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# Electromotive Drug Administration of Mitomycin C (EMDA/MMC) versus Intravesical Immunotherapy with Bacillus Calmette-Guérin (BCG) in Intermediate and High Risk Non Muscle Invasive Bladder Cancer

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**Keywords**

Bladder cancer · Electromotive drug administration · Bacillus Calmette-Guérin · Intravesical treatment · Non-muscle-invasive bladder cancer

**Abstract**

***Background:*** Although TURB of tumor (TURBT) by itself can eradicate a non-muscle-invasive bladder cancer (NMIBC) completely, these tumors commonly recur and can progress to MIBC. It is, therefore, necessary to consider adjuvant therapy in most patients. The primary objective of the present study was to report our experience with EMDA/MMC and BCG, considering efficacy, progression, and recurrence, as adjuvant therapy in NMIBC patients; the secondary objective was to assess the efficacy of EMDA/MMC versus BCG as a comparative treatment. ***Methods:*** Between April 2016 and February 2020, a series of 216 patients, with a diagnosis of intermediate- and high-risk NMIBC after TURBT, underwent adjuvant intravesical therapy. In 26 cases with a failure of the treatment, in patients unfit and unwilling for radical cystectomy, a repeated intravesical therapy was performed (2 had a twice repetition). Out of 244 adjuvant therapies, 140 EMDA/MMC and 104 BCG treatments were done. The following data were collected for each patient: baseline demographics and clinical data and perioperative and postoperative data. Overall patients' adjuvant intravesical therapies were included in a prospectively maintained institutional database, and a retrospective chart review was performed. We collected data on 2 main outcomes, recurrence-free survival (defined as a negative cystoscopy, cytology, and/or histology at the evaluation time point) and progression-free survival (defined as a negative cystoscopy or a nonprogressive tumor recurrence). ***Results:*** The NMIBC progression rate was higher in BCG than EMDA/MMC but not statistically significant (respectively, 4.2% vs. 2.5%; $p = 0.703$). In the overall population, the risk of NMIBC recurrence was higher after BCG than EMDA/MMC ($p = 0.025$). In the subgroups of 59 paired patients with similar characteristics, no difference was observed between groups in NMIBC progression and recurrence. ***Conclusions:*** Our findings suggest that EMDA/MMC and BCG are safe and reproducible approaches as adjuvant treatment in NMIBC. EMDA/MMC permits to achieve a fine oncological management as adjuvant treatment in NMIBC, which is not less than that obtained with BCG.



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## Introduction

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered. Patients with non-muscle-invasive BC (NMIBC), approximately 75%, have a high prevalence, due to long-term survival in many cases and lower risk of cancer-specific mortality, compared to MIBC ones [1–3].

These tumors can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations. The TURB's aim, in NMIBC, is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of NMIBC. In order to predict patient's prognosis, disease recurrence, and progression risks, the EORTC Genito-Urinary Cancer Group has developed a scoring system and risk tables [4]. To facilitate treatment recommendations, it is important to categorize patients into risk groups. Based on available prognostic factors and in particular data from the EORTC risk tables, the EAU Guidelines Panel recommends stratification of patients into 3 risk groups. Although TURB of tumor (TURBT) by itself can eradicate an NMIBC completely, these tumors commonly recur and can progress to MIBC. It is, therefore, necessary to consider adjuvant therapy in most patients [5].

The primary objective of the present study was to report our experience with electromotive drug administration of mitomycin C (EMDA/MMC) and intravesical immunotherapy with bacillus Calmette-Guérin (BCG), considering efficacy, progression, and recurrence, as adjuvant therapy in NMIBC patients. The secondary objective was to assess the efficacy of EMDA/MMC versus BCG as a comparative treatment.

