

**EMDA<sup>®</sup>**

Electromotive Drug Administration

Executive Summary  
Electromotive Drug Administration  
(EMDA)  
Non-Muscle Invasive Bladder Cancer

**PHYSION<sup>®</sup>**

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## I) BACKGROUND

Bladder cancer worldwide is the 7<sup>th</sup> most common cancer in men and the 10<sup>th</sup> in women.

Most bladder tumors (75-80%) are non-muscle invasive transitional cell carcinomas (Stage Ta, T1 and Tis).

Incidence rate is consistently lower in women than men, although sex differences varied greatly between countries.

There were almost 500.000 new cases in 2018.

Even in case of an adequate and complete TURBT about 50-70% of patients will recur in time and 20-40% will progress to muscle invasive disease: in order to reduce recurrent adjuvant therapy has been adopted by urologists (bladder instillation of cytotoxic and immunotherapeutic agents).

The key challenge is to prevent recurrence and disease progression.

## II) ELECTROMOTIVE DRUG ADMINISTRATION (EMDA)

Electromotive Drug Administration (EMDA) is a non-invasive method of enhancing local drug penetration across the urothelium of the bladder.

EMDA can be used either prior to or after TURBT.

The purpose of EMDA is to augment the effect of intravesical chemotherapy by creating an electric field across the bladder wall which increase urothelium's permeability.

The electric field stimulates directional ionic and solute movement of intravesical fluid: drug is delivered to a greater tissue depth and results in greater concentration than is possible with passive diffusion.

Furthermore the rate of drug administration is controllable, varying the current intensity.

The applied electric current causes no biological damage to tissue and no chemical modification of drug.

## II.1) PROCEDURE

The procedure can be conducted on an outpatient basis. With the patient in a supine position electrodes are placed on the skin of the lower abdominal wall, an intravesical electrode contained in a specially designed catheter is then inserted into the bladder through the urethra, using an anesthetic gel as lubricant. A chemotherapeutic drug solution, usually mitomycin C (MMM-C) in bidistilled water, is instilled intravesical into the bladder through the catheter, as in standard intravesical chemotherapy. The cutaneous and intravesical electrodes are connected to a generator that creates an electric field. Treatment lasts for 20-30 minutes. After the procedure the bladder is drained and the catheter is removed.



## II.2) PHARMACODINAMICS

Mechanism of transport with Electromotive Drug Administration (EMDA) to the urinary bladder

- Electromotive drug administration to the urinary bladder: an animal model and preliminary results – Journal of Urology, 1996, Gürpınar T et al.  
Anesthetized adult mongrel dogs were studied. An intravesical anode was inserted through a Foley catheter into the urinary bladder. Two patch electrodes were positioned on the animals' abdominal skin. Both skin and intravesical electrodes were attached to a direct current generator.

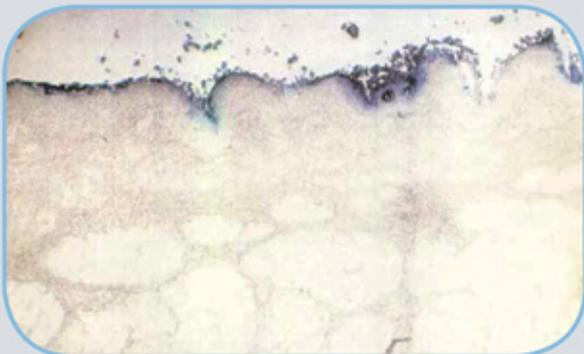
The bladder was then distended with an anionic blue dye (methylene blue). 15 mA pulsed direct current was applied for 40 minutes. After EMDA, the bladder was surgically removed and representative sections of full thickness bladder wall were immediately frozen in liquid nitrogen. Methylene blue was used to visually demonstrate EMDA-enhanced anion penetration into bladder submucosa and muscularis. This experimental model demonstrates significant submucosal and muscularis methylene blue penetration in the presence of an electric field. Same results were achieved with MMC-C in humans.

- Electromotive delivery of Mitomycin C into human bladder wall - Cancer Research 1997, Di Stasi SM et al.
- Electromotive versus Passive Diffusion of Mitomycin C into human bladder wall – Cancer research 1999, Di Stasi SM et al.

