NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer

Non-muscle-invasive bladder cancer is only in the lining of the bladder. It has not grown into the deeper muscle layer. This procedure is used before or after surgery. A catheter (thin tube) is inserted through the urethra (the tube that carries urine out of the body from the bladder. Chemotherapy drugs are passed through this tube into the bladder (intravesical therapy). An electrode is also passed into the bladder, to create a small electrical current. The aim is to make the chemotherapy work better.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make 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 June 2018.

Procedure name

- Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer

Specialist societies

- British Association of Urological Surgeons (BAUS)
- British Uro-Oncology Group (BUG)
- Royal College of Surgeons.

Description of the procedure

Indications and current treatment

The most common form of bladder cancer is transitional cell carcinoma (TCC). Non-muscle-invasive TCC is classified as stage Ta when the tumour is confined to the urothelium with no spread into the wall of the bladder or beyond, and stage T1 when there is spread into the connective tissue layer between the urothelium and the muscle wall. It is graded from G1 (low grade, least aggressive) to G3 (high grade, most aggressive). Another type of non-muscle-invasive cancer is carcinoma in situ, in which aggressive cancer cells spread within the surface lining of the bladder.

Conventional treatment for non-muscle-invasive cancer is transurethral resection of bladder tumour (TURBT), in which malignant tissue is removed with an electrocautery device during cystoscopy. Intravesical chemotherapy with Bacillus Calmette-Guérin (BCG) vaccine or other chemotherapeutic drugs may also be

used. The aim is to reduce the risk of cancer recurrence. Intravesical microwave hyperthermia may also be used, in combination with intravesical chemotherapy. Cystectomy may be needed in some patients.

What the procedure involves

Electrically stimulated intravesical chemotherapy (also known as electromotive drug administration [EMDA]) can be used as neoadjuvant treatment before TURBT, or as adjuvant treatment after TURBT. The procedure involves the use of a device to create an electric field across the bladder wall, with the aim of stimulating directional ionic and solute movement of the intravesical fluid. This increases absorption of the drug into the bladder lining.

The procedure is usually done using local anaesthesia. With the patient in a supine position, electrode pads are placed on the skin of the lower abdomen and a catheter (with an intravesical electrode) is inserted into the bladder through the urethra. When the catheter and electrodes are in place the chemotherapeutic drug solution (usually mitomycin C [MMC] in saline or distilled water) is instilled into the bladder through the catheter. The cutaneous and intravesical electrodes are connected to a generator that creates a current of up to 25 milliamps. Treatment sessions last about 30 minutes and are repeated, often weekly, for 4 to 8 weeks, or longer for adjuvant treatment. After the procedure, the bladder is drained and the catheter is removed.

Outcome measures

<u>Bladder cancer classification:</u>

Tumour

<table>
<tr><td>Tx</td><td>No primary tumour can be evaluated</td><td rowspan="2"></td></tr>
<tr><td>T0</td><td>There is no evidence of a primary tumour in the bladder</td></tr>
<tr><td>Ta</td><td>Non-invasive papillary carcinoma</td><td rowspan="3">Non-muscle invasive bladder cancer</td></tr>
<tr><td>Tis</td><td>Carcinoma in situ (CIS) or ‘flat tumour’. Cancer is only found on or near the surface of the bladder</td></tr>
<tr><td>T1</td><td>Tumour has spread to the subepithelial connective tissue (lamina propria only)</td></tr>
<tr><td>T2</td><td colspan="2">Muscle-invasive bladder cancer</td></tr>
</table>

Grade

Grade 1 – the cancer cells look a lot like normal bladder cells. They are usually slow-growing and are less likely to spread.

Grade 2 – the cancer cells look more abnormal and grow slightly more quickly than grade 1 cancer.

Grade 3 – the cancer cells look very abnormal and are likely to grow quickly.

Common terminology criteria for adverse events

Grade 1 – Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 – Moderate: minimal, local or non-invasive; intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 - Severe or medically significant: not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.

Grade 4 - Life-threatening consequences; urgent intervention indicated.

Grade 5 - Death related to adverse events.

Efficacy summary

Time to recurrence

Post-operative mitomycin C with electromotive drug administration (MMC-EMDA) compared with post-operative BCG induction therapy (3-month follow-up)

In a Cochrane review of 3 randomised controlled trials (RCTs) that included 5 randomised comparisons, 1 study (72 patients with non-muscle invasive bladder cancer [NMIBC]) comparing MMC-EMDA intravesical instillation (n=36) with BCG (n=36) about 3 weeks after transurethral resection of bladder tumour (TURBT) reported that at 3-month follow-up (before additional therapy and cross-over), the effect of post-operative MMC-EMDA on time to recurrence is uncertain (risk ratio [RR] 1.06, 95% confidence interval [CI] 0.64 to 1.76).[1]

Postoperative MMC-EMDA induction compared with MMC-passive diffusion (PD) induction therapy (3-month follow-up)

In the Cochrane review of 3 RCTs, 1 study (72 patients with NMIBC) comparing post-operative MMC-EMDA (n=36) with MMC-PD (n=36) about 3 weeks after TURBT reported that at 3-month follow-up MMC-EMDA may reduce disease recurrence but this is not clinically significant (RR 0.65, 95% CI 0.44 to 0.98).[1]

Postoperative MMC-EMDA with sequential BCG induction and maintenance compared with postoperative BCG induction and maintenance therapy (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (212 patients with NMIBC) comparing MMC-EMDA with sequential BCG (n=107) with BCG alone (n=105) about 3 weeks after TURBT reported that at a median 88-month follow-up, post-operative MMC-EMDA with sequential BCG may result in a longer time to recurrence than BCG alone, but this is not clinically significant (hazard ratio [HR] 0.51, 95% CI 0.34 to 0.77).[1]

Single-dose, preoperative MMC-EMDA compared with single-dose, postoperative MMC-PD (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (236 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with MMC-PD immediately after TURBT (n=119) reported that at median 86-month follow-up, pre-operative MMC-EMDA resulted in a longer time to recurrence (HR 0.47, 95% CI 0.32 to 0.69).[1]

Single-dose, preoperative MMC-EMDA compared with TURBT alone (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (233 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with TURBT alone (n=116) reported that at median 86-month follow-up, pre-operative MMC-EMDA resulted in a longer time to recurrence (HR 0.40, 95% CI 0.28 to 0.57).[1]

Time to progression, disease-specific survival and time to death because of any cause

Post-operative MMC-EMDA induction compared with post-operative BCG induction therapy (3-month follow-up)

In the Cochrane review of 3 RCTs, 1 study (72 patients with NMIBC) comparing MMC-EMDA (n=36) with BCG (n=36) about 3 weeks after TURBT reported that at 3-month follow-up there were no events of disease progression or death from any cause in either group.[1]

Postoperative MMC-EMDA induction compared with MMC-PD induction therapy (3-month follow-up)

In the Cochrane review of 3 RCTs, 1 study (72 patients with NMIBC) comparing MMC-EMDA (n=36) with MMC-PD (n=36) about 3 weeks after TURBT reported that at 3-month follow-up there was no disease progression or death from any cause in either group.[1]