## Materials and Methods

Between April 2016 and February 2020, a series of 216 patients, with a diagnosis of intermediate- and high-risk NMIBC after TURBT, underwent adjuvant intravesical therapy, in 2 medical centers located in Italy and Switzerland. We considered both naïve patients and those recurrent to other treatments. All patients performed thorax and abdomen CT preoperatively. In 26 cases with a failure of the treatment, in patients unfit and unwilling for radical cystectomy, a repeated intravesical therapy was performed (2 had a twice repetition). The total number of adjuvant intravesical therapies was 244: 140 EMDA/MMC and 104 BCG treatments were done. In detail, EMDA/MMC and BCG were, respectively, 120 and 96 at the first treatment during the study period, 19 and 7 in the case of second treatment, and 1 and 1 at the eventual third. Out of 26 patients that repeated intravesical therapy, 15 (58%) switched between the 2 regimes. Overall patients' adjuvant intravesical therapies were included in a prospectively maintained institutional database, and a retrospective chart review was performed for the purpose of the present study.

About EMDA/MMC, the treatment consisted in 30-min sessions of EMDA/MMC (Physion Mini 30N2, 20–23 mA, 40% [wt/vol] mitomycin in distilled water). Patients underwent up to 8 EMDA/MMC treatment sessions (1 per week) and up to 12 maintenance sessions (1 per month, minimum 6 sessions) in the induction and maintenance cycle, respectively.

BCG, provided as a freeze-dried powder, is diluted with saline and is administered through a catheter directly into the bladder. After the instillation of the intravesical agent into the bladder, the solution should be retained for 1.5–2 h. After this time, the patient voids to remove the solution. Patients underwent up to 6 BCG treatment sessions (1 per week) and up to 9 maintenance sessions (1 year; 3 instillations, 1 per week, at 3, 6, and 12 months) in the induction and maintenance cycle, respectively.

The following data were collected for each patient: baseline demographics and clinical data (age, gender, performance status according to ECOG [6], comorbidities according to the Charlson comorbidity index [7], number and type of previous NMIBC recurrences, previous treatments, clinical stage according to TNM staging [8] at the enrollment, and severity of carcinoma at the enrollment [classification into low-, intermediate-, and high-risk according to the EORTC [4]]); perioperative and postoperative data (number of EMDA/MMC treatment induction and maintenance sessions, number of BCG treatment induction and maintenance sessions, and tumor recurrence and progression during treatment). The patients were evaluated every 3 months with cystoscopy, cytology, and imaging staging. We collected data on 2 main outcomes, recurrence-free survival (defined as a negative cystoscopy, cytology, and/or histology at the evaluation time point) and progression-free survival (defined as a negative cystoscopy or a nonprogressive tumor recurrence).

This study did not receive any funding. All patients provided written informed consent for the procedures described herein. All surgical procedures were performed by expert surgeons.

*Statistical Analysis*

Data are reported as mean and standard deviation or frequency with percentage. We used the Student's *t* test to compare continuous variables. Associations between categorical variables were evaluated by using the $\chi^2$ test or Fisher test as appropriate. Since many variables were different between study groups, we paired patients 1:1 according to gender, age, staging and grade of tumor, previous treatment, and risk group. A conditional logistic regression model, appropriate for matched data, was used to compare paired patients. Cumulative NMIBC recurrence was estimated using the Kaplan-Meier curves, and between-group comparison was performed with the log-rank test. A $p$ value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, TX, USA).

