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Intravesical therapy for non-muscle invasive bladder cancer: a network meta-analysis (Protocol)

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[Intervention Protocol]

Intravesical therapy for non-muscle invasive bladder cancer: a network meta-analysis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess via network analysis the effects of different intravesical adjuvant therapies for early stage, non-muscle invasive bladder cancer.

BACKGROUND

Description of the condition

Bladder cancer, or urothelial carcinoma of the bladder, is the seventh most common cancer among men and the seventeenth most common among women worldwide (Ploeg 2009). An estimated 429,000 new cases of bladder cancer were diagnosed worldwide in 2012 (Ferlay 2015). In the United States, bladder cancer accounts for 6.6% of new adult malignancies in men and 2.2% of new adult malignancies in women (Siegel 2015). In all, there were 74,000 newly diagnosed cases of bladder cancer and 16,000 deaths from bladder cancer in the United States in 2015 (Siegel 2015). With appropriate treatment, non-muscle invasive tumours are considered curable (Clark 2013).

Bladder cancer is a heterogeneous group of malignancies that occur in the epithelial lining of the urinary bladder. A number of diverse molecular pathways have been proposed for its development (Ahmad 2012).

Non-muscle invasive bladder cancer can be subdivided into two categories: papillary and non-papillary (also known as flat or sessile) tumours. Papillary tumours grow out of the inner layer of the bladder, while non-papillary tumours lie flat against the inner layer of cells. When the tumours are high grade, they carry an increased risk of progression. According to the TNM classification system, papillary non-invasive bladder cancers are designated Ta when they are confined to the outermost layer of bladder cells or

T1 when they invade the lamina propria (basement membrane beneath the outer layer of cells). Non-papillary cancers are designated Tis (in situ) if they are confined to the outer layer of the bladder (Sobin 2009).

Non-muscle invasive bladder tumours account for approximately 80% of primary cancers of the urinary bladder (Herr 1997). Of non-muscle invasive bladder tumours, 50% to 70% will recur, and about 10% to 20% will progress to invasive disease (Herr 1997; Rübben 1988). Overall, 15-year progression-free survival among people with low to high grade papillary tumour (Ta) is 95% to 61%, respectively, and 15-year bladder cancer-specific survival is 74% among high grade papillary tumours. Among people with T1 tumour, 15-year progression-free survival is 44%, and 15-year bladder cancer-specific survival is 62% (Kaufman 2009).

Bladder cancer most often clinically presents as painless intermittent haematuria. Other symptoms include urinary frequency, urgency, or irritative voiding. Diagnosis is made by cystoscopic evaluation of the bladder and urine cytology. Directed bladder biopsies are used in case of positive urinary cytology with no visible tumour detected by cystoscopy.

Description of the intervention

The mainstay treatment for people with superficial bladder cancer is surgical resection in the form of transurethral resection (TUR). However, based on pathological grade and stage at presentation, as well as other factors summarised in the European Organisation for Research and Treatment of Cancer (EORTC) scoring system (Sylvester 2006), rates of recurrence and disease progression can be unacceptably high, thereby providing the rationale for adjuvant intravesical therapy (Clark 2013). Intravesical infusion of antitumour agents allows for the drug to be delivered directly into the bladder via a urinary catheter. The drug administration can vary in the dosage administered and the amount of time the drug can work prior to allowing the patient to void the bladder.

Immunotherapies

Immunotherapies for management of non-muscle invasive bladder cancer include Bacillus Calmette-Guérin (BCG) and interferon (IFN) therapy. BCG is an attenuated vaccine commonly used for the prevention of tuberculosis but has also been used in the treatment of early stage bladder cancer. While the exact mechanism of action in bladder cancer remains unclear, BCG appears to stimulate a local immune response against the tumour. Some proposed mechanisms include promotion of proinflammatory cytokines (IL-1, IL-6, IL-8, and tumour necrosis factor) and chemoattractants, and the activation and promotion of cellular immune response (macrophages and neutrophils) (Luo 2013).