Postoperative MMC-EMDA with sequential BCG induction and maintenance compared with postoperative BCG induction and maintenance therapy (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (212 patients with NMIBC) comparing MMC-EMDA with sequential BCG (n=107) with BCG alone (n=105) about 3 weeks after TURBT reported that at median 88-month follow-up, post-operative MMC-EMDA with sequential BCG may result in a longer time to progression (HR 0.36, 95% CI 0.17 to 0.75), improved disease-specific survival (HR 0.31, 95% CI 0.12 to 0.80), and little or no difference in time to death (HR 0.59, 95% CI 0.35 to 1.00) than BCG alone, but this is not clinically significant.[1]

Single-dose, preoperative MMC-EMDA compared with single-dose, postoperative MMC-PD (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (236 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with MMC-PD immediately after TURBT (n=119) reported that at median 86-month follow-up the effect of pre-operative MMC-EMDA on time to progression is uncertain (HR 0.81, 95% CI 0.00 to 259.93) and there is little or no difference in disease-specific survival (HR 0.99, 95% CI 0.74 to 1.32) and time to death (HR 0.89, 95% CI 0.62 to 1.28).[1]

Single-dose, preoperative MMC-EMDA compared with TURBT alone (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (233 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with TURBT alone (n=116) reported that at median 86-month follow-up the effect of pre-operative MMC-EMDA on time to progression is uncertain (HR 0.74, 95% CI 0.00 to 247.93) and there is little or no difference in disease-specific survival (HR 1.06, 95% CI 0.80 to 1.40) and time to death (HR 1.07, 95% CI 0.73 to 1.57).[1]

Recurrence-free survival

In a case series of 22 patients with superficial carcinoma of the bladder having MMC-EMDA, 57% (9/16) of patients were recurrence-free at 14-month follow-up.[5]

Disease-free survival

A non-randomised controlled trial of 28 patients with superficial transitional cell carcinoma of the bladder, comparing MMC-EMDA (n=15) with MMC-PD (n=13), reported a mean disease-free interval of 14.5 months after MMC-EMDA compared with 10.5 months after MMC-PD (measure of significance not stated).[4]

Complete response

In a case series of 107 patients with new or recurrent high risk NMIBC who had BCG for 2 weeks after TURBT, followed by MMC-EMDA for 9 weeks, 87% (90/104) of patients were recurrence-free at the first check cystoscopy, 86% (74/86) at 1-year and 93% (66/71) at 2-year follow-up. There was no significant difference in recurrence-free rates between patients who had a full 9-week treatment (n=77) or a reduced treatment schedule (n=30) at first check (87% [65/75] compared with 86% [25/29], p=0.95), at 1-year follow-up (86% [55/64] compared with 86% [19/22], p=0.96) or at 2 years (91% [49/54] compared with 100% [17/17], p=0.19).[2]

A non-randomised controlled trial of 80 patients reported a complete response to treatment (no macroscopic evidence of disease at cystoscopy, negative cytology, and negative histology) in 40% (6/15) of patients who had MMC-EMDA, 28% (10/36) of patients who had MMC-PD and 66% (19/29) of patients who had microwave hyperthermia MMC (measure of significance not stated)[3] at 7 to 10-day follow-up.[3]

In a case series of 32 patients with small single or multiple papillary bladder tumours who had a single dose of 60 mg MMC-EMDA before TURBT, complete response was reported in 25% (8/32) of patients at 2 to 4-week follow-up. In patients with multiple tumours some tumours disappeared but others remained.[6]

Safety summary

Serious adverse events

Post-operative MMC-EMDA induction compared with post-operative BCG induction therapy (3-month follow-up)

In the Cochrane review of 3 RCTs, 1 study (72 patients with NMIBC) comparing MMC-EMDA instillation (n=36) with BCG (n=36) about 3 weeks after TURBT reported that at 3-month follow-up the effect of MMC-EMDA on serious adverse events is uncertain (RR 0.75, 95% CI 0.18 to 3.11).[1]

Postoperative MMC-EMDA induction compared with MMC-PD induction therapy (3-month follow-up)

In the Cochrane review of 3 RCTs, 1 study (72 patients with NMIBC) comparing MMC-EMDA (n=36) with MMC-passive diffusion [PD, n=36] about 3 weeks after TURBT reported that at 3-month follow-up the effect of post-operative MMC-EMDA on serious adverse events is uncertain (RR 1.50, 95% CI 0.27 to 8.45).[1]

Postoperative MMC-EMDA with sequential BCG induction and maintenance compared with postoperative BCG induction and maintenance therapy (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (212 patients with NMIBC) comparing MMC-EMDA with sequential BCG (n=107) with BCG alone (n=105) about 3 weeks after TURBT reported that at median 88-month follow-up the effect of post-operative MMC-EMDA with sequential BCG on serious adverse events is uncertain (RR 1.02, 95% CI 0.21 to 4.94).[1]

Single-dose, preoperative MMC-EMDA compared with single-dose, postoperative MMC-PD (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (236 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with MMC-PD immediately after TURBT (n=119) reported that at median 86-month follow-up, the effect of pre-operative MMC-EMDA on serious adverse events is uncertain (RR 0.79, 95% CI 0.30 to 2.05).[1]

Single-dose, preoperative MMC-EMDA compared with TURBT alone (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (233 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with TURBT alone (n=116) reported that at median 86-month follow-up the effect of pre-operative MMC-EMDA on serious adverse events is uncertain (HR 1.74, 95% CI 0.52 to 5.77).[1]

Minor adverse events

Single-dose, preoperative MMC-EMDA compared with single-dose, postoperative MMC-PD (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (236 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with MMC-PD immediately after TURBT (n=119) reported that at median 86-month follow-up, pre-operative MMC-EMDA reduces minor adverse events (HR 0.55, 95% CI 0.42 to 0.72).[1]

Single-dose, preoperative MMC-EMDA compared with TURBT alone (long-term follow-up)

In the Cochrane review of 3 RCTs, 1 study (233 patients with NMIBC) comparing MMC-EMDA before TURBT (n=117) with TURBT alone (n=116) reported that at median 86-month follow-up, pre-operative MMC-EMDA may increase minor adverse events (HR 1.07, 95% CI 0.73 to 1.57).[1]

Haematuria

Across the included studies, haematuria following EMDA–MMC happened in 0% (0/15) of patients (Barusi 1998)[2] to 22% (8/36) of patients (Di Stasi 2003)[1] . However, the definition of haematuria varied across the studies.

