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[Intervention Protocol]

Postoperative interventions for preventing bladder dysfunction after radical hysterectomy in women with early-stage cervical cancer

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effectiveness and safety of postoperative interventions for preventing bladder dysfunction following radical hysterectomy in women with early-stage cervical cancer (FIGO stage IA2 to IIA).

BACKGROUND

Description of the condition

Cervical cancer is the fourth most common cancer affecting women worldwide, with an estimated 528,000 new cases and 266,000 cervical cancer-related deaths globally in 2012 (GLOBOCAN 2012). Cervical cancer is a major health problem among women in developing countries since almost 70% of the global burden and 90% of cervical cancer-related deaths occur in these regions (Ferlay 2015; GLOBOCAN 2012). The high burden of cervical cancer among less economically developed settings is secondary to the failure to provide effective, large-scale screening programmes (Torre 2015).

Treatment of cervical cancer depends on the stage of disease. Appendix 1 displays a summary of the International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer (FIGO Committee 2014). Women with FIGO stage IA2 to IIA cervical cancer can be treated with either radical hysterectomy with pelvic lymphadenectomy or pelvic chemoradiation (Landoni 1997). In premenopausal women, radical hysterectomy with pelvic lymphadenectomy may be preferable to pelvic radiation in order to preserve ovarian function and vaginal elasticity, as well as prevent the long-term risks of pelvic radiation (Cull 1993; Viswanathan 2014).

The aim of radical hysterectomy is to remove the primary tumour with an adequate margin of normal tissue to ensure complete resection (Piver 1974; Querleu 2008; Verleye 2009). Appendix 2 lists details of the three systems for the classification of radical hysterectomy (Piver-Rutledge-Smith, Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer, and Querleu and Morrow). The stage of cervical cancer is the fundamental factor to be taken into consideration when considering radical hysterectomy. Women with early-stage cervical cancer are traditionally treated with Piver type III radical hysterectomy. However, a previous randomised controlled trial (RCT) demonstrated that women with cervical cancer stage IB to IIA who underwent Piver type II hysterectomy (also called modified radical hysterectomy) had comparable oncological outcomes to those who underwent type III hysterectomy (Landoni 2001). Pelvic lymphadenectomy is performed to look for metastatic lesions in the pelvic lymph nodes. The survival of women who undergo radical hysterectomy with pelvic lymphadenectomy for cervical cancer stage IA2 to IIA is excellent. Estimated five-year survival rates range between 70% and 90% (Kim 2000; Mahawerawat 2013; Srisomboon 2011; Suprasert 2010).

One of the most distressing morbidities that can occur following radical hysterectomy is bladder dysfunction (Laterza 2015; Lin 1998; Plotti 2011). The incidence of bladder dysfunction after radical hysterectomy varies from 12% to 85% depending on the method used in evaluating bladder dysfunction and the duration of follow up (Wit 2014; Zullo 2003). In addition, the risk of bladder dysfunction depends on the radicality of surgery. Women undergoing type II radical hysterectomy are at lower risk of postoperative bladder dysfunction than those who undergo type III radical hysterectomy (Landoni 2001; Raspagliesi 2006). By magnifying anatomical structures in the pelvis, laparoscopic approaches may help reduce the denervation of pelvic nerves during radical hysterectomy; however, it has yet to be shown that these approaches have a significant effect on the prevention of bladder dysfunction (Laterza 2015).

Causes of bladder dysfunction following radical hysterectomy are secondary to the damage of pelvic autonomic nerves that innervate the muscles of the bladder (detrusor muscle), urethral sphincter and pelvic floor fasciae (Sellers 2012; Zullo 2003). Bladder dysfunction following radical hysterectomy includes various functional disorders of the lower urinary tract, such as urinary retention, voiding difficulty, urinary hesitancy, urinary tract infection and urinary stress incontinence (Chen 2002). Bladder dysfunction increases the rates of urinary tract infection, hospital visits/admission, patient dissatisfaction and the need for intermittent self-catheterisation (Manchana 2010). Bladder dysfunction can also negatively impact patient quality of life (QoL), which can lead to embarrassment or even social isolation (Zhou 2016).

