EMDA MMC prior to TURBT
it's not all about visualisation

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Disclosure

I have no relevant relationships to disclose.

Mitomycin C Pharmacodynamics in Cultured Human Bladder Tumors

MMC concentrations needed to produce 90% inhibition of tumor cell proliferation

- **Urothelium** — **16 μg/ml**
- **Lamina Propria** — **25 μg/ml**
- **Muscolaris** — **43 μg/ml**

Schmittgen et al, Cancer Res 1991

Bladder Wall Penetration of Intravesical Mitomycin C in Dogs

Inhibitory Concentrations

- **Urothelium** **100%**
- **Lamina Propria** **20%**
- **Muscolaris** **17%**

Wientjes et al., Cancer Res., 1991

EMDA

ElectroMotive Drug Administration

IONTOPHORESIS

+

ELECTROOSMOSIS/ELECTROPHORESIS

(solute-solvent and solute-solute coupling)

+

ELECTROPORATION

(“flip-flop gating mechanism”)

Stephen RL et al., Artif. Org., 1994

EMDA: Laboratory Summary

1. **MMC administration rates**
   - **EMDA > PD by a factor of 4-7**
2. **Coefficient of Variation (CV)**
   - **EMDA < PD**

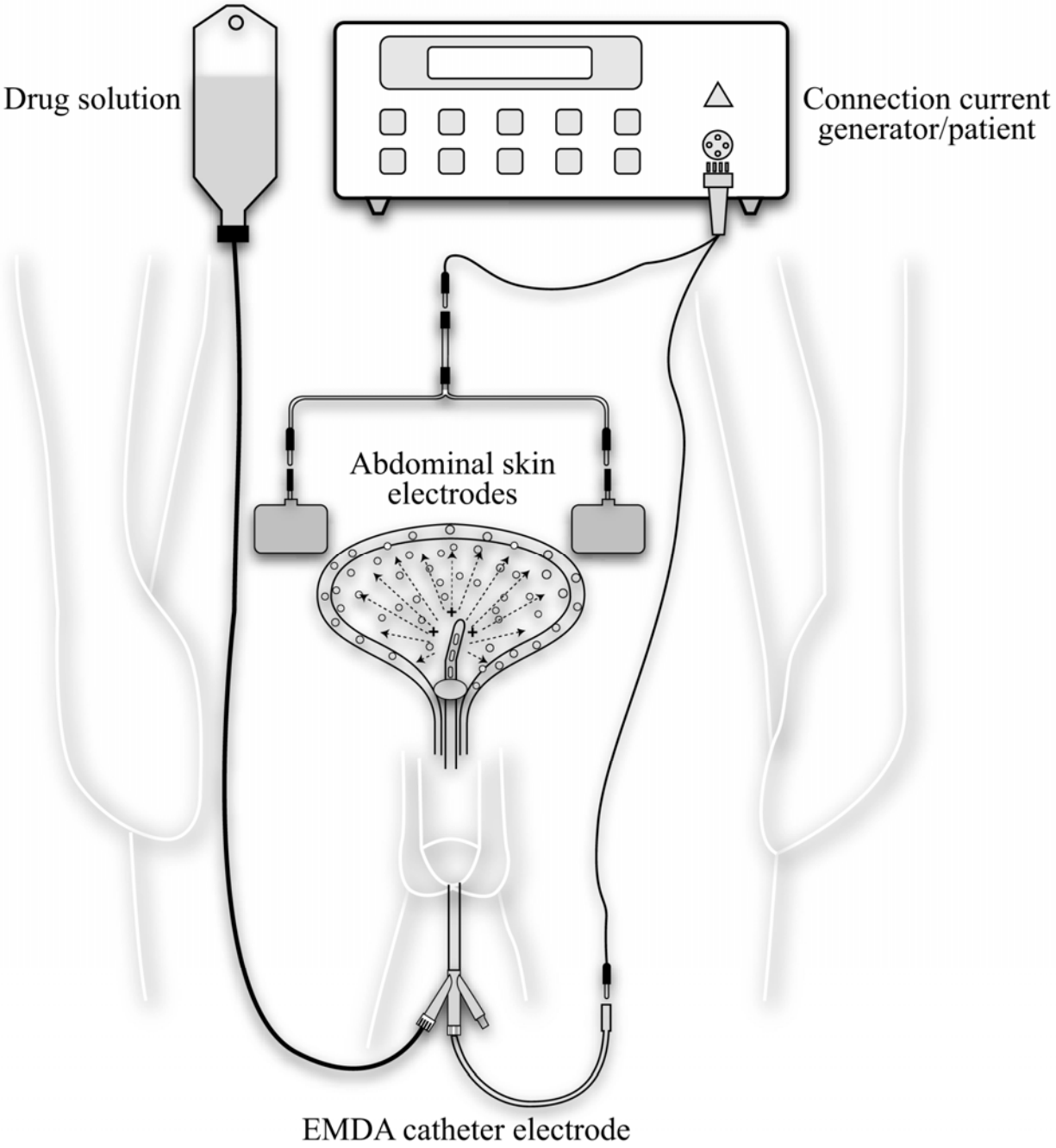
Di Stasi SM et al, Cancer Res 1997

3. **Labelling index: IC90**

Urothelium	**EMDA=14/14**	**PD=13/14**
Lamina propria	**EMDA=14/14**	**PD= 3/14**
Muscularis	**EMDA= 1/14**	**PD= 0/14**

4. **Rapid PD equilibrium by 15 min**
   - **? MMC metabolism**
   - **? Absorption blockade**

Di Stasi SM et al, Cancer Res 1999


Drug solution
Connection current generator/patient
Abdominal skin electrodes
EMDA catheter electrode

EMDA/MMC vs PD/MMC vs BCG
Cis of the bladder: long-term follow-up