**Table 1.** Characteristics of overall patients: demographic-clinical parameters

| Parameter | Total value | BCG value | EMDA/MMC value |
|---|---|---|---|
| Patients' treatments | 244 | 104 | 140 |
| Patients' age (at the moment of treatment), years | 68±10 | 67±10 | 70±10 |
| ECOG score (at the moment of treatment), *n* (%) | | | |
| 0 | 69 (28.3) | 33 (31.7) | 36 (25.7) |
| 1 | 105 (43.0) | 42 (40.4) | 63 (45) |
| 2 | 70 (28.7) | 29 (27.9) | 41 (29.3) |
| Charlson score (at the moment of treatment), *n* (%) | | | |
| 0 | 62 (25.4) | 29 (27.9) | 33 (23.6) |
| 1 | 69 (28.3) | 33 (31.7) | 36 (25.7) |
| 2 | 67 (27.5) | 21 (20.2) | 46 (32.9) |
| 3 | 32 (13.1) | 15 (14.4) | 17 (12.1) |
| 4 | 8 (3.3) | 3 (2.9) | 5 (3.6) |
| 5 | 4 (1.6) | 1 (1) | 3 (2.1) |
| 6 | 1 (0.4) | 1 (1) | 0 (0) |
| 7 | 1 (0.4) | 1 (1) | 0 (0) |
| Charlson score age adjusted (at the moment of treatment), *n* (%) | | | |
| 0 | 6 (2.5) | 2 (1.9) | 4 (2.9) |
| 1 | 28 (11.5) | 14 (13.5) | 14 (10) |
| 2 | 29 (11.9) | 17 (16.3) | 12 (8.6) |
| 3 | 38 (15.6) | 17 (16.3) | 21 (15) |
| 4 | 56 (23.0) | 23 (22.1) | 33 (23.6) |
| 5 | 38 (15.6) | 10 (9.6) | 28 (20) |
| 6 | 31 (12.7) | 12 (11.5) | 19 (13.6) |
| 7 | 12 (4.9) | 7 (6.7) | 5 (3.6) |
| 8 | 4 (1.6) | 2 (1.9) | 2 (1.4) |
| 9 | 2 (0.8) | 0 (0) | 2 (1.4) |
| Previous treatment (at the moment of treatment), *n* (%) | | | |
| None | 53 (21.7) | 14 (13.5) | 39 (27.9) |
| Yes | 191 (78.3) | 90 (86.5) | 101 (72.1) |
| Risk groups (at the moment of treatment), *n* (%) | | | |
| Intermediate | 37 (15.2) | 7 (6.7) | 30 (21.4) |
| High | 207 (84.8) | 97 (93.3) | 110 (78.6) |

Data represent the mean±standard deviation, median (interquartile range), or number (percentage). EMDA/MMC, electromotive drug administration of mitomycin C; BCG, bacillus Calmette-Guérin.

## Results

*Baseline Characteristics (Overall Treatments)*

Overall, 244 patients' treatments were evaluated. Table 1 summarizes baseline demographics and clinical characteristics of patients at the moment of the treatment. The overall mean patient age was 68 ± 10 years; in detail, in the BCG group, the mean patient age was 67 ± 10 years, while in the EMDA/MMC group, the mean patient age was 70 ± 10 years. Overall, 37 patients (15.2%) in the intermediate-risk group and 207 patients (84.8%) in the high-risk group were stratified. Considering the type of adjuvant therapy, in the BCG group, 7 patients (6.7%) in the intermediate-risk group and 97 patients (93.3%) in the high-risk group were stratified, while in the EMDA/MMC group, 30 patients (21.4%) in the intermediate-risk group and 110 patients (78.6%) in the high-risk group were stratified.

*Perioperative Outcomes (Overall Treatments)*

Table 2 summarizes intraoperative and perioperative parameters of patients at the moment of the treatment. Overall, 244 patients' treatments were evaluated.

Recurrence was observed in overall 45 patients (18.4%) during or immediately after induction therapy; in detail, in 25 patients (24%) during or immediately after BCG induction therapy and in 20 patients (14.3%) during or immediately after EMDA/MMC induction therapy, recurrence was observed. About maintenance therapy, when made and not interrupted before starting, recurrence was

**Table 2.** Characteristics of overall patients: perioperative-postoperative parameters

| Parameter | Total value | BCG value | EMDA/MMC value |
|---|---|---|---|
| Recurrence in induction TH, *n* (%) | 45 (18.4) | 25 (24) | 20 (14.3) |
| Recurrence type in induction TH, *n* (%) | | | |
| NMIBC LG | 3 (23.1) | 1 (25) | 2 (22.2) |
| NMIBC HG | 8 (61.5) | 3 (75) | 5 (55.6) |
| MIBC | 2 (15.4) | 0 (0) | 2 (22.2) |
| Recurrence in maintenance TH | 26 (16.5) | 13 (20) | 13 (14) |
| Recurrence type in maintenance TH, *n* (%) | | | |
| NMIBC LG | 11(42.3) | 5 (38.5) | 6 (46.2) |
| NMIBC HG | 10 (38.5) | 6 (46.2) | 4 (30.8) |
| MIBC | 5 (19.2) | 2 (15.4) | 3 (23.1) |
| Progression during induction TH, *n* (%) | | | |
| No | 236 (96.7) | 100 (96.2) | 136 (97.1) |
| Yes | 8 (3.3) | 4 (3.8) | 4 (2.9) |
| Progression during maintenance TH, *n* (%) | | | |
| No | 152 (96.2) | 63 (96.9) | 89 (95.7) |
| Yes | 6 (3.8) | 2 (3.1) | 4 (4.3) |