Description of the intervention

Postoperative interventions for preventing bladder dysfunction after radical hysterectomy can be classified broadly into two groups: pharmacological interventions and non-pharmacological interventions. Pharmacological interventions use parasympathomimetic agents to stimulate contraction of the smooth muscles of the detrusor muscle and can improve the symptoms associated with bladder hypotonia (Sellers 2012). The drugs frequently used in treating bladder dysfunction following radical hysterectomy are bethanechol chloride and cisapride (Kemp 1997; Madeiro 2006). A wide range of non-pharmacological interventions have been used to reduce bladder dysfunction following radical hysterectomy, including postoperative suprapubic catheterisation, intermittent self-catheterisation, bladder training and acupuncture (Fernandez 2005; Geller 2014; Kidd 2015; Naik 2005).

How the intervention might work

Previous studies have demonstrated that a malfunctioning bladder detrusor muscle is a major cause of bladder dysfunction following radical hysterectomy (Laterza 2015; Plotti 2011). Contraction of the detrusor muscle of the urinary bladder is stimulated by parasympathetic nerve impulses mediated by the neurotransmitter acetylcholine (Sellers 2012). Pharmacological therapy for voiding disorders consists of drugs that improve detrusor muscle contraction and those that reduce urethral resistance, which may have a role in the prevention of postoperative bladder dysfunction. Bethanechol, a cholinergic agent, is a synthetic ester, and is structurally and pharmacologically related to acetylcholine. Bethanechol increases the tone of the detrusor muscle by stimulating the parasympathetic nervous system (Kemp 1997; Madeiro 2006).

Cisapride is a prokinetic agent. It is principally prescribed for treating gastro-oesophageal reflux in children. The mechanism of action of cisapride is to stimulate the release of acetylcholine, thus promoting detrusor muscle contractility. Hence, as a result of its parasympathomimetic effect, cisapride may be effective for treating bladder hypotonia after surgery (Madeiro 2006). Cisapride, however, has been restricted to a limited access programme in the USA and Europe because it is associated with serious side effects, including cardiac arrhythmias (irregular heart rhythms) and death (Henney 2000).

The insertion of a suprapubic catheter (via postoperative suprapubic cystostomy) has been proposed to hasten the recovery of bladder function compared with an indwelling urethral catheter by minimising the risks of a urinary tract infection and asymptomatic bacteriuria, which can impede bladder function activity from returning to normal (Kidd 2015).

Bladder training is an important form of behaviour therapy that can be effective in treating bladder dysfunction following radical hysterectomy (Goldfarb 1967). Bladder training targets the detrusor muscle and aims to promote bladder filling and emptying according to a normal pattern (Oberst 1981). As bladder training has been acknowledged as an effective intervention for managing

individuals with neurogenic bladder (Wallace 2004), this intervention may be effective for managing bladder dysfunction following radical hysterectomy.

Acupuncture is a treatment derived from traditional Chinese medicine. Fine needles are inserted at certain sites in the body for either therapeutic or preventative purposes. A small electrical current passing between pairs of acupuncture needles may be used at the same time, a technique called electroacupuncture (Yi 2011). Previous studies have reported the efficacy of acupuncture for the treatment of postoperative urinary retention after gynaecological surgery (Geller 2014; Wang 2007). However, the actual mechanism of action remains unknown.

Why it is important to do this review

Although survival outcomes of women with early-stage cervical cancer after radical hysterectomy with pelvic lymphadenectomy are excellent, surgery is frequently associated with postoperative complications, particularly bladder dysfunction (Suprasert 2010). As bladder dysfunction diminishes QoL and is one of the most distressing complications following radical hysterectomy (Zhou 2016), effective interventions are needed in order to prevent or reduce the severity of the symptoms of this condition. Several postoperative interventions have been proposed to prevent bladder dysfunction following radical hysterectomy. To our knowledge there has been no systematic review evaluating the effectiveness and safety of postoperative interventions for preventing bladder dysfunction following radical hysterectomy in women with cervical cancer.

Please see Appendix 3 for a glossary of terms.

OBJECTIVES

To evaluate the effectiveness and safety of postoperative interventions for preventing bladder dysfunction following radical hysterectomy in women with early-stage cervical cancer (FIGO stage IA2 to IIA).

