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Single-dose intravesical chemotherapy after nephroureterectomy for upper tract urothelial carcinoma (Review)

Hwang EC, Sathianathen NJ, Jung JH, Kim MH, Dahm P, Risk MC

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[Intervention Review]

Single-dose intravesical chemotherapy after nephroureterectomy for upper tract urothelial carcinoma

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ABSTRACT

Background

Single-dose, postoperative intravesical chemotherapy reduces the risk of bladder cancer recurrence after transurethral resection of bladder tumours. However, there is limited evidence whether single-dose intravesical chemotherapy is similarly effective at preventing bladder cancer recurrence after nephroureterectomy.

Objectives

To assess the effects of single-dose intravesical chemotherapy instillation after nephroureterectomy for upper tract urothelial carcinoma.

Search methods

We performed a comprehensive literature search using multiple databases (MEDLINE, Cochrane Library, Embase, Scopus, Web of Science, and LILACS), trials registries, other sources of grey literature, and conference proceedings published up to April 15 2019, with no restrictions on language or status of publication.

Selection criteria

We included randomised controlled trials in which participants either received or did not receive single-dose intravesical chemotherapy instillation after nephroureterectomy.

Data collection and analysis

Two review authors screened and independently assessed studies and extracted data from included studies. We performed statistical analyses using a random-effects model. We rated the certainty of evidence according to the GRADE approach.

Main results

The search identified two studies (a multicenter study from Japan and the United Kingdom) with 361 participants.

Primary outcomes

Our results indicate that single-dose intravesical chemotherapy instillation may reduce the risk of bladder cancer recurrence over time compared to no instillation (hazard ratio [HR]: 0.51, 95% confidence interval [CI]: 0.32 to 0.82, low-certainty evidence). After 12 months follow-up, this would result in 127 fewer bladder cancer recurrences (95% CI: 182 to 44 fewer bladder cancer recurrences) per 1000 participants. We downgraded the certainty of evidence by two levels due to study limitations and imprecision.

We found no trials that reported on the outcomes of time to death from upper tract urothelial carcinoma. The effect of single-dose intravesical chemotherapy instillation on serious adverse events is uncertain (risk ratio [RR]: not estimable, 95% CI: not estimable, there were no events, very low-certainty evidence). We downgraded the certainty of evidence by one level due to study limitations and by two levels due to imprecision.

Secondary outcomes

We found no trials that reported on the outcomes of time to death from any cause and participants' disease-specific quality of life. The effect of single-dose intravesical chemotherapy instillation on minor adverse events is uncertain (risk ratio [RR]: not estimable, 95% CI: not estimable, there were no events, very low-certainty evidence). We downgraded the certainty of evidence by one level due to study limitations and by two levels due to imprecision.

Authors' conclusions

For patients who have undergone nephroureterectomy for upper tract urothelial carcinoma, single-dose intravesical chemotherapy instillation may reduce bladder cancer recurrence after nephroureterectomy. However, we are uncertain as to the risk of serious (and minor) adverse events. We found no evidence for the outcome of time to death from upper tract urothelial carcinoma. We were unable to conduct any of the preplanned subgroup analyses, particularly those based on operative approach, pathologic stage, and method of bladder cuff excision.

PLAIN LANGUAGE SUMMARY

Should we administer single-dose chemotherapy to the bladder after removing the kidney and ureter for the treatment of renal pelvis and ureter cancer?

Review question

In people with cancer of the inner lining of their kidney and ureter (the tube that transports urine from the kidney to the bladder) who are having surgery to remove the kidney and ureter, what are the effects of a one-time dose of chemotherapy into their bladder after surgery.

Background

In people with cancer of the inner lining of the bladder, one-time chemotherapy put into the bladder (after the tumour has been removed) is helpful in making the cancer less likely to come back. We don't know whether the same is true for people in whom the same type of cancer is found in the inner lining of the kidney and ureter. Even if it does, it may also make these people have serious unwanted effects. We performed this study to summarise the best available evidence on the effects of one-time dose of chemotherapy in these people after removal of the kidney and ureter for cancer.

Study characteristics

We found two randomised controlled studies (RCTs), with a total of 361 participants that compared a single-dose chemotherapy placed in the bladder to no chemotherapy in people having their kidney and ureter removed for cancer of the inner lining of the kidney or ureter, or both. These findings are based on a literature search up to April 15, 2019.

Key results

We found that a one-time dose of chemotherapy put into the bladder after surgery may reduce the risk of this type of tumor coming back in the bladder over time compared to no chemotherapy. We found no evidence whether this affects the time to death from this type of cancer. Serious unwanted effects appear to be rare and not increased with chemotherapy, but we are uncertain of this finding.

Certainty of the evidence

Our confidence in the evidence for the effect on the risk of recurrence within the bladder is low. This means that the true effect may be very different from what this review shows. The certainty of evidence for the effects of one-time chemotherapy put into the bladder on serious unwanted effects was very low. This means that we are very uncertain about this result.

Summary of findings for the main comparison. Single-dose intravesical chemotherapy instillation versus placebo or observation after nephroureterectomy for upper tract urothelial carcinoma

Single-dose intravesical chemotherapy instillation versus placebo or observation after nephroureterectomy for upper tract urothelial carcinoma

participants: people who received nephroureterectomy due to UTUC
Setting: a multicenter study from Japan and the United Kingdom (likely inpatients)
Intervention: single-dose intravesical chemotherapy instillation (pirarubicin and mitomycin)
Comparison: no instillation (observation)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no instillation (observation)	Risk difference with single-dose intravesical chemotherapy instillation
Time to bladder cancer recurrence (absolute effect size estimates based on recurrence rate at 12 months) Follow-up: median 12 to 24.9 months	311 (2 RCTs)	⊕⊕⊖⊖ LOW [1,2]	HR 0.51 (0.32 to 0.82)	Study population	
				283 per 1,000 [3]	127 fewer per 1,000 (182 fewer to 44 fewer)
				High	
				500 per 1,000 [4]	202 fewer per 1,000 (301 fewer to 66 fewer)
				Low	
				150 per 1,000 [4]	70 fewer per 1,000 (99 fewer to 25 fewer)
Time to death from UTUC [5] Follow-up: median 12 to 24.9 months	Not reported	-	-	Study population	
				-	-
Serious adverse events Follow-up: median 12 to 24.9 months	311 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1,6]	No events	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Time to death from any cause [5]	Not reported	-	-	Study population	

Follow-up: median 12 to 24.9 months				-	-
Minor adverse events Follow-up: median 12 to 24.9 months	72 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [6]	No events	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Disease-specific quality of life [5] Follow-up: median 12 to 24.9 months	Not reported	-	-	-	-

*__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; **RR:** Risk ratio; **RCT**: Randomised controlled trial; **UTUC**: Upper tract urothelial carcinoma

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

[1] Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains
[2] Downgraded by one level for imprecision: confidence interval crossed assumed threshold of clinical importance
[3] Baseline risk for bladder cancer recurrence in the no instillation (observation) group was assumed to be 28.3% (moderate risk) at 12 months based on pooled estimates from the two included studies
[4] Baseline risk for bladder cancer recurrence in the no instillation (observation) group was assumed to be 15% (low risk) and 50% (high risk) at 12 months as reported by Azémar 2011 and Xylinas 2013, respectively (both observational studies)
[5] Time to death from upper tract urothelial carcinoma; time to death from any cause; disease-specific quality of life: no available data
[6] Downgraded by two level for imprecision: no events

BACKGROUND

Description of the condition

Upper tract urothelial carcinoma (UTUC) is an urothelial malignancy involving the renal pelvis or ureter. It is a relatively rare disease and accounts for approximately 5% to 10% of all urothelial carcinomas (Siegel 2014). Ureteral tumours are even less common and have an incidence of approximately one-quarter that of renal pelvic tumours (Hall 1998). UTUC is mostly found in people from the age of 50 to 80 years, and its incidence is twice as high in men than in women (Siegel 2014). UTUC and bladder carcinomas have common pathogenic mechanisms and show analogous tumour characteristics with similar prognostic risk factors (Novara 2007; Sylvester 2006). Hence, much of the clinical decision-making for UTUC is extrapolated from the larger evidence base on bladder cancer (Green 2013; Kim 2015). The cause of UTUC is still not known, but many environmental factors, such as smoking cigarettes, medication (e.g. Chinese herbs and aristolochic acid), chronic infection, exposure to carcinogenic chemicals, and occupational carcinogenesis, have been linked to the development of UTUC (Colin 2009).

Given that symptoms of both localised diseases (hematuria, dysuria) and advanced diseases (weight loss, fatigue, anaemia, bone pain) are similar to those of bladder cancer, their diagnostic approaches also overlap. The recommended evaluation of UTUC includes computed tomography urography (CTU) or magnetic resonance urography (usually only performed when CTU is contraindicated), cystoscopy, and urine cytology (NCCN Guideline 2018; Rouprêt 2018). Other commonly used local imaging modalities include retrograde ureteropyelography or ureteroscopy. Chest radiography and CT chest and bone scans are often also part of the diagnostic pathway for the staging of the disease to rule out metastatic spread (NCCN Guideline 2018). The stages of UTUC are classified as follows: Stage 0a: TaN0M0, Stage 0is: TisN0M0, Stage I: T1N0M0, Stage II: T2N0M0, Stage III: T3N0M0 and Stage IV: T4NXM0, or Any T N1M0, Any T N2M0, Any T, and Any N M1 (Amin 2017).

Currently, the gold standard of treatment for UTUC is radical nephroureterectomy (RNU) with bladder cuff excision. This procedure is associated with a risk of chronic kidney disease due to the loss of a kidney. This procedure is generally performed in cases of high-risk UTUC with a normal contralateral kidney (NCCN Guideline 2018; Rouprêt 2018). Kidney-sparing surgeries, such as ureteroscopic and percutaneous tumour removal (e.g. endoscopic tumour ablation or resection) and segmental ureterectomy, are alternatives to RNU when patients have impaired renal function, low-risk disease, or prohibitive surgical risks (Bagrodia 2013; Oya 2015).

Following RNU, there is a risk of intravesical recurrence (IVR; recurrence in the bladder), which is estimated to occur in 22% to 47% of patients within an approximate two-year postoperative time period (Cho 2014; Lee 2017; Xylinas 2014). Several studies have elucidated the identification of postoperative prognostic factors in order to be able to propose adjuvant intravesical chemotherapy and risk-based surveillance to patients at high risk of disease recurrence (Azémar 2011; Lee 2017; Mbeutcha 2017). The proposed prognostic factors of IVR are aggressiveness of the tumour (i.e. advanced stage), tumour size, a tumour located in the ureter, laparoscopic surgical approaches, and positive surgical margins (Azémar 2011; Lee 2017; Mbeutcha 2017). Given that these factors are derived from retrospective studies, the true value of these factors remains unclear but provides the rationale of adjuvant intravesical chemotherapy (Mbeutcha 2017).

In this Cochrane Review, we define IVR as bladder cancer recurrence after RNU for UTUC. IVR is managed in the same way as recurrent bladder tumours in other settings, namely by transurethral resection, intravesical instillation immunotherapy or chemotherapy, and close surveillance using cystoscopy and urinary cytology (Griffiths 2013). This results in substantial economic costs due to the continued surveillance, diagnosis, and treatment of bladder cancer recurrences (Svatek 2014). This societal cost is compounded by the decrease in productivity of participants and their time lost from work (Svatek 2014).

Description of the intervention

Following the transurethral resection of bladder tumour (TURBT), the single-dose intravesical instillation of chemotherapy has been shown to decrease the risk of recurrence if a noninvasive disease is suspected (Abern 2013; Perlis 2013; Sylvester 2004). Mitomycin C (MMC) is the most commonly used intravesical chemotherapeutic agent in this setting, but epirubicin and pirarubicin (THP) have also been shown to be beneficial in reducing the risk of recurrence (NCCN Guideline 2018; Sylvester 2016). The rationale and explanation for its efficacy is thought to be based on its antitumour effect, as it can destroy tumour cells floating in the irrigation fluid and urine after TURBT, and its ablative effect on residual tumour cells at sites of resection and on small overlooked tumours (Sylvester 2016). These, or similar agents, may be used in a similar context to prevent IVR after RNU.