Median follow-up 82.5 months

	PD/MMC (n=36)	EMDA/MMC (n=36)	BCG (n=36)	p-value
Complete Response Rates				
• 6 months	27.8	52.8	55.5	0.0361
• 3 months	30.5	58.3	63.9	0.0123
• Crossover	----	23.1	35.0	0.5114
Recurrence				
• % Patients	82.8	66.7	65.7	0.2211
• Median time to rec. mos	9.1	15.0	17.8	<0.0001
Disease progression				
• % Patients	44.4	30.6	27.8	0.0612
• Median time to pro. mos	21.5	26.9	27.3	
Mortality rates				
• Any cause	52.8	47.2	52.8	0.4964
• Bladder cancer	30.6	22.2	22.2	0.4941

Di Stasi SM et al, J Urol 2003

Sequential BCG & EMDA/MMC vs BCG alone

Treatment Efficacy

Median follow-up 88 months

	BCG alone (n=105)	BCG/MMC (n=107)	P value
Recurrrence			
Patients (%)	**61/105 (58.1)**	**45/107 (42.1)**	**0.0012**
Median disease-free-time mos (CI)	**21 (15-54)**	**69 (55-86)**	**0.0221**
Progression to muscle invasive disease			
Patients (%)	**23/105 (21.9)**	**10/107 (9.4)**	**0.0047**
Median time to progression mos (CI)	**16.0 (10.0-21.0)**	**37.5 (17.8-58.0)**	**0.0030**
Mortality			
Death from any cause (%)	**34/105 (32.4)**	**23/107 (21.5)**	**0.0450**
Death from bladder cancer (%)	**17/105 (16.2)**	**6/107 (5.6)**	**0.0100**

Di Stasi SM et al, Lancet Oncol 2006

Peri-Operative Chemotherapy

Effect on recurrence rate

- **Meta-analysis of 7 randomized trials (1993-2002)**
- **1,467 patients; median follow-up: 3.4 years**
- **Relative risk of recurrence decreased of 40%**
- **Disease-Free Survival**
  - **TUR+Chemo = 63%**
  - **TUR alone = 52%**
  - **Single tumors = 64%**
  - **Multiple tumors = 35%**