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs. We will not include quasi-RCT or controlled clinical trials.

Types of participants

Women aged 18 years or over with early-stage cervical cancer who have undergone radical hysterectomy (Piver type II, Piver type III, Querleu-Morrow class B2 or class C1). If studies include women with other types of gynaecological cancer (i.e. endometrial cancer), we will contact the trial authors to retrieve data related to participants with cervical cancer only. If this is not possible, we will include the study only if at least 80% of participants were diagnosed with cervical cancer.

Types of interventions

We will include any trial that attempted to compare the following.

- A pharmacological agent and placebo or standard care.
- A non-pharmacological intervention and a standard care.

Specific interventions include postoperative suprapubic catheterisation, bladder training and acupuncture.

- A pharmacological agent and a non-pharmacological intervention.
- A pharmacological agent and another agent.
- A non-pharmacological intervention and another intervention.
- Combinations of intervention and placebo or standard care.
- Combinations of intervention and single intervention.
- Combinations of intervention and other combinations

Types of outcome measures

Primary outcomes

- Rate of spontaneous voiding recovery one week after surgery
- QoL, determined using a scale that has been validated in accordance with the norms reported in a peer-reviewed publication (i.e. the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CX24 cervical cancer-specific QoL questionnaire (Greimel 2006))

Secondary outcomes

- Time to post-void residual volume of urine $\leq$ 50 mL after surgery (days)
- Adverse events (excluding bladder dysfunction). We will categorise the severity of the following adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE 2010). (A) Acute complications including: postoperative mortality; digestive complications (e.g. bowel injuries, bowel obstruction); urological injuries; haematological complications (e.g. anaemia from acute blood loss); and cardiovascular and thromboembolic complications (e.g. myocardial infarction, arterial thrombosis, venous thrombosis, pulmonary embolism). (B) Late complications including:

symptomatic lymphocysts; incisional hernia; digestive complications (e.g. intestinal obstruction and fistular formation); and urological complications (e.g. ureteral stenosis and fistulae)

- Post-void residual urine volume (amount of urine measured by clean intermittent catheterisation after the participant feels that her bladder is empty) at 1, 6 and 12 months after surgery (mL)
- Rate of urinary tract infections in the first month after surgery, diagnosed by urine culture

- Subjective urinary symptoms, determined using a standard questionnaire (i.e. International Prostate Symptom Score (Barry 1992))
- Flow rate (mL per second), obtained by urodynamic measurement
- Maximum flow rate (mL per second) and number of women with low maximum flow rate (< 15 mL per second as defined by Abrams 2003), obtained by urodynamic measures
- Detrusor pressure at maximum flow and number of women with low detrusor pressure at maximum flow (< 25 cmH_2O)
- Poor bladder compliance

We will present a 'Summary of findings' table reporting the following outcomes listed in order of priority (see Appendix 4).

- Rate of spontaneous voiding recovery one week after surgery.
- QoL.
- Time to post-void residual volume of urine $\leq$ 50 mL after surgery (days).
- Adverse events.
- Post-void residual urine volume one month after surgery.
- Urinary tract infections over the one-month period following surgery.
- Subjective urinary symptoms.

Search methods for identification of studies

We will include RCTs, irrespective of the language of publication, publication status or sample size.

Electronic searches

We will search the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue).
- MEDLINE (1946 to present date).
- Embase (1980 to present date).

We present the Ovid MEDLINE search strategy in Appendix 5. For databases other than MEDLINE, we will adapt the search strategy accordingly.

Searching other resources

We will search the World Health Organization International Clinical Trials Registry Platform (who.int/ictrp/en/) and ClinicalTrials.gov to identify any ongoing trials. If ongoing trials that have not been published are identified, we will approach the principal investigators and major co-operative groups active in this area to ask for relevant data. We will search the following databases for grey literature: Open-Grey (opengrey.eu/) and Index to theses (proquest.com/products-services/pqdt_uk_ireland.html).

Handsearching

We will handsearch reports of conferences from the following sources.

