NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer

This procedure is used for treating early-stage bladder cancer, before or after surgery. A tube (catheter) is inserted into the bladder through the urethra (the tube that carries urine out of the body from the bladder). Chemotherapy drugs are then passed through this tube into the bladder. The catheter also gives out microwaves that heat up the bladder wall. The aim is to improve 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 and updated in July 2018.

Procedure name

- Intravesical microwave hyperthermia and 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

Transitional cell carcinoma is the most common form of bladder cancer. Non-muscle-invasive transitional cell carcinoma is classified as stage Ta when the tumour is confined to the uroepithelium with no spread into the bladder wall or beyond. It is classified as stage T1 when there is spread into the connective tissue layer between the urothelium and the muscle wall. Non-muscle-invasive 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 non-muscle-invasive transitional cell carcinoma include transurethral resection, in which malignant tissue is removed with an electrocautery device during cystoscopy. Bacillus Calmette-Guérin (BCG) vaccine or chemotherapy drugs may be put directly into the bladder, either as a treatment in itself, or as adjuvant therapy after transurethral resection. Cystectomy may also be necessary in some patients.

What the procedure involves

Intravesical hyperthermia and chemotherapy can be used as neoadjuvant therapy before transurethral resection, with the aim of eradicating tumours. Alternatively the procedure can be used after transurethral resection, as adjuvant therapy (sometimes referred to as prophylactic treatment), aiming to prevent 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 anaesthetic urethral gel, a balloon catheter (containing a radiofrequency 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 radiofrequency antenna gives off microwaves which heat the superficial layers of the bladder wall. The thermocouples are spread out from the catheter and pushed against the bladder lining. They monitor temperature to help prevent overheating. A solution of a cytostatic agent, usually mitomycin C, is put 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 between 40 minutes and60 minutes and are usually repeated weekly for 4 to 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

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 but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.

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

Grade 5 Death related to adverse event.

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 plus 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 happened 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 plus MMC (6% [2/35]) compared to patients treated by MMC alone (8% [3/40], p>0.05)[1-3].

CHT plus MMC compared to BCG vaccine

One RCT (n=190) included in the review of 26 studies reported no statistically significantly difference in recurrence free survival in the intention to treat population (ITT) between patients having CHT plus MMC (78% [65 to 87%]) compared to Bacilli Calmette-Guérin vaccine (BCG, 65% [52 to 75%], p=0.08), at the 24-month follow-up. In the per protocol population (PP, n=147) recurrence free survival was statistically significantly lower in patients having CHT plus MMC (82% [69 to 90%]) compared to BCG vaccine (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 treated by CHT plus MMC (89%) compared to BCG vaccine (86%, p=1). Progression was reported as less than 2% in both comparators[1-4].

CHT plus MMC used after transurethral resection of bladder tumour (TURBT, prophylactic or adjuvant treatment)

The review of 26 studies included 4 peer reviewed case series, 1 conference abstract and 1 unpublished non-randomised controlled study, reporting on outcomes of intermediate to high risk non-muscle invasive bladder cancer (n=922) after CHT plus MMC as adjuvant therapy after TURBT. In 1 case series (n=111) recurrence free survival was 85% at 1 year and 56% at 2 years follow-up. Median time to recurrence was 16 months. Disease free survival was 50% at the 2 years follow-up and progression happened in 3% (1/38) of patients. Another case series (n=42) reported 89% disease free survival 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) recurrence free survival was 60% at 1 year and 46% at the 2-year follow-up. Progression happened in 4% (7/160) of patients. In a case series (n=97) included in the same review overall survival was 82% (80/97), disease specific survival was 93% (90/97), progression was 36% (35/97) and cystectomy was 19% (18/97), at a median 27-month follow-up. In 1 unpublished non-randomised controlled study (n=366), done by the author of the review, recurrence was statistically significantly lower in patients having CHT plus MMC (25%) compared to patients having standard of care (39%, p<0.006), at a minimum 2 years follow-up. The frequency of radical cystectomy 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 plus MMC, recurrence was reported in 12% (3/26) patients, disease free survival in 88% and there was no progression, at the 16.4-months follow-up[7].