For intravesical chemotherapy instillation, a two-way catheter is inserted into the bladder in a sterile manner inside the operative field at the beginning of the surgical procedure. After surgery, when the bladder has been completely drained, chemotherapeutic agents (e.g. 40 mg of MMC in 40 mL of sterile water or 30 mg of THP in 30 mL of sterile water) are passed into the bladder through the catheter and the catheter is then clamped. After a certain period of time (typically 30 to 60 minutes with or without position changes), the catheter is unclamped, and the chemotherapeutic agents are allowed to drain passively. The catheter bag is then discarded as cytotoxic waste. The bladder is occasionally irrigated with saline at the physician's discretion. Post-RNU intravesical instillation is usually recommended within 24 to 72 hours post-operation (NCCN Guideline 2018; Rouprêt 2018), but can also be performed later (up to a week after RNU).

Adverse event of the intervention

Adverse events can be categorised as local or systemic. The incidence of local adverse events related to single-dose intravesical installations is approximately 10%, according to perioperative trials conducted after the TURBT, with the most common adverse events being increased urinary frequency, urinary urgency, dysuria, hematuria, and bladder or pelvic pain and prostatitis. These adverse events are usually self-limiting (Sylvester 2004; Williams 2010). The most severe adverse events related to this setting are extravasation from the bladder with local toxicity in the pelvis, peritoneum, or both. Even though the bladder wall is usually closed post-RNU, this site is potentially more vulnerable to extravasation after intravesical chemotherapy administration. Other systemic and serious local adverse events, such as perivesical fat necrosis,

bladder ulceration, perirectal fat necrosis with abscesses, and myelosuppression, are relatively rare (Griffin 2013; Lu 2017).

How the intervention might work

There are two main theories that may explain the occurrence of IVR after RNU. The first theory suggests that preoperative carcinogen exposure in the entire urothelium accounts for independent tumour development following RNU. Alternatively, the intraluminal seeding and implantation theory proposes that the bladder is continuously exposed to cancer cells dropping from the upper urinary tract before and during RNU, which may be responsible for IVR (Habuchi 1993; Jones 2005). The mechanism of action for intravesical chemotherapy involves the delivery of high concentrations of anticancer drugs to the bladder, potentially destroying circulating tumour cells within the urine that remain after RNU and preventing the seeding of cancer cells shed from UTUC. Moreover, intravesical chemotherapy may suppress the implantation of cancer cells, thereby reducing the likelihood of IVR following RNU.

Why it is important to do this review

There is limited evidence regarding the effectiveness of single-dose intravesical chemotherapy in preventing IVR after RNU. Although several systematic reviews and meta-analyses have been conducted on this topic (Fang 2013; Wu 2015; Yuan 2015), there is still considerable uncertainty in this area. In addition, none of the aforementioned published reviews have been conducted using rigorous methodologies, nor have they used the GRADE methodology to rate the certainty of evidence. This systematic review evaluates the best available evidence on the effectiveness of single-dose intravesical chemotherapy in preventing IVR after nephroureterectomy that exists to date and includes an independent assessment of the risks of bias and the rating of the certainty of evidence using the GRADE methodology. A survey of urologic oncologists regarding the use of intravesical chemotherapy after nephroureterectomy reported that almost half of the included urologists (44%) did not use intravesical chemotherapy due to the lack of supporting data (Lu 2017). We expect this review to be helpful for clinicians', guideline developers' and policy-makers' decisions seeking to establish the current role for single-dose intravesical chemotherapy after RNU.

OBJECTIVES

To assess the effects of single-dose intravesical chemotherapy instillation after nephroureterectomy for upper tract urothelial carcinoma.

METHODS

Criteria for considering studies for this review

Types of studies

This review is based on a previously published protocol (Hwang 2018). For details on the differences between that protocol and this review, please refer to the 'Differences between protocol and review' section. We included randomised controlled trials (RCTs), as they offer the most reliable results. We excluded quasi-randomised and non-randomised studies, cohort studies, case series, cross-over trials, and cluster-randomised trials. We did not exclude studies on the basis of publication status or language.

Types of participants

We included studies that used participants with localised or locally-advanced UTUC (Stage 0a, Stage 0is, and Stages I - IV) (Amin 2017), as determined via cross-sectional imaging, biopsy, or both. We excluded trials that had participants with known metastatic diseases. We also excluded trials that had participants who underwent kidney-sparing surgery, segmental ureterectomy, or endoscopic tumour removal (e.g. ureteroscopic tumour removal or ablation), and those that had participants with a history of bladder tumours or intravesical chemotherapy. We included studies using diverse methods of bladder cuff management due to the lack of a gold standard. We included studies irrespective of intravesical chemotherapy instillation timing, the duration of how long the chemotherapeutic agent remains in the bladder, and the change of the participants' position after instillation.

Types of interventions

We planned to investigate the following experimental and comparator intervention comparisons.

Experimental interventions

- Single dose of any intravesical chemotherapeutic agent instillation (e.g. mitomycin, epirubicin, pirarubicin, gemcitabine, etc.) after RNU (Rouprêt 2018)

Comparator interventions

- Observation
- Placebo

Concomitant interventions had to be the same in the experimental and comparator groups to ensure fair comparisons.

Types of outcome measures

We did not exclude trials if they met inclusion criteria but did not report one or several of our primary or secondary outcomes.

Primary outcomes

- Time to bladder cancer recurrence (time-to-event outcome)
- Time to death from UTUC (time-to-event outcome)
- Serious adverse events (dichotomous outcome)

Secondary outcomes

- Time to death from any cause (time-to-event outcome)
- Minor adverse events (dichotomous outcome)
- Disease-specific quality of life (continuous outcome)

We used a previously-reported minimum clinically important difference (MCID) to assess participants' disease-specific quality of life (e.g. European Organisation for Research and Treatment of Cacer core quality of life questionnaire version 3.0 (EORTC QLQ-C30 v. 3.0) > 10 points) in order to rate the certainty of evidence for imprecision, and these results can be found in our 'Summary of findings for the main comparison' (Cocks 2008; Johnston 2013). We could not find any published information about a clinically important difference for time-to-event outcomes (i.e. time to bladder cancer recurrence, time to death from UTUC and from any cause) and dichotomous outcomes (i.e. adverse events). We, therefore, used a relative risk reduction (RRR), risk ratio (RR), or

hazard ratio (HR) of at least 25%, based on the guidance in Guyatt 2011a.

Method and timing of outcome measurement

- Time to bladder cancer recurrence: as measured from the time of randomisation to the time of the first confirmed bladder cancer recurrence
  - Definition of recurrence: judged based on the cystoscopic visual appearance of the tumour or histopathologic proof of recurrence
- Time to death from UTUC: as measured from the time of randomisation to the time of death due to UTUC
- Time to death from any cause: as measured from the time of randomisation to the time of death due to any cause
- Adverse events: determined by the Common Terminology Criteria for Adverse Events (CTCAE). We classified grade 3 or higher complications as serious (e.g. bladder perforation and the need for invasive intervention, gross hematuria, and the need for hospitalisation), and grade 1 and 2 complications as minor (e.g. dysuria, hematuria, and the need for bladder irrigation). If the authors did not use the CTCAE, we graded the adverse events as described in their respective studies.

We considered adverse events that appeared within six months after randomisation. If we were unable to retrieve the necessary information to assess time-to-event outcomes, we tried to assess the number of events per the total number of included participants in each relevant study for dichotomised outcomes at 12 months, 24 months, 36 months, and 60 months for bladder cancer recurrence, death from UTUC, and death from any cause.

Search methods for identification of studies

We performed a comprehensive literature search with no restrictions on language or the status of publication. We planned to rerun searches within three months prior to the anticipated publication of the review.

Electronic searches

We searched the following sources for relevant literature that was published since the inception of each database (Appendix 1). The date of the last search for all databases was April 15, 2019.

- MEDLINE via Ovid (from 1946);
- Cochrane Library (Issue 4, April 2019);
- Embase (Elsevier, 1947 - present);
- Scopus (1966 - present);
- Web of Science (1900 - present);
- LILACS (Latin American and the Caribbean Health Sciences Literature; www.bireme.br/; 1982 - present).

We also searched the following.

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/);
- 'Grey literature' repository from the current Grey Literature Report (www.greylit.org/).

If we detected additional relevant key words during our literature search, we modified our electronic search strategies to incorporate these terms and documented the changes.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, reviews, and meta-analyses. We also contacted the authors of included trials to identify any further studies that we may have missed. We searched the abstract proceedings of any relevant meetings conducted during the last three years (2016 to 2018) by the American Urological Association, European Association of Urology, and American Society of Clinical Oncology to search for unpublished studies.

Data collection and analysis

In this review, we followed the methodological recommendations given by Cochrane (Higgins 2017a).

Selection of studies

We used EndNote reference management software to identify and remove potential duplicate records. Two review authors (ECH and JHJ) independently assessed abstracts and titles to determine which studies should be assessed further using Covidence software. Two review authors (ECH and JHJ) investigated all potentially relevant records, such as full texts, mapped records to studies, and classified them as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a). We resolved any discrepancies through consensus or by recourse to a third review author (PD). If a resolution was not possible, we designated the study as 'awaiting classification'. We documented the reasons for the exclusion of studies in the 'Characteristics of excluded studies' table. We presented an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

Two review authors (ECH and NS) independently extracted relevant data using a data extraction form. We based this form on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a) and pilot tested it before using it for our analysis. We resolved any potential disagreements by consensus or through discussion with a third review author (PD). In addition, when necessary, we contacted the original study authors. We collected and used the most detailed numerical data that might facilitate the similar analyses of included studies. When studies reported the median and range rather than the mean and standard deviation for continuous outcomes, we used the method provided by Hozo 2005. We detailed all characteristics of the included studies in the 'Characteristics of included studies' table.

- Record citation (e.g. authors' names and article title).
- Details of methods: study design and date when the study was conducted.
- Details of participants: setting; country; number of included participants; age; sex; inclusion and exclusion criteria; participants' risk factors for bladder cancer recurrence, death from UTUC, and death from any cause; and previous or

concomitant bladder tumours, including information on tumour stage (T category), tumour grade, tumour location (ureteral), the presence of concurrent carcinoma in situ, tumour multifocality, and the use of the bladder cuff excision method (Mbeutcha 2017).
- Details of interventions: the number of participants randomly assigned to each intervention group and drug use, including dosage and dilution details, and the time point of instillation.
- Details of outcomes: outcomes included in this review that were assessed in each study, including how each was measured and the times at which they were measured.
- Study funding sources.
- Declarations of interest among the primary study authors.

Dealing with duplicate and companion publications: In the event of duplicate publications, companion documents or multiple reports for a primary study, we maximised the yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data set 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

Two review authors (ECH and NS) independently assessed the risks of bias for each included study. We resolved disagreements by consensus, or by consulting with a third review author (PD). We used the Cochrane 'Risk of bias' assessment tool for the following domains (Higgins 2017b).

- 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 potential sources of bias (e.g. baseline imbalance).

We judged 'Risk of bias' domains as 'low risk,' 'high risk' or 'unclear risk'. We presented the results of this assessment graphically. For selection bias (random sequence generation and allocation concealment) and reporting bias (selective reporting), we evaluated the risks of bias at a trial level.

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

For detection bias (blinding of outcome assessments), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective) outcomes.
We defined the following outcome measures as subjective:

- time to bladder cancer recurrence
- time to death from UTUC
- serious and minor adverse events
- disease-specific quality of life.

We defined the following outcome as objective:

- time to death from any cause.

