Cochrane Library

Cochrane Database of Systematic Reviews

Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy (Review)

Hwang EC, Sathianathen NJ, Imamura M, Kuntz GM, Risk MC, Dahm P

Hwang EC, Sathianathen NJ, Imamura M, Kuntz GM, Risk MC, Dahm P.
Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy.
Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD013336.
DOI: 10.1002/14651858.CD013336.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Eu Chang Hwang[1], Niranjan J Sathianathen[2], Mari Imamura[3], Gretchen M Kuntz[4], Michael C Risk[5], Philipp Dahm[5]

[1]Department of Urology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea, South. [2]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [3]Academic Urology, University of Aberdeen, Aberdeen, UK. [4]Borland Health Sciences Library, University of Florida-Jacksonville, Jacksonville, Florida, USA. [5]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact address: Eu Chang Hwang, Department of Urology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea, South. urohwang@gmail.com, urohwang@naver.com.

Editorial group: Cochrane Urology Group.
Publication status and date: New, published in Issue 5, 2019.

Citation: Hwang EC, Sathianathen NJ, Imamura M, Kuntz GM, Risk MC, Dahm P. Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy. *Cochrane Database of Systematic Reviews* 2019, Issue 5. Art. No.: CD013336. DOI: 10.1002/14651858.CD013336.

ABSTRACT

Background

In the treatment of urothelial carcinoma of the bladder, we are currently uncertain of the benefits and harms of standard pelvic lymph node dissection (PLND) compared to extended PLND.

Objectives

To assess the effects of extended versus standard PLND in patients undergoing cystectomy to treat muscle-invasive (cT2 and cT3) and treatment-refractory, non-muscle-invasive (cT1 with or without carcinoma in situ) urothelial carcinoma of the bladder.

Search methods

We performed a comprehensive literature search using multiple databases (PubMed, Embase, Cochrane Controlled Trials, Web of Science, and LILACS), trial registries, and conference proceedings published up to April 29, 2019, with no restrictions on the language or status of publication.

Selection criteria

We included randomized controlled trials in which participants underwent radical cystectomy (RC) for muscle-invasive or therapy-refractory non-muscle-invasive urothelial carcinoma of the bladder with either an extended PLND with a superior extent reaching as far cranially as the inferior mesenteric vein, or a standard PLND with a superior extent of the bifurcation of the internal and external iliac artery, with otherwise the same anatomical boundaries.

Data collection and analysis

Two review authors independently assessed the included studies and extracted data from them for the primary outcomes: time to death from any cause, time to death from bladder cancer and Clavien-Dindo classification of surgical complications grade III-V, and the secondary outcomes: time to recurrence, Clavien-Dindo I-II complications and disease-specific quality of life.

We performed statistical analyses using a random-effects model and rated the certainty of evidence according to the GRADE approach.

Main results

The search identified one multicenter trial based in Germany that enrolled 401 participants with histologically confirmed T1 grade 3 or muscle-invasive urothelial carcinoma. The median age was 67 years (range: 59 to 74) and the majority of participants were male (78.3%). No participant received neoadjuvant chemotherapy; a small subset received adjuvant chemotherapy (14.5%).

Primary outcomes

Our results indicate that extended PLND may reduce the risk of death from any cause over time as compared to standard PLND, but the confidence interval includes the possibility of no effect (hazard ratio [HR]: 0.78, 95% confidence interval [CI]: 0.57 to 1.07, 401 participants, low-certainty evidence). After five years of follow-up, this may result in 83 fewer deaths (95% CI: 174 fewer to 24 more overall deaths) per 1000 participants: 420 deaths for extended PLND compared to 503 deaths per 1000 for standard PLND. We downgraded the certainty of evidence by two levels due to study limitations and imprecision.

Our results indicate that extended PLND may reduce the risk of death from bladder cancer over time as compared to standard PLND but, again, the confidence interval includes the possibility of no effect (HR: 0.70, 95% CI: 0.45 to 1.07, participants = 401, low-certainty evidence). After five years of follow-up, this corresponds to 91 fewer deaths per 1000 participants (95% CI: 176 fewer to 19 more bladder cancer deaths): 264 deaths for extended PLND compared to 355 deaths per 1000 for standard PLND. We downgraded the certainty of evidence by two levels due to study limitations and imprecision.

Based on follow-up of up to 30 days, we are uncertain whether extended PLND leads to more grade III-V complications as compared to standard PLND, because of study limitations and imprecision (risk ratio [RR]: 1.13, 95% CI: 0.84 to 1.52, participants = 401, very low-certainty evidence).

Secondary outcomes

We are uncertain whether extended PLND reduces the risk of recurrence over time as compared to standard PLND, because of study limitations and imprecision (HR: 0.84, 95% CI: 0.58 to 1.22, participants = 401, very low-certainty evidence).

Based on follow-up of up to 30 days, we are uncertain whether extended PLND leads to similar grade I-II complications as compared to standard PLND because of study limitations and imprecision (RR: 0.94, 95% CI: 0.74 to 1.19, participants = 401, very low-certainty evidence).

We found no trials that reported on disease-specific quality of life.

Authors' conclusions

Results from a single trial indicate that extended PLND in patients undergoing radical cystectomy for invasive urothelial carcinoma of the bladder may reduce death from any cause and death from bladder cancer over time; however, the results include the possibility of no effect. We are uncertain whether the risk of serious complications up to 30 days may be increased. We are also uncertain as to whether the risk of recurrence over time or the risk of minor complications up to 30 days changes. We were unable to conduct any of the preplanned subgroup analyses, in particular, analyses based on extended lymph node dissection templates, clinical tumor stage, and use of neoadjuvant chemotherapy that may be important effect modifiers. Important additional data is expected from a larger, ongoing trial that will also consider the role of neoadjuvant chemotherapy. Inclusion of this trial in the meta-analysis may help address the issue of imprecision which was a common reason for downgrading the certainty of the evidence.

PLAIN LANGUAGE SUMMARY

Extended versus standard lymph node dissection in patients with bladder cancer undergoing total bladder removal

Review question

When removing the whole bladder for bladder cancer, how does removing the lymph nodes from a large area (extended lymph node dissection) compare to only from a smaller area (standard lymph node dissection)?

Background

People with advanced cancer of the bladder that has spread into the deep muscle layers (but not outside the bladder) often have an operation to remove the whole bladder. As part of this operation, surgeons remove lymph nodes in that part of the body, which is

an important part of the immune system. Traditionally, only the lymph nodes close to the bladder and its major blood vessels were removed. This is called a standard lymph node dissection which removes lymph nodes as high up as to where the main blood vessels for the pelvis and the leg split up. Some people think that also removing lymph nodes further away from the bladder is better in getting rid of cancer. This is called an extended lymph node dissection. It removes lymph nodes as high up as the blood vessels that supply the lower part of the intestines. We don't know whether this indeed helps people live longer and not die from bladder cancer and how the unwanted effects compare.

Study characteristics

We included only studies in which chance determined whether people got a standard or extended lymph node dissection that was reported in literature up to April 29, 2019.

Key results

We found only one such study that answered our review question. This study was done at 16 large hospitals in Germany and included 401 men and women with bladder cancer.

We found that having an extended node dissection may make people less likely to die for any reason or to die from bladder cancer over time, although our confidence in this result is limited.

We are uncertain whether an extended node dissection causes more serious unwanted effects than a standard lymph node dissection.

We are also uncertain whether an extended node dissection makes cancer less likely to come back over time and causes a similar risk of not-so-serious unwanted effects compared to a standard lymph node dissection.

Certainty of the evidence

The certainty of evidence for these findings was low or very low, meaning that the true outcomes may be very different from what this review found.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Participant or population: Partcipants with bladder cancer undergoing radical cystectomy (male n = 314, female n = 87; age (interquartile range) 59 to 74)
Country: Germany
Setting: Muticenter/Inpatient
Intervention: Extended lymph node (LN) dissection
Comparison: Standard lymph node (LN) dissection

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard LN dissection	Risk difference with Extended LN dissection
Time to death from any cause (absolute effect size estimates based on death rate at 5 years) follow-up: median 43 months	401 (1 RCT)	⊕⊕◯◯ LOW [1,2]	HR 0.78 (0.57 to 1.07)	Study population	
				503 per 1,000	83 fewer per 1,000 (174 fewer to 24 more)
				High	
				600 per 1,000 [3]	89 fewer per 1,000 (193 fewer to 25 more)
Time to death from bladder cancer (absolute effect size estimates based on death rate at 5 years) follow-up: median 43 months	401 (1 RCT)	⊕⊕◯◯ LOW [1,2]	HR 0.70 (0.45 to 1.07)	Study population	
				355 per 1,000	91 fewer per 1,000 (176 fewer to 19 more)
				Moderate	
				491 per 1,000 [4]	114 fewer per 1,000 (229 fewer to 24 more)

Clavien-Dindo grade ≥ 3 complications assessed with: Clavien-Dindo classification (Grade 1 to 5; high grade represents severe complication) follow-up: 30 days	401 (1 RCT)	⊕○○○ VERY LOW [15]	RR 1.13 (0.84 to 1.52)	Study population	
				286 per 1,000	37 more per 1,000 (46 fewer to 149 more)
				High	
				565 per 1,000 [6]	73 more per 1,000 (90 fewer to 294 more)
Time to recurrence (absolute effect size estimates based on recurrence rate at 5 years) follow-up: median 43 months	401 (1 RCT)	⊕○○○ VERY LOW [15]	HR 0.84 (0.58 to 1.22)	Study population	
				408 per 1,000	52 fewer per 1,000 (146 fewer to 64 more)
				Moderate	
				453 per 1,000 [7]	55 fewer per 1,000 (158 fewer to 68 more)
				High	
				574 per 1,000 [7]	62 fewer per 1,000 (184 fewer to 73 more)
Clavien-Dindo grade ≤ 2 complications [8] assessed with: Clavien-Dindo classification (Grade 1 to 5; high grade represents severe complication) follow-up: 30 days	401 (1 RCT)	⊕○○○ VERY LOW [15]	RR 0.94 (0.74 to 1.19)	Study population	
				414 per 1,000	25 fewer per 1,000 (108 fewer to 79 more)
Disease-specific quality of life [9]	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; **LN:** Lymph node; **RR:** Risk ratio; **RCT**: Randomized controlled trial

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: high risk of performance and detection bias
[2] Downgraded by one level for imprecision: confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included benefit and no benefit)
[3] Baseline risk for death from any cause in the standard LN dissection group was assumed to be 60% (high risk) at 5 years as reported in Abd El-Latif 2012; observational study.
[4] Baseline risk for death from bladder cancer in the standard LN dissection group was assumed to be 49.1% (high risk) at 5 years as reported in Simone 2013; observational study.
[5] Downgraded by two levels for imprecision: confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference; wide confidence interval (included both benefit and harm)
[6] Baseline risk for Clavien-Dindo grade $\geq$ 3 complications in the standard LN dissection group was assumed to be 56.5% (high risk) at 30 days as reported in Brossner 2004; observational study.
[7] Baseline risk for recurrence in the standard LN dissection group was assumed to be 45.3% (moderate risk) and 57.3% (high risk) at 5 years as reported in Abol-Enein 2011 and in Simone 2013, respectively; both observational studies.
[8] We could not ascertain this outcome in observational studies
[9] Disease-specific quality of life: no available data

BACKGROUND

Description of the condition

In accordance with 2018 GLOBOCAN data, urothelial carcinoma of the bladder is the 10th most common malignancy worldwide, with 549,393 new cases and 200,000 cancer-related deaths (Bray 2018). In the United States, bladder cancer comprises 5% of new cancer diagnoses and is the sixth most prevalent malignancy (American Cancer Society).

