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Lymphadenectomy for the management of endometrial cancer (Review)

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[Intervention Review]

Lymphadenectomy for the management of endometrial cancer

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ABSTRACT

Background

This is an update of a previous Cochrane review published in Issue 1, 2010 and updated in Issue 9, 2015. The role of lymphadenectomy in surgical management of endometrial cancer remains controversial. Lymph node metastases can be found in approximately 10% of women who before surgery are thought to have cancer confined to the womb. Removal of all pelvic and para-aortic lymph nodes (lymphadenectomy) at initial surgery has been widely advocated, and pelvic and para-aortic lymphadenectomy remains part of the FIGO (International Federation of Gynaecology and Obstetrics) staging system for endometrial cancer. This recommendation is based on data from studies that suggested improvement in survival following pelvic and para-aortic lymphadenectomy. However, these studies were not randomised controlled trials (RCTs), and treatment of pelvic lymph nodes may not confer a direct therapeutic benefit, other than allocating women to poorer prognosis groups. Furthermore, the Cochrane review and meta-analysis of RCTs of routine adjuvant radiotherapy to treat possible lymph node metastases in women with early-stage endometrial cancer found no survival advantage. Surgical removal of pelvic and para-aortic lymph nodes has serious potential short-term and long-term sequelae. Therefore, it is important to investigate the clinical value of this treatment.

Objectives

To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase to June 2009 for the original review, updated the search to June 2015 for the last updated version and further extended the search to March 2017 for this version of the review. We also searched registers of clinical trials, abstracts of scientific meetings, and reference lists of included studies, and we contacted experts in the field.

Selection criteria

RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias. Hazard ratios (HRs) for overall and progression-free survival and risk ratios (RRs) comparing adverse events in women who received lymphadenectomy versus those with no lymphadenectomy were pooled in random-effects meta-analyses. We assessed the quality of the evidence using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.

Main results

978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria; for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting.

Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence).

We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation, respectively) (1922 participants, two studies; high-quality evidence).

Authors' conclusions

This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.

PLAIN LANGUAGE SUMMARY

The role of removing lymph nodes as part of standard surgery for endometrial cancer

The issue

Cancer of the lining of the womb (endometrial cancer) is now the most common gynaecological cancer among women in western Europe and North America. Most of these women (75%) have tumours confined to the body of the womb at the time of diagnosis, and three-quarters of women will survive for 10 years after diagnosis. Lymph node metastases can be found in one in 10 women who appear to have cancer confined to the womb at the time of diagnosis, and removal of all pelvic and para-aortic lymph nodes has been advocated, even for women with presumed early-stage cancer. This recommendation is based on non-randomised studies that suggested improvement in survival following removal of pelvic and para-aortic lymph nodes. However, treatment of pelvic lymph nodes may not be beneficial, and additional treatment to lymph nodes might not necessarily be better treatment, especially as surgical removal of lymph nodes has serious potential short-term and long-term harmful effects.

The aim of the review

To evaluate the safety and efficacy of lymphadenectomy in the management of endometrial cancer.

What are the main findings?

We found only three trials that compared lymphadenectomy with no lymphadenectomy among women with endometrial cancer. One of these trials could not be included in the meta-analysis of this review, as it provided insufficient information about outcomes for women. When we combined findings from the two remaining trials, which included 1945 women, we found no evidence that women

who received lymphadenectomy were less likely to die or have a relapse of their cancer. In addition, severe adverse events experienced as a consequence of lymphadenectomy outnumbered those reported when no lymphadenectomy was performed.

Quality of the evidence

The overall quality of the evidence for lymphadenectomy versus standard surgery was moderate for survival outcomes and adverse events (other than evidence for presence or absence of lymphoedema or lymphocyst, which was of high quality). The quality of evidence for quality of life was very low, as this outcome was not reported.

What are the conclusions?