Three main types of IFN therapy have been studied in bladder cancer: IFN-α, IFN-β, and IFN-γ; however, the majority of studies focus on IFN-α-2b. IFN-α is an immune response modifier that mounts an anti-tumour response through direct and indirect pathways. Reports from murine studies show IFN-α is capable of inhibiting tumour growth and vascularisation, as well as down-regulating basic fibroblast growth factor, matrix metalloprotease-9 mRNA, and protein expression (Slaton 1999). In studies utilising human bladder cancer cell lines, IFN-α has been shown to act via a tumour necrosis factor-related mechanism to induce apoptosis among bladder cancer cells (Papageorgiou 2004).

Chemotherapies

Chemotherapies for management of non-muscle invasive bladder cancer include doxorubicin, epirubicin, gemcitabine, mitomycin C, thiotepa, and valrubicin, among others. Doxorubicin, epirubicin, and valrubicin fall into the anthracycline drug class. They interact with the cell DNA and topoisomerase II enzyme, vital for DNA replication, to stop cells from multiplying and thus contributing to cell death (Pommier 2010). Gemcitabine is a nucleoside analogue (i.e. mimics DNA building blocks), which assimilates into the DNA during replication, resulting in tumour cell death (Cerqueira 2007). Mitomycin C is an antitumour antibiotic that induces tumour cell death by forming cross links with DNA, resulting in DNA breakage. Thiotepa is an alkylating agent (i.e. attaches alkyl groups to quickly replicating DNA, resulting in DNA damage and cell death).

How the intervention might work

Several systematic reviews and meta-analyses have compared a specific intravesical agent to no treatment (e.g. BCG versus no treatment; mitomycin C versus no treatment), demonstrating the significant impact of adjuvant therapy on controlling tumour recurrence and progression (Shelley 2000; Shelley 2003; Sylvester 2008). Intravesical agents reduce tumour recurrence and prevent or delay tumour progression to muscle invasion and metastases as either immune modulators (BCG, interferon) or chemotherapeutic agents (mitomycin, epirubicin, doxorubicin, thiotepa) (Clark 2013).

Immunotherapies

A systematic review of TUR plus BCG therapy versus TUR alone reported that people who received BCG had a 67% lower rate of bladder cancer recurrence at 12 months. The most common adverse events associated with BCG were cystitis (67%), haematuria (23%), fever (25%) and urinary frequency (71%) (Shelley 2000). One randomised trial enrolling people with pathological T1 (pT1) bladder cancer found that there was no significant difference between IFN-α following TUR and TUR alone for the outcomes of relapse rate, disease progression, mortality, and adverse events (Portillo 1997). However, when used in combination with mitomycin C or epirubicin, IFN has demonstrated efficacy

in comparison to either treatment alone among people with stage Ta and T1 bladder cancer (Engelmann 1992, Raitanen 1995).

Chemotherapies

Several randomised controlled trials comparing doxorubicin versus TUR alone have been performed, reporting a 20% average decrease in tumour recurrence with the use of doxorubicin (Thrasher 1992). A systematic review of doxorubicin versus BCG for non-muscle invasive bladder cancer identified four studies and found doxorubicin to be inferior for preventing tumour recurrence (Shelley 2010). Likewise, a systematic review of epirubicin versus BCG reported that BCG was assoicated with a lower risk of tumour recurrence than epirubicin (RR 0.69, 95% CI 0.60 to 0.79). There was no significant difference observed for the outcomes of disease progression or overall survival between the two treatment strategies. However, BCG was associated with a significantly higher rate of adverse events (Shang 2011). Studies have evaluated valrubicin in BCG refractory non-invasive bladder cancer patients, finding good response rates (21% complete response) (Steinberg 2000).

A systematic review of intravesical gemcitabine for the treatment of non-muscle invasive bladder cancer identified six studies (Jones 2012). In comparison to TUR alone, one study reported that gemcitabine was not associated with a significant difference in tumour recurrence rates (Böhle 2009). However, studies comparing gemcitabine versus mitomycin C found gemcitabine to be associated with lower tumour recurrence rates (28% versus 39%), but the results were not statistically significant (Addeo 2010; Jones 2012). In a comparison of BCG versus gemcitabine, rates of tumour recurrence among low-risk patients were similar (25% on BCG versus 30% on gemcitabine); however, gemcitabine was associated with higher recurrence rates in high-risk patients (28% versus 53%) (Jones 2012).

