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Intravesical Bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer (Review)

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[Intervention Review]

Intravesical Bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer

Stefanie Schmidt[1], Frank Kunath[1,2], Bernadette Coles[3], Desiree Louise Draeger[1,4], Laura-Maria Krabbe[1,5], Rick Dersch[6], Samuel Kilian[7], Katrin Jensen[7], Philipp Dahm[8,9], Joerg J Meerpohl[10]

[1]UroEvidence@Deutsche Gesellschaft für Urologie, Berlin, Germany. [2]Department of Urology, University Hospital Erlangen, Erlangen, Germany. [3]Velindre NHS Trust, Cardiff University Library Services, Cardiff, UK. [4]Department of Urology, University of Rostock, Rostock, Germany. [5]Department of Urology, University of Muenster Medical Center, Muenster, Germany. [6]Department of Neurology and Neurophysiology, Medical Center – University of Freiburg, Freiburg, Germany. [7]Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany. [8]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA. [9]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [10]Institute for Evidence in Medicine, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Contact address: Stefanie Schmidt, UroEvidence@Deutsche Gesellschaft für Urologie, Martin-Buber-Str. 10, Berlin, 14163, Germany. schmidt@dgu.de.

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ABSTRACT

Background

People with urothelial carcinoma of the bladder are at risk for recurrence and progression following transurethral resection of a bladder tumour (TURBT). Mitomycin C (MMC) and Bacillus Calmette-Guérin (BCG) are commonly used, competing forms of intravesical therapy for intermediate- or high-risk non-muscle invasive (Ta and T1) urothelial bladder cancer but their relative merits are somewhat uncertain.

Objectives

To assess the effects of BCG intravesical therapy compared to MMC intravesical therapy for treating intermediate- and high-risk Ta and T1 bladder cancer in adults.

Search methods

We performed a systematic literature search in multiple databases (CENTRAL, MEDLINE, Embase, Web of Science, Scopus, LILACS), as well as in two clinical trial registries. We searched reference lists of relevant publications and abstract proceedings. We applied no language restrictions. The latest search was conducted in September 2019.

Selection criteria

We included randomised controlled trials (RCTs) that compared intravesical BCG with intravesical MMC therapy for non-muscle invasive urothelial bladder cancer.

Data collection and analysis

Two review authors independently screened the literature, extracted data, assessed risk of bias and rated the quality of evidence according to GRADE per outcome. In the meta-analyses, we used the random-effects model.

Main results

We identified 12 RCTs comparing BCG versus MMC in participants with intermediate- and high-risk non-muscle invasive bladder tumours (published from 1995 to 2013). In total, 2932 participants were randomised.

Time to death from any cause: BCG may make little or no difference on time to death from any cause compared to MMC (hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.79 to 1.20; participants = 1132, studies = 5; 567 participants in the BCG arm and 565 in the MMC arm; low-certainty evidence). This corresponds to 6 fewer deaths (40 fewer to 36 more) per 1000 participants treated with BCG at five years. We downgraded the certainty of the evidence two levels due to study limitations and imprecision.

Serious adverse effects: 12/577 participants treated with BCG experienced serious non-fatal adverse effects compared to 4/447 participants in the MMC group. The pooled risk ratio (RR) is 2.31 (95% CI 0.82 to 6.52; participants = 1024, studies = 5; low-certainty evidence). Therefore, BCG may increase the risk for serious adverse effects compared to MMC. This corresponds to nine more serious adverse effects (one fewer to 37 more) with BCG. We downgraded the certainty of the evidence two levels due to study limitations and imprecision.

Time to recurrence: BCG may reduce the time to recurrence compared to MMC (HR 0.88, 95% CI 0.71 to 1.09; participants = 2616, studies = 11, 1273 participants in the BCG arm and 1343 in the MMC arm; low-certainty evidence). This corresponds to 41 fewer recurrences (104 fewer to 29 more) with BCG at five years. We downgraded the certainty of the evidence two levels due to study limitations, imprecision and inconsistency.

Time to progression: BCG may make little or no difference on time to progression compared to MMC (HR 0.96, 95% CI 0.73 to 1.26; participants = 1622, studies = 6; 804 participants in the BCG arm and 818 in the MMC arm; low-certainty evidence). This corresponds to four fewer progressions (29 fewer to 27 more) with BCG at five years. We downgraded the certainty of the evidence two levels due to study limitations and imprecision.

Quality of life: we found very limited data for this outcomes and were unable to estimate an effect size.

Authors' conclusions

Based on our findings, BCG may reduce the risk of recurrence over time although the Confidence Intervals include the possibility of no difference. It may have no effect on either the risk of progression or risk of death from any cause over time. BCG may cause more serious adverse events although the Confidence Intervals once again include the possibility of no difference. We were unable to determine the impact on quality of life. The certainty of the evidence was consistently low, due to concerns that include possible selection bias, performance bias, given the lack of blinding in these studies, and imprecision.

PLAIN LANGUAGE SUMMARY

Bacillus Calmette-Guérin or mitomycin C for treatment of non-muscle-invasive bladder cancer

Review question

In people with cancer of the inner lining of the bladder, how do two different medicines, that are called Bacillus Calmette-Guérin (BCG) and mitomycin (MMC), that are put into the bladder, after the tumour is taken out, compare?

Background

Tumours of the superficial layers of the bladder, so-called non-muscle-invasive bladder cancer, are treated by putting small instruments into the bladder and shaving them out. This works well but these tumours often come back. When they do come back they can be more aggressive and advanced than before. Different types of medicines put into the bladder afterwards can make that happen less often, with BCG and MMC being those used most often. We are not sure how the two treatments compare when it comes to wanted and unwanted effects.

Study characteristics

The content of this review is current to September 2019. We included only studies where chance determined what treatment people in the study would get.

Key results

We found 12 studies including 2932 people who matched our question.

We found that BCG may lead to similar risk of dying from any cause over time (low-quality evidence), but may increase the risk of serious unwanted effects (low-quality evidence), although it is possible that it does not make a difference.

BCG may reduce the risk that the tumour comes back over time (low-quality evidence), although it is possible that it does not make a difference.

BCG may have little or no effect on the risk that the tumour gets worse over time (low-quality evidence).

We found no data on quality of life.

Quality of the evidence

The quality of the evidence was consistently rated as low, meaning that our confidence is limited, and future research may change these findings.

Summary of findings for the main comparison. Bacillus Calmette-Guérin (BCG) compared to mitomycin C (MMC) for Ta and T1 bladder cancer

BCG compared to MMC for Ta and T1 bladder cancer

Participants: Adults (≥18 years) with intermediate and high-risk non-muscle invasive urothelial bladder cancer

Setting: hospital

Intervention: BCG

Comparison: MMC

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with MMC	Risk difference with BCG
Time to death from any cause (absolute effect size estimates based on event rate at 5 years). Follow-up: range 3.5–20 years	1132 (5 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**HR 0.97** (0.79 to 1.20)	**Study population**	
				210 per 1000[c]	6 fewer per 1000 (40 fewer to 36 more)
Serious adverse effects Follow-up: range 1.6–10 years	1024 (5 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**RR 2.31** (0.82 to 6.52)	**Study population**	
				7 per 1000	9 more per 1000 (1 fewer to 37 more)
Time to recurrence (absolute effect size estimates based on event rate at 5 years) Follow-up: range 3–20 years	2616 (11 RCTs)	⊕⊖⊖⊖ **Low**[a,b,d]	**HR 0.88** (0.71 to 1.09)	**Study population**	
				450 per 1000[e]	41 fewer per 1000 (104 fewer to 29 more)
Time to progression (absolute effect size estimates based on event rates at 5 years) Follow-up: range 1.6–20 years	1622 (6 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**HR 0.96** (0.73 to 1.26)	**Study population**	
				112 per 1000[c]	4 fewer per 1000 (29 fewer to 27 more)
Quality of life (measured using EORTC QLQ-BLS24 at baseline and after each installation weekly for 6 weeks)	110 (1 RCT)	Not estimable[f]	Not estimable	There was no evidence of a difference between BCG and MMC groups, except for abdominal bloating and flatulence, which was worse in the BCG group.[f]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded one level for study limitations: concerns with performance or detection bias (or both), as well as with regard to allocation concealment and selective outcome reporting.
[b]Downgraded one level for imprecision: 95% CI was consistent with the possibility for important benefit and large harm.
[c]The assumed risk was based on five-year mortality rate from Gardmark 2007.
[d]Downgraded one level for inconsistency: variation in point estimates or substantial heterogeneity among studies (or both).
[e]The assumed risk is based on five-year mortality rate based on Ojea 2007b
[f]More detailed results on quality of life were not available (conference abstract only)

BACKGROUND

Description of the condition

Urinary bladder cancer affects men and women worldwide, though it is more common in the Western world. Bladder cancer is the fourth most common cancer diagnosed in men in the USA and Europe. It is placed at seventh and eighth position in cancer-related mortality in the USA (Siegel 2018) and Europe, respectively (Ferlay 2013). The tumour appears three to four times more frequently in men than in women (Fajkovic 2011). One in 26 men will develop bladder cancer in their lifetime (Siegel 2018). Overall five-year survival rates in Europe are around 68% (De Angelis 2014), but it has been noted that women present with more advanced disease and have a worse prognosis (Shariat 2010). Age, tobacco smoking and exposure to cancerous substances have been reported as potential risk factors (Burger 2013).

Approximately 75% of newly diagnosed cases are non-muscle invasive bladder cancers, where the tumour affects only the mucous membrane or submucosal layer (also called non-muscle invasive urothelial carcinoma of the bladder) (Babjuk 2018). About 25% of people diagnosed with bladder cancer have muscle invasive disease and will have poor prognosis even after receiving treatment. The prevalence of bladder cancer is high, as the tumour recurs frequently even after initial treatment and it requires long-term clinical monitoring. Therefore, this type of cancer is very bothersome to those affected, causes substantial morbidity and affects quality of life (Griffiths 2013).

In economic terms, bladder cancer has the highest lifetime treatment cost per patient. Compared to all other cancers, the per-patient expenditures range from USD 89,287 to USD 202,203 per patient from diagnosis to death (Sievert 2009), because of high medical expenditures on diagnosis, treatment and continued surveillance using invasive techniques (Svatek 2014). The disease is very costly for the healthcare system and for society, because of work loss and loss of productivity.

Description of the intervention

Although transurethral resection of the bladder (TURB) can eradicate Ta and T1 bladder tumours, intravesical therapy is recommended in most people with intermediate- or high-risk non-muscle invasive bladder tumours (Ta, T1 and Cis) due to the high chance of tumour recurrence (about 80%) or progression to muscle invasive disease (about 45%) (Babjuk 2018; van Rhijn 2009). Therapy includes either immunotherapy with Bacillus Calmette-Guérin (BCG) or chemotherapy with cytotoxics, the most commonly used being mitomycin C (MMC) (Ragonese 2016). Other intravesical cytotoxics include gemcitabine, epirubicin and doxorubicin. Intravesical therapies are used to prevent cancer recurrence after primary treatment, and have shown efficacy during recent years of regular utilisation (Abern 2013; Perlis 2013; Sylvester 2004). After the instillation of intravesical agents into the bladder, the solution should be retained for 1.5 to 2 hours. The patient is encouraged to move positions every 30 to 45 minutes to allow the intravesical solution to contact all parts of the bladder wall. After this time, the patient voids to remove the solution.

BCG is provided as a freeze-dried powder and is diluted with saline before it is instilled into the bladder. Different strains of BCG are available. The original BCG strain was developed at the Pasteur Institute from an attenuated strain of *Mycobacterium bovis*. Subcultures were made and sent to other parts of the world: Tice and TheraCys substrains are available in the USA, while the Tokyo 172 and the Danish substrains are available outside the USA. There is some evidence that different strains might differ in their clinical efficacy, but this evidence is still limited (Rentsch 2014; Sengiku 2013). Contraindications to BCG therapy are gross haematuria, traumatic catheterisation, recent bladder tumour resection (less than two weeks after TURB), urinary incontinence, symptomatic urinary tract infection and immunosuppression. A BCG sepsis might occur, which presents as an acute tuberculosis-like illness. Signs and symptoms of a life-threatening septicaemia are high-grade fevers, hepatotoxicity, respiratory distress, chills, haemodynamic instability and mental status changes. Local adverse effects might include symptoms of cystitis, haematuria, symptomatic granulomatous prostatitis and epididymo-orchitis.

MMC powder is diluted with saline and is administered through a catheter directly into the bladder. The recommended dosage depends on patient and tumour characteristics, such as age and prior cytostatic therapy. Although bladder cancer occurs mostly in older people, there are only limited data available about the use of MMC in people aged over 65 years. MMC was isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae* in the 1950s. Trade names are Amétycine, Mitem, Urocin and Mito-medac, as well as other diverse generic products. Contraindications to MMC use are: reduced bone marrow function; bleeding predisposition; damage to liver, lung or kidney; general bad health; and hypersensitivity against MMC; as well as haematuria, perforation of bladder, and urinary tract infection. It is systemically absorbed to a very limited degree when administered intravesically, and systemic adverse effects are rare. Common adverse effects might include cystitis, dysuria, nocturia, pollakisuria, haematuria, local bladder wall reactions and allergic reactions of the skin. The administration of MMC with local microwave-induced hyperthermia to enhance the effectiveness of therapy is still experimental, with limited evidence but promising results (Lammers 2011; Slater 2014). Also, the use of an electrical current to improve the delivery of intravesical agents (electromotive drug administration) has been a matter of research. Recent evidence suggests a delay in time to recurrence in selected people with non-muscle invasive bladder cancer, while the effect about its impact on serious adverse effects is still uncertain (Jung 2017). Other heating devices are currently tested in clinical trials.

The type of intravesical therapy which is chosen for the individual patient depends on the patient's risk group (Babjuk 2018). While for low-risk tumours (primary, solitary, Ta G1, less than 3 cm, no carcinoma in situ (Cis)) an immediate single instillation of chemotherapy is sufficient, intermediate-risk tumours (between the category of low and high risk) will need additional instillations of either chemotherapy (i.e. MMC) or immunotherapy (i.e. BCG) for one year (reference current European Association of Urology (EAU) guideline). For high-risk tumours (T1 or G3 or Cis or multiple, recurrent, greater than 3 cm Ta G1-2, or a combination of these) BCG instillations for one to three years may be more effective in preventing tumour recurrence than TURB alone or TURB and chemotherapy, but people experience significantly more adverse effects (Malmström 2009a; Shang 2011, current EAU guideline). There are still contradictory results concerning the beneficial effect

of BCG over MMC on tumour progression (Böhle 2004; Malmström 2009a; Shelley 2010; Sylvester 2004).

How the intervention might work

The mechanism of action of BCG therapy is not clearly understood. The therapeutic effect might be the result of an immune response against BCG surface antigens that cross-react with bladder tumour antigens. The BCG organisms enter macrophages, where they induce the same type of histological and immunological reaction as found in people with tuberculosis. BCG therapy also has been shown to have a predilection for entering bladder cancer cells, where the proteins are broken down and fragments are combined with histocompatibility antigens and displayed on the cell surface. This induces a cytokine and direct cell-to-cell cytotoxicity response, which targets these cells for destruction. The overall response to BCG is limited if the patient is immunosuppressed. BCG induction therapy (primary treatment) is usually given in six-week schedules. Many different maintenance schedules (following therapy) are used, ranging from a total of 10 instillations given at 18-week intervals to 27 instillations given over a three-year period (Lamm 2000: Packiam 2017).

MMC is a mutagenic substance and is used as a chemotherapeutic agent. The mechanism of effect is based preliminarily on alkylation of DNA with corresponding inhibition of DNA synthesis. The degree of damage correlates with the clinical effect and is less in resistant cells than in sensitive cells. The biological half-life time is short at about 40 to 50 minutes. A single and immediate instillation of chemotherapy is effective and reduces the recurrence rate by 12% to 13% compared to TURB alone (Abern 2013; Perlis 2013; Sylvester 2004). The agent acts by destroying free intravesical tumour cells resulting from the TURB and by an ablative effect on residual tumour cells at the resection site (Soloway 1980). Immediate instillation is necessary, as remaining free tumour cells in the bladder are implanted and covered by extracellular matrix within a few hours (Pode 1986). The prognostic factors of the patient indicate the further need for adjuvant intravesical instillations (chemotherapy or immunotherapy). There is still controversy about which patient groups might benefit the most from an immediate chemotherapy instillation (Abern 2013).

Why it is important to do this review

Although several systematic reviews and meta-analyses have been conducted on this topic (Böhle 2003; Shelley 2010), the debate on whether MMC or BCG is more effective with less toxicity is still ongoing. It furthermore remains unclear what the optimal treatment dose and schedule might be, as well as the question of which people benefit most from one or the other agent.

One systematic review by Shelley and colleagues identified over 80 randomised controlled trials (RCTs) and 11 meta-analyses that studied the effectiveness of different intravesical therapies in non-muscle invasive bladder cancer (Shelley 2010). Although in their general conclusion intravesical administration of BCG was judged to be superior to chemotherapy in terms of complete response and disease-free survival, there was no conclusive evidence to show the superiority of one agent over the other in terms of overall survival.

In the direct comparison of BCG versus MMC, BCG seemed to be superior to MMC in terms of preventing tumour recurrence in people with high-risk bladder cancer and reducing the risk of tumour progression in intermediate- and high-risk tumours, but it appeared to be more toxic (Shang 2011; Shelley 2010). There was no significant difference in disease progression and overall survival in this patient population. In intermediate-risk groups, MMC and BCG might be equally effective in preventing cancer recurrence (Shelley 2010).

The differences in findings among primary studies are the result of the clinical complexity of the disease: dosage, frequency and duration might vary considerably, also the time between TURB and intravesical therapy might differ, as well as patient characteristics, length of follow-up and study power. All these factors complicate and limit the value of the conclusions that can be drawn. The optimal schedule for BCG immunotherapy, in terms of number of inductions, and frequency and duration of maintenance, remains unknown.

The first Cochrane Review dealing with this topic was published in 2003 (Shelley 2003). This Cochrane Review serves to update the previous review, includes the new findings from the results of recent RCTs and addresses new subgroup analyses that incorporate new developments and clinical practice in this field. The methodology was adapted to the new standards of reporting and conducting Cochrane Reviews. Therefore, this systematic review provides the best available evidence that exists to date and includes independent 'Risk of bias' assessment and certainty rating according to the GRADE methodology.

OBJECTIVES

To assess the effects of Bacillus Calmette-Guérin (BCG) intravesical therapy compared to mitomycin C (MMC) intravesical therapy for treating adults with intermediate- and high-risk non-muscle invasive bladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials (RCTs), parallel-grouped or quasi-randomised trials that compared intravesical BCG with intravesical MMC therapy for non-muscle invasive urothelial bladder cancer were considered for inclusion. Studies were not excluded on the basis of publication status or language of publication. Studies that included other intravesical agents, but had treatment groups allowing a comparison of BCG and MMC were also considered for inclusion, if the results were reported separately. Studies comparing BCG to placebo/no intervention or MMC versus placebo/no intervention were excluded. We identified no cross-over trials.

Types of participants

This review considered studies reporting on adults (aged 18 years or greater) with intermediate- and high-risk non-muscle invasive urothelial bladder cancer (Sobin 2009). We also considered studies including participants with Cis of the bladder. If studies also included participants with muscle invasive bladder cancer, only data of the subset of participants with non-muscle invasive bladder cancer were considered, if these studies presented data stratified for people with intermediate- and high-risk non-muscle invasive bladder cancer.

Eligible people were those who were at intermediate or high risk of tumour recurrence or progression, or both. If studies also included participants with low risk for tumour recurrence and/or progression, we again assessed data of the subset of participants with intermediate or high risk (or both) if these data were reported separately.

The risk for recurrence and progression was defined using the EAU guidelines (Babjuk 2018), which refer to the European Organisation for Research and Treatment of Cancer (EORTC) risk tables (Sylvester 2006):

- low risk is defined as: primary, solitary, Ta G1 (papillary urothelial neoplasm of low malignant potential, low grade), less than 3 cm, no Cis;
- intermediate-risk tumours are defined as: all tumours between the categories of low and high risk;
- high risk refers to any of the following four requirements: T1 tumours; high grade G3 (high grade) tumour; Cis; multiple, recurrent and large (greater than 3 cm) Ta G1G2/low-grade tumours (all these conditions must be presented).

Following the latest clinical guideline (Babjuk 2018), we also included people at highest risk for recurrence/progression that was defined as T1 G3 tumours associated with concurrent bladder Cis or recurrent T1 G3 (or both), T1 G3 with Cis in prostatic urethra, atypical histology of urothelial carcinoma or lymphovascular invasion.

Types of interventions

Single agent intravesical therapy with BCG or MMC for the prevention or treatment of intermediate- and high-risk non-muscle invasive urothelial bladder cancer after TURB was eligible for inclusion. BCG of any schedule or strain was considered appropriate for inclusion, as well as any dose or schedule of MMC.

Types of outcome measures

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion for study inclusion.

Primary outcomes

- Time to death from any cause (defined as the time from the date of randomisation to the date of death).
- Serious adverse effects (adverse effects were considered serious when they required hospitalisation, were life-threatening or were reported as serious by the authors of the original publication).

Secondary outcomes

- Time to recurrence (defined as the date from randomisation to the date of diagnosis of recurrence or death).
- Time to progression (defined as the date from randomisation to the date of diagnosis of progression, in stage or grade or death).
- Adverse effects (such as dysuria, painful urination, haematuria, cystitis, nocturia, pollakisuria or allergic reactions).
- Quality of life (measured with validated instruments).

Main outcomes for 'Summary of findings' table

The 'Summary of findings' table included the following outcomes.

- Time to death from any cause.
- Serious adverse effects.
- Time to recurrence.
- Time to progression.
- Quality of life.

Findings and quality of the available evidence were reported according to the GRADE methodology (Schünemann 2011). For the time-to-event outcomes, we used published evidence to estimate the baseline risk (see Summary of findings for the main comparison).

Search methods for identification of studies

We performed a comprehensive literature search with no restrictions on the language of publication or publication status.

Electronic searches

We applied no date or language restrictions.

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL; included in the Cochrane Library; 2018, Issue 11) latest issue (Appendix 1), MEDLINE and MEDLINE in Process via Ovid from 1946 to 13 November 2017 (Appendix 2), Embase via Ovid from 1974 to 13 November 2017 (Appendix 3), Scopus from 1966 to 16 November 2017 (Appendix 4), Web of Science (Thomson Reuters Web of Knowledge) from 1900 to 16 November 2017 (Appendix 5), and LILACS from 1982 to 16 November 2017 (Appendix 6).

The electronic search were complemented by a search of the World Health Organization International Clinical Trials Registry Platform Search Portal (WHO ICTRP Search Portal; www.who.int/ictrp/en/, no restricted time period) (Appendix 7) and ClinicalTrials.gov (clinicaltrials.gov/, no restricted time period) (Appendix 8) to identify further completed or ongoing trials.

We updated the searches for all relevant databases shortly before publication of the review (23th September 2019) and screened the results for further potentially eligible studies. We documented and reported the search process in detail.

Searching other resources

We manually screened the reference lists of included articles to identify potentially relevant citations. We searched the American Society of Clinical Oncology (ASCO) database for grey literature (2011 to 2018; meetinglibrary.asco.org/). We contacted authors to request missing information.

Data collection and analysis

In this review, we followed the methodological recommendations given by Cochrane (Higgins 2011a).

Selection of studies

Two review authors (SS and RD or DD) independently reviewed titles and abstracts of identified references according to the predefined inclusion criteria. Two review authors (SS and RD or DD) independently assessed the full texts of all potentially relevant studies. We resolved disagreements by discussion or, if necessary, with the help of a third review author (JJM or FK). We recorded the reasons for study exclusion in the Characteristics

of excluded studies table. We identified duplicate publication of studies by checking potentially relevant references for author names, locations and settings, details of interventions, numbers of participants, baseline data, study date and duration of the study. We used EndNote software to manage the references (endnote.com/).

Data extraction and management

Two review authors (SS and DD) independently extracted relevant data on study characteristics, participant population and study setting, follow-up time, tumour characteristics and relevant comorbidities, intervention characteristics on agent and administration, study methodology, study results and author conclusion using a data extraction form. A third review author (KJ) checked the extracted outcome data relevant to this review as needed for calculation of summary statistics and measures of variance. The data extraction form was based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and was pilot tested before routine use. The review authors resolved any potential disagreement by consensus or through discussion with a third review author (JJM or FK). In addition, when necessary, we contacted the original investigators. We collected and used the most detailed numerical data in order to facilitate similar analyses of included studies. We displayed the information in the Characteristics of included studies table.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we maximised yield of information by mapping all publications to unique studies and collating all available data. We used the most complete dataset aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes

Assessment of risk of bias in included studies

For the 'Risk of bias' assessment, we used the Cochrane 'Risk of bias' tool for RCTs (Higgins 2011b). Two review authors (SS and DD or LMK) independently assessed all included studies for potential risk of bias. We resolved discrepancies through discussion or by contacting a third review author (JJM or FK). We assessed the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We judged risk of bias domains as 'low risk', 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We presented a 'Risk of bias' summary figure to illustrate these findings.

We further summarised the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

For performance bias (blinding of participants and personnel), we considered all outcomes similarly susceptible to performance bias and assessed them in one group.

For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective). Objective outcomes: time to death from any cause. Subjective outcomes: serious adverse effects, time to recurrence, time to progression, adverse effects and quality of life.

We assessed attrition bias (incomplete outcome data) on a per-outcome basis and created groups of outcomes based on similar reporting characteristics. Time-to-event outcomes: time to death from any cause, time to recurrence, time to progression; adverse effects outcomes: serious adverse effects, adverse effects; quality-of-life outcomes.

Measures of treatment effect

We extracted hazard ratios (HRs) with 95% confidence intervals (CIs) for time to event outcomes (time to recurrence, time to progression and time to death from any cause). Adjusted HRs based on multivariate analysis were preferred to univariate HRs. An indirect estimation method was used to calculate HRs and their variances if they were not reported (Parmar 1998; Tierney 2007; Williamson 2002). We expressed results of dichotomous outcomes (e.g. serious adverse effects, adverse effects) as risk ratios (RRs) with 95% CIs, results of continuous outcomes (e.g. quality of life) as mean difference (MD) with corresponding 95% CI, unless different studies use different measures to assess the same outcome, in which case we expressed data as standardised mean differences (SMDs) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant. In the event we identified trials with more than two intervention groups for inclusion in the review, we handled these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Dealing with missing data

We contacted the corresponding author of the original publication to request any missing data. We did not impute missing data and considered only the available data in the analyses. We did not conduct best-case and worst-case scenarios.

Assessment of heterogeneity

We examined statistical heterogeneity using the I^2 statistic. The thresholds for interpretation of the I^2 statistic are in accordance with the definitions presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 60% to 90% may represent substantial heterogeneity;
- 75% to 100% considerable heterogeneity.