We assessed attrition bias (incomplete outcome data) by outcome. We summarised the risk of attrition bias across domains for each outcome in each included study, as well as across the studies and domains for each outcome, in accordance with the approach for the summary assessment of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017b).

Measures of treatment effect

When at least two included trials were available for a given outcome, we expressed dichotomous data as RRs with a 95% confidence interval (CI). For continuous outcomes measured on the same scale, we estimated the intervention effect using the mean difference (MD) with a 95% CI. For continuous outcomes measuring the same underlying concept (e.g. disease-specific quality of life), but using different measurement scales, we planned to calculate the standardised mean difference (SMD). We expressed time-to-event data as HRs with 95% CIs or used an indirect estimation method if HRs were not given (Parmar 1998; Tierney 2007).

Unit of analysis issues

The units of analysis were each individual participant. If we had identified trials with more than two intervention groups for inclusion in this review, we would have handled these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We planned to obtain missing data from the original authors of each included study, if feasible, and planned to perform intention-to-treat analyses if data were available. Otherwise, we performed available-case analyses. We investigated attrition rates (e.g. dropouts, losses to follow-up, and withdrawals) and critically appraised issues of missing data. We did not plan to impute missing data.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through the visual inspection of forest plots to assess the amount of overlap between 95% CIs and used the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); we interpreted I^2 as follows (Deeks 2017).

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: may indicate considerable heterogeneity.

When we identified heterogeneity, we attempted to determine the possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We tried to obtain study protocols to assess selective outcome reporting. As we included only two studies for comparison in our review, we could not use funnel plots to assess any small study effects. Please refer to Differences between protocol and review.

Data synthesis

We performed data synthesis using Review Manager 5 (RevMan) software, provided by Cochrane (Review Manager 2014) in accordance with the guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a). In the meta-analyses, we used a random-effects model. For dichotomous outcomes, we used the Mantel-Haenszel method. For continuous outcomes, we used the inverse variance method. For time-to-event outcomes, we used the generic inverse variance method.

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity and planned to carry out subgroup analyses to investigate interactions.

- Operative approach (open RNU versus laparoscopic RNU).
- Pathologic stage (localised (Tis, Ta, T1, T2) versus locally advanced (T3, T4)).
- Bladder cuff excision method (endoscopic excision versus extravesical or intravesical excision).

These subgroup analyses were based on the following observations:

- High IVR rates are possibly associated with laparoscopic RNU, advanced tumour stage, and endoscopic bladder cuff excision (Xylinas 2014).

However, we could not perform any subgroup analyses due to the lack of relevant data.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size, if applicable:

- Restricting the analysis by taking the risk of bias into account and excluding studies classified as having a high risk or unclear risk of bias.

However, we could not perform any sensitivity analyses due to the lack of relevant data.

'Summary of findings' table

Main outcomes for 'Summary of findings' table

We present a 'Summary of findings for the main comparison' that reports on the following outcome measures listed according to priority. One review author (PD) determined outcome measure priority using content expertise:

- Time to bladder cancer recurrence
- Time to death from UTUC
- Serious adverse events
- Time to death from any cause
- Minor adverse events
- Disease-specific quality of life

We present the findings and the certainty of the available evidence according to the GRADE methodology (Schünemann 2017).

We assessed the overall certainty of evidence for each outcome according to the GRADE approach, which takes into account five criteria related, not only to internal validity (risk of bias, inconsistency, imprecision, and publication bias), but also to external validity (directness of results) (Guyatt 2008). Two review authors (ECH, JHJ) independently rated the certainty of evidence for each outcome as 'high', 'moderate', 'low', or 'very low'. We resolved discrepancies by consensus, or, if needed, by the arbitration of a third review author (PD). We present a summary of the evidence for the main outcomes in the 'Summary of findings for the main comparison', which we generated using the Gradepro GDT (gradepro.org/); This table provides key information about the best estimate of the magnitude of an effect in relative terms and presents absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of our overall confidence in the effect estimates for each outcome (Guyatt 2011b; Schünemann 2017).

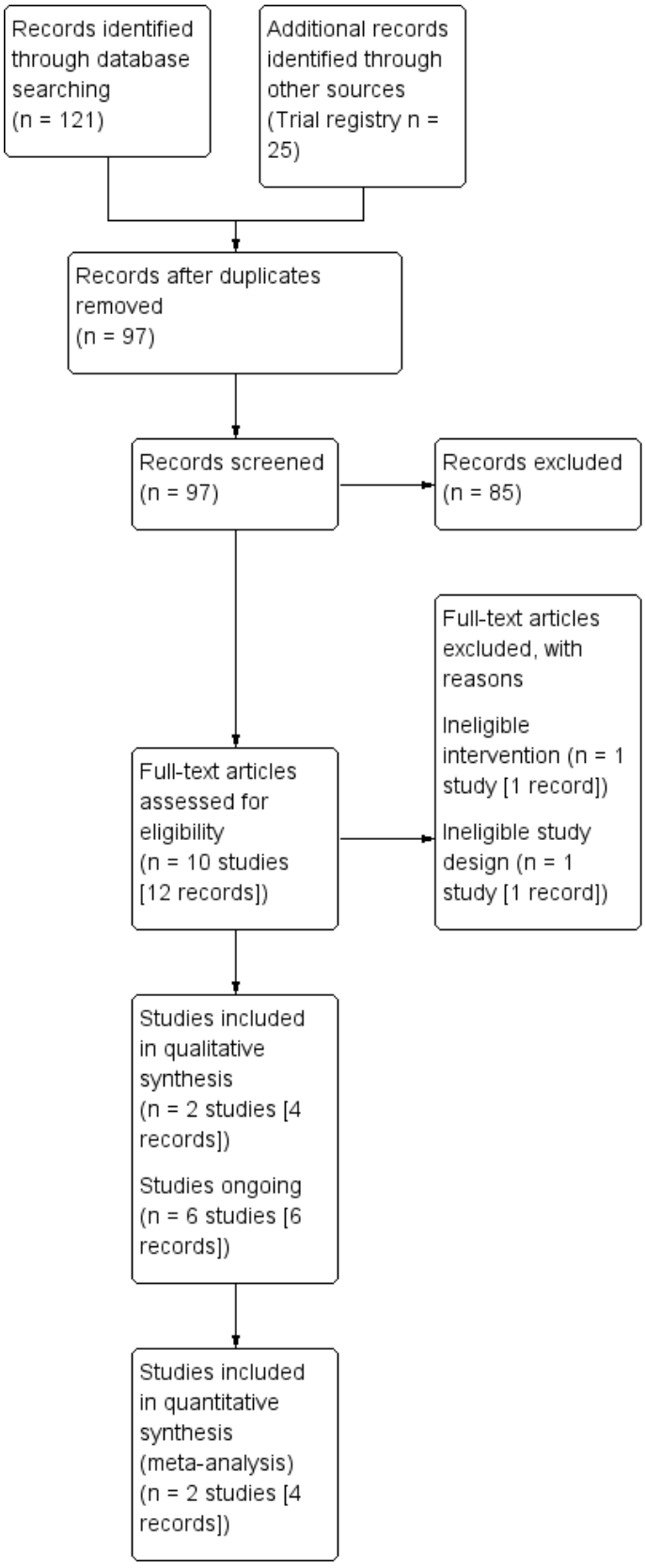
RESULTS

Description of studies

Results of the search

Our literature search yielded 121 references, to which we added an additional 25 studies that we identified by searching trial registries (Figure 1). After the exclusion of duplicates, we screened 97 references at the title and abstract stage. Of these 97 references, 12 references that were mapped to 10 unique studies entered the full-text screening stage. We ultimately included two studies in the quantitative analyses. The reasons for exclusion at the full-text screening stage are summarised in the PRISMA flow diagram (Figure 1), with further details provided in the 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram.



Included studies

The details of the included studies are presented in the 'Characteristics of included studies' table; Table 1; Table 2.

Source of data

All included trials were identified through the literature search (Ito 2013; O'Brien 2011).

Study design and settings

All included studies were parallel group RCTs (Ito 2013; O'Brien 2011). Both trials were open-label, multicentred, and likely conducted in an inpatient setting. The included studies were performed in Japan (Ito 2013) and the UK (O'Brien 2011). Accrual periods ranged from 2000 to 2008.

Participants

This review included a total of 361 randomised participants with UTUC, of which 250 completed the trials. The median follow-up period and age of participants ranged from 12 to 24.9 months (Ito 2013; O'Brien 2011) and 36 to 90 years old (O'Brien 2011), respectively. Participants were required to have an adequate functional status, as defined by the Eastern Cooperative Oncology Group as a score of less or equal to 2, and a life expectancy of more than one year. Prior or existing bladder cancer was not allowed in the included studies.

Interventions, comparators, and comparisons

The included trials administered single-dose intravesical chemotherapy. However, these trials used different drugs and doses and were administered at different time periods. The Ito 2013 study used 30 mg of THP with 30 mL of normal saline, which was administered within 48 hours after RNU, while the O'Brien 2011 study used 40 mg of MMC with 40 mL of normal saline, which was administered at various time periods after RNU due to their concerns over the extravasation of chemotherapy.

The comparator in the included trials was no chemotherapy instillation (observation).

Outcomes

The predefined primary outcomes of time to bladder cancer recurrence and serious adverse events were identified in both included studies, while minor adverse events were only available in one of the included trials (Ito 2013). However, we were unable to evaluate time to death from UTUC, time to death from any cause, and disease-specific quality of life because these outcomes were not investigated in the included studies.

Funding sources and conflicts of interest

All included studies reported receiving funding from multiple sources, including hospitals, pharmaceutical companies, and their respective governments (Ito 2013; O'Brien 2011). Conflicts of interests were reported as 'none' in the included studies.

Excluded studies

We excluded two studies on the basis that one had an ineligible intervention (multiple instillation (28 times) of chemotherapy) (Sakamoto 2001) and the other was a published trial protocol (not full text) with an ineligible study design (Van Doeveren 2018). The details of these excluded studies are presented in the 'Characteristics of excluded studies' table.

Studies awaiting classification and ongoing trials

There were no studies awaiting classification. We found six ongoing studies which did not provide usable outcome data at the time this review was written (JPRN-UMIN000009682; Miyamoto 2018; NCT02547350; NCT02923557; NCT03062059; NCT03209206) (see 'Characteristics of ongoing studies' table).

Risk of bias in included studies

The detailed results of the 'risk of bias' assessment are provided in Figure 2 and Figure 3, and the judgements regarding the individual domains are provided in the 'Characteristics of included studies' table.

