

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrically-stimulated intravesical chemotherapy for superficial bladder cancer

This procedure, also known as electromotive drug administration (EMDA) of intravesical chemotherapy, can be used for patients with bladder cancer, either before or after surgery. A solution including a chemotherapy drug is injected into the bladder using a thin tube inserted through the urethra. At the same time, an electrode is inserted in the bladder and other electrodes are placed on the skin of the lower abdomen. An electric current is then created with the aim of improving absorption of the chemotherapeutic drugs.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2008.

Procedure name

- Electrically-stimulated intravesical chemotherapy

Specialty societies

- British Association of Urological Surgeons

Description

Indications and current treatment

Bladder cancer.

Transitional cell carcinoma is the most common form of bladder cancer. It begins in the bladder lining (urothelium). Superficial disease is defined as cancer that is confined to the bladder lining and has not invaded the muscle layer.

Most patients with bladder cancer have superficial disease. For these patients, treatment consists mainly of transurethral resection (TUR), in which malignant tissue is removed by electrocautery under cystoscopic control. Intravesical chemotherapy with *Bacillus Calmette-Guérin* (BCG) vaccine or other chemotherapy agents may also be used, either on its own or as adjuvant therapy after TUR, to reduce the probability of cancer recurrence. Intravesical microwave hyperthermia combined with intravesical chemotherapy has also been used. Most patients treated with any of the above procedures (either alone or in combination) undergo periodic cystoscopy follow-up, and re-treatment may be necessary.

For patients with more advanced disease, radical cystectomy may be necessary.

What the procedure involves

Electrically-stimulated or electromotive drug administration (EMDA) of intravesical chemotherapy can be used either prior to or after TUR (neoadjuvant or adjuvant treatment, respectively). The purpose of EMDA is to augment the effect of intravesical chemotherapy by creating an electric field across the bladder wall. The electric field stimulates directional ionic and solute movement of the intravesical fluid, which increases absorption of the chemotherapeutic solution.

The procedure can be conducted on an outpatient basis under local anaesthesia. 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 anaesthetic urethral gel as a lubricant. A chemotherapeutic drug solution, usually mitomycin C (MMC) in saline or distilled water, is instilled into the bladder through the catheter, as in standard intravesical chemotherapy. The cutaneous and intravesical electrodes are connected to a generator that creates a current of up to 25 mA. After the procedure the bladder is drained and the catheter is removed. Treatment sessions usually last for approximately 30 minutes and are repeated weekly for 4–8 weeks, or longer for adjuvant treatment.

Efficacy

A randomised controlled trial of 212 patients with histologically proven pT1 transitional cell carcinoma of the bladder, including patients with carcinoma in situ, reported that there was a statistically significant higher disease-free survival rate with electromotive drug administration of

mitomycin C (EMDA–MMC) plus BCG (58%; 62/107) than with BCG alone (42%; 44/105) at a mean follow-up of 88 months ($p = 0.0012$)⁵.

A randomised controlled trial of 108 patients with either bladder carcinoma in situ or papillary transitional cell carcinoma reported that complete response (histologically negative biopsy and negative cytological findings) at 6 months was significantly higher in the EMDA–MMC treatment group (58%; 21/36), than in the passive MMC treatment group (31%; 11/36) ($p = 0.012$), and similar to the BCG treatment group (64%; 23/36)¹. In the same study the estimated 5-year survival (all-cause mortality) was not significantly different between the groups (EMDA–MMC 68.9%, passive MMC 63.1%, BCG 58.7%; $p = 0.782$). However, patients in this trial were allowed to cross over treatment arms if the treatment they were initially allocated to had failed at 6 months, so potential differences in efficacy between the two treatments could have been made less apparent by the study design.

A mean disease-free interval of 14.5 months was achieved following EMDA–MMC treatment in a non-randomised controlled trial of 28 patients compared with 10.5 months in patients treated by passive MMC (measure of significance not stated)². A second non-randomised controlled trial reported that a complete response to treatment (no macroscopic evidence of disease at cystoscopy, negative cytology, and negative histology) was achieved in 40% (6/15) of EMDA–MMC patients, 28% (10/36) of passive MMC patients and 66% (19/29) of microwave hyperthermia MMC patients (measure of significance not stated)³ at 7- to 10-day follow-up.

