, and MR: Having access to the data.

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