Data represent the mean±standard deviation, median (interquartile range), or number (percentage). EMDA/MMC, electromotive drug administration of mitomycin C; BCG, bacillus Calmette-Guérin; NMIBC, non-muscle-invasive bladder cancer.

**Table 3.** Characteristics of patients at the first procedure in the study period and in the subgroups of paired subjects

| | BCG, *n* = 96 | EMDA/MMC, *n* = 120 | *p* value | BCG, *n* = 59 | EMDA/MMC, *n* = 59 | *p* value |
|---|---|---|---|---|---|---|
| Male gender, *n* (%) | 79 (82.3) | 109 (90.8) | 0.063 | 54 (91.5) | 54 (91.5) | 1.000 |
| Age, years | 67±10 | 70±10 | 0.017 | 70±9 | 71±10 | 0.110 |
| ECOG PS 0, *n* (%) | 30 (31.3) | 28 (23.3) | 0.192 | 13 (22.0) | 10 (16.9) | 0.273 |
| ECOG PS 1, *n* (%) | 40 (41.7) | 55 (45.8) | 0.540 | 23 (39.0) | 31 (52.5) | 0.109 |
| ECOG PS 2, *n* (%) | 26 (27.1) | 37 (30.8) | 0.547 | 23 (39.0) | 18 (30.5) | 0.232 |
| Previous treatment, *n* (%) | 89 (92.7) | 99 (82.5) | 0.026 | 56 (94.9) | 56 (94.9) | 1.000 |
| Tx, *n* (%) | 0 (0.0) | 1 (0.8) | 1.000 | 0 (0.0) | 1 (1.7) | 1.000 |
| T0, *n* (%) | 1 (1.0) | 0 (0.0) | 0.444 | 0 (0.0) | 0 (0.0) | 1.000 |
| Ta, *n* (%) | 16 (16.7) | 43 (35.8) | 0.002 | 9 (15.3) | 9 (15.3) | 1.000 |
| TIS/CIS, *n* (%) | 4 (4.2) | 3 (2.5) | 0.703 | 2 (3.4) | 1 (1.7) | 1.000 |
| T1, *n* (%) | 75 (78.1) | 73 (60.8) | 0.007 | 48 (81.4) | 48 (81.4) | 1.000 |
| G1, *n* (%) | 0 (0.0) | 10 (8.3) | 0.003 | 1 (1.7) | 2 (3.4) | 0.571 |
| G2, *n* (%) | 20 (20.8) | 53 (44.2) | <0.001 | 15 (25.4) | 15 (25.4) | 1.000 |
| G3, *n* (%) | 71 (74.0) | 54 (45.0) | <0.001 | 41 (69.5) | 41 (69.5) | 1.000 |
| Risk group 2, *n* (%) | 6 (6.3) | 27 (22.5) | <0.001 | 2 (3.4) | 2 (3.4) | 1.000 |
| Risk group 3, *n* (%) | 90 (93.8) | 93 (77.5) | <0.001 | 57 (96.6) | 57 (96.6) | 1.000 |

Data represent the mean±standard deviation, median (interquartile range), or number (percentage). EMDA/MMC, electromotive drug administration of mitomycin C; BCG, bacillus Calmette-Guérin.

observed in overall 26 patients (16.5%); in detail, recurrence was observed in 20% and in 14% of patients during maintenance therapy of BCG and EMDA/MMC, respectively. Progression of disease was observed, during induction therapy, in overall 8 patients (3.3%); in detail, it was observed in 3.8% and in 2.9% of patients during induction therapy of BCG and EMDA/MMC, respectively. About maintenance therapy, when made and not interrupted before starting, progression of disease was observed in overall 6 patients (3.8%); in detail, it was observed in 3.1%