About 90% of affected patients are older than 55 years (median age: 73 years); men are three to four times more likely than women to develop the disease according to the key statistics for bladder cancer (American Cancer Society; NCCN Guideline 2019). Approximately 75% of the newly diagnosed patients have non-muscle invasive bladder cancer (tumor that spreads to the mucosa [carcinoma in situ, Ta] and lamina propria [stage T1]), while the remaining 25% of the patients have muscle-invasive carcinoma (tumor invasion to the muscle layer of the bladder; stage T2) (Burger 2013; Smith 2014). Prognosis depends on the types of bladder cancer, with five-year rates ranging from 96% for non-muscle invasive bladder cancer to 5% for metastatic cases (NCCN Guideline 2019). An estimated 17,240 deaths were caused by bladder cancer in the US in 2018 (American Cancer Society).

Risk factors for urothelial bladder cancer vary (Burger 2013; Chang 2017; EAU Guideline 2018). Smoking and occupational exposure to chemicals are well-known environmental risk factors. With regard to medical conditions, radiotherapy for other malignancies of pelvic organs and chronic urinary tract infections are strongly related to the development of bladder cancer. Other controversial risk factors are dietary factors, gender, race, and socioeconomic status (Burger 2013; Chang 2017; EAU Guideline 2018). Genetic instability may also be implicated in the genesis of bladder cancer (Chang 2017; Figueroa 2014).

Description of the intervention

Lymph node dissection (LND) is a surgical procedure in which the lymph nodes in the tumor area or in the whole lymphatic drainage area are also removed in addition to surgical management of primary cancer. Radical cystectomy (RC) (removal of the bladder) with bilateral pelvic lymph node dissection (PLND) and cisplatin-based neoadjuvant or adjuvant chemotherapy is the gold standard for the management of resectable (able to be removed by surgery) non-metastatic muscle-invasive bladder cancer and for non-muscle-invasive high grade urothelial carcinoma that is refractory to intravesical therapy (Chang 2017; EAU Guideline 2018; Herr 2001; NCCN Guideline 2019; Stein 2001; Shabsigh 2009). The suggested PLND templates for their treatment are as follows:

- Limited PLND: removal of lymph nodes limited to obturator or peri-vesical fossa, lying laterally by the external iliac vein and are present medial to the obturator nerve (Brossner 2004; Holmer 2009; Hori 2013)
- Standard PLND: removal of lymph nodes, along with the obturator and external, internal, and common iliac nodes up to the crossing of the ureter (Chang 2017; Simone 2013)
- Extended PLND: removal of lymph nodes, along with the aortic bifurcation and common iliac vessels, the genitofemoral nerve, the circumflex iliac vein and lymph node of Cloquet, and the internal iliac vessels (Holmer 2009; Simone 2013).
- Super-extended PLND: LND is performed up to the inferior mesenteric artery with a template of extended PLND (Abol-Enein 2011).

In this review, standard PLND refers to limited and standard PLND as defined above, and extended PLND refers to any template beyond the standard PLND.

Adverse events associated with the intervention

There are several complications inherent to PLND, including ureteral injury, major vascular injury, obturator nerve injury, pelvic lymphocele (a collection of lymphatic fluid not bordered by epithelial lining), deep venous thrombosis, and leg/scrotal edema (Kavoussi 1993). A large retrospective study reported 28% early complications and 2.6%-3% perioperative mortality rates for PLND (Stein 2001). However, when comparing complication rates according to the extent of PLND (i.e. extended versus standard or limited PLND) and age (octogenarians versus non-octogenarians), no detectable differences were reported except for prolonged operation time in extended PLND performed laparoscopically (Brossner 2004; Finelli 2004; Grabbert 2017; Holmer 2009; Poulsen 1998). Moreover, a prospective multicenter study reported no significant adverse events to be associated with extended PNLD (Leissner 2004).

How the intervention might work

The incidence of lymph node metastasis at RC for bladder cancer ranges from 13% to 26% and is associated with a high risk of tumor recurrence and progression (Leissner 2004; Poulsen 1998; Stein 2001). PLND potentially has therapeutic importance by removing undetected metastatic lymph nodes, and thus, for providing a chance of cure for some patients for whom radical cystectomy alone would have been insufficient. Furthermore, lymph node dissection is important for accurate pathological staging and helps stratify the risk, therefore, helping determine the need for adjuvant systemic chemotherapy after RC (Ku 2010; Youssef 2011).

Extended PLND also captures lymph node metastases beyond the common iliac bifurcation yielding an ever larger number of nodes (Vazina 2004). Removing more lymph nodes is hypothesized to reduce the incidence of recurrence and potentially provide better recurrence-free, cancer-specific, and overall survival (Herr 2002; Konety 2003; Leissner 2000; Steven 2007).

Why it is important to do this review

Until recently, the evidence for the benefits and harms of extended PLND over those of standard PLND originated only from non-randomized trials (Abd El-Latif 2012; Abol-Enein 2011; Brossner 2004; Ku 2010; Simone 2013; Wang 2013) which had many inherent limitations. Systematic reviews and meta-analyses based on these studies have been plagued by the same limitations (Bi 2014; Bruins 2014; Palmer 2011; Tilki 2013).

This Cochrane review was triggered by the publication of the first randomized controlled trial on this topic. In contrast to prior systematic reviews, this review stands out for its rigorous methodology which includes a registered protocol, a comprehensive search, a focus on patient-important outcomes and the application of GRADE. We expect this review to be helpful to clinicians, guideline developers, and policy-makers in helping them establish an evidence-based role for extended PLND when treating muscle-invasive bladder cancer.

OBJECTIVES

To assess the effects of extended versus standard PLND in patients undergoing cystectomy to treat muscle-invasive (cT2 and cT3) and treatment refractory, non-muscle-invasive (cT1 with or without carcinoma in situ) urothelial carcinoma of the bladder.

METHODS

Criteria for considering studies for this review

Types of studies

This review is based on a previously published protocol (CRD42018116290). For details on the differences between the previous protocol and the method followed here, please refer to the 'Differences between protocol and review' section. We included randomized controlled trials (RCTs) as they offer more reliable results. We excluded quasi-randomized and nonrandomized studies, cohort studies, case series, cross-over trials, and cluster-randomized trials. We did not exclude studies on the basis of publication status or language.

Types of participants

We included studies of participants with urothelial carcinoma of the bladder undergoing RC with PLND with curative intent. Participants of these trials underwent histological confirmation of urothelial carcinoma based on transurethral resection of the bladder (TURBT) and cross-sectional imaging (usually computer tomography (CT) and/or magnetic resonance imaging (MRI) indicating clinically localized disease with or without suspected locoregional lymphatic spread (N0 or N1) but without distant metastases (M0). Eligible clinical tumor stages were T2 and T3, as well as treatment-refractory T1 and carcinoma in situ. We excluded trials of participants with locally advanced, but unresectable, bladder urothelial carcinoma with pelvic fixation (clinical stage T4)

Types of interventions

We planned to investigate the following experimental and comparator interventions.

Experimental interventions

We planned to include studies that had used templates for extended PLND that varied somewhat due to the lack of a gold standard.

- Extended PLND
  - Anatomical boundaries
    - cranial: inferior mesenteric artery, caudal: pelvic floor (circumflex iliac vein), both lateral: genitofemoral nerve, both medial: ureter, dorsal: rectum, or
    - anything beyond boundaries of the comparator

Comparator interventions

- Standard PLND
  - Anatomical boundaries
    - cranial: common iliac bifurcation (bifurcation of the internal and external iliac artery), caudal: pelvic floor (circumflex iliac vein), both lateral: genitofemoral nerve, both medial: ureter, dorsal: obturator nerve

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 death from any cause (overall survival, time-to-event outcome)
- Time to death from bladder cancer (disease-specific survival, time-to-event outcome)
- Clavien-Dindo III-V complications (dichotomous outcome)

Secondary outcomes

- Time to recurrence (recurrence-free survival, time-to-event outcome)
- Clavien-Dindo I-II complications (dichotomous outcome)
- Disease-specific quality of life (continuous outcome)

Method and timing for outcome measures

- Time to death from any cause: as measured from the time of randomization to the time of death due to any cause
- Time to death from bladder cancer: as measured from the time of randomization to the time of death due to bladder cancer
- Time to recurrence: as measured from the time of randomization to the time of the first confirmed recurrence
    - Definition of recurrence: judged based on the imaging, such as computed tomography, with or without biopsy
- Clavien-Dindo I-V complications: we used the Clavien-Dindo classification system to assess surgical complications (Dindo 2004). If an eligible study's authors had not used the Clavien-Dindo system, we judged the adverse events by severity using the information available in the studies
- Disease-specific quality of life: measured by validated instruments (e.g. the 12-item Short Form (SF-12), 36-item Short Form (SF-36), Functional Assessment of Cancer Therapy (FACT) questionnaire, or EORTC Quality of Life Questionnaire version 3.0

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

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, should the original search date have fallen outside of this timeframe.

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 29, 2019.

- PubMed (late 1940s - present);
- Embase (Elsevier, 1947 - present);
- Cochrane Controlled Trials (Issue 4, April 2019);
- Web of Science (1900 - 2019);
- LILACS (Latin American and the Caribbean Health Sciences Literature; http://lilacs.bvsalud.org/en/).

We also searched the following:

- ClinicalTrials.gov (https://www.clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/).

If we detected any additional relevant keywords 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 trials included in this review to identify any further studies that we may have missed. We also searched the meeting proceedings of the American Urological Association, European Association of Urology, and American Society of Clinical Oncology annual meetings for the last three years (2016 to 2018) for relevant abstracts of unpublished studies.