Tissue sections of human bladder were inserted into two chamber diffusion cells with urothelium exposed one to passive diffusion of MMC (control) and one to “active” diffusion of MMC potentiated by electric current (EMDA).

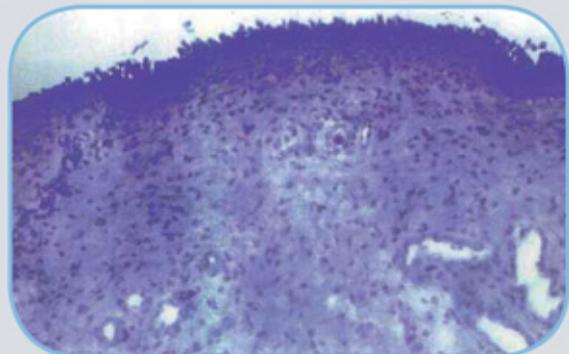
**Without EMDA:**

Less MMC in the bladder wall

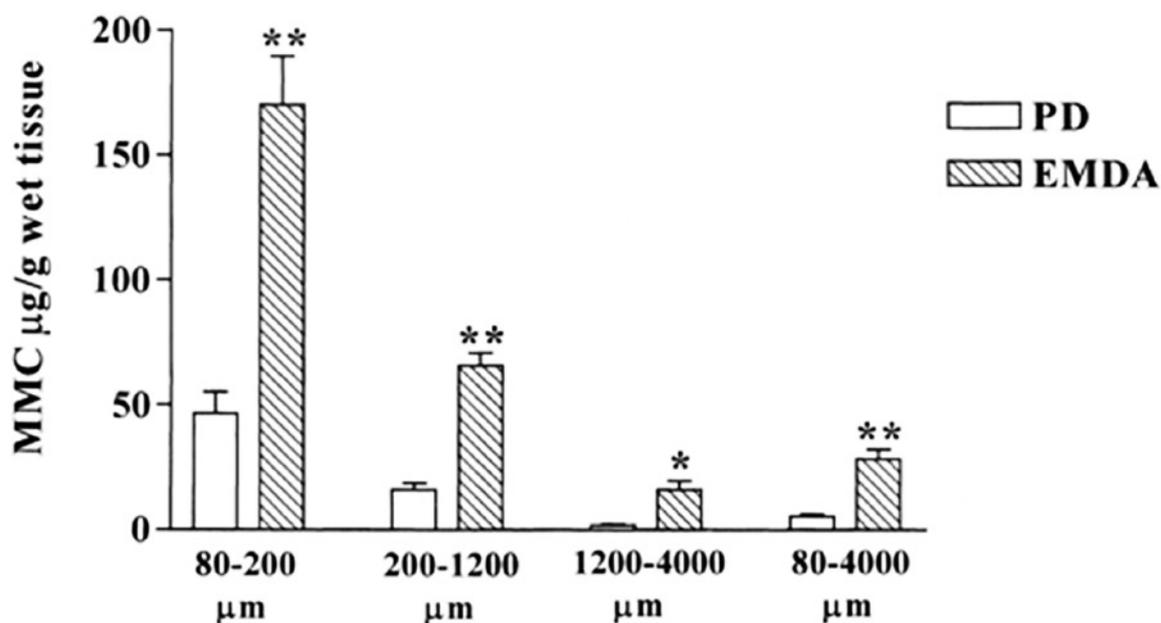


**With EMDA:**

More MMC in the bladder wall



EMDA significantly increases MMC-C concentration in all of the layers of the bladder wall (urothelium, lamina propria and superficial muscle layers): MMC-C concentration is 4-7 times increased (plasma levels remains well below toxic concentration).



Data below are expressed as µg of MMC/g of wet tissue, the means ± 1 SE of 14 experiments per group.  
 \*, p < 0.0005 and \*\*, p < 0.0001 versus PD

UROTHELIUM P<0.0001	PD MMC	46.6	<b>3.7</b>
	EMDA MMC	170.0	
LAMINA PROPRIA P<0.0001	PD MMC	16.1	<b>4.1</b>
	EMDA MMC	65.6	
MUSCULARIS P<0.0001	PD MMC	1.9	<b>8.4</b>
	EMDA MMC	15.9	

Concentration of MMC (µg/g of wet tissue) in bladder wall tissue layers after PD and EMDA

**EMDA enhances administration of MMC into bladder wall tissue and reduce variability in drug delivery rates**

### III) EVIDENCE-BASED TREATMENT

Many authors have published studies about Electromotive Drug Administration for non muscle invasive bladder cancer.

