NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer

This procedure may be done as an outpatient before or after surgery for early-stage bladder cancer. Chemotherapeutic drugs are instilled through a special tube called a catheter inserted into the bladder through the urethra (the tube that carries urine out of the body from the bladder). The catheter also emits microwaves which heat up the bladder wall. The heating is intended to enhance the effect of chemotherapy on the cancer cells.

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 January 2018.

Procedure name

- Intravesical microwave hyperthermia with intravesical chemotherapy for superficial 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

Transitional cell carcinoma (TCC) is the most common form of bladder cancer. Superficial TCC (not invading the muscle layer) is classified as stage Ta when the tumour is confined to the uroepithelium 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. Superficial transitional cell carcinomas can be graded from G1 (low grade, least aggressive) to G3 (high grade, most aggressive). Carcinoma in situ is a form of tumour consisting of aggressive cancer cells which spread within the surface lining of the bladder.

Surgical interventions for superficial transitional cell carcinoma include transurethral resection (TUR), in which malignant tissue is removed with an electrocautery device during cystoscopy. Bacillus Calmette-Guérin (BCG) vaccine or chemotherapeutic drugs may be instilled directly into the bladder, either as a treatment in itself, or as adjuvant therapy after TUR. Cystectomy may also be necessary in some patients.

What the procedure involves

Intravesical hyperthermia combined with intravesical chemotherapy can be used as neoadjuvant therapy prior to TUR, with the aim of eradicating tumours.

Alternatively the procedure can be used after TUR, as adjuvant therapy (sometimes referred to as prophylactic treatment), with the aim of preventing recurrence. Hyperthermia is believed to have a direct and immune-mediated cytotoxic effect on tumour cells and to improve the efficacy of chemotherapy drugs.

The procedure can be done on an outpatient basis. Using local anaesthetc urethral gel, a balloon catheter, containing an antenna and several insulated thermocouples, is inserted through the urethra into the bladder. Ultrasound is sometimes used to assess the position of the device. The antenna emits microwaves which heat the superficial layers of the bladder wall. The thermocouples, which are spread out from the catheter and pushed against the bladder lining, monitor temperature to help prevent overheating. A solution of a cytostatic agent, usually mitomycin C, is instilled into the bladder, between the bladder wall and the balloon surface. The solution is continuously pumped out of the bladder, cooled, and recirculated to prevent overheating. Treatment sessions typically last for 40–60 minutes and are usually repeated weekly for 4–8 weeks, or longer for adjuvant treatment.

Outcome measures

Bladder cancer classification:

Tumour

Tx	No primary tumour can be evaluated	
T0	There is no evidence of a primary tumour in the bladder	
Ta	Non-invasive papillary carcinoma	Non-muscle invasive bladder cancer
Tis	Carcinoma in situ (CIS) or “flat tumour”. Cancer is only found on or near the surface of the bladder.	
T1	Tumour has spread to the subepithelial connective tissue (lamina propria only).	
≥T2	Muscle invasive bladder cancer	

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. They are more likely to grow more quickly

Common terminology criteria for adverse events (CTCAE)

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 ADL.

Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 - Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.

Efficacy summary

Chemohyperthermia with mitomycin C compared to MMC alone.

In a review of 26 studies, 3 randomised control studies (RCT) and 1 non-randomised comparative study (NRCS) compared the outcome of patients with non-muscle invasive bladder cancer (NMIBC) treated by intravesical chemohyperthermia (CHT) with mitomycin C (MMC) compared to MMC alone. A meta-analysis of these studies suggested a statistically significantly lower risk of recurrence after CHT MMC (28% [26/93]) compared to MMC alone (68% [67/99]), risk ratio (RR) 0.41, 95% CI 0.29 to 0.58. In a RCT (n=83) reported in the same review, 2-year progression only occurred in the MMC alone group (3% [1/40]). At the 90-month follow-up, progression was not statistically significantly different in patients treated by CHT MMC (6% [2/35]) compared to patients treated by MMC alone (8% [3/40], p>0.05)[1-3].

CHT with MMC compared to BCG

One RCT (n=190) included in the review of 26 studies reported no statistically significantly difference in recurrence free survival (RFS) in the intention to treat population (ITT) between patients having CHT with MMC (78% [65 to 87%]) compared to bacilli Calmette-Guérin (BCG, 65% [52 to 75%], p=0.08), at the 24-month follow-up. In the per protocol population (PP, n=147) RFS was statistically significantly lower in patients having CHT MMC (82% [69 to 90%]) compared to

BCG (65% [52 to 75%], p=0.02). In the same study, complete response (CR) was not statistically significantly different in patients with carcinoma in situ tumours (CIS) treated by CHT MMC (89%) compared to BCG (86%, p=1). Progression was reported as less than 2% in both comparators[1-4].

CHT with MMC used after TURBT (prophylactic or adjuvant treatment)

The review of 26 studies included 4 peer reviewed case series, 1 conference abstract and 1 unpublished NRCS, reporting on outcomes of intermediate to high risk NMIBC (n=922) after CHT MMC as adjuvant therapy after TURBT. In 1 case series (n=111) RFS was 85% at 1 year and 56% at 2 years follow-up. Median time to recurrence was 16 months. DFS was 50% at the 2 years follow-up and progression occurred in 3% (1/38) of patients. Another case series (n=42) reported 89% DFS in the ITT population at 1 year follow-up. Recurrence was 31% (13/42), progression was 12% (5/42) and 17% (7/42) of patients ended up having a cystectomy. In 1 case series (n=160) RFS was 60% at 1 year and 46% at the 2-year follow-up. Progression occurred in 4% (7/160) of patients. In a case series (n=97) included in the same review OS was 82% (80/97), DSS 93% (90/97), progression: 36% (35/97) and cystectomy 19% (18/97), at a median 27-month follow-up. In 1 unpublished NRCS (n=366), conducted by the author of the review, recurrence was statistically significantly lower in patients having CHT MMC (25%) compared to patients having standard of care (39%, p<0.006), at a minimum 2 years follow-up. The frequency of RC was also statistically significantly lower in patients treated by CHT (2% [3/189]) compared to the standard care group (11% [20/180], p=0.0015). A conference abstract (n=146) included in the review reported PFS 98% at 1 year, 96% at 2 years and 84% at the 5 years follow-up[1-3].

In a case series of 26 patients treated by adjuvant CHT MMC, recurrence was reported in 12% (3/26) patients, DFS in 88% and there was no progression, at the 16.4-months follow-up[7].

CHT with MMC used after failed BCG as prophylactic or adjuvant treatment

In a case series (n=90) included in the review of 26 studies, recurrence was higher in patients treated by CHT MMC who had previously received BCG therapy (41%) than in patients treated by CHT MMC only (25%), at the 2 years follow-up. There was no progression during the median 18-month follow-up. In another case series (n=56) included in the same review there was no difference in recurrence between patients previously treated by BCG (46%) and patients treated by CHT MMC (44%, p=0.54) only, at the 4 years follow-up. In a case series of 38 high risk patients previously treated with BCG, recurrence was 50% and progression 3% (1/38), at the 2 years follow-up[1-3].

CHT with MMC used as neoadjuvant treatment

In a case series (n=12) reported in the review of 26 studies, CR was 42% (5/12), recurrence 20% (1/5) at 3 months after TURBT. In another case series (n=44) included in the review of 26 studies, CR was reported in 70% (31/44) patients and recurrence in 23% (7/31). There was no progression at the median 24 months follow-up. In a case series of 19 patients with multifocal therapy-resistant T1 tumours CHT MMC was used as debulking therapy allowing for 44% (16/19) of patients to have TURBT instead of RC. CR was reported in 47% (9/16) and recurrence in 89% (8/9) and there was no progression at the 33 month follow-up. The review of 26 studies included a conference abstract (case series, n=271) of patients having CHT MMC after non-compete resected NMIBC and failed BCG. CR was reported in 76% (206/271) and partial response in 8% (21/271). Overall recurrence was 19% (52/271) but higher in patients with BCG resistant tumours (42%) and in BCG relapse patients (67%), at the median 2.2 years (range 28 days to 12.9 years) follow-up[1-3].