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

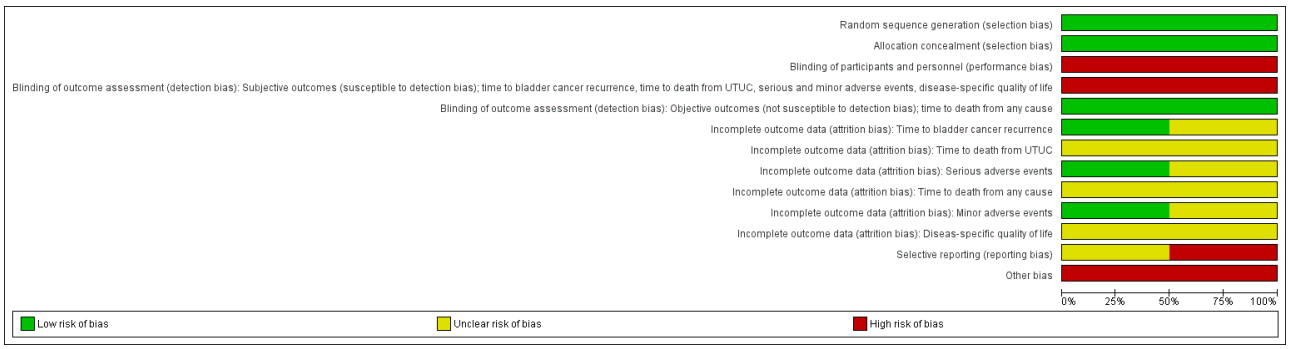


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

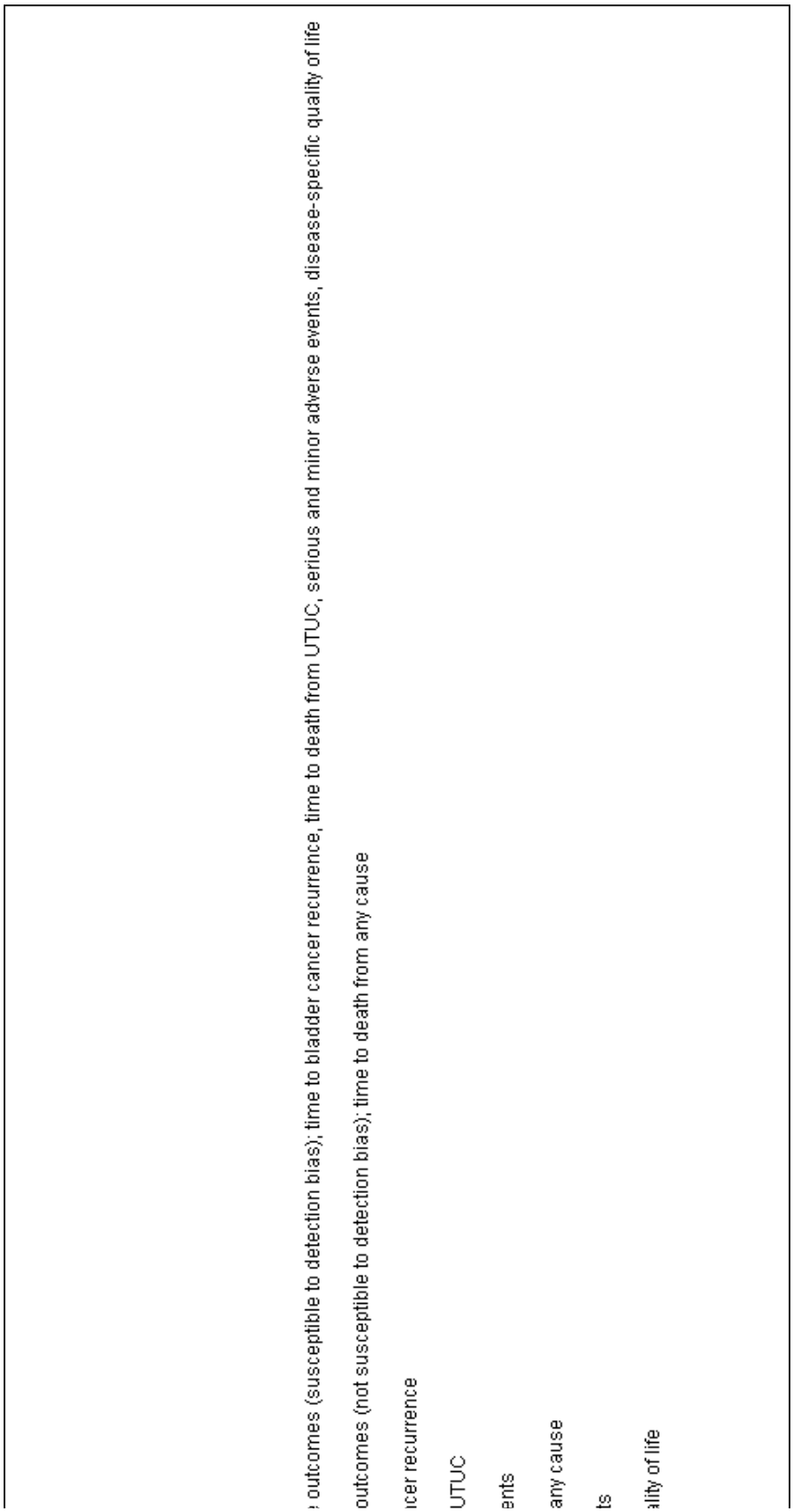
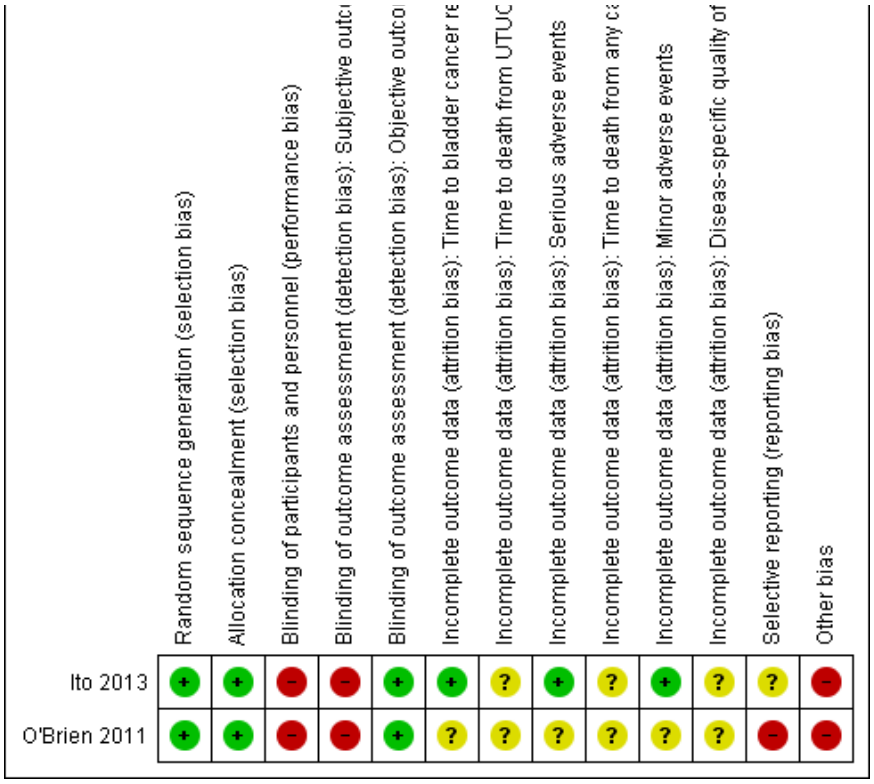


Figure 3. (Continued)



Allocation

Random sequence generation

Both included studies reported sufficient detail to provide the assurance of an adequate method of sequence generation and were rated as having a low risk of bias.

Allocation concealment

We rated all trials as having a low risk of bias as group allocation was performed centrally in both studies.

Blinding

Blinding of participants and personnel

We rated the included trials as having a high risk of performance bias because the participants and personnel were not blinded in either study.

Blinding of outcome assessments

We distinguished between the outcomes in which the blinding of outcome assessors appeared relevant (subjective outcomes; susceptible to detection bias) versus those in which it was not (objective outcomes; not susceptible to detection bias).

The subjective outcomes were time to bladder cancer recurrence, time to death from UTUC, serious and minor adverse events, and disease-specific quality of life. We rated the included studies as having a high risk of detection bias because unblinded assessors were responsible for these outcomes. The objective outcome, time to death from any cause, was rated as having a low risk of detection bias in the included trials because blinding was unlikely to influence this outcome in either of the studies.

Incomplete outcome data

Time to bladder cancer recurrence and serious adverse events

We rated the Ito 2013 study as having a low risk of attrition bias regarding these outcomes, while the O'Brien 2011 study was rated as having an unclear risk of attrition bias due to a moderate number of participants lost to follow-up.

Time to death from UTUC, time to death from any cause, and disease-specific quality of life

We did not rate these domains because these outcomes were not investigated in the trials. We report the risk of bias as unclear in the tables and figures only because this is the default value.

Minor adverse events

We rated one study as having a low risk of attrition bias (Ito 2013) regarding this outcome. We did not rate the other study as it did not investigate this outcome (O'Brien 2011). Therefore, the risk of bias is reported as unclear in the table and figures.

Selective reporting

We rated one study as having an unclear risk of reporting bias (Ito 2013) and one as having a high risk of reporting bias (O'Brien 2011), since several outcomes were not predefined in the protocol or were not analysed as intended.

Other potential sources of bias

We rated the included trials as having a high risk of other potential biases due to imbalances of baseline characteristics, mainly with regard to the proportion of participants with carcinoma in situ, as well as different tumor grades and stages.

Effects of interventions

See: **Summary of findings for the main comparison** Single-dose intravesical chemotherapy instillation versus placebo or observation after nephroureterectomy for upper tract urothelial carcinoma

Please refer to Analysis 1.1 to Analysis 1.3 and Summary of findings for the main comparison for the main comparison.

Single-dose intravesical chemotherapy instillation versus placebo or observation

Primary outcomes

Time to bladder cancer recurrence

Single-dose intravesical chemotherapy instillation may reduce the risk of bladder cancer recurrence over time compared to no instillation (HR: 0.51, 95% CI: 0.32 to 0.82, two studies, 311 participants, Analysis 1.1, low-certainty evidence). Based on the control event risk taken from the trials included in this analysis and 12 months follow-up, this corresponds to 127 fewer bladder cancer recurrences (95% CI: 182 fewer to 44 fewer) per 1000 participants for those that undergo single-dose intravesical chemotherapy. We rated the certainty of evidence as low due to study limitations and imprecision.

Based on low-risk and high-risk control groups as drawn from separate observational studies (Azémar 2011; Xylinas 2013) also at 12 months follow-up, single-dose intravesical chemotherapy may result in 70 fewer bladder cancer recurrences (95% CI: 99 fewer to 25 fewer) per 1000 participants or 202 fewer bladder cancer recurrences (95% CI: 301 fewer to 66 fewer) per 1000 participants, respectively.

Time to death from UTUC

We found no studies that reported this outcome.

Serious adverse events

We are uncertain whether single-dose intravesical chemotherapy instillation has little to no effect on serious adverse events compared to no instillation as there were no serious adverse events in either group (RR: not estimable, 95% CI: not estimable, two studies, 311 participants, Analysis 1.2, very low-certainty evidence). We downgraded the certainty of evidence by one level due to study limitations and by two levels for imprecision.

Secondary outcomes

Time to death from any cause

We found no studies that reported this outcome.

Minor adverse events

We are uncertain whether single-dose intravesical chemotherapy instillation has little to no effect on minor adverse events compared to no instillation as there were no minor adverse events in either group (RR: not estimable, 95% CI: not estimable, one study, 72 participants, Analysis 1.3, very low-certainty evidence). We downgraded the certainty of evidence by one level due to study limitations and by two levels for imprecision.

Disease-specific quality of life

We found no studies that reported this outcome.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses based on operative approach, pathologic stage and method of bladder cuff excision.

Sensitivity analysis

We rated both of the included studies as having a high or unclear risk of bias overall and were therefore unable to perform a meaningful sensitivity analysis.

DISCUSSION

Summary of main results

We included two RCTs with 361 participants. The findings of this systematic review indicate that single-dose intravesical chemotherapy instillation may increase the time to bladder cancer recurrence compared to no chemotherapy installation. We found no evidence on the risk of death from UTUC. We are uncertain whether single-dose intravesical chemotherapy instillation has little or no effect on serious (and minor) adverse events.

We also found no evidence about the effect of single-dose intravesical chemotherapy instillation on the time to death from any cause and disease-specific quality of life.

Overall completeness and applicability of evidence

The following issues deserve consideration:

- Findings of this review were based on only two, relatively small studies, which limits the generalisability of its findings.
- Information on time-to recurrence was limited to 12 months; therefore, is of very short-term nature.
- We stipulated that factors such as surgical approach, pathological stage, and technique of managing the bladder cuff could be important effect modifiers but were unable to conduct any relevant subgroup analyses.
- The included studies used two different chemotherapeutic agents and instillation time periods (please refer to the 'Characteristics of included studies' table). However, this review is unable to address whether one drug is more effective than another and what the optimal timing of instillation should be.
- Findings of this systematic review were limited to evidence from randomised controlled trials that yielded low quality at best. The consideration of non-randomised controlled trials may have provided some evidence for additional outcomes such as adverse events (Schünemann 2013). Also, while we believe this to be unlikely, it is possible that they could have provided higher quality for time-to-recurrence.