Sylvester R et al, J Urol 2004

Early single instillation of chemotherapy after TURBT

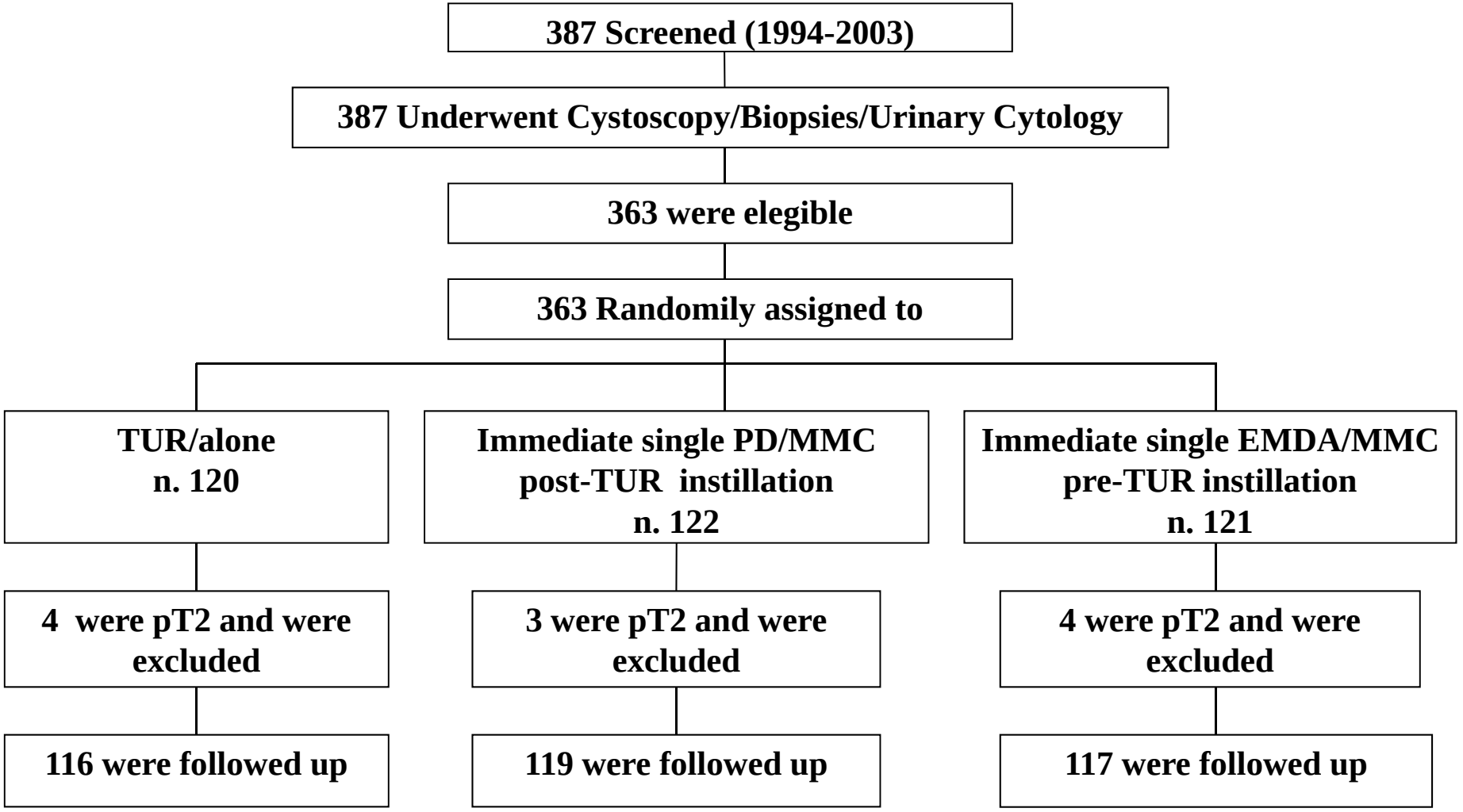
- **Significantly decreases the risk of recurrence (~50% at 2 yr & 15% at 5 yr) but is suboptimal in multifocal disease.**
- **Agent, optimal schedule and duration of treatment have not yet been standardized**
- **Sometimes the procedure is not tolerated for the full time of treatment and its potential benefits are probably decreased by premature evacuation of the drug because of spasms, leakage and hematuria**
- **If a bladder perforation occurs during TURBT, it can results in severe complications due to extravesical extravasation of the drugs**

Why an Immediate Single Pre-TUR Intravesical EMDA/MMC Instillation ?