CHT plus MMC used after failed BCG vaccine 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 plus MMC who had previously had BCG vaccine (41%) than in patients treated by CHT plus 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 with BCG vaccine (46%) and patients treated by CHT plus 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 vaccine, 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) of 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 plus MMC was used as debulking therapy allowing for 44% (16/19) of patients to have TURBT instead of radical cystectomy. CR was reported in 47% (9/16) of patients and recurrence in 89% (8/9). 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 plus MMC after non-compete resected NMIBC and failed BCG vaccine. CR was reported in 76% (206/271) and partial response in 8% (21/271) of patients. 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 plus MMC

The review of 26 studies included 5 non-randomised controlled studies and 1 case series (n=289) reporting outcomes of intermediate to high risk patients treated with adjuvant or neoadjuvant CHT plus MMC. In a non-randomised controlled study (n=52), recurrence was higher in patients treated with prophylactic CHT plus MMC (38% [9/24]) than in high risk patients having CHT before TURBT (19% [4/21]), at a mean 10 months follow-up. Recurrence free

survival was 63% (15/21) in patients having 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 plus MMC (9% [2/22], 10 months) than in the group having neoadjuvant therapy (20% [2/10], 9 months). There was no progression at the median 10 months follow-up. In a non-randomised controlled study of 51 patients with carcinoma in situ, 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 non-randomised controlled study (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 plus 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 non-randomised controlled study (n=30) reported similar recurrence in patients treated by adjuvant (56% [9/16]) and neoadjuvant CHT plus 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) of patients having neoadjuvant therapy[1-3].

In 1 case series (n=21) of patients treated by adjuvant (n=10) or neoadjuvant (n=11) CHT plus MMC, overall recurrence was 71% (15/21), disease specific survival was 90% (19/21) and overall survival was 67% (14/21). Progression happened in 19% (4/21) of patients and 29% (6/21) had radical cystectomy because of 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 plus MMC (adjuvant or neoadjuvant), during a follow-up range of 9 to 90 months[1-3].

Progression

The review reported 10 studies considering progression to muscle invasive bladder cancer as a secondary endpoint, progression varied between 0% and 8%. Median follow-up was 24 months or less in 8 of the 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 plus 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 posterior wall thermal reactions were found after CHT plus MMC, compared to more fever, fatigue, arthralgia, haematuria, incontinence and frequency after BCG vaccine [1-3].

Bladder spasms

Bladder spasms during treatment by CHT plus 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 treatment by CHT plus 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 plus MMC in the same RCT[4].

Pain

Pain during treatment by CHT plus MMC was reported in 18% (range 7 to 27%) of patients (8 studies, n=3454) included in the review of 26 studies. Pain during the 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 treatment by CHT plus MMC was reported in 14% (202/1431) of patients in the RCT of 190 patients (OR: 26.3, 95% CI 14.3 to 48.5). Bladder pain between intravesical chemotherapy sessions was more frequent in patients treated by CHT plus MMC compared to BCG vaccine (OR: 1.6, 95% CI 1.2 to 2.3), in the same RCT. Dysuria was also more frequent in patients treated by CHT plus MMC 12% [167/1431]) than by BCG vaccine (15% [229/1525])[4].

Pain was statistically significantly more frequent in patients treated by CHT plus MMC (41% [17/42]) compared to MMC alone (0%, p<0.001) in the RCT of 83 patients. Dysuria was more frequent in patients treated by CHT plus 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 plus 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 plus MMC 10% (147/1431) compared to patients treated by BCG vaccine (15% [227/1525], OR: 0.79, 95% CI 0.63 to 0.98) in the RCT of 190 patients. Urinary frequency was statistically significantly less frequent in patients treated by CHT plus MMC (10% [147/1431]) compared to BCG vaccine (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 plus MMC compared to BCG vaccine (OR: 0.22, 95% CI 0.12 to 0.37)[4].

Urinary retention was reported in 19% (5/26) of patients treated by CHT plus 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 plus MMC in the RCT of 190 patients. Haematuria was less frequent in patients treated by CHT plus MMC compared to BCG vaccine (OR: 0.56, 95% CI 0.42 to 0.74) in the same RCT[4].

Haematuria was more frequent in patients treated by CHT plus 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 plus 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 were commonly seen (frequency not reported). The author reported that during follow-up cystoscopy, an asymptomatic posterior wall thermal reactions could be seen in almost all patients (frequencies not reported)[1-3].

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

Posterior wall thermal reactions was reported in 27% (7/26) of patients treated by CHT plus MMC in the case series of 26[7].