A recent literature review reported that early instillation of mitomycin C seems effective in reducing the tumour recurrence rate in low and intermediate risk bladder cancers (Volpe 2010). Another systematic review of BCG versus mitomycin C reported no significant difference in the rate of recurrence, disease progression, or survival between the two treatment strategies. Additionally, there was no significant difference between the two strategies on adverse events, except for skin rash, which was more common with mitomycin (Shelley 2003).

Most early studies of thiotepa adjuvant therapy versus TUR alone reported lower tumour recurrence rates with the use of thiotepa (Lamm 1995). However, in comparison to mitomycin C or BCG, thiotepa is inferior in terms of tumour recurrence (Tomaszewski 2010).

Why it is important to do this review

Previous systematic reviews and meta-analyses have assessed the role of different intravesical agents such as mitomycin C, epirubicin, gemcitabine, and BCG in reducing tumour recurrence rates and preventing or delaying tumour progression to muscle invasion and metastasis, through action as either immune modulators or chemotherapeutic agents (Clark 2013). Specifically, systematic reviews and meta-analyses have compared an intravesical agent to no treatment (e.g. BCG versus no treatment, mitomycin C versus no treatment, etc.) (Shelley 2000; Shelley 2003); however, there have been few direct, head-to-head comparisons of intravesical agents to each other (e.g. BCG versus mitomycin C versus epirubicin versus gemcitabine) (Jones 2012). In the absence of data to inform a direct meta-analysis, network meta-analysis can be used to compare these treatments in an indirect way. In such a multitreatment network, meta-analytic techniques are used to compare the effect of all adjuvant therapies that may or may not have already been directly compared to a common treatment or control condition in clinical trials. The aim of this Cochrane review is therefore to perform a comprehensive network meta-analysis to assess the comparative effects of all agents used to treat non-muscle invasive bladder cancer.

OBJECTIVES

To assess via network analysis the effects of different intravesical adjuvant therapies for early stage, non-muscle invasive bladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials. We will exclude quasi-randomised trials, cluster-randomised trials, and cross-over design trials. We will include studies regardless of their publication status or language of publication.

Types of participants

We will include studies that enrolled adults (> 18 years) with newly diagnosed, clinically localised pathological Ta or T1 bladder cancer. We will exclude trials in participants with recurrent bladder cancer (participants who have had prior transurethral resection of a bladder tumour with or without subsequent intravesical therapy). We will also exclude trials that enrolled participants with

carcinoma in situ (CIS) or that did not report outcomes separately for the Ta/T1 group to permit a meaningful analysis.

Types of interventions

We will include any treatment used as adjuvant intravesical therapy in the management of non-muscle invasive bladder cancer (NMIBC), including:

- Bacillus Calmette-Guerin (BCG);
- doxorubicin;
- epirubicin;
- gemcitabine;
- mitomycin C;
- thiotepa;
- valrubicin;
- interferon (IFN).

We will exclude trials in which the delivery of the intravesical agent is delivered in conjunction with external energy delivered through a device, such as in electromotive intravesical therapy. We will also exclude studies in which BCG is administered in conjunction with intravesical interferon.
We will consider all doses and treatment durations of intravesical therapy.

Types of outcome measures

We will not use the measurement of the outcomes assessed in this review as an eligibility criterion. This review will focus on patient-important outcomes.

Primary outcomes

- Time to tumour recurrence (relapse), as measured from the time of randomisation to the date of pathological confirmation of recurrent bladder tumour of any grade/stage
- Time to tumour progression, as measured from the time of randomisation to the date of pathological confirmation of recurrent bladder tumour of higher stage (e.g. pTa to pT1/pT2/pT3; pT1 to pT2/3)
- Incidence of serious (grade 3 or 4) adverse events (e.g. BCG sepsis, bladder perforation, bladder contracture)

Secondary outcomes

- Overall survival, as measured from the time of randomisation to the date of death of any cause
- Disease-specific survival, as measured from the time of randomisation to the date of death from bladder cancer
- Quality of life, as assessed by validated, bladder-specific instruments (e.g. EORTC QLQ-BLS24, EORTC QLQ-BLM30)

We will not abstract data on frequent minor adverse events such as dysuria, frequency, haematuria, or others.
If we are unable to abstract and pool data for time-to-event rates, we will measure event rates at two- and five-year time intervals.