Quality of the evidence

We rated the certainty of evidence as low to very low. The reasons for downgrading the certainty of evidence were as follows:

- Study limitations: Neither of the studies blinded participants or personnel, which raises concerns about performance bias. For the subjective outcomes, there is also a similar concern over detection bias. In conjunction with incomplete outcome data and the concerns over other sources of bias (i.e. baseline imbalances in each group), this prompted us to downgrade the certainty of evidence.

- Imprecision: The finding of wide confidence intervals that crossed the thresholds of clinical relevance, rare events, or both led to the downgrading of the certainty of evidence.
- Selective reporting bias: We rated one study as unclear, the other as high risk of bias due to discordances between planned and actual outcome reporting and/or analyses.

Potential biases in the review process

- Despite our comprehensive literature searching strategy without any publication status or language restrictions, there is a possibility that we may have missed studies that were published in a language other than English, published in non-indexed journals, or not published at all.
- The number of studies included in this review was insufficient to generate funnel plots. Therefore, we may have underestimated the risk of publication bias.
- We contacted study authors on several occasions and they provided feedback to some of our queries, but only one (O'Brien 2011) provided the additional data we requested, which may also be a potential source of bias.

Agreements and disagreements with other studies or reviews

We identified existing systematic reviews on this topic (Deng 2014; Fang 2013; Wu 2015; Yuan 2015). Similar to our results, all of these reviews reported that intravesical chemotherapy reduces bladder cancer recurrence and causes little to no minor adverse events, even though they pooled single and multiple chemotherapy instillations and different study designs.

However, only our review applied the necessary methodological rigor. Unlike this review, previous systematic reviews did not publish protocols nor did they rate the certainty of evidence (Deng 2014, Fang 2013, Wu 2015, Yuan 2015). We believe that three studies did not apply the 'risk of bias' tool (Fang 2013; Wu 2015; Yuan 2015) appropriately and that two studies have unit of analysis errors (Deng 2014, Fang 2013). In addition, none of the existing systematic reviews included a certainty of evidence rating. We therefore believe that our systematic review provides the most reliable summary of evidence on this topic to date, thereby fulfilling an important role in guiding evidence-based decision-making.

AUTHORS' CONCLUSIONS

Implications for practice

Single-dose intravesical chemotherapy instillation after nephroureterectomy for UTUC may reduce the risk of recurrence over time. However, we are very uncertain as to the risk of serious (and minor) adverse events. This major uncertainty surrounding this outcome that is critical to the trade-off of desirable and undesirable effects of this treatment approach relates to the small number of included studies, their small sample size, and the possibility of selective reporting bias for harm outcomes. We also found no RCT evidence for other patient-important outcomes such as disease-specific survival, overall survival and quality of life.

Implications for research

Our knowledge on this topic can be improved by focusing on the following issues:

- The body of evidence in this review comes from relatively small studies of limited methodological quality. More rigorous, adequately powered trials are necessary.
- It is important that future trials assess the head-to-head comparisons of chemotherapeutic drugs, as well as the evidence for optimal chemotherapy instillation time periods. Moreover, recent evidence suggests that gemcitabine is more effective than mitomycin in preventing bladder cancer recurrence in non-muscle invasive bladder cancer (Addeo 2010). Future research should ascertain the efficacy and safety of gemcitabine instillation for preventing bladder cancer recurrence after nephroureterectomy for UTUC.
- Future studies with longer-term data (beyond 12 months) should also provide data on disease-specific survival, overall survival, and quality of life.
- There is a need for both randomised trials as well as prospective observational studies that assess the true burden of this intervention in terms of side effects and quality of life impact.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ito 2013

Methods	**Study design:** Prospective randomised phase II study **Statistical design:** N/A **Setting/Country:** Multicentre/Japan **Dates when study was conducted:** December 2005 to November 2008

Participants	**Ethnicity:** likely Japanese
	
	Inclusion criteria
	
	• Participants who were clinically diagnosed with UTUC
	• No distant metastasis
	• ECOG PS of ≤ 2
	• Participants who were expected to receive curative surgery
	• Normal organ function
	  ○ ALT/AST upper limit of normal range
	  ○ serum creatinine < 1.5 mg/dL
	  ○ WBC: more than 4000/mm^3 Hb: more than 10 mg/dL, PLT: more than 100,000/mm^3
	  ○ Electrocardiograph: normal
	
	Exclusion criteria
	
	• A prior history of bladder or synchronous bladder cancer
	• Administration of neoadjuvant chemotherapy
	• Presence of severe complications
	• Active other cancer
	
	Total number of participants randomly assigned:
	
	• Screened: N/A
	• Eligible: 77
	
	Group A (THP instillation)
	
	• number of all participants randomly assigned: 39
	• Age: < 69 years; n = 18 (50%), ≥ 69 years; n = 18 (50%)
	• Gender (M/F): 22/14 (61.1%/38.9%)
	• Death from UTUC: N/A; death from any cause: N/A
	• Previous or concomitant bladder tumour: exclusion criteria
	• Tumour stage (Ta/T1/T2/T3/T4, n, %): 10 (27.7)/9 (25)/6 (16.7)/11 (30.6)/0 (0); tumour grade (low/high, n, %): 24 (66.7)/12 (33.3)
	• Tumour location (n, %): calix or pelvis 21 (58.3), pelvis and ureter 2 (5.6%), ureter 13 (36.1)
	• Presence of concurrent carcinoma in situ: 4 (11.1%); tumour multifocality: N/A
	• Bladder cuff excision method: the distal ureter was dissected down to its intramural segment, and the entire ureter and orifice were completely excised through a posterolateral cystotomy
	
	Group B (No instillation)
	
	• number of all participants randomly assigned: 38
	• Age: < 69 years; n = 19 (52.8%), ≥ 69 years; n = 17 (47.2%)
	• Gender (M/F, n, %): 21/15 (58.3/41.7)
	• Death from UTUC: N/A; death from any cause: N/A

Ito 2013 *(Continued)*

- Previous or concomitant bladder tumour: exclusion criteria
- Tumour stage (Ta/T1/T2/T3/T4, n, %): 6 (16.7)/14 (38.9)/2 (5.6)/14 (38.9)/0 (0); tumour grade (low/high, n, %): 15 (41.7)/21 (58.3)
- Tumour location (n, %): calix or pelvis 19 (55.9), pelvis and ureter 1 (2.8), ureter 16 (44.4)
- Presence of concurrent carcinoma in situ: 0 (0%); tumour multifocality: N/A
- Bladder cuff excision method: same as group A

Interventions	**Group A:** Single-dose THP 30 mg in 30 mL of normal saline was delivered into the bladder through a catheter within 48 hours after nephroureterectomy and was retained for 30 minutes. **Group B:** No instillation **Follow-up:** median 24.9 months (range: 2.6 to 39.3 months) in group A; median 13.7 months (range: 2.8 to 34.1 months) in group B
Outcomes	**Primary outcome** • Bladder cancer recurrence • How measured: bladder cancer recurrence: cystoscopy, urine cytology and urine analysis • Time points to measurement of bladder cancer recurrence: 2 years • Time points reported: N/A **Safety outcome** • Adverse events • How measured: National Cancer Institute Common Toxicity Criteria version 2.0. • Time points to measurement: N/A • Time points reported: N/A **Subgroup:** none
Funding Sources	Supported in part by a Grant-In-Aid for Scientific Research from the Ministry of Education, Science and Culture (Grant No. 21390437) of the Japanese government (Y.A.)
Declarations of interest	None
Notes	**Protocol:** UMIN Clinical Trials Registry: Trial number UMIN000004039 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Randomly assigned using a minimization method" **Comment:** This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "Enrolled patients were stratified at University Hospital Medical Information Network Clinical Trials Registry according to institution, sex, location of urothelial tumour, and operative method and then randomly assigned". **Comment:** Central registration. This method may ensure allocation concealment.

Ito 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote from publication:** Open-label trial (reported in the study protocol) **Comment:** Participants and personnel were not blinded; therefore risk of performance bias was considered to be high.
Blinding of outcome assessment (detection bias) Subjective outcomes (susceptible to detection bias); time to bladder cancer recurrence, time to death from UTUC, serious and minor adverse events, disease-specific quality of life	High risk	**Quote from publication:** Open-label trial (reported in the study protocol) **Comment:** Outcome assessor was not blinded; therefore, risk of detection bias was considered to be high.
Blinding of outcome assessment (detection bias) Objective outcomes (not susceptible to detection bias); time to death from any cause	Low risk	**Comment:** Objective outcomes were not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to bladder cancer recurrence	Low risk	**Comment:** 3/39 (7.6%) in intervention arm and 2/38 (5.3%) in control arm were excluded from the analysis. Owing to the small number of participants lost to follow-up, risk of attrition bias was considered to be low.
Incomplete outcome data (attrition bias) Time to death from UTUC	Unclear risk	**Comment:** This study did not address this outcome.
Incomplete outcome data (attrition bias) Serious adverse events	Low risk	**Comment:** 3/39 (7.6%) in intervention arm and 2/38 (5.3%) in control arm were excluded from the analysis. Owing to the small number of participants lost to follow-up, risk of attrition bias was considered to be low.
Incomplete outcome data (attrition bias) Time to death from any cause	Unclear risk	**Comment:** This study did not address this outcome.
Incomplete outcome data (attrition bias) Minor adverse events	Low risk	**Comment:** 3/39 (7.6%) in intervention arm and 2/38 (5.3%) in control arm were excluded from the analysis. Owing to the small number of participants lost to follow-up, risk of attrition bias was considered to be low.
Incomplete outcome data (attrition bias) Diseas-specific quality of life	Unclear risk	**Comment:** This study did not address this outcome.
Selective reporting (reporting bias)	Unclear risk	**Comment:** Protocol was provided (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000004865; UMIN Clinical Trials Registry: Trial number UMIN000004039) but toxicity outcomes were not predefined.
Other bias	High risk	**Comment:** Difference in median follow-up between the groups (24.9 vs 13.7 months) and there was baseline imbalance in carcinoma in situ and tumour grade.