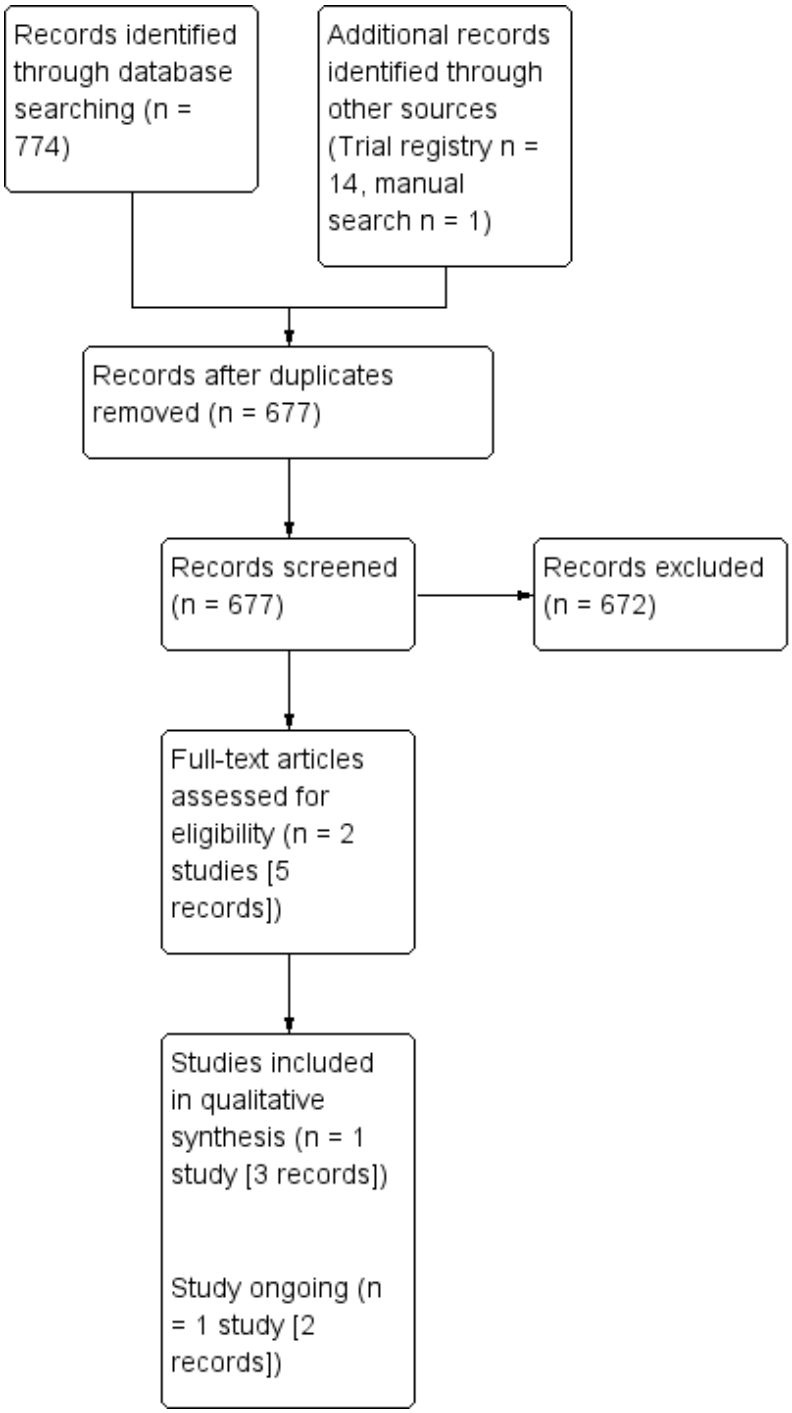
Data collection and analysis

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

Selection of studies

Two review authors (ECH and NS) independently assessed abstracts and titles to determine which studies should be assessed further using the Covidence software. They investigated all potentially relevant records, such as full texts and mapped records to studies, and classified them as studies that should be included, excluded, await classification, or as 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) (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

In this review, two 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 in our analysis. These authors resolved any potential disagreements by consensus or through discussion with a third author (PD). In addition, when necessary, we contacted the original authors of a given study. We collected and used the most detailed numerical data that might facilitate similar analyses of included studies. We have presented 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; the number of included participants; age; sex; inclusion and exclusion criteria; tumor stage (clinical or pathologic T category); pathologic nodal stage; positive surgical margin; neo- or adjuvant chemotherapy.
- Details of interventions: the number of participants randomly assigned to each intervention group and PLND boundaries in each group.
- 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.
- Funding sources for the study.
- 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 maximized 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 prioritized the publication that had reported the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two authors (ECH and NS) independently assessed the risks of bias for each included study. We resolved the disagreements by consensus or by consulting with a third 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 assessments (detection bias);
- Incomplete outcome data (attrition bias);
- Selective reporting (reporting bias);
- Other potential sources of bias (e.g. baseline imbalance).

We judged the risk of bias by categorizing them into domains, such as "low risk," "high risk," or "unclear risk." We presented the results of this assessment graphically. For selection bias and reporting bias, we evaluated the risks of bias at the 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 death from bladder cancer;
- time to recurrence;
- Clavien-Dindo I-II complications;
- disease-specific quality of life.

We defined the following outcomes as objective:

- time to death from any cause;
- Clavien-Dindo III-V complications.

We assessed attrition bias (incomplete outcome data) from an outcome-specific perspective. We summarized 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. This was done in accordance with the approach for summary assessment of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017b).

Measures of treatment effect

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 that measured the same underlying concept (e.g. disease-specific quality of life), but on different measurement scales, we calculated the standardized mean difference (SMD). We expressed time-to-event data as HRs with 95% CI 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 handled these in accordance with the 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 study included here, if feasible; we further 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 any issues of missing data. We did not plan to impute missing data.

Assessment of heterogeneity

We planned to assess heterogeneity. However, we included only one RCT and, therefore, the assessment of heterogeneity was not possible.

Assessment of reporting biases

We tried to obtain study protocols to assess selective outcome reporting. As we included only one study, we could not use funnel plots to assess small study effects.

Data synthesis

As we included only one RCT, we only re-analyzed and reported single study data using Review Manager 5 software (Review Manager 2014) in accordance with the guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a).

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.

- Extended PLND template (if different PLND templates were used in various studies);
- Clinical tumor stage (non-muscle invasive [e.g., T1G3] versus muscle-invasive disease [e.g. ≥ T2]);
- Neoadjuvant chemotherapy (neoadjuvant versus no neoadjuvant chemotherapy).

We restricted subgroup analyses to the primary outcomes only.

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 or unclear risk of bias.

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

'Summary of findings' table

Main outcomes for the 'Summary of findings' table

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

- Time to death from any cause;
- Time to death from bladder cancer;
- Clavien-Dindo III-V complications;
- Time to recurrence;
- Clavien-Dindo I-II complications;
- Disease-specific quality of life.

We presented 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 considers five criteria that are related not only to internal validity (risk of bias, inconsistency, imprecision, and publication bias) but also to external validity (the directness of results) (Guyatt 2008). Two authors (ECH, NS) of this review 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 author (PD). We presented a summary of the evidence for the main outcomes in the 'Summary of findings' table, which we generated using the Gradepro GDT (https://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, as well as the rating of our overall confidence in the effect estimates for each outcome (Guyatt 2011; Schünemann 2017).

RESULTS

Description of studies

Results of the search

Our literature search yielded 774 references to which we added an additional 15 records that were identified by searching trial registries and manual searches. After the exclusion of duplicates, we screened 677 references at the title and abstract stage. Of these 677 references, five references that were mapped to two unique studies entered the full-text screening stage. We ultimately included one study in the qualitative analyses (Figure 1).

Included studies

Source of data

We identified one RCT (Gschwend 2018). For details, please refer to the 'Characteristics of included studies' table, Table 1, and Table 2. The included trial compared extended PLND with standard PLND during RC for the treatment of bladder urothelial carcinoma. We contacted the corresponding author of this study to get additional information and received a response (Appendix 2).

Participants

A total of 458 participants were screened for enrolment. Between October 2006 and December 2010, 401 participants were randomly assigned to this trial (extended PLND, n = 198; standard PLND, n = 203). All randomized participants were included in the analysis.

Interventions and comparators

The study used extended PLND as an intervention and standard PLND as a comparator. The median follow-up duration was 43 months.

Outcomes

We found reporting of all primary outcomes in the included study for this comparison. In addition, all secondary outcomes were reported for the study included, except for disease-specific quality of life.

Funding sources and conflicts of interest

A pharmaceutical company supported the study, but all authors declared no conflicts of interest.

Excluded studies

There were no studies excluded at the full-text screening stage.

Studies awaiting classification and ongoing trials

There were no studies awaiting classification. We found one ongoing study, Southwest Oncology Group study S1011, which did not provide usable outcome data at the time that this review was written (NCT01224665; 'Characteristics of ongoing studies' table). Expected date of completion is August 2022.

Risk of bias in included studies

For details, please refer to 'Characteristics of included studies' section, the 'Risk of bias' table, and the 'Summary of findings for the main comparison' for information on the main comparison, as well as Figure 2 and Figure 3.