Recurrence-free survival at 14-month follow-up was achieved in 57% (9/16) of patients in a case series of 22 patients with superficial carcinoma of the bladder receiving EMDA–MMC⁴.

Safety

One randomised controlled trial reported that adverse events led to the suspension of treatment in 3% (3/107) of patients receiving EMDA–MMC plus BCG and in 3% (3/105) of patients receiving BCG alone⁵. In a case series of 22 patients, treatments were terminated owing to complications in 14% (3/22) of patients; in one patient, this was because of bladder ulcer and in the other two patients this was because of leakage of the instillate solution caused by bladder contractions in the other two patients⁴. In the same case series problems related to catheters (not further defined) occurred during 2% (2/91) of treatments.

Urinary frequency developed in 19% (7/36) of patients in a randomised controlled trial with a median follow-up of 43-months following the EMDA–MMC intravesical chemotherapy procedure¹. Bladder contracture/leakage occurred during 15% (14/91)⁴ of procedures in a case series of 22 patients.

Chemical/drug-induced cystitis occurred at a rate of 13% (2/15)² and 36% (13/36)¹ in one non-randomised controlled trial and one randomised controlled

trial, respectively, and bacterial cystitis was reported in 19% (7/36)¹ of patients in the latter trial¹.

Across the included studies haematuria following EMDA–MMC occurred in 0% (0/15)² to 22% (8/36)¹ of patients; however, the definitions used to describe this outcome varied across the studies.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to electrically-stimulated intravesical chemotherapy for superficial bladder cancer. Searches were conducted of the following databases, covering the period from their commencement to 9th April 2008: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.</p> <p>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.</p>
Patient	Patients with superficial bladder cancer.
Intervention/test	Electrically-stimulated intravesical chemotherapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 200 patients from two randomised controlled trials^{5,1}, two non randomised controlled trials^{2,3} and one case series⁴.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in appendix A.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed below.

Interventional procedures

- Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer. NICE interventional procedures guidance 235 (2007). Available from www.nice.org.uk/IPG235
- Laparoscopic cystectomy of the urinary bladder. NICE interventional procedures guidance 26 (2003). Available from www.nice.org.uk/IPG026

Cancer service guidance

- Improving outcomes in urological cancers .NICE cancer service guidance (2002). Available from <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10889>

Table 2 Summary of key efficacy and safety findings on electrically-stimulated intravesical chemotherapy for superficial bladder cancer