Different clinical protocols have been studied to evaluate the impact of EMDA/MMC-C and compare the different modalities of treatment with EMDA/MMC-C.

Publications	Type of trial	Patients	Tumors	Peer-reviewed journals
Brausi 1998	non-RCT	28	pTa and pT1	Urology
Riedl 1998	Case series	22	pTa, pT1 and pTis	Journal of Urology
Di Stasi 2003	RCT	108	pTis, pTis +pT1	Journal of Urology
Di Stasi 2006	RCT	212	pT1 and pTis; high risk	The Lancet Oncology
Sockett 2008	non-RCT	22	pTis, pTa/T1G3	BJU Int, BAUS 2008
Di Stasi 2011	RCT	374	pTa and pT1; intermediate and high-risk	The Lancet Oncology
Di Stasi 2012	RCT	212	pT1	Journal of Urology, AUA 2018
Rehme, Rubben 2015	Non-RCT	25	pTa, pT1	Der Urologe
O'Brien 2016	RCT	151	High grade Ta/T1 (48%) High grade Ta/T1 + Cis (32%) Primary Cis (18%) Recurrent large Volume low grade Ta ( 2%)	Journal of Urology
Racioppi, Bassi 2018	non-RCT	26	pTa, pT1 and pTis	BMC Cancer
Juvet, Zlotta 2018	non-RCT	30	TaG3 (15,4%), T1G3 (53,8%), Tis (15,4%), TaT1G3 +Tis (15,4 %)	Journal of Urology, AUA 2018
Di Modugno, Pagliarulo 2018	non-RCT	87	NMIBC high-risk	SIU 2018

### III.1.1)

Intravesical electromotive administration of drugs for treatment of superficial bladder cancer: a comparative phase II study - Urology 1998 Mar; 51(3): 506-9 – Brausi M, Ramazzini Hospital Center, Carpi , Modena, Italy.

Patients	Primary endpoint	Efficacy results
28 patients with multifocal Ta-T1, G1-G2, primary or recurrent NMIBC - 13 were assigned to receive 40 mg mitomycin C once a week for 8 weeks (group A) - 15 were treated with EMDA-MMC C once a week for 8 weeks All lesions in the bladder were previously resected except one (marker) Marker lesion diameter: 0,4-1,5 cm	Evaluate the efficacy of electromotive drug administration ( EMDA ) of mitomycin-C  Median follow-up : 16,3 months	<b>Group A</b> Complete responder * ( CR ): 41.6 % In responder patients recurrence rate was 60 % and disease free interval was 10.5 months  <b>Group B:</b> CR* : 40% In responder patients recurrence rate was <b>33%</b> and and disease free interval was <b>14.5</b> months

\*Complete responder: patients who demonstrate complete macroscopic and histological disappearance of the marker lesion with negative cytology (CR)

	Group A	Group B
RECURRENCE RATE	60%	33%
DISEASE FREE INTERVAL (months)	10.5	14.5

**Patients in EMDA-MMC group have a longer disease free interval and a lower recurrence rate**

### III.1.2)

Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study vs BCG - Journal of Urology 2003; 170 (3):777-782-  
Di Stasi SM, Stephen RL et al.