Subgroup analyses was done for the examination of clinical heterogeneity. For details, see Subgroup analysis and investigation of heterogeneity.

Assessment of reporting biases

To account for possible publication bias, we conducted a combination of electronic and manual searches of multiple databases without language restrictions. In case of sufficient data, we created funnel plots to assess the likelihood of publication bias. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. Therefore, we interpreted results with caution (Sterne 2011).

Data synthesis

We performed data synthesis using Review Manager 5 software provided by Cochrane (Review Manager 2014).

In the meta-analyses, we used the random-effects model that assumes that the treatment effect among studies varies and, therefore, incorporates the heterogeneity among studies in the synthesis of primary study results. We combined the estimated log HRs using the generic inverse-variance method, the result of which is presented as pooled HR with 95% CI on a logarithmic scale. HRs were given for BCG compared to MMC, therefore, an HR less than 1 indicates a benefit of BCG. We calculated summary statistics with respect to the RR and its 95% CI using the Mantel-Haenszel method (Lane 2013).

Three-arm trials comparing two BCG arms with one MMC arm but without clinical relevant difference in the BCG treatment approaches were included in the meta-analysis with both treatment arms of BCG versus MMC (Ojea 2007a; Ojea 2007b; Witjes 1996a; Witjes 1996b). The standard error of the HRs were adjusted according to Woods 2010 in order to avoid a unit-of-analysis error (i.e. using the participants of the MMC group twice). In Friedrich 2007, we included one MMC arm (six weeks) in the primary meta-analysis to give attention to the comparable duration of medication in the BCG and the MMC arm. The second MMC arm (three years) was used for a sensitivity analysis.

For adverse effect outcomes, we did not pool study data to give an overall result on adverse effects, as in all studies (except Ojea 2007b) adverse effects were not reported on a per-patient basis, but as the number of the different adverse effects that had occurred. We chose to present cystitis as a patient-relevant outcome in Summary of findings for the main comparison.

Subgroup analysis and investigation of heterogeneity

We explored the following potential sources of clinical heterogeneity using the following subgroup analyses:

- different doses of BCG installations;
- different doses of MMC installations;
- different strains of BCG;
- different BCG maintenance therapies (posthoc subgroup analyses).

We used the fixed-effect models for the subgroup analyses due to the limited number of available studies (Bender 2018).

Sensitivity analysis

We aimed at examining the methodological quality according to risk of bias, by conducting separate meta-analyses for low risk of bias studies, excluding studies judged as high or unclear (or both) risk of bias. As there were no studies with low risk of bias, this analysis was not performed.

Instead we tested the robustness of results using sensitivity analysis. The fixed-effect model was used to explore visually if results of the meta-analysis varied substantially when using a model that does assume homogeneity of effects among studies and gives greater weight to larger studies. Furthermore, the second MMC arm in Friedrich 2007 (three years) was used instead of the six weeks MMC arm for a sensitivity analysis.

'Summary of findings' table

We presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account five criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (SS and JJM) independently rated the certainty of evidence for each outcome as 'high', 'moderate', 'low' or 'very low' using GRADEpro GDT. We resolved any discrepancies by consensus, or, if needed, by arbitration by a third review author (PD). For each comparison, we presented a summary of the evidence for the main outcomes in Summary of findings for the main comparison, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011).

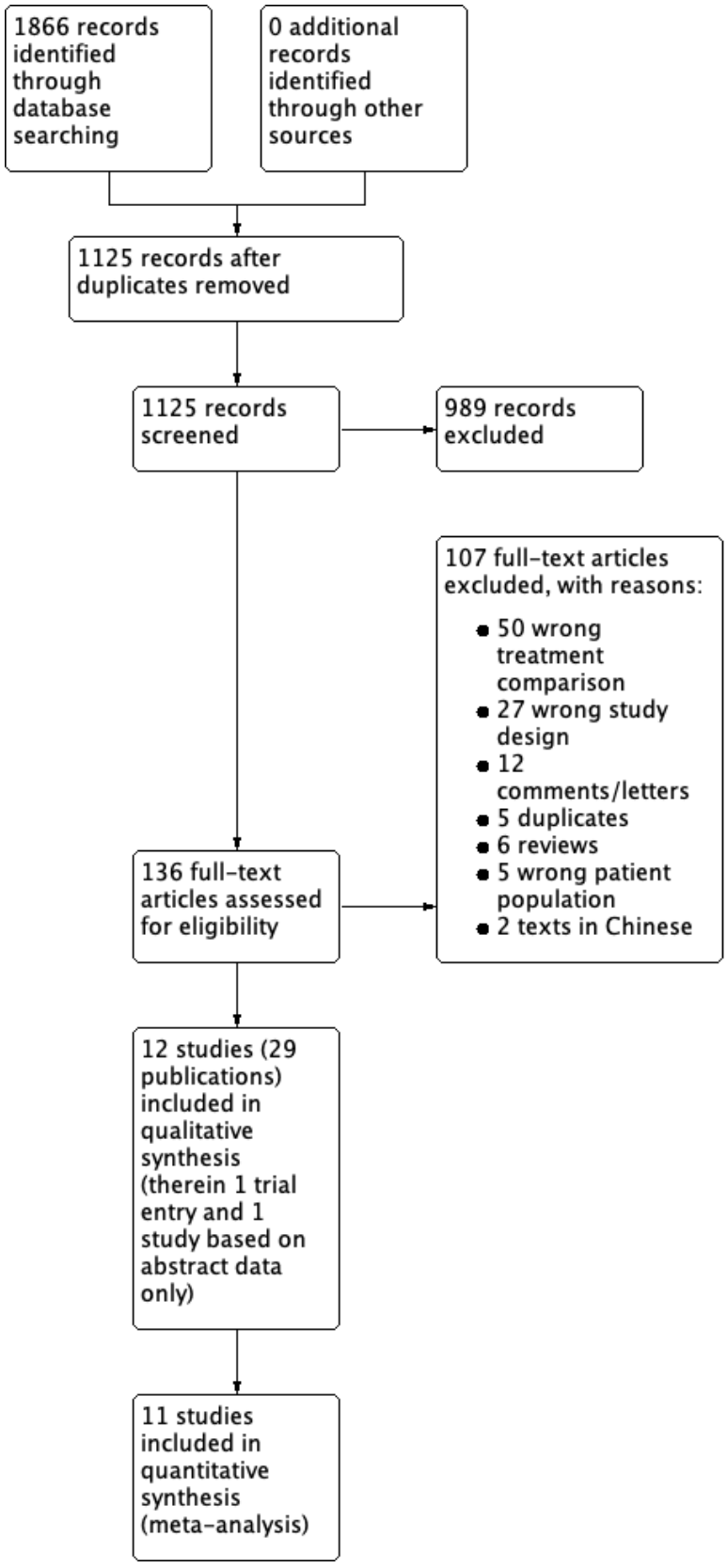
RESULTS

Description of studies

Results of the search

The literature search identified 1125 records, of which 12 studies fulfilled our inclusion criteria (based on 29 publications). Eleven were included in the meta-analyses. The one study that was not included in the meta-analysis was only available as a conference proceeding (Michielsen 2013), which did not provide sufficient data for inclusion in the analysis. Figure 1 shows the flow chart for the selection of studies. For one study, there was only the trial registry entry available (NCT00974818). This study has been terminated early due to accrual problems. For this review, we used the results available from the clinical trial website for analyses (clinicaltrials.gov/ct2/show/NCT00974818). We identified no relevant ongoing trials.

Figure 1. Study flow diagram.



Included studies

The 12 included studies are: Di Stasi 2003; Friedrich 2007; Krege 1996; Lamm 1995; Malmström 1999; Mangiarotti 2008; Michielsen 2013; NCT00974818; Ojea 2007b and Ojea 2007a; Rintala 1991; Witjes 1998a; and Witjes 1996a and Witjes 1996b. In total, the studies randomised 3080 participants. Table 1 gives a detailed description of interventions of included studies, and the Characteristics of included studies table and Table 2 give a detailed description of included studies.

Study design and settings

Most of the studies were multicentre prospective RCTs, except Mangiarotti 2008, which was a single-centre study. Di Stasi 2003; Friedrich 2007; Krege 1996; Ojea 2007b; Ojea 2007a; Witjes 1996a; Witjes 1996b were three arm studies. The studies of Ojea and Witjes are introduced twice in the reference section, as we have used the arms separately in the analyses. All trials were conducted in the hospital setting and most were conducted in Europe. Studies were published from 1991 to 2013.

Participants

A total of 2932 participants were randomised to either BCG or MMC. Follow-up ranged from 20 month to 20 years. Rintala 1991 reported the longest follow-up. Trials included men and women with histologically confirmed pTa/T1 grades 1 to 3 of intermediate- or high-risk non-muscle invasive transitional cell carcinoma of the bladder. Participants had undergone a prior transurethral resection without prior adjuvant therapy. Major exclusion criteria were: prior cancer, muscle invasive disease, concurrent treatment with chemotherapy or radiotherapy and pregnancy.

Interventions and comparators

BCG dosages ranged from 120 mg (Krege 1996; Malmström 1999) to 13.5 mg (very low dose, Ojea 2007a). Studies used different BCG strains (Tice, RIVM, Connaught and Pasteur). Most studies administered BCG weekly for six weeks, followed by different maintenance schemes. Rintala 1991 started BCG therapy with weekly instillations for four weeks. MMC dosages were 20 mg (Friedrich 2007; Krege 1996; Lamm 1995), 30 mg (Ojea 2007b; Witjes 1996a; Witjes 1996b; Witjes 1998a), or 40 mg (Di Stasi 2003; Malmström 1999; Mangiarotti 2008; Michielsen 2013). Rintala 1991 administered MMC 20 mg to 40 mg. Instillations were mostly given weekly for six weeks. Mangiarotti 2008 used a weekly schedule of eight weeks, Witjes 1996a; Witjes 1996b; Witjes 1998a; and Rintala 1991 used weekly for four weeks and Krege 1996 used every two weeks instillations for 12 months.

Outcomes

Most data were available for time to recurrence (11 studies, 2616 participants), followed by adverse effects. Five studies reported time to death from any cause (Di Stasi 2003; Lamm 1995; Malmström 1999; Rintala 1991; Witjes 1998a; 1132 participants). Six studies provided information on time to progression (Di Stasi 2003; Lamm 1995; Malmström 1999; Ojea 2007a; Ojea 2007b; Witjes 1998a; 1622 participants). Reporting of adverse effects was inhomogeneous. Studies reported on 18 different adverse effects. Only one study aimed at evaluating quality of life in these participant groups (Michielsen 2013). Information was only available in abstract form (conference proceeding) and hence gave no further insights.

Funding sources and conflicts

Three studies had at least one coauthor with a financial relationship with a company or the study was at least partly financed by a company (Di Stasi 2003; Friedrich 2007; Malmström 1999). Four studies provided no information on funding (Mangiarotti 2008; Michielsen 2013; Ojea 2007b; Witjes 1996a).

Excluded studies

A list of 95 excluded studies is in the Characteristics of excluded studies table.

Risk of bias in included studies

The Characteristics of included studies table, Figure 2, and Figure 3 show the detailed risk of bias evaluation. In summary, unclear or incomplete reporting in primary studies seriously hindered definitive risk of bias assessment.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

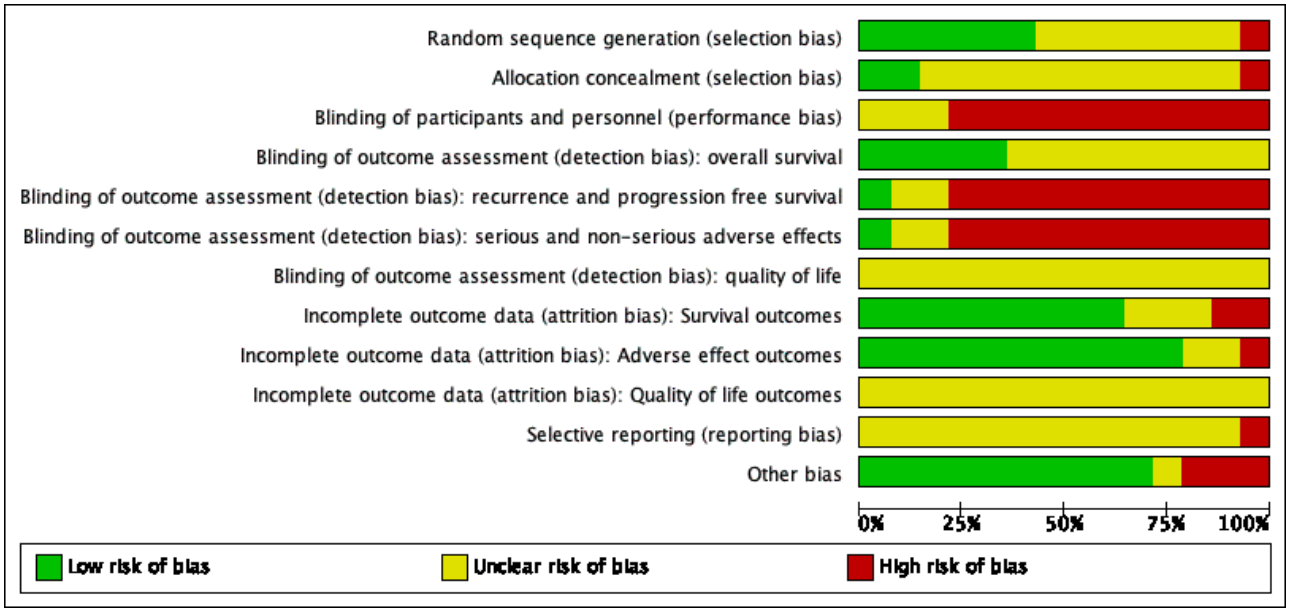


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

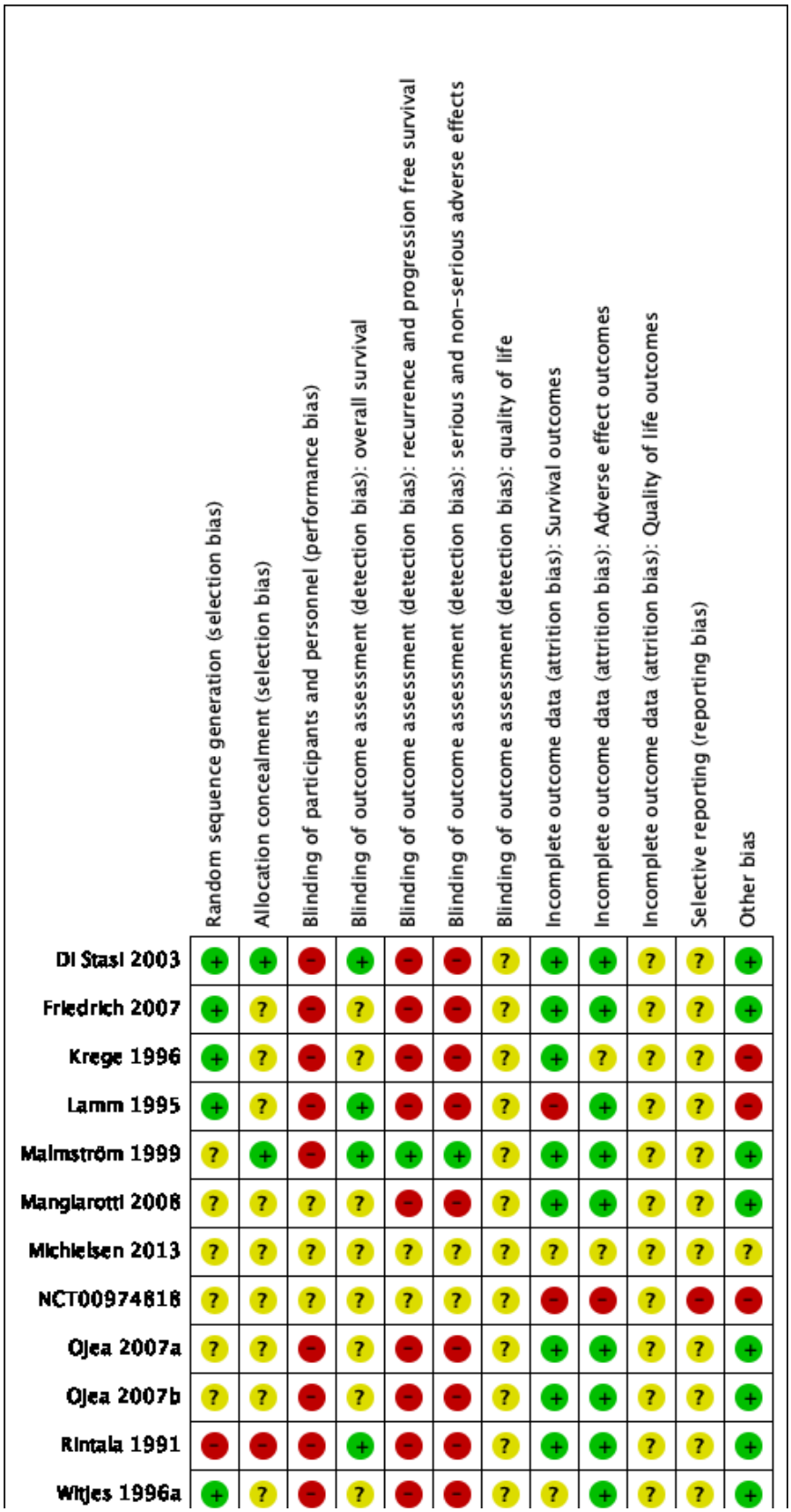
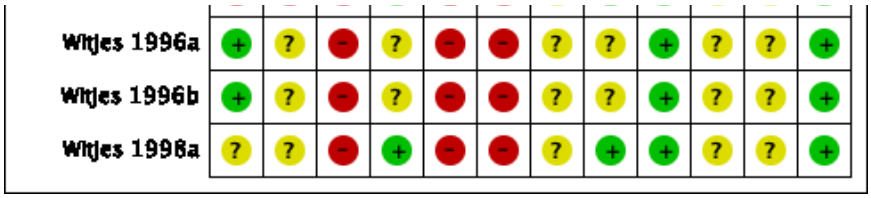


Figure 3. (Continued)



Allocation

Random sequence generation

Malmström 1999; Mangiarotti 2008; Michielsen 2013; NCT00974818; Ojea 2007b; Ojea 2007a; and Witjes 1998a had unclear random sequence generation. One study randomised participants to treatment arms, but based allocation on date of birth and so was judged at high risk of bias (Rintala 1991). The remaining studies had low risk of random sequence generation (Di Stasi 2003; Friedrich 2007; Krege 1996; Lamm 1995; Witjes 1996a; Witjes 1996b).

Allocation concealment

Most studies did not report allocation concealment and, therefore, this domain was at unclear risk of bias (Friedrich 2007; Krege 1996; Lamm 1995; Mangiarotti 2008; Ojea 2007a; Witjes 1996a; Witjes 1996b; Witjes 1998a). Only Di Stasi 2003 and Malmström 1999 reported the method for allocation concealment, which was adequate and at low risk. Rintala 1991 was at high risk as participant selection was based on date of birth, which might have influenced the concealment of the allocation.

Blinding

Blinding of participants and personnel

None of the studies reported that blinding was done. Given that blinding is a well-known mechanism to reduce bias in trials, we assumed that if blinding was not reported, it was not done. Therefore, we judged this domain at high risk of bias for most outcomes. For the clinical trial entry (NCT00974818) and the study that was only available as conference proceeding (Michielsen 2013), we rated this domain as unclear.

Blinding of outcome assessment

We judged that a lack of blinding had no effect on assessment of objective outcomes, such as survival or death. For the studies that evaluated time to death from any cause, this domain was rated at low risk of bias, although blinding was not performed.

For outcomes based on a more subjective assessment (time to recurrence and time to progression, adverse effects and serious adverse effects), we judged this domain at high risk of bias.

Only one study assessed quality of life (Michielsen 2013), Unfortunately, the conference proceeding did not provide sufficient information on trial methodology and conduct. Therefore, all studies were at unclear risk of bias for quality of life.

Incomplete outcome data

Most studies clearly reported participant flow and there was no indication of important attrition bias.

Time-to-event outcomes

In the study of Lamm 1995 there was a concern regarding the time to death from any cause outcomes as only 85% (BCG) and 84% (MMC) of participants were included in the analyses. In NCT00974818, there was no analysis for time to death from any cause due to a lack of accrual. Also, the number of participants throughout the website entry was not congruent. Thus, we rated it at high risk of bias.

Adverse effect outcomes

The only concern was in the NCT00974818 study where the number of participants throughout the website entry was not congruent, which might indicate a possible bias. In the Krege 1996 study, there was no precise information on the number of patients included in this analysis. In the conference proceeding of Michielsen 2013 there is insufficient information to rate the bias due to attrition.

Quality of life outcomes

One study assessed quality of life but the conference proceeding gave no detailed results and was at high risk of bias (Michielsen 2013). Therefore, all studies were at unclear risk of bias.

Selective reporting

Most studies had no study protocol available. Therefore, we judged this domain as unclear in all but one study (NCT00974818). In NCT00974818, there was no information why data on the primary outcome (relapse rate) were not reported but data on the secondary outcomes (adverse effects) were. Therefore, we rated this domain at high risk of bias.

Other potential sources of bias

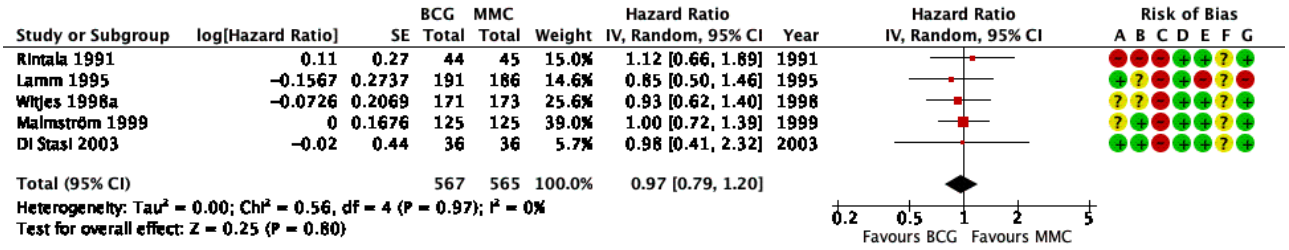
We identified no other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Bacillus Calmette-Guérin (BCG) compared to mitomycin C (MMC) for Ta and T1 bladder cancer

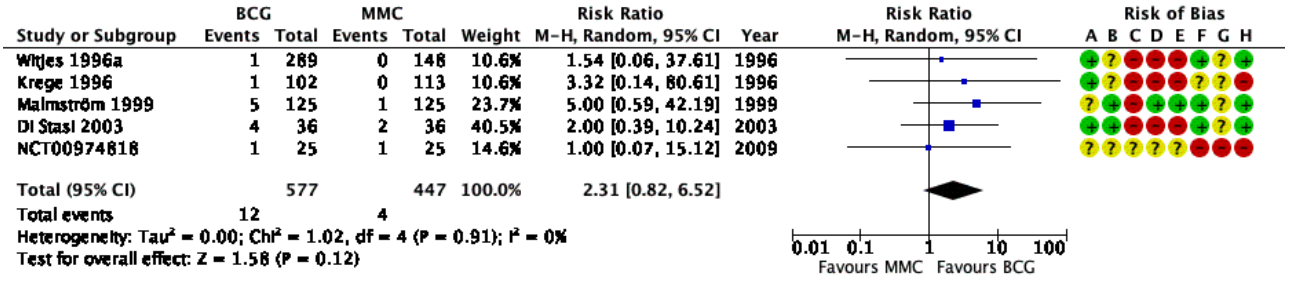
The effects of the intervention are presented in Summary of findings for the main comparison for the main outcomes. All other effects are presented in Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; and Figure 9. None of the included studies calculated the sample size with respect to time to death from any cause to achieve a certain power.

Figure 4. Forest plot of comparison: 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), outcome: 1.1 Time to death from any cause.



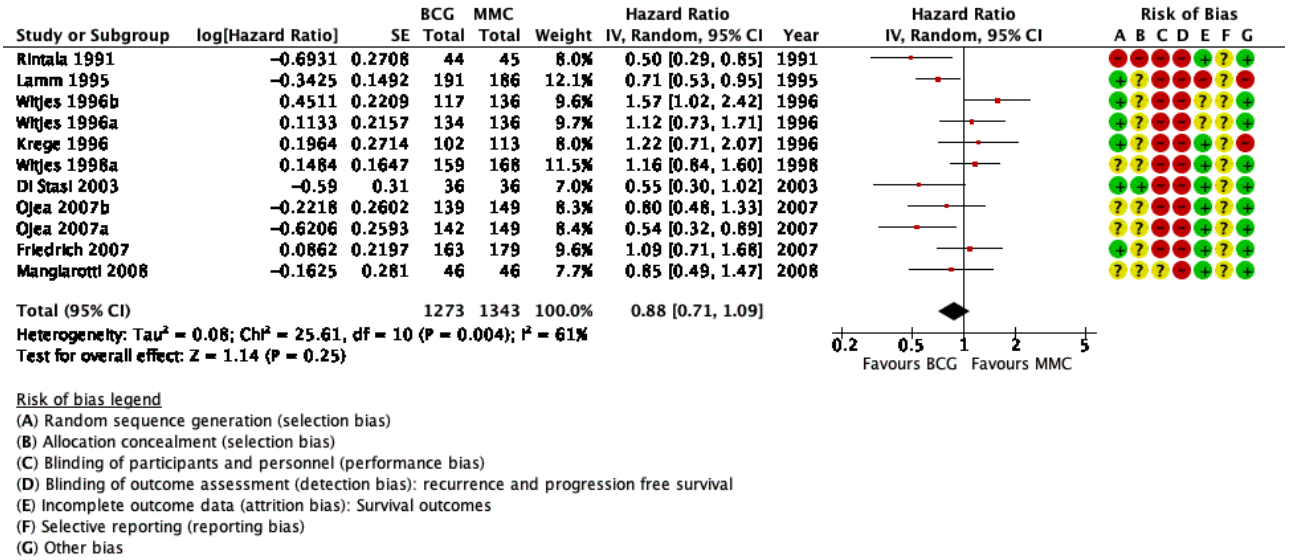
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): overall survival
(E) Incomplete outcome data (attrition bias): Survival outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 5. Forest plot of comparison: 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), outcome: 1.2 Serious adverse effects.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): recurrence and progression free survival
(E) Blinding of outcome assessment (detection bias): serious and non-serious adverse effects
(F) Incomplete outcome data (attrition bias): Adverse effect outcomes
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 6. Forest plot of comparison: 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), outcome: 1.3 Time to recurrence.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): recurrence and progression free survival
(E) Incomplete outcome data (attrition bias): Survival outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 7. Funnel plot of comparison: 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), outcome: 1.3 Time to recurrence.