Drug-induced cystitis

Drug-induced cystitis was reported in 13% (2/15) of patients in 1 non-randomised controlled trial (Barusi 1998)[2] and in 36% (13/36) of patients in 1 RCT (Di Stasi 2003)[1]. Bacterial cystitis was reported in 19% (7/36) of patients in the Di Stasi trial (2003).[1]

Urinary frequency

Urinary frequency developed in 19% (7/36) of patients in an RCT with a median follow-up of 43 months following MMC-EMDA intravesical chemotherapy (Di Stasi 2003)[1]. Bladder contracture or leakage happened during 15% (14/91) of procedures in a case series of 22 patients.[5]

Urination immediately or during an MMC-EMDA procedure was reported in 2 patients in the case series of 32 patients who had a single dose of MMC-EMDA before TURBT. Treatment could not be completed in these 2 patients.[6]

Termination of treatment because of complications

One RCT reported that adverse events caused treatment to be suspended in 3% (3/107) of patients having MMC-EMDA plus BCG and in 3% (3/105) of patients having BCG alone (Di Stasi 2006)[1]. In a case series of 22 patients, treatment was stopped because of complications in 14% (3/22) of patients; in 1 patient, this was because of bladder ulcer and in the other 2 patients it was because of leakage of the instillate solution caused by bladder contractions.[5]

In the case series of 107 patients with new or recurrent high risk NMIBC who had sequential BCG/MMC-EMDA for 9 weeks after TURBT, treatment was stopped because of side effects in 16 patients (lower urinary tract symptoms or haematuria in 9 patients, arthralgia in 3, recurrent urinary tract infection in 2, rash in 1 and a rare granulomatous disease in 1), EMDA catheter insertion problems in 6, unrelated illness in 4, BCG shortage in 3, and 1 patient withdrew from the study.[2]

Catheter problems

In a case series of 22 patients, problems related to catheters happened during 2% (2/91) of treatments[5].

In the case series of 107 patients with new or recurrent high risk NMIBC who had sequential BCG/MMC-EMDA for 9 weeks after TURBT, EMDA catheter insertion problems were reported in 6 patients[2].

Severe bladder spasms

Severe bladder spasms during current-application were reported in 2 patients in the case series of 32 patients with small NMIBC who had MMC-EMDA before TURBT[6].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse event: mitomycin ulceration in the bladder. They did not describe any theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer. The following databases were searched, covering the period from their start to 10.05.2018: 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 the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. 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.
Patient	Patients with non-muscle invasive 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 IP overview

This IP overview is based on 802 patients from 1 Cochrane review[1], 2 non-randomised controlled trials[3,4] and 3 case series[2, 5,6].

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 the appendix.

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

Study 1 Jung JH (2017)

Details

Study type	Systematic review (Cochrane review)
Country	South Korea, UK
Study period & search methods	Search period: inception -2017; comprehensive search done using Cochrane CENTRAL, MEDLINE, EMBASE databases, 2 registries, grey literature and reference lists of relevant publications and urological societies abstract proceedings with no language restrictions were also searched. Authors, experts and manufacturers in the field were contacted.
Study population and number	n=**3 randomised controlled trials (RCTs) with 672 patients with non-muscle invasive bladder cancer (NMIBC) treated with intravesical electromotive drug administration (EMDA)**. NMIBC evaluation: CIS or concurrent T1 (or both) [Di Stasi 2003, Di Stasi 2006]; Ta or T1 [Di Stasi 2011]. Stage of disease: primary [Di Stasi 2003, Di Stasi 2011]; or both primary and recurrent disease [Di Stasi 2006]
Age and sex	mean age range 64.5 to 68.5 years; 78.5% (528/672) male
Patient selection criteria	Inclusion criteria: randomised and quasi-randomised studies comparing EMDA of any intravesical agent (mitomycin C, epirubicin, gemcitabine or other) with placebo, passive instillation of any chemotherapeutic agent, BCG instillation, or transurethral resection of bladder tumour (TURBT) without intravesical instillation. Patients with NMIBC (Ta, T1 or CIS), as determined by pathological evaluation of the TURBT, with no lymph node involvement and no metastases (clinically N0, M0).We considered studies of participants with both primary and recurrent disease. Exclusion criteria: patients with known MIBC, non-urothelial type bladder cancer or upper urinary tract urothelial carcinoma; other types of drug delivery methods such as chemo-hyperthermia.

<table>
<tr><td>Technique</td><td>Mitomycin C was the only intravesical agent used for EMDA in all studies.
Di Stasi 2011 (parallel multicentre RCT):
<table>
<tr><th>Interventions and comparators</th><th>Intervention given</th></tr>
<tr><td>single-dose, intravesical instillation of MMC-EMDA before TURBT</td><td>Single intravesical instillation 30 minutes before anaesthesia for TURBT</td></tr>
<tr><td>single-dose MMC-passive diffusion[PD] immediately after TURBT</td><td>Single intravesical instillation within 6 hours after TURBT</td></tr>
<tr><td>TURBT alone</td><td>No intravesical instillation</td></tr>
</table>
Participants received adjuvant intravesical therapy if indicated based on EAU guidelines
Di Stasi 2006 (parallel multicentre RCT):
<table>
<tr><th>Interventions and comparators</th><th>Intervention given</th></tr>
<tr><td>MMC-EMDA with sequential BCG installation and maintenance after TURBT</td><td>3 cycles of treatment per week for 9 weeks [initial 1 cycle of 2 BCG +1 MMC-EMDA 3 weeks after TURBT,
Maintenance with 1 instillation per month for 9 months: 3 cycles of 2 MMC-EMDA + 1 BCG.</td></tr>
<tr><td>BCG instillation alone and maintenance after TURBT</td><td>6 BCG instillations at weekly intervals 3 weeks after TURBT and monthly BCG instillations for 10 months</td></tr>
</table>
Di Stasi 2003 (parallel RCT with additional sessions of EMDA at 3 months and cross over at 6 months)
<table>
<tr><th>Interventions and comparators</th><th>Intervention given</th></tr>
<tr><td>MMC-EMDA instillation after TURBT</td><td>6 intravesical instillations at weekly intervals at 3 weeks after TURBT</td></tr>
<tr><td>MMC-passive diffusion [PD] instillation after TURBT</td><td>An additional 6 MMC-PD intravesical instillations at weekly intervals if cancer persisted at 3 months.</td></tr>
<tr><td>BCG instillation after TURBT</td><td>Patients in this group were crossed over to a six-week MMC-EMDA course.</td></tr>
</table>
If disease persisted at 6 months, there was cross over to a 6-week additional course of BCG for people who underwent the MMC-EMDA with MMC-PD instillation.</td></tr>
<tr><td>Follow-up</td><td>Median range 43 to 88 months</td></tr>
<tr><td>Conflict of interest/source of funding</td><td>None. Study supported by Cochrane Urology Group, University of Minnesota and Minneapolis VA healthcare System USA.</td></tr>
</table>

Analysis

Follow-up issues: in the cross over study (Di Stasi 2003) data up to 3 months after intervention (before additional sessions and cross over) was only used due to the study design.