Search methods for identification of studies

We will perform a comprehensive search with no restrictions on the language of publication or publication status. We plan to rerun searches within three months prior to anticipated publication of the review and incorporate any additional eligible studies. For non-English language studies, we will seek assistance with translation within and outside Cochrane. If we are unable to translate one or more study reports deemed to be relevant, we will discuss this as a limitation of the review.

Electronic searches

We will search the following sources from inception of each database.

- Cochrane Central Register of Controlled Trials (CENTRAL; for the search strategy, see Appendix 1).
- MEDLINE (via PubMed; see Appendix 2).
- EMBASE.

We will also search the following trials registers.

- ClinicalTrials.gov (www.clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/).
- MetaRegister of Controlled Trials (mRCT; www.isrctn.com/page/mrct).

Searching other resources

In order to identify any recently completed studies that have not yet been published in full, we will handsearch the abstracts from the last two annual meetings of the American Society of Clinical Oncology (ASCO), the American Urological Association (AUA), and the European Association of Urology (EAU). Finally, we will handsearch the references of identified systematic and narrative reviews as well as all included studies in order to find any other relevant studies (Montori 2005). We will provide documentation of the search process (sources searched, when, by whom and using what terms) in the published review.
We will also seek to contact the manufacturers of intravesical agents as well as experts in the field to identify unpublished or ongoing trials.

Data collection and analysis

Selection of studies

We will use reference management software to identify and remove potential duplicate records. Two review authors will independently scan the abstract, title, or both, of remaining records retrieved, to determine which studies should be assessed further. Two review authors will investigate all potentially relevant records as full text, map records to studies, and classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will resolve any discrepancies through consensus or recourse to a third review author. If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification', and we will contact study authors for clarification. We will document reasons for exclusion of studies that readers may have reasonably expected to be included in the review in a 'Characteristics of excluded studies' table. We will present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of study selection (Moher 2009).

Data extraction and management

Two review authors will independently extract data from all studies using a standardised data extraction form that we will pilot test according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will collect data on the following items.

- General study information: study title, authors, source.
- Study characteristics: study design, study dates, country, setting, duration of follow-up.
- Participant characteristics: participant inclusion and exclusion criteria, number of participants enrolled overall and by study arm, number of participants randomised, number of participants included in the analysis, specific disease diagnosis including stage (Ta/T1) and grade, mean participant age, participant sex.
- Interventions: name, dose, route, administration schedule, and any associated therapies.
- Outcomes: definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups.
- Study funding sources and declarations of interest by authors.
- Study limitations to determine the risk of bias.

We will extract outcomes data relevant to this Cochrane review as needed for calculation of summary statistics and measures of variance.
We will resolve any disagreements by discussion, or, if required, by consultation with a third review author.
We will provide information, including trial identifier, about potentially relevant ongoing studies in the table 'Characteristics of ongoing studies'.
We will attempt to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

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

Assessment of risk of bias in included studies

Two review authors will assess the risk of bias of each included study independently. We will resolve disagreements by consensus, or by consultation with a third review author.
We will assess risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011c). We will assess 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 will judge risk of bias domains as 'low risk' (plausible bias unlikely to seriously alter the results; if all criteria were met), 'high risk' (plausible bias that seriously weakens confidence in the results; if one or more criteria were not met), or 'unclear risk' (plausible bias that raises some doubt about the results; if one or more criteria were assessed as unclear) and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We will present a 'Risk of bias' summary figure to illustrate these findings.
For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we will evaluate the risk of bias separately for each outcome, and we will group outcomes according to whether they are measured subjectively or objectively when reporting our findings in the 'Risk of bias' tables.
We define the following endpoints as subjective outcomes.

- Time to tumour recurrence (relapse).
- Time to tumour progression.
- Quality of life.
- Incidence of serious (grade 3 or 4) adverse events.
- Disease-specific survival.

We define the following endpoints as objective outcomes.

- Overall survival.

We will also assess attrition bias (incomplete outcome data) on an outcome-specific basis.
We will further summarise the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

Measures of treatment effect

Time-to-event data

For time-to-event data (i.e. time to tumour recurrence, time to tumour progression, overall survival and disease specific survival), for each included study we will calculate the observed minus expected events (O minus E) and variance from the reported time-to-event estimates to obtain the log hazard ratio (LnHR) and standard error (SE) of LnHR. Where trials do not report time-to-event estimates, we will extract data from papers using the methods described by Parmar 1998 and Tierney 2007. We will report summary estimates as hazard ratios (HRs) with 95% confidence intervals (CIs).