- Annual Meeting of the Society of Gynecologic Oncology.
- Annual Meeting of the International Gynecologic Cancer Society.
- Annual Meeting of the European Society of Medical Oncology.
- Annual Meeting of the British Gynaecological Cancer Society.
- Biennial Meeting of the Asian Society of Gynecologic Oncology.
- Biennial Meeting of Asia and Oceania Federation of Obstetrics and Gynaecology.
- Biennial Meeting of the European Society of Gynaecologic Oncology.

We will check the citation lists of the included studies and key textbooks for potentially relevant references. We will search for papers in all languages and will translate them, if necessary. We will include unpublished trials only if trial data and methodological descriptions are provided in written form or via direct contact with the trial authors.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved via electronic search of the Endnote reference management database. After duplicates are removed, we will transfer these data to Covidence (covidence.org). Two review authors (AA and CK) will examine the remaining references independently. We will exclude those studies which clearly do not meet the inclusion criteria, and we will obtain full-text copies of potentially relevant references. Two review authors (AA and CK) will independently assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third review author (KG/PL). We will identify and exclude duplicates and collate multiple reports of the same study so that each study

rather than each report is the unit of interest in the review. We will use the details obtained from the selection process in Covidence to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (AA and CK) will independently extract study characteristics and outcome data from included studies using Covidence. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (KG/TT). One review author (CK) will check study characteristics for accuracy against the trial report.

For included studies, we will extract the following data.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study methodology.
- Study population and disease characteristics:
  - total number enrolled;
  - participant characteristics;
  - age;
  - comorbidities;
  - other baseline characteristics;
  - percentage of participants with non-cervical cancer (only RCTs involving mixed gynaecologic malignancies);
  - FIGO stage of cervical cancer;
  - histopathological subtype of cervical cancer;
  - tumour size (largest tumour diameter);
  - radicality of surgery (Piver or Querleu-Morrow).
- Intervention details:
  - schedule of bladder training;
  - suprapubic cystostomy technique;
  - acupuncture;
  - cholinergic agents (dose, duration).
- Comparison:
  - Placebo.
- Risk of bias in study (see below).
- Duration of follow-up.
- Outcomes: for each outcome, we will extract the outcome definition and unit of measurement (if relevant); for adjusted estimates, we will record variables adjusted for in analyses.
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome and the missing participants.
- Notes: funding for trial and notable conflicts of interest of trial authors.

Assessment of risk of bias in included studies

We will assess and report on the methodological quality and risk of bias in included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs.

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel (treatment providers).
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting of outcomes.
- Other possible bias.

We will regard outcome data as complete if at least 80% of participants undergo follow-ups and are assessed for primary outcomes. Two review authors (AA and CK) will independently apply the 'Risk of bias' tool and differences will be resolved by discussion or by appeal to a third review author (KG/PL). We will judge each item as being at high, low or unclear risk of bias as set out in the criteria displayed in Appendix 6. We will provide a quote from the study report or a statement, or both as justification for our judgement for each item in the 'Risk of bias' table. We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias in the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the table.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For dichotomous outcomes (e.g. rate of spontaneous voiding recovery one week after surgery, rate of urethral catheter removal, rate of urinary tract infections, number of participants with normal detrusor pressure at maximum flow, adverse events, recurrences and death), we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio and 95% confidence interval.
- For continuous outcomes (e.g. duration of postoperative retained urethral catheterisation, post-void residual urine volume and QoL measures), we will analyse data based on the means, standard deviations and number of people assessed for both the intervention and comparison groups to calculate the mean difference between treatment arms with a 95% confidence interval. If the mean difference is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference and 95% confidence interval using the inverse variance method.

- For time-to-event data (e.g. time to post-void residual volume of urine $\leq$ 50 mL after surgery), we will extract the log of the hazard ratio ($\log_{HR}$) and its standard error from trial reports. If these have not been reported, we plan to estimate the $\log_{HR}$ and its standard error using the methods of Parmar 1998.

Unit of analysis issues

We will include studies in which individual participants were randomised. In a study with multiple intervention groups, we will combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison, where possible (Higgins 2011). It is unlikely that cross-over or cluster-RCTs could be designed to evaluate the interventions that this review aims to evaluate.