The uncertainty of whether lymphadenectomy or no lymphadenectomy is best in the management of early-stage endometrial cancer probably reflects the fact that evidence shows no reduction in death or in disease relapse when lymphadenectomy is performed, rather than lack of evidence. In addition, women undergoing lymphadenectomy experienced more severe adverse events than those who did not undergo lymphadenectomy.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Lymphadenectomy for the management of endometrial cancer						
Patient or population: women with stage I endometrial cancer Settings: inpatient or outpatient Intervention: lymphadenectomy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lymphadenectomy				
Overall survival Follow-up: median 37 to 49 months ^a			HR 1.07 (0.81 to 1.43)	1851 (2 studies)	⊕⊕⊕○ Moderate^b	As a result of the way HRs are calculated, assumed and corresponding risks were not estimated
Recurrence-free survival Follow-up: median 37 to 49 months ^a			HR 1.23 (0.96 to 1.58)	1851 (2 studies)	⊕⊕⊕○ Moderate^b	As a result of the way HRs are calculated, assumed and corresponding risks were not estimated
Direct surgical morbidity	Study population		RR 1.93 (0.79 to 4.71)	1922 (2 studies)	⊕⊕⊕○ Moderate^b	
	17 per 1000	33 per 1000 (13 to 80)				
	Moderate-risk population					

	19 per 1000	37 per 1000 (15 to 89)			
Surgery-related systemic morbidity	Study population		RR 3.72 (1.04 to 13.27)	1922 (2 studies)	⊕⊕⊕○ Moderate^b
	3 per 1000	11 per 1000 (3 to 40)			
	Moderate-risk population				
	5 per 1000	19 per 1000 (5 to 66)			
Lymphoedema or lymphocyst	Study population		RR 8.39 (4.06 to 17.33)	1922 (2 studies)	⊕⊕⊕⊕ High
	8 per 1000	67 per 1000 (32 to 139)			
	Moderate-risk population				
	11 per 1000	92 per 1000 (45 to 191)			

* The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio.

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.

^aMedian follow-up was 37 months (interquartile range (IQR) 24 to 58 months) in the Kitchener trial and 49 months (IQR 27 to 79 months) in the trial of Panici.

^bEstimate is imprecise, as a fair degree of uncertainty can be seen in the pooled estimate, as indicated by a 95% confidence interval.

BACKGROUND

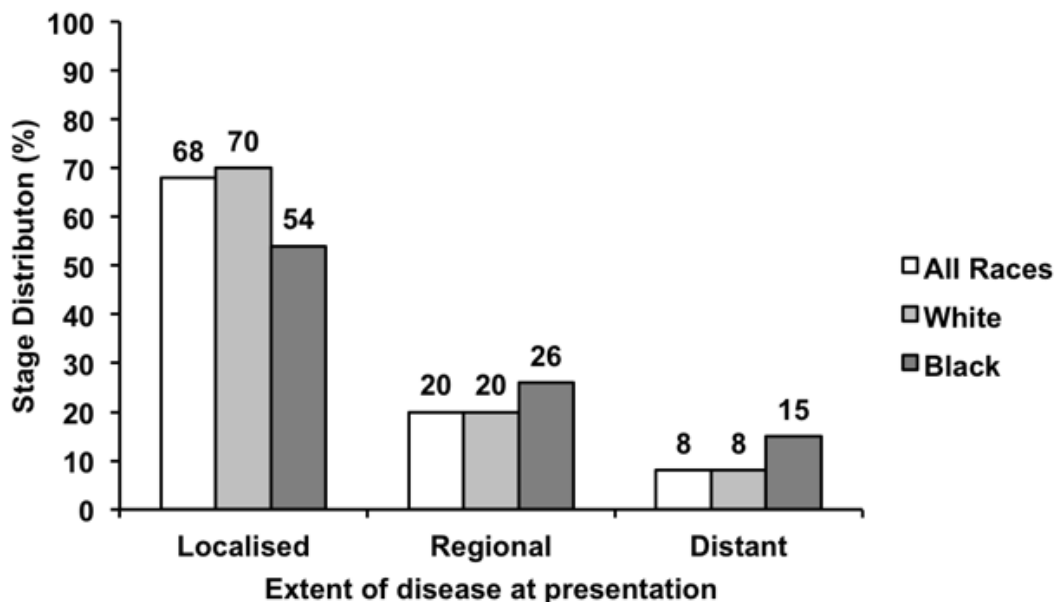
Description of the condition

Endometrial cancer affects the lining of the womb and is the fifth most common cancer among women worldwide (Ferlay 2012). The disease occurs predominantly in postmenopausal women (91% of cases are reported in women over 50 years old) (Parkin 2005). Global incidences vary as a result of differences in risk factors, with higher risk associated with a 'western' lifestyle; the age-standardised incidence is 14.7 per 100,000 women per year in more developed countries, compared with 5.5 per 100,000 per year in less developed countries (Ferlay 2012). One of the main risk factors for endometrial cancer is unopposed oestrogen, which may come from exogenous (from outside of the body) sources, such as oestrogen-only hormone replacement therapy (HRT), or endogenous (from within the body) overproduction, as is seen

with polycystic ovarian syndrome, oestrogen-producing tumours and excessive adipose tissue in obese women (Park 2010; Renehan 2008).