Dichotomous data

We will summarise dichotomous data (i.e. incidence of serious (grade 3 or 4) adverse events) as risk ratios (RRs) with 95% CIs.

Continuous data

For continuous data (i.e. quality of life), we will obtain the mean and standard error from each trial or use the methods by Hozo 2005 to approximate the mean if the primary study reports a median. We will express continuous data as standardised mean differences (SMDs) with 95% CIs.

Unit of analysis issues

Due to the nature of the disease and treatment, we expect to only include parallel randomised controlled trials in this systematic review. In the case of repeated follow-up (e.g. reporting of survival at 6 months and 12 months), we will use the longest follow-up from each study. We will treat recurring events as a single event occurring in one participant (e.g. four instances of grade III nausea in one participant will be considered as one participant with grade III nausea). Additionally, provided the nature of the disease, we do not expect unit of analysis issues associated with multiple treatment attempts or use of multiple body parts. Finally, in the case of multiple intervention arms (e.g. different doses), we will combine similar arms together to create a single pair-wise comparison (Higgins 2011d).

Dealing with missing data

For any study with missing data, we will attempt to contact the study's principal investigator, corresponding author, or both, as suggested in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). If we are unable to obtain missing data that would be required in order to include the study in a particular meta-analysis, we will include the study in the systematic review but exclude it from the meta-analysis for the outcome with missing data, discussing any potential impacts. We will not apply imputation methods.
We will perform intention-to-treat analyses if data is available; we will otherwise perform available case analyses and will identify these analyses as such.

Assessment of heterogeneity

We will assess heterogeneity by identifying methodological differences between studies such as the impact of potential risk of bias on results. Clinical heterogeneity will be assessed by comparing details among participants, interventions, comparisons, and outcomes among trials. We will assess statistical heterogeneity (inconsistency) using the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis. An I^2 value greater than 50% will be considered substantial, and we will conduct further exploration of the cause behind said heterogeneity via subgroup analysis (Higgins 2003; Higgins 2011a).

Assessment of reporting biases

We will assess the possibility of publication bias using a funnel plot in the case that there are at least 10 studies in the meta-analysis (Sterne 2011). Within each study, we will evaluate selective reporting of outcomes by comparing outcomes reported with outcomes specified in the protocol, if available.

Data synthesis

We will only perform meta-analysis if participants, interventions, comparisons and outcomes are sufficiently similar to ensure that the pooled estimate will be clinically meaningful.

Meta-analysis of direct evidence (direct comparison of treatment effects)

We will summarise data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we will use the Mantel-Haenszel method; for continuous outcomes, we will use the

inverse variance method; and for time-to-event outcomes, we will use the generic inverse variance method.

If data are reported in factorial trials, we will adhere to the guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* in regards to whether to extract data from one or more comparisons (Higgins 2011d). Similarly, we will follow the advice from Chapter 16.4.5 related to the incorporation of cross-over trials into a meta-analysis (Higgins 2011d). We will perform analyses using Review Manager (RevMan).

Indirect comparison of treatment effects

We will use two methods to perform the indirect meta-analysis.

1. The frequentist method as described by Lumley 2002.
2. The Bayesian method as described by Lu 2004.

All analyses will be performed using STATA and WinBUGS (version 1.4) software (WinBUGS 2000; Stata 2009).

For studies with multiple intervention groups (more than two), we will apply standard methods as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.5 (Higgins 2011d).

Subgroup analysis and investigation of heterogeneity

We will investigate the effect of the intervention in a small number of subgroups and assess the difference in the treatment effects between these subgroups using a test for interaction between subgroups.

Predefined subgroups will be short-term ($\leq$ 8 weeks) versus long-term (> 8 weeks) duration of intravesical therapy.

We will also test for heterogeneity with Cochrane's Q and will quantify its extent with I^2. We will consider I^2 of 30% to 60% as moderate and of 50% to 90% as substantial (Higgins 2003; Higgins 2011a).