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

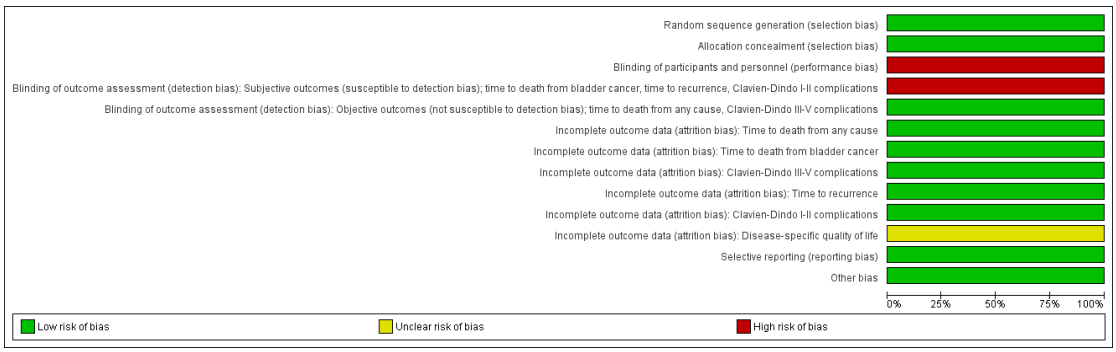
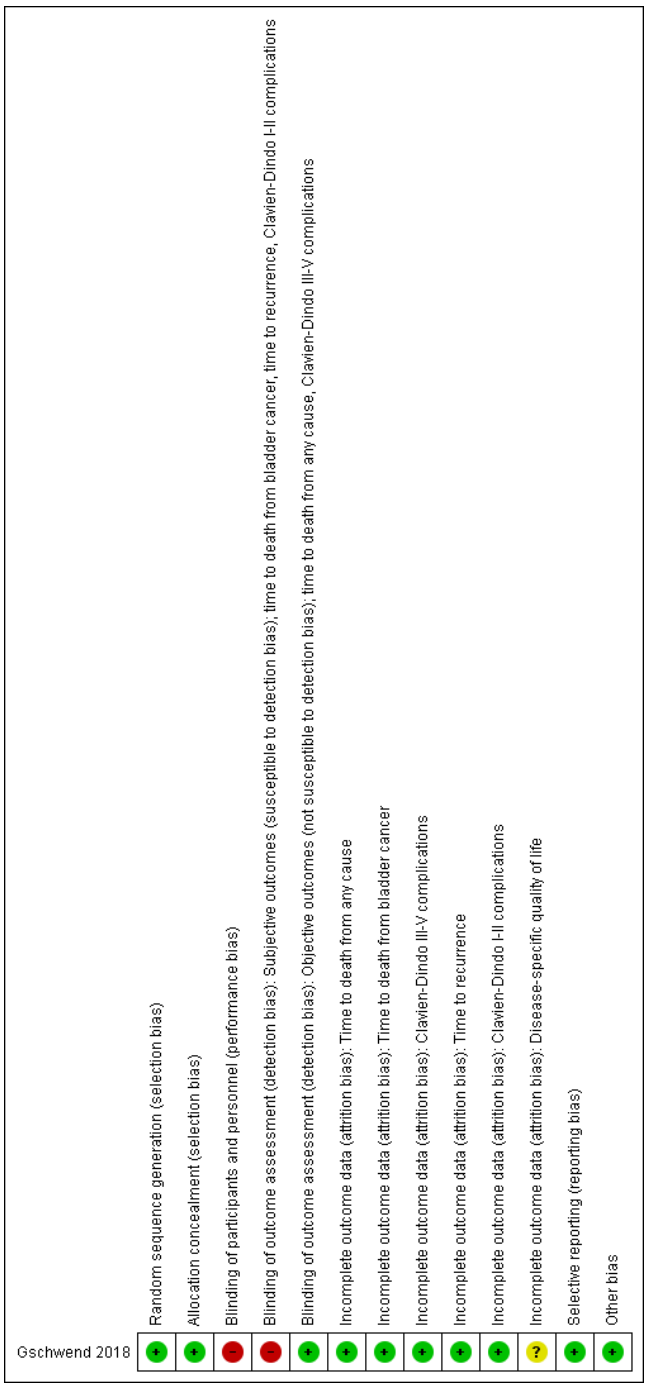


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation and allocation concealment were performed adequately; we rated the risk of bias as low.

Blinding

Performance bias

Participants and personnel (surgeons) were not blinded. We rated the risk of bias as high.

Detection bias

Susceptible (subjective) outcomes (time to death from bladder cancer, time to recurrence, Clavien-Dindo I-II complications): the assessors of these outcomes were reported to be unblinded. We rated the risk of bias for these outcomes to be high.
Not susceptible (objective) outcomes (time to death from any cause, Clavien-Dindo III-V complications): blinding of outcome assessors did not appear relevant to these outcomes, therefore, we rated the risk of bias for them as low.

Incomplete outcome data

Among 203 participants assigned to standard PLND, 13 participants did not receive standard PLND. Also, in the extended PLND group (n = 198), 25 participants did not receive extended PLND. However, all randomized participants (n = 401) were included in the analysis as intended. We judged the risk of bias as low risk for all outcomes.
We did not rate the domain of disease-specific quality of life because this outcome was not investigated in the trial. We reported the risk of bias as unclear in the table and figures only because this was the default value.

Selective reporting

Since the study had a planned protocol, and all reported outcomes and associated analyses corresponded to how these had been planned, we assigned a judgement of low risk of reporting bias.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** Impact of extended versus standard lymph node dissection on overall survival among patients with urothelial cancer of the bladder
Please refer to the Analysis 1.1 to Analysis 1.7 and Summary of findings for the main comparison. We also analysed the 90-day results for complications in the Analysis 1.4 and Analysis 1.7; we did not describe this below.

Primary outcomes

Time to death from any cause

Extended PLND may reduce the risk of death from any cause over time as compared to standard PLND (HR: 0.78, 95% CI: 0.57 to 1.07, participants = 401; studies = 1, Analysis 1.1, low-certainty evidence). Based on the control event risk in this trial at 5-year follow-up, this corresponds to 83 fewer deaths from any cause (95% CI: 174 fewer to 24 more) per 1000 participants: 420 deaths for extended PLND compared to 503 deaths per 1000 for standard PLND.
Based on high-risk control groups as drawn from an observational study (Abd El-Latif 2012), also at 5-year follow-up, extended PLND may result in 89 fewer overall deaths (95% CI: 193 fewer to 25 more) per 1000 participants: 511 deaths for extended PLND compared to 600 deaths per 1000 participants for standard PLND.
We rated the certainty of evidence as low due to study limitations (performance bias) and imprecision, given that the CI was consistent both with an appreciable reduction in the risk of overall deaths as well as a small or no increase in the risk of overall deaths.

Time to death from bladder cancer

Extended PLND may reduce the risk of death from bladder cancer over time as compared to standard PLND (HR: 0.70, 95% CI: 0.45 to 1.07, participants = 401; studies = 1, Analysis 1.2, low-certainty evidence). Based on the control event risk of the included trial at 5-year follow-up, this corresponds to 91 fewer deaths from bladder cancer (95% CI: 176 fewer to 19 more) per 1000 participants: 264 deaths for extended PLND compared to 355 deaths per 1000 participants for standard PLND.
Based on moderate-risk control groups as drawn from an observational study (Simone 2013), also at 5-year follow-up, extended PLND may result in 114 fewer bladder cancer deaths (95% CI: 229 fewer to 24 more) per 1000 participants: 377 deaths for extended PLND compared to 491 deaths per 1000 participants for standard PLND.

We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was consistent both with an appreciable reduction in the risk of bladder cancer deaths as well as a small or no increase in the risk of bladder cancer deaths.

Clavien-Dindo grade ≥ 3 complications

We are uncertain whether extended PLND results in more Clavien-Dindo grade ≥ 3 complications as compared to standard PLND (RR: 1.13, 95% CI: 0.84 to 1.52, participants = 401; studies = 1, Analysis 1.3, very low-certainty evidence). Based on the control event risk in the trial and 30-day follow-up, this corresponds to 37 more complications (95% CI: 46 fewer to 149 more) per 1000 participants: 323 complications for extended PLND compared to 286 complications per 1000 participants for standard PLND.

Based on the high-risk control groups as coming from an observational study (Brossner 2004) also at 30-day follow-up, extended PLND may result in 73 more complications (95% CI: 90 fewer to 294 more) per 1000 participants: 638 complications for extended PLND compared to 565 complications per 1000 participants for standard PLND.

We downgraded the certainty of evidence by one level due to study limitations, namely performance bias, and by two levels due to imprecision, given that the CI was consistent both with a small reduction in complications, as well as an appreciable increase in the Clavien-Dindo grade ≥ 3 complications.

Secondary outcomes

Time to recurrence

We are uncertain whether extended PLND reduces the risk of recurrence over time as compared to standard PLND (HR: 0.84, 95% CI: 0.58 to 1.22, participants = 401; studies = 1, Analysis 1.5, very low-certainty evidence). Based on the control event risk in the trial included in this analysis and 5-year follow-up, this corresponds to 52 fewer recurrences (95% CI: 146 fewer to 64 more) per 1000 participants: 356 recurrences for extended PLND compared to 408 recurrences per 1000 participants for standard PLND.

Based on the moderate- and high-risk control groups, as drawn from separate observational studies (Abol-Enein 2011; Simone 2013) at 5-year follow-up, extended PLND may result in 55 fewer recurrences (95% CI: 158 fewer to 68 more) per 1000 participants: 398 recurrences for extended PLND compared to 453 recurrences per 1000 participants for standard PLND or 62 fewer recurrences (95% CI: 184 fewer to 73 more) per 1000 participants: 512 recurrences for extended PLND compared to 574 recurrences per 1000 participants for standard PLND, respectively. We rated the certainty of evidence to be very low due to study limitations (due to performance and detection bias) as well as imprecision, given that the CI was consistent both with an appreciable reduction in the risk of recurrence, as well as a small increase in the risk of recurrences.

Clavien-Dindo grade ≤ 2 complications

The evidence is uncertain whether extended PLND results in similar Clavien-Dindo grade ≤ 2 complications compared to standard PLND.(RR: 0.94, 95% CI: 0.74 to 1.19, participants = 401; studies = 1, Analysis 1.6, very low-certainty evidence). Based on the control event risk in the trial included in this analysis and a 30-day follow-up, this corresponds to 25 fewer complications (95% CI: 108 fewer to 79 more) per 1000 participants: 389 complications for extended PLND compared to 414 complications per 1000 participants for standard PLND. We downgraded the certainty of evidence by one level due to study limitations, namely performance bias and detection bias, and by two levels due to imprecision, given that the CI was consistent both with an appreciable reduction in complications, as well as a small increase in the Clavien-Dindo grade ≤ 2 complications.

Disease-specific quality of life

We found no studies that reported this outcome.

Subgroup analysis

We were unable to obtain sufficient information to perform the planned subgroup analyses.

DISCUSSION

Summary of main results

We included only one RCT with 401 participants. The findings of this systematic review indicate that extended PLND may reduce overall mortality and bladder cancer mortality over time but both results include the possibility of no effect. The evidence is uncertain about the effect of extended PLND on time to recurrence.

With regard to complications, we are uncertain whether extended PLND increases Clavien-Dindo grade ≥ 3 complications and results in similar Clavien-Dindo grade ≤ 2 complications for up to 30 days.

We were unable to find evidence for the effect of extended PLND on disease-specific quality of life and were unable to conduct any of our preplanned secondary analyses based on lymph node dissection templates, tumor stage or receipt of neoadjuvant chemotherapy.

Overall completeness and applicability of evidence

Findings of this review were based on only one RCT that was performed by experienced high-volume surgeons at tertiary medical centers which may limit the generalizability of its findings. Quality control of the treatment arms could have been improved by measures such as intraoperative photographs taken to ensure the completeness of extended PLND and to document that dissection in the standard PLND arm did not extend beyond the intended boundaries. Moreover, the study did not investigate the effect of extended PLND in a neoadjuvant or adjuvant setting which are recommended by current guidelines (Chang 2017; EAU Guideline 2018; NCCN Guideline 2019) and may represent effect modifiers.