Patients	Primary endpoint	Efficacy results
<p>108 patients with histologically proven multifocal carcinoma in situ (Tis) of the bladder (most had concurrent pT1 papillary transitional cell carcinoma) were randomly assigned to three groups:</p> <ul style="list-style-type: none"><li>- 81 mg BCG (n° 36)</li><li>- 40 mg EMDA/MMC (n° 36)</li><li>- 40 mg PD/MMC (n° 36)</li></ul> <p>Patients in the 3 groups who had complete response to the initial 6 weekly treatments underwent a further 10 monthly instillations. If cancer persisted at 3 months, a second 6-week course was given. If disease persisted at 6 months, there was a crossover to a 6-week second line course of BCG for patients in the two MMC groups and EMDA/MMC for patients in the BCG group.</p>	<p>The primary study endpoint was a complete response at 3 and 6 months following treatment. The aim was to evaluate differences between responses to PD/MMC estimated at 33% and to EMDA/MMC, anticipated to be equivalent to that of a BCG response rate of 70%</p>	<p>The complete response for EMDA/MMC vs PD/MMC at 3 and 6 months was 53% versus 28% (p&lt;0.036) and 58% vs 31% (p&lt;0.012). For BCG the responses were 56% and 64%. Median time to recurrence was 35 vs 19.5 months (p&lt;0.013) and for BCG it was 26 months.</p>

	MMC	EMDA MMC	BCG
N°	36	36	36
COMPLETE RESPONSE AT 3 MONTHS	28%	<b>53%</b>	56%
COMPLETE RESPONSE AT 6 MONTHS	31%	<b>58%</b>	64%
TIME TO RECURRENCE (months)	19,5	<b>35</b>	26

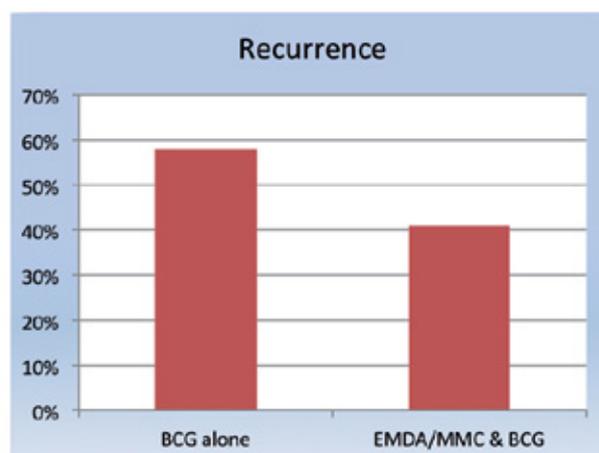
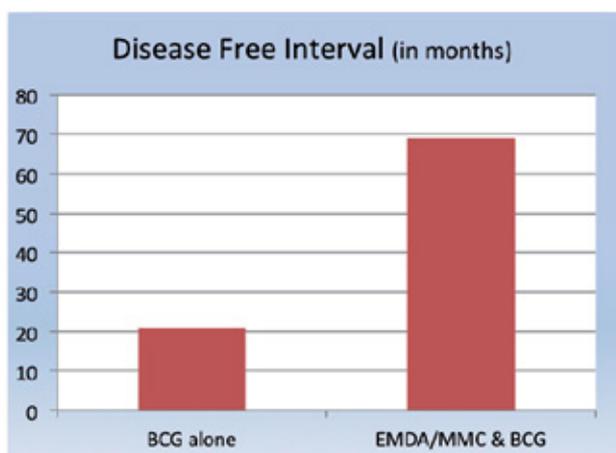
**EMDA increases bladder uptake of MMC, resulting in an improved response rate and an improved median time to recurrence**

### III.1.3)

Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial – The Lancet Oncology 2006; 7 (1):43-51- Di Stasi SM, University Tor Vergata, Rome, Italy.

Patients	Primary endpoint	Efficacy results
<p>212 patients with stage pT1 bladder cancer were randomly assigned to two groups:</p> <ul style="list-style-type: none"><li>- 81 mg BCG a week for 6 weeks (n°105)</li><li>- 81 mg BCG once a week for two weeks, followed by 40 mg EMDA/MMC once a week as one cycle for three cycles (n° 107)</li></ul> <p>Complete responders underwent maintenance treatment:</p> <ul style="list-style-type: none"><li>- those assigned BCG alone had one infusion of BCG once/months for 10 months</li><li>- those assigned BCG and EMDA/MMC had 40 mg EMDA/MMC once a month for 2 months, followed by 81 mg BCG once a month as one cycle for three cycle</li></ul>	<p>The primary endpoint was</p> <ul style="list-style-type: none"><li>- either disease-free survival in patients without carcinoma in situ</li><li>- or period from randomisation to first recurrence noted by cystoscopy in patients with TCC</li></ul>	<p>At a mean follow-up of 88 months patients assigned to sequential BCG-EMDA/MMC group had a higher disease-free interval than did those assigned to BCG alone (69 months vs 21 months).</p> <p>Patients assigned to sequential BCG-EMDA/MMC also group had lower recurrence (41,9% vs 57.9%), progression (9.3% vs 21.9%) and overall mortality (21.5% vs 32.5%)</p>