Study design issues: methodologically high quality systematic review with a comprehensive search strategy; only 3 RCTs were included. Two review authors independently screened the literature (according to criteria in Cochrane handbook for Systematic Reviews of Interventions), extracted data, assessed risk of bias (using Cochrane 'risk of bias' tool) and rated quality of evidence according to GRADE working group grades of evidence (high, moderate low or very low quality) on a per outcome basis. Any discrepancies were resolved by consensus after discussion with a third reviewer. The rating for most comparisons in studies was low or very low (studies used stratified block randomisation, but did not report methods of allocation concealment, had inadequate blinding of patients and personnel and outcomes). Patient-important outcomes were reported. Data were analysed according to different comparisons, and both pre-operative and post-operative settings. A meta-analysis was done if sufficient data was available and if unavailable a narrative synthesis was done. Subgroup analysis and heterogeneity were also investigated.

Study population issues: patients who had NMIBC were classified as low, intermediate or high-risk categories in accordance with the European Association of Urology (EAU) classification system.

Other issues: all included studies were from the same research team and mitomycin C was the only chemotherapeutic drug used. Concomitant interventions were same in the experimental and comparator groups.

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **3 RCTs (n=672 patients)**

Comparison 1 Postoperative MMC-EMDA induction versus postoperative BCG induction therapy (short term) [Di Stasi 2003]

Outcomes (at mean 3 months follow-up)	No of patients (studies)	MMC-EMDA % (n)	BCG % (n)	Effect size (RR, 95% CI)
Time to recurrence	72 (1 RCT)	47% (17/36)	44% (16/36)	1.06 (0.64, 1.76)
Time to progression	72 (1 RCT)	0	0	0.0 (0.0, 0.0)
Serious adverse events	72 (1 RCT)	8% (3/36)	11% (4/36)	0.75 (0.18, 3.11)
Disease-specific survival	72 (1 RCT)	0	0	0.0 (0.0, 0.0)
Time to death	72 (1 RCT)	0	0	0.0 (0.0, 0.0)

Comparison 2 Postoperative MMC-EMDA induction versus MMC-PD induction therapy (short term) [Di Stasi 2003]

Outcomes (at mean 3 months follow-up)	No of patients (studies)	MMC-EMDA % (n)	BCG % (n)	Effect size (RR, 95% CI)
Time to recurrence	72 (1 RCT)	47% (17/36)	72% (26/36)	0.65 (0.44, 0.98)
Time to progression	72 (1 RCT)	0	0	0.0 (0.0, 0.0)
Serious adverse events	72 (1 RCT)	8 % (3/36)	5% (2/36)	1.50 (0.27, 8.45)
Disease-specific survival	72 (1 RCT)	0	0	0.0 (0.0, 0.0)
Time to death	72 (1 RCT)	0	0	0.0 (0.0, 0.0)

Comparison 3 Postoperative MMC-EMDA with sequential BCG induction and maintenance versus postoperative BCG induction and maintenance therapy (long term) [Di Stasi 2006]

Outcomes (at median 88 months follow-up)	No of patients (studies)	MMC-EMDA with BCG % (n)	BCG %(n)	Effect size (HR, 95% CI)
Time to recurrence	212 (1 RCT)	105	107	0.51 (0.34, 0.77)
Time to progression	212 (1 RCT)	105	107	0.36 (0.17, 0.75)
Serious adverse events	212 (1 RCT)	3 % (3/105)	3% (3/107)	1.02 (0.21, 4.94)
Disease-specific survival	212 (1 RCT)	105	107	0.31 (0.12, 0.80)
Time to death	212 (1 RCT)	105	107	0.59 (0.35, 1.00)

Comparison 4 Single-dose, preoperative MMC-EMDA versus single-dose, postoperative MMC-PD (long term) [Di Stasi 2011]

Outcomes (at median 86 months follow-up)	No of patients (studies)	Pre-operative MMC-EMDA %(n)	MMC-PD % (n)	Effect size (HR, 95% CI)
Time to recurrence	236 (1 RCT)	117	119	0.47 (0.32, 0.69)
Time to progression	236 (1 RCT)	117	119	0.81 (0.00, 259.93)
Serious adverse events	236 (1 RCT)	6% (7/117)	7% (9/119)	0.79 (0.30, 2.05)
Disease-specific survival	236 (1 RCT)	117	119	0.99 (0.74, 1.32)
Time to death	236 (1 RCT)	117	119	0.89 (0.62, 1.28)
Minor adverse events	236 (1 RCT)	37% (44/117)	68% (81/119)	0.55 (0.42, 0.72)

Comparison 5 Single-dose, preoperative MMC-EMDA versus TURBT alone (long term) [Di Stasi 2011]

Outcomes (at median 86 months follow-up)	No of patients (studies)	Pre-operative MMC-EMDA %(n)	TURBT alone %(n)	Effect size (HR, 95% CI)
Time to recurrence	233 (1 RCT)	117	116	0.40 (0.28, 0.57)
Time to progression	233 (1 RCT)	117	116	0.74 (0.00, 247.93)
Serious adverse events	233 (1 RCT)	6% (7/117)	3% (4/116)	1.74 (0.52, 5.77)
Disease-specific survival	233 (1 RCT)	117	116	1.06 (0.80,1.40)
Time to death	233 (1 RCT)	117	116	1.07 (0.73, 1.57)
Minor adverse events	233 (1 RCT)	37% (44/117)	22% (26/116)	1.68 (1.11, 2.53)

Abbreviations used: BCG vaccine, Bacillus Calmette-Guerin vaccine; CI, confidence interval; EMDA, electromotive drug administration; HR, hazard ratio; MMC-EMDA, electromotive drug administration of mitomycin C; MMC-PD, passive diffusion of mitomycin C; RCT, randomised controlled trial; RR, risk ratio; TURBT, transurethral resection of bladder tumour.

Study 2 Gan C (2016)

Details

Study type	**Case series**
Country	UK
Study period	2009-2013
Study population and number	n=**107 patients with new or recurrent high risk, non-muscle invasive bladder cancer undergoing bladder conservation.** **Tumour stage** Ta/T1 in 80% (86/107), primary CIS 18% (19/107), recurrent large volume low grade Ta 2% (2/107) **Disease type:** new 74% (79/107),recurrent 26% (28/107)
Age and sex	Mean age 68 years, 87% (93/107) male
Patient selection criteria	Exclusion criteria: patients with a history of tuberculosis infection unable to receive BCG and those with permanent cardiac pacemakers unsuitable for EMDA-MMC.
Technique	Sequential BCG /electromotive drug administration of mitomycin C (EMDA-MMC) following complete, transurethral resection of bladder tumour (TURBT). Treatment schedule: 9 weeks BCG/EMDA-MMC induction schedule 3-4 weeks after TURBT. BCG was administered in weeks 1 and 2 and Mitomycin C was administered in EMDA fashion (40mg and 20mA current for 30 minutes) in week 3 and repeated three times for a total of 9 weeks. Response was assessed by rigid cystoscopy 8 weeks after treatment. Patients who tolerated and recurrent free proceeded to maintenance treatment. As maintenance 3 doses of BCG were given 3 months after induction and then every 6 months for 3 years. Cystoscopic surveillance at 6 month intervals was done if the patient remained recurrence free.
Follow-up	**2 years**
Conflict of interest/source of funding	Not stated; no commercial incentive received.