- **An early single intravesical EMDA/MMC instillation after TURBT is strongly not recommended because**
  - **Further injury to resected urothelium**
  - **Further thrauma from catheterization**
  - **Consenquent bladder spasms**

- **Haematuria and bladder perforation are contraindications to intravesical EMDA /MMC**

STUDY DESIGN



Di Stasi SM et al, Lancet Oncol 2011; 12: 871–79

Methods

Randomization into 3 groups

- **TUR/alone**
- **Post-TUR (within 6 h) PD/MMC 40 mg/50 ml x 60 min**
- **Pre-TUR (immediately before anesthesia induction) EMDA/MMC 40 mg/100 ml + 20 mA x 30 min**
- **Intermediate (MMC) and high risk (BCG) NMIBC underwent adjuvant standard intravesical therapy.**

Follow-up

- **3 month interval: 2 years**
- **6 month interval: 3 years**
- **yearly: forever**

Data analysis

- **Primary endpoint: time to recurrence**
- **Intention-to-treat**

Baseline Characteristics by Treatment Group

	TUR alone (n=116)	MMC/PD Post-TUR (n=119)	MMC/EMDA Pre-TUR (n=117)
Sex			
• Male	92	92	92
• Female	24	27	25
Age (years)			
• Median (IQR)	66.5 (60-73)	67 (61-72)	67 (63-74)
Follow up (months)			
• Median (IQR)	92 (61-126)	82 (50-125)	85 (57-126)
Disease characteristics			
• Low risk	9	10	11
• Intermediate risk	75	77	73
* Unifocal	22	20	29
* Multifocal	53	57	54
• High risk	32	32	33
* Unifocal	5	5	6
* Multifocal	27	27	27