Quality of the evidence

Overall, we judged the potential risk of bias of the included trial as unclear. While the study used appropriate methods of randomization and allocation concealment, thereby raising no concerns about selection bias, it used an open-label design (no blinding of participants and personnel) raising concerns about performance bias. Also, outcome assessors were not blinded raising concerns about detection bias. The latter does not apply to outcomes that could be objectively measured such as time to death from any cause and Clavien-Dindo III-V complications for which we judged the risk of detection bias as low. Since all randomized participants were included in the analyses for all investigated outcomes, we judged the risk of attrition bias as low.

We judged the certainty of the evidence body as low or very low for most outcomes due to these study limitations as well as wide confidence intervals and resulting clinically important imprecision of the results. For the Clavien-Dindo complications and time to recurrence outcomes, we judged the certainty of the evidence body as very low, due to the aforementioned reasons. In addition, very wide confidence intervals led to downgrading (two levels) for imprecision.

Potential biases in the review process

- It is possible (although unlikely) that additional studies may have been conducted but not yet published, or that we failed to identify additional studies that do exist despite our comprehensive search.
- The study included some clinical stage T1 disease participants. Given that the aggressiveness of cancer is somewhat different from that of muscle-invasive disease (clinical stage ≥ T2 disease), this could be a source of bias, possibly resulting in an underestimate of the effect size.

Agreements and disagreements with other studies or reviews

We identified four systematic reviews with nonrandomized controlled trials on this topic (Bi 2014; Bruins 2014; Palmer 2011; Tilki 2013).

Bi 2014 performed a systematic review that included six studies comparing extended PLND and nonextended PLND. The definition of LND template in their review was similar to that used in our review. In line with our results, the pooled data indicated that extended PLND provided a better recurrence-free survival as compared to nonextended PLND. Subgroup analysis showed that participants with ≥ pathologic T3 disease and regardless of lymph node involvement, also had a recurrence-free survival benefit from extended PLND. The level of evidence (LOE) of the included studies was rated according to the criteria developed by the Centre for Evidence-Based Medicine in Oxford, UK, (OCEBM Levels of Evidence Working Group) but the risk of bias was not assessed.

Bruins 2014 performed a systematic review that included 23 studies to evaluate the impact of the extent of LND on oncologic outcomes. They could not perform a meta-analysis due to study heterogeneity; instead, they assessed the risk of bias using the risk of bias tool developed by Cochrane (Reeves 2011). They concluded that despite the poor quality of the data, extended PLND might improve oncologic outcomes as compared to lesser degrees of dissection, although extending the dissection up to inferior mesenteric artery was unlikely to yield any further benefits. Moreover, extended PLND seemed to not increase perioperative morbidity. These results are somewhat different from our results.

Palmer 2011 performed a systematic review, including three studies that compared extended and limited PLND. The pooled relative risk for recurrence-free survival was 1.23 (95% CI 1.07 to 1.42; P = 0.004) in favour of extended PLND. However, they did not provide information on the overall or disease-specific survival or detailed findings regarding the complications. They rated the certainty of evidence using GRADE and assessed the risk of bias using the risk of bias tool developed by Cochrane (Reeves 2011).

Tilki 2013 summarized the existing data on the value of lymphadenectomy for staging and disease-free survival. They concluded that extended PLND may influence disease-free survival. However, they included several studies that evaluated the use of lymph node retrieval count as a surrogate for the extent of LND. It seems inaccurate to use the LN count to represent the extent of the LND template, instead of using an anatomic landmark (Dorin 2011; Meijer 2012).

This systematic review is the first to focus on the RCT results for both oncologic outcomes and intervention-related complications and providing absolute effect size estimates. We believe that our systematic review provides the most reliable summary of evidence on this topic to date.

AUTHORS' CONCLUSIONS

Implications for practice

This is the first systematic review based on the only available RCT in this field. Based on the findings of this review, extended PLND may improve overall survival and cancer-specific survival, although our results include the possibility of no effect. We are uncertain whether extended PLND results in more Clavien-Dindo grade ≥ 3 complications for up to 30 days. We are also uncertain whether recurrence-free survival is improved by extended PLND and whether Clavien-Dindo grade ≤ 2 complications rates are similar to standard PLND up to 30 days. We found no evidence from the RCT for other patient-important outcomes, such as quality of life. As a result, there is insufficient information to balance the possible advantages of extended PLND against the potential adverse effects on patients.

Implications for research

Given that the certainty of evidence for the patient-important outcomes considered in this review was only low or very low, future studies are required. Important additional data is expected from a larger, ongoing trial (NCT01224665) that will also consider the role of neoadjuvant chemotherapy. We expect to update this review once the result becomes available; inclusion of this trial in the meta-analysis may help address the issue of imprecision which was a common reason for downgrading. Based on its protocol, we do not expect it to provide information on quality of life as an important secondary outcome. In the absence of additional trials, important information on treatment-related harms, in particular, surgical complications rates of extended PLND, when performed in the community setting outside of tertiary care centers, could come from well designed, ideally prospective observational studies.

ACKNOWLEDGEMENTS

We acknowledge the support received from the author of the included study, Jürgen E. Gschwend who provided information on the method of blinding.

We are very grateful to Annemarie Uhlig, Guillaume Ploussard, Wassim Kassouf, Caroline Raw and Martin Burton for having served as peer reviewers. We thank Cochrane Urology, Managing Editor Robert Lane and Cochrane Fast-Track Service, Managing Editor Helen Wakeford, for the support we received.

REFERENCES

References to studies included in this review

Gschwend 2018 *{published data only}*

Gschwend JE, Heck MM, Lehmann J, Ruebben H, Albers P, Heidenreich A, et al. Limited versus extended pelvic lymphadenectomy in patients with bladder cancer undergoing radical cystectomy: survival results from a prospective, randomized trial (LEA AUO AB 25/02). *Journal of Clinical Oncology* 2016;**34**(15 suppl):4503. DOI: 10.1200./JCO.2016.34.15˙suppl.4503

* Gschwend JE, Heck MM, Lehmann J, Rübben H, Albers P, Wolff JM, et al. Extended versus limited lymph node dissection in bladder cancer patients undergoing radical cystectomy: survival results from a prospective, randomized trial. *European Urology* 2019;**75**(4):604–11. DOI: 10.1016/j.eururo.2018.09.047; PUBMED: 30337060

NCT01215071. A prospective randomized study for the comparison, an extended versus a limited pelvic lymphadenectomy, in the surgical therapy of bladder cancer [Prospektiv randomisierte Studie zum Vergleich einer ausgedehnten mit einer eingeschränkten pelvinen Lymphadenektomie bei der operativen Therapie des Harnblasenkarzinoms]. https://clinicaltrials.gov/ct2/show/record/NCT01215071 (first received 6 October 2010).

References to ongoing studies

NCT01224665 *{unpublished data only}*

Lerner SP, Li H, Svatek RS, Koppie TM, Alva AS, La Rosa FG, et al. Prerandomization factors and utilization of neoadjuvant chemotherapy in a clinical trial of extended versus standard pelvic lymphadenectomy at the time of radical cystectomy for bladder cancer. *Journal of Clinical Oncology* 2014;**32**(4 suppl):295. DOI: 10.1200/jco.2014.32.4˙suppl.295

* NCT01224665. S1011 Standard or extended pelvic lymphadenectomy in treating patients undergoing surgery for invasive bladder cancer [A phase III surgical trial to evaluate the benefit of a standard versus an extended pelvic lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer]. https://clinicaltrials.gov/ct2/show/record/NCT01224665 (first received 20 October 2010).

Additional references

Abd El-Latif 2012

Abd El Latif A, Miocinovic R, Stephenson AJ, Campbell S, Fergany A, Gong MC. Impact of extended versus standard lymph node dissection on overall survival among patients with urothelial cancer of the bladder. *Journal of Urology* 2012;**187**(Suppl 4):e707. DOI: 10.1016/j.juro.2012.02.1768

Abol-Enein 2011

Abol-Enein H, Tilki D, Mosbah A, El-Baz M, Shokeir A,

Nabeeh A, et al. Does the extent of lymphadenectomy in radical cystectomy for bladder cancer influence disease-free survival? A prospective single-center study. *European Urology* 2011;**60**(3):572–7. [PUBMED: 21684070]

American Cancer Society
American Cancer Society. Key statistics for bladder cancer. www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-keystatistics (accessed 7 January 2019).

Bi 2014
Bi L, Huang H, Fan X, Li K, Xu K, Jiang C, et al. Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: a systematic review and meta-analysis of comparative studies. *BJU International* 2014;**113**(5b):E39–48. [PUBMED: 24053715]

Bray 2018
Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians* 2018;**68**(6):394–424. [PUBMED: 30207593]

Brossner 2004
Brossner C, Pycha A, Toth A, Mian C, Kuber W. Does extended lymphadenectomy increase the morbidity of radical cystectomy?. *BJU International* 2004;**93**(1):64–6. [PUBMED: 14678370]

Bruins 2014
Bruins HM, Veskimae E, Hernandez V, Imamura M, Neuberger MM, Dahm P, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. *European Urology* 2014;**66**(6):1065–77. [PUBMED: 25074764]

Burger 2013
Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. *European Urology* 2013;**63**(2):234–41. [PUBMED: 22877502]

Chang 2017
Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of non-metastatic muscle-Invasive bladder cancer: AUA/ASCO/ASTRO/SUO Guideline. *Journal of Urology* 2017;**198**(3):552–9. [PUBMED: 28456635]

Dindo 2004
Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery* 2004;**240**(2):205–13. [PUBMED: 15273542]

Dorin 2011
Dorin RP, Daneshmand S, Eisenberg MS, Chandrasoma S, Cai J, Miranda G, et al. Lymph node dissection technique is more important than lymph node count in identifying nodal metastases in radical cystectomy patients: a comparative mapping study. *European Urology* 2011;**60**(5):946–52. [PUBMED: 21802833]

EAU Guideline 2018
European Association of Urology. Muscle-invasive and metastatic bladder cancer. uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/ (accessed 7 January 2019).