Abbreviations used: BCG, Bacillus Calmette-Guérin; EMDA, electromotive drug administration; MMC, mitomycin C; MW, microwave; TCC, transitional cell carcinoma																																				
Study details	Key efficacy findings	Key safety findings	Comments																																	
<p>Di Stasi SM (2006)⁵</p> <p>Study type: randomised controlled trial</p> <p>Country: Italy</p> <p>Study period: Jan 1994 to Jun 2002</p> <p>Study population: patients with histologically proven pT1 transitional cell carcinoma of the bladder including patients with carcinoma in situ at high risk of recurrence and a medium to high risk of progression</p> <p>Previous treatment with epirubicin n = 46, mitomycin n = 30, interferon n = 4, gemcitabine n = 9</p> <p>n = 212 (n = 107 BCG plus EMDA MMC)</p> <p>Age: mean 67 years</p> <p>Sex: 82% male</p> <p>Exclusion criteria: treatment with BCG or EMDA chemotherapy in past 6 months</p> <p>Technique: BCG 81mg for 120 min once a week for 12 weeks. Followed by MMC 40 mg in 100 ml saline with maximum 20 mA pulsed electric current for 30 min vs BCG only</p> <p>Follow-up: median 88 months</p> <p>Conflict of interest: none</p>	<p>Survival</p> <p>The primary endpoint was either disease-free survival in patients without carcinoma in situ, or period from randomisation to first recurrence noted by cystoscopy in patients with TCC. Response to treatment was assessed by ultrasonography, cystoscopy and urinary cytology. In patients who were disease-free at 3 months, assessment was repeated every 3 months for 3 years and 6-monthly thereafter. Patients with carcinoma in situ additionally underwent bladder biopsies at 3 and 6 months. If at 3 months carcinoma in situ persisted or a tumour had recurred the patient underwent multiple biopsy and transurethral resection, and received a second course of treatment.</p> <p>At a mean follow-up of 88 months 58% (62/107) of the patients in the BCG plus EMDA chemotherapy group were found to be disease-free compared with 42% (44/105) patients in the BCG alone group (p = 0.0012).</p> <p>Patients in the BCG plus EMDA chemotherapy group had a lower overall mortality (22%; 23/107) (95% CI 13.5 to 29.5) compared with patients in the BCG alone group (32%; 34/105) (95% CI 23.4 to 41.4) at a mean follow-up of 88 months Hazard ratio 0.586 (p = 0.045).</p>	<p>Complications</p> <p>3% (3/107) of patients in the EMDA plus BCG group and 3% (3/105) of the patients in the BCG alone group did not complete the treatment protocol due to adverse events.</p> <table border="1"> <thead> <tr> <th>Adverse event</th> <th>BCG plus EMDA-MMC</th> <th>BCG alone</th> </tr> </thead> <tbody> <tr> <td>Dysuria</td> <td>50% (54/107)</td> <td>49% (51/105)</td> </tr> <tr> <td>Bacterial cystitis</td> <td>15% (16/107)</td> <td>13% (14/105)</td> </tr> <tr> <td>Drug-induced cystitis</td> <td>46% (49/107)</td> <td>44% (46/105)</td> </tr> <tr> <td>Macroscopic haematuria</td> <td>60% (64/107)</td> <td>58% (61/105)</td> </tr> <tr> <td>Prostatitis</td> <td>0%</td> <td>1% (1/105)</td> </tr> <tr> <td>Epididymitis</td> <td>1% (1/107)</td> <td>0%</td> </tr> <tr> <td>Fever</td> <td>20% (21/107)</td> <td>23% (24/105)</td> </tr> <tr> <td>Influenza symptoms</td> <td>31% (33/107)</td> <td>32% (34/105)</td> </tr> <tr> <td>Fatigue</td> <td>30% (32/107)</td> <td>30% (32/105)</td> </tr> <tr> <td>Temporary suspension of treatment.</td> <td>37% (40/107)</td> <td>35% (37/105)</td> </tr> </tbody> </table> <p>Time of occurrence of complication and duration not reported</p>	Adverse event	BCG plus EMDA-MMC	BCG alone	Dysuria	50% (54/107)	49% (51/105)	Bacterial cystitis	15% (16/107)	13% (14/105)	Drug-induced cystitis	46% (49/107)	44% (46/105)	Macroscopic haematuria	60% (64/107)	58% (61/105)	Prostatitis	0%	1% (1/105)	Epididymitis	1% (1/107)	0%	Fever	20% (21/107)	23% (24/105)	Influenza symptoms	31% (33/107)	32% (34/105)	Fatigue	30% (32/107)	30% (32/105)	Temporary suspension of treatment.	37% (40/107)	35% (37/105)	<p>Computer-generated block randomisation in strata across 4 factors: primary or recurrent tumours, multifocal or unifocal tumours, grade 3 vs grade 2, presence or absence of carcinoma in situ.</p> <p>Multicentre study with 4 sites.</p> <p>Maintenance treatment for both groups was given by the same dose and method as the initially allocated treatment.</p> <p>All analysis undertaken on intention-to-treat principle.</p> <p>Power calculation used to calculate sample size.</p>