Rash and allergy

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

Skin allergy was more frequent in patients treated by CHT plus 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 plus MMC in the case series of 26 patients[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 plus 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 alone 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 plus MMC compared to BCG vaccine (OR: 2.3, 95% CI 1.3 to 4.1) in the RCT of 190 patients[4].

Urethral stenosis was more frequent in patients treated by CHT plus 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 plus MMC compared to BCG vaccine (OR: 16.7, 95% CI 5.1 to 54) in the RCT of 190 patients[4].

Systemic symptoms

Subjective symptom scoring (4 studies) using a 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 plus MMC treated patients (9.1 [1.8]) compared to BCG vaccine (9.4 [1.7], in the RCT of 83 patients. After induction cycle, subjective symptoms were higher in the CHT plus MMC group (18.4 [2.6]) than in the BCG vaccine 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 plus MMC compared to BCG vaccine (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 vaccine 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 because of scarring.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer. The following databases were searched, covering the period from their start to 30 April 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 non-muscle invasive bladder cancer.
Intervention/test	Intravesical microwave hyperthermia and 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 appendix A.

Table 2 Summary of key efficacy and safety findings on Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive 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 done 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 CIS patients only **CR**: 89% CHT, 86% BCG, p=1 **Progression**: <2% in both groups

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
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) **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)

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 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)
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

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
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 by 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 cases of concomitant papillary lesions or many CIS lesions (group 2, n=33); prophylactic schedule in other patients (group 1, n=18)	51	22 (3 to 77)	Only CIS	60	41 to 44	Group 1: 20 mg in 50 ml Group 2: 40 mg in 50 ml	Group 1: 6 Group 2: 8	Yes: 6 times every 6 weeks	Total evaluable patients: 49 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)

Author	Study design, study description	n	Median FU months	Patient population	Treatment					Outcomes recurrence and progression
					Duration (min)	T°C	Dose	N. treatments	Maintenance	
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 happened 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 non-muscle-invasive bladder cancer varied between studies.

Existing assessments of this procedure

The European Association of Urology has published guidelines on Non-muscle-invasive Bladder Cancer (NMIBC), TaT1 and carcinoma in situ (CIS).[8]

The guidelines state:

'Microwave-induced hyperthermia

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk bladder cancer, a reduced RFS at 24 months in the MMC group was demonstrated (LE: 1b).'

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 sent 20 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 12 completed questionnaires (including 2 that were completed online).

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.

The company submitted an 'academic in confidence' paper, which was reviewed by the committee for safety events.

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
8. Babjuk M, Burger M, Compérat E et al. European Association of Urology (EAU) Guidelines for Non-muscle-invasive Bladder Cancer (NMIBC), TaT1 and carcinoma in situ (CIS).

   Retrieved from: http://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/

   Access date [17/07/2018].

Additional relevant papers

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
Arends TJH, Nativ O, Maffezzini M, et al. (2016) Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin C versus Bacillus Calmette-Guérin for adjuvant treatment of patients with intermediate- and high-risk non-muscleinvasive bladder cancer. European Urology 69(6):1046-1052	RCT n=190 FU=26 months	CHT is a safe and effective treatment option in patients with intermediate- and high-risk papillary NMIBC. A significantly higher 24-mo RFS in the CHT group was seen in the PP analysis. Based on the results above, CHT is an option for BCG therapy as adjuvant treatment for intermediate- and high-risk papillary NMIBC.	Reported in paper 1 in table 2.
Arends TJH, van der Heijden AG, Witjes JA (2014) Combined chemohyperthermia: 10-year single center experience in 160 patients with nonmuscle invasive bladder cancer. Journal of Urology 192(3): 708-713	Case series n=160 FU=76 months	Chemohyperthermia is an effective approach to non-muscle invasive bladder cancer for which standard intravesical treatments fail. Patients with highly recurrent disease before chemohyperthermia have lower recurrence-free survival. Furthermore, recurrence-free survival appears to improve with earlier chemohyperthermia. No significant differences were observed between the 2 chemotherapy agents.	Reported in paper 1 in table 2.
Ayres BE, Connor A, Corbishley C et al. (2010) Radiofrequency hyperthermia and mitomycin C for the management of frail patients with high-risk non-muscle invasive bladder cancer who fail intravesical BCG treatment. BJU International 106(s1):8	Case series n=38 FU=9	Although radical cystectomy remains the gold standard treatment for BCG failures in high-risk non-muscle invasive bladder cancer these results suggest that hyperthermic mitomycin may have a role in a sub-group of patients. The forthcoming randomised controlled trial will investigate this further.	Reported in paper 1 in table 2.
Colombo R, Da Pozzo LF, Lev A et al. (1998) Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors. J Urology 159(3):783-787.	Case series n=18 FU=33	Microwave induced hyperthermia combined with intravesical mitomycin C seems to be a feasible, safe and elective approach for conservative treatment of multifocal and recurrent superficial bladder tumours when other treatment strategies have failed.	Reported in paper 1 in table 2.