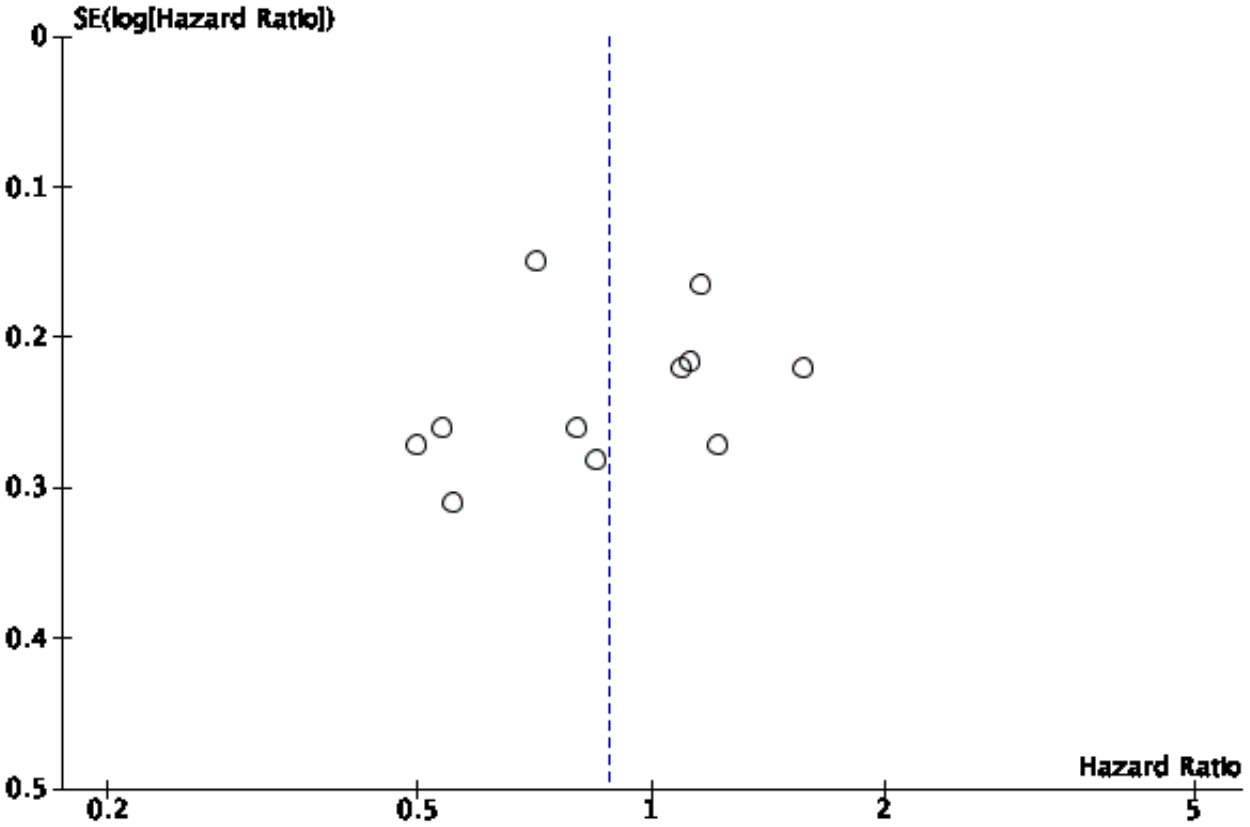
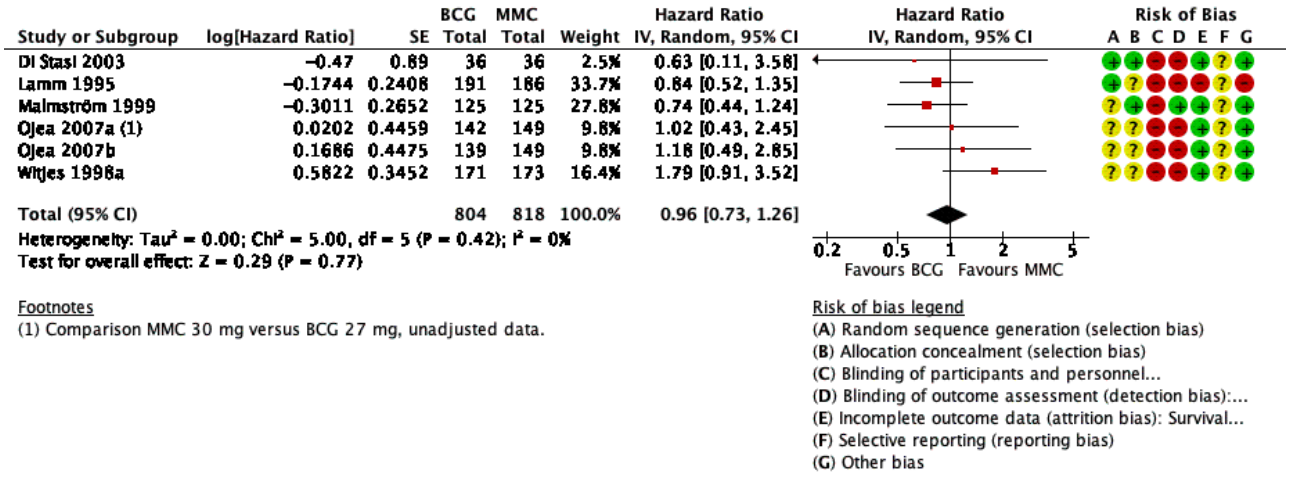


Figure 8. Forest plot of comparison: 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), outcome: 1.4 Time to progression.



Footnotes
(1) Comparison MMC 30 mg versus BCG 27 mg, unadjusted data.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel...
(D) Blinding of outcome assessment (detection bias):...
(E) Incomplete outcome data (attrition bias): Survival...
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 9. Forest plot of comparison: 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), outcome: 1.5 Adverse effects.

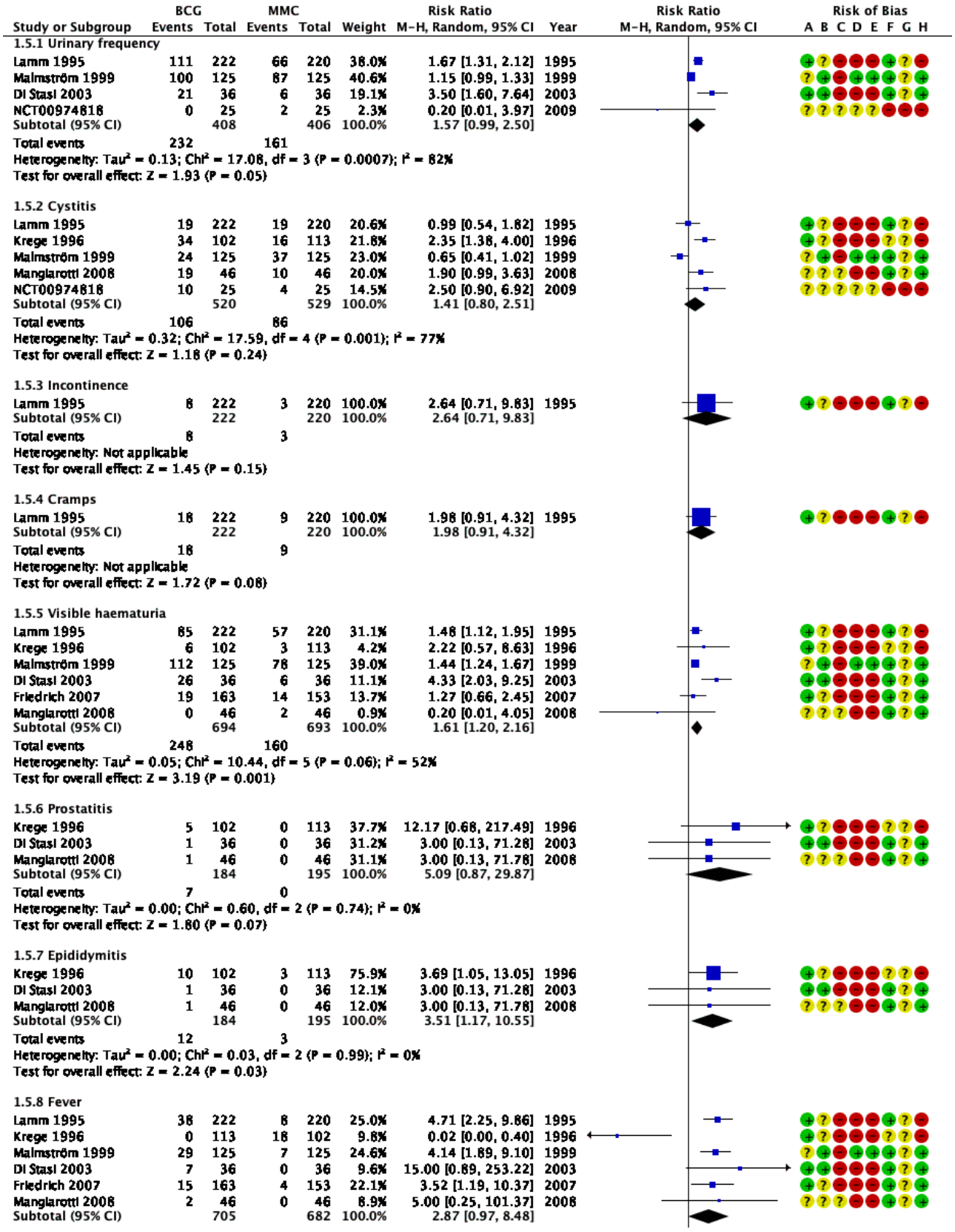


Figure 9. (Continued)

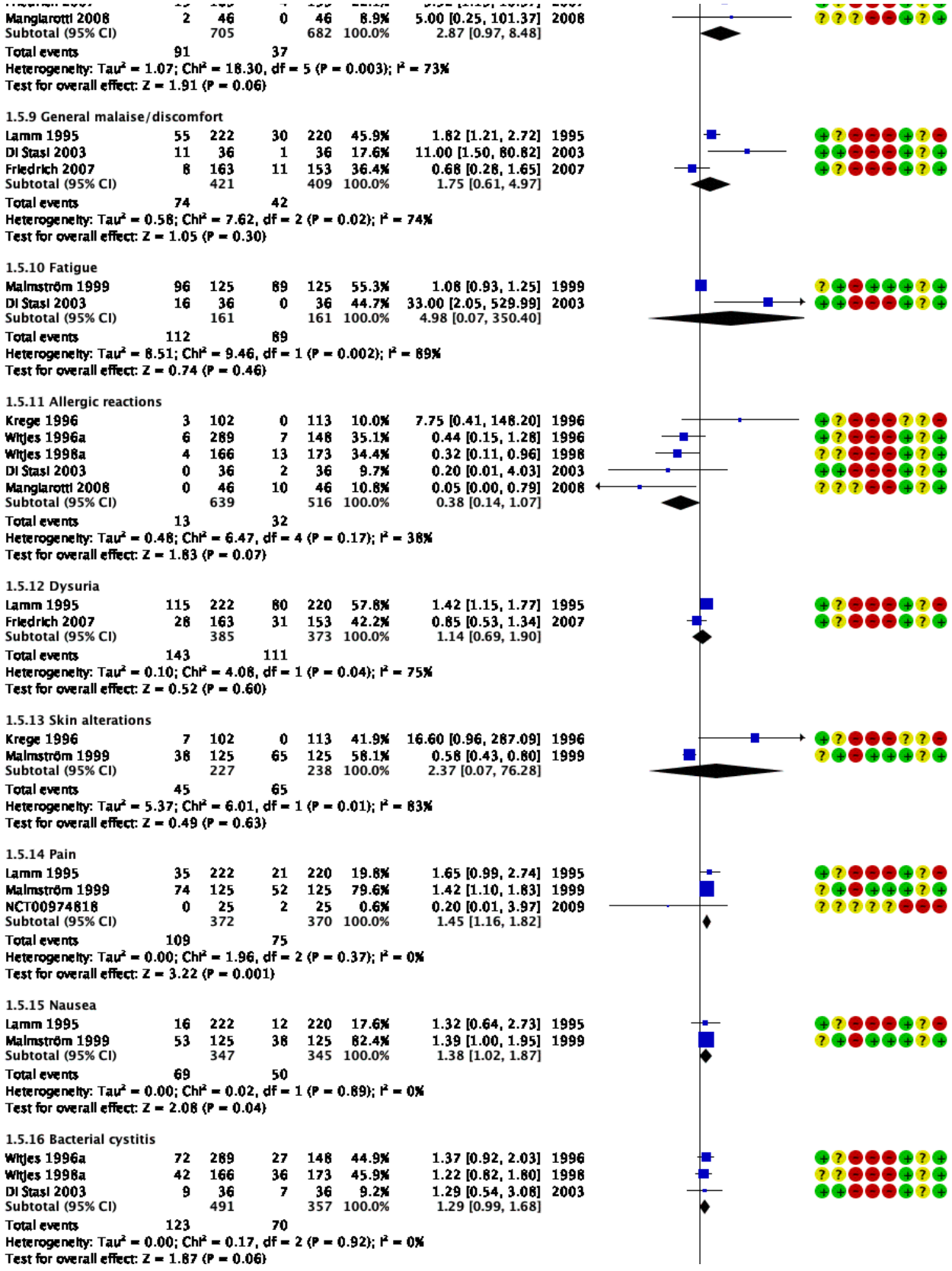
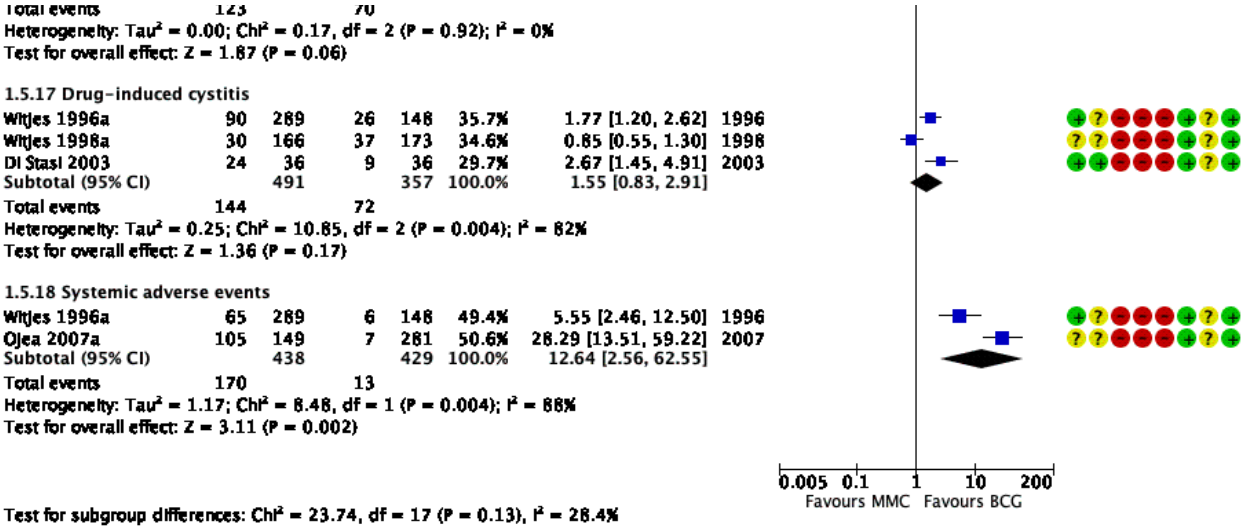


Figure 9. (Continued)



1 Bacillus Calmette-Guérin versus mitomycin C

1.1 Primary outcomes

1.1.1 Time to death from any cause

BCG may have little or no effect on time to death from any cause in adults with intermediate- and high-risk non-muscle invasive bladder cancer (HR 0.97, 95% CI 0.79 to 1.20; studies = 5, participants = 1132; 567 participants in the BCG arm and 565 in the MMC arm; I^2 = 0%; Analysis 1.1; Figure 4). This corresponds to six fewer deaths (40 fewer to 36 more) per 1000 participants with BCG at five years.

Certainty of the evidence was low because of study limitations (performance bias and allocation concealment) and imprecision (the CIs were wide with a possibility for either important benefit or harm). The results are based on study data with different lengths of follow-up (3.5 to 20 years).

1.1.2 Serious adverse effects

Twelve of 577 participants on BCG had serious non-fatal adverse effects compared to four of 447 participants in the MMC group. BCG may increase the risk of experiencing a serious adverse event. The pooled RR was 2.31 (95% CI 0.82 to 6.52; studies = 5, participants = 1024; I^2 = 0%; Analysis 1.2; Figure 5); although BCG may increase the risk for serious adverse effects compared to MMC, the 95% CI includes the possibility of no difference. This corresponds to nine more serious adverse effects (1 fewer to 37 more) with BCG. Certainty of the evidence was low because of study limitations (performance bias and allocation concealment) and the CIs were wide and were consistent with both no effect and clinically relevant harm). Length of follow-up among the studies ranged from 1.6 to 10 years.

1.2 Secondary outcomes

1.2.1 Time to recurrence

Pooled data demonstrated a 12% hazard reduction over time for BCG (HR 0.88, 95% CI 0.71 to 1.09; studies = 11, participants = 2616; 1273 participants in the BCG arm and 1343 in the MMC arm; I^2 = 61%; Analysis 1.3; Figure 6). This corresponds to 41 fewer recurrences (104 fewer to 29 more) with BCG at five years. These data are based on a follow-up from 3 to 20 years.

Certainty of the evidence was low because of study limitations (performance bias and allocation concealment), the CIs were imprecise (possibility for either important benefit or large harm), and the results of the point estimates of primary studies varied substantially and showed inconsistency. In aggregate, we downgraded twice. The funnel plot showed no asymmetry (Figure 7). Hence, we did not downgrade for publication bias.

1.2.2 Time to progression

BCG may have little to no effect on time to progression in adults with intermediate- and high-risk non-muscle invasive bladder cancer (HR 0.96, 95% CI 0.73 to 1.26; studies = 6, participants = 1622; 804 participants in the BCG arm and 818 in the MMC arm; I^2 = 0%; Analysis 1.4; Figure 8). This corresponds to four fewer progressions (29 fewer to 27 more) with BCG at five years. Certainty of the evidence was low because of study limitations (performance bias and allocation concealment) and the CIs were imprecise (possibility for both important benefit or large harm). Length of follow-up ranged from 1.6 to 20 years.

1.2.3 Adverse effects

Reporting of adverse effects was heterogeneous in the included studies. The studies reported 18 different adverse effects. Adverse events were as follows (Analysis 1.5; Figure 9):

- urinary frequency: RR 1.57, 95% CI 0.99 to 2.50; studies = 4, participants = 814; I^2 = 82%;
- cystitis: RR 1.41, 95% CI 0.80 to 2.51; studies = 5, participants = 1049; I^2 = 77%;
- incontinence: RR 2.64, 95% CI 0.71 to 9.83; studies = 1, participants = 442; I^2 = 0%;
- cramps: RR 1.98, 95% CI 0.91 to 4.32; studies = 1, participants = 442; I^2 = 0%;
- visible haematuria: RR 1.61, 95% CI 1.20 to 2.16; studies = 6, participants = 1387; I^2 = 52%;
- prostatitis: RR 5.09, 95% CI 0.87 to 29.87; studies = 3, participants = 379; I^2 = 0%;
- epididymitis: RR 3.51, 95% CI 1.17 to 10.55; studies = 3, participants = 379; I^2 = 0%;
- fever: RR 2.87, 95% CI 0.97 to 8.48; studies = 6, participants = 1387; I^2 = 73%;
- general malaise/discomfort: RR 1.75, 95% CI 0.61 to 4.97; studies = 3, participants = 830; I^2 = 74%;
- fatigue: RR 4.98, 95% CI 0.07 to 350.40; studies = 2, participants = 322; I^2 = 0%;
- allergic reactions: RR 0.38, 95% CI 0.14 to 1.07; studies = 5, participants = 1155; I^2 = 38%);
- dysuria: RR 1.14, 95% CI 0.69 to 1.90; studies = 2, participants = 758; I^2 = 75%);
- skin alterations: RR 2.37, 95% CI 0.07 to 76.28; studies = 2, participants = 465; I^2 = 83%);
- pain: RR 1.45, 95% CI 1.16 to 1.82; studies = 3, participants = 742; I^2 = 0%);
- nausea: RR 1.38, 95% CI 1.02 to 1.87; studies = 2, participants = 692; I^2 = 0%);
- bacterial cystitis: RR 1.29, 95% CI 0.99 to 1.68; studies = 3, participants = 848; I^2 = 0%);
- drug-induced cystitis: RR 1.55, 95% CI 0.83 to 2.91; studies = 3, participants = 848; I^2 = 82%);
- systemic adverse effects: RR 12.64, 95% CI 2.56 to 62.55; studies = 2, participants = 867; I^2 = 88%).

1.2.4 Quality of life

One study evaluated quality of life (Michielsen 2013). Information was only available as a conference proceeding. The study used the EORTC-BLS-24 instrument. There were no statistical differences when comparing groups, except for abdominal bloating and flatulence, which was worse in the BCG group.

More detailed results on quality of life were not available.

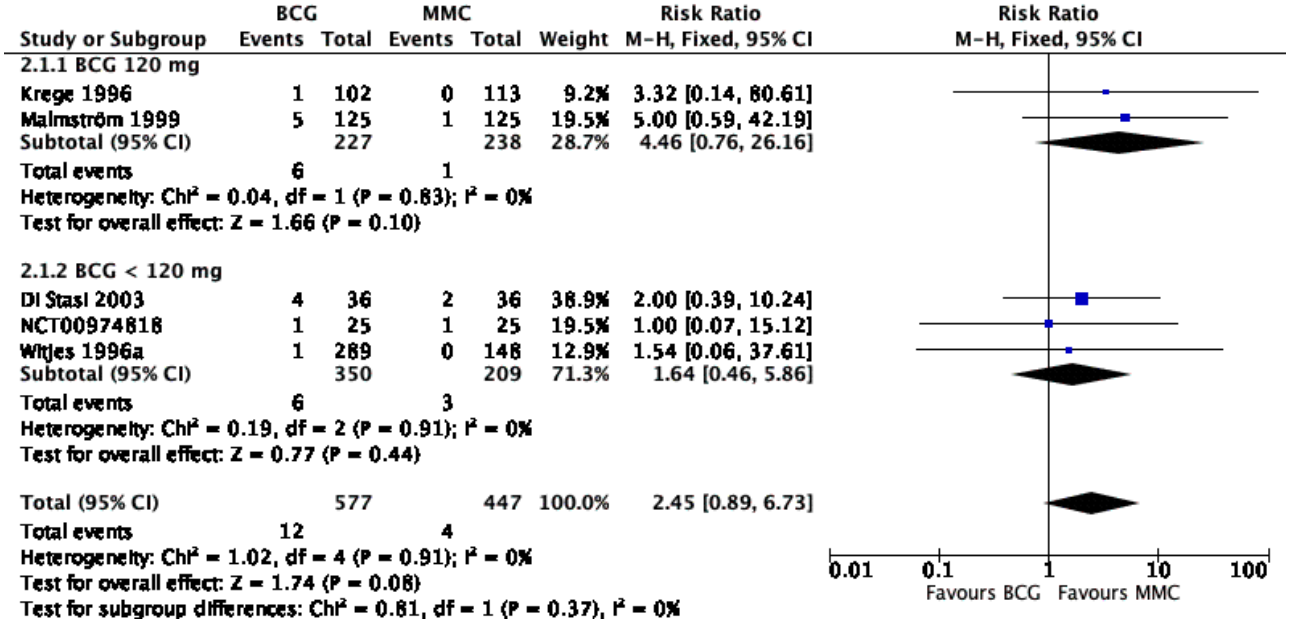
2 Subgroup analyses

Below we present the results of the subgroup analyses. All other initially planned subgroup analyses could not be conducted due to a lack of data.

2.1 Different doses of Bacillus Calmette-Guérin installations (subgroup analyses)

In Analysis 2.1, we tested the effect of different doses of BCG on serious adverse effects. Compared to MMC, BCG 120 mg (RR 4.46, 95% CI 0.76 to 26.16; studies = 2, participants = 465; I^2 = 0%) showed higher serious adverse effects than BCG administered in lower doses (less than 120 mg: RR 1.64, 95% CI 0.46 to 5.86; studies = 3, participants = 559; I^2 = 0%). The difference of the subgroup test showed no statistical difference (P = 0.37, I^2 = 0%). This was the only subgroup analysis possible in this context. Results are shown graphically in Figure 10.

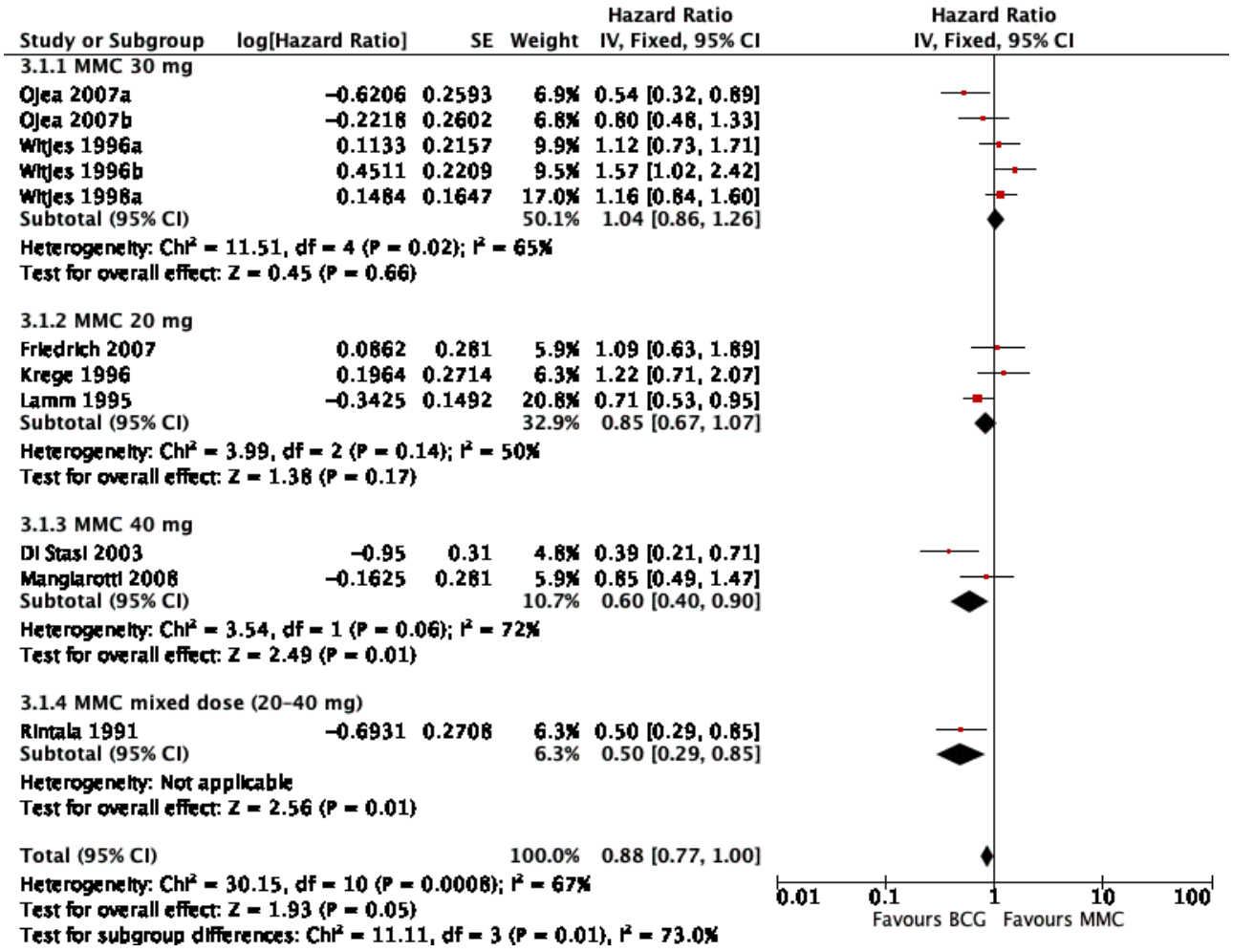
Figure 10. Forest plot of comparison: 2 Different doses of Bacillus Calmette-Guérin (BCG) (subgroup analyses), outcome: 2.1 Serious adverse effect (subgroup analyses).