88 months Follow-up	BCG	BCG-EMDA MMC
N°	105	107
DISEASE FREE INTERVAL (months)	21	<b>69</b>
RATE OF RECURRENCE	57,9%	<b>41,9%</b>
PROGRESSION	21,9%	<b>9,3%</b>
OVERALL MORTALITY	32,4%	<b>21,5%</b>
DISEASE-SPECIFIC MORTALITY	16,2%	<b>5.6%</b>



**Patients in sequential BCG-EMDA MMC group have a higher disease free interval (69 months) and a lower recurrence than patients in BCG alone group (21 months)**

### III.1.4)

Sequential bacillus Calmette-Guérin/Electromotive Drug Administration of Mitomycin C as the Standard Intravesical Regimen in high-risk non muscle invasive bladder cancer: 2-year Outcomes - Journal of Urology Vol.195, 1697-1703 June 2016 – Christine Gan, Tim O’Brien, Guy’s and St. Thomas’ National Health Service Trust, London, UK.

Patients	Primary endpoint	Efficacy results
<p>Of the 151 patients with high risk, non-muscle invasive bladder cancer treated between June 2009 and 2013, 44 underwent primary cystectomy and 107 received BCG plus EMDA/MMC.</p> <p>Disease was high grade Ta/T1 in 86 patients (80%), of whom 34 (32%) also had Tis. A total of 19 patients (18%) had primary Tis and 2 (2%) had recurrent large volume, low grade disease.</p>	<p>Primary outcomes were the recurrence rate at first, 1-year and 2-years cystoscopy</p>	<p>Of the 107 patients receiving BCG plus EMDA/MMC 104 underwent first check cystoscopy, including 90 (87 %) who were clear. Of the 90 complete responders 86 underwent 1-year cystoscopy, including 74 (86 %) who were recurrence-free.</p> <p>Of these 74 patients, 71 underwent 2-year cystoscopy, of whom 66 (93 %) remained recurrence-free</p>

COMPLETE RESPONSE RATE	<b>87%</b> (n°90)
DISEASE FREE RATE AT 1 YEAR	<b>86%</b> (n°74)
DISEASE FREE RATE AT 2 YEARS	<b>93%</b> (n°66)
PROGRESSION RATE AT 2 YEARS	<b>3%</b>

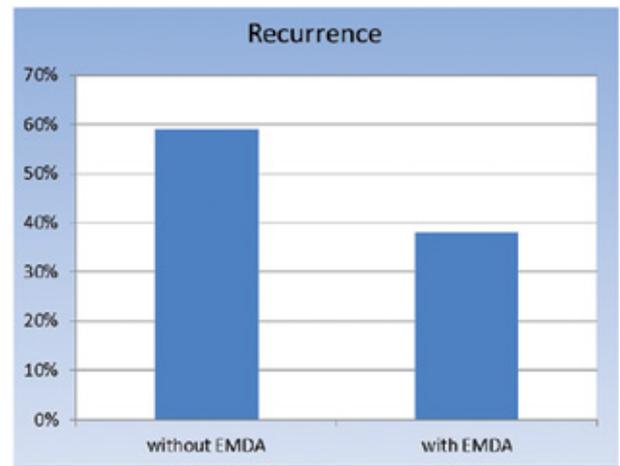
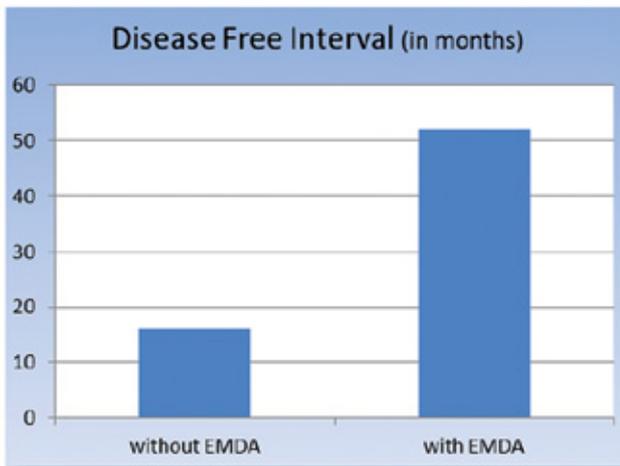
**This study confirms the excellent oncology efficacy of sequential BCG/Electromotive Drug Administration of MMC-C in cases of high-risk non muscle invasive bladder cancer**