Comparison between adjuvant and neoadjuvant treatment of CHT with MMC

The review of 26 studies included 5 NRCS and 1 case series (n=289) reporting outcomes of intermediate to high risk patients treated by adjuvant or neoadjuvant CHT with MMC. In a NRCS (n=52) recurrence was higher in patients treated by prophylactic CHT MMC (38% [9/24]) than in high risk patients having CHT before TURBT (19% [4/21]), at a mean 10 months follow-up. RFS was 63% (15/21) in patients receiving prophylactic CHT and there was no progression in both groups at the median 15.2 months follow-up. In another case series (n=47), recurrence was lower in patients having prophylactic CHT MMC (9% [2/22], 10 months) thank in the group having neoadjuvant therapy (20% [2/10], 9 months). There was no progression at the median 10 months follow-up. In a NRCS of 51 patients with CIS, there was no difference between adjuvant and neoadjuvant therapies as patient data were analysed together. CR was 92% (45/49), recurrence was 49% (22/45) and there was no progression, at the 2 years follow-up. Another NRCS (n=88) included in the review of 26 studies reported a higher recurrence (28% [18/64]) and progression (5% [3/64]) in patients having adjuvant CHT MMC compared to neoadjuvant (recurrence: 16% [3/19], progression: 0/19), at a median 23-month follow-up. Cystectomy was less frequent in the adjuvant CHT group (5% [3/64]) than in the neoadjuvant group (8% [2/24]). Another NRCS (n=30) reported similar recurrence in patients treated by adjuvant (56% [9/16]) and neoadjuvant CHT MMC (57% [8/14]) at a median 14-month follow-up. There was no progression in the adjuvant CHT group compared to 18% (3/14) in patients having neoadjuvant therapy[1-3].

In 1 case series (n=21) of patients treated by adjuvant (n=10) or neoadjuvant (n=11) CHT with MMC, overall recurrence was 71% (15/21), DSS was 90% (19/21) and OS was 67% (14/21). Progression happened in 19% (4/21) of patients and 29% (6/21) had RC due to multifocal recurrence or progression[1-3].

Bladder sparing

In 8 studies included in the review bladder sparing was achieved in 88% (range 47 to 98%) of patients treated by CHT MMC (adjuvant or neoadjuvant), follow-up range 9 to 90 months[1-3].

Progression

The review reported 10 studies considering progression to MIBC as a secondary endpoint, progression varied between 0% and 8%. Median follow-up was ≤24 months in 8/10 studies, 33 months in 1 study and 90 months in another[1-3].

Safety summary

Adverse events were more frequent in patients treated by CHT MMC (12% [5/42]) compared to MMC alone (37% [15/41], p value not reported) in a RCT of 83 patients[5, 6].

More allergic reactions, pain, bladder spasms, strictures, catheter issues and PWTR were found after CHT MMC, compared to more fever, fatigue, arthralgia, haematuria, incontinence and frequency after BCG treatments[1-3].

Bladder spasms

Bladder spasms during CHT MMC were reported in 22% (range 2 to 36%) of patients in 8 studies (n=3454) included in the review of 26 studies. Bladder spasms were more frequent with the prophylactic schedule (18%) than with the ablative schedule (11%) but the difference was not statistically significant (p=0.398)[1-3].

Bladder spasms during CHT MMC were reported in 14% (206/1431) of patients in the RCT of 190 patients (OR: 15.5, 95% CI 9.7 to 25). Serious bladder contraction happened in 1/90 patient treated by CHT MMC in the same RCT[4].

Pain

Pain during CHT MMC was reported in 18% (range 7 to 27%) of patients (8 studies, n=3454) included in the review of 26 studies. Pain during procedure was not statistically significantly more frequent in the prophylactic (17%) compared to the ablative schedule (16%, p=0.366)[1-3].

Bladder pain during CHT MMC was reported in 14% (202/1431) of patients in the RCT of 190 (OR: 26.3, 95% CI 14.3 to 48.5). Bladder pain between intravesical chemotherapy sessions was more frequent in patients treated by CHT MMC compared to BCG (OR: 1.6, 95% CI 1.2 to 2.3), in the same RCT. Dysuria was also more frequent in patients treated by CHT MMC 12% [167/1431]) than BCG (15% [229/1525])[4].

Pain was statistically significantly more frequent in patients treated by CHT MMC (41% [17/42]) compared to MMC alone (0%, p<0.001) in the RCT of 83. Dysuria was more frequent in patients treated by CHT MMC (24% [10/42]) compared to MMC alone (10% [4/41]), in the same RCT (p value not reported)[5, 6].

Pain during procedure was reported in 38% (10/26) patients and dysuria after the procedure in 42% (11/26) of patients treated by CHT MMC in a case series of 26 patients[7].

Lower urinary tract symptoms (LUTS)

LUTS were reported in 27% (range 4 to 74%) of patients in 8 studies (n=1865) included in the review of 26 studies[1-3].

Nocturia was statistically significantly more frequent in patients treated by CHT MMC 10% (147/1431) compared to patients treated by BCG (15% [227/1525], OR: 0.79, 95% CI 0.63 to 0.98) in the RCT of 190. Urinary frequency was statistically significantly less frequent in patients treated by CHT MMC (10% [147/1431]) compared to BCG (18% [274/1525], OR: 0.61, 95% CI 0.49 to 0.75) in the same RCT. Incontinence was statistically significantly less frequent in patient treated by CHT MMC compared to BCG (OR: 0.22, 95% CI 0.12 to 0.37)[4].

Urinary retention was reported in 19% (5/26) of patients treated by CHT MMC in the case series of 26[7].

Bleeding

Haematuria was reported in 6% (range 2 to 26%) of patients in 6 studies (n=1196) included in the review of 26 studies[1-3].

Urethral bleeding happened in 1/90 patient treated by CHT MMC in the RCT of 190. Haematuria was less frequent in patients treated by CHT MMC compared to BCG (OR: 0.56, 95% CI 0.42 to 0.74) in the same RCT[4].

Haematuria was more frequent in patients treated by CHT MMC (7% [3/42]) compared to MMC alone (5% [2/41]), in the same RCT (p value not reported)[5, 6].

Haematuria was reported in 15% (4/26) of patients treated by CHT MMC in the case series of 26[7].

Bladder burn injuries

Burn injuries to the bladder were not reported in the studies included in the review but posterior wall thermal reactions (PWTR) were commonly seen (frequency not reported). The author reported that during follow-up cystoscopy, an asymptomatic PWTR could be seen in almost all patients (frequencies not reported)[1-3].

PWTR was more frequent in patients treated by CHT MMC (14% [10/42]) compared to MMC alone (2% [1/41]), in the same RCT (p value not reported)[5, 6].

PWTR was reported in 27% (7/26) of patients treated by CHT MMC in the case series of 26[7].

Rash and allergy

Bladder tissue reaction was statistically significantly more frequent in patients treated by CHT MMC that BCG (OR: 5.8, 95% CI 4 to 8.3) in the RCT of 190[4].

Skin allergy was more frequent in patients treated by CHT MMC (12% [5/42]) compared to MMC alone (5% [2/41]), in the same RCT (p value not reported)[5, 6].

Allergic reaction was reported in 8% (2/26) of patients treated by CHT MMC in the case series of 26[7].

Systemic absorption of MMC

Systemic absorption of MMC was reported in the review of 26 studies. Serum levels of MMC were 19.4 nanograms/ml in patients treated by CHT MMC with 40 mg dose and 5.56 nanograms/ml in patients treated with the 20 mg dose (frequencies not reported). The author reported that both of these values were significantly higher than those after MMC only instillation but below the threshold for myelosuppression (400 nanograms/ml)[1-3].

Urethral damage

Urethral strictures were statistically significantly more frequent in patients treated by CHT MMC compared to BCG (OR: 2.3, 95% CI 1.3 to 4.1) in the RCT of 190[4].

Urethral stenosis was more frequent in patients treated by CHT MMC (7% [3/42]) compared to MMC alone (2% [1/41]), in the same RCT (p value not reported)[5, 6].