2.2 Different doses of mitomycin C installations (subgroup analyses)

In Analysis 3.1, we tested the effect of different doses of MMC on time to recurrence (see Figure 11). Compared to BCG, MMC 30 mg (HR 1.04, 95% CI 0.86 to 1.26; studies = 5, participants = 0; I^2 = 65%) showed little or no effect compared to MMC 20 mg (HR 0.85, 95% CI 0.67 to 1.07; studies = 3, participants = 0; I^2 = 50%). MMC 40 mg had a longer time to recurrences (HR 0.60, 95% CI 0.40 to 0.90; studies = 2, participants = 0; I^2 = 72%), but data were based on two studies with high heterogeneity. The difference of the subgroup test showed statistical difference (P = 0.01, I^2 = 73%). This was the only outcome we could address.

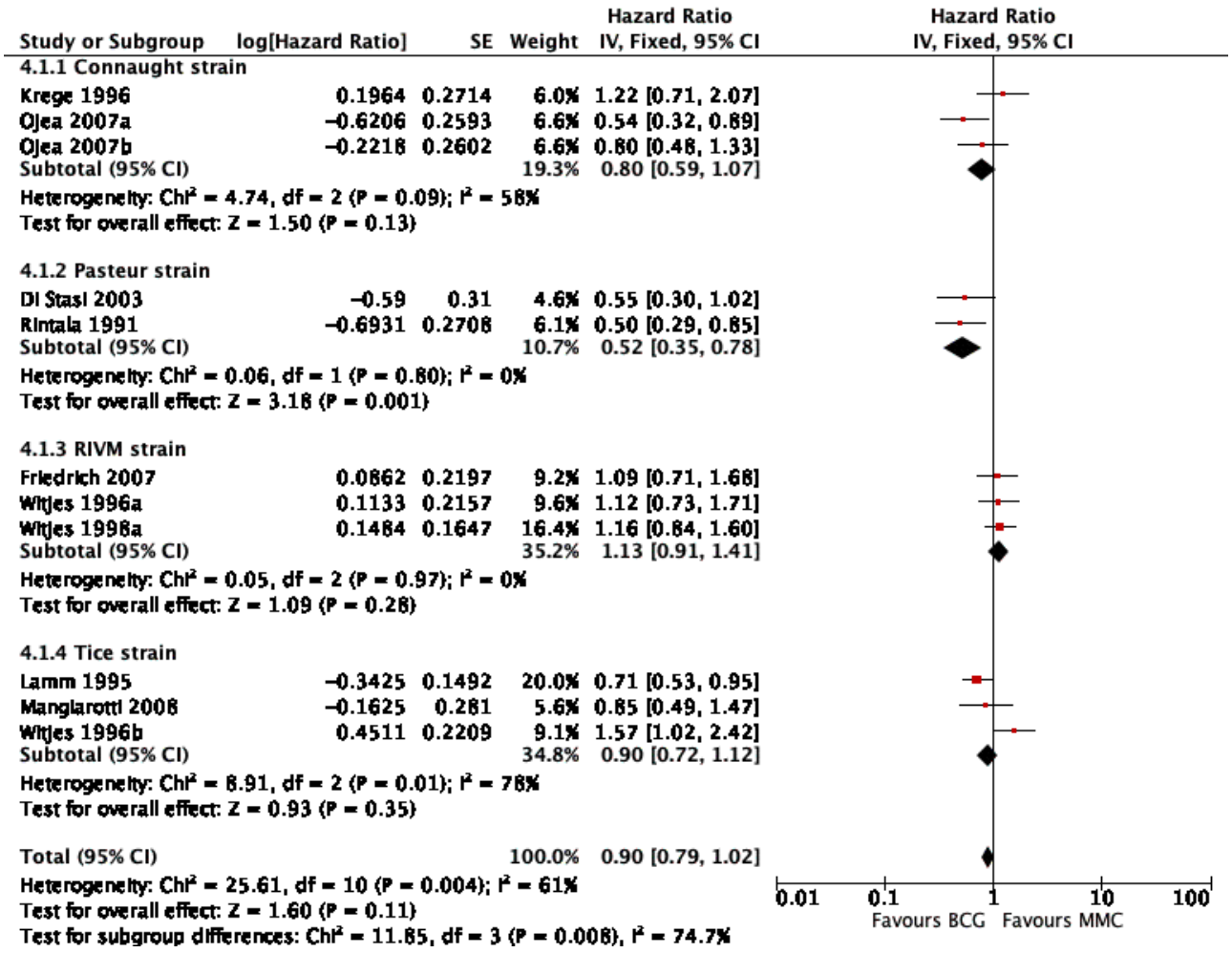
Figure 11. Forest plot of comparison: 3 Different doses of mitomycin C (MMC) (subgroup analyses), outcome: 3.1 Time to recurrence (subgroup analyses).



2.3 Different strains of Bacillus Calmette-Guérin (subgroup analyses)

In Analysis 4.1, we tested the effect of different BCG strains compared to MMC on time to recurrence. Findings suggested that there might be relevant differences among BCG strains regarding time to recurrence. Especially the Pasteur strain, but also the Connaught and Tice strains showed some effects on recurrence. The RIVM strain might be less effective. Results are presented in Figure 12.

Figure 12. Forest plot of comparison: 4 Different Bacillus Calmette-Guérin (BCG) strains (subgroup analyses), outcome: 4.1 Time to recurrence (subgroup analyses).



- Connaught strain: HR 0.80, 95% CI 0.59 to 1.07; studies = 3; I^2 = 58%.
- Pasteur strain: HR 0.52, 95% CI 0.35 to 0.78; studies = 2; I^2 = 0%.
- RIVM strain: HR 1.13, 95% CI 0.91 to 1.41; studies = 3; I^2 = 0%.
- Tice strain: HR 0.90, 95% CI 0.72 to 1.12; studies = 3; I^2 = 78%.

The test for subgroup differences was statistically significant (P = 0.008, I^2 = 74.7%).

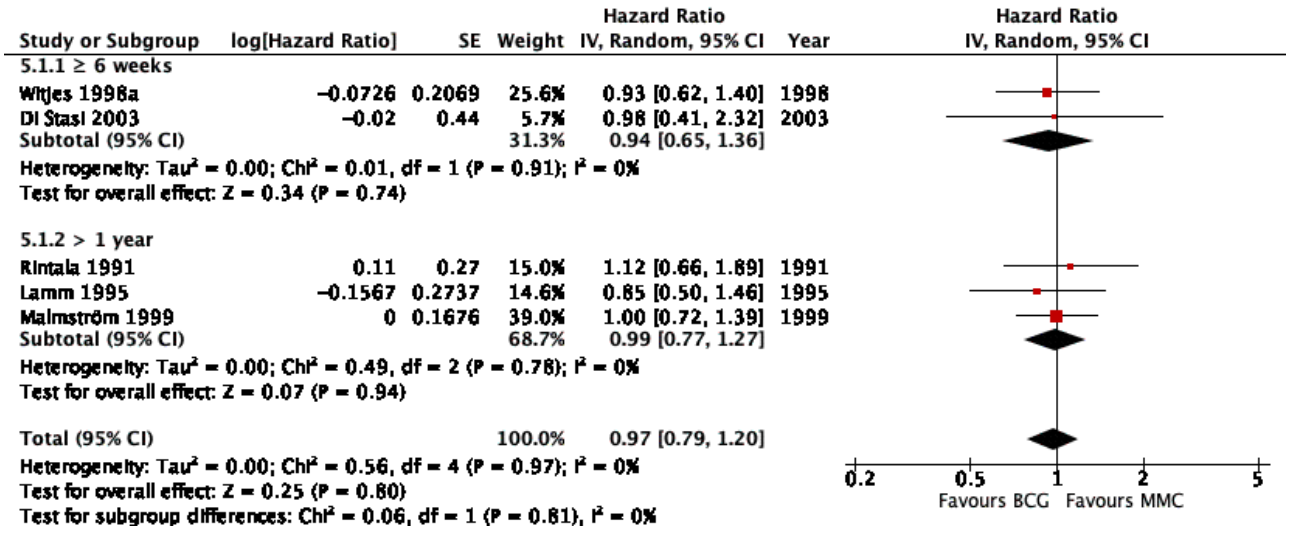
2.4 Different Bacillus Calmette-Guérin maintenance therapies (subgroup analyses)

In Analysis 5.1; Analysis 5.2; Analysis 5.3; and Analysis 5.4, we tested the effect of different BCG maintenance therapies between each other. We compared induction regimens (six weeks or greater) versus maintenance regimens (greater than one year).

2.4.1 Time to death from any cause

Figure 13 shows the results of the time to death from any cause analysis. Results were as follows: six weeks or greater: HR 0.94, 95% CI 0.65 to 1.36; studies = 2, participants = 416; greater than one year group: HR 0.99, 95% CI 0.77 to 1.27; studies = 3, participants = 339 (Analysis 5.1). The test for subgroup effect was not significant (P = 0.81).

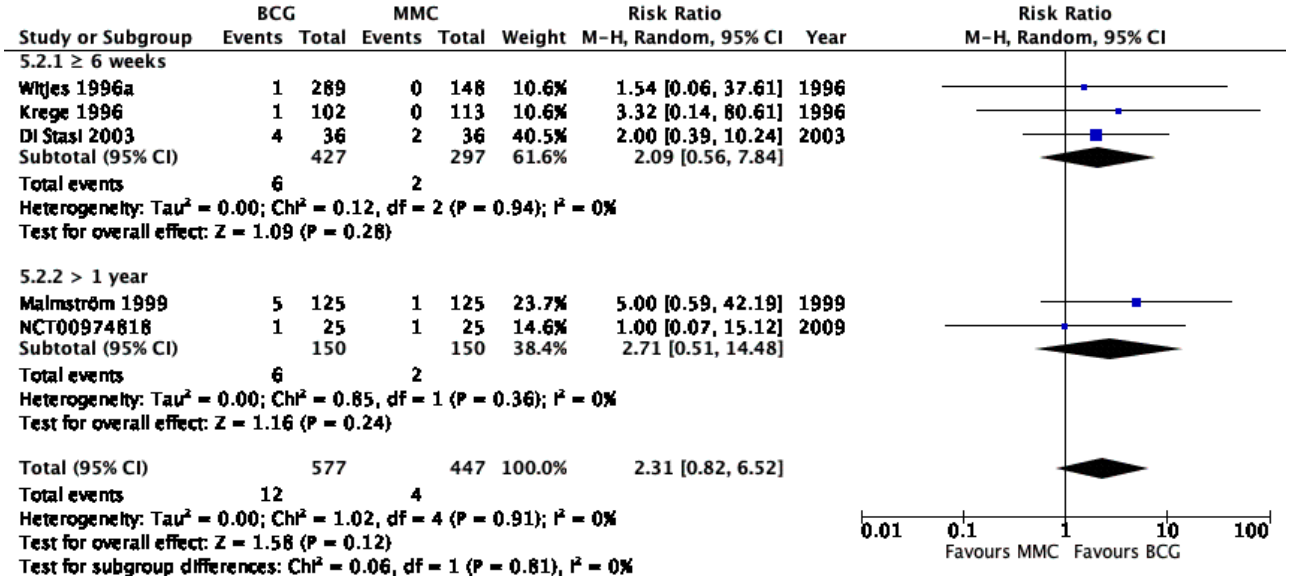
Figure 13. Forest plot of comparison: 5 Different maintenance therapies (posthoc subgroup analyses), outcome: 5.1 Time to death from any cause.



2.4.2 Serious adverse effects

Results for the subgroup analyses for serious adverse effects were as follows: BCG induction therapy six weeks or greater: RR 2.09, 95% CI 0.56 to 7.84; studies = 3, participants = 724; I^2 = 0%); BCG maintenance therapy greater than one year: RR 2.71, 95% CI 0.51 to 14.48; studies = 2, participants = 300; I^2 = 0%) (Analysis 5.2; Figure 14). The test for subgroup effect was not significant (P = 0.81).

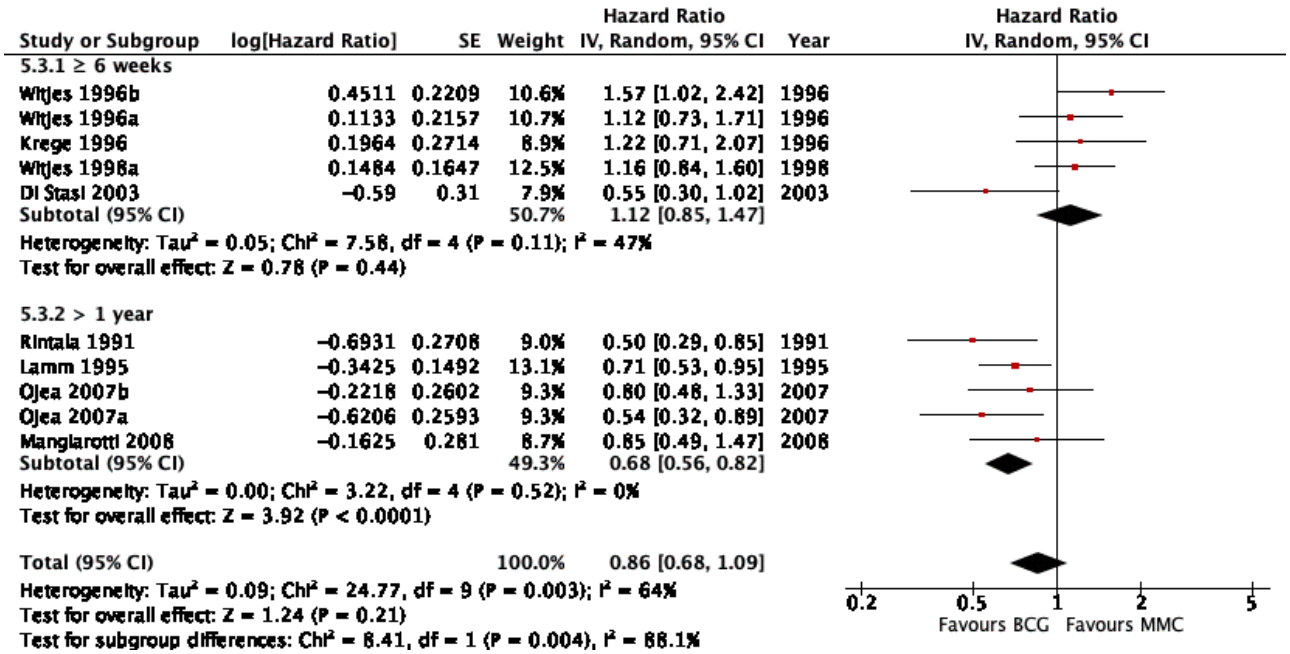
Figure 14. Forest plot of comparison: 5 Different maintenance therapies (posthoc subgroup analyses), outcome: 5.2 Serious adverse effects (greater than six weeks).



2.4.3 Time to recurrence

Eight studies reported data on time to recurrence for this subgroup analysis. Results were as follows: six weeks or greater group (HR 1.12, 95% CI 0.85 to 1.47; participants = 1137; studies = 4; Analysis 5.3; Figure 15). BCG maintenance therapy greater than one year (HR 0.68, 95% CI 0.56 to 0.82; studies = 4, participants = 89). The test for subgroup effect was significant (P = 0.004), but showed high heterogeneity (I^2 = 88%).

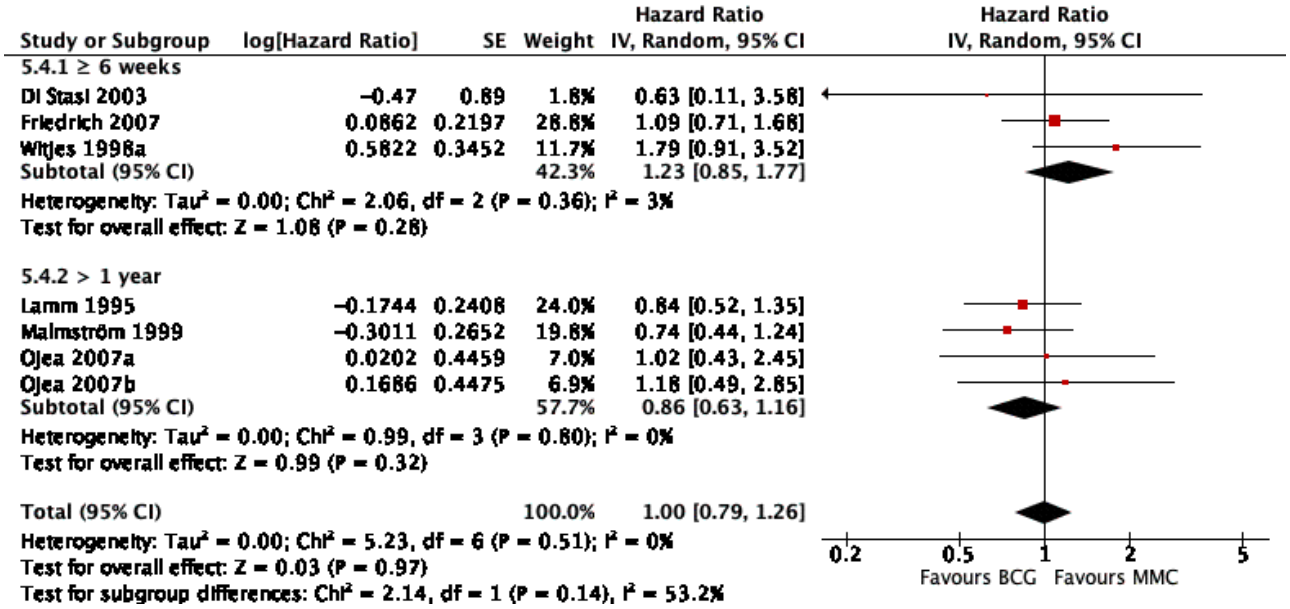
Figure 15. Forest plot of comparison: 5 Different maintenance therapies (posthoc subgroup analyses), outcome: 5.3 Time to recurrence.



2.4.4 Time to progression

Six studies reported data on time to progression for this subgroup analysis. Results were as follows: six weeks or greater group (HR 1.23, 95% CI 0.85 to 1.77; participants = 416; studies = 3); BCG maintenance therapy greater than one year (HR 0.86, 95% CI 0.63 to 1.16; studies = 3, participants = 250). The test for subgroup effect was not significant (P = 0.14; Analysis 5.4; Figure 16).

Figure 16. Forest plot of comparison: 5 Different maintenance therapies (posthoc subgroup analyses), outcome: 5.4 Time to progression.



3 Sensitivity analyses

The use of the fixed-effect model compared to the random-effect model showed no relevant differences (data not shown). Friedrich 2007 only reported summary data for time to recurrence. In a sensitivity analysis using the BCG six weeks arm versus the MMC three years arm for Friedrich 2007 (instead of MMC six weeks arm; adjusted HR 2.87, 95% CI 1.67 to 4.90) resulted in an overall HR of 0.95 (95% CI 0.71 to 1.26; I^2 = 76%; random-effect model) and thus a smaller treatment difference for recurrence-free survival.

DISCUSSION

Summary of main results

This latest update of a prior Cochrane Review (Shelley 2003) on the question of BCG versus MMC for people with intermediate- or high-grade non-muscle invasive bladder tumours based on 12 RCTs provides evidence of low certainty for all outcomes except quality of life to inform clinical and health policy decision-making.

Data suggested that BCG probably reduces the risk of recurrence over time (450 recurrences per 1000 participants treated with MMC and 41 fewer recurrences with BCG), but may result in more serious adverse effects (7 serious adverse effects per 1000 participants treated with MMC and 9 more serious adverse effects with BCG). BCG may have little or no effect on time to death from any cause or time to progression. Studies reported several adverse effects with BCG and MMC treatment. We found no available RCT evidence for quality of life.

Overall completeness and applicability of evidence

This review was based on 12 RCTs of people with intermediate- and high-risk non-muscle invasive bladder tumours. Results were based on a systematic literature search including several databases. Two review authors assessed studies for inclusion and evaluated the certainty of the evidence. The characteristics of participants and treatments are likely to reflect daily clinical practice. Thus, included studies provide direct evidence to the review question.

The first Cochrane Review on this topic was published in 2003 (Shelley 2003), and included seven trials based on 1901 participants. This review update includes further five trials and was based on 3080 participants. It now reflects also the current Cochrane methodology, which includes the certainty of the evidence assessment according to the GRADE approach.

We identified substantial heterogeneity in our analyses (I^2 = 66% for the analyses of time to recurrence and I^2 = 77% for cystitis). This may be due to differences in study design (e.g. in length of follow-up, BCG strains used, treatment dosage and schedule) as well as due to different baseline risks for recurrence and progression of included participants.

In this review, we used the EAU risk categories, which differ from the risk categories set up by the American Urological Association (AUA). Applying the AUA risk categories would likely impact the results of this review.

We were unable to assess treatment effects between intermediate- and high-risk groups, which may differ.

Quality of the evidence

The judgement of low certainty of the evidence for all outcomes with available data means that further research is very likely to have an important impact on the confidence in the estimates of effects and is likely to change the estimates.

Of the 12 identified studies, six were planned and conducted in the 1990s and do not meet 2019s methodological quality standards. Only one trial was conducted after 2010 but results of this trial have not been published yet. One trial (recruitment 2009 to 2012) was closed prior to finalisation due to a lack of accrual. Blinding of participants did not take place in any of the 12 trials. General concerns, which led to downgrading, were study limitations (performance bias and allocation concealment), wide CIs resulting in imprecision (possibility for either important benefit or large harm) and study heterogeneity.

The availability of low-certainty evidence for non-muscle-invasive bladder cancer only is not surprising. One meta-analysis revealed that the evidence on transurethral resection versus transurethral resection plus chemotherapy (MMC and other) was also low to very low (Perlis 2013). Although this is not the study question addressed in the review here, it highlights similar methodological issues.

Potential biases in the review process

We conducted an extensive systematic literature search without language or publication date restrictions as well as a search in clinical trial registries for unpublished, planned or ongoing studies. Therefore, we have probably identified all relevant information on this topic. However, there is always a possibility that relevant publications may not have been identified.

This review follows standard Cochrane methodology including the latest MECIR standards. No funding was received for this review and the authors state that they have no financial conflicts of interests.

Agreements and disagreements with other studies or reviews

The Agency for Healthcare Research and Quality conducted a systematic review with quality evaluation of included evidence (AHRQ 2016). The authors identified no difference between BCG and MMC therapy for cancer recurrence (RR 0.95, 95% CI 0.81 to 1.11; 10 trials). This is in contrast to our results that included two additional studies (Michielsen 2013; Rintala 1991). Our findings suggested an effect (HR 0.88, 95% CI 0.71 to 1.09) although the CIs did cross the line of no effect. Based on a subgroup analysis, the AHRQ review further indicated a decreased risk for cancer recurrence using BCG versus MMC (RR 0.79, 95% CI 0.71 to 0.87; 5 trials). It found no difference between BCG and MMC for all-cause mortality, bladder cancer-specific mortality or progression (all-cause mortality: RR 0.94, 95% CI 0.83 to 1.0, 7 trials; bladder cancer-specific mortality: RR 0.77, 95% CI 0.54 to 1.10, 5 trials; progression: RR 0.88, 95% CI 0.66 to 1.17, 7 trials). However, BCG also increased the risk of local adverse events and fever when compared with MMC (AHRQ 2016).

One individual participant data meta-analysis based on 9/12 RCTs included in this review concluded that only when BCG was used in the form of maintenance therapy was it superior to MMC with regard to prevention of recurrences (Malmström 2009a). There was no meaningful difference between BCG and MMC unless treatment was stratified by the receipt of maintenance therapy. Also, there was no difference concerning overall survival, cancer-specific survival, and progression. The effect on recurrence for the BCG maintenance therapy group remained statistically significant independently of prior chemotherapy treatment (Malmström 2009a). Three per cent of included participants belonged to the low-risk group, 74% to the intermediate-risk group and 23% to the high-risk group (median follow-up of 4.4 years, maximum 17.7 years). This meta-analysis further concluded that the optimal strain, dosage and duration of BCG maintenance therapy remains unknown (Malmström 2009b).

One systematic review with network meta-analyses (including 65 trials of 12,246 participants) not limited to MMC as a comparator concluded that no definitive conclusion could be drawn regarding

superiority of a given BCG strain and recurrence reduction (Boehm 2017). Available clinical trials lack important methodological safeguards against bias; therefore, higher-quality head-to-head comparisons are needed to address this question (Boehm 2017; Miyazaki 2018). Our subgroup results suggested a relevant positive effect among BCG strains, especially for the Pasteur strain, but also for the Connaught and Tice strains on time to recurrence. The RIVM strain may be less effective. However, these subgroup analyses are based on few studies and few participants and should be interpreted with caution.

Differences in the results of existing systematic reviews might be due to differences in included participants of primary trials. The non-muscle invasive bladder cancer participant group is highly heterogeneous, and may include BCG-refractory, BCG-relapsing, BCG-intolerant and BCG-unresponsive participants (Packiam 2017). A mixture of these participants in trials can cause difficulty in interpreting the results, especially because some failure types such as BCG-relapsing participants have superior outcomes in comparison with others (Packiam 2017). Also, different dosing of BCG and MMC regimens (dosage and schedules) may result in heterogeneity of data, making it difficult to draw definite conclusions. Results should also be interpreted with caution due to the methodological limitations of primary studies as reflected in the low certainty of evidence rating.