O'Brien 2011

Methods	**Study design:** Prospective randomised nonblinded study **Statistical design:** N/A **Setting/Country:** Multicentre/United Kingdom **Dates when study was conducted:** July 2000 to December 2006
Participants	**Ethnicity:** likely English **Inclusion criteria** • A new clinical diagnosis of a transitional cell tumour of the upper urinary tract above the intramural ureter • A negative cystoscopy for urothelial cell carcinoma of bladder within one month of the nephroureterectomy • A nephroureterectomy that is planned to be performed in such a way that there is early distal ligation of the ureter prior to the mobilisation of the tumour • The intramural portion of the ureter may be resected prior to the open part of the operation, taken at the open operation with a cuff of bladder or everted at the end of the operation and resected endoscopically according to surgical preference. • Have a life expectancy of at least one year • Informed consent to participate (written and witnessed) • Adult **Exclusion criteria** • The histology of the upper tract tumour does not confirm a transitional cell carcinoma. • Stage N1 or M1 • Had additional systemic chemotherapy or additional intravesical mitomycin at follow-up cystoscopies • Existing or previous urothelial cell carcinoma of bladder • Children, pregnant women excluded • Life expectancy less than one year • Known sensitivity to mitomycin **Total number of participants randomly assigned:** • Screened: N/A • Eligible: 284 **Group A** (MMC instillation) • Number of all participants randomly assigned: 144 • Age: median: 70 years (range 44 to 87) • Gender (M/F): N/R • Death from UTUC: N/A; death from any cause: N/A • Previous or concomitant bladder tumour: exclusion criteria • Tumour stage (Ta/T1/T2/T3/T4, n, %): 28 (23.3)/40 (33.3)/19 (15.8)/29 (24.1)/2 (1.8)/not stated 2 (1.8); tumour grade (low/high, n, %): 67 (55.8)/50 (41.7)/not stated 3 (2.5) • Tumour location: N/A • Presence of concurrent carcinoma in situ: N/A; tumour multifocality (n, %): 15 (12.5) • Bladder cuff excision method: rip and pluck, laparoscopic, open **Group B** (No instillation) • Number of all participants randomly assigned: 140 • Age: 71 years (range 36 to 90)

O'Brien 2011 *(Continued)*

- Gender (M/F): N/R
- Death from UTUC: N/A; death from any cause: N/A
- Previous or concomitant bladder tumour: exclusion criteria
- Tumour stage (Ta/T1/T2/T3/T4, n, %): 45 (37.8)/26 (21.8)/13 (10.9)/28 (23.5)/2 (1.7)/not stated 5 (4.3); tumour grade (low/high, n, %): 73 (61.3)/42 (35.3)/not stated 4 (3.4)
- Tumour location: N/A
- Presence of concurrent carcinoma in situ: N/A; tumour multifocality (n, %): 15 (12.6)
- Bladder cuff excision method: same as group A

Interventions	**Group A:** Single-dose MMC 40 mg in 40 mL of normal saline was delivered into the bladder prior to removal of the urethral catheter and was retained for 1 hour (the timing of the administration of the intravesical chemotherapy was chosen to minimise the risk of extravasation). **Group B:** No instillation **Follow-up:** 12 months
Outcomes	**Primary outcome** • Bladder cancer recurrence at 1 year • How measured: bladder cancer recurrence: cystoscopy (visual); histologic proof of recurrence was not required • Time points to measurement: cystoscopy at 3, 6, and 12 months post-nephroureterectomy • Time points to reported: N/A **Secondary outcome** • Post-surgical survival of participants over five years • How measured: N/R • Time points to measurement: not reported • Time points to reported: not reported **Safety outcome** • Adverse events • How measured: not reported • Time points to measurement: not reported • Time points reported: not reported **Subgroup** • Recurrence by grade, recurrence by multifocality, recurrence by stage, recurrence by method of nephroureterectomy
Funding Sources	The trial was funded through Guys and St Thomas' Hospitals Urology Research Fund. Kyowa Hakko gave two unrestricted donations totaling £7000 to offset some administrative expenses. No payments were made to recruiting centres. None of the team at Guys Hospital had financial links with Kyowa.
Declarations of interest	None
Notes	**Protocol:** ISRCTN36343644 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement

O'Brien 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Comment:** Randomisation stated and trial author provided random sequence generation method "used 'Tombola' blinded selection of treatment from within the block"; therefore selection bias was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "Randomisation was performed at Guys Hospital following the nephroureterectomy and was by means of sealed envelopes in blocks of 20". **Comment:** Since this study was multicentre and allocation was performed by central allocation (randomisation was performed at Guys Hospital with sealed envelopes), we assumed that this method may ensure allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote from publication:** "nonblinded trial" **Comment:** Participants and personnel were not blinded; therefore risk of performance bias was considered to be high.
Blinding of outcome assessment (detection bias) Subjective outcomes (susceptible to detection bias); time to bladder cancer recurrence, time to death from UTUC, serious and minor adverse events, disease-specific quality of life	High risk	**Quote from publication:** "nonblinded trial" **Comment:** Participants and personnel were not blinded; therefore risk of performance bias was considered to be high.
Blinding of outcome assessment (detection bias) Objective outcomes (not susceptible to detection bias); time to death from any cause	Low risk	**Comment:** Objective outcomes were not likely to be affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to bladder cancer recurrence	Unclear risk	**Comment:** 24/144 (16.6%) in intervention arm and 21/140(15%) in control arm were excluded from the analysis; owing to the moderate number of participants lost to follow-up (> 10%), risk of attrition bias was considered to be unclear.
Incomplete outcome data (attrition bias) Time to death from UTUC	Unclear risk	**Comment:** This study did not address this outcome.
Incomplete outcome data (attrition bias) Serious adverse events	Unclear risk	**Comment:** 24/144 (16.6%) in intervention arm and 21/140(15%) in control arm were excluded from the analysis; owing to the moderate number of participants lost to follow-up (> 10%), risk of attrition bias was considered to be unclear.
Incomplete outcome data (attrition bias) Time to death from any cause	Unclear risk	**Comment:** This study did not address this outcome.
Incomplete outcome data (attrition bias) Minor adverse events	Unclear risk	**Comment:** This study did not address this outcome.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment:** This study did not address this outcome.

O'Brien 2011 *(Continued)* Diseas-specific quality of life		
Selective reporting (reporting bias)	High risk	**Comment:** Protocol was provided (ISRCTN36343644) but secondary outcomes were not reported and subgroup analyses were not predefined.
Other bias	High risk	**Comment:** There was baseline imbalance in Ta disease and high grade tumour.

ALT: alanine aminotransferase
AST: aspartate aminotransferase
ECOG PS: Eastern Cooperative Oncology Group performance status
F: female
Hb: haemoglobin
M: male
M1: metastasis
MMC: mitomycin
n: number of participants
N1: lymph node involvement
N/A: not available
N/R: not reported
PLT: platelet
THP: pirarubicin
UTUC: upper tract urothelial carcinoma
WBC: white blood cell

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

Study	Reason for exclusion
Sakamoto 2001	Ineligible intervention; multiple instillation (28 times) of chemotherapy
Van Doeveren 2018	Published study protocol, not full-text, and ineligible study design

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

JPRN-UMIN000009682

Trial name or title	Randomised controlled trial of a single postoperative intravesical instillation of THP for prevention of intravesical recurrence after nephroureterectomy
Methods	Open-label randomised parallel group trial
Participants	**Estimated enrollment:** 90 participants **Inclusion Criteria** • Obtained informed consent • Pathologically confirmed urothelial carcinoma • No previous treatment of upper urinary tract tumours • No metastasis and resectable tumours • No previous bladder tumours and concomitant bladder tumours • ECOG PS 0-3

JPRN-UMIN000009682 *(Continued)*

	• Have sufficient major organ functions **Exclusion Criteria** • Need adjuvant chemotherapy according to pathological result • Have active cancer except for upper urinary tract tumours • Inappropriate patients for this study judged by the physicians
Interventions	**Group A** • Intravesical instillation of THP (dose: not available) **Group B** • No treatment
Outcomes	**Primary outcomes** • Intravesical recurrence rate (time to measurement: not available) **Secondary outcomes** • None
Starting date	August 22, 2012; **Expected date of completion:** June 2020
Contact information	shingoy@hyo-med.ac.jp; tosuzuki@hyo-med.ac.jp
Notes	**Funding source:** Self funding

Miyamoto 2018

Trial name or title	A Phase III trial of a single early intravesical instillation of pirarubicin to prevent bladder cancer recurrence after radical nephroureterectomy for upper tract urothelial carcinoma (JCOG1403, UTUC THP Phase III)
Methods	A multi-institutional open-label randomised phase III study

Participants	**Estimated enrollment:** 310 participants
	
	Inclusion Criteria
	
	First registration (before undergoing radical nephrectomy)
	
	• UTUC diagnosed using CT with (i) the primary site in the renal pelvis or ureter, (ii) not bilateral, (iii) both solitary/multiple lesions eligible
	• Clinical stage 0a–III (cTa-T3N0M0) disease diagnosed using CT
	• Age of 20–80 years
	• ECOG performance status of 0–1
	• No history of treatment for UTUC
	• No cystoscopic diagnosis of bladder cancer
	• No history of bladder cancer
	• No history of irradiation, including bladder irradiation
	• Intact and functional kidneys
	• Sufficient organ functions:
	  ◦ WBC count ≥ 1500/mm^3
	  ◦ Hb ≥ 10.0 g/dL

Miyamoto 2018 *(Continued)*

- PLT count ≥ $10 \times 10^4/mm^3$
- AST ≤ 100 U/L
- ALT ≤ 100 U/L
- serum creatinine of ≤ 1.5 mg/dL
- written informed consent

Second registration (after undergoing radical nephrectomy)

- Macroscopically confirmed Ta-3N0M0 disease
- No lymph node metastasis if intraoperative pathological examinations performed
- No serious intraoperative complications
- No leakage after bladder wall sutured after cuff resection around the ureteral orifice
- Macroscopically negative ureter resection margins
- Within 56 days from the date of cystoscopy
- Within 91 days from the date of CT

Exclusion Criteria

- Synchronous or metachronous malignancies (within 5 years)
- Infectious diseases requiring systemic treatment
- Pyrexia of ≥ 38°C
- Females who are pregnant, have given birth within 28 days, or are lactating
- Severe psychiatric disorders
- Receiving continuous systemic corticosteroid or immunosuppressant treatment
- History of abnormal cardiac function or having received the limit dose of medications with cardiac toxicity, such as anthracyclines
- Positive for antibodies to the human immunodeficiency virus

Interventions	**Group A** • Intravesical instillation of THP at 30 mg following radical nephroureterectomy • Postoperative chemotherapy of 2 cycles of gemcitabine at 1000 mg/m^2 and cisplatin at 70 mg/m^2 every 4 weeks for only high risk patients with pT3/T4 or pN+ **Group B:** • No instillation following radical nephroureterectomy • Postoperative chemotherapy of 2 cycles of gemcitabine at 1000 mg/m^2 and cisplatin at 70 mg/m^2 every 4 weeks for only high risk patients with pT3/T4 or pN+
Outcomes	**Primary outcomes** • Relapse-free survival **Secondary outcomes** • Overall survival • Intravesical relapse-free survival, adverse events, and serious adverse events Follow-up: at least 3 years after the patient recruitment is completed
Starting date	October 03, 2016; **Expected date of completion:** October 2025
Contact information	itoaki@uro.med.tohoku.ac.jp
Notes	**Funding source:** National Cancer Center Research and Development Fund (26-A-4)

NCT02547350

Trial name or title	Prophylactic intravesical chemotherapy to prevent bladder tumors after nephroureterectomy for primary upper urinary tract urothelial carcinomas
Methods	Open-label randomised parallel group phase II study
Participants	**Estimated enrollment:** 200 participants **Inclusion Criteria** • Patients who were clinically diagnosed with UTUC • Treated with radical nephroureterectomy **Exclusion Criteria** • Distant metastasis • Prior history of bladder or synchronous bladder cancer • Administration of neoadjuvant chemotherapy • Presence of severe complications
Interventions	**Group A** • No Intervention; blank control, do not use prophylactic intravesical chemotherapy **Group B** • Single intravesical instillation, intravesical instillation within 24 hours postoperatively using pharmorubicin 50 mg or pirarubicin 30 mg **Group C** • Multiple intravesical instillation, intravesical instillation every 1 week for the first 2 months, then once a month for the remaining 10 months using pharmorubicin 50 mg or pirarubicin 30 mg
Outcomes	**Primary outcomes** • Intravesical recurrence-free survival (time to measurement: two years after surgery) **Secondary outcomes** • Cancer-specific survival (time to measurement: two years after surgery)
Starting date	September 2015; **Expected date of completion:** December 2020
Contact information	Xuesong Li, Professor, Peking University First Hospital
Notes	**Funding source:** Not available

NCT02923557

Trial name or title	Prophylactic intravesical chemotherapy to prevent bladder cancer recurrence after nephroureterectomy for primary upper tract urothelial carcinoma patients
Methods	Single-blinded randomised parallel group phase II study
Participants	**Estimated enrollment:** 200 participants