Catheterisation difficulties were statistically significantly more frequent in patient treated by CHT MMC compared to BCG (OR: 16.7, 95% CI 5.1 to 54) in the RCT of 190[4].

Systemic symptoms

Subjective symptom scoring (4 studies) using non-validated questionnaire (higher score meaning worse symptoms) suggest worse symptoms during CHT treatment (18.3) compared to MMC alone (13.1, $p>0.05$)[1-3].

Before treatment subjective symptoms assessed with a symptom questionnaire (minimum=7, maximum=24) were lower in the CHT MMC treated patients (9.1 [1.8]) compared to BCG (9.4 [1.7], in the RCT of 83 patients. After induction cycle, subjective symptoms were higher in the CHT MMC group (18.4 [2.6]) than

in the BCG group (14.6 [1.5]) which was still the case after maintenance cycle (CHT: 12.7 [1.5}, BCG: 12.2 [1.5]), in the same RCT[5, 6].

Fatigue was statistically significantly less frequent in patients treated by CHT MMC compared to BCG (OR: 0.17, 95% CI 0.11 to 0.28) and so was arthralgia (OR: 0.09, 95% CI 0.03 to 0.31) and fever (OR: 0.09, 95% CI 0.04 to 0.1). Serious episodes of fever were reported in 3% (3/90) patients treated by CHT compared to 1\94 in the BCG group, in the same RCT of 190 patients[4].

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 events: reduction in bladder capacity and compliance and urethral strictures. They considered that the following were theoretical adverse events: reduced bladder capacity due to scarring.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer. The following databases were searched, covering the period from their start to January 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 appendix C for details of 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 superficial bladder cancer.
Intervention/test	Intravesical microwave hyperthermia with 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 2,426 patients from 3 literature reviews, 2 randomised controlled trials (one of which resulted in 2 publications) and 1 case series. [1–7]

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

Table 2 Summary of key efficacy and safety findings on intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer

Study 1, 2 and 3 Colombo R (2016), van Valenberg H (2016), Lammers RJ (2011)

Details

Study type	**Review**
Country	Netherlands, Israel, Italy, Austria
Recruitment period	Databases searched for 2016 publications. Previous publications (Lammers 2011 and van Valenberg 2016), have searched for publications from 1950 to 2015.
Study population and number	**n= 26 studies** (22 published, 3 conference abstracts and 1 unpublished data analysis from the author) reporting on patients with NMIBC treated by CHT using the Synergo system (Medical Enterprises Europe, Amsterdam)
Age and sex	Not reported
Patient selection criteria	Patient inclusion criteria: - Intermediate to high risk NMIBC under standard therapy - BCG refractory NMIBC - Therapy resistant CIS Patient exclusion criteria: - Small bladder capacity (<150 mL) - Urinary bladder diverticulum larger than 1 cm - Uncontrolled bladder overactivity - Urethral strictures and active urinary tract infection. - For patients hypersensitive to MMC, epirubicin was used as an alternative drug.
Technique	An extensive search was conducted in in Medline, Embase, Cochrane and ClinicalTrials.gov. The results from this search come to update the previously published literature reviews.
Follow-up	**Median 9 to 90 months**
Conflict of interest/source of funding	One of the authors is an investigator for Medical Enterprise Ltd. Amsterdam, without financial compensation. Another author was supported by the European Urological Scholarship programme.

Analysis

Follow-up issues: There is substantial variability between the studies reported in this publication.

Study design issues: The SR and meta-analysis by Lammers 2011 followed the PRISMA guidelines. Two independent reviewers have independently searched the databases, assessed candidate manuscripts for inclusion criteria and extracted primary data. Candidate manuscripts were limited to English language with publication range from 1990 to 2011. Abstracts from annual meetings were also searched manually. When possible data were combined using random effects meta-analytic techniques. The subsequent published updates of the SR consisted of update searches done by the same research collaboration with less a less systematic methodology.

Primary endpoint was time to recurrence. Secondary endpoints included time to progression, bladder preservation and adverse event rate. Progression was defined as worsening pathological stage, including muscle invasion or metastases.

In earlier studies, recurrence rates are different from later studies, since the principal exploratory studies all made use of CR or PR scoring with subsequent recurrence rates, regardless of dose and treatment schedule. Later studies used specific ablative or prophylactic treatment protocols.

Progression was reported less frequently that recurrence as a longer follow-up of NMIBC were required. Reporting of progression rates was wide spread in the publications as most recent studies had definitions of progression that did not confine to the development of muscle invasive bladder cancer. Some of the most recent studies also included further treatment, extravesical disease or distant metastases.

Study population issues: The studies reported patient outcomes on different recognised settings for CHT. The most frequently were prevention of tumour recurrence after TURBT (prophylaxis or adjuvant therapy) and before ablation of bladder tumour (ablative or neoadjuvant therapy). Commonly the prophylactic treatment schedule consists of an induction phase of 6 once-weekly sessions. In each session, patient receives 40 mg MMC (2 x 20 mg). The induction phase of the ablative protocol consists in general of 8 once-weekly sessions, with 80 mg MMC (2 x 40 mg). Both protocols generally include the induction phase and a maintenance phase extended for 4 to 12 monthly or quarterly sessions. Other specific settings were the use of CHT MMC after failed BCG treatment

Other issues: The author reported that this review is an update to previous literature reviews (Lammers 2011 and van Valenberg 2016), produced by the same research collaboration group. For completions, the analysts has merged data from the 3 publications and completed the table of evidence with evidence from the original studies publications. The publications by Arends (2016) and Colombo (2003, 2011) were reported separately in table 2.

CHT with MMC compared to MMC alone

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Colombo 1996	**RCT**, marker lesion comparison of CHT with MMC (group 1: n=29) vs MMC alone (group 2: n=23). Neoadjuvant schedule.	52	38 in group 1 (NA), 36 in group 2 (NA)	Ta/1 G1 to 3	60	42.5 to 46.0	40 mg in 50 ml	6 to 8	No	**CR:** 66% (19/29) group1 versus 22% (5/23) group 2, p<0.001 **Recurrence:** group 1: 28% (8/29) after 2 to 22 months versus group 2: 39% (9/23) after 7 to 19 months **Progression**: N/A
Colombo 2001	**NRCS**, retrospective, marker lesion comparison of MMC alone (group 1, n=36) VS CHT with MMC (group2, n=29) and VS EMDA with MMC (group 3, n=15). Neoadjuvant schedule.	80	None	Single small (<2 cm) Ta/1 G1 to 2 that were not earlier treated with MMC	MMC alone and CHT: 60 EMD: 20	Mean 42.5	MMC alone and CHT with MMC: 40 mg in 50 ml EMDA: 40 mg in 150 ml	4	No	**CR:** 28% (10/36) group 1, 66% (19/29) group 2 and 40% (6/15) group 3 (p value not reported) **Progression**: N/A
Colombo 2003	**RCT**, multicentre phase 3 study, comparison of CHT with MMC (group 1, n=41) vs MMC alone (group 2, n=41). Closed envelope randomisation. Adjuvant schedule.	83	>24 (NA)	Intermediate or high risk UCC, with confirmed complete TURBT	40 to 60	40 to 44	20 mg in 50 ml	8	Yes: 4 times monthly	Total evaluable patients: 75 **Recurrence:** 17% (6/35) group 1 vs 58% (23/40) group 2, p=0.002 **Progression**: 3% (1/40) in group 2; none in group 1
Colombo 2011	**RCT,** closed envelope randomisation, multicentre. Long term follow-up of 2003 study. Comparison of CHT with MMC (group 1, n=42) vs MMC alone (group 2, n=41). Adjuvant schedule.	83	90 (6 to 154)	Intermediate or high risk, with complete TURBT	60	40 to 44	20 mg in 50 ml	8	Yes: 4 times month	Total evaluable population: 75 **Recurrence**: 40% (14/35) group 1 vs 80% (32/40) group 2 (p<0.001) **DFS**: 53% group 1, 15% group 2, at 10 years **Progression**: 6% (2/35) group 1 vs 8% (3/40) group 2 (p>0.05)