Figueroa 2014
Figueroa JD, Ye Y, Siddiq A, Garcia-Closas M, Chatterjee N, Prokunina-Olsson L, et al. Genome-wide association study identifies multiple loci associated with bladder cancer risk. *Human Molecular Genetics* 2014;**23**(5):1387–98. [PUBMED: 24163127]

Finelli 2004
Finelli A, Gill IS, Desai MM, Moinzadeh A, Magi-Galluzzi C, Kaouk JH. Laparoscopic extended pelvic lymphadenectomy for bladder cancer: technique and initial outcomes. *Journal of Urology* 2004;**172**(5 Pt 1):1809–12. [PUBMED: 15540725]

Grabbert 2017
Grabbert M, Grimm T, Buchner A, Kretschmer A, Apfelbeck M, Schulz G, et al. Risks and benefits of pelvic lymphadenectomy in octogenarians undergoing radical cystectomy due to urothelial carcinoma of the bladder. *International Urology and Nephrology* 2017;**49**(12):2137–42. [PUBMED: 28900840]

Guyatt 2008
Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**(7651):995–8. [PUBMED: 18456631]

Guyatt 2011
Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94. [PUBMED: 21195583]

Herr 2001
Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? . *Journal of Urology* 2001;**166**(4):1296–9. [PUBMED: 11547061]

Herr 2002
Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *Journal of Urology* 2002;**167**(3):1295–8. [PUBMED: 11832716]

Higgins 2011
Higgins JPT, Deeks JJ, Altman DG, editor(s), Cochrane Statistical Methods Group. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2017a
Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of

Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Higgins 2017b
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Holmer 2009
Holmer M, Bendahl PO, Davidsson T, Gudjonsson S, Mansson W, Liedberg F. Extended lymph node dissection in patients with urothelial cell carcinoma of the bladder: can it make a difference?. *World Journal of Urology* 2009;**27**(4): 521–6. [PUBMED: 19145436]

Hori 2013
Hori J, Tamaki G, Kita M, Iwata S, Matsumoto S, Kakizaki H. Survival impact of the extent of pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer. *European Journal of Cancer* 2013;**49**:S16. DOI: 10.1016/S0959-8049(13)70039-X

Kavoussi 1993
Kavoussi LR, Sosa E, Chandhoke P, Chodak G, Clayman RV, Hadley HR, et al. Complications of laparoscopic pelvic lymph node dissection. *Journal of Urology* 1993;**149**(2): 322–5. [PUBMED: 8426411]

Konety 2003
Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. *Journal of Urology* 2003;**169**(3):946–50. [PUBMED: 12576819]

Ku 2010
Ku JH. Role of pelvic lymphadenectomy in the treatment of bladder cancer: a mini review. *Korean Journal of Urology* 2010;**51**(6):371–8. [PUBMED: 20577602]

Leissner 2000
Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder: significance for staging and prognosis. *BJU International* 2000;**85**(7):817–23. [PUBMED: 10792159]

Leissner 2004
Leissner J, Ghoneim MA, Abol-Enein H, Thuroff JW, Franzaring L, Fisch M, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *Journal of Urology* 2004;**171**(1):139–44. [PUBMED: 14665862]

Liberati 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLOS Medicine* 2009;**6**(7):e1000100. [PUBMED: 19621070]

Meijer 2012
Meijer RP, Nunnink CJ, Wassenaar AE, Bex A, Van der Poel HG, Van Rhijn BW, et al. Standard lymph node dissection for bladder cancer: significant variability in the number of reported lymph nodes. *Journal of Urology* 2012;**187**(2): 446–50. [PUBMED: 22177147]

NCCN Guideline 2019
Bladder Cancer, NCCN Clinical Practice Guidelines in Oncology. www.nccn.org/professionals/physician_gls/default.aspx#site (accessed 7 January 2019), issue 1.

OCEBM Levels of Evidence Working Group
Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. Oxford Center for Evidence-Based Medicine. "The Oxford 2011 Levels of Evidence".. www.cebm.net/index.aspx?o=5653 (accessed 3 January 2019).

Palmer 2011
Palmer D, Clubb A, Duboy AJ, Neuberger MM, Gilbert SM, Dahm P. The therapeutic benefit of an extended lymph node dissection in radical cystectomy: a systematic review and meta-analysis of observational studies applying the novel Cochrane risk of bias tool. *Journal of Urology* 2011; **185**(4):e742. DOI: 10.1016/j.juro.2011.02.1883

Parmar 1998
Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34. [PUBMED: 9921604]

Poulsen 1998
Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *Journal of Urology* 1998;**160**(6 Pt 1): 2015–20. [PUBMED: 9817313]

Reeves 2011
Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2017
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Akl E, et al. Cochrane GRADEing Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Completing 'Summary of findings' tables and grading the confidence in or quality of the evidence. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS

(editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Shabsigh 2009
Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *European Urology* 2009;**55**(1):164–74. [PUBMED: 18675501]

Simone 2013
Simone G, Papalia R, Ferriero M, Guaglianone S, Castelli E, Collura D, et al. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *International Journal of Urology* 2013;**20**(4): 390–7. [PUBMED: 22970939]

Smith 2014
Smith AB, Deal AM, Woods ME, Wallen EM, Pruthi RS, Chen RC, et al. Muscle-invasive bladder cancer: evaluating treatment and survival in the National Cancer Data Base. *BJU International* 2014;**114**(5):719–26. [PUBMED: 24325202]

Stein 2001
Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *Journal of Clinical Oncology* 2001;**19**(3):666–75. [PUBMED: 11157016]

Steven 2007
Steven K, Poulsen AL. Radical cystectomy and extended pelvic lymphadenectomy: survival of patients with lymph node metastasis above the bifurcation of the common iliac vessels treated with surgery only. *Journal of Urology* 2007; **178**(4 Pt 1):1218-23; discussion 1223-4. [PUBMED: 17698113]

Tierney 2007
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [PUBMED: 17555582]

Tilki 2013
Tilki D, Brausi M, Colombo R, Evans CP, Fradet Y, Fritsche HM, et al. Lymphadenectomy for bladder cancer at the time of radical cystectomy. *European Urology* 2013;**64**(2): 266–76. [PUBMED: 23648149]

Vazina 2004
Vazina A, Dugi D, Shariat SF, Evans J, Link R, Lerner SP. Stage specific lymph node metastasis mapping in radical cystectomy specimens. *Journal of Urology* 2004;**171**(5): 1830–4. [PUBMED: 15076287]

Wang 2013
Wang G. Clinical significance of radical cystectomy with extended lymphadenectomy and influencing factors associated with recurrence of bladder cancer. *Journal of Endourology* 2013;**27**(S1):A142. DOI: 10.1089/end.2013.2001

Youssef 2011
Youssef RF, Raj GV. Lymphadenectomy in management of invasive bladder cancer. *International Journal of Surgical Oncology* 2011;**2011**:758189. [PUBMED: 22312522]

References to other published versions of this review

CRD42018116290
Hwang EC, Sathianathen NJ, Imamura M, Kuntz GM, Risk MC, Dahm P. Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy. www.crd.york.ac.uk/prospero/ (accessed 18 December 2018).

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Gschwend 2018

Methods	**Study design:** Prospective randomized phase-III trial (1:1) study **Statistical design:** N/A **Setting/Country:** Multicenter/Germany **Dates when study was conducted:** February 2006 to August 2010
Participants	**Ethnicity:** likely German **Inclusion criteria** • Histologically proven, locally completely resectable (T1G3 - T4a, Nx), invasive urothelial bladder cancer • Age ≥ 18 years • Written consent of the patient • Patient compliance and geographic proximity to allow adequate follow-up **Exclusion criteria** • Histologically or by imaging diagnostics-proven organ metastases • Radiographic evidence of enlarged lymph nodes (> 1 cm) above the aortic bifurcation in conjunction with pelvic lymph node metastases • Radiographic or other evidence of T4b-tumor (infiltration of the pelvic wall or other organ systems) • Prior neoadjuvant chemotherapy of bladder cancer • Prior previous pelvic lymphadenectomy • Prior radiotherapy to the pelvis • Internal medical or anesthetic risk factors that require a short operation time • Palliative cystectomy (e.g. bulky-disease, infiltration of adjacent structures) • Evidence of another tumor restricting life expectancy of the patient **Total number of participants randomly assigned** • Screened: 458 • Eligible: 401 **Group A** (Extended lymph node dissection) • Number of all participants randomly assigned: 198 • Age: median 67 (IQR: 59-74) • Gender (male/female): 151/47 • Tumor clinical stage: N/A • Tumor pathologic T stage (T1/T2/T3/T4, %): 31 (16)/88 (44)/63 (32)/16 (8.1) • Removed LN number: median 31 (IQR 22-47) • Pathologic N stage (Nx/N0/N+, %): 2 (1.0)/152 (77)/44 (22) • Positive surgical margin (R0/Rx/R+, %): 179 (90)/2 (1.0)/17 (8.6) • Neoadjuvant chemotherapy: N/A • Adjuvant chemotherapy (%): 28 (14) **Group B** (Standard lymph node dissection) • Number of all participants randomly assigned: 203 • Age: median 68 (IQR:61-73) • Gender (male/female): 163/40 • Tumor clinical stage: N/A

	• Tumor pathologic T stage (T1/T2/T3/T4, %): 24 (12)/81(40)/68(34)/30 (15) • Removed LN number: median 19 (IQR 12-26) • Pathologic N stage (Nx/N0/N+, %): 0 (0)/147 (72)/56 (28) • Positive surgical margin (R0/Rx/R+, %): 181 (89)/4 (2.0)/18 (8.9) • Neoadjuvant chemotherapy: N/A • Adjuvant chemotherapy (%): 30 (15)
Interventions	**Group A** (Extended lymph node dissection)**:** Removal of at least 10 out of 14 LND fields and resection of 12 or more LNs were mandatory • Lymph node dissection template ○ Proximal: inferior mesenteric artery ○ Distal: pelvic floor ○ Both lateral: genitofemoral nerve ○ Dorsal: pelvis and rectum **Group B** (Standard lymph node dissection)**:** Removal of at least four out of six LND fields as well as resection of four or more LNs was demanded • Lymph node dissection template ○ Proximal: bifurcation of internal and external iliac artery ○ Distal: pelvic floor ○ Both lateral: the genitofemoral nerve ○ Dorsal: obturator nerve **Follow-up:** median 43 months
Outcomes	**Primary outcomes** • Recurrence-free survival (RFS) • How measured: computed tomography (CT), or death • Time points measured: every 3 months in the first year and then every 6 months up to five years postoperatively • Time point reported: postoperative 5 years **Secondary outcomes** • Cancer-specific survival (CSS), overall survival (OS), localization of tumor recurrence, influence of adjuvant chemotherapy, influence on histopathologic N stage • How measured: CSS: death from bladder cancer, OS: death from any cause, localization of tumor recurrence: CT scan, influence of adjuvant chemotherapy: survival analysis, influence on histopathologic N stage: survival analysis • Time points measured: every 3 months in the first year and then every 6 months up to five years postoperatively • Time points reported: postoperative 5 years **Safety outcomes** • Complication rate • How measured: Clavien-Dindo grades ($\geq$ 3 and $\leq$ 2) • Time points measured: postoperative 30 days and 90 days • Time points reported: postoperative 5 years
Funding Sources	The study was funded by Lilly Deutschland GmbH, The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor of the trial was the AUO of the German Cancer Society. Trial design, conduct, and analysis were done by the AUO, independent of all funding bodies