Dealing with missing data

We will contact the original investigators to request missing data. If we cannot contact the investigators or cannot obtain the requested missing data, we will analyse only the available data and will not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

We will clinically assess heterogeneity by visual inspection of forest plots. We will assess statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test (Higgins 2003). We will regard heterogeneity as substantial if the I^2 statistic value is greater than 50% or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity (Deeks 2001; Higgins 2011). If there is substantial statistical heterogeneity, we will carry out subgroup analyses to assess differences among the included studies. However, if there is both clinical and methodological heterogeneity across included studies, we will not report pooled results from meta-analysis, but will instead use a narrative approach to data synthesis.

Assessment of reporting biases

We will examine funnel plots corresponding to a meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias if more than 10 studies are identified. We plan to assess funnel plot asymmetry visually, and if asymmetry of funnel plots is identified, we will perform exploratory analyses to investigate it (Sterne 2011).

Data synthesis

We will use the random-effects model with inverse variance weighting for all meta-analyses (DeSimonian 1986). We will perform statistical analysis using Review Manager 5.3 (RevMan 2014).

- For time-to-event data, we will pool hazard ratios using the generic inverse variance.
- For any dichotomous outcomes, we will calculate the relative risks for each study and then pooled them.
- For continuous outcomes, we will pool the mean differences among the treatment arms, if all trials measure the outcome on the same scale; otherwise we will pool standardised mean differences.

Main outcomes of the 'Summary of findings' table for assessing the quality of the evidence

Appendix 4 displays a 'Summary of findings' table, which we will use to summarise the results of the meta-analyses conducted for each of the outcomes, as outlined in the section Types of outcome measures. We will grade the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results (Langendam 2013). We will create a 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011) and will use GRADEpro GDT.

- High quality: the true effect lies close to that of the estimate of the effect.
- Moderate quality: 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 quality: the true effect may be substantially different from the estimate of the effect.
- Very low quality: the true effect is likely to be substantially different from the estimate of effect.

We will downgrade the evidence from 'high' quality by one level for each serious (or by two for each very serious) limitation.

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analyses in order to assess the effect of the following factors.

- Tumour size (2 cm or less versus more than 2 cm).
- Surgical approach (laparotomy versus minimal invasive surgery).
- Nerve-sparing approach during radical hysterectomy (yes versus no).
- Radicality of surgery (Piver type II versus Piver type III, or Querleu-Morrow class B2 versus class C1).
- Extent of pelvic lymph node dissection determined by number of lymph nodes removed.

We will assess subgroup differences using the interaction tests available within RevMan 2014. We will report the results of subgroup analyses by quoting the Chi^2 statistic and P value, the interaction test and the I^2 statistic.

Sensitivity analysis

We will perform sensitivity analyses in order to assess the effect of the following factors.

- Repeating the analysis excluding unpublished studies (if any).
- Repeating the analysis excluding studies judged to be at "high" or "unclear" risk of bias for allocation concealment.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. FIGO staging classification for cervical cancer

FIGO* Stage	Description
I	The carcinoma is confined to the cervix
IA	Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
IA1	Measured invasion of stroma ≤ 3 mm in depth and ≤ 7 mm width
IA2	Measured invasion of stroma > 3 mm and < 5 mm in depth and ≤ 7 mm width
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
IB1	Clinical lesions no greater than 4 cm in size
IB2	Clinical lesions > 4 cm in size
II	The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina
IIA	Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement
IIA1	Clinically visible lesion ≤ 4 cm
IIA2	Clinically visible lesion > 4 cm
IIB	Parametrial involvement but not onto the pelvic sidewall
III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum, or both
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