Further administration modes have been developed and tested. Intravesical substances can be delivered via electromotive drug administration (EMDA). One small RCT demonstrated the efficacy of MMC using EMDA sequentially combined with BCG in people with high-risk tumours (Di Stasi 2006a). One Cochrane Review concluded that the use of EMDA to administer intravesical MMC may result in a delay in time to recurrence in selected participant populations, but that there is no information on serious adverse effects yet (Jung 2017). Hyperthermic intravesical chemotherapy administration can also be used for MMC delivery. This procedure increases the temperature of instilled MMC. This RCT compared one year of BCG with one year of MMC and microwave-induced hyperthermia in people with intermediate- and high-risk bladder cancer and found reduced time to recurrence at 24 months in the MMC group (Arends 2016). However, these newer techniques of application of MMC are not included in this review, which addresses the standard mode of administration.

There is also the option of sequential BCG and MMC administration, but there is still controversy about the effectiveness of this approach (AHRQ 2016; Kaasinen 2016; Solsona 2016). One phase III trial of high-risk participants is currently ongoing (NCT02948543). Furthermore, BCG and MMC efficacy and toxicity may depend on manufacturing components, which might influence participant outcomes.

Patient care might not always follow scientific evidence but is dependent on practical issues, such as supply shortages. Due to the current worldwide need of BCG and manufacturing problems in the past, there has been a delay in BCG supply for some countries (Abufaraj 2018; Cernuschi 2018). This issue has to be kept in mind when prospectively planning patient care. Therefore, BCG usage must be further studied to predict patients who respond most to BCG therapy, and to determine the optimal schedule and amount of BCG delivery per patient.

AUTHORS' CONCLUSIONS

Implications for practice

Treatment decisions and patient counselling for intermediate- and high-risk bladder cancer on choice of Bacillus Calmette-Guérin (BCG) or mitomycin C (MMC) is based on evidence of low certainty. BCG may improve time to recurrence but may not impact time to death from any cause or time to progression. Serious adverse events may be increased as might minor adverse events. There is no meaningful data concerning patient-reported quality of life.

Implications for research

High-quality randomised controlled trials in people with intermediate- and high-risk bladder cancer with adequate randomisation and blinding are warranted. They should address quality of life, adverse effects and time to progression to provide more reliable results for this patient population.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Di Stasi 2003

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** unclear **Study dates:** June 1994 to March 2001, follow-up 42–45 months **Participants randomly assigned:** 108 (36 in each group)
Participants	**Inclusion criteria:** • histologically confirmed multifocal Cis • concurrent pT1 papillary transitional cell carcinoma • adequate bone marrow reserve, normal renal function, normal liver function • Karnofsky performance score 50–100 **Exclusion criteria:** • prior carcinoma of the bladder or upper urinary tract, or both • other malignancies within 5 years of registration • pregnancy
Interventions	**Group A:** MMC 40 mg with 960 mg excipient saline dissolved in 100 mL water instilled and retained in the bladder for 60 minutes **Group B:** 81 mg wet weight (mean 10.2, SEM 9.0 × 10^8 cfu) intravesical Pasteur BCG. Lyophilised BCG was suspended in 50 mL bacteriostatic-free saline 0.9% solution. Instillations retained for 120 minutes. **Group C:** MMC 40 mg with 960 mg excipient saline dissolved in 100 mL water instilled and retained in the bladder for 30 minutes with 20 mA pulsed electric current (600 mA minute) **Procedure:** • all groups were scheduled to receive an initial 6 intravesical treatments at weekly intervals commencing approximately 3 weeks after multiple biopsy/TUR procedures; • participants who had a complete response to the initial 6 weekly treatments underwent a further 10 monthly instillations; • if cancer persisted at 3 months, a second 6-week course was given. If disease persisted at 6 months, there was a cross-over to a 6-week second-line course of BCG for participants in the 2 MMC groups and electromotive MMC for participants in the BCG group.
Outcomes	Time to first recurrence, time to progression, time to death from any cause, adverse effects
Funding sources	Supported by grants Progetti di Ricerca di Ateneo ex 60% 1999–2000 and 2000–2001 from Tor Vergata University of Rome. Electromotive equipment provided by Physion Srl, Medolla, Italy.
Declarations of interest	No interest, except 1 coauthor, who reported financial interest with the company.
Notes	53 participants underwent cross-over: 25 with electromotive MMC and 15 with MMC switched to a 6-week BCG course; 13 with BCG failure switched to electromotive MMC. Here we only considered the

Di Stasi 2003 *(Continued)*

MMC data with passive administration, not the electromotive MMC data. 1 of the study authors declared financial interest with the company providing the electromotive equipment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization and data collection were performed using a central computer." Comment: we assumed a low risk for the domain.
Allocation concealment (selection bias)	Low risk	Quote "Randomization and data collection were performed using a central computer. Patients were allocated to 1 of 3 treatment arms by blocked randomisation across 8 (2x2x2) strata resulting from 3 factors, namely Tis [Cis] only vs Tis with concurrent T1 papillary tumours, grades III vs II concurrent T1 papillary tumours and multifocal vs unifocal concurrent T1 papillary tumours." Comment: we assumed a low risk for the domain.
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Low risk	Comment: no information on blinding. We assumed that there was no blinding but that the absence of blinding had not affected this objective outcome.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: all randomised participants (72/72) were considered in the analyses. Participant flow was clearly reported.
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all randomised participants (72/72) were considered in the analyses. Participant flow is clearly reported.
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.

Di Stasi 2003 *(Continued)*

Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Friedrich 2007

Methods	**Study design:** multicentre, prospective, randomised open-label clinical trial **Number of study centres:** unclear **Study dates:** 1995–2002, follow-up 2.9 years **Participants randomly assigned:** 495
Participants	**Inclusion criteria:** • histologically confirmed primary transitional cell carcinoma of the bladder or tumour recurrence after TUR without prior adjuvant therapy with intermediate-risk pTa G1 tumour (size > 3 cm, recurrent or multifocal tumour) or pTa G2 up to pT1 tumour (G1–3) • pT1 G3 tumours in case of a unifocal small tumour (diameter 2.5 cm) **Exclusion criteria:** • muscle-invasive tumour or a concomitant Cis • evidence of lymph node or distant metastasis • pT1 G3 tumour > 2.5 cm • pregnancy, mental disease, reduced kidney function or a second malignant disease
Interventions	**Group A:** 6 weekly instillations of MMC 20 mg (MMC 6 week) **Group B:** 6 weekly instillations of BCG RIVM (BCG 6 week) **Group C:** 6 weekly instillations of MMC 20 mg followed by monthly instillations of MMC 20 mg for 3 years (MMC 3 years) **Procedure:** • instillation was performed with a volume of 20 mL after emptying the bladder; • participants received 20 mg of MMC or RIVM 2 10^8 cfu; • adjuvant intravesical therapy was started 4 weeks after TUR (after second TUR in case of a pT1 tumour). In case of recurrence, treatment was stopped.
Outcomes	Recurrence-free survival, adverse effects
Funding sources	Quote: "The work was supported in part by Fa. Medac GmbH, Wedel, Germany. Dr Pichlmeier is an employee of Medac GmbH."
Declarations of interest	Quote: "None of the authors will benefit financially from the publication of the manuscript."
Notes	Quote: "None of the authors will benefit financially from the publication of the manuscript. The work was supported in part by Fa. Medac GmbH, Wedel, Germany. Dr Pichlmeier is an employee of Medac GmbH." Our meta-analyses included groups A and B. Group C was considered in the sensitivity analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement

Friedrich 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by use of a stratified permuted block randomisation scheme, balanced for treatment groups. Stratification was performed by hospital or private urologists." Comment: therefore, we assumed this item to be of low risk for bias.
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not reported.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: all participants were considered in the analysis (Group A 179/179, Group B 163/163, Group C 153/153).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants were considered in the analyses (Group A 179/179, Group B 163/163, Group C 153/153).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Krege 1996

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** 14 **Study dates:** August 1985 to September 1992, follow-up 20.2 months

Krege 1996 *(Continued)*

	Participants randomly assigned: 327
Participants	**Inclusion criteria:** • histologically confirmed stage pTa/T1 grades 1–3 bladder cancer • complete resection of tumour, inconspicuous cystoscopy after 6 weeks • > 3000/mL leukocytes; > 100,000/mL thrombocytes; serum creatinine < 2.0 mg **Exclusion criteria:** • primary stage pTa grade 1 tumours • metastasis, upper urinary tract tumour, hydronephrosis, other malignant disease or active tuberculosis • intravesical chemotherapy during the last 6 months or previous radiation • acute urinary infection
Interventions	**Group A:** 112 participants randomised to TUR alone **Group B:** 113 participants randomised to TUR followed by intravesical MMC 20 mg in 50 mL saline **Group C:** 102 participants randomised to TUR followed by intravesical BCG 120 mg Connaught strain in 50 mL saline, plus concomitant subcutaneous BCG 0.5 mg. **Procedure:** • at 6 weeks after TUR, participants underwent subsequent urethrocystoscopy, and in case of residual tumour a second TUR was performed; • instillation was done only after complete resection of the tumour, 7 days after secondary resection at the earliest; • MMC was instilled via a catheter and kept in the bladder for 2 hours. Instillations were performed every 2 weeks during year 1 and once a month during year 2; • BCG was instilled intravesically for 1 hour. At the same time BCG 0.5 mg was applied subcutaneously. Therapy was continued once weekly for 6 weeks and once a month for 4 months; • in case of tumour recurrence TUR was repeated.
Outcomes	Time to recurrence, progression rate and adverse effects
Funding sources	Supported by a grant from the Ministry of Science and Technology, Germany.
Declarations of interest	No information reported.
Notes	Sample size calculations demanded the admission of 402 participants into the study. However, despite an extended recruitment phase to September 1992, only 337 participants were enrolled.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: randomised by permuted block method after stratification with respect to primary or recurrent tumours, as well as the canters involved to ensure balanced group sizes within strata after every 6 participants. We assumed that sequence generation was done adequately.
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias)	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.

Krege 1996 *(Continued)*

all outcomes		
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not reported.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: nearly all participants were included in statistical analysis (Group B 112/113, Group C 102/102).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Unclear risk	Comment: no precise information on participants included in analyses.
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	High risk	Quote: "(...) despite an extended recruitment phase (...), only 337 patients were found." Comment: sample size calculations showed a need for 134 participants per treatment arm. Thus, the reduced number of study participants might have had led to reduced power to detect any effects. Study was supported by a grant from the Ministry of Science and Technology, Germany. Conflicts of interests are not reported. We assumed there was no other potential risk of bias.

Lamm 1995

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** 65 institutions **Study dates:** not reported **Participants randomly assigned:** 447
Participants	**Inclusion criteria:** • histologically confirmed Ta or T1 transitional cell carcinoma at increased risk for tumour recurrence; • participants with stage Ta or T1 tumour with concurrent Cis were also eligible;

Lamm 1995 *(Continued)*

	• life expectancy ≥ 6 months, performance status of ≥ 2 according to Southwest Oncology Group criteria. **Exclusion criteria:** • tumours of stage T2 or higher; • concurrent treatment with chemotherapy or radiotherapy.
Interventions	**Group A:** lyophilised Tice BCG 50 mg (5×10^8 cfu) diluted in 50 mL of sterile, preservative-free saline **Group B:** MMC 20 mg in 20 mL of sterile water **Procedure:** • treatment not sooner initiated than 1 week, and no later than 2 weeks, after tumour resection; • the suspensions were instilled into the bladder by gravity flow; • participants instructed to lie on their abdomen for 15 minutes and on their left, right and back for 15 minutes each and to retain the suspension, if possible, for 2 hours; • treatments were repeated weekly for 6 weeks and at 8 and 12 weeks, then monthly to 1 year.
Outcomes	Recurrence-free survival, worsening-free survival (progression to higher-stage disease), overall survival, adverse effects
Funding sources	investigation was supported in part by the following PH.5 Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA46113, CA22433, CA13612, CA42777, C.446441, CA46282, CA13238, 'X45560, CA20319, C-427057, CA16385, 'X28862. CA35192, CA35431, CA12213, 'X22411, CA35090, CA32734, CA35178, C-435281, CA14028, CA35261, CA35117, CA45450, CA52420, CA37981, CA04919, CA36020. CA38926, CA32102, CA49957, CA21076.
Declarations of interest	No information on declaration of interests reported.
Notes	Trial of the Southwest Oncology Group. Early Trial Closure: quote: "The trial opened for accrual in December of 1988. The first planned interim analysis was performed in May 1992. It provided strong evidence of BCG arm superiority over the MMC arm with respect to prolonging the time to first recurrence in patients without Cis. Based primarily on the strength of this evidence the trial was closed by its data monitoring committee prior to the completion of planned accrual. The intent-to treat analysis presented in this article preserves the between arm comparability implemented through randomisation. However, because the trial was closed early with an indication of BCG superiority it is possible that patients randomised to MMC were switched to BCG treatment. If a large number of patients randomised to the MMC arm were switched to BCG treatment then the intent-to-treat analysis will underestimate the relative magnitude of the BCG effect size (as compared to MMC)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: randomisation according to dynamic balancing algorithm. Balancing factor was the absence of Cis.
Allocation concealment (selection bias)	Unclear risk	Comment: this trial forms part of the Southwest Oncology Group Study. Nevertheless, there was no information on allocation concealment in the text.
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Low risk	Comment: no information on blinding. We assumed that there was no blinding but that the absence of blinding did not affect this objective outcome.

Lamm 1995 *(Continued)*

Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	High risk	Quote: "All subsequent analyses are based on eligible patients." Comment: participants included in the survival analyses: Group A 191/225 (85%), Group B 186/222 (84%).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: nearly all participants were included in statistical analysis (Group A 222/225, Group B 220/222).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol was available.
Other bias	High risk	Quote: "Early Closure: The trial opened for accrual in December of 1988. The first planned interim analysis was performed in May 1992. It provided strong evidence of BCG arm superiority over the MMC arm with respect to prolonging the time to first recurrence in patients without Cis. Based primarily on the strength of this evidence the trial was closed by its data monitoring committee prior to the completion of planned accrual. The intent-to-treat analysis presented in this article preserves the between arm comparability implemented through randomisation. However, because the trial was closed early with an indication of BCG superiority it is possible that patients randomised to MMC were switched to BCG treatment. If a large number of patients randomised to the MMC arm were switched to BCG treatment then the intent-to-treat analysis will underestimate the relative magnitude of the BCG effect size (as compared to MMC)." Quote: "There were 43 patients for which pre-randomisation pathologic stage from review is unavailable and 39 patients for whom pathologic grade from review is unavailable, primarily because a box of specimens was lost." Comment: this might have affected the results.

Malmström 1999

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** 12 **Study dates:** 1987–1992, follow-up of 10 years

Malmström 1999 *(Continued)*

	Participants randomly assigned: 261
Participants	**Inclusion criteria:** • people with stage Ta, grades 1–3 or stage T1, grades 1 and 2 tumours with ≥ 3 tumour effects during the prior 18 months • people with stage T1, grade 3 and people with primary or concomitant dysplasia or carcinoma **Exclusion criteria:** • previous or ongoing intravesical treatment with MMC, BCG or radiotherapy, chemotherapy during the prior 6 months • any secondary malignancy except treated Cis of the uterine cervix or basal cell carcinoma of the skin • ongoing corticosteroid therapy • leukocytes < 3000/mL, thrombocytes < 100,000/mL • untreated urinary tract infection, urethral stricture preventing cystoscopy, active tuberculosis, pregnancy • Karnofsky performance index < 50
Interventions	**Group A:** MMC 40 mg dissolved in 50 mL phosphate buffer (pH 7.4) **Group B:** BCG (Danish strain 1331) 120 mg containing 1 × 10^9 cfu, dissolved in 50 mL saline **Procedure:** • therapy begun 1–3 weeks after TUR or biopsies, and was given weekly for 6 weeks, then monthly for up to 1 year and every 3 months during year 2; • treatment cross-over for people with stage Ta, grades 1–3 or stage T1, grades 1 and 2 disease if tumour relapsed at 2 consecutive follow-up visits. Cross-over was performed at initial relapse in people with stage T1, grade 3 tumour, and if cytology and biopsies showed malignancy after 6 months of treatment in people with stage Cis disease or dysplasia.
Outcomes	Recurrence-free survival, progression-free survival, overall survival
Funding sources	No information on funding in the first study publication reported. The later publications referred to governmental funding sources.
Declarations of interest	No information on declaration of interests in the first study publication. In the publication of 1999, 1 author reported "financial interest and/or other relationship with Statens Serum Institute;" in the publication of 2007, the authors declared no conflicts of interests.
Notes	Supported by Grant 2323-Bg5-09XBB from the Swedish Cancer Society. First author declared financial interest or other relationship with Statens Serum Institute, or both.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information
Allocation concealment (selection bias)	Low risk	Comment: randomisation via centralised procedure.
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.

Malmström 1999 *(Continued)*

Blinding of outcome assessment (detection bias) overall survival	Low risk	Comment: no information on blinding. We assumes that there was no blinding but that the absence of blinding did not affect this objective outcome.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	Low risk	Quote: "Immunostaining evaluation was performed blindly, without knowledge of clinical history, by 2 observers (K. W. and C. B.) in collaboration over a conference microscope." (for the 5-year outcome paper). Comment: we assumed there was low risk for this item.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	Low risk	Quote: "Immunostaining evaluation was performed blindly, without knowledge of clinical history, by 2 observers (K. W. and C. B.) in collaboration over a conference microscope." (for the 5-year outcome paper). Comment: we assumed there was low risk for this item.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: 125/130 participants in the MMC group and 125/131 (95%) in the BCG group were included in the analyses.
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: 125/130 participants in the MMC group and 125/131 (95%) in the BCG group were included in the analyses.
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Mangiarotti 2008

Methods	**Study design:** prospective, randomised clinical trial **Number of study centres:** 1 **Study dates:** recruitment period not reported, follow-up 12–108 months **Participants randomly assigned:** 92
Participants	**Inclusion criteria:** • histologically confirmed Ta-T1 G1-2 stage tumour **Exclusion criteria:** • no previous intravesical treatment
Interventions	**Group A:** MMC 40 mg in 50 mL saline **Group B:** BCG Tice

Mangiarotti 2008 *(Continued)*

Procedure:

- therapy started 1 month after TUR;
- MMC once a week for 8 weeks, thereafter for once a month for 1 year;
- BCG weekly for 6 weeks, thereafter once a month for 1 year.

Outcomes	Recurrence rate, recurrence-free survival, adverse effects
Funding sources	Not reported.
Declarations of interest	No information on interests reported.
Notes	Sample size estimation required 97 participants to allow a 5% dropout and 92 remaining participants (46 in each group). The article reported on the 92 participants and on the 46 per group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	Unclear risk	Comment: no information
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not reported.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: all participants entered the analysis (46/46 in each group).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants entered the analysis (46/46 in each group).
Incomplete outcome data (attrition bias)	Unclear risk	Outcome not reported.

Mangiarotti 2008 *(Continued)*
Quality of life outcomes

Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Michielsen 2013

Methods	**Study design:** prospective, randomised controlled clinical trial **Number of study centres:** 1 probably **Study dates:** not reported **Participants randomly assigned:** unclear
Participants	**Inclusion criteria:** • people with intermediate risk of non-muscle invasive urothelial carcinoma of the bladder **Exclusion criteria:** • not reported
Interventions	**Group A:** MMC 40 mg in 50 mL 0.9% saline **Group B:** BCG full dose **Procedure:** • treatments weekly for 6 weeks, each group had a specific maintenance programme.
Outcomes	Disease-specific quality of life, measured with EORTC QLQ BLS24
Funding sources	No information reported.
Declarations of interest	No information reported.
Notes	Congress abstract available only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information reported to allow a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of participants and personnel (performance bias) all outcomes	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: no information reported to allow a judgement.

Michielsen 2013 *(Continued)*

overall survival		
Blinding of outcome assessment (detection bias) recurrence and progression free survival	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Comment: no information reported to allow a judgement.
Incomplete outcome data (attrition bias) Survival outcomes	Unclear risk	Comment: no information reported to allow a judgement.
Incomplete outcome data (attrition bias) Adverse effect outcomes	Unclear risk	Comment: no information reported to allow a judgement.
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Comment: no information reported to allow a judgement.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Unclear risk	Comment: no information reported to allow a judgement.

NCT00974818

Methods	**Study design:** prospective, randomised clinical trial **Number of study centres:** 3 **Study dates:** September 2009 to March 2012 **Participants randomly assigned:** 50
Participants	**Inclusion criteria:** • pathologically confirmed Ta or T1 non-muscle invasive urothelial bladder tumours at intermediate risk **Exclusion criteria:** • any intravesical therapy within the past 6 months prior to current diagnosis • radiation treatment or surgery for the bladder or chemotherapy during the study
Interventions	**Group A:** MMC 40 mg, dissolved in 20 mL sterile water **Group B:** BCG 81 mg, dissolved in 53 mL of diluent and saline **Procedure:**

NCT00974818 *(Continued)*

- MMC: induction course of 6 cycles of weekly intravesical therapy of MMC, followed by a maintenance schedule consisting of 3 weekly cycles of the same drug at 3, 6, 12, 18 and 24 months;
- BCG: induction course of 6 cycles of weekly intravesical therapy of either BCG, followed by a maintenance schedule consisting of 3 weekly cycles of the same drug at 3, 6, 12, 18 and 24 months. Participants received 3 weekly cycles of intravesical BCG 27 mg 3, 6, 12, 18 and 24 months after the induction course.

Outcomes	Response to treatment (relapse rate), serious adverse effects, adverse effects
Funding sources	Sponsor was Memorial Sloan Kettering Cancer Center.
Declarations of interest	No information reported.
Notes	Study has been terminated due to lack of accrual. Only the trial entry is available: NCT00974818. Official name: mitomycin C versus Bacillus Calmette-Guérin in the intravesical treatment of non-muscle-invasive bladder cancer participants: a randomized phase III non-inferiority trial. Quote: "Due to a lack of patients accrued to the protocol the protocol was closed and the analysis of the 2 year relapse rates could not be compared."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information reported to allow a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of participants and personnel (performance bias) all outcomes	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	Unclear risk	Comment: no information reported to allow a judgement.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not assessed.
Incomplete outcome data (attrition bias) Survival outcomes	High risk	Comment: analysis was not done due to a lack of participants. Unclear why this analysis could not be done.

NCT00974818 *(Continued)*

Incomplete outcome data (attrition bias) Adverse effect outcomes	High risk	Comment: we judged this item at high risk, as the reported numbers on the webpage were not congruent. But analyses here included the 50 participants (25 per arm).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not assessed.
Selective reporting (reporting bias)	High risk	Comment: no information why data on the primary outcome (relapse rate) was not reported but there were data on the secondary outcomes (adverse effects).
Other bias	High risk	Comment: study was affected by a lack of reporting.

Ojea 2007a

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** unclear **Study dates:** March 1995 to May 1998, follow-up 52.6 months **Participants randomly assigned:** 430
Participants	**Inclusion criteria:** • intermediate-risk people with stages Ta G2 and T1 G1-2 tumours, without Cis **Exclusion criteria:** • Ta G1 tumours, high-risk tumours • concurrent or previous muscle-invasive disease, concurrent or previous tumour in the upper urinary tract or prostatic urethra • chronic urinary tract infection, cured or active tuberculosis • < 2 years of life expectancy, physical or psychic disability • any other malignancy except basal cell carcinoma of skin, previous pelvic irradiation • pregnancy or lactation • any other disease with immunodeficiency
Interventions	**Group A:** low-dose BCG 27 mg Connaught strain **Group B:** very low-dose BCG 13.5 mg Connaught strain **Group C:** MMC 30 mg **Procedure:** • Instillations started 14–21 days after TUR with histological confirmation of bladder cancer and were repeated once a week for 6 weeks followed by another 6 instillations given once every 2 weeks for 12 weeks.
Outcomes	Disease-free interval, time to progression, overall survival, adverse effects
Funding sources	No information
Declarations of interest	The authors reported that they had nothing to disclose.

Ojea 2007a *(Continued)*

Notes	CUETO study 95011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not reported.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: all participants entered the analysis (Group A 142/142, Group B 139/139, Group C 149/149).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants entered the analysis (Group A 142/142, Group B 139/139, Group C 149/149).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Ojea 2007b

Methods	**Study design:** multicentre, prospective, randomised clinical trial

Ojea 2007b *(Continued)*

	Number of study centres: unclear **Study dates:** March 1995 to May 1998, follow-up 52.6 months **Participants randomly assigned:** 430
Participants	**Inclusion criteria:** • intermediate-risk people with stages Ta G2 and T1 G1–2 tumours, without Cis **Exclusion criteria:** • Ta G1 tumours, high-risk tumours • concurrent or previous muscle-invasive disease, concurrent or previous tumour in the upper urinary tract or prostatic urethra • chronic urinary tract infection, cured or active tuberculosis • < 2 years of life expectancy, physical or psychic disability • any other malignancy except basal cell carcinoma of skin, previous pelvic irradiation • pregnancy or lactation • any other disease with immunodeficiency
Interventions	**Group A:** low-dose BCG 27 mg Connaught strain **Group B:** very low-dose BCG 13.5 mg Connaught strain **Group C:** MMC 30 mg **Procedure:** • instillations started 14–21 days after TUR with histological confirmation of bladder cancer and were repeated once a week for 6 weeks followed by another 6 instillations given once every 2 weeks for 12 weeks.
Outcomes	Disease-free interval, time to progression, overall survival, adverse effects
Funding sources	No information
Declarations of interest	The authors reported that they had nothing to disclose.
Notes	CUETO study 95011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not reported.

Ojea 2007b *(Continued)*

Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: all participants entered the analysis (Group A 142/142, Group B 139/139, Group C 149/149).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants entered the analysis (Group A 142/142, Group B 139/139, Group C 149/149).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Rintala 1991

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** unclear **Study dates:** 1984–1987, for a subgroup of participants there is a follow-up of 20 years **Participants randomly assigned:** 89
Participants	**Inclusion criteria:** • people with Cis grade 1–3 • frequently recurrent Ta-T1 papillary transitional cell cancer grade 1–3 • histologically confirmed malignancy or 3 consecutive malignant cytological findings, or both **Exclusion criteria:** • not reported.
Interventions	**Group A:** BCG Pasteur Strain F, 75 mg **Group B:** MMC 20–40 mg (AUC method) **Procedure:**

Rintala 1991 *(Continued)*

- instillations (for 2 hours) started 2 weeks after TUR. Weekly repetition during the first month, then once a month for 2 years.