Analysis

Follow-up issues: 10 patients were lost follow –up (3 at first check, 4 at 1 year [1 terminated due to comorbidities, 1 died, 1 had cystectomy, 1 care transferred], and another 3 at 2 years).

Study design issues: prospective data collection. All patients had sequential BCG/EMDA-MMC but some minor and major alterations to treatment schedule had been made. Repeat TURBT prior to sequential BCG/EMDA-MMC was done if there is no muscle in original specimen, or incomplete tumour resection, or extensive HR-NMIBC or for tertiary referral patents who have undergone initial resection elsewhere. Induction regime described by Di Stasi was used.

Data analysis was on an intention to treat basis and also by the actual treatment received.

Efficacy

Number of patients analysed: **107**

Intention to treat analysis-response rate

	After treatment N=104	1 year follow-up N=86	2 year follow-up N=71
Recurrence free	87% (90/104)	86% (74/86)	93% (66/71)
Recurred or progressed	13% (14/104)	14% (12/86)	7% (5/71)

Disease recurrence and subsequent management

Recurrence	No of patients	Management
Progression		
MIBC	3	Radical cystectomy
Higher stage NMIBC	2	Endoscopic surveillance (1), radical cystectomy(1)
Same or lower stage recurrence	26	Radical cystectomy (6), further intravesical therapy (5), endoscopic surveillance with/without maintenance treatment (13), palliation(1), other (1)

Analysis of treatment received: Response rate by treatment schedule

	Recurrence free % (n)		
Treatment schedule	**After treatment**	**1 year follow-up**	**2 year follow-up**
Full 9 week treatment	87 (65/75)	86 (55/64)	91 (49/54)
Reduced schedule	86 (25/29)	86 (19/22)	100 (17/17)
P value	0.95	0.96	0.19

Safety

Tolerability

Full 9 week treatment was not completed in 28% (30/107) patients. Of these patients, 16 had a minor alteration to treatment schedule and received 7-8 doses, remaining 14 patients had a major alteration which included all other dose permutations.

Reasons for treatment discontinuation

Adverse event	No of patients
Lower urinary tract symptoms/hematuria	9
Arthralgia	3
Recurrent urinary tract infection	2
Rash	1
BCGosis	1
EMDA catheter not tolerated	6
Unrelated illness	4
Other reasons	
BCG shortage	3
Defaulted	1

3 patients who had salvage cystectomy died.

Abbreviations used: BCG vaccine, Bacillus Calmette-Guerin vaccine; EMDA, electromotive drug administration; MMC, mitomycin C; NMIBC, non-muscle invasive bladder cancer.

Study 3 Colombo R (2001)

Details

Study type	**Non-randomised controlled trial**
Country	Italy
Study period	1996-1998
Study population and number	n=**80 (n = 29 MMC MW, n= 36 MMC alone, n = 15 MMC EMDA) patients with superficial (Ta–T1), low-grade (G1–G2), recurrent, single, small (< 2 cm) bladder tumours**
Age and sex	Not stated
Patient selection criteria	Exclusion criteria: previous treatment with MMC
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.
Follow-up	**7–10 days after last treatment**
Conflict of interest/source of funding	Not stated

Analysis

Follow-up issues:

Study design issues: The method of patient selection was not described.

Subjective symptom scores were collected using a non-validated questionnaire regarding 7 factors. Low scores indicate better status.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **80 (n = 29 MMC MW, n= 36 MMC alone, n = 15 MMC EMDA)**

Tumour response

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.

MMC plus MW: 19/29 (66.0%)

MMC plus EMDA 6/15 (40.0%)

Passive MMC alone: 10/36 (27.8%)

(No p values reported)

Safety

Complications

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.

Subjective symptom scores: 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)

There were no significant differences between the treatment groups (p value not stated).

Abbreviations used: BCG vaccine, Bacillus Calmette-Guerin vaccine; EMDA, electromotive drug administration; MMC, mitomycin C; MMC-PD, MW, microwave; passive diffusion of mitomycin C; SD, standard deviation; TCC, transitional cell carcinoma.

Study 4 Barusi M (1998)

Details

Study type	**Non-randomised controlled trial**
Country	Italy and US
Study period	Nov 1993 to Jan 1995
Study population and number	n=**28 (n = 15 MMC plus EMDA versus 13 MMC-PD) patients with superficial transitional cell carcinoma (TCC) of the bladder.** Range of tumour diameter 0.4 to 1.5 cm. Tumour stage Ta = 50%, T1 = 50%. Tumour grade G1 = 36%, grade 2 = 64%.
Age and sex	Mean age 70 years, 75% male
Patient selection criteria	Exclusion criteria: infiltrating tumour > T1. Random biopsies of the bladder mucosa and prostatic urethra taken to exclude carcinoma in situ
Technique	eight 20-min sessions MMC 40 mg in 50 ml distilled water with maximum 15 mA pulsed electric current externally vs passive MMC.
Follow-up	**mean 16 months**
Conflict of interest/source of funding	Not stated

Analysis

Follow-up issues: One patient in the passive MMC group died at 10 weeks follow-up from myocardial infarction and was excluded from efficacy analysis.

Study design issues: 28 patients recruited across 7 participating centres. Some sites will have treated only a small number of patients.

Authors state that patient sample is too small to draw definite conclusions

Key efficacy and safety findings

Efficacy

Number of patients analysed: 28 (n=15 MMC plus EMDA)

Tumour response

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.

Outcomes	EMDA MMC	Passive MMC
Complete response % (n)	40% (6/15)	42% (5/12)
Tumour-free at final follow-up % (n)	67% (4/6)	40% (2/5)
Mean disease-free interval	14.5 months	10.5 months

Measure of significance not reported.

Long-term follow-up was recorded for patients who were complete responders at initial assessment (3 months).

Safety

Complications

No severe systemic side effects were recorded in either group.

Adverse events	EMDA MMC % (n)	Passive MMC % (n)
Transient macroscopic haematuria	0%	7% (1/13)
Chemical cystitis (requiring suspension or delay of treatment)	13% (2/15)	0%

Measure of significance not reported. Time of occurrence of complication and duration not reported.

Abbreviations used: BCG vaccine, Bacillus Calmette-Guerin vaccine; EMDA, electromotive drug administration; MMC, mitomycin C; MMC-PD, passive diffusion of mitomycin C; TCC, transitional cell carcinoma.

Study 5 Riedl CR (1998)

Details

Study type	**Case series**
Country	Austria
Study period	Not stated
Study population and number	n=**22 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%.**
Age and sex	Mean age 72 years, 68% male
Patient selection criteria	Not stated
Technique	Following transurethral resection EMDA with MMC 40 mg in 100 ml distilled eater with maximum. 15 mA pulsed electric current for 4 treatment sessions
Follow-up	**Mean 14 months**
Conflict of interest/source of funding	Not stated

Analysis

Follow-up issues: Insufficient follow-up data were available on 14% (3/22) of patients.