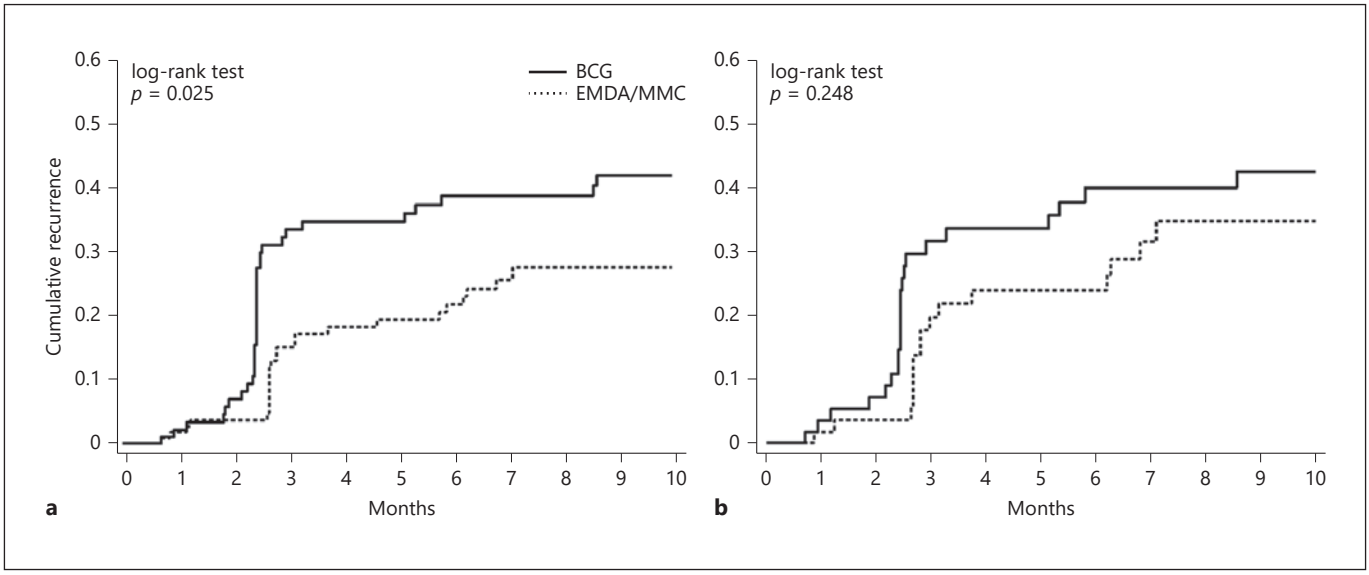


**Fig. 1.** Kaplan-Meier estimates of bladder cancer recurrence in the overall population (**a**) and in patients paired with similar characteristics (**b**). EMDA/MMC, electromotive drug administration of mitomycin C; BCG, bacillus Calmette-Guérin.

and 4.3% of patients, during maintenance therapy of BCG and EMDA/MMC, respectively.

The overall severity of complications was low. In 91.5% of cases, no complication was recorded. In overall 16 patients (6.5%), particularly in 9 patients in the BCG group and in 7 patients in the EMDA/MMC group, grade I complications, such as urinary infection, skin erythema (only in the EMDA/MMC group), fever, and bladder pain treated with antibiotics, antipyretics, and analgesics, were noted. No major complications (grade II–V) were noted. Overall, 5 patients (2.0%), exclusively in the EMDA/MMC group, had to stop the treatment because of the catheter intolerance.

*Baseline Characteristics and Perioperative Outcomes in Patients at the First Procedure in the Study Period and in the Subgroups of Paired Subjects*

Table 3 shows baseline characteristics of patients (first procedure in the study period, 216 single cases) and those of paired subjects selected as most similar for characteristics at the time of treatment (118 patients, 59 in each group; in 5, data were from the second procedure). Compared to the 120 patients in the EMDA/MMC group, 96 in BCG were younger, more frequently at the first therapy, more frequently T1G3, and in the high-risk group. The NMIBC progression rate was higher in BCG than EMDA/MMC but not statistically significant (respectively, 4.2% vs. 2.5%; $p = 0.703$). Figure 1 shows the cumulative values of NMIBC recurrence: in the overall population, the risk was higher after BCG than EMDA/MMC (Fig. 1b; $p = 0.025$). In the subgroups of 59 paired patients with similar characteristics, no difference was observed between groups in NMIBC progression (3.4% in each cohort) and recurrence (Fig. 1b).