We will also calculate the measure of inconsistency for network meta-analysis, and explain any inconsistency between direct and indirect comparisons.

Sensitivity analysis

We will investigate the robustness of the analysis by assessing the effect of methodological quality on the results. (e.g. we will evaluate if the results differ in the trials with adequate versus non-adequate allocation concealment). In the case of moderate or substantial heterogeneity (I^2 > 50%), we will perform a sensitivity analysis according to methodological domains of risk of bias and the differences among included RCTs according to patient population, interventions, and comparisons.

Summary of findings table

In the 'Summary of findings table', we will include the outcomes of time to tumour recurrence, time to tumour progression, incidence of serious (grade 3 or 4) adverse events, overall survival, disease specific survival and quality of life.

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors will independently rate the quality of evidence for each outcome as high, moderate, low, or very low using GRADEpro GDT (GRADEpro GDT). We will resolve any discrepancies by consensus, or, if needed, through arbitration by a third review author. For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, 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). We will provide justification for each assessment about the confidence in the estimates of effect (for example, reasons for downgrading the quality of the evidence). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
#2 MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
#3 (tcc or transitional cell)
#4 MeSH descriptor: [Ureteral Neoplasms] explode all trees
#5 (bladder or urotheli* or urethera* or ureter* or urin* or "renal pelvis" or calice*)
#6 (cancer* or neoplas* or tumor* or toumor* or carcino* or adenoma* or adenocarcin* or squamous* or malignan*)
#7 (#5 AND #6)
#8 (#1 OR #2 OR #3 OR #4 OR #7)
#9 MeSH descriptor: [BCG Vaccine] explode all trees
#10 (calmette* and vaccin*) or BCG

#11 MeSH descriptor: [Interferons] explode all trees
#12 (Interferon* or IFN or Intron-A)
#13 MeSH descriptor: [Doxorubicin] explode all trees
#14 (doxorubicin* or caelyx or doxil or myocet or adriblastin* or adriablastin* or doxolem)
#15 MeSH descriptor: [Epirubicin] explode all trees
#16 (epirubicin* or farmorubicin* or pharmorubicin* or IMI-28 or ellence)
#17 (gemcitabin* gemcetabin* or gemcatabin* or gemzar*)
#18 MeSH descriptor: [Mitomycin] explode all trees
#19 (mitomycin* or mitomicin* or mitocin* or ametycin* or mutamycin*)
#20 MeSH descriptor: [Thiotepa] explode all trees
#21 (thiotepa or tespa* or thio-tepa)
#22 (valrubicin* or valtaxin* or valstar)
#23 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24 MeSH descriptor: [Administration, Intravesical] explode all trees
#25 (intraves* or instill* or region* or install*)
#26 (#24 OR #25)
#27 (#23 AND #26)
#28 (#8 AND #27)

Appendix 2. MEDLINE search strategy (via PubMed)

#1 Urinary Bladder Neoplasms[Mesh]
#2 Carcinoma, Transitional Cell[Mesh]
#3 (tcc OR transitional cell)
#4 "Ureteral Neoplasms"[Mesh]
#5 (bladder OR urotheli* OR urethera* OR ureter* OR urin* OR "renal pelvis" OR calice*)
#6 (cancer* OR neoplas* OR tumor* OR toumor* OR carcino* OR adenoma* OR adenocarcin* OR squamous* OR malignan*)
#7 (#5 AND #7)
#8 (#1 OR #2 OR #3 OR #4 OR #7) [disease term]
#9 BCG Vaccine[Mesh] OR (calmette* AND vaccin*) OR BCG
#10 Interferons[Mesh] OR (Interferon* OR IFN OR Intron-A)
#11 "Doxorubicin"[Mesh] OR (doxorubicin* OR caelyx OR doxil OR myocet OR adriblastin* OR adriablastin* OR doxolem)
#12 "Epirubicin"[Mesh] OR (epirubicin* OR farmorubicin* OR pharmorubicin* OR IMI-28 OR ellence)
#13 "gemcitabine" [Supplementary Concept] OR (gemcitabin* gemcetabin* OR gemcatabin* OR gemzar*)
#14 "Mitomycin"[Mesh] OR (mitomycin* OR mitomicin* OR mitocin* OR ametycin* OR mutamycin*)
#15 "Thiotepa"[Mesh] OR (thiotepa OR tespa* OR thio-tepa)
#16 "valrubicin" [Supplementary Concept] OR (valrubicin* OR valtaxin* OR valstar)
#17 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 Administration, Intravesical[Mesh] OR (intraves* OR instill* OR region* OR install*)
#19 (#17 AND #18) [treatment term]
#20 randomized controlled trial[Publication Type]
#21 controlled clinical trial[Publication Type]
#22 randomi*[Title/Abstract]
#23 placebo[Title/Abstract]
#24 drug therapy[MeSH Subheading]
#25 randomly[Title/Abstract]
#26 trial[Title/Abstract]
#27 groups[Title/Abstract]
#28 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #27) [RCT filter]
#29 (#8 AND #19)
#30 (#29 AND #28)