Outcomes	Recurrence rate, recurrence index, overall mortality, progression, disease-specific mortality
Funding sources	Finnish Cancer Foundation, Academy of Finland Paolo Foundation and Research and Science Foundation of Farmos
Declarations of interest	No information reported.
Notes	FinnBladder I study group. Jarvinen reported 20-year follow-up data based on a subgroup of participants with TaT1 disease and without Cis (91/109 participants).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: method of randomisation was based on date of birth.
Allocation concealment (selection bias)	High risk	Comment: method of randomisation was based on date of birth.
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Low risk	Comment: no information on blinding. We assumed that there was no blinding but that the absence of blinding has not affected this objective outcome.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: all participants were considered in the analyses (Group A 44/44, Group B 45/45).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants were considered in the analyses (Group A 44/44, Group B 45/45).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.

Rintala 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Witjes 1996a

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** 27 **Study dates:** 1987–1990, follow-up 36 months (2–81 months) **Participants randomly assigned:** 437
Participants	**Inclusion criteria:** • histologically confirmed primary or recurrent papillary transitional cell carcinoma stage Ta or T1 after complete TUR; • people with primary or concomitant Cis were also eligible. **Exclusion criteria:** • previously treated with intravesical or systemic cytotoxic agents or radiotherapy • recurrent severe bacterial urinary tract infections • bladder cancer other than transitional cell carcinoma or with a second primary malignancy (exception of basal cell or squamous cell carcinoma of the skin)
Interventions	**Group A:** MMC 30 mg in 50 mL saline **Group B:** BCG-RIVM 5×10^8 bacilli in 50 mL saline **Group C:** BCG-Tice 5×10^8 bacilli in 50 mL saline **Procedure:** • MMC instilled once a week for 1 month (weeks 1–4) and thereafter once a month for 6 months; • BCG was administered once a week for 6 weeks. Treatments start 7–20 days after TUR; • if a recurrence was detected in the MMC group, complete resection was carried out and the MMC treatment continued monthly for another 3 months; • if disease recurred within 6 months in the BCG treatment group, a second course of 6 weekly instillations was administered after complete tumour resection; • if a recurrence was observed after completion of intravesical treatment or if the T category increased to T2 or higher, participants went off the study; • further treatment was left to the discretion of the individual urologist.
Outcomes	Recurrence-free survival, progression-free survival, adverse effects
Funding sources	No information reported.
Declarations of interest	No information reported.
Notes	Dutch South East Cooperative Trial. 1 pathologist determined stage and grade.
Risk of bias	

Witjes 1996a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: restricted block-wise (block size 6 equals 3 treatments times 2 participants per treatment) randomisation was used.
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Unclear risk	Outcome not reported.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants were considered in the analyses (Group A 136/136, Group B 134/134, Group C 140/140).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Witjes 1996b

Methods	**Study design:** multicentre, prospective, randomised clinical trial **Number of study centres:** 27 **Study dates:** 1987–1990, follow-up 36 months (2–81 months)

Witjes 1996b *(Continued)*

	Participants randomly assigned: 437
Participants	**Inclusion criteria:** • histologically confirmed primary or recurrent papillary transitional cell carcinoma stage Ta or T1 after complete TUR; • people with primary or concomitant Cis were also eligible. **Exclusion criteria:** • previously treated with intravesical or systemic cytotoxic agents or radiotherapy; • recurrent severe bacterial urinary tract infections; • bladder cancer other than transitional cell carcinoma or with a second primary malignancy (exception of basal cell or squamous cell carcinoma of the skin).
Interventions	**Group A:** MMC 30 mg in 50 mL saline **Group B:** BCG-RIVM 5×10^8 bacilli in 50 mL saline **Group C:** BCG-Tice 5×10^8 bacilli in 50 mL saline **Procedure:** • MMC instilled once a week for 1 month (weeks 1–4) and thereafter once a month for a total of 6 months; • BCG was administered once a week for 6 weeks. Treatments start 7–20 days after TUR; • if a recurrence was detected in the MMC group, complete resection was carried out and the MMC treatment continued monthly for another 3 months; • if disease recurred within 6 months in the BCG treatment group, a second course of 6 weekly instillations was administered after complete tumour resection; • if a recurrence was observed after completion of intravesical treatment or if the T category increased to T2 or higher, participants went off the study; • further treatment was left to the discretion of the individual urologist.
Outcomes	Recurrence-free survival, progression-free survival, adverse effects
Funding sources	No information reported.
Declarations of interest	No information reported.
Notes	Dutch South East Cooperative Trial. 1 pathologist determined stage and grade.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: restricted block-wise (block size 6 equals 3 treatments times 2 participants per treatment) randomisation was used.
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome not reported.

Witjes 1996b *(Continued)*
overall survival

Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: all participants were considered in the analyses (Group A 136/136, Group B 134/134, Group C 140/140).
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

Witjes 1998a

Methods	**Study design:** prospective, randomised clinical trial **Number of study centres:** 24 **Study dates:** January 1985 to October 1986, median follow-up 7.2 years **Participants randomly assigned:** 344
Participants	**Inclusion criteria:** • people with primary or recurrent pTa and pT1 bladder tumours, including Cis **Exclusion criteria:** • not reported
Interventions	**Group A:** MMC 30 mg in 50 mL saline **Group B:** BCG-RIVM 5×10^8 bacilli in 50 mL saline **Procedure:** • intravesical therapy was started 7–15 days after resection; • MMC was given weekly for 4 consecutive weeks and thereafter monthly for 5 months;

Witjes 1998a *(Continued)*

- BCG was given weekly for 6 consecutive weeks;
- in case of a recurrence at 3 months, a complete resection was performed, where after in BCG-treated participants a second course was given and in MMC-treated participants instillations were continued;
- in case of a recurrence at or after 6 months, or in case of progression to muscle invasion, the participant was withdrawn from the study.

Outcomes	Time to first recurrence, time to progression, adverse effects
Funding sources	This work was supported by grants 5U10 CA11488-26 and 5U10 CA11488-27 from the National Cancer Institute, Bethesda, MD.
Declarations of interest	No information reported.
Notes	Joint effort of the European Organisation for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Collaborative Group and the Dutch South East Cooperative Urological Group (protocol 30845).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all outcomes	High risk	Comment: no information on blinding. We assumed that there was no blinding and that the outcomes might have been influenced by differences in performance due to a lack of blinding.
Blinding of outcome assessment (detection bias) overall survival	Low risk	Comment: no information on blinding. We assumed that there was no blinding but that the absence of blinding has not affected this objective outcome.
Blinding of outcome assessment (detection bias) recurrence and progression free survival	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) serious and non-serious adverse effects	High risk	Comment: no information on blinding. We assumed that there was no blinding. We assumed that the absence of blinding might have had an effect on the detection and measurement of subjective outcomes.
Blinding of outcome assessment (detection bias) quality of life	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Survival outcomes	Low risk	Comment: participants considered in the analyses were: BCG 159/171 (93%), MMC 168/173 (97%).
Incomplete outcome data (attrition bias) Adverse effect outcomes	Low risk	Comment: participants considered in the analyses were: BCG 166/171 (97%), MMC 173/173.

Witjes 1998a *(Continued)*

Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no study protocol available.
Other bias	Low risk	Comment: we assumed that there was no risk for other bias.

AUC: area under the curve; BCG: Bacillus Calmette-Guérin; cfu: colony-forming units; Cis: carcinoma in situ; EORTC QLQ BLS24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – 24-question Superficial Bladder Cancer; MMC: mitomycin C; SEM: standard error of the mean; TUR: transurethral resection.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12613000513718	Wrong treatment comparison.
Allona 1988	Wrong treatment comparison.
Altay 2000	Wrong treatment comparison.
Arends 2014	Wrong treatment comparison.
Ayres 2010	Wrong study design.
Badalato 2011	Wrong study design.
Bassi 2001	Wrong study design.
Bismarck 2004	Comment/letter.
Boccafoschi 1991	Wrong study design.
Bochner 2006	Comment/letter.
Bohle 2008	Comment/letter.
Braasch 2008	Wrong study design.
Brausi 1998	Wrong study design.
Chen 2012	Wrong study design.
Chen 2019	Wrong study design.
Cho 2012	Wrong study design.
Crawford 1995	Comment/letter.
Dalbagni 2009	Comment/letter.
de Jong 1989	Wrong study design.

Study	Reason for exclusion
deVere 2000	Wrong study design.
Di Stasi 2004a	Wrong treatment comparison.
Di Stasi 2004b	Wrong treatment comparison.
Di Stasi 2006b	Wrong treatment comparison.
Di Stasi 2012a	Wrong treatment comparison.
Di Stasi 2012b	Wrong treatment comparison.
Di Stasi 2013	Wrong treatment comparison.
Di Stasi 2015	Wrong treatment comparison.
El Kader 2010	Wrong treatment comparison.
EUCTR2008-005428-99-GB	Wrong treatment comparison.
EUCTR2011-000607-41-BE	Wrong treatment comparison.
FinnBladder 4	Wrong treatment comparison.
FinnBladder II	Wrong treatment comparison.
Gao 2002	Wrong study design.
Gazzaniga 2009	Wrong study design.
Gelabert-Mas 1993	Wrong treatment comparison.
Gelabert-Mas 1997	Wrong treatment comparison.
Gianneo 1997	Wrong study design.
Grossman 2006	Comment/letter.
Guerrero-Ramos 2019	Wrong treatment comparison.
Gulpinar 2012	Wrong treatment comparison.
Han 2015	Wrong study design.
Hausladen 2003	Wrong study design.
Hayne 2011	Wrong treatment comparison.
Huang 2010	Wrong treatment comparison.
Iavarone 1996	Wrong study design.
ISRCTN85785327	Duplicate.
Jarvinen 2012	Wrong treatment comparison.

Study	Reason for exclusion
Jarvinen 2013	Comment/letter.
Jarvinen 2014	Wrong treatment comparison.
Jarvinen 2015	Wrong treatment comparison.
Jauhiainen 1993	Wrong study design.
Kaasinen 2000	Wrong treatment comparison.
Kaasinen 2002	Wrong treatment comparison.
Kaasinen 2003	Wrong treatment comparison.
Kaasinen 2014	Wrong treatment comparison.
Kelly 2015	Wrong treatment comparison.
Kirkali 2010	Wrong treatment comparison.
Kurth 2000	Wrong study design.
Lamm 1991	Wrong study design.
Leblanc 1999	Wrong study design.
Liberati 2012	Wrong treatment comparison.
Lundholm 1999	Duplicate.
Malmström 2009b	Comment/letter.
Matsumoto 2010	Wrong study design.
Matsumoto 2012	Wrong study design.
Mondal 2016	No distinction of low- and mid-/high-risk participants.
Morales 1999	Wrong treatment comparison.
Murillo 2019	Wrong study design.
NCT00023842	Wrong treatment comparison.
NCT00384891	Wrong treatment comparison.
NCT01094964	Duplicate.
NCT01442519	Wrong treatment comparison.
Nishimura 1996	Wrong study design.
Nohales 1996	Wrong study design.
Nouhaud 2017	Wrong treatment comparison.

Study	Reason for exclusion
Ooi 2011	Comment/letter.
Peyromaure 2004	Wrong study design.
Raviv 2005	Wrong study design.
Saxena 2006	Wrong study design.
Sekine 2001	Wrong treatment comparison.
Shelley 2015b	Wrong study design.
Smits 1998	Wrong study design.
Soloway 1990	Wrong study design.
Stasi 2004	Wrong treatment comparison.
Steinberg 2017	Wrong treatment comparison.
Study 30993	Wrong treatment comparison.
Sylvester 2009	Wrong study design.
Tong 2003	Duplicate.
van der Meijden 1989	Duplicate.
van Gils-Gielen 1995	Wrong study design.
Wang 1992	Wrong participant population.
Wang 2011	No distinction of low- and mid-/high-risk participants.
Witjes 1998b	Wrong treatment comparison.
Witjes 1999a	Wrong treatment comparison.
Witjes 1999b	Comment/letter.
Yabusaki 1991	Wrong treatment comparison.
Yang 1999	Wrong study design.
Yari 2010	Wrong treatment comparison.

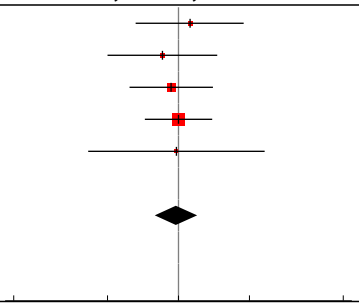
DATA AND ANALYSES

Comparison 1. Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to death from any cause	5	1132	Hazard Ratio (Random, 95% CI)	0.97 [0.79, 1.20]
2 Serious adverse effects	5	1024	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.82, 6.52]
3 Time to recurrence	11	2616	Hazard Ratio (Random, 95% CI)	0.88 [0.71, 1.09]
4 Time to progression	6	1622	Hazard Ratio (Random, 95% CI)	0.96 [0.73, 1.26]
5 Adverse effects	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Urinary frequency	4	814	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.99, 2.50]
5.2 Cystitis	5	1049	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.80, 2.51]
5.3 Incontinence	1	442	Risk Ratio (M-H, Random, 95% CI)	2.64 [0.71, 9.83]
5.4 Cramps	1	442	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.91, 4.32]
5.5 Visible haematuria	6	1387	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.20, 2.16]
5.6 Prostatitis	3	379	Risk Ratio (M-H, Random, 95% CI)	5.09 [0.87, 29.87]
5.7 Epididymitis	3	379	Risk Ratio (M-H, Random, 95% CI)	3.51 [1.17, 10.55]
5.8 Fever	6	1387	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.97, 8.48]
5.9 General malaise/discomfort	3	830	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.61, 4.97]
5.10 Fatigue	2	322	Risk Ratio (M-H, Random, 95% CI)	4.98 [0.07, 350.40]
5.11 Allergic reactions	5	1155	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.14, 1.07]
5.12 Dysuria	2	758	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.69, 1.90]
5.13 Skin alterations	2	465	Risk Ratio (M-H, Random, 95% CI)	2.37 [0.07, 76.28]
5.14 Pain	3	742	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.16, 1.82]
5.15 Nausea	2	692	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.02, 1.87]
5.16 Bacterial cystitis	3	848	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.99, 1.68]
5.17 Drug-induced cystitis	3	848	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.83, 2.91]
5.18 Systemic adverse events	2	867	Risk Ratio (M-H, Random, 95% CI)	12.64 [2.56, 62.55]

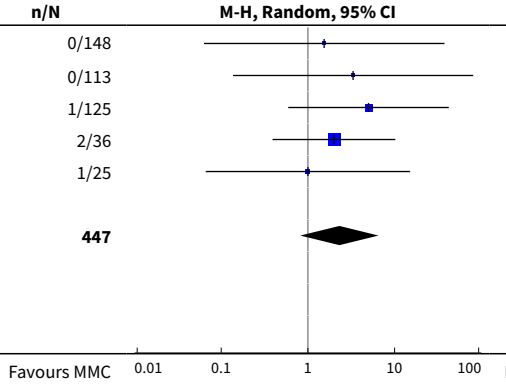
Analysis 1.1. Comparison 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), Outcome 1 Time to death from any cause.

Study or subgroup	BCG N	MMC N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Rintala 1991	44	45	0.1 (0.27)		15.04%	1.12[0.66,1.89]
Lamm 1995	191	186	-0.2 (0.274)		14.64%	0.85[0.5,1.46]
Witjes 1998a	171	173	-0.1 (0.207)		25.62%	0.93[0.62,1.4]
Malmström 1999	125	125	0 (0.168)		39.04%	1[0.72,1.39]
Di Stasi 2003	36	36	-0 (0.44)		5.66%	0.98[0.41,2.32]
Total (95% CI)					**100%**	**0.97[0.79,1.2]**
Heterogeneity: Tau²=0; Chi²=0.56, df=4(P=0.97); I²=0%						
Test for overall effect: Z=0.25(P=0.8)						



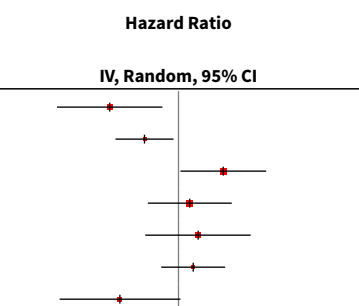
Analysis 1.2. Comparison 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), Outcome 2 Serious adverse effects.

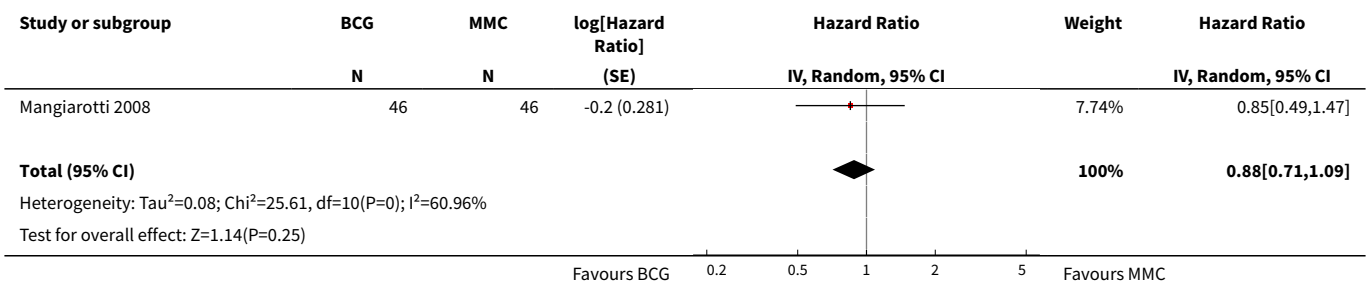
Study or subgroup	BCG n/N	MMC n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Witjes 1996a	1/289	0/148		10.58%	1.54[0.06,37.61]
Krege 1996	1/102	0/113		10.61%	3.32[0.14,80.61]
Malmström 1999	5/125	1/125		23.73%	5[0.59,42.19]
Di Stasi 2003	4/36	2/36		40.46%	2[0.39,10.24]
NCT00974818	1/25	1/25		14.63%	1[0.07,15.12]
Total (95% CI)	**577**	**447**		**100%**	**2.31[0.82,6.52]**
Total events: 12 (BCG), 4 (MMC)					
Heterogeneity: Tau²=0; Chi²=1.02, df=4(P=0.91); I²=0%					
Test for overall effect: Z=1.58(P=0.12)					



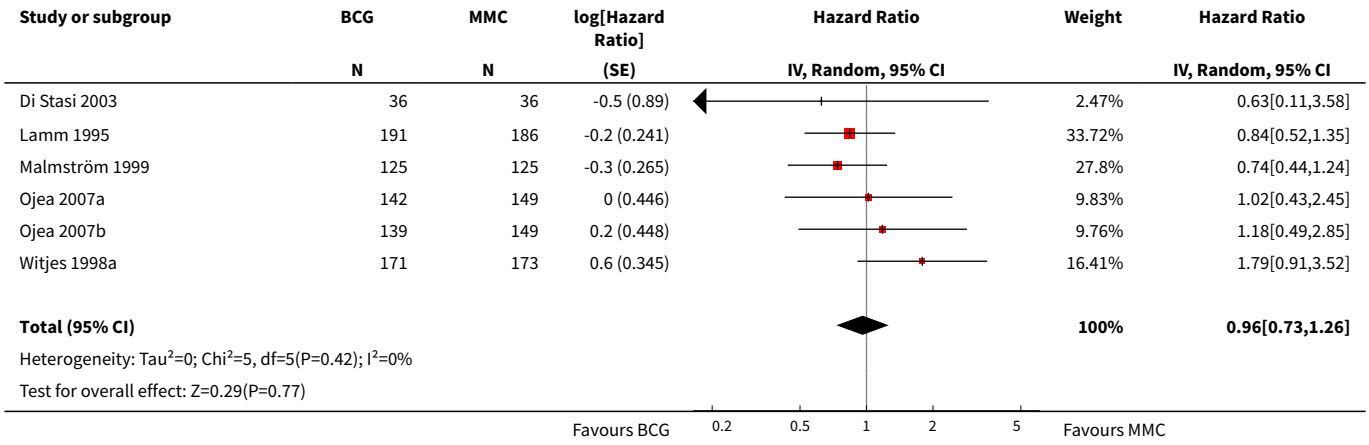
Analysis 1.3. Comparison 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), Outcome 3 Time to recurrence.

Study or subgroup	BCG N	MMC N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Rintala 1991	44	45	-0.7 (0.271)		8.03%	0.5[0.29,0.85]
Lamm 1995	191	186	-0.3 (0.149)		12.09%	0.71[0.53,0.95]
Witjes 1996b	117	136	0.5 (0.221)		9.57%	1.57[1.02,2.42]
Witjes 1996a	134	136	0.1 (0.216)		9.75%	1.12[0.73,1.71]
Krege 1996	102	113	0.2 (0.271)		8.01%	1.22[0.71,2.07]
Witjes 1998a	159	168	0.1 (0.165)		11.53%	1.16[0.84,1.6]
Di Stasi 2003	36	36	-0.6 (0.31)		6.98%	0.55[0.3,1.02]
Ojea 2007b	139	149	-0.2 (0.26)		8.33%	0.8[0.48,1.33]
Ojea 2007a	142	149	-0.6 (0.259)		8.36%	0.54[0.32,0.89]
Friedrich 2007	163	179	0.1 (0.22)		9.61%	1.09[0.71,1.68]