Study design issues: In 3 patients' resection was incomplete owing to large tumour size, and EMDA–MMC was used with the intention of residual tumour control.

The study report describes outcome of EMDA with a variety of other drugs for other indications. Data not extracted here.

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. Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 22
Tumour response
Cystoscopy and cytology were performed 6 weeks following final treatment session, and every 3 months thereafter. However, complete response was not defined
Recurrence-free survival was achieved in 57% (9/16) of patients, at a mean follow-up of 14 months
In 3 patients with incomplete resection, tumour reduction was observed but complete remission was not achieved</td><td>Complications
Treatments were terminated owing to complications in 14% (3/22) of patients.
<table>
<tr><th>Event</th><th>Rate % (n)</th></tr>
<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>
</table></td></tr>
<tr><td colspan="2">Abbreviations used: BCG vaccine, Bacillus Calmette-Guerin vaccine; EMDA, electromotive drug administration; MMC, mitomycin C.</td></tr>
</table>

Study 6 Decaestecker (2018)

Details

Study type	**Case series**
Country	Belgium
Study period	2012-2015
Study population and number	n=**32 patients with small non-muscle invasive bladder cancer (NMIBC).** **Disease type:** primary (n=12), recurrent (n=20)
Age and sex	Mean age 75 years, 84% (27/32) male
Patient selection criteria	All patients will small (<2cm) single or multiple papillary bladder tumours were included. Recurrent patients treated with intravesical MMC within the last year or patients with a history of Tis of the bladder were excluded.
Technique	Electromotive drug administration of mitomycin C (EMDA-MMC) instillation using a single dose of 60mg intravesical MMC (with 25mA current for 25 minutes) before planning TURBT. 36 instillations were given, 4 patients received a second EMDA-MMC at a new recurrence after complete response at the first EMDA-MMC.
Follow-up	**4 weeks**
Conflict of interest/source of funding	No potential conflict of interest reported.

Analysis

Follow-up issues: 1 patient refused TURBT and lost to further follow-up. In 2 others TURBT was not done due to serious disease.

Study design issues: very small study, some patients had previous MMC (n=13) and BCG (n=4).

Efficacy

Number of patients analysed: **32**

Tumour response % (n)

Complete response*	**% (n)**
No of patients	25% (8/32)
No of sessions^	28% (10/36)
No change	**61% (22/36)**

*defined as complete disappearance of all papillary tumours at cystoscopy at 2-4 weeks after the treatment, to avoid TURBT)

^including 2 of the 4 repeated sessions who had a complete response 1 year earlier.

In patients with multiple tumours (n=16), tumours disappeared in 4 patients and remained unchanged in others.

Safety

Adverse events

	n
Severe bladder spasms when EMDA was applied, (treatment stopped early)	2
Urination immediately/during treatment, treatment failed	2

Abbreviations used: EMDA, electromotive drug administration; MMC, mitomycin C; NMIBC, non-muscle invasive bladder cancer; TURBT, transurethral resection of bladder tumour.

Validity and generalisability of the studies

- Mitomycin C with electromotive drug administration (MMC-EMDA) has been used for both immediate (before or after transurethral resection of bladder tumour [TURBT]) induction and maintenance treatment for non-muscle invasive bladder cancer (NMIBC). 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.
- The Cochrane review included 3 randomised controlled trials (RCTs) that compared 5 ways of using this treatment. One study included looked at MMC-EMDA in addition to BCG treatment. All trials were from the same study group who founded this procedure. The quality of evidence was rated as low to very low for the comparisons, therefore the findings are uncertain.
- Drug delivery preparation, dosage, duration and intensity of interventional and comparator interventions varied across studies. The composition of the solution may have an influence on the safety and efficacy of the procedure.
- Mitomycin C was the only intravesical agent used with EMDA in all studies. There is no evidence on the effect of EMDA with other chemotherapeutic agents.
- One study had very short follow-up (≤10 days).
- The definition of “complete response” differed across studies, and in some it is not well defined. None of the studies reported quality of life data.
- The surveillance protocol during follow-up varied 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.
- The Cochrane review authors state that EMDA is not compared to established standard of practice in this patient group. Current guidelines state that after TURBT, patient should undergo immediate postoperative instillation of MMC followed by an induction course of MMC or BCG, with or without maintenance

therapy based on their risk of recurrence. Therefore clinical applicability and generalisability is limited.

Existing assessments of this procedure

European Association of Urology guidelines on microwave-induced hyperthermia and electromotive drug administration (EMDA) non-muscle-invasive bladder cancer (Ta, T1 and CIS) published in 2016 states that

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia or the efficacy of MMC using electromotive drug administration (EMDA) in patients with high-risk tumours. The current evidence, however, is limited and both treatment modalities are considered to be experimental (LE: 2b).[7]

Canadian guidelines on the management of NMIBC including intravesical therapy published in 2015 suggest that device assisted therapies have shown promising results; however multicentre studies are needed to further validate their efficacy as first and second-line treatments in the North American population.[8]

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer. Interventional procedures IPG 235 (2007). Available from https://www.nice.org.uk/guidance/ipg235 (This guidance is currently under review and is expected to be updated in 2009. For more information, see http://www.nice.org.uk/guidance/IPG235).

NICE guidelines

- Bladder cancer: diagnosis and management. NICE guideline 2 (2015). Available from https://www.nice.org.uk/guidance/ng2
- Bladder cancer. NICE quality standard 106 (2015). Available from https://www.nice.org.uk/guidance/qs106
- Suspected cancer: recognition and referral. NICE guideline 12 (2015). Available from https://www.nice.org.uk/guidance/ng12

Additional information considered by IPAC

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 is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Specialist Advisor Questionnaires for electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

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.
- Ongoing trials
  - **NCT01920269** Intravesical Adjuvant Electromotive Mitomycin-C in Patients With pTa-pT1 and G1-G2 Non-muscle Invasive Bladder Cancer: a Randomized Controlled Trial**;** Group A-Transurethral resection alone; Group B-Intravesical MMC-PD after TURBT, Group C-Intravesical electromotive mitomycin after TURBT. Primary outcome Disease-free interval (time frame: 120 months). Completion date: June 2013 (This study has been completed, but the results have not published)
  - **NCT02202044** Adjuvant Sequential Intravesical BCG (Bacillus Calmette-Guérin) and Electromotive Mitomycin-C (EMDA/MMC) After Transuretheral Resection (TUR) in Patients With Primary High Risk Non-Muscle Invasive Transitional Cell Carcinoma of the Bladder location: USA; Status: terminated

References

1. Jung JH, Gudeloglu A et al (2017). Intravesical electromotive drug administration for non-muscle invasive bladder cancer. Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD011864. DOI: 10.1002/14651858.CD011864.pub2.
2. Gan C, Amery S et al (2016). Sequential bacillus Calmette-Guerin/Electromotive Drug Administration of mitomycin C as the standard intravesical regimen in high risk nonmuscle invasive bladder cancer: 2 year outcomes. The Journal of Urology. 195, 1697-1703.
3. 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.
4. 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.
5. 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.
6. Decaestecker K, Lumen N et al (2018). Single ablative intravesical electromotive mitomycin C administration for small non-muscle invasive bladder cancer; a prospective study. Acta Clinica Belgica 16
7. Babjuk M, Böhle A, Burger M (2016). EAU guidelines on non-muscle-invasive bladder cancer (Ta, T1 and CIS). European Association of Urology. Available online https://uroweb.org/wp-content/uploads/2016-Non-muscle-invasive-Bladder-Cancer-Guidelines.pdf
8. Kassouf W, Traboulsi SL et al (2015). CUA guidelines on the management of non-muscle invasive bladder cancer. Can Urol Assoc J 2015; 9(9-10):E690-704.