## Discussion

In order to predict risks of disease recurrence and progression in individual NMIBC patients, the EORTC Genito-Urinary Cancer Group has developed a scoring system and risk tables [4]; the total scores are stratified into categories that reflect various probabilities of recurrence and progression at 1 and 5 years. It is important to categorize into risk groups to facilitate treatment recommendations. Adjuvant treatment should be based on a patient's prognosis.

According to EAU guidelines, in patients with tumors presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (<1 recurrence per year) and expected EORTC recurrence score <5, one immediate chemotherapy instillation is recommended. In patients with intermediate-risk tumors, 1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3–6–12 months), or instillations of chemotherapy (optimal schedule not known),

for a maximum of 1 year, is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. In patients with high-risk tumors, full-dose intravesical BCG for 1–3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months) is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences [5].

Under the circumstances that 12% of patients do not complete maintenance for up to 3 years [9] and that availability of BCG has become an issue in some countries, we have considered 12 months as the limit of maintenance therapy. Since 2012, availability of BCG has become an issue in some countries; thus, the development of alternative intravesical treatments for NMIBC has been become imperative. Moreover, the available intravesical chemotherapy and immunotherapy options are suboptimal in efficacy and toxicity. Novel therapies are thought in order to improve efficacy and potentially preserve the patient's bladder.

Developments for the treatment of NMIBC have focused on optimizing the delivery of established therapies or potentiating the effects of chemotherapy, using intravesical device-assisted technology to deliver hyperthermia to the bladder wall or circulating chemotherapy and ionization of chemotherapy to improve drug tissue penetration; EMDA/MMC is one of the most used devices [10, 11].

EMDA enhances the delivery of chemotherapy by electro-osmosis, iontophoresis, and electroporation, whereby an electrical charge is generated between a catheter electrode and a cutaneous electrode to aid the transport of drug molecules into tissues. MMC was detected in all layers of the bladder wall in both treatment modalities, passive diffusion and EMDA; however, MMC concentration in the urothelium was 30-fold greater using EMDA/MMC than passive MMC and 3-fold greater in the lamina propria and muscularis [10, 11].

Intravesical EMDA/MMC is administered using a battery-powered generator to deliver a controlled electric current of up to 30 mA. The electrical current passes between the intravesical active electrode at the tip of a catheter to a dispersive ground electrode positioned on the lower abdomen. The specialized 16-Fr catheter is inserted, and the bladder is washed with water, after which 40 mg MMC in 100 mL of water is instilled with the operating current maintained at 20-mA pulsed electrical current. Treatment time is 30 min per session, and the peak concentration of MMC in the bladder wall is achieved after 15 min of initiating treatment [10, 11].

Di Stasi et al. [12] assessed the effect of EMDA/MMC before TURBT. Patients were randomized to perform TURBT alone, immediate post-TURBT instillation of MMC, or immediate pre-TURBT instillation of EMDA/MMC. After a median follow-up of 86 months, patients who performed MMC/EMDA before TURBT had a lower recurrence rate than those performed TURBT alone or MMC after TURBT. Disease progression was observed in 6% of patients performed MMC/EMDA before TURBT.

Gan et al. [13] reported results of sequential BCG and EMDA/MMC as the treatment of high-risk NMIBC. Patients performed an induction dose of BCG at weeks 1 and 2, followed by EMDA/MMC in week 3 and repeated thrice for a total of 9 weeks. A maintenance scheme was offered with 3 doses of BCG given 3 months after induction and every 6 months for 3 years. In 67% of patients, recurrence was not observed; moreover, no progression of disease was assessed in 95.3% of patients.