*FIGO, International Federation of Gynecology and Obstetrics

Appendix 2. Classification of radical hysterectomies

Piver-Rutledge-Smith		GCG-EORTC*		Querleu and Morrow	
Class I	Extrafascial hysterectomy Deflection and retraction of the ureters without dissection of the ureteral bed Uterine artery, uterosacral ligament and cardinal ligament are not removed No vaginal cuff removed	Type I	Simple hysterectomy	Type A	Extrafascial hysterectomy Visualisation or palpation, or both, of the ureters without dissection of the ureteral bed Uterine artery, uterosacral ligament and cardinal ligament are not transected at a distance from the uterus Minimal vaginal cuff removed (< 10 mm)
Class II	Modified radical hysterectomy (Wertheim) Ureters are freed from the paracervical position but are not dissected out of the pubovesical ligament Uterine arteries divided just medial to the ureter Uterosacral ligaments resected midway between the uterus and their sacral attachments Medial half of the cardinal ligaments removed Upper one-third of the vagina removed Elective pelvic lymphadenectomy	Type II	Modified radical hysterectomy The uterus, paracervix and upper vagina (10-20 mm) are removed after dissection of the ureters to the point of their entry to the bladder Uterine arteries are cut off and ligated Medial half of parametria and proximal uterosacral ligaments are transected	Type B	Ureters are unroofed and rolled laterally Partial removal of uterosacral and vesicouterine ligaments Transection of the paracervix at the level of the ureteral tunnel At least 10 mm of the vagina from the cervix or tumour is resected

(*Continued*)

					B1	Without removal of lateral paracervical lymph nodes
					B2	With additional removal of lateral paracervical lymph nodes
Class III	Classic radical hysterectomy (Meigs) Complete dissection of the ureter from the pubovesical ligament to entry in the bladder except a small lateral part so that the superior vesicle artery is conserved Uterine vessels divided at origin from the internal iliac artery Uterosacral ligaments resected at their sacral attachments Cardinal ligaments resected at the pelvic wall Upper half of the vagina removed Routine pelvic lymphadenectomy	Type III	Radical hysterectomy En bloc removal of the uterus with the upper third of the vagina along with the paracervical and paravaginal tissues Uterine arteries are cut off and ligated at their origin The entire width of the parametria is resected bilaterally The entire uterosacral ligament is resected	Type C	Ureters are completely mobilised Transection of the uterosacral ligament at the rectum Transection of the vesicouterine ligament at the bladder Complete transection of the paracervix 15-20 mm of the vagina from the cervix or tumour and the corresponding paracolpos is resected routinely	
					C1	With preservation of autonomic nerves
					C2	Without preservation of autonomic nerves
Class IV	More radical than class III in three aspects: (i) Complete dissection of the ureter from the pubovesical ligament	Type IV	Extended radical hysterectomy Differs from class III in that three-fourths of the vagina and paravaginal tis-	Type D	D1	Resection of the entire paracervix at the pelvic side wall together with the hypogastric vessels, exposing the

(*Continued*)

	(ii) The superior vesicle artery is sacrificed (iii) Upper three-quarters of the vagina removed		sues are resected			roots of the sciatic nerve
					D2	Type D1 plus resection of the entire paracervix with the hypogastric vessels and adjacent fascial or muscular structures
Class V	More radical than class IV Excision of involved portion of distal ureter or bladder and reimplantation of ureter into the bladder	Type V	Partial exenteration Terminal ureters or segments of bladder or rectum are resected along with the uterus and parametria			
For all types, lymphadenectomy is described separately according to four levels (external and internal iliac, common iliac, aortic inframesenteric and aortic infrarenal) and radicality (sentinel node sampling, random sampling, removal of enlarged nodes only, systematic lymph node dissection or debulking)						

* Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer

Appendix 3. Glossary

Pelvic chemoradiation: a combination of medication and radiotherapy given at the same time to destroy cancer cells.
Radical hysterectomy: the surgical removal of the womb, the cervix, the upper part of the vagina and the tissues around the cervix.
Pelvic lymphadenectomy: the surgical removal of the lymph glands found in the pelvis.
Bladder dysfunction (also referred to as voiding dysfunction): a general term to describe abnormalities in either the filling or emptying of the bladder (e.g. urinary retention, voiding difficulty and urgency).
Detrusor muscle: the smooth muscle of the urinary bladder.
Bladder hypotonia: the bladder does not press strongly enough to become completely empty.
Postoperative suprapubic catheterisation: a procedure that creates a connection between the urinary bladder and the skin to drain urine from the bladder.
Acetylcholine: the chemical substance released by the distal part of the nervous system to activate muscles.
Parasympathomimetic agents (also referred to as cholinergic drugs): substances that provoke the autonomic nervous system to promote contraction of the smooth muscle of the urinary bladder.
Prokinetic agent: a drug which enhances gastrointestinal motility by increasing the frequency of contractions in the small intestine.
Poor bladder compliance: a significant increase in bladder pressure with small increments in bladder volume, as measured in a urodynamic study.