### III.1.5)

Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial – The Lancet Oncology Vol 12 September 2011 – Di Stasi SM, University of Rome Tor Vergata, Italy.

Patients	Primary endpoint	Efficacy results
<ul style="list-style-type: none"> <li>- 124 patients were randomly assigned to receive TURBT alone</li> <li>- 126 to receive immediate post-TURBT PD/MMC</li> <li>- 124 to receive immediate pre-TURBT EMDA/MMC</li> </ul> <p>Eligible participants had histologically proven primary pTa and pT1 urothelial carcinoma of the bladder</p>	<p>The primary endpoint were:</p> <ul style="list-style-type: none"> <li>- recurrence rate</li> <li>- disease-free interval for patients who were disease-free after treatment</li> </ul>	<p>Patients assigned to receive EMDA/MMC before TURBT had a lower rate of recurrence (38%) than those assigned to receive PD/MMC (59%) after TURBT and TURBT alone (64%)</p> <p>Patients assigned to receive EMDA/MMC before TURBT also had a higher disease-free interval (52 months) than those assigned to receive PD/MMC after TURBT (16 months) and TURBT alone (12 months)</p>

86 months Follow-up	TURBT	PD MMC POST-TURBT	EMDA MMC PRE-TURBT
N°	116	119	117
DISEASE FREE INTERVAL (months)	12	16	<b>52</b>
RATE OF RECURRENCE	64%	59%	<b>38%</b>



**Intravesical EMDA-MMC pre-Turbt reduces recurrence rates and enhances the disease free interval (compared with intravesical PD MMC post-Turbt and Turbt alone) because tumor cells that could implant were killed**

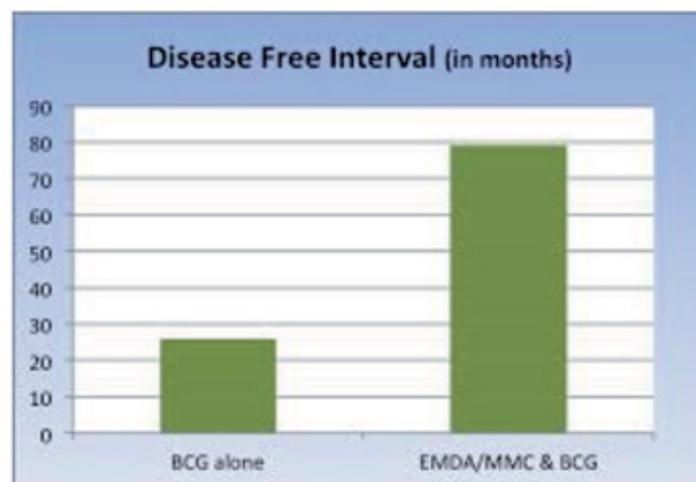
### III.1.6)

Intravesical sequential bacillus Calmette-Guérin and electromotive mitomycin versus bacillus Calmette-Guérin alone for stage pT1 urothelium bladder cancer – AUA annual meeting 2012, abstract 1670.22-5-2012 – Di Stasi SM.

Is Intravesical BCG alone still the only truly effective intravesical therapy for non-muscle invasive bladder cancer ? - Journal of Urology Vol.193, No. 4S, Supplement, Saturday, May 16, 2015 – Di Stasi SM.