Adverse event	BCG plus EMDA-MMC	BCG alone																																		
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Study details	Key efficacy findings				Key safety findings			Comments		
Di Stasi SM (2003) ¹	Complete response Defined as histology negative for malignancy and resolution of abnormal cytological findings. All patients were assessed by cystoscopy, biopsy and cytology. Patients underwent bladder biopsies at 3 and 6 months, and thereafter only as indicated by cytology or cystoscopy findings. In tumour-free patients cystoscopy and cytology were repeated every 3 months for 2 years and every 6 months thereafter.				Complications			<p>Study period overlaps with Di Stasi (2006); however, the EMDA–MMC group are patients not reported elsewhere as they received no BCG treatment. The randomisation protocol for each study makes this impossible.</p> <p>Randomisation by computer generation in blocks to account for 3 factors: presence or absence of concurrent T1 papillary tumours, grade II or grade III tumours, and multifocal or unifocal tumours.</p> <p>There were no statistically significant differences between the 3 study arms at baseline in demographic or clinical characteristics, including grade of cancer.</p> <p>A total of 36% (13/36) of patients in the BCG arm, 69% (25/36) of patients in the passive MMC arm, and 42% (15/36) of patients in the EMDA MMC arm crossed over treatment at 6 months. This makes comparison and interpretation of subsequent outcomes difficult.</p>		
Study type: randomised controlled trial					EMD A– MMC	Passive MMC	BCG		P=	
Country: Italy					Urinary frequency	19% (7/36)	17% (6/36)		58% (21/36)	0.001
Study period: Jun 1994 to March 2001					Bacterial cystitis	19% (7/36)	19% (7/36)		25% (9/36)	0.874
Study population: patients with histologically proven multifocal carcinoma in situ of the bladder and most (91%) with pT1 papillary transitional cell carcinoma.0					Drug- induced cystitis	36% (13/36)	25% (9/36)		67% (24/36)	0.001
n= 108 (n = 36 MMC plus EMDA)					Visible haematuria	22% (8/36)	17% (6/36)		72% (26/36)	0.001
Age: mean 66 years					Prostatitis	0%	0%		3% (1/36)	1.000
Sex: 73% male					Epididymitis	0%	0%		3% (1/36)	1.000
Inclusion/exclusion criteria: not stated					Fever	0%	0%		19% (7/36)	0.001
Technique: following complete transurethral resection of all visible bladder tumour, six 30-min sessions of MMC 40 mg with NaCl 960 mg in 100 ml saline with maximum 20 mA pulsed electric current externally vs BCG 81 mg for 120 min vs passive MMC. Repeat schedules of treatment for non-responders and crossover treatment BCG or EMDA–MMC if cancer persisted at 6 months.	Re-currence (median follow-up = 43 months)	52.8% (35.5 to 69.6)	75.0% (57.8 to 87.9)	52.8% (35.5 to 69.6)	0.092	General malaise	0%		3% (1/36)	31% (11/36)
Follow-up: median 43 months	Pro-gression (median follow-up = 43 months)	16.7% (6.4 to 32.8)	22.2% (10.1 to 39.1)	16.7% (6.4 to 32.8)	0.861	Fatigue	3% (1/36)	0%	44% (16/36)	0.001
Conflict of interest: supported by academic grant and equipment supplied by manufacturer	p values for EMDA–MMC vs MMC group for tumour response, or overall log rank test between the three groups for recurrence and progression					Allergic reactions	8% (3/36)	6% (2/36)	0%	1.000
						Time of follow up/events not stated.				
						There were no life-threatening events or permanent bladder contractures				