Recurrence Rate

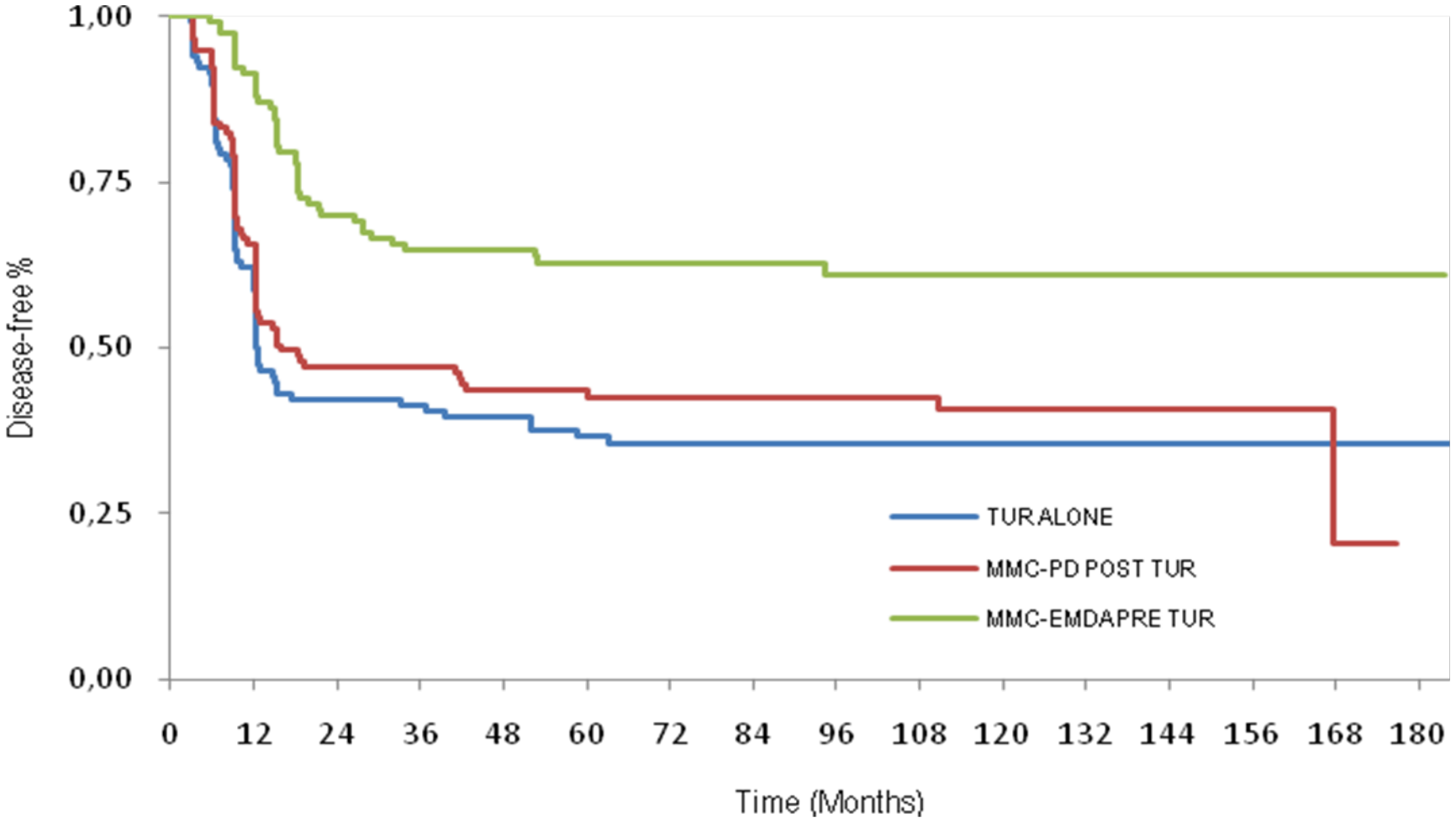
Median follow-up: 85.4 months

	TUR alone	post-TUR PD/MMC	pre-TUR EMDA/MMC	P value
No. of pts with recurrence				
Overall	**74/116 (64%)**	**70/119 (59%)**	**44/117 (38%)**	**<0.001**
Low-Risk	**0/9 (0%)**	**0/10 (0%)**	**1/11 (9%)**	**0.409**
Intermediate-Risk	**47/75 (63%)**	**46/77 (60%)**	**26/73 (36%)**	**0.001**
Single	**14/22 (64%)**	**12/20 (60.%)**	**6/19 (32%)**	**0.087**
Multiple	**33/53 (62%)**	**34/57 (60%)**	**20/54 (37%)**	**0.015**
High-Risk	**27/32 (84%)**	**24/32 (75%)**	**17/33 (51%)**	**0.012**
Single	**4/5 (80%)**	**3/5 (60%)**	**3/6 (50%)**	**0.587**
Multiple	**23/27 (85%)**	**21/27 (78%)**	**14/27 (52%)**	**0.017**