CHT with MMC compared to BCG

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Arends 2016	**RCT,** multi-institution (n=11), comparing CHT MMC to BCG after TURNBT over 1 year. Adjuvant schedule.	190	25.7 (3.9 to 34)	Intermediate and high risk NMIBC (EAU criteria)	2x30=60	42±2	MMC: 20+20 mg in 50 ml	6 times weekly	6 times every 6 weeks	24 months follow-up: **ITT RFS:** 78% CHT, 65% BCG, p=0.08 **Per protocol RFS (n=147)**: 82% CHT, 65% BCG, p=0.02 <u>CIS patients only</u> **CR**: 89% CHT, 86% BCG, p=1 **Progression**: <2% in both groups
Kelly 2015 *conference abstract*	**RCT** phase III, multicentre. CHT after BCG vs second course BCG or institutional standard therapy. Adjuvant schedule.	104	N/A but goal 24 months	Recurrence after BCG but unfit or unwilling for RC	2x30=60	42±2	MMC	6 times week	Every 6 weeks (year 1), every 8 weeks (year 2)	No difference in DFS. **DFS** in patients with papillary disease alone (n=33): HR 0.4, 95% CI 0.16 to 0.98, p=0.05 (favours CHT)

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
										CR in CIS patients (n=71) at 3 months: 81% CHT vs 86% BCG **DFS:** HR 2.17, 95% CI 1.15 to 4.08, p=0.02 (favours BCG)

CHT with MMC compared to radical cystectomy

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Nair 2014 *conference abstract*	**Case series**, prospective, single centre. CHT (n=103) matched with RC (n=51). 5 year survival.	154	40 (9 to 92)	High risk NMIBC (EAU criteria) overlaps in patients with Sooriakumaran 2015	2x30=60	42±2	MMC: 40+40 mg in 50 ml (all in 50 ml)	6 to 8 times week, median 6 times	If CR or PR: 20 mg MMC in 50 ml every 6 weeks (year 1) and every 8 weeks (year 2)	**DSS (5 years):** 75% RC vs 85% CHT **OS (5 years):** 68% RC vs 62% CHT **90 day mortality:** 4% RC vs 0% CHT **Significant AE:** 21% RC vs 0% CHT

CHT with MMC– Prophylactic (adjuvant) schedule

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Nativ 2009	**Case series**, retrospective, multicentre study. CHT after TURBT (Adjuvant schedule)	111	16 (2 to 74)	Ta/1 G1 to 3, after confirmed complete TURBT	60	40 to 44	20 mg in 50 ml	6	Yes: 6 times every 4 to 6 weeks	Total evaluable patients: 105 Kaplan-Meier RFS: 85% at 1 years, 56% at 2 years **Recurrence**: median time to recurrence is 16 months **DFS**: 50% at 2 years **Progression**: 3% (1/38)
Maffezzini 2014	**Case series**, single centre. CHT with MMC in adjuvant setting. Epirubicin in cases of persistant intolerance to MMC (n=10)	42	38 (4 to 73)	High risk NMIBC (EAU criteria): EORTC recurrence score≥5 or progression score ≥7	2x30=60	42.5±1.5	MMC: 40+40 mg or Epirubicin: 50+50 mg Both in 50 ml	4 times week, every 2 weeks (total=10)	Yes: 4 times every 3 weeks	32 patients completed protocol, ITT: 1 year **DFS:** before study 15% vs 89% after CHT. **Recurrence**: 31% (13/42) **Progression (ITT)**: 12% (5/42) **Cystectomy (ITT)**: 17% (7/42)
Arends 2014	**Case series**, prospective, single centre. CHT with MMC in adjuvant setting. Epirubicin in cases of persistent intolerance to MMC (n=20)	160	75.6	Intermediate and high risk NMIBC (EAU criteria)	2x30=60	42±2	Prophylactic: 20+20 mg MMC or 25+25 mg epirubicin Abaltive: 40+40 mg MMC or 50+50 mg epirubicin	6 to 8 times week	Yes: every 6 weeks, up to 1 year	MMC: **1 year RFS**: 60% **2 years RFS**: 46% Epirubicin: **1 year RFS**: 64% **2 years RFS**: 55% **Progression**: 4% (7/160)

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Sooriakumaran 2016	**Case series**, prospective, time to progression study in ablative protocol. CHT MMC after TURBT, adjuvant schedule.	97	27 (16 to 47)	High risk NMIBC (EAU criteria)	2x30=60	41 to 44	MMC: 40+40 mg in 50 ml	6 to 8 times week, median 6 times	If CR or PR: 20 mg MMC in 50 ml every 6 weeks (year 1) and every 8 weeks (year 2)	**OS**: 82% (80/97) **DSS**: 93% (90/97) **Progression**: 36% (35/97) **Cystectomy**: 19% (18/97)
Lombardia project *unpublished data, Colombo R., Milan, Italy*	**NRCS,** prospective, single centre, adjuvant CHT with MMC (n=189) compared to current treatment (EAU guidelines, n=180). Controls collected retrospectively from chart review.	366	55.3 (N/A)	Ta/1 G1 to 3 confirmed complete TURBT	N/A	N/A	N/A	6	Yes: 6 time every 6 weeks	Total evaluable patients: 189+180 **Recurrence after minimum 2 years**: 25% CHT MMC vs 39% controls, p<0.006) **Cystectomies**: 2% (3/189) CHT MMC vs 11% (20/180) controls, p=0.0015
Canepa 2016 *conference abstract*	**Case series**, retrospective, single centre, CHT single arm	146	N/A	Intermediate or high risk (EAU criteria)	N/A	NA	MMC: 40+40 mg in 50 ml; 2 times 30	6 times week + 4 times month	N/A	**PFS 1 year**: 98% **PFS 2 years**: 96% **PFS 5 years**: 84%

CHT with MMC after failed BCG – Prophylactic (adjuvant) schedule

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
van der Heijden 2004	**Case series**, multicentre study. CHT MMC given in average 55 days after TURBT, adjuvant.	90	18 (2 to 24)	Intermediate or high risk Ta/1, with confirmed complete TURBT (22 had failed previous BCG therapy)	60	41 to 44	20 mg in 50 ml	6 to 8	Yes: 4 to 6 times monthly	**Kaplan-Meier recurrence chance**: Patients failing BCG: 41% after 2 years Patients treated by CHT MMC only: 14% after 1 year, 25% after 2 years **Progression**: None
Halamachi 2011	**Case series**, retrospective, multicentre study. ACH as adjuvant therapy after TURBT.	56	>24 (2 to 49)	Only T1G3 after complete TURBT. Overlap in patients (n=7) with Moskovitz and Halachmi	60	40 to 44	20 mg	6	Yes: 6 times every 4 to 6 weeks	Total evaluable patients: 51 **Kaplan-Meier recurrence chance**: 46% at 2 years, 51% at 4 years **Progression**: 8% (4/52) No difference in 4-year recurrence between patients previously failing BCG (46%) and those that had not (44%, p=0.54)
Ayres 2010	**Case series**, prospective, N/A	38	9 (2 to 34)	Only high risk with failure after BCG	60	40 to 44	Induction: 40 mg, Maintenance: 20 mg	6	Yes: 3 times monthly	**DFS:** 50% at 2 years **Progression**: 3% (1/38)