Abbreviations used: BCG, Bacillus Calmette-Guérin; EMDA, electromotive drug administration; MMC, mitomycin C; MW, microwave; TCC, transitional cell carcinoma																					
Study details	Key efficacy findings				Key safety findings	Comments															
Di Stasi SM (2003) Cont.	<p>Survival</p> <p>Defined as period from randomisation to death by any cause.</p> <table border="1"> <thead> <tr> <th></th> <th>EMDA MMC</th> <th>Passive MMC</th> <th>BCG</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>5-year estimated survival – all-cause mortality</td> <td>68.9% (46.6 to 83.4)</td> <td>63.1% (41.6 to 78.5)</td> <td>58.7% (35.9 to 75.8)</td> <td>0.782</td> </tr> <tr> <td>5 year estimated survival – bladder cancer-related mortality</td> <td>78.5% (57.9 to 89.8)</td> <td>75.3% (89.6 to 88.3)*</td> <td>78.0% (54.1 to 90.4)</td> <td>0.943</td> </tr> </tbody> </table> <p>p values for likelihood ratio test between the three groups</p> <p>*95% CI figure extracted from study report but falls outside point estimate.</p>					EMDA MMC	Passive MMC	BCG	p	5-year estimated survival – all-cause mortality	68.9% (46.6 to 83.4)	63.1% (41.6 to 78.5)	58.7% (35.9 to 75.8)	0.782	5 year estimated survival – bladder cancer-related mortality	78.5% (57.9 to 89.8)	75.3% (89.6 to 88.3)*	78.0% (54.1 to 90.4)	0.943		<p>Sample size calculated assuming 80% power.</p> <p>Pharmacokinetic results are also presented in the paper but not extracted here.</p>
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<p>Brausi M (1998)²</p> <p>Study type: non-randomised controlled trial</p> <p>Country: Italy and USA</p> <p>Study period: Nov 1993 to Jan 1995</p> <p>Study population: patients with superficial transitional cell carcinoma of the bladder.</p> <p>Range of tumour diameter 0.4 to 1.5 cm. Tumour stage Ta = 50%, T1 = 50%. Tumour grade G1 = 36%, grade 2 = 64%.</p> <p>n= 28 (n = 15 MMC plus EMDA)</p> <p>Age: mean 70 years</p> <p>Sex: 75% male Male = 75%</p> <p>Exclusion criteria: infiltrating tumour > T1. Random biopsies of the bladder mucosa and prostatic urethra taken to exclude carcinoma in situ</p> <p>Technique: eight 20-min sessions MMC 40 mg in 50 ml distilled water with maximum 15 mA pulsed electric current externally vs passive MMC.</p> <p>Follow-up: mean 16 months</p> <p>Conflict of interest: not stated</p>	<p>Tumour response</p> <p>Patients were classified as having a complete response if no visible or microscopic carcinoma on biopsy and negative cytological findings. Failure in all other circumstances. Progression if tumour at stage >T1.</p> <table border="1"> <thead> <tr> <th></th> <th>EMDA MMC</th> <th>Passive MMC</th> </tr> </thead> <tbody> <tr> <td>Complete response</td> <td>40% (6/15)</td> <td>42% (5/12)</td> </tr> <tr> <td>Tumour-free at final follow-up</td> <td>67% (4/6)</td> <td>40% (2/5)</td> </tr> <tr> <td>Mean disease-free interval</td> <td>14.5 months</td> <td>10.5 months</td> </tr> </tbody> </table> <p>Measure of significance not reported.</p> <p>Long-term follow-up was recorded for patients who were complete responders at initial assessment (3 months)</p>		EMDA MMC	Passive MMC	Complete response	40% (6/15)	42% (5/12)	Tumour-free at final follow-up	67% (4/6)	40% (2/5)	Mean disease-free interval	14.5 months	10.5 months	<p>Complications</p> <p>No severe systemic side effects were recorded in either group.</p> <table border="1"> <thead> <tr> <th></th> <th>EMDA MMC</th> <th>Passive MMC</th> </tr> </thead> <tbody> <tr> <td>Transient macroscopic haematuria</td> <td>0%</td> <td>7% (1/13)</td> </tr> <tr> <td>Chemical cystitis (requiring suspension or delay of treatment)</td> <td>13% (2/15)</td> <td>0%</td> </tr> </tbody> </table> <p>Measure of significance not reported. Time of occurrence of complication and duration not reported.</p>		EMDA MMC	Passive MMC	Transient macroscopic haematuria	0%	7% (1/13)	Chemical cystitis (requiring suspension or delay of treatment)	13% (2/15)	0%	<p>28 patients recruited across 7 participating centres. Some sites will have treated only a small number of patients.</p> <p>One patient in the passive MMC group died at 10 weeks follow-up from myocardial infarction and was excluded from efficacy analysis.</p> <p>Authors state that patient sample is too small to draw definite conclusions.</p>
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Study details	Key efficacy findings	Key safety findings	Comments																				