Declarations of interest	None
Notes	**Protocol:** NCT01215071 **Language of publication:** English

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication:** The randomization list was created upfront by a statistician and organized with blocks per 8 patients. The blocks were assigned to trial sites consecutively. For randomization, the patient was assigned to the next free consecutive randomization number of the site's open block **Comment:** This method of random sequence generation was considered to have low risk of bias
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "a randomization fax was sent from the individual participating site to the AUO head-office (H. Rexer) who managed the concealed randomisation list" **Comment:** Central registration. This method may ensure allocation concealment
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 death from bladder cancer, time to recurrence, Clavien-Dindo I-II complications	High risk	**Quote from publication:** "The outcome was assessed by the local investigator (CRFs, Questionaires, CT scans etc.). There was no blinding (reply from study investigator) **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, Clavien-Dindo III-V complications	Low risk	**Comment:** Objective outcomes are not likely affected by lack of blinding

Incomplete outcome data (attrition bias) Time to death from any cause	Low risk	**Comment:** Intention-to-treat analysis was performed. All participants included in the analysis
Incomplete outcome data (attrition bias) Time to death from bladder cancer	Low risk	**Comment:** Intention-to-treat analysis was performed. All participants included in the analysis
Incomplete outcome data (attrition bias) Clavien-Dindo III-V complications	Low risk	**Comment:** Intention-to-treat analysis was performed. All participants included in the analysis
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** Intention-to-treat analysis was performed. All participants included in the analysis
Incomplete outcome data (attrition bias) Clavien-Dindo I-II complications	Low risk	**Comment:** Intention-to-treat analysis was performed. All participants included in the analysis
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	**Comment:** The included study did not investigate this outcome.
Selective reporting (reporting bias)	Low risk	**Comment:** Protocol was provided and all predefined outcomes were reported
Other bias	Low risk	**Comment:** Not detected

AUO:AssociationofUrologicOncology

CRF: case report forms
CSS : cancer-specific survival
CT: computerized tomography
IQR: interquartile range
LN: lymph node
LND:lymphnodedissection

N (Nx/N0/N+): extent of cancer within nearby lymph nodes (Nx: the lymph nodes could not be assessed, N0: no cancer found in the lymph nodes, N+ cancer found in the lymph nodes)
N/A:notavailable

OS: overall survival
R (R0/Rx/R+): residual tumor (R0: no cells at surgical margin, Rx: residual tumor cannot be assessed, R+: residual tumor present at surgical margin)
RFS: recurrence-free survival
T (1, 2, 3, 4): size and extension of tumor (low to high)

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

NCT01224665

Trial name or title	A phase III surgical trial to evaluate the benefit of a standard versus an extended pelvic lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer
Methods	Open-label multicenter randomized parallel study
Participants	**Estimated enrollment:** 620 participants **Eligible ages:** 18 years to 120 years (adult, older adult) **Eligible sexes:** All **Eligibility Criteria** Disease characteristics: • Histologically-confirmed urothelial carcinoma of the bladder; Stage T2, T3, or T4a disease; no clinical stage consistent with a low risk of node metastasis (CIS only, T1); No T4b disease (fixed lesion); disease that requires primary radical cystectomy and lymph node dissection for definitive treatment; no laparoscopic surgery • Predominant urothelial carcinoma with any of the following elements allowed: adenocarcinoma, squamous cell carcinoma, micropapillary or minor components of other rare phenotype, no pure squamous cell carcinoma or adenocarcinoma • No visceral or nodal metastatic disease proximal to the common iliac bifurcation by 2-view chest x-ray and abdominal-pelvic imaging by computerized tomography or MRI of the abdomen and pelvis • No intraoperative pelvic lymph node involvement (confirmed by frozen section) at or above the bifurcation of the common iliac vessels in any of the extended template Patient characteristics: • Zubrod performance status 0-2 • ALT and AST $\leq$ upper limit of normal (ULN)* • Alkaline phosphatase $\leq$ ULN* • Not pregnant or nursing • Fertile patients must use an effective contraception • No other prior malignancy except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or stage I or II cancer from which the patient is in complete remission for the past 5 years • Medically suitable to undergo cystectomy, in the physician's opinion Prior concurrent therapy: • No prior partial cystectomy for invasive bladder cancer • No prior pelvic surgery that would obviate a complete extended lymphadenectomy (e.g. aorto-femoral/ iliac bypass) • Prior neoadjuvant chemotherapy for this cancer allowed provided it has been completed and patient has recovered • No prior pelvic irradiation
Interventions	**Intervention** • Patients undergo radical cystectomy and extended pelvic lymphadenectomy **Comparator** • Patients undergo radical cystectomy and standard pelvic lymphadenectomy
Outcomes	**Primary outcomes** • Disease-free survival (time point measured: 6 years) **Secondary outcomes** • Overall survival (time point measured: 6 years)

NCT01224665 (*Continued*)

	• Morbidity (time point measured: 6 years)
Starting date	August 2011; **Expected date of completion:** August 2022
Contact information	Contact: Jennifer I Scott; jscott@swog.org Contact: Dana B Sparks, M.A.T; dsparks@swog.org
Notes	**Funding source:** not reported; **Sponsors and Collaborators:** Southwest Oncology Group; National Cancer Institute (NCI)

$^{*Levels maybe} \geq$ upper limit of normal (ULN) provided metastatic disease is excluded using dedicated liver imaging, bone scan, or biopsy
$^{ALT: alanine transaminase}$

AST: aspartate transaminase
CIS: carcinoma in situ
MRI: magnetic resonance imaging
T (1, 2, 3, 4): size and extension of tumor (low to high)
ULN: upper limit of normal

DATA AND ANALYSES

Comparison 1. Extended versus standard lymph node dissection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to death from any cause	1		Hazard Ratio (Random, 95% CI)	Totals not selected
2 Time to death from bladder cancer	1		Hazard Ratio (Random, 95% CI)	Totals not selected
3 Clavien-Dindo III-V complications (up to 30 days)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Clavien-Dindo III-V complications (up to 90 days)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Time to recurrence	1		Hazard Ratio (Random, 95% CI)	Totals not selected
6 Clavien-Dindo I-II complications (up to 30 days)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Clavien-Dindo I-II complications (up to 90 days)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

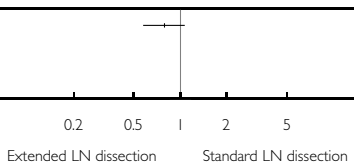
Analysis 1.1. Comparison 1 Extended versus standard lymph node dissection, Outcome 1 Time to death from any cause.

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 1 Time to death from any cause

Study or subgroup	Extended LN dissection N	Standard LN dissection N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Hazard Ratio IV,Random,95% CI
Gschwend 2018	198	203	-0.25 (0.16)		0.78 [0.57, 1.07]



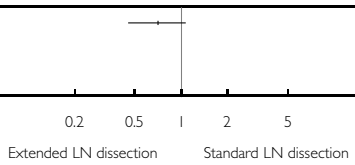
Analysis 1.2. Comparison 1 Extended versus standard lymph node dissection, Outcome 2 Time to death from bladder cancer.

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 2 Time to death from bladder cancer

Study or subgroup	Extended LN dissection N	Standard LN dissection N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Hazard Ratio IV,Random,95% CI
Gschwend 2018	198	203	-0.36 (0.22)		0.70 [0.45, 1.07]



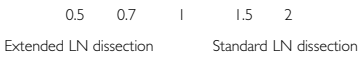
Analysis 1.3. Comparison 1 Extended versus standard lymph node dissection, Outcome 3 Clavien-Dindo III-V complications (up to 30 days).

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 3 Clavien-Dindo III-V complications (up to 30 days)

Study or subgroup	Extended LN dissection n/N	Standard LN dissection n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Gschwend 2018	64/198	58/203		1.13 [0.84, 1.52]

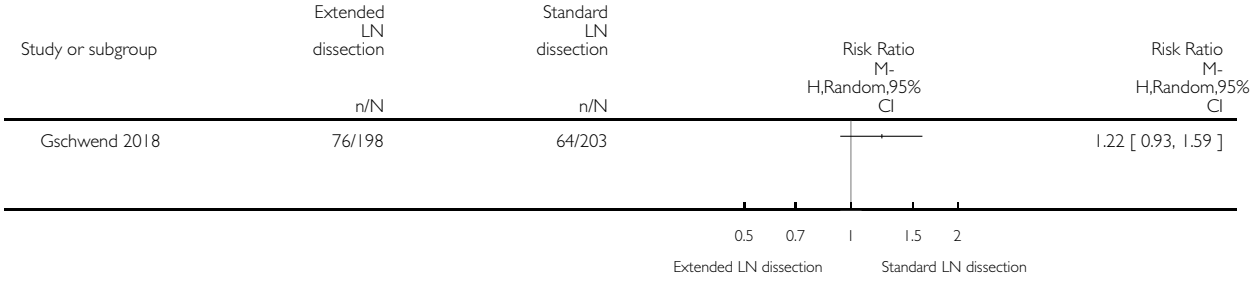


Analysis 1.4. Comparison 1 Extended versus standard lymph node dissection, Outcome 4 Clavien-Dindo III-V complications (up to 90 days).

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 4 Clavien-Dindo III-V complications (up to 90 days)

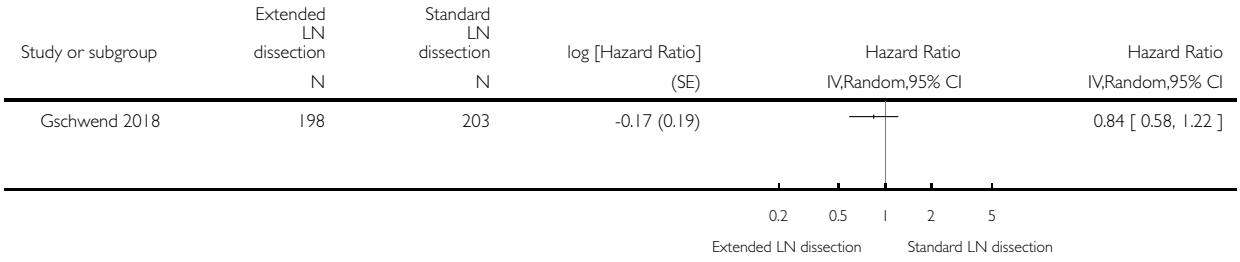


Analysis 1.5. Comparison 1 Extended versus standard lymph node dissection, Outcome 5 Time to recurrence.