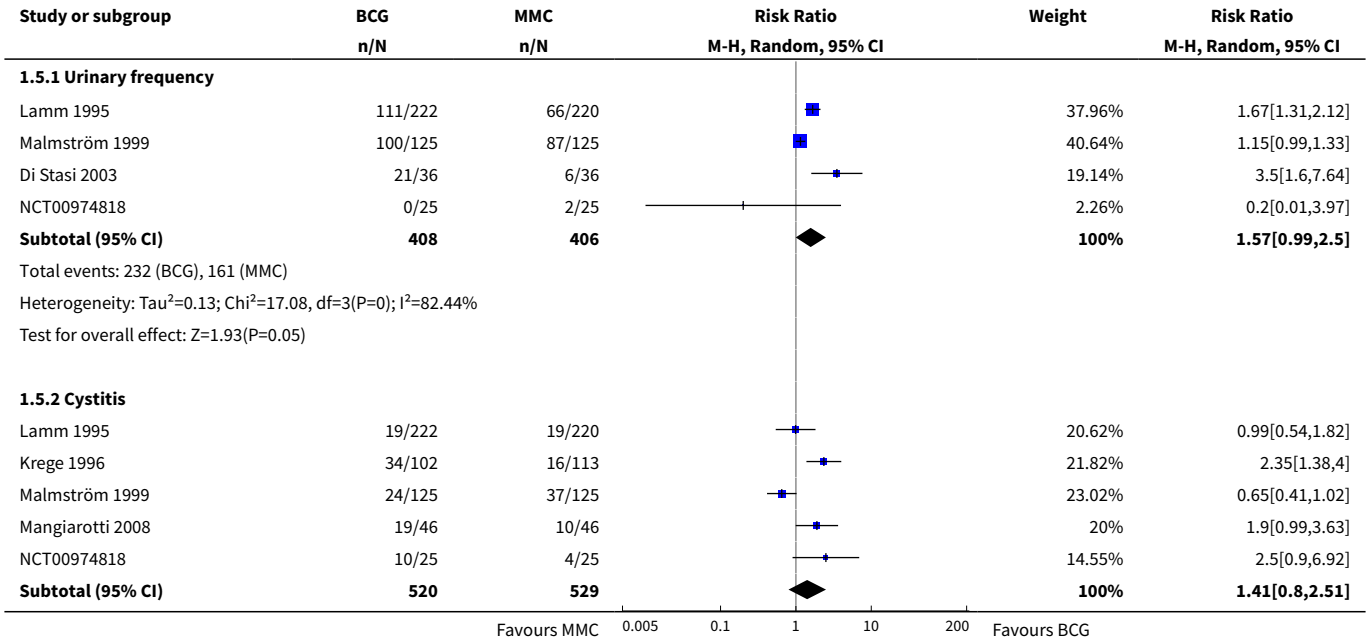


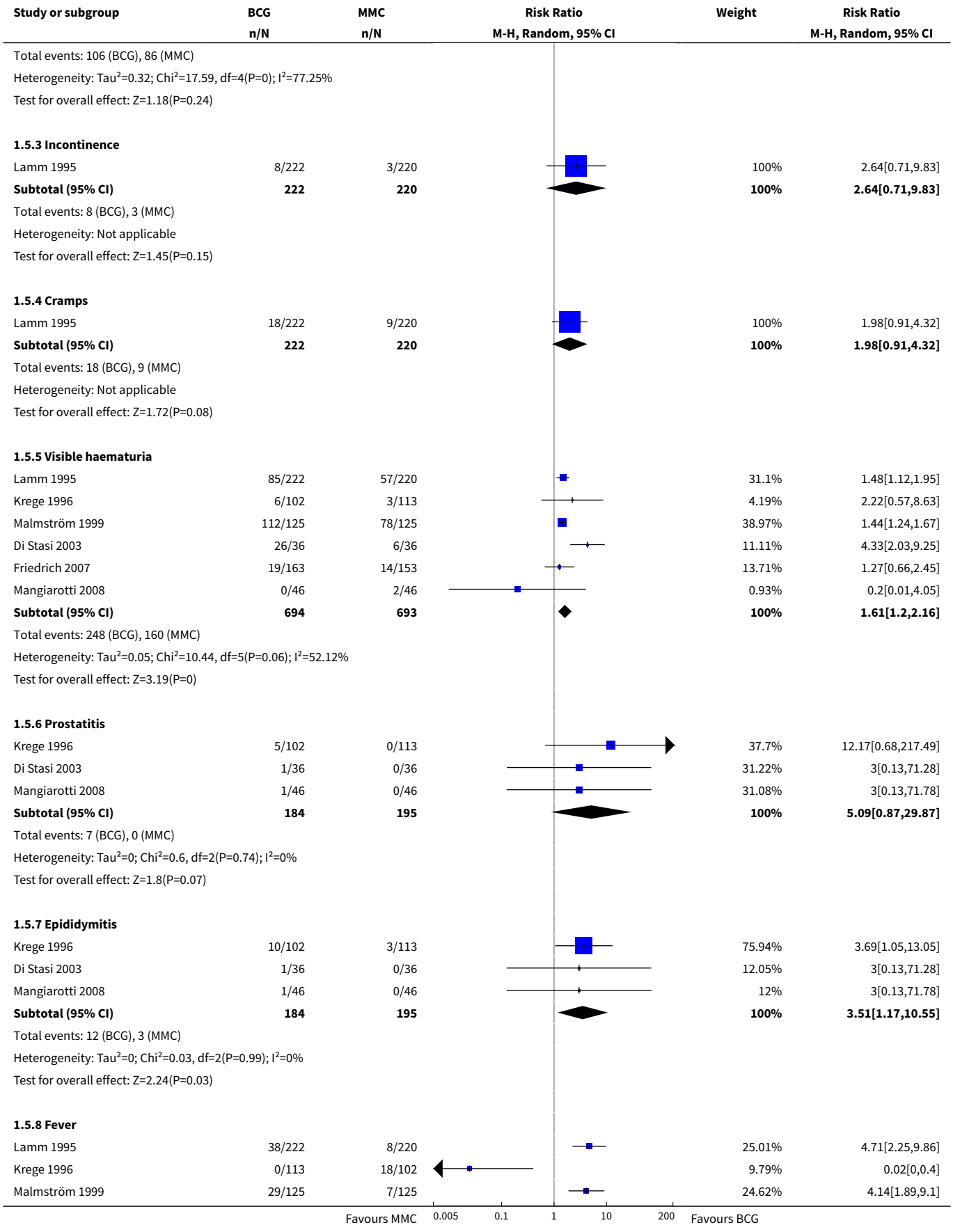


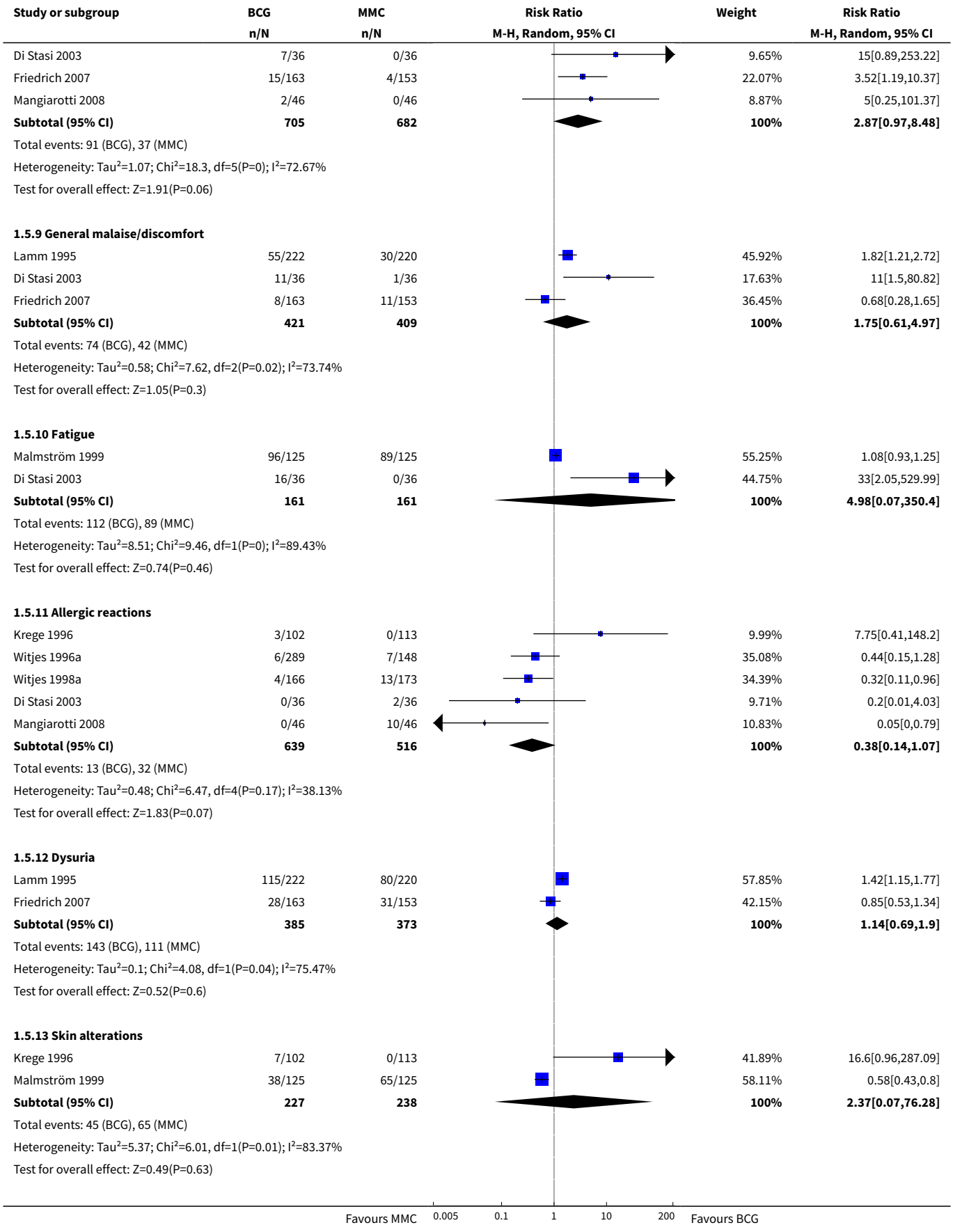
Analysis 1.4. Comparison 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), Outcome 4 Time to progression.

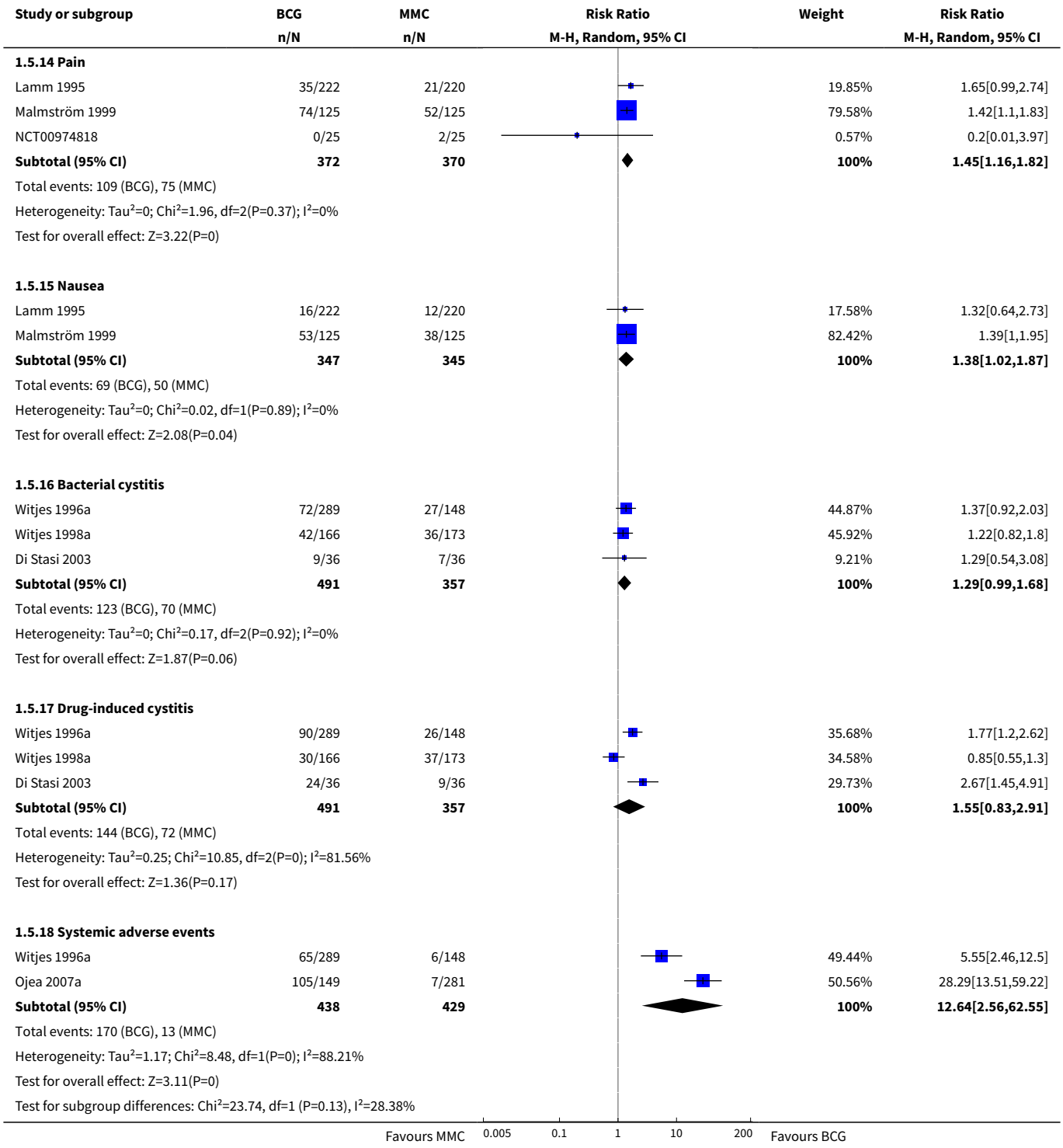


Analysis 1.5. Comparison 1 Bacillus Calmette-Guérin (BCG) versus mitomycin C (MMC), Outcome 5 Adverse effects.





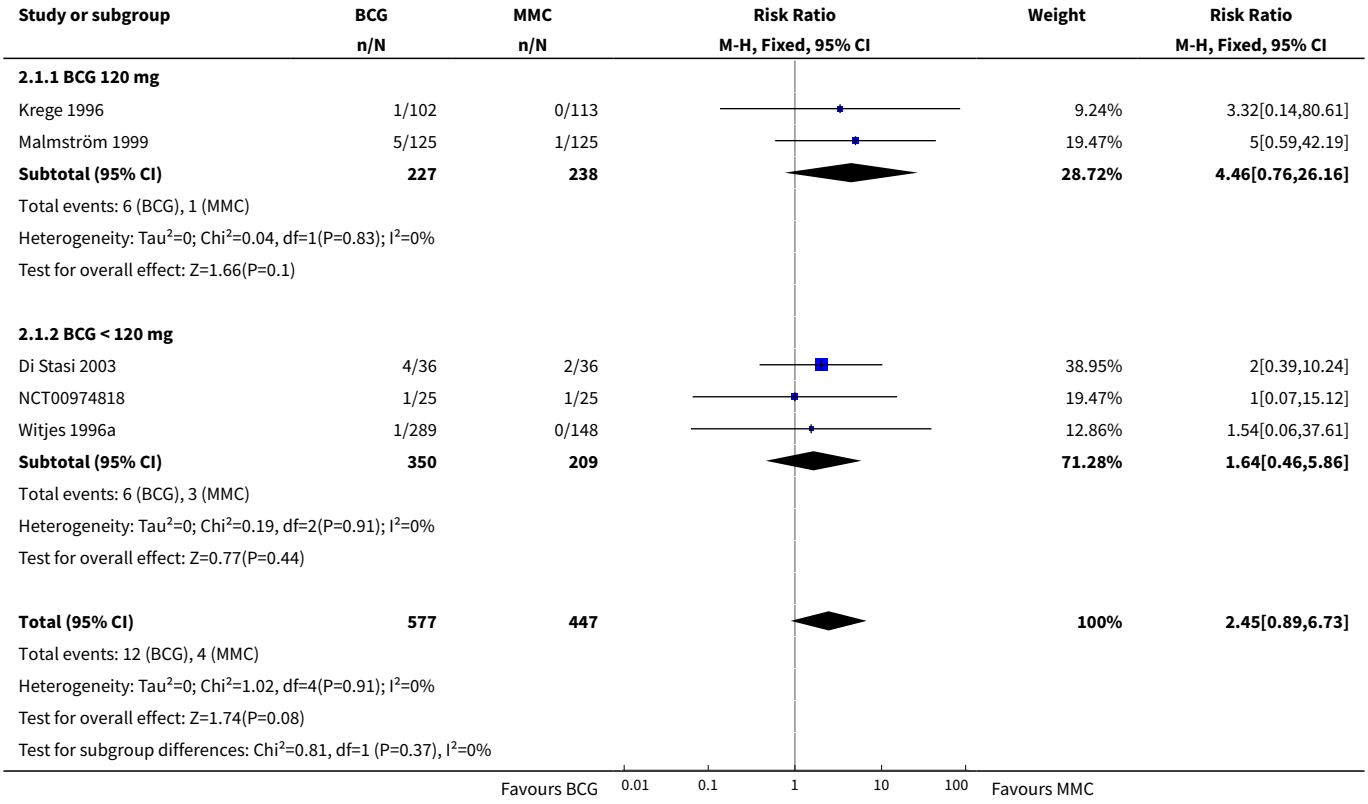




Comparison 2. Different doses of Bacillus Calmette-Guérin (BCG) (subgroup analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse effect (subgroup analyses)	5	1024	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.89, 6.73]
1.1 BCG 120 mg	2	465	Risk Ratio (M-H, Fixed, 95% CI)	4.46 [0.76, 26.16]
1.2 BCG < 120 mg	3	559	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.46, 5.86]

Analysis 2.1. Comparison 2 Different doses of Bacillus Calmette-Guérin (BCG) (subgroup analyses), Outcome 1 Serious adverse effect (subgroup analyses).



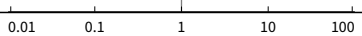
Comparison 3. Different doses of mitomycin C (MMC) (subgroup analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to recurrence (subgroup analyses)	11		Hazard Ratio (Fixed, 95% CI)	0.88 [0.77, 1.00]
1.1 MMC 30 mg	5		Hazard Ratio (Fixed, 95% CI)	1.04 [0.86, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 MMC 20 mg	3		Hazard Ratio (Fixed, 95% CI)	0.85 [0.67, 1.07]
1.3 MMC 40 mg	2		Hazard Ratio (Fixed, 95% CI)	0.60 [0.40, 0.90]
1.4 MMC mixed dose (20–40 mg)	1		Hazard Ratio (Fixed, 95% CI)	0.50 [0.29, 0.85]

Analysis 3.1. Comparison 3 Different doses of mitomycin C (MMC) (subgroup analyses), Outcome 1 Time to recurrence (subgroup analyses).

Study or subgroup	BCG N	MMC N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
3.1.1 MMC 30 mg						
Ojea 2007a	0	0	-0.6 (0.259)		6.87%	0.54[0.32,0.89]
Ojea 2007b	0	0	-0.2 (0.26)		6.83%	0.8[0.48,1.33]
Witjes 1996a	0	0	0.1 (0.216)		9.93%	1.12[0.73,1.71]
Witjes 1996b	0	0	0.5 (0.221)		9.47%	1.57[1.02,2.42]
Witjes 1998a	0	0	0.1 (0.165)		17.04%	1.16[0.84,1.6]
Subtotal (95% CI)					**50.14%**	**1.04[0.86,1.26]**
Heterogeneity: Tau²=0; Chi²=11.51, df=4(P=0.02); I²=65.26%						
Test for overall effect: Z=0.45(P=0.66)						
3.1.2 MMC 20 mg						
Friedrich 2007	0	0	0.1 (0.281)		5.85%	1.09[0.63,1.89]
Krege 1996	0	0	0.2 (0.271)		6.27%	1.22[0.71,2.07]
Lamm 1995	0	0	-0.3 (0.149)		20.76%	0.71[0.53,0.95]
Subtotal (95% CI)					**32.89%**	**0.85[0.67,1.07]**
Heterogeneity: Tau²=0; Chi²=3.99, df=2(P=0.14); I²=49.84%						
Test for overall effect: Z=1.38(P=0.17)						
3.1.3 MMC 40 mg						
Di Stasi 2003	0	0	-0.9 (0.31)		4.81%	0.39[0.21,0.71]
Mangiarotti 2008	0	0	-0.2 (0.281)		5.85%	0.85[0.49,1.47]
Subtotal (95% CI)					**10.66%**	**0.6[0.4,0.9]**
Heterogeneity: Tau²=0; Chi²=3.54, df=1(P=0.06); I²=71.77%						
Test for overall effect: Z=2.49(P=0.01)						
3.1.4 MMC mixed dose (20–40 mg)						
Rintala 1991	0	0	-0.7 (0.271)		6.3%	0.5[0.29,0.85]
Subtotal (95% CI)					**6.3%**	**0.5[0.29,0.85]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.56(P=0.01)						
Total (95% CI)					**100%**	**0.88[0.77,1]**
Heterogeneity: Tau²=0; Chi²=30.15, df=10(P=0); I²=66.84%						
Test for overall effect: Z=1.93(P=0.05)						
Test for subgroup differences: Chi²=11.11, df=1 (P=0.01), I²=73%						

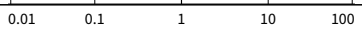


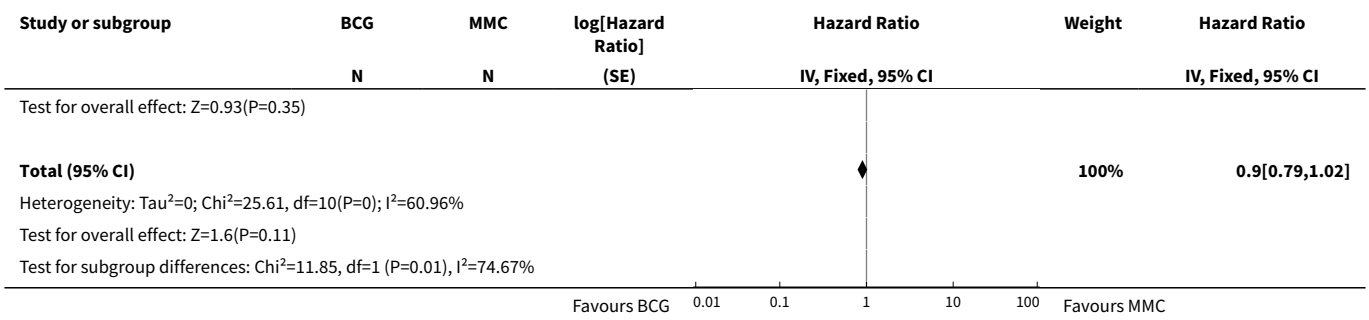
Comparison 4. Different Bacillus Calmette-Guérin (BCG) strains (subgroup analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to recurrence (subgroup analyses)	11		Hazard Ratio (Fixed, 95% CI)	0.90 [0.79, 1.02]
1.1 Connaught strain	3		Hazard Ratio (Fixed, 95% CI)	0.80 [0.59, 1.07]
1.2 Pasteur strain	2		Hazard Ratio (Fixed, 95% CI)	0.52 [0.35, 0.78]
1.3 RIVM strain	3		Hazard Ratio (Fixed, 95% CI)	1.13 [0.91, 1.41]
1.4 Tice strain	3		Hazard Ratio (Fixed, 95% CI)	0.90 [0.72, 1.12]

Analysis 4.1. Comparison 4 Different Bacillus Calmette-Guérin (BCG) strains (subgroup analyses), Outcome 1 Time to recurrence (subgroup analyses).

Study or subgroup	BCG N	MMC N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
4.1.1 Connaught strain						
Krege 1996	0	0	0.2 (0.271)		6.05%	1.22[0.71,2.07]
Ojea 2007a	0	0	-0.6 (0.259)		6.63%	0.54[0.32,0.89]
Ojea 2007b	0	0	-0.2 (0.26)		6.58%	0.8[0.48,1.33]
Subtotal (95% CI)					**19.26%**	**0.8[0.59,1.07]**
Heterogeneity: Tau²=0; Chi²=4.74, df=2(P=0.09); I²=57.79%						
Test for overall effect: Z=1.5(P=0.13)						
4.1.2 Pasteur strain						
Di Stasi 2003	0	0	-0.6 (0.31)		4.64%	0.55[0.3,1.02]
Rintala 1991	0	0	-0.7 (0.271)		6.08%	0.5[0.29,0.85]
Subtotal (95% CI)					**10.71%**	**0.52[0.35,0.78]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.8); I²=0%						
Test for overall effect: Z=3.18(P=0)						
4.1.3 RIVM strain						
Friedrich 2007	0	0	0.1 (0.22)		9.23%	1.09[0.71,1.68]
Witjes 1996a	0	0	0.1 (0.216)		9.58%	1.12[0.73,1.71]
Witjes 1998a	0	0	0.1 (0.165)		16.43%	1.16[0.84,1.6]
Subtotal (95% CI)					**35.24%**	**1.13[0.91,1.41]**
Heterogeneity: Tau²=0; Chi²=0.05, df=2(P=0.97); I²=0%						
Test for overall effect: Z=1.09(P=0.28)						
4.1.4 Tice strain						
Lamm 1995	0	0	-0.3 (0.149)		20.02%	0.71[0.53,0.95]
Mangiarotti 2008	0	0	-0.2 (0.281)		5.64%	0.85[0.49,1.47]
Witjes 1996b	0	0	0.5 (0.221)		9.13%	1.57[1.02,2.42]
Subtotal (95% CI)					**34.79%**	**0.9[0.72,1.12]**
Heterogeneity: Tau²=0; Chi²=8.91, df=2(P=0.01); I²=77.56%						

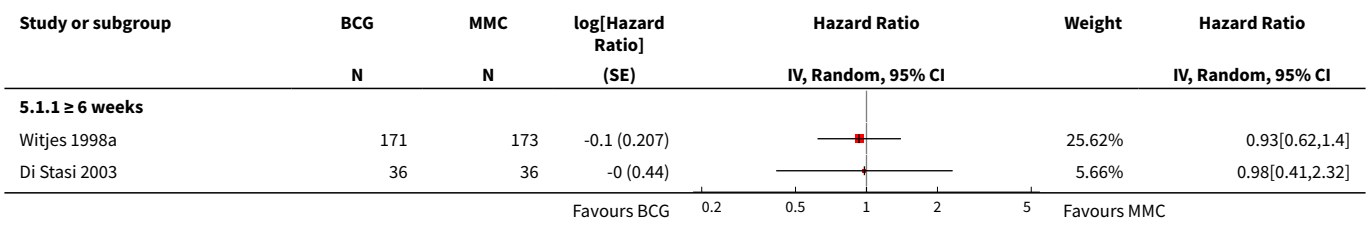


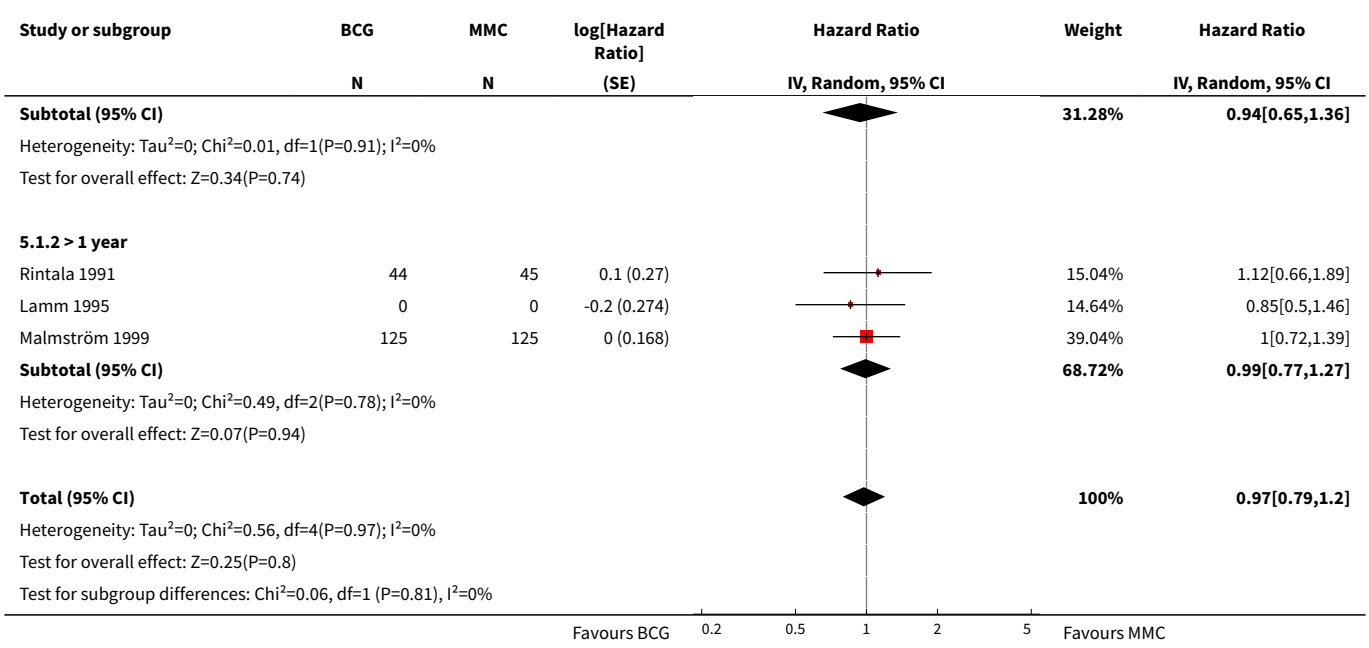


Comparison 5. Different maintenance therapies (posthoc subgroup analyses)

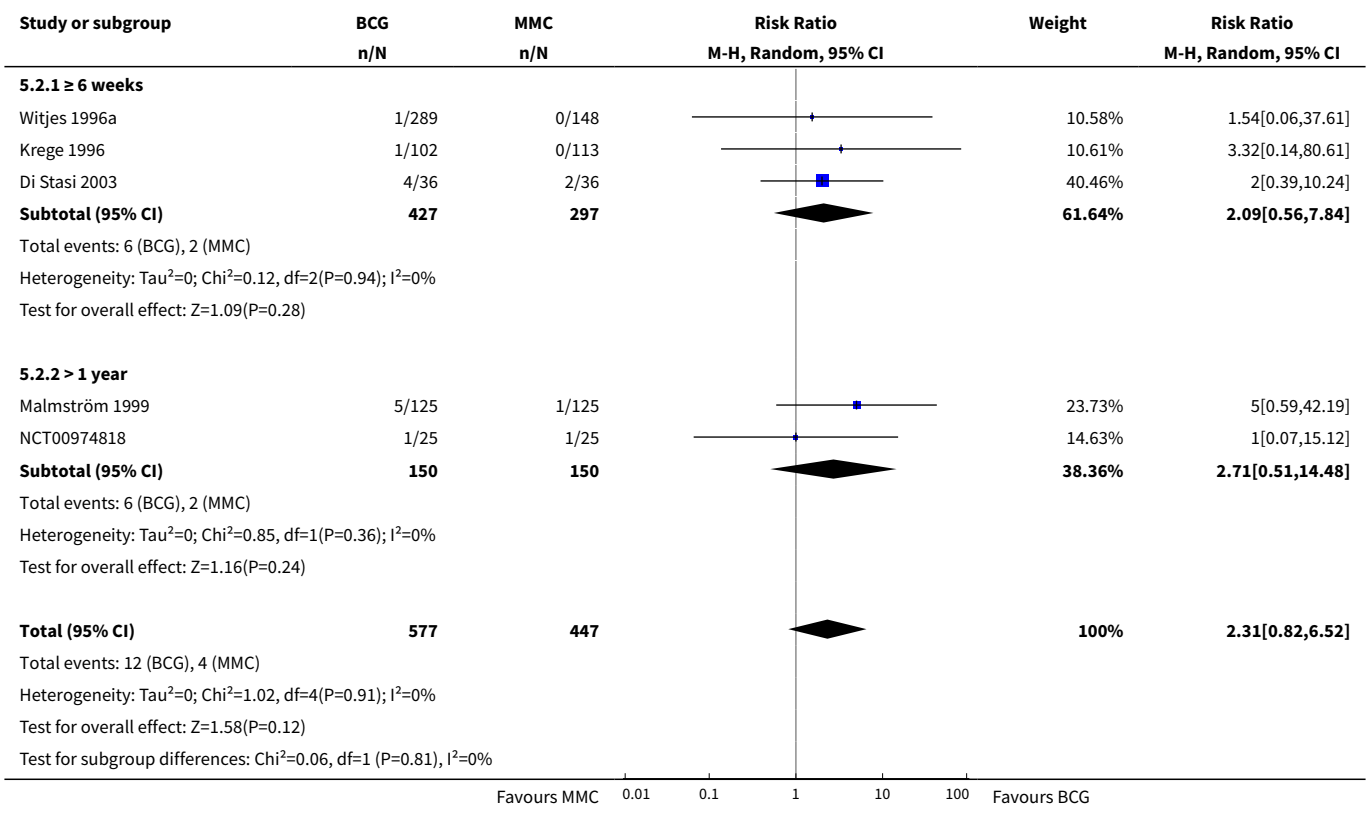
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to death from any cause	5		Hazard Ratio (Random, 95% CI)	0.97 [0.79, 1.20]
1.1 ≥ 6 weeks	2		Hazard Ratio (Random, 95% CI)	0.94 [0.65, 1.36]
1.2 > 1 year	3		Hazard Ratio (Random, 95% CI)	0.99 [0.77, 1.27]
2 Serious adverse effects (≥ 6 weeks)	5	1024	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.82, 6.52]
2.1 ≥ 6 weeks	3	724	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.56, 7.84]
2.2 > 1 year	2	300	Risk Ratio (M-H, Random, 95% CI)	2.71 [0.51, 14.48]
3 Time to recurrence	10		Hazard Ratio (Random, 95% CI)	0.86 [0.68, 1.09]
3.1 ≥ 6 weeks	5		Hazard Ratio (Random, 95% CI)	1.12 [0.85, 1.47]
3.2 > 1 year	5		Hazard Ratio (Random, 95% CI)	0.68 [0.56, 0.82]
4 Time to progression	7		Hazard Ratio (Random, 95% CI)	1.00 [0.79, 1.26]
4.1 ≥ 6 weeks	3		Hazard Ratio (Random, 95% CI)	1.23 [0.85, 1.77]
4.2 > 1 year	4		Hazard Ratio (Random, 95% CI)	0.86 [0.63, 1.16]

Analysis 5.1. Comparison 5 Different maintenance therapies (posthoc subgroup analyses), Outcome 1 Time to death from any cause.