<p>Colombo R et al (2001)³</p> <p>Study type: non-randomised controlled trial</p> <p>Country: Italy</p> <p>Study period: 1996 to 1998</p> <p>Study population: superficial (Ta–T1), low-grade (G1–G2), recurrent, single, small (< 2 cm) bladder tumours</p> <p>n = 80 (n = 29 MMC MW, n = 36 MMC alone, n = 15 MMC EMDA)</p> <p>Age: not stated</p> <p>Sex: not stated</p> <p>Exclusion criteria: previous treatment with MMC</p> <p>Technique: neoadjuvant treatment with MMC 40 mg in 50 ml saline; Synergo device used; mean temperature 42.5°C; session duration at least 60 minutes; treatment regimen 4 sessions, 1 per week; vs MMC alone vs MMC 40 mg in 150 ml distilled water at 20mA current for 20 min; 4 sessions</p> <p>Follow-up: 7–10 days after last treatment</p> <p>Conflict of interest: not stated</p>	<p>Tumour response</p> <p>Complete response was defined as no macroscopic evidence of disease at cystoscopy, negative cytology and negative histology in TUR specimens (where taken), at a maximum follow up of 7–10 days.</p> <p>MMC plus MW: 19/29 (66.0%)</p> <p>MMC plus EMDA 6/15 (40.0%)</p> <p>Passive MMC alone: 10/36 (27.8%)</p> <p>(No p values reported)</p>	<p>Complications</p> <p>Most patients complained about a cystitis syndrome. Local side effects related to thermo-chemotherapy were mainly described as urgency and nocturia. Inflammatory symptoms disappeared almost completely within a few days after the last session in all patient groups.</p> <p>Subjective symptom scores</p> <table border="1"> <thead> <tr> <th></th> <th colspan="3">Mean score (SD)</th> </tr> <tr> <th></th> <th>MMC + EMDA</th> <th>MMC + MW</th> <th>Passive MMC</th> </tr> </thead> <tbody> <tr> <td>Before treatment</td> <td>9.4 (± 1.7)</td> <td>11.6 (± 1.8)</td> <td>10.3 (± 1.2)</td> </tr> <tr> <td>Immediately after last session</td> <td>14.6 (± 1.5)</td> <td>17.4 (± 2.6)</td> <td>13.2 (± 1.6)</td> </tr> <tr> <td>7–10 days after last session*</td> <td>12.2 (± 1.5)</td> <td>12.7 (± 1.5)</td> <td>11.0 (± 0.8)</td> </tr> </tbody> </table> <p>There were no significant differences between the treatment groups (p value not stated).</p>		Mean score (SD)				MMC + EMDA	MMC + MW	Passive MMC	Before treatment	9.4 (± 1.7)	11.6 (± 1.8)	10.3 (± 1.2)	Immediately after last session	14.6 (± 1.5)	17.4 (± 2.6)	13.2 (± 1.6)	7–10 days after last session*	12.2 (± 1.5)	12.7 (± 1.5)	11.0 (± 0.8)	<p>The method of patient selection was not described</p> <p>Subjective symptom scores were collected using a non-validated questionnaire regarding 7 factors. Low scores indicate better status.</p>
	Mean score (SD)																						
	MMC + EMDA	MMC + MW	Passive MMC																				
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Abbreviations used: BCG, Bacillus Calmette-Guérin; EMDA, electromotive drug administration; MMC, mitomycin C; MW, microwave; TCC, transitional cell carcinoma													
Study details	Key efficacy findings	Key safety findings	Comments										
<p>Riedl CR (1998)⁴</p> <p>Study type: case series</p> <p>Country: Austria</p> <p>Study period: not stated</p> <p>Study population: patients with superficial carcinoma of the bladder, treated for recurrence prophylaxis. Tumour stage TaG1 = 5%, TaG2 = 64%. T1G2 = 9%, T1G3 = 14%; carcinoma in situ G3 = 9%.</p> <p>n= 22</p> <p>Age: mean 72 years</p> <p>Sex: 68% male</p> <p>Inclusion/exclusion criteria: not stated</p> <p>Technique: following transurethral resection EMDA with MMC 40 mg in 100 ml distilled water with maximum. 15 mA pulsed electric current for 4 treatment sessions</p> <p>Follow-up: mean 14 months</p> <p>Conflict of interest: not stated</p>	<p>Tumour response</p> <p>Cystoscopy and cytology were performed 6 weeks following final treatment session, and every 3 months thereafter. However, complete response was not defined</p> <p>Recurrence-free survival was achieved in 57% (9/16) of patients, at a mean follow-up of 14 months</p> <p>In 3 patients with incomplete resection, tumour reduction was observed but complete remission was not achieved</p>	<p>Complications</p> <p>Treatments were terminated owing to complications in 14% (3/22) of patients</p> <table border="1"> <thead> <tr> <th>Event</th> <th>Rate</th> </tr> </thead> <tbody> <tr> <td>Bladder ulcer</td> <td>1% (1/91)</td> </tr> <tr> <td>Bladder contractions/leakage</td> <td>15% (14/91)</td> </tr> <tr> <td>Moderate pain</td> <td>4% (4/91)</td> </tr> <tr> <td>Catheter problems</td> <td>2% (2/91)</td> </tr> </tbody> </table>	Event	Rate	Bladder ulcer	1% (1/91)	Bladder contractions/leakage	15% (14/91)	Moderate pain	4% (4/91)	Catheter problems	2% (2/91)	<p>Insufficient follow-up data were available on 14% (3/22) of patients.</p> <p>In 3 patients resection was incomplete owing to large tumour size, and EMDA–MMC was used with the intention of residual tumour control.</p> <p>The study report describes outcome of EMDA with a variety of other drugs for other indications. Data not extracted here.</p> <p>Safety outcomes are presented per number of treatments not per patient. It is possible that some patients had the same event at different treatment sessions.</p>
Event	Rate												
Bladder ulcer	1% (1/91)												
Bladder contractions/leakage	15% (14/91)												
Moderate pain	4% (4/91)												
Catheter problems	2% (2/91)												