NCT02923557 *(Continued)*

	Inclusion Criteria • Suspected UTUC patients without history of bladder tumour • Suspected UTUC patients without synchronous bladder tumour • Suspected UTUC patients without contralateral UTUCs **Exclusion Criteria** • Patients with history of bladder tumour • Patients with synchronous bladder tumour • Patients with contralateral UTUCs • Patients with advanced stage (T4) • Patients with other malignant tumours
Interventions	**Group A** • No Intervention; blank control, do not use prophylactic intravesical chemotherapy **Group B** • Single immediate intravesical dose of THP intravesical therapy (THP 40 mg for 30 min) within 24 hours of nephroureterectomy
Outcomes	**Primary outcomes** • Intravesical recurrence-free survival (time to measure: three years after surgery) **Secondary outcomes** • Cancer-specific survival (time to measure: three years after surgery)
Starting date	November 2016; **Expected date of completion:** November 2021
Contact information	Xuesong Li, Associated Professor, Peking University First Hospital
Notes	**Funding source:** Not available

NCT03062059

Trial name or title	The effectiveness and safety of intravesical gemcitabine instillation during operation to prevent intravesical recurrence after radical nephroureterectomy in upper urinary tract urothelial carcinoma: prospective, phase II Study
Methods	A multicentre open-label randomised parallel group phase II study

Participants	**Estimated enrollment:** 134 participants
	Inclusion Criteria
	• Subjects who will undergo nephroureterectomy due to ureter or renal pelvis urothelial carcinoma
	• Male or female aged 18 years or over and not more than 85 years who were diagnosed with upper urinary tract urothelial carcinoma
	• Normal bone marrow function: Hb > 10 g/dL, ANC > 1500/mm^3, PLT count > 100,000/mm^3
	• Normal bladder volume and function
	• Normal liver function
	  ○ Bilirubin ≤ 1.5 times of upper normal limit
	  ○ AST/ALT ≤ 1.8 times of upper normal limit

NCT03062059 *(Continued)*

	○ Alkaline phosphatase ≤ 1.8 times of upper normal limit • Subjects who voluntarily decided to participate and signed the written informed consent **Exclusion Criteria** • Concomitant bladder cancer • Subjects who underwent any treatment due to bladder cancer within 3 years • Prior hypersensitivity reaction history to gemcitabine • Neurogenic bladder • Subjects who underwent chemotherapy due to any cancer within 6 months • Subjects who underwent neoadjuvant chemotherapy due to ureter or renal pelvis urothelial carcinoma • Hypersensitivity to gemcitabine or component of gemcitabine • In case of co-administration of gemcitabine and cisplatin in severe renal failure patients • Moderate to severe liver dysfunction or renal dysfunction (glomerular filtration rate < 30 mL/min) • Severe bone marrow suppression • Severe infection • Female who is pregnant or has a possibility of pregnancy • Nursing female • Interstitial pneumonia or pulmonary fibrosis which is evident on chest x-ray and symptomatic • Subjects who are undergoing radiotherapy on chest
Interventions	**Group A** • No intervention **Group B** • Intravesical 2000 mg/52.6 mL gemcitabine instillation during radical nephroureterectomy
Outcomes	**Primary outcomes** • Recurrence-free survival (time to measurement: two years, how to measure: CT scan and cystoscopic exam) **Secondary outcomes** • Time to recurrence (time to measurement: six years, how to measure: CT scan and cystoscopic exam) • Overall survival (time to measurement: six years) • CT cystography finding (e.g. leakage) at one week after surgery (time to measurement: one week) • International Prostate Symptom Score questionnaire at one week after surgery (time to measurement: one week)
Starting date	March 1, 2018; **Expected date of completion:** December 31, 2022
Contact information	seohk@ncc.re.kr; 12754@ncc.re.kr
Notes	**Funding source:** Chong Kun Dang Pharmaceutical Corp

NCT03209206

Trial name or title	The effectiveness and safety of intravesical docetaxel instillation after operation to prevent intravesical recurrence after radical nephroureterectomy or distal ureterectomy in upper urinary tract urothelial carcinoma: a prospective study

NCT03209206 *(Continued)*

Methods	Open-label randomised parallel group phase II study
Participants	**Estimated enrollment:** 84 participants **Inclusion Criteria** • Age 19 to 85 years • UTUC • Hb > 10g/dL, ANC > 1500/mm^3, PLT > 100 x 10^3/mm^3 • Total bilirubin : 1.5 times lower than the normal upper limit • AST/ALT: 1.8 times lower than the normal upper limit • ALP: 1.8 times lower than the normal upper limit **Exclusion Criteria** • Concomitant bladder tumour • Patients diagnosed with bladder cancer within the last 3 years • Previous history of hypersensitivity to docetaxel • Neurogenic bladder • Patients who received chemotherapy for cancer within the last 6 months • Patients with active disease not fit for this study • ANC < 1500mm^3 • Pregnant or lactating women • Patients with severe hepatic dysfunction • Patients with severe renal impairment • Patients with hypersensitivity to mannitol, paraplatin, platinum compounds • Patients with complications of infection • Patients suspected of having infectious fever
Interventions	**Group A** • Intravesical instillation of docetaxel (docetaxel 75 mg diluted in 100 cc of normal saline) after operation of UTUC (within 48 hours) **Group B** • Intravesical instillation of normal saline (100 cc of normal saline) after operation of UTUC (within 48 hours)
Outcomes	**Primary outcomes** • Recurrence in bladder (time to measurement: two years, how to measure: CT scan and cystoscopic exam) **Secondary outcomes** • Incidence of treatment-emergent adverse events (presence of adverse event(s) after intervention) • Overall survival (time to measurement: two years) • Time to recurrence (time to measurement: two years, how to measure: CT scan and cystoscopic exam)
Starting date	June 28, 2017; **Expected date of completion:** April 1, 2022
Contact information	randyku@hanmail.net
Notes	**Funding source:** Seoul National University Hospital

ANC: absolute neutrophil count
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CT: computed tomography
ECOG PS: Eastern Cooperative Oncology Group performance status
Hb: haemoglobin
PLT: platelet
THP: pirarubicin
UTUC: upper tract urothelial carcinoma
WBC: white blood cell

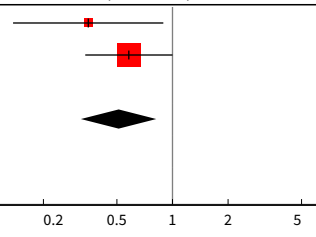
DATA AND ANALYSES

Comparison 1. Single-dose intravesical chemotherapy instillation versus placebo or observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to bladder cancer recurrence	2	311	Hazard Ratio (Random, 95% CI)	0.51 [0.32, 0.82]
2 Serious adverse events	2	311	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Minor adverse events	1	72	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Single-dose intravesical chemotherapy instillation versus placebo or observation, Outcome 1 Time to bladder cancer recurrence.

Study or subgroup	Single dose intravesical chemotherapy instillation N	Placebo or observation N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Ito 2013	36	36	-1 (0.478)		25.27%	0.35[0.14,0.89]
O'Brien 2011	120	119	-0.5 (0.278)		74.73%	0.58[0.34,1]
Total (95% CI)					**100%**	**0.51[0.32,0.82]**
Heterogeneity: Tau^2=0; Chi^2=0.84, df=1(P=0.36); I^2=0%						
Test for overall effect: Z=2.8(P=0.01)						



Analysis 1.2. Comparison 1 Single-dose intravesical chemotherapy instillation versus placebo or observation, Outcome 2 Serious adverse events.

Study or subgroup	Single dose intravesical chemotherapy instillation	Placebo or observation	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Ito 2013	0/36	0/36			Not estimable
O'Brien 2011	0/120	0/119			Not estimable
Total (95% CI)	**156**	**155**			**Not estimable**
Total events: 0 (Single dose intravesical chemotherapy instillation), 0 (Placebo or observation)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Single dose intravesical chemotherapy instillation — Placebo or observation

Analysis 1.3. Comparison 1 Single-dose intravesical chemotherapy instillation versus placebo or observation, Outcome 3 Minor adverse events.

Study or subgroup	Single dose intravesical chemotherapy instillation	Placebo or observation	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Ito 2013	0/36	0/36			Not estimable
Total (95% CI)	**36**	**36**			**Not estimable**
Total events: 0 (Single dose intravesical chemotherapy instillation), 0 (Placebo or observation)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Single dose intravesical chemotherapy instillation — Placebo or observation

ADDITIONAL TABLES

Table 1. Baseline characteristics of included study

Study name	Trial period (year to year)	Setting/Country	Description of participants	Intervention(s) and comparator(s)	Duration of follow-up	Age	Gender
Ito 2013	2005 to 2008	Multicentre/Japan	Participants with UTUC who underwent nephroureterectomy	Intervention: pirarubicin 30 mg in 30 mL of normal saline	24.9 months (range: 2.6 to 39.3 months)	< 69 years; n = 18 (50%) ≥ 69 years; n = 18 (50%)	Male: n = 22 (61.1%) Female: n = 14 (38.9%)
				Comparator: no instillation	13.7 months (range: 2.8 to 34.1 months)	< 69 years; n = 19 (52.8%), ≥ 69 years; n = 17 (47.2%)	Male: n = 21 (58.3%) Female: n = 15 (41.7%)
O'Brien 2011	2000 to 2006	Multicentre/United Kingdom	Participants with UTUC who underwent nephroureterectomy	Intervention: mitomycin 40 mg in 40 mL of normal saline	12 months	median 70 years (range: 44 to 87)	not reported
				Comparator: no instillation		median 71 years (range: 36 to 90)	not reported

UTUC: upper tract urothelial carcinoma

Table 2. Participants in included study

Study name	Intervention(s) and comparator(s)	Screened/ eligible (N)	Randomised (N)	Analysed (N): efficacy[a]	Analysed (N): safety[b]	Finishing trial (N (%))
Ito 2013	Intervention: pirarubicin 30mg in 30 mL of normal saline	N/A/77	39	36	36	32
	Comparator: no instillation		38	36	36	31
	Total		77	72	72	63
O'Brien 2011	Intervention:mitomycin 40 mg in 40 mL of normal saline	N/A/284	144	120	120	92
	Comparator: no instillation		140	119	119	95
	Total		284	239	239	187
Grand total			361	311	311	250

N/A: not available

a: The number of participants analysed for bladder cancer recurrence

b: The number of participants with adverse events

APPENDICES

Appendix 1. Search strategy

MEDLINE	
1	exp NEPHRECTOMY/
2	Kidney Neoplasms/su [Surgery]
3	Ureteral Neoplasms/su [Surgery]
4	(Nephrectom$ or Nephroureterectom$ or Nephro-ureterectom$ or Ureteronephrectom$).tw.
5	1 or 2 or 3 or 4
6	exp DOXORUBICIN/
7	(23214-92-8 or 25316-40-9).rn,tw.
8	(Doxorubicin$ or Caelyx or Doxil or Myocet or Adriblastin$ or Adriablastin$ or Doxolem or Adrimedac or Farmiblastina or Ribodoxo or DOXO-cell or Onkodox).nm,tw.
9	exp EPIRUBICIN/
10	(56390-09-1 or 56420-45-2).rn,tw.