CHT with MMC– Ablative (neoadjuvant) schedule

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Rigatti 1991	**Case series**, prospective, phase 1 study, preoperative treatment before TURBT, neoadjuvant schedule.	12	16	Ta/1 G1 to 3	60	41.5 to 43.5	30 mg in 60 ml	6 to 8	No	**CR:** 42% (5/12) **Recurrence:** 20% (1/5) at 3 months after TURBT **Progression**: NA
Colombo 1995	**Case series**, prospective, phase 1 study preoperative treatment. Neoadjuvant schedule.	44	24 (3-57)	Ta/1 G1 to 3	60	42.5 to 44.5	30 mg in 60 ml	8	No	**CR:** 70% (31/44) **Recurrence:** 23% (7/31) **Progression**: None
Colombo 1998	**Case series**, CHT after recurrence post intravesical chemotherapy. CHT as debulking therapy. When TURBT impossible: cystectomy after last treatment. Neoadjuvant schedule.	19	33 (12-60)	Multifocal therapy-resistant T1 tumours	40 to 60	42.5 to 46.0	40 mg in 40 ml	8	No	In 16 of 19 TURBT were possible after treatment with CHT. **CR:** 47% (9/16) • **Recurrence:** 89% (8/9) **Progression:** none
Ludecke 2015 *conference abstract*	**Case series**, prospective, multi-institution (n=7) study on the long term effect of CHT. Ablative schedule after non-compete resected NMIBC and failed BCG. Cystectomy 3 weeks after last CHT MMC.	271	Mean 2.2 years (28 days to 12.9 years)	High risk (CIS, T1 G3), (EAU criteria) Overlaps patients with other 2 abstracts	N/A	N/A	MMC: 40+40 mg in 50 ml	8 times week	6 times every 6 weeks 2x20 mg MMC if tumour free on re-TURBT	**Patients completing full protocol** **CR**: 76% (206/271) **PR**: 8% (21/271) **2 years recurrence**: 19% (52/271) **Recurrence in patients with BCG resistant tumours**: 42% **Recurrence in BCG relapse patients:** 67%

CHT with MMC prophylactic compared to ablative schedule

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
Gofrit 2004	**NRCS**, prospective, multicentre study, prophylactic schedule compared to ablative schedule. Prophylactic schedule in case of confirmed complete TURBT (group 1, n=24); ablative in other patients (group2, n=28)	52	15.2 (6 to 90)	Ta/1 G2 to 3 high risk	40	40 to 44	Group 1: 20 mg in 50 ml; Group 2: 40 mg in 50 ml	8	Yes: 4 times monthly	CR in group 2: 75% (21/28) **Recurrence**: 38% (9/24) group1 after mean 10 months; 19% (4/21) group 2 after mean 13.7 months **RSF**: 63% (15/21) group 1 **Progression**: None in both groups
Moskovitz 2005	**NRCS**, prospective, prophylactic schedule compared to ablative schedule. Prophylactic schedule in case of confirmed TURBT (group 1, n=22); ablative schedule in other patients (group 2, n=10)	47	10 (N/A)	Intermediate and high risk. Overlap in patients (n=7) between Moskovitz and Halachmi	60	40 to 44	Group 1: 20 mg in 50 ml; group 2: 40 mg in 50 ml	6 to 8	Yes: only in case of CR, 4 to 6 times monthly	Total evaluable patients: 32 **Recurrence:** 9% (2/22) in group 1 at 10 months, 20% (2/10) in group 2 at 9 months **Progression**: none
Witjes 2009	**NRCS**, retrospective, multicentre study. Prophylactic schedule compared to ablative schedule. Ablative schedule in	51	22 (3 to 77)	Only CIS	60	41 to 44	Group 1: 20 mg in 50 ml	Group 1: 6 Group 2: 8	Yes: 6 times every 6 weeks	Total evaluable patients: 49

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
	cases of concomitant papillary lesions or many CIS lesions (group 2, n=33); prophylactic schedule in other patients (group 1, n=18)						Group 2: 40 mg in 50 ml			Because no difference between groups (p=0.94), data were analysed together. **CR**: 92% (45/49) **Recurrence**: 49% (22/45) at 2 years **Progression**: none
Moskovitz 2012	**NRCS**, retrospective, single centre. Adjuvant (n=64) and neoadjuvant (n=24) treatment with MMC	88	23 months (3 months up to 7 years)	Intermediate and high risk NMIBC (EAU criteria)	2x30=60	42	Adjuvant: 20+20 mg Neoadjuvant: 40+40 mg Both in 50 ml	Adjuvant: 6 times week Neoadjuvant: 8 times week	Adjuvant or if CR in neoadjuvant: 6 times every 5 week, 1 year	Adjuvant: **Recurrence**: 28% (18/64) **Progression**: 5% (3/64) **Cystectomy**: 5% (3/64) Neoadjuvant: CR: 79% (19/24) **Recurrence**: 16% (3/19) **Progression**: 0/19 **Cystectomy**: 8% (2/24)
Volpe 2012	**NRCS,** prospective, single centre. CHT with MMC. Prophylactic (n=16) and ablative (n=14) treatment. Both had TURBT before start	30	Mean: 14±8.48	Ta/1 G2/3 or Tis	2x 20 to 30 (40 to 60)	42±2	Prophylactic: 20+20 mg Ablative: 40+40 mg Both in 50 ml	Prophylactic: 6 times week Ablative: 8 times week	Yes: 6 times month	**Overall recurrence**: 57% (17/30) Prophylactic: **Recurrence**: 56% (9/16) **Progression**: 0/16 Ablative: **CR**: 43% (6/14) **Recurrence**: 57% (8/14) **Overall DFS**: 77% at 1 year, 55% at 2 years **Progression**: 18% (3/14)
Kiss 2015	**Case series**, prospective, single centre CHT in prophylactic (n=10) and ablative (n=11) setting	21	50 (1 to 120)	Intermediate and high risk NMIBC (EAU criteria)	2x30=60	42±2	Prophylactic: 20+20 mg Ablative: 12 times weekly Overall median: 6 times	Prophylactic: 6 times week Ablative: 12 times week Overall: 6 times	N/A	**Overall recurrence:** 71% (15/21) **DSS:** 90% (19/21) **OS:** 67% (14/21) **Progression**: 19% (4/21) **Cystectomy**: 29% (6/21) due to multifocal recurrence or progression

Key efficacy and safety findings

Efficacy

CHT MMC alone

Adjuvant approach

(single arm studies for intermediate to high risk NMIBC patients)

Recurrence: 16 to 89%

Overall progression: 0 to 36%

Progression in studies with FU>2 years: 0 to 12%

Neoadjuvant approach

Complete response (CR) after ablative therapies: 42 to 86%

Recurrence: 16 to 30%, follow-up 16 to 38 months

Progression: 0 to 27%

Bladder preservation after ablative treatment: 71 to 100%

The author reports a high level of methodological heterogeneity in patient characteristics, treatment schedule and follow-up time.

CHT MMC versus MMC alone (4 studies):

Recurrence: 28% (26/93) CHT MMC vs 68% (67/99) MMC alone

RR 0.41, 95% CI 0.29 to 0.58 [favours CHT MMC compared to MMC alone]

CR: 66% CHT MMC vs 22% MMC alone, p=0.001

CR: 66% CHT MMC vs 27% MMC alone, p value not reported

Progression after CHT:

In 10 studies considering progression to MIBC as a secondary endpoint, progression varies between 0% and 8%. Median follow-up is ≤24 months in 8/10 studies, 33 months in 1 study and 90 months in another.

Bladder sparing

Study	Follow-up, months, median	% patients with bladder in situ
Colombo 1998	33	47% (9/19)
Gofrit 2004 prophylactic treatment	15.2	96% (23/24)
Gofrit 2004 ablative treatment	20	79% (22/28)
Witjes 2009	22	89% (40/45)
Halachmi 2011	18	88% (45/51)
Ayres 2010	9	82% (31/38)
Colombo 2011	90	86% (N/A)
Lombardia project (unpublished)	23	98% (149/152)
Overall	**NA**	**88%**

Safety

Frequency of adverse events during CHT with MMC

Study	Bladder spasms	Pain
Rigatti 1991	40% (5/12)	25% (3/12)
Grofit 2004	15% (8/52)	23% (12/52)
Moskovitz 2005	2% (8/398)	8% (31/398)
Witjes 2009	13% (66/503)	13% (64/503)
Nativ 2009	31% (34/111)	27% (30/111)
Halachmi 2011	24% (13/56)	11% (6/56)
Lombardia project	36% (483/1354)	21% (278/1354)
Witjes unpublished data	21% (202/968)	7% (65/968)
Overall	**22%**	**18%**

Bladder spasms were not statistically significantly different between prophylactic (18%) and ablative schedule (11%, p=0.398).

Pain was not statistically significantly different between prophylactic (17%) and ablative schedules (16%, p=0.366).