Validity and generalisability of the studies

- In some studies EMDA–MMC intravesical chemotherapy was used as an adjunct to TUR for superficial bladder tumours. However, in some studies it was not clear whether this was being used as a first-line therapy or not.
- The stage and grade of bladder cancer varied across studies, and some studies included patients with carcinoma in situ.
- One study⁵ looked at EMDA–MMC in addition to BCG treatment.
- Different preparations of chemotherapeutic solutions were used in the studies included in this overview. The composition of the solution may have an influence on the safety and efficacy of the procedure.
- One study³ appears to have had a particularly short follow-up (≤ 10 days).
- The definition of “complete response” differs across studies, and in some it is not well defined.
- The surveillance protocol during follow-up varies between studies. In some studies it was not standardised for all patients, but altered depending on outcomes during short-term (3- or 6-month) follow-up.

Specialist Advisers’ opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr N Clarke (British Association of Urological Surgeons), Mr W Turner (British Association of Urological Surgeons).

- One Specialist Adviser considered this procedure to be novel and of uncertain safety and efficacy, and a second that it was the first in a new class of procedure.
- Known adverse events or those reported in the literature include urinary frequency, haematuria, urinary tract infection, cystitis and allergic reaction.
- Additional theoretical adverse events may include urethral stricture, systemic drug toxicity, bladder contracture and transitory incontinence.

- One Adviser noted that there may be potential interaction between the chemotherapeutic drug, its intravesical use, and EMDA.
- It was noted that there is a limited number of trials and the procedure needs to be studied in larger randomised controlled trials.
- Training needs to include the safe use of EMDA equipment over and above training for intravesical chemotherapy procedures.
- The key efficacy outcomes identified were tumour recurrence, tumour progression and mortality.
- Both Advisers thought that the procedure would be used in the majority of district general hospitals if it were found to be safe and efficacious.

Issues for consideration by IPAC

- EMDA is a registered trade name of the manufacturer
- Only studies using EMDA with MMC were found in the published literature to date. However, other chemotherapeutic drugs may also be used for this procedure.

References

- 1 Di Stasi SM, Giannantoni A, Stephen RL et al. (2003) Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. *Journal of Urology* 170: 777–782.
- 2 Brausi M, Campo B, Pizzocaro G et al. (1998) Intravesical electromotive administration of drugs for treatment of superficial bladder cancer: a comparative Phase II study. *Urology* 51: 506–509.
- 3 Colombo R, Brausi M, Da Pozzo L et al. (2001) Thermo-chemotherapy and electromotive drug administration of mitomycin C in superficial bladder cancer eradication. a pilot study on marker lesion. *European Urology* 39: 95–100.
- 4 Riedl CR, Knoll M, Plas E et al. (1998) Intravesical electromotive drug administration technique: preliminary results and side effects. *Journal of Urology* 159:1851–1856.
- 5 Di Stasi SM, Giannantoni A, Giurioli A et al. (2006) Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncology* 7:4351.