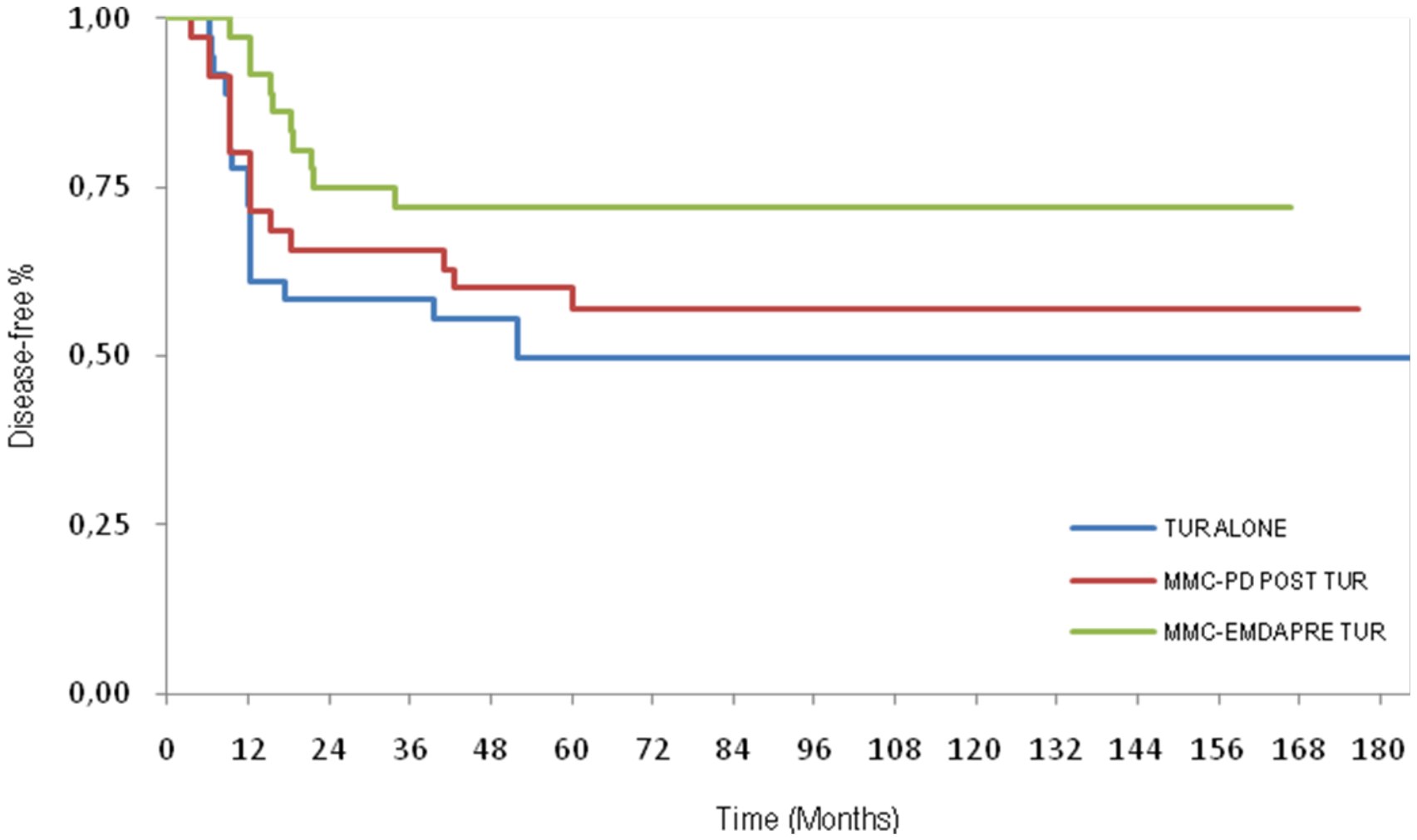
Disease-Free Interval

	TUR alone	post-TUR PD/MMC	pre-TUR EMDA/MMC	P value
Median Disease-Free Interval, Months (range)				
Overall	**13 (3-184)**	**16 (4-174)**	**57 (6-182)**	**<0.001**
Low-Risk	**121 (54-153)**	**128 (51-174)**	**66 (25-164)**	**0.387**
Intermediate-Risk	**13(3-184)**	**19 (6-166)**	**60 (56-182)**	**<0.001**
Single	**23 (7-184)**	**42 (7-156)**	**73 (10-165)**	**0.085**
Multiple	**13 (3-174)**	**16 (6-166)**	**58 (6-182)**	**0.004**
High-Risk	**11 (3-157)**	**11 (4-137)**	**19 (10-175)**	**<0001**
Single	**12 (7-85)**	**10 (4-137)**	**57 (12-146)**	**0.408**
Multiple	**10 (3-157)**	**12 (4-131)**	**18 (10-175)**	**<0.001**