Analysis 5.2. Comparison 5 Different maintenance therapies (posthoc subgroup analyses), Outcome 2 Serious adverse effects (≥ 6 weeks).

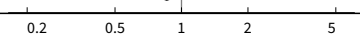


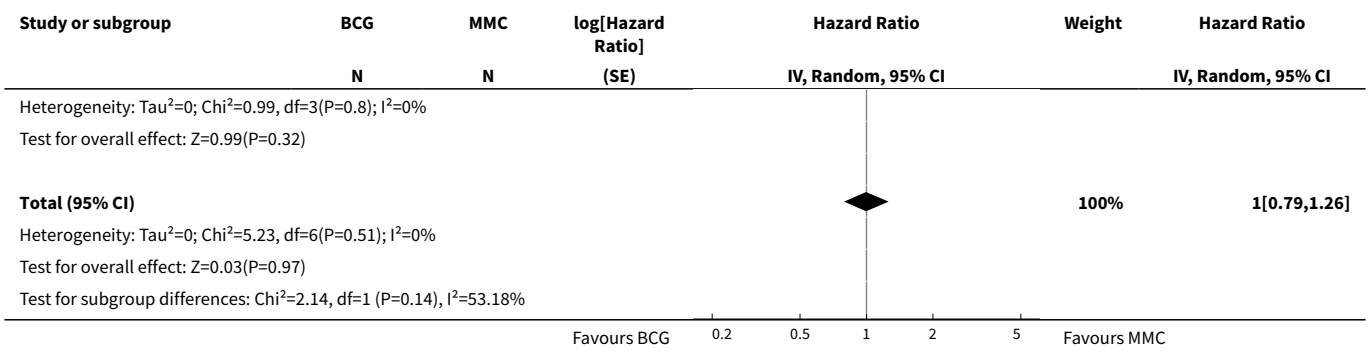
Analysis 5.3. Comparison 5 Different maintenance therapies (posthoc subgroup analyses), Outcome 3 Time to recurrence.

Study or subgroup	BCG N	MMC N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
5.3.1 ≥ 6 weeks						
Witjes 1996b	117	136	0.5 (0.221)		10.57%	1.57[1.02,2.42]
Witjes 1996a	134	136	0.1 (0.216)		10.74%	1.12[0.73,1.71]
Krege 1996	102	113	0.2 (0.271)		8.95%	1.22[0.71,2.07]
Witjes 1998a	159	168	0.1 (0.165)		12.54%	1.16[0.84,1.6]
Di Stasi 2003	36	36	-0.6 (0.31)		7.86%	0.55[0.3,1.02]
Subtotal (95% CI)					**50.67%**	**1.12[0.85,1.47]**
Heterogeneity: Tau²=0.05; Chi²=7.58, df=4(P=0.11); I²=47.26%						
Test for overall effect: Z=0.78(P=0.44)						
5.3.2 > 1 year						
Rintala 1991	44	45	-0.7 (0.271)		8.97%	0.5[0.29,0.85]
Lamm 1995	0	0	-0.3 (0.149)		13.09%	0.71[0.53,0.95]
Ojea 2007b	0	0	-0.2 (0.26)		9.29%	0.8[0.48,1.33]
Ojea 2007a	0	0	-0.6 (0.259)		9.32%	0.54[0.32,0.89]
Mangiarotti 2008	0	0	-0.2 (0.281)		8.67%	0.85[0.49,1.47]
Subtotal (95% CI)					**49.33%**	**0.68[0.56,0.82]**
Heterogeneity: Tau²=0; Chi²=3.22, df=4(P=0.52); I²=0%						
Test for overall effect: Z=3.92(P<0.0001)						
Total (95% CI)					**100%**	**0.86[0.68,1.09]**
Heterogeneity: Tau²=0.09; Chi²=24.77, df=9(P=0); I²=63.66%						
Test for overall effect: Z=1.24(P=0.21)						
Test for subgroup differences: Chi²=8.41, df=1 (P=0), I²=88.11%						

Analysis 5.4. Comparison 5 Different maintenance therapies (posthoc subgroup analyses), Outcome 4 Time to progression.

Study or subgroup	BCG N	MMC N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
5.4.1 ≥ 6 weeks						
Di Stasi 2003	36	36	-0.5 (0.89)		1.76%	0.63[0.11,3.58]
Friedrich 2007	0	0	0.1 (0.22)		28.83%	1.09[0.71,1.68]
Witjes 1998a	171	173	0.6 (0.345)		11.68%	1.79[0.91,3.52]
Subtotal (95% CI)					**42.27%**	**1.23[0.85,1.77]**
Heterogeneity: Tau²=0; Chi²=2.06, df=2(P=0.36); I²=2.95%						
Test for overall effect: Z=1.08(P=0.28)						
5.4.2 > 1 year						
Lamm 1995	0	0	-0.2 (0.241)		24%	0.84[0.52,1.35]
Malmström 1999	125	125	-0.3 (0.265)		19.79%	0.74[0.44,1.24]
Ojea 2007a	0	0	0 (0.446)		7%	1.02[0.43,2.45]
Ojea 2007b	0	0	0.2 (0.448)		6.95%	1.18[0.49,2.85]
Subtotal (95% CI)					**57.73%**	**0.86[0.63,1.16]**





ADDITIONAL TABLES

Table 1. Description of interventions

Study	Intervention (route, frequency, total dose/day)	Comparator (route, frequency, total dose/day)
Michielsen 2013	I1: BCG group (full dose) for 6 weeks; each group had a specific maintenance programme.	C1: MMC group (40 mg in 50 mL saline) weekly for 6 weeks; each group had a specific maintenance programme.
NCT00974818	I1: MMC 40 mg, dissolved in 20 mL sterile water.	C1: BCG 81 mg, dissolved in 53 mL of diluent and saline.
Mangiarotti 2008	I1: therapy started 1 month after TUR. BCG Tice, weekly instillations for 6 weeks, thereafter once a month for 1 year.	C1: therapy started 1 month after TUR. MMC 40 mg in 50 mL saline for once a week for 8 weeks, thereafter for once a month for 1 year.
Friedrich 2007	I1: 6 weekly instillations of BCG RIVM 2×10^8 cfu (BCG 6 week). Therapy started 4 weeks after TUR.	C1: 6 weekly instillations of MMC 20 mg (MMC 6 week). Therapy started 4 weeks after TUR. C2: 6 weekly instillations of MMC 20 mg followed by monthly instillations of MMC 20 mg for 3 years (MMC 3 year). Therapy started 4 weeks after TUR.
Ojea 2007b; Ojea 2007a	I1: low-dose BCG 27 mg. Connaught strain. Instillations started 14–21 days after TUR. The instillations were repeated once a week for 6 weeks followed by another 6 instillations given once every 2 weeks for 12 weeks. I2: very low-dose BCG 13.5 mg. Connaught strain. Instillations started 14–21 days after TUR. The instillations were repeated once a week for 6 weeks followed by another 6 instillations given once every 2 weeks for 12 weeks.	C1: MMC 30 mg, instillations started 14–21 days after TUR. The instillations were repeated once a week for 6 weeks followed by another 6 instillations given once every 2 weeks for 12 weeks.
Di Stasi 2003	I1: Pasteur BCG instillations with 81 mg wet weight (mean 10.2, SEM 9.0×10^8 cfu). Lyophilised BCG was suspended in 50 mL bacteriostatic-free 0.9% saline solution. Suspension was instilled and retained for 120 minutes. Treatment started 3 weeks after TUR.	C1: participants were placed on fluid restriction and oral sodium bicarbonate before intravesical MMC treatments. Under ultrasound control, the bladder was thoroughly drained by repositioning the catheter or participant, or both. MMC 40 mg with 960 mg excipient NaCl dissolved in 100 mL water was instilled

Table 1. Description of interventions *(Continued)*

	Participants who had a complete response to the initial 6 weekly treatments underwent a further 10 monthly instillations. If cancer persisted at 3 months, a second 6-week course was given. If disease persisted at 6 months, there was a cross-over to a 6-week second-line course of BCG for participants in the 2 MMC groups and electromotive MMC for participants in the BCG group.	and retained in the bladder for 60 minutes. Treatment started 3 weeks after TUR. C2: participants were placed on fluid restriction and oral sodium bicarbonate before intravesical MMC treatments. Under ultrasound control the bladder was thoroughly drained by repositioning the catheter or participant. Electromotive instillations of MMC 40 mg with 960 mg excipient NaCl dissolved in 100 mL water, retained for 30 minutes with 20 mA pulsed electric current (600 mA minute). Treatment started 3 weeks after TUR.
Malmström 1999	I1: BCG (Danish strain 1331) 120 mg containing 1 × $l0^9$ cfu, dissolved in 50 mL saline. Therapy was begun 1–3 weeks after TUR or biopsies, and was given weekly for 6 weeks, then monthly for up to 1 year and every 3 months during year 2.	C1: MMC 40 mg dissolved in 50 mL phosphate buffer (pH 7.4). Therapy was begun 1–3 weeks after TUR or biopsies, and was given weekly for 6 weeks, then monthly for up to 1 year and every 3 months during year 2.
Witjes 1998a	I1: Intravesical therapy was started 7–15 days after resection. BCG-RIVM (5 × 10^8 bacilli in 50 mL saline) was given weekly for 6 consecutive weeks. In case of a recurrence at 3 months, a complete resection was performed, where after in BCG-treated participants a second course was given.	C1: intravesical therapy was started 7–15 days after resection. MMC 30 mg in 50 mL saline was given weekly for 4 consecutive weeks and thereafter monthly for 5 months. In case of a recurrence at 3 months, a complete resection was performed, and instillations were continued.
Krege 1996	I1: 6 weeks after TUR, BCG 120 mg Connaught strain in 50 mL sodium chloride was instilled intravesically for 1 hour. At the same time, BCG 0.5 mg was applied subcutaneously by multiple punctures in the forearm. Therapy was continued once weekly for 6 weeks and once a month for 4 months.	C1: 6 weeks after TUR, MMC 20 mg in 50 mL sodium chloride was instilled via a catheter and kept in the bladder for 2 hours. Instillations were performed every 2 weeks during year 1 and once a month during year 2.
Witjes 1996a; Witjes 1996b	I1: Treatment start 7–20 days after TUR. BCG-RIVM 5 × 10^8 bacilli in 50 mL saline was administered once a week for 6 weeks. If disease recurred within 6 months in the BCG treatment group, a second course of 6 weekly instillations was administered after complete tumour resection. I2: Treatment start 7–20 days after TUR. BCG-Tice 5 × 10^8 bacilli in 50 mL saline was administered once a week for 6 weeks. If disease recurred within 6 months in the BCG treatment group, a second course of 6 weekly instillations was administered after complete tumour resection.	C1: treatment start 7–20 days after TUR. MMC 30 mg in 50 mL saline instilled once a week for 1 month (weeks 1–4) and thereafter once a month for 6 months. If a recurrence was detected in the MMC group, complete resection was carried out and the MMC treatment continued monthly for another 3 months.
Lamm 1995	I1: lyophilised Tice BCG 50 mg 5 × 10^8 cfu diluted in 50 mL of sterile, preservative-free saline. The 50 mL suspension was instilled into the bladder by gravity flow. Participants were instructed to lie on their abdomen for 15 minutes and on their left, right and back for 15 minutes each and to retain the suspension, if possible, for 2 hours. Treatments were repeated weekly for 6 weeks and at 8 and 12 weeks, then monthly to 1 year. Treatment was initiated no sooner than 1 week and no later than 2 weeks after TUR.	C1: MMC 20 mg in 20 mL of sterile water. Treatments were repeated weekly for 6 weeks and at 8 and 12 weeks, then monthly to 1 year. Treatment was initiated no sooner than 1 week and no later than 2 weeks after TUR.

Table 1. Description of interventions *(Continued)*

Rintala 1991	I1: Intravesical BCG 75 mg in 50 mL distilled water for 2 hours 6×10^8 cfu Pasteur Strain F. Instillations started 2 weeks after TUR. Weekly repetition during the first month, then once a month for 2 years.	C1: MMC 20–40 mg (AUC method) for 2 hours. Instillations started 2 weeks after TUR. Weekly repetition during the first month, then once a month for 2 years.

[a]The term 'clinical practice setting' refers to the specification of the intervention/comparator as used in the course of a standard medical treatment (such as dose, dose escalation, dosing scheme, provision for contraindications and other important features).
AUC: area under the curve; BCG: Bacillus Calmette Guérin; C: comparator; cfu: colony-forming units; I: intervention; MMC: mitomycin C; NaCl: sodium chloride, TUR: transurethral resection.

Table 2. Baseline characteristics

Study	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up)	Description of participants	Trial period	Country	Setting
Michielsen 2013	I1: BCG full dose C1: MMC 40 mg	Weekly for 6 weeks, each group with specific maintenance programme.	Intermediate-risk non-muscle invasive urothelial carcinoma of the bladder	—	Belgium	Hospital
Mangiarotti 2008	I1: BCG Tice C1: MMC 40 mg	BCG weekly for 6 weeks, then 1 × month for 1 year. MMC 1 × week for 8 weeks, then 1 × month for 1 year (follow-up 42–45 months).	Intermediate-risk non-muscle invasive urothelial carcinoma of the bladder, Ta-T1 G1-2	—	Italy	Hospital
Friedrich 2007	I1: BCG RIVM 2×10^8 cfu C1: MMC 20 mg C2: MMC 20 mg long-term	All 3 treatments for 6 weeks; long-term MMC continued for 3 years	Intermediate-risk pTa G1 tumours or pTa G2 up to pT1 tumours (G1-3)	1995–2002	Germany	Hospital
Ojea 2007b; Ojea 2007a	I1: BCG Connaught strain low-dose 27 mg I2: BCG Connaught strain very low-dose 13.5 mg C1: MMC 30 mg	Once a week for 6 weeks, followed by another 6 instillations every 2 weeks for 12 weeks.	Intermediate-risk Ta G2 and T1 G1-2 without Cis	1995–1998	Spain	Hospital, multicentre
Di Stasi 2003	I1: BCG Pasteur 81 mg C1: MMC 40 mg C2: MMC 40 mg electromotive	Weekly for 6 weeks, a further 6 weeks for non-responders and a follow-up 10 monthly treatments.	Multifocal Cis and most had concurrent pT1	1994–2001	Italy	Hospital, multicentre

Table 2. Baseline characteristics *(Continued)*

Malmström 1999	I1: BCG 120 mg Danish strain C1: MMC 40 mg	Weekly for 6 weeks, then monthly for 1 year and then every 3 months for 3 years.	Ta G1-3 or T1 G1-2	1987–1992	Sweden-Norway	Hospital, multicentre
Witjes 1998a	I1: BCG RIVM C1: MMC 30 mg	MMC: weekly for 4 weeks, then monthly for 5 months. BCG: weekly for 6 weeks.	pTa and pT1 including Cis	1985–1986	Europe	Hospital, multicentre
Krege 1996	I: TUR C1: BCG 120 mg Connaught strain C2: MMC 20 mg	BCG: weekly for 6 weeks, then monthly for 4 months. MMC: every 2 weeks for 12 months, then once a months for 2 years.	pTa/1 G1-3	1985–1992	Germany	Hospital, multicentre
Witjes 1996a; Witjes 1996b	I1: BCG RIVM 5 × 10^8 bacilli I2: BCG Tice 5 × 10^8 bacilli C1: MMC 30 mg	BCG: weekly for 6 weeks, a further 6 weeks for non-responders. MMC: once a week for 1 month, then once a month for 6 months, for non-responders monthly another 3 months.	Ta or T1 including Cis	1987–1990	—	Hospital, multicentre
Lamm 1995	I1: BCG Tice 50 mg (5 × 10^8 cfu) C1: MMC 20 mg	Weekly for 6 weeks and at 8 and 12 weeks, then monthly to 1 year.	Ta or T1 at increased risk	—	—	Hospital, multicentre
Rintala 1991	I1: BCG Pasteur strain 75 mg C1: MMC 20–40 mg	Weekly for 1 month, then once per months for 2 years.	Cis G1-3, Ta-T1 G1-3	1984–1987	—	Hospital, multicentre

BCG: Bacillus Calmette-Guérin; Cis: carcinoma in situ; cfu: colony-forming units; MMC: mitomycin C; NaCl: sodium chloride, TUR: transurethral resection.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees

#2 bladder*:ti,ab,kw near/3 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan*):ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor: [BCG Vaccine] explode all trees

#5 (bacillus calmette guerin or BCG or calmette guerin):ti,ab,kw

#6 calmette*:ti,ab,kw near/3 vaccine*:ti,ab,kw

#7 #4 or #5 or #6

#8 MeSH descriptor: [Mitomycin] explode all trees

#9 (mitomycin or mitocinc or mitocin c or ametycine or mutamycin or mitocin-c or nsc26980 or nsc-26980 or nsc 26980 or mitomycin-c or 50SG953SK6):ti,ab,kw

#10 #8 or #9

#11 #3 and #7 and #10

Appendix 2. MEDLINE (Ovid) search strategy

1	exp urinary bladder neoplasms/
2	(bladder* adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan*)).tw.
3	1 or 2
4	BCG vaccine/
5	(bacillus calmette guerin or BCG or calmette guerin).mp.
6	(calmette* adj3 vaccine*).mp.
7	or/4-6
8	Mitomycin/
9	50SG953SK6.rn.
10	(mitomycin or mitocinc or mitocin c or ametycine or mutamycin or mitocin-c or nsc26980 or nsc-26980 or nsc 26980 or mitomycin-c).mp.
11	or/8-10
12	3 and 7 and 11
13	randomized controlled trial.pt.
14	controlled clinical trial.pt.
15	randomized.ab.
16	placebo.ab.
17	drug therapy.fs.
18	randomly.ab.
19	trial.ab.
20	groups.ab.
21	or/13-20
22	exp animals/ not humans.sh.
23	21 not 22
24	12 and 23

Appendix 3. Embase (Ovid) search strategy

1	exp bladder tumor/
2	(bladder* adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan*)).tw.
3	1 or 2
4	exp BCG vaccine/
5	(bacillus calmette guerin or BCG or calmette guerin).mp.
6	(calmette* adj3 vaccine*).mp.
7	or/4-6
8	exp mitomycin C/
9	mitomycin.rn.
10	(mitomycin or mitocinc or mitocin c or ametycine or mutamycin or mitocin-c or nsc26980 or nsc-26980 or nsc 26980 or mitomycin-c or 50SG953SK6).mp.
11	or/8-10
12	3 and 7 and 11
13	Crossover Procedure/
14	double-blind procedure/
15	randomized controlled trial/
16	single-blind procedure/
17	(random$ or factorial$ or crossover$ or cross over$ or placebo$ or assign$ or allocat$ or volunteer$).mp.
18	((doubl$ or singl$) adj blind$).mp.
19	or/13-18
20	12 and 19

Appendix 4. Scopus search strategy

((TITLE-ABS-KEY(bladder* W/3 (cancer* OR carcinoma* OR tumor* OR tumour* OR neoplas*))) AND (TITLE-ABS-KEY(“bacillus calmette Guerin” OR bcg OR calmette)) AND (TITLE-ABS-KEY(mitomycin OR mitocinc OR mitocin c OR ametycine OR mutamycin OR mitocin-c OR nsc26980 OR nsc-26980 OR nsc 26980 OR mitomycin-c OR 50sg953sk6))) AND (TITLE-ABS-KEY("clinical trial*" OR "research design" OR "comparative stud*" OR "evaluation stud*" OR "controlled trial*" OR "follow-up stud*" OR "prospective stud*" OR random* OR placebo* OR "single blind*" OR "double blind*"))

Appendix 5. Web of Science search strategy

# 1	TS=(bladder* NEAR/3 (cancer* or carcinoma* or tumor* or tumour* or neoplas*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 2	TS=(BCG vaccine) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 3	TS=(bacillus calmette guerin or BCG or calmette guerin) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 4	TS=(calmette* NEAR/3 vaccine*). *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 5	#4 OR #3 OR #2 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 6	TS=(mitomycin or mitocinc or mitocin c or ametycine or mutamycin or mitocin-c or nsc26980 or nsc-26980 or nsc 26980 or mitomycin-c or 50SG953SK6) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 7	#6 AND #5 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 8	TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*
# 9	#8 AND #7 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2015*

Appendix 6. LILACS search strategy

(bladder* OR vejiga OR bexiga OR vesical) AND (bcg OR bacillus calmette guerin OR calmette) AND (mitomycin OR mitocinc OR mitocin c OR ametycine OR mutamycin OR mitocin-c) AND ((PT randomized controlled trial OR PT controlled clinical trial OR PT multicenter study OR MH randomized controlled trials as topic OR MH controlled clinical trials as topic OR MH multicenter study as topic OR MH random allocation OR MH double-blind method OR MH single-blind method) OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT in vitro)

Appendix 7. WHO ICTRP search strategy

1. Bladder* AND BCG AND mitomycin
2. Bladder* AND “Bacillus Calmette Guerin” AND mitomycin

Appendix 8. ClinicalTrials.gov search strategy

1. Bladder* AND BCG AND mitomycin
2. Bladder* AND “Bacillus Calmette Guerin” AND mitomycin

CONTRIBUTIONS OF AUTHORS

SS: project co-ordination of this update, protocol writing, data extraction, quality assessment, analyses and draft manuscript.

FK: critical feedback, review protocol and manuscript.

BC: search strategy, and protocol and manuscript review.

DD: manuscript review, data extraction and quality assessment.

LMK: protocol and manuscript review, data extraction and quality assessment.

RD: protocol and manuscript review, study selection and quality assessment.

SK: statistical advice, statistical analyses and manuscript review.

KJ: statistical advice, statistical analyses, and protocol and manuscript review.

PD: critical feedback, protocol and manuscript review.

JJM: methodological guidance, critical feedback, protocol and manuscript review.

All authors approved the final version of this review.

DECLARATIONS OF INTEREST

SS: none.

FK: none.

BC: none.

DD: none.

LMK: none.

RD: received lecture fees by Roche and travel grants by Biogen.

SK: employed by the Institute of Medical Biometry and Informatics, University Heidelberg, which receives support by the German Society for Urology (Deutsche Gesellschaft für Urologie, DGU) for conducting urology-related systematic reviews.

KJ: employed by the Institute of Medical Biometry and Informatics, University Heidelberg, which receives support by the German Society for Urology (Deutsche Gesellschaft für Urologie, DGU) for conducting urology-related systematic reviews.

PD: none.

JJM: none.

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Internal sources

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a published protocol (Schmidt 2015).

Adverse effects: we omitted adverse effects from the list of main outcomes for the 'Summary of findings' table, as adverse effects were reported very heterogeneously and were not clearly defined among included studies.

Secondary outcomes: We have added "quality of life" to the list of secondary outcomes.

Sensitivity analyses: we planned to examine the methodological quality according to risk of bias, by conducting separate meta-analyses for low risk of bias studies, excluding studies judged as high or unclear (or both) risk of bias. As there was no study rated as low risk of bias, we could not perform these sensitivity analyses.

Subgroup: we planned to explore clinical heterogeneity by testing high risk versus intermediate risk of tumour recurrence. These analyses were not conducted as included studies did not report information for these subgroups separately. We also aimed at exploring effects of different schedules of BCG installations versus different schedules of MMC (less than one year versus more than one year) at the protocol stage. Due to the heterogeneity and paucity of data, these subgroup analyses were not conducted.

Subgroup (posthoc): we added the comparison of different BCG maintenance therapy strategies (BCG administration greater than six weeks and BCG administration greater than one year) as posthoc subgroup analyses as we found this to be of clinical importance.

We have excluded two studies in Chinese, as we were unable to translate them.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Intravesical; Antibiotics, Antineoplastic [administration & dosage] [*therapeutic use]; BCG Vaccine; Carcinoma, Transitional Cell [*drug therapy]; Mitomycin [administration & dosage] [*therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome; Urinary Bladder Neoplasms [*drug therapy]

MeSH check words

Humans