Appendix A: Additional papers on electrically-stimulated intravesical chemotherapy for superficial bladder cancer

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
No additional relevant studies were located by the literature search			

Appendix B: Related NICE guidance for electrically-stimulated intravesical chemotherapy for superficial bladder cancer

Guidance	Recommendations
Interventional procedures	<p>Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer]. NICE interventional procedures guidance 235 (2007)</p> <p>1.1 The current evidence on intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer is based on small numbers of patients but raises no major safety concerns. The evidence on efficacy is very limited and treatment protocols have varied between the published studies. Therefore, this procedure should only be used in the context of</p>

	<p>controlled clinical research.</p> <p>Laparoscopic cystectomy of the urinary bladder. NICE interventional procedures guidance 26 (2003)</p> <p>1.1 Current evidence on the safety and efficacy of laparoscopic cystectomy does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake laparoscopic cystectomy should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present.</p> <p>1.2 Special training is required to perform the procedure. The British Association of Urological Surgeons has agreed to produce standards for training.</p>
Clinical guidelines	<p>Improving outcomes in urological cancers. .NICE cancer service guidance (2002)</p> <p>Superficial tumours</p> <p>Patients with newly diagnosed, apparently superficial, tumours should be treated by complete trans-urethral resection (TUR), which should be carried out by designated urologists in local district general hospitals (DGHs). After recovery from resection, these</p>

	<p>patients should normally have a single instillation of chemotherapy (mitomycin or epirubicin) or glycine into the bladder (intravesical therapy). They should be allocated to one of the groups described below when the results of pathological review are available.</p> <p>Lower-risk superficial cancer (pTa G1 or G2 or T1, G1 or G2)</p> <p>About 50% of newly diagnosed patients have superficial tumours which carry a relatively low risk of progression after treatment but the majority of tumours will recur locally in the bladder. Guidelines for the frequency and timing of follow-up cystoscopy should be agreed and adopted throughout each network.</p> <p>High-risk superficial cancer (pTa G3, or T1 G3 tumours, extensive, recurrent or multifocal G2 tumours, and carcinoma in situ)</p> <p>These tumours are associated with higher risk of progression and death, and many patients are not receiving adequate treatment at present. Protocols for treatment and follow-up of patients with highrisk superficial tumours should be jointly agreed by the urological cancer multidisciplinary teams (MDTs) of each network and adopted throughout the network. Although these patients may be treated – at least initially – by urologists who are members of local urological cancer teams, the options should be discussed with each patient in a joint meeting which includes a urologist, an oncologist and a nurse specialist who are also members of the MDT. The range of appropriate options may include intravesical treatment with bacillus Calmette-Guerin (BCG) or referral to the specialist urological cancer team for possible radical treatment. If the tumour fails to respond to BCG or recurs within a short time, radical treatment (normally cystectomy) should be offered.</p>
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	Patients with high-risk tumours should be encouraged, when appropriate, to participate in randomised trials such as the MRC BS06 trial comparing radical radiotherapy with intravesical therapy.
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Appendix C: Literature search for electric field-stimulated intravesical chemotherapy for superficial bladder cancer

IP 697: Electric field-stimulated intravesical chemotherapy for superficial bladder cancer		
Database	Date searched	Version searched
Cochrane Library	09/04/2008	Issue 1, 2008
CRD databases (DARE & HTA)	09/04/2008	January/February 2008
Embase	09/04/2008	1980 to 2008 Week 14
Medline	09/04/2008	1950 to March Week 4 2008
Premedline	09/04/2008	April 07, 2008
CINAHL	09/04/2008	1982 to date (via Dialog)
British Library Inside Conferences	09/04/2008	-
NRR	09/04/2008	-
Controlled Trials Registry	09/04/2008	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1. Electric Stimulation Therapy/
2. Electrochemotherapy/
3. electrochemotherap\$.tw.
4. Iontophoresis/
5. (Iontotherap\$ or iontophores\$).tw.
6. electromotive\$.tw.
7. EMDA.tw.
8. or/1-7
9. Urinary Bladder Neoplasms/

10. (bladder adj3 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinom\$ or tumo?r\$ or malignan\$)).tw.
11. (sarcoma adj3 bladder).tw.
12. (transitional adj3 cell adj3 carcinoma\$ adj3 bladder).tw.
13. or/9-12
14. 8 and 13
15. Animals/
16. Humans/
17. 15 not (15 and 16)
18. 14 not 17