Racioppi et al. [14] evaluated the efficacy and the safety of EMDA/MMC treatment in BCG-refractory NMIBC on a 3-year follow-up. At the end of follow-up, 61% patients reserved their native bladder. At the end of follow-up, recurrence-free rates were 75, 71.4, 50, and 25% in TaG3, T1G3, CIS, and TaT1G3 + CIS patients, respectively; progression-free rate was 61%.

Carando et al. [15, 16] reported the data of 65 patients and 112 patients affected by NMIBC that performed a complete TURBT followed by EMDA/MMC. At the end of follow-up, recurrence-free rates were 84 and 75% in 65 and 112 patients, respectively. Progression-free rate, evaluated in the cohort of 112 patients, was 90%.

In the present study, recurrence was observed in 24% of treatments, during or immediately after BCG induction therapy, and in 14.3% of treatments, during or immediately after EMDA/MMC induction therapy. About maintenance therapy, when made and not interrupted before starting, recurrence was observed in 20% and in 14% of treatments, during maintenance therapy of BCG and EMDA/MMC, respectively. Progression of disease was observed, during induction therapy, in 3.8% and in 2.9% of treatments during induction therapy of BCG and EMDA/MMC, respectively. About maintenance therapy, when made and not interrupted before starting, progression of disease was observed in 3.1% and 4.3% of treatments, during maintenance therapy of BCG and EMDA/MMC, respectively.

In patients at the first procedure in the study period, the NMIBC progression rate was higher in BCG than

**Table 4.** Overview of main series of EMDA/MMC treatments reported in the literature

| Series | Publication year | EMDA/MMC treatments, *n* | Recurrence-free rates, % | Progression-free rates, % | EMDA/MMC versus BCG (*p* value) |
|---|---|---|---|---|---|
| Di Stasi et al. [12] | 2011 | 124 | Neoadjuvant<br>EMDA/MMC + TURBT: 62 | Neoadjuvant<br>EMDA/MMC + TURBT: 94 | NP |
| Gan et al. [13] | 2016 | 107 | 68 | 95.3 | NP |
| Racioppi et al. [14] | 2018 | 26 | TaG3: 75<br>T1G3: 71.4<br>CIS: 50<br>TaT1G3 + CIS: 25 | 61 | NP |
| Carando et al. [15] | 2019 | 65 | 84 | Not reported | NP |
| Carando et al. [16] | 2020 | 112 | 75 | 90 | NP |
| Present study | 2021 | 140 | 85.7 (induction th)<br>86 (maintenance th) | 97.1 (induction th)<br>95.7 (maintenance th) | $p = 0.025$ |

Data represent number or percentage. EMDA/MMC, electromotive drug administration of mitomycin C; BCG, bacillus Calmette-Guérin; NP, not performed.

EMDA/MMC but not statistically significant (respectively, 4.2% vs. 2.5%; $p = 0.703$). As shown in Figure 1a, the risk of NMIBC recurrence, in the overall population, was higher after BCG than EMDA/MMC ($p = 0.025$). However, a selection bias was performed because the patients' characteristics were heterogeneous in 2 groups; in fact, compared to the 120 patients in the EMDA/MMC group, the 96 in BCG were younger, more frequently at the first therapy, more frequently T1G3, and in the risk class 3; this was a limit of the study. Moreover, considering the subgroups of 59 paired patients with similar characteristics, no difference was observed between groups in NMIBC progression (3.4% in each cohort) and recurrence as shown in Figure 1b.

Overall severity of complications was low. In 91.5% of cases, no complication was recorded, and almost all patients reached to perform the treatment. This study reports our high experience with EMDA/MMC and BCG, considering efficacy, progression, and recurrence, as adjuvant therapy in NMIBC patients and assesses the efficacy of EMDA/MMC versus BCG as a comparative treatment.

The largest reported study to date evaluated 124 EMDA/MMC treatments [11–16]. Thus, this research adds to the current literature by describing patient characteristics, efficacy, and recurrence as well as progression outcomes after EMDA/MMC treatments in the largest study reported to date, as shown in Table 4.