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 5 Time to recurrence

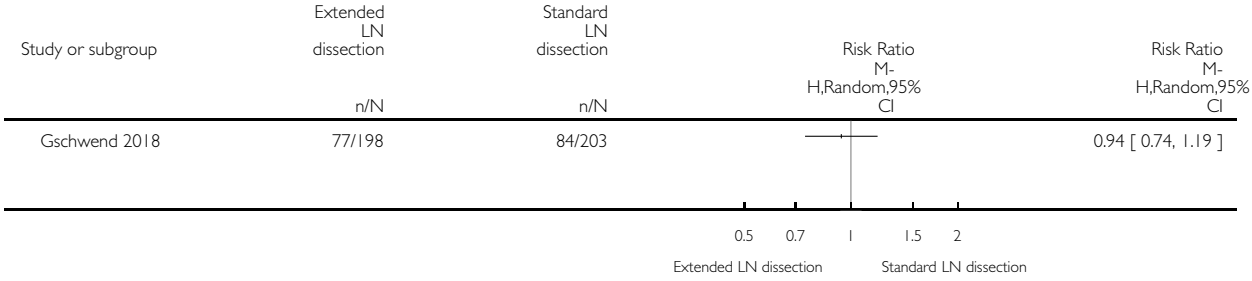


Analysis 1.6. Comparison 1 Extended versus standard lymph node dissection, Outcome 6 Clavien-Dindo I-II complications (up to 30 days).

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 6 Clavien-Dindo I-II complications (up to 30 days)

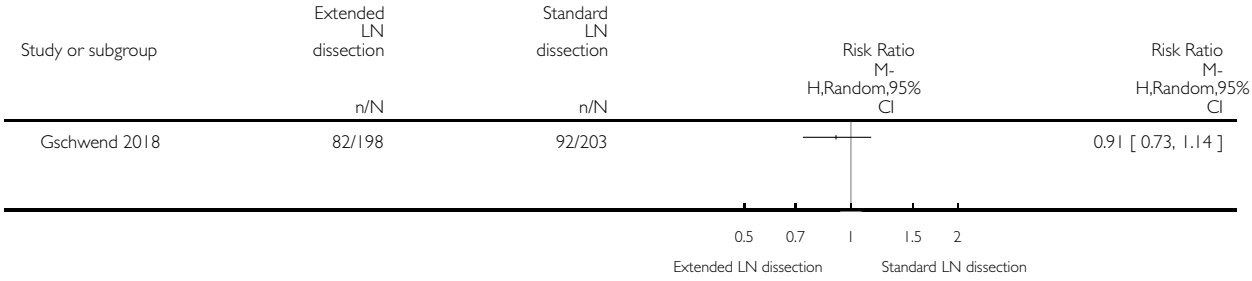


Analysis 1.7. Comparison 1 Extended versus standard lymph node dissection, Outcome 7 Clavien-Dindo I-II complications (up to 90 days).

Review: Extended versus standard lymph node dissection for urothelial carcinoma of the bladder in patients undergoing radical cystectomy

Comparison: 1 Extended versus standard lymph node dissection

Outcome: 7 Clavien-Dindo I-II complications (up to 90 days)



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	Pathologic T stage	Pathologic N stage
Gschwend 2018	2006 to 2010	Multicenter/ Germany	Participants with urothelial carcinoma of the bladder who underwent radical cystectomy	Intervention: Extended lymph node dissection	43 months	median 67 (IQR:59-74)	Male: n = 151 (76.3%) Female: n = 47 (23.7%)	T1: 31 (16%) T2: 88 (44%) T3: 63 (32%) T4: 16 (8.1%)	Nx: 2 (1.0%) N0: 152 (77%) N+: 44 (22%)
				Comparator: Standard lymph node dissection		median 68 (IQR:61-73)	Male: n = 163 (80.3%) Female: n = 40 (19.7%)	T1: 24 (12%) T2: 81 (40%) T3: 68 (34%) T4: 30 (15%)	Nx: 0 (0%) N0: 147 (72%) N+: 56 (28%)

IQR:interquartilerange

Nx:thelymphnodescouldnotbeassessed

N0:nocancerfoundinthenearbylymphnodes

N+:cancerfoundinthelymphnodes

T(1,2,3,4):sizeandextensionoftumor(lowtohigh)

Table 2. Participants in included study

Study name	Intervention(s) and comparator (s)	Screened/ eligible (N)	Randomized (N)	Analysed (N): efficacy	Analysed (N): safety	Finishing trial (N (%))
Gschwend 2018	Intervention: Extended lymph node dissection	458/401	198	198	198	173 (87.3)
	Comparator: Standard lymph node dissection		203	203	203	190 (93.5)
	Total		401	401	401	363 (90.5)

APPENDICES

Appendix 1. Search strategies

PubMed (late 1940s-present)

1. "urinary bladder neoplasms"[MeSH Terms] OR bladder neoplasm[tw] OR bladder neoplasms[tw]
2. "carcinoma, transitional cell"[MeSH Terms] OR transitional cell carcinoma[tw] OR transitional cell carcinomas[tw]
3. bladder cancer[tw] OR bladder cancers[tw] OR cancer of the bladder[tw] OR cancers of the bladder[tw] OR bladder tumor[tw] OR bladder tumors[tw] OR bladder tumor[tiab] OR bladder tumors[tw] OR tumours of the bladder[tw] OR tumors of the bladder[tw]
4. 1 OR 2 OR 3
5. "lymph node excision"[MeSH Terms] OR lymph node excision[tw] OR excision of the lymph node*[tiab] OR lymph node dissection[tiab] OR dissection of the lymph node*[tw]
6. lymphadenectomy[tw] OR lymphadenectomies[tw]
7. 5 OR 6
8. "cystectomy"[MeSH Terms] OR cystectomy[tw] OR cystectomies[tw]
9. 4 AND 7 AND 8
10. (((((((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR randomized[tiab]) OR placebo[tiab]) OR clinical trials as topic[mesh:noexp]) OR randomly[tiab]) OR trial[ti])) NOT (animals[mh] NOT humans[mh])
11. 9 AND 10

Embase (Elsevier, 1947-present)

('cystectomy'/exp OR 'cystectomy' OR 'cystectomies') AND ('lymph node dissection'/exp OR 'lymph node dissection' OR 'lymph node excision'/exp OR 'lymph node excision' OR 'excision of the lymph node' OR 'dissection of the lymph node' OR 'pelvis lymphadenectomy'/exp OR 'pelvis lymphadenectomy' OR 'lymphadenectom*') AND ('bladder cancers' OR 'bladder cancer'/exp OR 'bladder cancer' OR 'bladder carcinoma'/exp OR 'bladder carcinoma' OR 'bladder carcinomas' OR 'bladder neoplasm'/exp OR 'bladder neoplasm' OR 'bladder neoplasms'/exp OR 'bladder neoplasms' OR 'transitional cell carcinoma'/exp OR 'transitional cell carcinoma' OR 'transitional cell carcinomas' OR 'urothelial bladder cancer'/exp OR 'urothelial bladder cancer' OR 'urothelial bladder carcinoma'/exp OR 'urothelial bladder carcinoma' OR 'bladder tumor'/exp OR 'bladder tumor') AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('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)

Cochrane Controlled Trials (Issue 4, April 2019)

#1 MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
#2 MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
#3 bladder NEXT cancer:ti,ab,kw OR bladder NEXT cancers:ti,ab,kw OR bladder NEXT tumor*:ti,ab,kw OR bladder NEXT tumour*:ti,ab,kw OR cancer NEAR/3 of the bladder:ti,ab,kw OR Urothelial NEXT carcinoma*:ti,ab,kw OR transitional NEXT cell NEXT cancer*:ti,ab,kw
#4 MeSH descriptor: [Lymph Node Excision] explode all trees
#5 excision of the lymph node:ti,ab,kw OR dissection of the lymph node:ti,ab,kw OR lymph node dissection:ti,ab,kw
#6 #1 OR #2 OR #3
#7 #4 OR #5
#8 MeSH descriptor: [Cystectomy] explode all trees
#9 cystectom*:ti,ab,kw
#10 #8 OR #9
#11 #6 AND #7 AND #10

(*Continued*)

Web of Science (1900-2019)
1. TS=bladder tumor* 2. TS=urinary bladder neoplasm* 3. TS=bladder cancer* 4. TS=transitional cell carcinoma* 5. TS=cancer of the bladder* 6. TS=urothelial carcinoma* 7. #1 OR #2 OR #3 OR #4 OR #5 or #6 8. TS=lymph node excision* 9. TS=excision of lymph node* 10. TS=lymph node dissection* 11. TS=dissection of the lymph mode* 12. TS=lymphadenedtom* 13. #8 OR #9 OR #10 OR #11 OR #12 14. TS=cystectom* 15. #7 AND #13 AND #14 16. TS=randomized controlled trial* 17. TS=clinical trial* 18. #16 OR #17 19. #15 and #18
LILACS/clinical trials
Bladder cancer AND lymph node resection AND cystectomy
ClinicalTrials.gov
Condition: Bladder cancer **Other Terms:** lymph node resection AND cystectomy
World Health Organization (WHO) International Clinical Trials Registry Platform search portal
Bladder cancer AND lymphadenectomy AND cystectomy

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)
Gschwend 2018	18 Dec 2018	19 Dec 2018	Blinding of outcome assessor

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 J Sathianathen (NS): study selection, extracting data, assessing risk of bias, performing data analysis, and interpretation of data

Mari Imamura (MI): providing clinical and methodological guidance for this review

Gretchen M Kuntz (GK): creating search strategies and searching for trials

Michael C Risk (MR): providing clinical and methodological guidance for this review

Philipp Dahm (PD): conception and study design, providing clinical and methodological advice on the review, and final approval

DECLARATIONS OF INTEREST

ECH: none known.

NS: Niranjan J Sathianathen was a previous recipient of a Royal Australasian College of Surgeons (RACS) scholarship awarded for the undertaking of a separate, non-related project that was completed in March 2018.

GK: none known.

MI: none known.

MR: 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. The editorial process was conducted in collaboration with the Fast-Track Service, which is independent of Cochrane Urology, and the review was signed off by members of Cochrane's Editorial and Methods Department.

SOURCES OF SUPPORT

Internal sources

- Chonnam National University Hwasun Hospital, Hwasun, Korea, South.

Salary support for Eu Chang Hwang

- Minneapolis VA Medical Center, Minneapolis, Minnesota, USA.

Salary support for Philipp Dahm

- Minneapolis VA Medical Center, Minneapolis, Minnesota, USA.

Salary support for Michael C Risk

- Department of Urology, Chonnam National University Medical School, Gwangju, Korea, South.
- Department of Urology, University of Minnesota, Minneapolis, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a registered protocol (PROSPERO; CRD42018116290).

The study included here investigated complication rates 30 and 90 days after the intervention; we have included both results in the analysis.

NOTES

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