Appendix

The following table outlines the studies that are considered potentially relevant to the IP 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
Annette F (2011). BLADDER CANCER- EMDA mitomycin before TURBT is the best treatment for non-muscle-invasive disease. Nature Reviews Urology 8, 472.	Review	Intravesical EMDA mitomycin before TURBT provided significant long-term benefit in all stratification groups including intermediate-risk and high-risk patients and those with multifocal disease.	Article on research highlights.
Bachir BG, Dragomir A, Aprikian AG et al. Contemporary cost-effectiveness analysis comparing sequential bacillus Calmette-Guerin and electromotive mitomycin versus bacillus Calmette-Guèrin alone for patients with high-risk Non-Muscle-Invasive bladder cancer. Cancer 2014: 00 : 1-7	Retrospective cost effectiveness analysis N=212 Ta-T1 and Cis		Cost effectiveness study (out of remit).
Brausi M (2017). Is Bacillus Calmette-Guerin (BCG) still the best adjuvant treatment after Trans Urethral Resection (TUR) for Ta-T1 high grade (G3) bladder cancer. 14th Meeting of the EAU Section of Oncological Urology (ESOU). Eur Urol Suppl; 16(2):94	Review	The good results obtained with the administration of MMC with EMDA in low, intermediate and high risk patients after TUR have been reported extensively in literature. Also the efficacy of chemo-hyperthermia with MMC in intermediate, high risk and BCG resistant TCC of the bladder has been documented. Studies demonstrate that the combination of immuno and chemotherapy administered with new technologies, Electromotive Drug Administration-EMDA and the use of Chemo-hyperthermia with MMC can obtain better results in terms of disease free interval and progression	Review

		compared to BCG alone in patients at high risk.	
Brausi M, Olaru V (2012). Management of high-risk non-muscle invasive bladder cancer. Minerva urologica e nefrologica 64 (4), 255-260.	Review	Device assisted chemotherapy (EMDA with MMC) may have a role in BCG failure or BCG resistant patients who cannot receive or refuse cystectomy. Postponing radical cystectomy until progression to muscle invasive disease may have a negative impact on survival.	Review
Canadian Agency for Drugs and Technologies in Health (2014). The use of the electromotive drug administration system in patients with superficial bladder cancer: a review of the clinical effectiveness, safety, and cost-effectiveness. Canadian Agency for Drugs and Technologies in Health. Rapid Response Report. www.ncbi.nlm.nih.gov pubmedhealth/PMH0069840/	Review (limited search)	The results of this review suggest EDMA mitomycin before TURBT is a promising alternative to passive diffusion mitomycin post-TURBT or TURBT alone, with little (or even fewer) adverse effects. However more trials in different contexts would likely be needed to evaluate effectiveness and safety before a policy recommendation. There was also no evidence on cost-effectiveness which would be required to better understand policy implications.	Rapid review (included only 1 trial Di Stasi 201).
Campodonico F, Di Stasi S et al (2017). Intravesical Chemotherapy and Chemohyperthermia in Non-Muscle-Invasive Bladder Cancer; An Overview on Drug Administration Technologies and Pharmacokinetics. Current Drug Metabolism, 18, 657-665	Review on principles of pharmacokinetics and absorption of chemotherapy agents administered intravesically for NMIBC are described, as well as the techniques to maximize drug delivery and contact time and strategies to enhance the absorption and action of these agents.	Knowledge of drug diffusion mechanisms into the tissue and cellular cytoplasm following bladder instillation is a key to understand the safety profile and clinical activity of chemotherapy.	Review
Houghton B, Hayne D et al (2010). Intravesical chemotherapy plus BCG in non-muscle invasive bladder cancer-A systematic review with meta-analysis. BJU International 111, 977-983.	Systematic review and meta-analysis of RCTs that compared sequential intravesical chemotherapy plus maintenance BCG versus maintenance BCG alone for NMIBC	Four trials were identified, including 801 patients. Adding chemotherapy to maintenance BCG did not result in a significant reduction in recurrence (relative risk [RR] 0.92; 95% confidence interval [CI] 0.79–1.09; P = 0.32) or	Heterogeneous mix of studies with different interventions and sequencing. Only one study (Stasi 2006) used electromotive

		progression (RR 0.88; 95% CI 0.61–1.27; P = 0.5). The risk of recurrence (RR 0.75; 95% CI 0.61–0.92; P = 0.006) and progression (RR 0.45; 95% CI 0.25–0.81; P = 0.007) were reduced when the single trial that included isolated Tis was excluded. Toxicity was similar for both groups.	mitomycin C. this study has been included in the Cochrane review added to table 2.
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.	Randomised controlled trial n= 212 intermediate risk patients with TCC of the bladder 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) (n = 107 BCG plus EMDA MMC) Follow-up: median 88 months	Patients assigned sequential BCG and electromotive mitomycin had higher disease-free interval than did those assigned BCG alone (69 months [95% CI 55–86] *vs* 21 months [15–54]; difference between groups 48 months [42–54], log-rank p=0·0012). Patients assigned sequential BCG and electromotive mitomycin also had lower recurrence (41·9% [32·7–51·5] *vs* 57·9% [48·7–67·5]; difference between groups 16·0% [2·7–29·3], log-rank p=0·0012); progression (9·3% [3·8–14·8] *vs* 21·9% [17·9–25·9]; difference between groups 12·6% [3·0–22·2], log-rank p=0·004); overall mortality (21·5% [13·5–29·5] *vs* 32·4% [23·4–41·4], difference between groups 10·9% [0·6–21·2], log-rank p=0·045); and disease-specific mortality (5·6% [1·2–10·0] *vs* 16·2% [6·1–23·3], difference between groups 10·6% [2·5–18·7], log-rank p=0·01). Side-effects were mainly localised to the bladder.	Included in Cochrane review added to table 2.
Di Stasi SM, Riedl C (2009). Updates in intravesical electromotive drug administration of mitomycin-C for non-muscle invasive bladder cancer. World J Urol. 27:325–330	Review	EMDA of intravesical mitomycin-C (MMC) has been used for treatment of non-muscle invasive bladder cancer (NMIBC). Studies demonstrated an enhanced administration rate of MMC into all bladder	Review