Colombo R, Da Pozzo L, Lev A et al. (1996) Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer. J Urology 155(4):1227-1232	RCT n=52 FU=38 months	According to these preliminary data, microwave induced hyperthermia combined with local intravesical chemotherapy seems to be a feasible, safe and promising approach for neoadjuvant and minimally invasive treatment of superficial bladder cancer.	Reported in paper 1 in table 2.
Colombo R, Lev A, Da Pozzo LF et al. (1995) A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment. Journal of Urology 153: 959-963	Case series n=44 FU=24 months	Endoscopic and histological evaluations proved that combined local hyperthermia and chemotherapy can induce necrosis of transitional tumours. The overall response rate was 90.8%, with 70.4% complete and 20.4% partial, leaving 4 patients (9.2%) non-responders. Clinical and histological evaluations have confirmed the feasibility and safety of this combined treatment. Further multicentre studies have been initiated.	Reported in paper 1 in table 2.
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(1):95-100	NRCS n=80 FU=NA	The intravesical administration of mitomycin C can be safely performed in the form of both thermo-chemotherapy and electromotive drug approach with an increased ablative success rate on small superficial tumour involving only minimal local side effects	Reported in paper 1 in table 2.
Colombo R, Da Pozzo LF, Salonia A et al. (2003) Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. Journal Clinical Oncolology 21(23): 4270-4276	RCT n=52 FU=24 months	Endovesical thermochemotherapy appears to be more effective than standard endovesical chemotherapy as an adjuvant treatment for superficial bladder tumours at 24-month follow-up, despite an increased but acceptable local toxicity.	Reported in paper 1 in table 2.
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. BJU Int. 107(6):912-918	RCT n=52 FU=90 months	This is the first analysis of long-term follow-up of patients treated with intravesical thermochemotherapy. The high rate (53%) of patients who were tumour-free 10 years after treatment completion, as well as the high rate (86%) of bladder preservation, confirms the efficacy of this adjuvant approach for NMIBC at long-term follow-up, even in patients with multiple tumours.	Reported in paper 1 in table 2.

Gofrit ON, Shapiro A, Pode D et al. (2004) Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer. Urology 63(3):466-471	NRCS n=52 Fu=15 months	Combined local bladder hyperthermia and intravesical chemotherapy has a beneficial prophylactic effect in patients with G3 superficial bladder cancer. Ablation of high-grade bladder tumours is feasible, achieving a complete response in about three quarters of the patients.	Reported in paper 1 in table 2.
Kiss B, Schneider S, Thalmann GN et al. (2015) Is thermochemotherapy with the Synergo system a viable treatment option in patients with recurrent non-muscle-invasive bladder cancer? International Journal of Urology 22(2):158-162.	Case series n=21 FU=50 months	Given the high rate of severe side-effects leading to treatment discontinuation, as well as the limited tumour response, thermochemotherapy should be offered only in highly selected cases of recurrent non-muscle-invasive bladder cancer.	Reported in paper 1 in table 2.
Maffezzini M, Campodonico F, Canepa G et al. (2014) Intravesical mitomycin C combined with local microwave hyperthermia in non-muscle-invasive bladder cancer with increased European Organization for Research and Treatment of Cancer (EORTC) score risk of recurrence and progression. Cancer Chemotherapy Pharmacology 73(5):925-930	Case series n=42 FU=38 Months	Intravesical chemotherapy and local microwave hyperthermia significantly increases the disease free interval of non-muscle invasive bladder cancer patients with high European Organization for Research and Treatment of Cancer core for recurrence and progression. Toxicity of the intensive treatment schedule was generally mild.	Reported in paper 1 in table 2.
Moskovitz B, Halachmi S, Moskovitz M et al (2012) 10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. Future Oncology 8(8):1041-1049	NRCS n=88 FU=23 months	Microwave-induced chemohyperthermia is a safe and effective treatment option for patients with NMIBC, both in the adjuvant and neoadjuvant settings. The use of this treatment modality did not expose the patients to an increased risk of progression.	Reported in paper 1 in table 2.
Moskovitz B, Meyer G, Kravtzov A et al. (2005) Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients. Annals Oncology 16(4):585-589.	NRCS n=47 Fu=10 months	Our efficacy and safety results confirm those reported in previously published studies, suggesting the promising value of this combined treatment modality for both prophylactic and ablative patients. The ablative protocol offers an alternative therapy for a selected patient population for whom no other treatment option exists.	Reported in paper 1 in table 2.