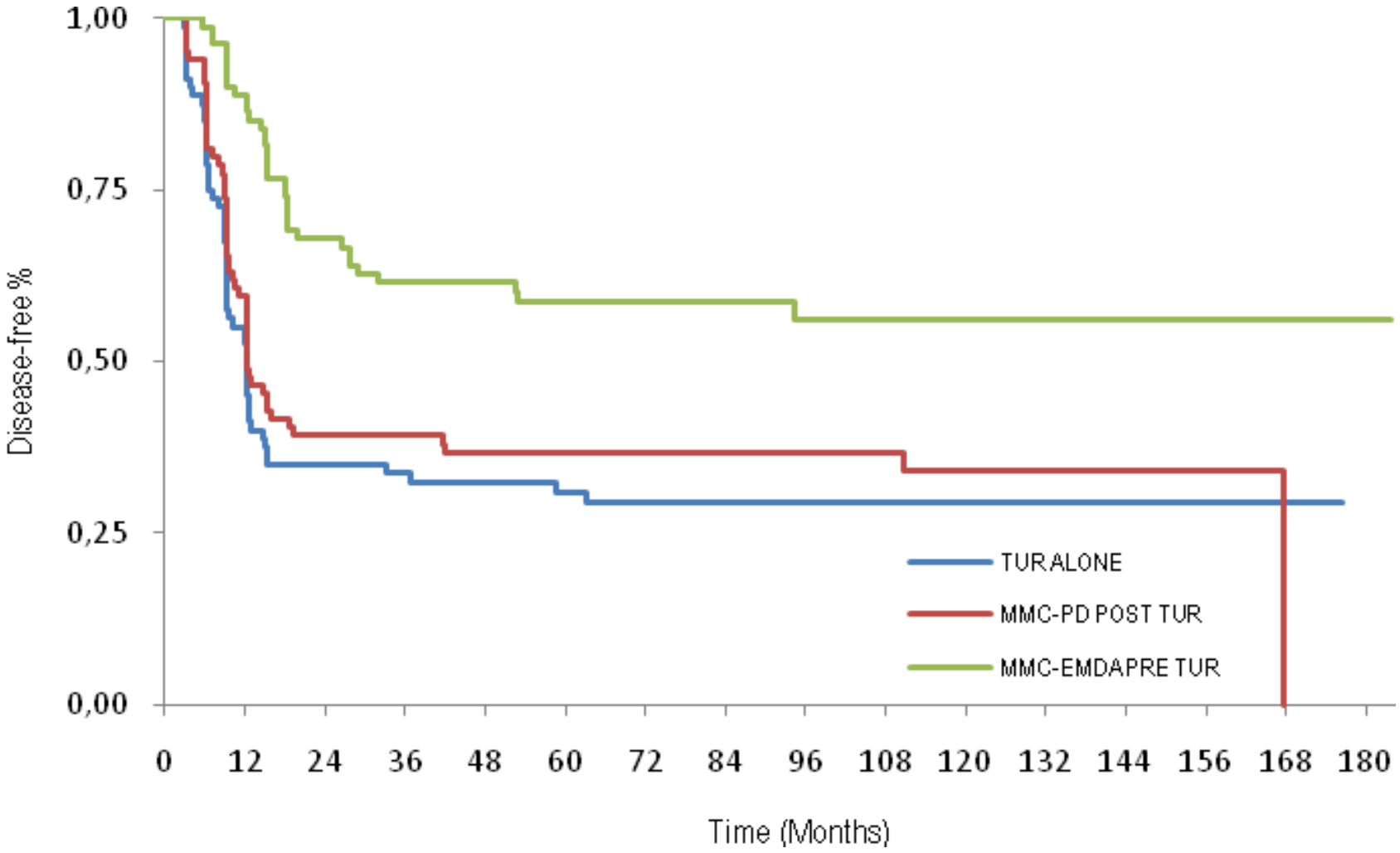
Overall Disease-Free Interval



Disease-Free Interval: Unifocal Disease



Disease-Free Interval: Multifocal Disease



Feasibility & Safety

Post-TUR PD/MMC group

- **Not administered** **21%**
  - **Overt bladder perforation** **8%**
  - **Macroscopic haematuria:** **13%**
- **Treatment stopped after 10-15 min** **24%**
  - **Discomfort/Pain**
  - **Bladder spasms**
  - **Leakage of drug solution**
- **Persistent lower urinary-tract symptoms**
  - **Unrecognized drug extravasion?**

Pre-TUR EMDA/MMC group

- **99% of patients completed treatment**

Conclusions

- **Intravesical EMDA/MMC is feasible, safe and effective**
- **EMDA/MMC is more effective than PD/MMC in high risk non-muscle invasive bladder cancer**
- **Sequential EMDA/MMC and BCG: reduced recurrence, tumour progression and mortality**
- **Pre-TUR EMDA/MMC: reduced recurrence and was tolerated better than post-TUR PD/MMC**
- **More controlled clinical trials are required to confirm these benefits, and examine the role of EMDA in the overall management of non-muscle invasive bladder cancer**

Intravesical MMC Solutions Employed Clinically

	Dose (mg)	Excipient (mg)	Volume (ml)	MosM
USA	40	Mannitol 80	40 H_2O	14
EUROPE	40	NaCl 960	50 NaCl 0.9%	960