Frequency of adverse events after CHT wit MMC

Study	LUTS[1]	Haematuria
Gofrit 2004	58% (30/52)	N/A
Van der Heijden2004	24% (22/90)	9% (8/90)
Moskovitz 2005	4% (2/47)	2% (8/398)
Witjes 2009	10% (50/503)	3% (15/503)
Halachmi 2011	12% (7/56)	2% (1/56)
Nativ 2009	16% (18/111)	19% (21/111)
Ayres 2010	74% (28/38)	26% (10/38)
Witjes (unpublished data)	42% (407/968)	N/A
Overall	**27%**	**6%**

More allergic reactions, pain, bladder spasms, strictures, catheter issues and PWTR are found after CHT MMC, compared to more fever, fatigue, arthralgia, haematuria, incontinence and frequency after BCG treatments.

Other AEs

Cystitis	16% (3/18)
Non-specific rash	7.5% (25/339*) range 0 to 24%
Urethral strictures	4% (9/245*)
PWTR (mild)	40%(76/189*)
PWTR (severe and prolonged)	1% (2/173*)
Contracted bladder	N/A
Severe urinary incontinence	N/A
AE related drop-out rate	4% (38%) in one study of patient not fit or refusing cystectomy

Burn injuries to the bladder were not reported but posterior wall thermal reactions were commonly seen (frequency not reported).

PWTR - The author reported that during follow-up cystoscopy, an asymptomatic PWTR can be seen in almost all patients

Author has reported that comparison of AE is difficult because older studies used non-validated questionnaires, whereas more recent studies use the CTCAE. Some studies used ITT and others used per-protocol analysis. Most studies did not mention administration of painkillers which may have led to underestimation of AE.

Systemic absorption of MMC

CHT MMC 40 mg treatment: 19.4 ng/ml

CHT MMC 20 mg treatment: 5.56 ng/ml

Both of these values were significantly higher than those after MMC only instillation. Plasma values were below the threshold for myelosuppression (400 ng/ml).

In comparison with MMC instillations, local toxicity was slightly higher after CHT MMC although not statistically significant (frequencies and level of significance not reported).

Subjective symptom scoring (4 studies) using non-validated questionnaire (higher score meaning worse symptoms) suggest worse symptoms during CHT treatment (18.3) compared to MMC alone (13.1, p>0.05)

[1]Frequency, dysuria, urgency, nocturia. Most studies classified these as mild (CTCAE grade 1) and transient, resolving spontaneously within a few days.

*Frequencies calculated by the IP analyst.

Abbreviations used: AE, adverse event; BCG, bacilli Calmette-Guérin; CHT, chemohyperthermia; CI, confidence interval; CIS, carcinoma in situ; CR, compete response; CTCAT, Common Toxicity Criteria for Adverse Events; DFS, disease free survival; DSS, disease specific survival; EAU, European Association of Urology; EMDA, electromotive drug administration; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; ITT, intention to treat analysis; LUTS, lower urinary tract symptoms; MIBC, muscle invasive bladder cancer; MMC, mitomycin C; NA, not applicable; N/A, not available; ng, nanogram;

NMIBC, non-muscle invasive bladder cancer; NRCS, non-randomised comparative study; OS, overall survival; PR, partial response; RC, radical cystectomy; RFS, recurrence free survival; RCT, randomised comparative study; RF, radiofrequency; PRISMA, preferred reported items for systematic reviews and meta-analysis guidelines; PWTR, posterior wall thermal reaction; RR, risk ratio; SR, systematic review; TURBT, transurethral resection of bladder tumour.

Study 4 Arends TJH (2017)

Details

Study type	**RCT**
Country	Netherlands, Israel, Italy, Austria, France and Belgium
Recruitment period	2002 to 1012
Study population and number	**n=190 patients** (92 CHT MMC, 98 BCG) with intermediate and high risk NMIBC (EAU definition) treated by intravesical chemotherapy after TURBT (adjuvant setting)
Age and sex	**CHT**: 67.4±10.08 years , 83% males **BCG**: 65.1±10.67 years; 84% males (Demographics available on 184 patients (89 CHT, 95 BCG)
Patient selection criteria	Inclusion criteria: - T1 or grade 3 urothelial carcinoma, CIS, multifocal (6 of more) Ta lesions or multiple (3 or more) recurrences of Ta lesions in the previous 24 months. - Previous TURBT confirmed by negative cytology and video cystoscopy with negative biopsies from suspected are before intravesical therapy started - World Health Organisation performance status ≤2 - Life expectancy ≥24 months Exclusion criteria - Histology other than urothelial carcinoma - Another primary malignancy (basal cell carcinoma excluded) - Urothelial carcinoma involving the urethra or upper urinary tract - Previous history of urothelial carcinoma stage T2 or higher - Intravesical MMC treatments during the previous 12 months - BCG treatment in previous 48 months - Previous pelvic radiotherapy or systemic chemotherapy - Partial cystectomy - Bladder diverticulum >1 cm - Residual urine >100 ml - Bladder volume <150 ml - Urinary incontinence - Urethral stricture impeding 20F catheterisation - Persistent haematuria - Active intractable or uncontrollable urinary tract infection - Active tuberculosis - Known impaired immune response - Positive HIV serology - Receipt of systemic steroids or immunosuppressive therapy - Haematological disorders - Leucocytes<3,500, platelets <100,00 - Liver or kidney function disorders (>1.5 times upper normal limit) - Pregnant or lactating women
Technique	After randomisation patients in the CHT group were treated with MMC weekly for 6 weeks, followed by 6 maintenance sessions at 6 weeks interval during the rest of year 1. Sessions consisted of 2x30 minutes treatments with 20 mg MMC in 50 ml of distilled water, combined with hyperthermia at 42±2 °C. In the control group BCG was given as a 1-year schedule: 6 weekly induction sessions and 3 weekly repeated maintenance sessions at months 3, 6 and 12. Patients retained BCG in the bladder for 120 minutes. Intravesical therapy started between 38 weeks after initial TURBT in case of high risk tumours. All treatments in the CHT group were delivered with the Synergo system (Medical Enterprises Europe, Amsterdam)
Follow-up	**ITT:** median 25.6 (0 to 34) months **PP:** median 25.3 (3.9 to 34) months
Conflict of interest/source of funding	One of the authors was a Medical Enterprises consultant for the US Food and Drug Administration meeting in 2014. Medical Enterprises provided support and was involved in the design and conduct of the study and the collection and management of the data. No personal grants were provided.

Analysis

Follow-up issues: Patients follow-up was done at least 24 months after randomisation at 3-month intervals, including blood analysis, urinalysis, cytology, cystoscopy and biopsies of the suspicious areas. Study termination was defines as adverse events causing treatment delay for ≥2 weeks or withdrawal of consent.

There were 6 patients not receiving instillation, 2 were refused CHT treatment by the insurance company, 2 had protocol violations noted (1 CHT, 1 BCG) and 2 refused additional therapy (CHT).

Study design issues: Randomisation was done on a 1:1 allocation ratio stratified by centre using the permutable block method. Randomisation assignment was done using closed numbered sealed envelopes. There was no blinding for physicians or patients.

Sample size calculation assumed a 25% 2-year recurrence rate for CHT MMC and 40% for BCG from published literature. A total population of 237 NMIBC patients was deemed necessary to test the null hypothesis of RFS with a power of 80% (alpha=0.05). Expecting a 20% dropout rate, a target recruitment of 150 patients in each comparator was.

Patients with tumour recurrence during the 12 months of treatment had TURBT and continued treatment as planned, unless recurrence was T1G3 or muscle invasive. Patients with second recurrence went off study and were followed-up for 24 months.

Primary endpoint was 24-month RFS in the ITT and PP analysis. Secondary endpoints were proportion of CR in CIS patients, progression to disease higher than T1 or metastatic disease and safety of both treatments. CR in CIS was defined as negative biopsies or cytology at 3 months.

Side effects were recorded using the CTCAE 2.0 at every treatment and during follow-up. In case of side-effects no dose modifications were allowed, only treatment delay.

Study population issues: There were 67% of patients with high risk tumour in the CHT group compared to 63% in the BCG group. Forty-four percent of patients had previous chemotherapy (including MMC), 33% had previous MMC and 22% previous BCG in the CHT group compared to 52% having had previous chemotherapy, 24% MMC instillations and 24% BCG in the BCG group. There were 147 patients with pure papillary tumours (71 in the CHT and 76 in the BCG group) and 43 had concomitant CIS (21 CHT and 22 BCG).