Nativ O, Witjes JA, Hendricksen K et al. (2009) Combined thermochemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin. Journal of Urology 182(4):1313-1317	Case series n=111 FU=16 months	Thermo-chemotherapy may be effective for papillary non-muscle invasive urothelial cell carcinoma of the bladder that recurs after BCG treatment without increasing the risk of tumour progression. Maintenance therapy is important and improves the outcome.	Reported in paper 1 in table 2.
Rigatti P, Lev A, Colombo R (1991) Combined intravesical chemotherapy with mitomycin C and local bladder microwave-induced hyperthermia as a preoperative therapy for superficial bladder tumors. A preliminary clinical study. European Urology 20(3): 204-210	Case series n=12 FU=16 months	Local intravesical concurrent chemotherapy and hyperthermia administration is found to be a safe and well-tolerated approach for superficial bladder tumour treatment. The preliminary results encourage further studies to define the limits and prospects of this regimen, in both superficial bladder tumour ablation and prophylaxis of recurrences.	Reported in paper 1 in table 2.
Sooriakumaran P, Chiocchia V, Dutton S et al. (2016) Predictive factors for time to progression after hyperthermic mitomycin C treatment for high-risk non-muscle invasive urothelial carcinoma of the bladder: an observational cohort study of 97 patients. Urology International 96(1):83-90	Case series n=97 FU=27	High-risk non-muscle invasive bladder cancer patients can be safely treated with hyperthermic mitomycin and have good oncological outcome. However, those without an initial complete response have a poor prognosis and should be counselled towards adopting other treatment methodologies such as cystectomy. Female gender and lack of carcinoma in situ may be good prognostic indicators for response to hyperthermic mitomycin.	Reported in paper 1 in table 2.
Witjes JA, Hendricksen K, Gofrit O et al. (2009) Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo working party. World Journal of Urology 27(3):319-324	Case series n=51 FU=22	In patients with primary or BCG-failing carcinoma in situ, treatment with intravesical hyperthermia and mitomycin appears a safe and effective treatment. The initial complete response rate is 92%, which remains approximately 50% after 2 years.	Reported in paper 1 in table 2.
van der Heijden AG, Kiemeney LA, Gofrit ON et al. (2004) Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder. European Urology 46(1): 65-71	Case series n=90 FU=18 months	Microwave induced hyperthermia combined with MMC has promising value in intermediate or high risk superficial bladder cancer patients compared to literature data of BCG and/or intravesical chemotherapy, particularly where other treatments, i.e. BCG, have failed.	Reported in paper 1 in table 2.
Volpe A, Racioppi M, Bongiovanni L,et al. (2012) Thermochemotherapy for non-muscle-invasive bladder	NRCS n=30 Fu=14 months	Thermochemotherapy could be considered an additional tool in patients refractory to intravesical	Reported in paper 1 in table 2.

cancer: is there a chance to avoid early cystectomy? Urology International 9(3):311-318		therapies before considering early cystectomy.	

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/04/2018	Issue 4 of 12, April 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/04/2018	Issue 3 of 12, March 2018
HTA database (Cochrane Library)	30/04/2018	Issue 4 of 4, October 2016
MEDLINE (Ovid)	30/04/2018	1946 to present with Daily Update
MEDLINE In-Process (Ovid) &	30/04/2018	April 27, 2018
Medline ePub ahead (Ovid)	30/04/2018	April 27, 2018
EMBASE (Ovid)	30/04/2018	1974 to 2018 Week 18

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