Appendix 3. EMBASE search strategy

Search Query
#1 urinary AND ('bladder'/exp OR bladder) AND ('neoplasms'/exp OR neoplasms)
#2 ('carcinoma'/exp OR carcinoma AND transitional AND ('cell'/exp OR cell)
#3 (ureteral AND neoplasms)
#4 (bladder OR urotheli$ OR urethera$ OR ureter$ OR urin$ OR 'renal pelvis' OR calice$) AND (cancer$ OR neoplas$ OR tumor$ OR toumor$ OR carcino$ OR adenoma$ OR adenocarcin$ OR squamous$ OR malignan$)
#5 #1 OR #2 OR #3 OR #4
#6 (bcg AND vaccine OR (calmette$ AND vaccin$) OR bcg)
#7 interferon OR interferon$ OR ifn OR 'intron a'
#8 doxorubicin'/exp OR doxorubicin$ OR caelyx OR doxil OR myocet OR adriblastin$ OR adriablastin$ OR doxolem
#9 epirubicin'/exp OR epirubicin$ OR farmorubicin$ OR pharmorubicin$ OR 'imi 28' OR ellence
#10 gemcitabine'/exp OR gemcitabine OR (gemcitabin$ AND gemcetabin$) OR gemcatabin$ OR gemzar$
#11 mitomycin'/exp OR mitomycin OR mitomycin$ OR mitomicin$ OR mitocin$ OR ametycin$ OR mutamycin$
#12 thiotepa'/exp OR thiotepa OR tespa$ OR 'thio tepa'
#13 valrubicin'/exp OR valrubicin OR valrubicin$ OR valtaxin$ OR valstar)
#14 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #5 AND #14
#16 #15 AND 'intravesical drug administration'/lnk

CONTRIBUTIONS OF AUTHORS

Mia Djulbegovic (MD): contributed to the initiation and design of this review and drafting of the protocol; will aid in study selection, data extraction, and interpretation of analyses and will contribute clinical expertise.

Rahul Mhaskar (RM): contributed to the initiation and design of this review. Will conduct the search; aid in study selection, data extraction, and interpretation of analyses; and contribute methodological expertise.

Tea Reljic (TR): contributed to the initiation and design of this review; will conduct the search, aid in study selection and data extraction, perform and interpret analysis of direct evidence, and contribute statistical and methodological expertise.

Robert S Ackerman (RSA): contributed to the initiation and design of this review; will aid in study selection and data extraction and will contribute clinical expertise:

Branko Miladinovic (BM): contributed to the initiation and design of this review; will contribute to performance and interpretation of all analyses and will contribute statistical and methodological expertise.

Iztok Hozo (IH): contributed to the initiation and design of this review; will perform and interpret analysis of indirect comparisons and will contribute statistical expertise.

Philipp Dahm (PD): contributed to the initiation and design of this review; will resolve any disagreements regarding study inclusion and data extraction, aid in interpretation of analyses, and contribute clinical expertise.

Ambuj Kumar (AK): contributed to the initiation and design of this review; will resolve any disagreements regarding study inclusion and data extraction, aid in interpretation of analyses, and contribute statistical and methodological expertise.

DECLARATIONS OF INTEREST

MD: none known.

RM: none known.

TR: none known.

RSA: none known.

BM: none known.

IH: none known.

PD: employed as a urologist.

AK: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

No support was received.

External sources

- None, Other.

No support was received.

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by the Cochrane Urology Group.