Other issues: This study was prematurely closed due to slow accrual on December 2011 and is therefore underpowered.

This publications was also reported in paper 1-3 in table 2.

Key efficacy and safety findings

Efficacy

n= 190 patients (92 CHT, 98 BCG)

ITT: 68 CHT, 74 BCG

PP: 60 CHT, 72 BCG (at least 6 instillations)

Summary efficacy

	ITT analysis	PP analysis
Median follow-up (months)	25.6 (0 to 34)	25.3 (3.9 to 34)
24-month RFS, CHT	78% (65 to 87%)	82% (69 to 90%)
24-month RFS, BCG	65% (52 to 75%)	65% (52 to 75%)
P value	0.08	0.02
24-months PFS, CHT	100%	100%
24-months PFS, BCG	99%	97%

CR in CIS patients at 3 months: 89% CHT, 86% BCG, p=1

Progression to MIBC: 0/68 CHT, 1% (1/74) BCG, p=1

Safety

n=184 patients (90 CHT, 94 BCG)

CHT: 1540 treatments, 1431 AE

BCG: 1923 treatments, 1525 AE

Serious AE:

5 CHT: 1 contracted bladder, 1 urethral bleeding, 3 fever

4 BCG: 1 retention, 1 haematuria, 1 urinary tract infection, 1 fever

AE	CHT*	BCG*
During treatment		
Bladder spasms	14% (206/1431) **OR**: 15.5, 95% CI 9.7 to 25	Not reported
Bladder pain	14% (202/1431) **OR**: 26.3, 95% CI 14.3 to 48.5	
After treatment		
Dysuria	12% (167/1431)	15% (229/1525)
Nocturia	10% (147/1431) **OR**: 0.79, 95% CI 0.63 to 0.98	15% (227/1525)
Urinary frequency	10% (147/1431) **OR**: 0.61, 95% CI 0.49 to 0.75	18% (274/1525)
Haematuria	**OR**: 0.56, 95% CI 0.42 to 0.74	11% (170/1525)
Fatigue	**OR**: 0.17, 95% CI 0.11 to 0.28	9% (129/1525)
Incontinence	**OR**: 0.22, 95% CI 0.12 to 0.37	Not reported
Fever	**OR**: 0.09, 95% CI 0.04 to 0.1	
Arthralgia	**OR**: 0.09, 95% CI 0.03 to 0.31	
Catheterisation difficulties	**OR**: 16.7, 95% CI 5.1 to 54	
Urethral strictures	**OR**: 2.3, 95% CI 1.3 to 4.1	
Bladder tissue reaction	**OR**: 5.8, 95% CI 4 to 8.3	
Bladder pain between sessions	**OR**: 1.6, 95% CI 1.2 to 2.3	
Allergy	**OR**: 2.7, 95% CI 1.6 to 4.6.	

*OR<1 favour CHT, OR>1 favour BCG

Abbreviations used: BCG, bacilli Calmette-Guérin; CHT, chemohyperthermia; CI, confidence interval; CIS, carcinoma in situ; CR, compete response; CTCAT, Common Toxicity Criteria for Adverse Events; EAU, European Association of Urology; EMDA, electromotive drug administration; ITT, intention to treat analysis; MIBC, muscle invasive bladder cancer; MMC, mitomycin C; N/A, not available; NMIBC, non-muscle invasive bladder cancer; OR, odds ratio; OS, overall survival; PR, partial response; RC, radical cystectomy; RCT, randomised control trial; RFS, recurrence free survival; TURBT, transurethral resection of bladder tumour.

Study 5 and 6 Colombo R (2003, 2011)

Details

Study type	**RCT**
Country	Italy and Israel
Recruitment period	1994 to 1999
Study population and number	**n=83** (42 CHT MMC, 41 MMC) patients with primary or recurrent NMIBC and treated by TURBT
Age and sex	**CHT**: 41% over 65 years of, 83% males **MMC alone**: 61% over 65 years, 83% males
Patient selection criteria	Inclusion criteria - Intermediate and high-risk disease (Ta–T1, G1–G2, multifocal, primary or recurrent) or high-risk disease (T1, G3 and CIS in association with papillary tumours) - Patients had already had complete TUR, confirmed by cystoscopy, biopsy and cytology. Patients excluded: - Patients with low-risk disease (Ta, G1, single, primary cancer) - Residual tumours after TURBT - Pre-treatment with systemic chemotherapy or radiotherapy within past 3 months - TCC of prostatic urethra - Allergy to MMC - Large benign prostatic hyperplasia - Residual urine > 100 ml - Bladder capacity < 150 ml - Neurogenic hypotonic bladder
Technique	Adjuvant treatment, 20 to 40 days after complete TURBT. MMC dose: 20 mg in 50 ml water, replaced after 30 minutes; Synergo device used; placement of device assessed by ultrasound; session duration: 40 to 60 minutes; treatment regimen: induction cycle of 8 treatments, 1 per week, followed by maintenance cycle of 4 treatments, 1 per month.
Follow-up	**Colombo 2003 :** 24 months **Colombo 2011:** median 91 months
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: Of 83 patients, 8 did not complete the study (4 withdrew and 4 did not comply with protocol), but outcomes are presented for all patients on the 24 month follow-up.

Updated complete data was available for 87% (65/75) patients at the 10 years follow-up. One patient was not evaluated for recurrence on the CHT group and 3 in the MMC alone group.

Study design issues: The study statistician assessed sample size adequately. The method of randomisation was well described and adequate.

Study population issues: No significant difference in demographic or baseline tumour characteristics was found between treatment groups.

Other issues: The percentages given in the paper for frequency of recurrence do not correspond with the absolute numbers given. Therefore the figures presented here are the analyst's own calculations based on the numbers given in the paper. This publications was also reported in paper 1-3 in table 2.

Key efficacy and safety findings

Efficacy

n=83 (42 CHT, 41 MMC)

Recurrence within 24 months

CHT MMC: 14% (6/42)

MMC alone: 56% (23/41)

Recurrence was significantly more frequent and earlier among patients who received MMC alone (p = 0.0002).

HR 4.8, 95% CI 2 to 11.9 [favours CHT MMC]

(Median) 91 months follow-up

Outcome	CHT MMC	MMC alone	p
Median follow-up (months)			
Of tumour free patients	91	87	
To recurrence	29	10	
DFS rates			
Crude rate	60% (21/35)	20% (8/40)	<0.001
5-year KM estimate	62%	21%	
10-year KM estimate	53%	15%	
Progression and RC			
Tumour progression (T>T1)	2	3	
RC for superficial disease	1	3	0.129
Bladder preservation rate			
10-year KM estimate	86%	79%	p>0.05
Death			
Total	6	9	0.558
Specific	N/A	N/A	

Safety

	CHT MMC (n=42)	MMC alone (n = 41)
No side effects	12% (5/42)	37% (15/41)
Tissue reaction	50% (21/42)	49% (20/41)
Pain*	41% (17/42)	0
Dysuria	24% (10/42)	10% (4/41)
Haematuria	7% (3/42)	5% (2/41)
Urethral stenosis	7% (3/42)	2% (1/41)
Posterior-wall thermal reaction*	24% (10/42)	2% (1/41)
Skin allergy	12% (5/42)	5% (2/41)

* p < 0.001 between treatment groups

Pain occurred only during heating, and resolved after each treatment. In the CHT MMC group; 3 patients (7.1%) said the pain was severe.

Thermal reaction resolved in a few days in most patients but lasted for 3 months in one case (healed spontaneously).

Other clinical complications
There was one case of reduced bladder capacity with urge incontinence in the CHT MMC group.

Voiding patterns
No change was found in residual urine or uroflowmetry after treatment.

Subjective symptom questionnaire
Minimum possible score is 7 and maximum is 24

	Mean score (SD)	
	CHT MMC	**MMC alone**
Before treatment	9.1 (1.8)	9.4 (1.7)
After induction cycle	18.4 (2.6)	14.6 (1.5)
After maintenance cycle	12.7 (1.5)	12.2 (1.5)

Statistical significance was not stated.