		wall layers after EMDA compared to standard instillation/passive diffusion (PD). BCG combined with EMDA/MMC as well as preoperative EMDA/MMC are new therapeutic strategies with promising preliminary results in terms of higher remission rates and longer remission times. These findings suggest that EMDA for MMC delivery in the bladder could be a major therapeutic breakthrough in the treatment of NMIBC.	
Di Stasi SM, Liberati E et al (2008). Intravesical electromotive drug administration of mitomycin-C for non-muscle invasive bladder cancer. Archivio Italiano di Urologia e Andrologia 80 (4), 157-161	Review	Article reviews EMDA for non-muscle invasive bladder cancer treatment and evidence in support of this. two recent RCTs adopting protocols that use EMDA to enhance urothelial transport of intravesical mitomycin C showed it proved a therapeutic advantage and suggested that further studies are required to demonstrate feasibility and advantage if intravesical EMDA of mitomycin C.	Review
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.	Randomised controlled trial Patients with high risk superficial bladder cancer (histologically proven multifocal carcinoma in situ of the bladder and most (91%) with pT1 papillary transitional cell carcinoma). n= 108 (n = 36 MMC plus EMDA) Follow-up: median 43 months	The complete response for electromotive vs passive MMC at 3 and 6 months was 53% versus 28% (p = 0.036) and 58% versus 31% (p = 0.012). For BCG the responses were 56% and 64%. Median time to recurrence was 35 vs 19.5 months (p = 0.013) and for BCG it was 26 months. Peak plasma MMC was significantly higher following electromotive MMC than after MMC ((43 vs 8 ng/ml), consistent with bladder content absorption	Included in Cochrane review added to table 2.
Di Stasi SM, Valenti M, Verri C et al. Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle	RCT N=374 patients with non-muscle invasive bladder cancer. (124 TURBT alone versus	Patients assigned to receive EMDA mitomycin before TURBT had a lower rate of recurrence (44 [38%] of 117) than those assigned to receive PD mitomycin after TURBT (70	Included in Cochrane review added to table 2.

invasive bladder cancer: a randomized controlled trial. Lancet Oncol 2011; 12: 871-979	126 post-TURBT PD MMC [immediate post-TURBT instillation of 40 mg PD mitomycin dissolved in 50 mL sterile water infused over 60 min], versus 124 pre-TURBT EMDA MMC [immediate pre-TURBT instillation of 40 mg EMDA mitomycin dissolved in 100 mL sterile water with intravesical 20 mA pulsed electric current for 30 min]). Median follow-up was 86 months.	[59%] of 119) and TURBT alone (74 [64%] of 116; log-rank p<0·0001). Patients assigned to receive EMDA mitomycin before TURBT also had a higher disease-free interval (52 months, IQR 32–184) than those assigned to receive PD mitomycin after TURBT (16 months, 12–168) and TURBT alone (12 months, 12–37; log-rank p<0·0001). We recorded persistent bladder symptoms after TURBT in 18 (16%) of 116 patients in the TURBT-alone group (duration 3–7 days), 37 (31%) of 119 in the PD mitomycin post-TURBT group (duration 20–30 days), and 24 (21%) of 117 in the EMDA mitomycin pre-TURBT group (duration 7–12 days); haematuria after TURBT in eight (7%) of 116 patients in the TURBT-alone group, 16 (13%) of 119 in the PD mitomycin post-TURBT group, and 11 (9%) of 117 in the EMDA mitomycin pre-TURBT group; and bladder perforation after TURBT in five (4%) of 116 patients in the TURBT-alone group, nine (8%) of 119 in the PD mitomycin post-TURBT group, and seven (6%) of 117 in the EMDA mitomycin pre-TURBT group.	
Porten SP, Leapmean MS et al (2015). Intravesical chemotherapy in non-muscle-invasive bladder cancer. Indian Journal of Urology. 31, 4, 297-303.	Narrative review	Chemohyperthermia and electromotive instillation have been associated with improved freedom from recurrence intervals but may be associated with increased urinary toxicity. Improvements in therapeutic selection may be heralded by novel opportunities for genomic profiling and refinements in clinical risk stratification.	Review
Slater SE, Patel R et al (2014). The effects and effectiveness of	Non-systematic review describing the scientific basis and	EMDA takes advantage of three phenomena: iontophoresis, electro-	Review.

electromotive drug administration and chemohyperthermia for treating non-muscle invasive bladder cancer. Ann R Coll Surg Engl; 96: 415–419.	mechanisms of action of electromotive drug administration (EMDA) and chemohyperthermia (CHT).	osmosis and electroporation. It has been found to reduce recurrence rates in NMIBC patients and has been proposed as an addition or alternative to bacillus Calmette–Guérin (BCG) therapy in the treatment of high risk NMIBC. CHT improves the efficacy of mitomycin C by three mechanisms: tumour cell cytotoxicity, altered tumour blood flow and localised immune responses. Fewer studies have been conducted with CHT than with EMDA but they have demonstrated utility for increasing disease-free survival, especially in patients who have previously failed BCG therapy. EMDA and CHT will play important roles in the management of NMIBC in the future. Techniques of delivery should be standardised, and there is a need for more randomised controlled trials to evaluate the benefits of the treatments alongside quality of life and cost-effectiveness.	
Veeratterapillay R, Heer R et al (2016). High-risk non-muscle-invasive bladder cancer – therapy options during intravesical BCG shortage. Current Urology Reports 2016; 17(9):68.	Review	BCG has been shown to reduce recurrence in high-risk NMIBC and is more effective that other intravesical agents including mitomycin C, epirubicin, interferon-alpha and gemcitabine. Primary cystectomy offers a high change of cure in this cohort (80–90 %) and is a more radical treatment option which patients need to be counselled carefully about. Bladder thermotherapy and electromotive drug administration with mitomycin C are alternative therapies with promising short-term results although long-term follow-up data are lacking.	Review

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	10/05/2018	Issue 5 of 12, May 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	10/05/2018	Issue 4 of 12, April 2018
HTA database (Cochrane Library)	10/05/2018	Issue 4 of 4, October 2016
MEDLINE (Ovid)	10/05/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid) &	10/05/2018	May 09, 2018
Medline ePub ahead (Ovid)	10/05/2018	May 09, 2018
EMBASE (Ovid)	10/05/2018	1974 to 2018 Week 19

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

MEDLINE search strategy

1 Electric Stimulation Therapy/
2 Electrochemotherapy/
3 (electrochemotherap* or electro chemotherap*).tw.
4 Iontophoresis/
5 (Iontotherap$ or iontophores$).tw.
6 (electromotive* or electro-motive*).tw.
7 EMDA.tw.
8 or/1-7
9 Urinary Bladder Neoplasms/
10 carcinoma, transitional cell/ and bladder.af.
11 (bladder adj4 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumo?r$ or malignan$)).tw.
12 (sarcoma adj4 bladder).tw.
13 (transitional adj4 cell adj4 carcinoma$ adj4 bladder).tw.
14 or/9-13
15 8 and 14
16 animals/ not humans/
17 15 not 16
18 limit 17 to ed=20171013-20181231