Moreover, this study is the first one reported to date to assess the efficacy of EMDA/MMC versus BCG as a comparative treatment. Considering recurrence and progression rates after BCG and EMDA/MMC, as a comparative treatment, our findings suggest that EMDA/MMC and BCG seem not different in NMIBC progression (3.4% in each cohort) and recurrence, as shown in Figure 1b. The present study had limitations: data were collected prospectively but reviewed in a retrospective manner which introduced a selection bias; moreover, no control group was available for this analysis, and this was not a randomized blinded study.

## Conclusions

Our findings suggest that EMDA/MMC and BCG are safe and reproducible approaches as adjuvant treatment in NMIBC. EMDA/MMC permits to achieve a fine oncological management as adjuvant treatment in NMIBC, which is not less than that obtained with BCG, without any major complications noted. However, further comparative studies are needed to define the definitive role of EMDA/MMC in the management of NMIBC.

## Acknowledgment

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## Statement of Ethics

Participants (or their parent/legal guardian/next of kin) have given their written informed consent to participate in this study. The Independent Ethics Committee – Policlinico Hospital of Bari – approved the study (Decision No. 6331). The Swiss Local Ethics Committee – Comitato etico del Canton Ticino – approved the study (Decision No. 2018-01470/CE 3390).

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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The authors have received no external funding.


## Author Contributions

M. Zazzara, A. Nazaraj, M. Scarcia, G. Cardo, R. Carando, and G.M. Ludovico contributed equally to data collection and preparation of the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## References


1 Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019 Apr 15;144(8):1941–53.

2 Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013 Feb;63(2):234–41.

3 Compérat E, Larré S, Roupret M, Neuzillet Y, Pignot G, Quintens H, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. Virchows Arch. 2015 May;466(5):589–94.

4 Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006 Mar;49(3):466–5; discussion 475–7.

5 Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) – 2019 update. Eur Urol. 2019 Nov;76(5):639–57.

6 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

7 Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. J Clin Epidemiol. 2006 Mar;59(3):265–73.

8 Sobin LH, Compton CC. TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer. 2010 Nov 15;116(22):5336–9.

9 Ojea A, Nogueira JL, Solsona E, Flores N, Gómez JM, Molina JR, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. Eur Urol. 2007 Nov;52(5):1398–406.

10 Di Stasi SM, Giannantoni A, Massoud R, Dolci S, Navarra P, Vespasiani G, et al. Electromotive versus passive diffusion of mitomycin C into human bladder wall: concentration-depth profiles studies. Cancer Res. 1999 Oct 1;59(19):4912–8.

11 Carando R, Pradere B, Afferi L, Marra G, Aziz A, Roghmann F, et al. The role of device-assisted therapies in the management of non-muscle invasive bladder cancer: a systematic review. Prog Urol. 2020 May;30(6):322–31.

12 Di Stasi SM, Valenti M, Verri C, Liberati E, Giurioli A, Leprini G, et al. Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. Lancet Oncol. 2011 Sep;12(9):871–9.

13 Gan C, Amery S, Chatterton K, Khan MS, Thomas K, O'Brien T. Sequential bacillus Calmette-Guérin/electromotive drugadministration of mitomycin C as the standard intravesicalregimen in high-risk non-muscle invasive bladder cancer: 2-year outcomes. J Urol. 2016 Jun;195(6):1697–703.

14 Racioppi M, Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi PF. Electromotive drug administration (EMDA) of mitomycin C as first-line salvage therapy in high risk "BCG failure" non muscle invasive bladder cancer: 3 years follow-up outcomes. BMC Cancer. 2018 Dec 6;18(1):1224.

15 Carando R, Zazzara M, Cotrufo S, Ludovico GM. Intravesicaltreatment with electro-mediated administration of mytomicin C as prophylaxis for intermediate and high-risk non-muscle-invasive bladder cancer: a retrospective multicenter study. Urol Int. 2019;103(3):285–90.

16 Carando R, Soldini E, Cotrufo S, Zazzara M, Ludovico GM. Electro-mediated drug administration of mitomycin C in preventing non-muscle-invasive bladder cancer recurrence and progression after transurethral resection of the bladder tumour in intermediate- and high-risk patients. Arab J Urol. 2020;19(1):71–7.