Abbreviations used: CHT, chemohyperthermia; DFS, disease free survival; HR, hazard ratio; KM, Kaplan-Meier; MMC: mitomycin C; N/A, not available; NMIBC, non-muscle invasive bladder cancer; RC, radical cystectomy; SD, standard deviation; TURBT, transurethral resection of bladder tumour.

Study 7 Erturhan S (2015)

Details

Study type	**Case series**
Country	Turkey
Recruitment period	Not reported
Study population and number	**n=26** patients with high risk primary NMIBC treated by adjuvant CHT using the Synergo system (Medical Enterprise, Netherlands)
Age and sex	Mean 62.4 (51 to 78) years, 9% (24/26) males
Patient selection criteria	Inclusion criteria: - T1 or grade 3 or CIS or multiple recurrent >3 cm Ta Grade 1 to 2 tumours Exclusion criteria: - Previous malignancy (bladder or elsewhere) - Concurrent upper urinary system urothelial carcinoma - Not tumour free after TURBT - Bladder capacity < 150 cc - Bladder diverticulum
Technique	All patients with diagnose of NMIBC were treated by TURBT. All patients included in the study received a single dose of CHT MMC 40 mg within 1 hour after TURBT. Treatment was scheduled for once a week for the first six weeks and once a month for 6 months. In each application the bladder was emptied and then MMC 20 mg in 50 ml of saline was administered for 30 minutes. Patients were sedated for the procedure.
Follow-up	**Median 16.4 (6 to 48) months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Cryptoscopy and urine cytology examination were done once every 3 months for the first 2 years for all patients. MRI was done once every 6 months for urinary system assessment. All patients completed the treatment protocol.

Study design issues: Primary endpoint was tumour cell detection in pathological examination of the lesion identified during cystoscopy or MRI.

Study population issues: There were 13 patients with T1 grade 3, 6 patients with T1 grade 3 CIS, 4 patients with Ta grade 3 and 3 patients with Ta grade 2 multiple > 5 cm tumours.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>n=26 patients

<u>Median follow-up 16.4 months</u>
Recurrence: 12% (3/26)
DFS: 88%
Progression: 0%</td><td>No patients discontinued treatment due to side effects.

<table><tr><th>Adverse events</th><th>%</th></tr><tr><td>Dysuria</td><td>42% (11/26)</td></tr><tr><td>Urinary retention</td><td>19% (5/26)</td></tr><tr><td>Haematuria</td><td>15% (4/26)</td></tr><tr><td>Pain during procedure</td><td>38% (10/26)</td></tr><tr><td>Allergic reaction</td><td>8% (2/26)</td></tr><tr><td>Thermal reaction in the posterior wall</td><td>27% (7/26)</td></tr></table></td></tr>
<tr><td colspan="2">Abbreviations used: CIS, cancer in situ; CHT, chemohyperthermia; DFS, disease free survival; MMC, mitomycin C; MRI, magnetic resonance imaging; NMIBC, non-muscle invasive bladder cancer; TURBT, transurethral resection of bladder tumour.</td></tr>
</table>

Validity and generalisability of the studies

- All studies used MMC and the Synergo device. Protocols for each session were similar across studies. Treatment regimens varied between studies.
- The proportion of patients with each grade and stage of superficial bladder cancer varied between studies.

Existing assessments of this procedure

2013 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

7.2.1.3.2 Microwave-induced hyperthermia and electromotive drug administration (EMDA) 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 [182-184] and both treatment modalities are considered to be experimental (LE: 2b)

Related NICE guidance

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

Interventional procedures

- Electrically-stimulated intravesical chemotherapy for superficial bladder cancer. Interventional procedures guidance 277 (2008). Available from https://www.nice.org.uk/guidance/ipg277

- Laparoscopic cystectomy. NICE interventional procedures guidance 287 (2003). Available from https://www.nice.org.uk/guidance/ipg287.

NICE guidelines

- Bladder cancer. NICE quality standard 106 (2015). Available from https://www.nice.org.uk/guidance/qs106

- Bladder cancer: diagnosis and management. NICE guideline 2 (2015). Available from https://www.nice.org.uk/guidance/ng2

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. Two Specialist Advisor Questionnaires for intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

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

- The studies identified did not compare different chemostatic agents or attempt to determine the optimal dosage or treatment regimen.
- The author has included 3 conference abstracts and 1 set of unpublished data in the literature review.

Emerging trials:

NCT03335059 - Mitomycin C intravesical chemotherapy in conjunction with Synergo® radiofrequency-induced hyperthermia for treatment of carcinoma in

situ non-muscle invasive bladder cancer patients unresponsive to bacillus Calmette-Guérin, with or without papillary tumors (RITE-USA). Case series, n=106, FU=, predicted start date: January 2018, predicted completion date: December 2024. [Not yet recruiting]

NCT02471495 - RITE-EUROPE (radiofrequency-induced thermochemotherapy effect-EUROPE), European multicentre, case series, n=116, FU=12 months, start date: September 2016, estimated completion date: January 2020. [Not yet recruiting]

References

1. Colombo R, van Valenberg H , Moschini M et al. (2016) Radiofrequency-induced thermo-chemotherapy effect (RITE) for non muscle invasive bladder cancer treatment: current role and perspectives. Urologia (Treviso) 83 (Suppl 2), 7-17
2. van Valenberg H, Colombo R, Witjes F (2016) Intravesical radiofrequency-induced hyperthermiacombined with chemotherapy for non-muscle-invasive bladder cancer. Review article. International Journal of Hyperthermia 32(4), 351-362
3. Lammers RJ, Witjes JA, Inman BA et al. (2011) The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. European Urology 60(1), 81-93
4. Arends TJH, Nativ O, Maffezzini M et al. (2016) Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin C versus bacillus Calmette-Guerin for adjuvant treatment of patients with intermediate- and high-risk non-muscle-invasive bladder cancer. European Urology 69(6), 1046-1052
5. Colombo R, Da Pozzo LF, Salonia A, Rigatti P, Leib Z, Baniel J et al. (2003) Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *Journal of Clinical Oncology* 21: 4270–6.
6. Colombo R, Salonia A, Leib Z et al. (2011) Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). BJU International 107(6), 912-8
7. Erturhan S, Sen H, Demirbag A et al. (2015) Thermochemotherapy in adjuvant treatment of primary high risk non muscle invasive bladder cancers: Single center results. Archivos Espanoles de Urologia 68(8), 666-71

Appendix

There were no additional papers identified.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	08/01/2018	Issue 1 of 12, January 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	08/01/2018	Issue 12 of 12, December 2017
HTA database (Cochrane Library)	08/01/2018	Issue 4 of 4, October 2016
MEDLINE (Ovid)	08/01/2018	1946 to present with daily update
MEDLINE In-Process (Ovid)	08/01/2018	January 05, 2018
MEDLINE Epubs ahead of print (Ovid)	08/01/2018	January 05, 2018
EMBASE (Ovid)	08/01/2018	1974 to 2018 January 05

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

The MEDLINE search strategy was adapted for use in the other sources.

1 Hyperthermia, Induced/
2 ((intravesic* or endovesic*) adj4 (chemo* or mitomycin*)).tw.
3 ((hypertherm* or heat*) adj4 (chemo* or mitomycin* or induce* or deliver* or insert* or catheter*)).tw.
4 (thermochemo* or thermo-chemo* or chemotherm* or chemo-therm*).tw.
5 (chemohypertherm* or chemo-hypertherm*).tw.
6 (thermocouple* thermo-couple* or thermo-therap* or thermotherap*).tw.
7 or/1-6
8 Urinary Bladder Neoplasms/
9 Carcinoma, Transitional Cell/
10 ((bladder* or urinary or urothelial* or transitional) adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas*)).tw.
11 STCCB.tw.
12 or/8-11
13 7 and 12
14 animals/ not humans/
15 13 not 14
16 limit 15 to ed=20170822-20181231
17 (synergo or (Combat* adj1 BRS) or Unithermia or BSD-2000).tw.
18 16 or 17