Appendix 4. 'Summary of findings' table

Title: Postoperative interventions for preventing bladder dysfunction after radical hysterectomy in women with cervical cancer

Population: women with stage IA2-IIA cervical cancer undergoing radical hysterectomy
Settings: specialist hospital
Intervention: non-pharmacological or pharmacological interventions
Comparison: placebo or no treatment or different interventions (non-pharmacological versus pharmacological interventions)

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Rate of spontaneous voiding recovery one week after surgery						
Quality of life						
Time to post-void residual volume of urine ≤ 50 mL after surgery (days)						
Adverse events						
Post-void residual urine volume one month after surgery						
Urinary tract infections during the one-month period following surgery						
Subjective urinary symptoms						

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) 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; MD: mean difference; RR: risk ratio; OR: odds ratio

(*Continued*)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate.

Appendix 5. MEDLINE Ovid search strategy

1. Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. exp Hysterectomy/
5. hysterectom*.mp.
6. ((uter* or womb) adj5 (remov* or excis*)).mp.
7. 4 or 5 or 6
8. Urinary Bladder/
9. Urinary Catheterization/
10. exp Urinary Bladder Diseases/
11. exp Lower Urinary Tract Symptoms/
12. exp Urination Disorders/
13. exp Urinary Tract Infections/
14. Urination/
15. ((bladder* or urethra* or ureter* or urin* or urologic*) adj5 (dysfunction* or disorder* or disease* or infect* or incontinence* or urgency* or injur* or damage* or hypotonia* or resist* or malfunction*)).mp.
16. (suprapubic adj3 (cystostomy* or catheter*)).mp.
17. Acupuncture Therapy/
18. exp Cholinergic Agents/
19. ((bladder* or detrusor muscle* or urin*) adj3 (train* or fill* or empty* or pattern* or intervention*)).mp.
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 3 and 7 and 20

Appendix 6. 'Risk of bias' assessment

Assessment of risk of bias will be based on chapter 8 of Higgins 2011.

- Random sequence generation
  - Low risk of bias, e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers.
  - High risk of bias, e.g. participants assigned to treatments on the basis of date of birth, clinic ID number or surname, or no attempt to randomise participants.
  - Unclear risk of bias, e.g. not reported, information not available.
- Allocation concealment
  - Low risk of bias, e.g. where the allocation sequence could not be foretold.
  - High risk of bias, e.g. allocation sequence could be foretold by participants, investigators or treatment providers.
  - Unclear risk of bias, e.g. not reported.
- Blinding of participants and personnel
  - Low risk of bias if participants and personnel were adequately blinded.

- High risk of bias if participants were not blinded to the intervention that the participant received.
- Unclear risk of bias if this was not reported or unclear.

- Blinding of outcomes assessors
  - Low risk of bias if outcome assessors were adequately blinded.
  - High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
  - Unclear risk of bias if this was not reported or is unclear.
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
  - Low risk of bias, e.g. if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
  - High risk of bias, e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
  - Unclear risk of bias, e.g. if loss to follow-up was not reported.
- Selective reporting of outcomes
  - Low risk of bias, e.g. review reports all outcomes specified in the protocol.
  - High risk of bias, e.g. it is suspected that outcomes have been selectively reported in the study.
  - Unclear risk of bias, e.g. it is unclear whether outcomes have been selectively reported.

- Other bias

i) Low risk of bias, e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound.

ii) High risk of bias, e.g. the review authors suspect that the trial was prone to an additional bias.

iii) Unclear risk of bias, e.g. the review authors are uncertain whether an additional bias may have been present.

CONTRIBUTIONS OF AUTHORS

Apiwat Aue-aungkul: conceived the review question, and developed, co-ordinated and completed the protocol

Chumnan Kietpeerakool: conceived the review question, and developed and completed the protocol

Khadra Galaal: conceived the review question, and developed and completed the protocol

Teerayut Temtanakitpaisan: completed the protocol

Chetta Ngamjarus: had an editing and advisory role

Pisake Lumbiganon: co-ordinated the development of the protocol and had an editing and advisory role

DECLARATIONS OF INTEREST

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