121-month follow up of the 212 patients included in the study “Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial - The Lancet Oncology 2006”

121 months Follow-up	BCG-EMDA MMC	BCG
DISEASE FREE INTERVAL (months)	<b>79</b>	26
RATE OF RECURRENCE	<b>45%</b>	62%
RATE OF PROGRESSION	<b>12%</b>	28%
OVERALL MORTALITY	<b>44%</b>	59%
DISEASE-SPECIFIC MORTALITY	<b>9%</b>	23%



**Patients assigned to BCG-EMDA MMC group have a higher disease free interval and a lower recurrence than patient in BCG alone group: in patients with pT1 NMIBC, BCG-EMDA MMC provided better results than BCG alone**

### III.1.7)

Intravesical sequential BCG/Electromotive drug administration Mitomycin C ( EMDA-MMC ) in high risk non muscle invasive bladder cancer- results from a retrospective analysis- Di Modugno, Pagliarulo, Ditunno et al., Policlinico di Bari Urologia II, Italy.

<p>This study confirms the efficacy of sequential administration of intravesical BCG and EMDA-MMC in terms of clinical response, complication rate and patients' compliance</p>	<p>87 patients with high-risk non muscle invasive bladder cancer</p> <p>Median follow-up 43 months</p>	<p>Disease recurrence was found in 17/87 patients (19,5%)</p> <p>Only 2/87 patients had a disease progression (2,3 %)</p>
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### III.1.8)

Studies on high-risk “BCG failure“ NMIBC

- Electromotive drug administration (EMDA) of intravesical MMC C in patients with high risk and failure of BCG immunotherapy, BJU Int. 2008, Sockett L, Borwell L et al.
- 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 December 6, 2018 – Racioppi M, Bassi PF et al. – Policlinico Gemelli, Rome, Italy.

Patients	Primary endpoint	Efficacy results
<p>26 patients with high grade NMIBC unresponsive after at one cycle of intravesical immunotherapy with BCG. Patients received 6 weekly instillation of MMC (40 mg) and then a monthly treatment for a total of 6 treatments.</p>	<p>Determinate the efficacy (in terms of recurrence and progression) of EMDA MMC in patients having failed treatment with BCG</p>	<p>After 3 years of follow-up, 16 patients (61,5 %) preserved their bladder, 10 patients (38,4 %) underwent radical cistectomy. Disease-free rates at 3 years follow-up were: 75% (TaG3), 71,4% (T1G3), 50% (Cis) and 25% (TaT1G3+Cis)</p>

	DISEASE-FREE RATES AT 3 YEARS
TaG3	75%
T1G3	71,4%
Tis	50%
TaT1G3 + Tis	25%

- Sequential administration of BCG and electromotive drug administration (EMDA) of mitomycin C (MMC) in non muscle invasive bladder cancer having previously received intravesical therapy – Journal of Oncology Vol.199, No.4S, Supplement, Monday, May 21, 2018 – Juvet T, Zlotta A et al. Princess Margaret Hospital Cancer Center, Toronto, Canada.

**The EMDA MMC treatment is an efficacy tool in the long term conservative strategy of the high-risk non-muscle invasive bladder cancer unresponsive to BCG**

## IV) SAFETY

In different studies, the groups did not differ in the frequency or severity of side effects.

For examples, the tables below display the percentage of side effects in the study published in the Journal of Urology 2003 and in the Lancet Oncology 2006.

TABLE 2. Adverse effects in patients who received at least 1 or more intravesical treatments

Adverse Effect	No. BCG (%)	No. Passive MMC (%)	No. Electromotive MMC (%)	p Value (Fisher exact test)
Urinary frequency	21 (58.3)	6 (16.7)	7 (19.4)	0.001
Bacterial cystitis	9 (25.0)	7 (19.4)	7 (19.4)	0.874
Drug induced cystitis	24 (66.7)	9 (25.0)	13 (36.1)	0.001
Visible hematuria	26 (72.2)	6 (16.7)	8 (22.2)	0.001
Prostatitis	1 (2.8)	0	0	1.000
Epididymitis	1 (2.8)	0	0	1.000
Fever	7 (19.4)	0	0	0.001
General malaise	11 (30.5)	1 (2.8)	0	0.001
Fatigue	16 (44.4)	0	1 (2.8)	0.001
Allergic reactions	0	2 (5.6)	3 (8.3)	1.000
Treatment modified:				
No	10 (27.8)	26 (72.2)	21 (58.4)	
Yes, continued	22 (61.1)	8 (22.2)	12 (33.3)	0.003
Yes, stopped	4 (11.1)	2 (5.6)	3 (8.3)	

Local and systemic side effects are significantly more prominent in the BCG arm than in EMDA MMC arm.