(Continued)

11	(Epirubicin$ or Farmorubicin$ or Pharmorubicin$ or IMI28 or Ellence or Epidoxorubicin or Epi-Doxorubicin or Epiadriamycin or Epi-Adriamycin or EPI-cell or EPIcell or Epilem).nm,tw.
12	exp MITOMYCIN/
13	(1404-00-8 or 50-07-7 or 74349-48-7).rn,tw.
14	(Mitomycin$ or Mitomicin$ or Mitocin$ or Ametycin$ or Mutamycin$).nm,tw.
15	exp THIOTEPA/
16	52-24-4.rn,tw.
17	(Thiotepa or Thio-tepa or Tespa$ or Thiophosphamide or Girostan).nm,tw.
18	(Gemcitabin$ or Gemcetabin$ or Gemcatabin$ or Gemzar$).nm,tw.
19	103882-84-4.rn,tw.
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Administration, Intravesical/
22	((Bladder or Intravesical) adj2 (Administration$ or Injection$ or Instillation$)).tw.
23	exp Urinary Bladder Neoplasms/su [Surgery]
24	exp Urinary Bladder Neoplasms/pc [Prevention & Control]
25	21 or 22 or 23 or 24
26	20 and 25
27	5 and 26
28	randomized controlled trial.pt.
29	controlled clinical trial.pt.
30	randomized.ab.
31	placebo.ab.
32	drug therapy.fs.
33	randomly.ab.
34	trial.ab.
35	groups.ab.
36	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37	exp animals/ not humans.sh.
38	36 not 37

(Continued)

39	27 and 38
Cochrane Library	
1	MeSH descriptor: [Nephrectomy] explode all trees
2	MeSH descriptor: [Kidney Neoplasms] explode all trees and with qualifier(s): [surgery - SU]
3	MeSH descriptor: [Ureteral Neoplasms] explode all trees and with qualifier(s): [surgery - SU]
4	(Nephrectom* OR Nephroureterectom* OR Nephro-ureterectom* OR Ureteronephrectom*):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	MeSH descriptor: [Doxorubicin] explode all trees
7	('23214 92 8' OR '25316 40 9'):ti,ab,kw
8	(Doxorubicin* OR Caelyx OR Doxil OR Myocet OR Adriblastin* OR Adriablastin* OR Doxolem OR Adrimedac OR Farmiblastina OR Ribodoxo OR DOXO-cell OR Onkodox):ti,ab,kw
9	MeSH descriptor: [Epirubicin] explode all trees
10	('56390 09 1' OR '56420 45 2'):ti,ab,kw
11	(Epirubicin* OR Farmorubicin* OR Pharmorubicin* OR IMI28 OR Ellence OR Epidoxorubicin OR Epi-Doxorubicin OR Epiadriamycin OR Epi-Adriamycin OR EPI-cell OR EPIcell OR Epilem):ti,ab,kw
12	MeSH descriptor: [Mitomycins] in all MeSH products
13	('1404 00 8' OR '50 07 7' OR '74349 48 7'):ti,ab,kw
14	(Mitomycin* OR Mitomicin* OR Mitocin* OR Ametycin* OR Mutamycin*):ti,ab,kw
15	MeSH descriptor: [Thiotepa] explode all trees
16	('52 24 4'):ti,ab,kw
17	(Thiotepa OR Thio-tepa OR Tespa* OR Thiophosphamide OR Girostan):ti,ab,kw
18	(Gemcitabin* OR Gemcetabin* OR Gemcatabin* OR Gemzar*):ti,ab,kw
19	('103882 84 4'):ti,ab,kw
20	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21	MeSH descriptor: [Administration, Intravesical] explode all trees
22	((Bladder OR Intravesical) near/2 (Administration* OR Injection* OR Instillation*)):ti,ab,kw
23	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees and with qualifier(s): [prevention & control - PC, surgery - SU]
24	#21 OR #22 OR #23

(Continued)

25	#5 AND #20 AND #24
Embase	
1	'nephrectomy'/exp
2	'kidney tumor'/exp/dm_su
3	'ureter tumor'/exp/dm_su
4	(Nephrectom* OR Nephroureterectom* OR Nephro-ureterectom* OR Ureteronephrectom*):ab,ti
5	#1 OR #2 OR #3 OR #4
6	doxorubicin'/exp
7	('23214 92 8' OR '25316 40 9'):rn
8	(Doxorubicin* OR Caelyx OR Doxil OR Myocet OR Adriblastin* OR Adriablastin* OR Doxolem OR Adrimedac OR Farmiblastina OR Ribodoxo OR DOXO-cell OR Onkodox):ab,ti
9	'epirubicin'/exp
10	('56390 09 1' OR '56420 45 2'):rn
11	(Epirubicin* OR Farmorubicin* OR Pharmorubicin* OR IMI28 OR Ellence OR Epidoxorubicin OR Epi-Doxorubicin OR Epiadriamycin OR Epi-Adriamycin OR EPI-cell OR EPIcell OR Epilem):ab,ti,tn
12	'mitomycin'/exp
13	('1404 00 8' OR '50 07 7' OR '74349 48 7'):rn
14	(Mitomycin* OR Mitomicin* OR Mitocin* OR Ametycin* OR Mutamycin*):ab,ti,tn
15	thiotepa'/exp
16	52 24 4':rn
17	(Thiotepa OR Thio-tepa OR Tespa* OR Thiophosphamide OR Girostan):ab,ti,tn
18	gemcitabine'/exp
19	(Gemcitabin* OR Gemcetabin* OR Gemcatabin* OR Gemzar*):ab,ti,tn
20	'103882 84 4':rn
21	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	intravesical drug administration'/exp
23	((Bladder OR Intravesical) NEAR/2 (Administration* OR Injection* OR Instillation*)):ab,ti
24	bladder tumor'/exp/dm_pc,dm_su
25	#22 OR #23 OR #24

(Continued)

26	#5 AND #21 AND #25
27	''crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
28	('animals'/exp) NOT ('humans'/exp and 'animals'/exp)
29	#27 NOT #28
30	#26 AND #29
Scopus	
1	TITLE-ABS-KEY ((nephrectom* OR nephroureterectom* OR nephro-ureterectom* OR ureteronephrectom*))
2	TITLE-ABS-KEY ((doxorubicin* OR caelyx OR doxil OR myocet OR adriblastin* OR adriablastin* OR doxolem OR adrimedac OR farmiblastina OR ribodoxo OR doxo-cell OR onkodox OR epirubicin* OR farmorubicin* OR pharmorubicin* OR imi28 OR ellence OR epidoxorubicin OR epi-doxorubicin OR epiadriamycin OR epi-adriamycin OR epi-cell OR epicell OR epilem OR mitomycin* OR mitomicin* OR mitocin* OR ametycin* OR mutamycin* OR thiotepa OR thio-tepa OR tespa* OR thiophosphamide OR girostan OR gemcitabin* OR gemcetabin* OR gemcatabin* OR gemzar*))
3	CASREGNUMBER ("23214 92 8" OR "25316 40 9" OR "56390 09 1" OR "56420 45 2" OR "1404 00 8" OR "50 07 7" OR "74349 48 7" OR "52 24 4" OR "103882 84 4")
4	#2 OR #3
5	TITLE-ABS-KEY (((bladder OR intravesical) W/2 (administration* OR injection* OR instillation*)))
6	#1 AND #2 AND #3
7	(INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomisation" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical trial* OR trial* OR rct* OR random* OR blind*))
8	#4 AND #5
Web of Science	
1	TS= ((Nephrectom* OR Nephroureterectom* OR Nephro-ureterectom* OR Ureteronephrectom*))
2	TS= ((Doxorubicin* OR Caelyx OR Doxil OR Myocet OR Adriblastin* OR Adriablastin* OR Doxolem OR Adrimedac OR Farmiblastina OR Ribodoxo OR DOXO-cell OR Onkodox OR Epirubicin* OR Farmorubicin* OR Pharmorubicin* OR IMI28 OR Ellence OR Epidoxorubicin OR Epi-Doxorubicin OR Epiadriamycin OR Epi-Adriamycin OR EPI-cell OR EPIcell OR Epilem OR Mitomycin* OR Mitomicin* OR Mitocin* OR Ametycin* OR Mutamycin* OR Thiotepa OR Thio-tepa OR Tespa* OR Thiophosphamide OR Girostan OR Gemcitabin* OR Gemcetabin* OR Gemcatabin* OR Gemzar* OR "23214 92 8" OR

(Continued)

	"25316 40 9" OR "56390 09 1" OR "56420 45 2" OR "1404 00 8" OR "50 07 7" OR "74349 48 7" OR "52 24 4" OR "103882 84 4"))
3	TS= (((Bladder OR Intravesical) NEAR/2 (Administration* OR Injection* OR Instillation*)))
4	#1 AND #2 AND #3
5	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*)
6	#3 AND #4
LILACS	
1	(mh:("Nephrectomy" OR "Kidney Neoplasms/SU" OR "Ureteral Neoplasms/SU")) OR (tw:(Nephrectom* or Nephroureterectom* or Nephro-ureterectom* or Ureteronephrectom*))
2	(mh:("Doxorubicin" OR "Epirubicin" OR "Mitomycin" OR "Thiotepa")) OR (tw:(Doxorubicin* OR Caelyx OR Doxil OR Myocet OR Adriblastin* OR Adriablastin* OR Doxolem OR Adrimedac OR Farmiblastina OR Ribodoxo OR DOXO-cell OR Onkodox OR Epirubicin* OR Farmorubicin* OR Pharmorubicin* OR IMI28 OR Ellence OR Epidoxorubicin OR Epi-Doxorubicin OR Epiadriamycin OR Epi-Adriamycin OR EPI-cell OR EPIcell OR Epilem OR Mitomycin* OR Mitomicin* OR Mitocin* OR Ametycin* OR Mutamycin* OR Thiotepa OR Thio-tepa OR Tespa* OR Thiophosphamide OR Girostan OR Gemcitabin* OR Gemcetabin* OR Gemcatabin* OR Gemzar* OR 23214-92-8 OR 25316-40-9 OR 56390-09-1 OR 56420-45-2 OR 1404-00-8 OR 50-07-7 OR 74349-48-7 OR 52-24-4 OR 103882-84-4))
3	(mh:("Administration, Intravesical")) OR (mh:("Urinary Bladder Neoplasms/SU")) OR (mh:("Urinary Bladder Neoplasms/PC")) OR (tw:("Bladder Drug Administration" OR "Bladder Instillation" OR "Intravesical Administration" OR "Intravesical Drug Administration" OR "Intravesical Injection" OR "Intravesical Instillation"))
4	((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")
5	1 AND 2 AND 3 AND 4
ClinicalTrials.gov	
1	(Nephrectomy OR Nephroureterectomy OR Nephro-ureterectomy OR Ureteronephrectomy)
2	(Bladder OR Intravesical)
3	1 AND 2
World Health Organization (WHO) International Clinical Trials Registry Platform search portal	
1	In the title = (Nephrectom* OR Nephroureterectom* OR Nephro-ureterectom* OR Ureteronephrectom*) AND In the intervention= (Bladder OR Intravesical)
Grey Literature (Open Grey)	

(Continued)

1	(Nephrectom* OR Nephroureterectom* OR Nephro-ureterectom* OR Ureteronephrectom*) AND (Bladder OR Intravesical)

Appendix 2. Survey of trial investigators providing information on included trials

Study	Date trial author contacted (first)	Date trial author provided data (latest)	Data trial author provided (short summary)
O'Brien 2011	3 Nov 2018	5 Nov 2018	Random sequence generation method and baseline characteristics

CONTRIBUTIONS OF AUTHORS

Eu Chang Hwang (ECH): study selection, extracting data, assessing risk of bias, performing data analysis, interpretation of data, and drafting the review.

Niranjan Sathianathen (NS): extracting data, assessing risk of bias, performing data analysis, and providing clinical advice and critical content.

Jae Hung Jung (JHJ): study selection and interpretation of data.

Myung Ha Kim (MHK): creating search strategies and searching for trials.

Philipp Dahm (PD): providing clinical and methodological guidance for this review.

Michael C Risk (MR): conception and study design, providing clinical and methodological advice on the review, and final approval.

DECLARATIONS OF INTEREST

ECH: none known.

NS: none known.

JHJ: none known.

MHK: none known.

PD: serves as Co-ordinating Editor of Cochrane Urology. However, he was not involved in the editorial processing or decision-making for this review. Other editors of Cochrane Urology managed the editorial process, including final sign-off for this review through the Cancer Network.

MR: none known.

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- Department of Urology, Chonnam National University Medical School, Korea, South.
- Department of Urology, Yonsei University Wonju College of Medicine, Korea, South.
- Department of Urology, University of Minnesota, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a previously published protocol (Hwang 2018). There were no relevant departures from this protocol.

NOTES

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Administration, Intravesical; Antineoplastic Agents [*administration & dosage] [therapeutic use]; Carcinoma [*drug therapy]; Nephroureterectomy; Randomized Controlled Trials as Topic; Treatment Outcome; Ureteral Neoplasms [*drug therapy]

MeSH check words

Humans