LANCET Oncology 2006; 7(1):43-51	BCG (%) (n=105)	Seq BCG and EMDA mitomycin C (%) (n=107)
Dysuria	51 (48.5%)	54 (50.5%)
Bacterial cystitis	14 (13.3%)	16 (14.9%)
Drug-induced cystitis	46 (43.8%)	49 (45.8%)
Macroscopic haematuria Prostatitis	61 (58.1%)	64 (59.8%)
Protatitis	1 (1%)	0
Fever	24 (22.8%)	21 (19.6%)
Influenza-like symptoms	34 (32.4%)	33 (30.8%)
Fatigue	32 (30.5%)	32 (29.9%)

Toxic effects associated with sequential BCG-EMDA MMC are no worse than those associated with BCG alone and were mainly localised to the bladder.

A recent study shows safety of EMDA-assisted instillation:

- Non muscle invasive bladder cancer. Safety of postoperative EMDA-assisted instillation of miyomycin – Der Urologe 2015 – Rehme C, Rubben H., University Hospital Essen

25 patient diagnosed with NMIBC underwent post-TURBT EMDA/MMC instillations. Blood sample was taken before starting the procedure and 15, 30, 60 and 120 min after starting the procedure for quantification of MMC serum level

In 24 patients the measured serum level of MMC was below 50 ng/ml.  
In 1 patients serum level was elevated 15 min (155 ng/ml) and 30 min (65 ng/ml) after instillation

**EMDA is a safe procedure: the measured mitomycin serum level were always below toxic concentration (400 ng/ml)**

## V) CONCLUSION

The studies discussed above evidenced 3 different modalities of treatment with EMDA/MMC-C :

1. EMDA/MMC-C instillation in intermediate-risk non muscle-invasive bladder cancer and for BCG “failure“ and intolerance patients
2. Sequential BCG – EMDA/MMC treatment for high-risk non muscle-invasive bladder cancer
3. Pre-TURBT instillation of EMDA/MMC non muscle invasive bladder cancer

The results of these studies in intermediate and high risk NMIBC patients treated with EMDA/MMC, show significant short and long-term benefits with median disease-free interval longer and lower rate of recurrence.

An appropriate patients follow-up was done during two to twelve years post treatment administration.

EMDA technology reduces medium term and long term costs ( less cystectomies, less cystoscopies) and improve patients confort, tolerance and clinical data.

In addition, the 10-year cost-effectiveness randomized study comparing sequential treatments with BCG/EMDA MMC-C versus BCG alone, shows that the sequential therapy is a cost-effective treatment for patients with high risk non muscle invasive bladder cancer.

## VI) PUBLICATIONS

- Gürpınar T, Truong LD, Wong HY, Griffith DP, Electromotive drug administration to the urinary bladder: an animal model and preliminary results – Journal of Urology, Vol.156, No.4,01.10.1996,p.1496-1501
- Di Stasi SM, Vespasiani G, Giannantoni A et al. Electromotive delivery of Mitomycin C into human bladder wall - Cancer Research March 1, 1997 Vol 57, 875-880
- Di Stasi SM, Stephen RL, Electromotive versus Passive Diffusion of Mitomycin C into human bladder wall – Cancer research October 1999 Vol 59, Issue 19
- Di Stasi SM, Giannantoni A, Stephen RL et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer:a prospective randomized study vs BCG - Journal of Urology 2003; (3): 777-782
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- Christine Gan, Tim O'Brien, Guy's and St. Thomas' National Health Service, Trust Sequential bacillus Calmette-Guérin/Electromotive Drug Administration of Mitomycin C as the Standard Intravesical Regimen in high-risk non muscle invasive bladder cancer: 2-year Outcomes - Journal of Urology June 2016 Vol.195, 1697-1703
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The background of the entire page is a solid blue color. Overlaid on this is a complex geometric pattern of thin, light-colored lines. These lines form a series of concentric, overlapping curves that create a sense of depth and perspective, resembling a tunnel or a funnel that narrows towards the center. The lines are most densely packed in the center and become more sparse towards the edges.

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