Most women present with symptoms of abnormal vaginal bleeding. This typically is reported as postmenopausal bleeding, as most cases occur in those over the age of 50, although younger women may present with intermenstrual bleeding, menorrhagia (heavy periods), or a change in bleeding pattern, and in those over 45 years, changes in menstruation should be investigated (NICE 2007). Less common symptoms include low pelvic pain and vaginal discharge. Most women (75% to 80%) with postmenopausal bleeding present with early-stage disease (International Federation of Gynaecology and Obstetrics (FIGO) stage I), in which the disease is confined to the womb (Shepherd 1989 - Table 1), (Siegel 2015 - Figure 1). It should be noted that FIGO staging was changed in 2009, following publication of the main studies included in this analysis (Pecorelli 2009 - Table 2). The 2009 staging system will be used in this review, unless otherwise stated.

Figure 1. Distribution of stage of endometrial cancer at presentation, USA 2004-2010. Adapted from Siegel 2015.



Histologically most endometrial cancers are endometrioid adenocarcinomas. Other histological subtypes tend to have a poorer prognosis, as they typically are more aggressive (high grade = G3) and present at a more advanced FIGO stage. These include

adenosquamous, clear cell and serous carcinomas.

Endometrial cancer directly invades surrounding tissues, most commonly the myometrium and the cervix. Lymphatic spread

also occurs, primarily to the pelvic lymph nodes, including external and common iliac lymph nodes, and then to the para-aortic lymph nodes. Results of histopathological studies have demonstrated spread to pelvic and para-aortic lymph nodes in up to 10% of cases of early-stage disease (Creasman 1987). Metastasis to more distant organs is typically haematological.

Description of the intervention

Standard treatment for early-stage endometrial cancer consists of total hysterectomy, bilateral salpingo-oophorectomy (BSO) and washings. This may be performed via a laparotomy or by a laparoscopic approach. For patients with risk factors for spread beyond the womb, adjuvant radiotherapy (and increasingly chemotherapy) is administered to reduce the risk of recurrence.

Randomised controlled trials (RCTs) have demonstrated that adjuvant radiotherapy does not improve overall survival in early-stage disease (FIGO stage I without G3 disease or without evidence of invasion into the lymphovascular space), although it does reduce the number of pelvic recurrences (Kong 2012). Reducing the number of pelvic recurrences does not affect survival rates, probably because pelvic recurrences usually can be treated effectively with radiotherapy in women who have not previously received pelvic radiotherapy.

Lymphadenectomy can be considered as clearance of all lymph nodes or sampling of a few lymph nodes from an anatomical area. Lymphadenectomy is used to drain the site of cancer when cancers have spread to the lymph nodes, for example, in breast cancer surgery. Lymphadenectomy often refers to the systematic removal of all lymph nodes within a defined area, as opposed to lymph node sampling, which refers to removal of a few representative lymph nodes or removal of suspiciously enlarged nodes. Use of sentinel lymph node biopsy in the management of endometrial carcinoma is a topic of increasing interest, and studies assessing the diagnostic accuracy of this procedure have yielded promising results (Ansari 2013; Kang 2011).

How the intervention might work

Knowledge of cancer spread gives prognostic information and guides the decision to provide adjuvant treatment in the form of radiotherapy and chemotherapy. Lymphadenectomy can be directly therapeutic, as surgery removes involved lymph nodes, which may be the source of pelvic recurrences. However, lymph node involvement is rare if the tumour is of low grade (G1) or is confined to the inner half of the myometrium (FIGO stage IA). Hence, surgical staging involving a lymphadenectomy may be recommended only for women who are at increased risk of pelvic lymph node involvement (e.g. those with higher-grade tumours identified by biopsy) (Kim 1993).

Nevertheless, lymphadenectomy is not performed without serious short-term and long-term morbidity. Many women with endometrial cancer are elderly or obese and have serious comorbidities, and the increase in operative time required to perform a full

lymphadenectomy may increase risks of surgery and anaesthesia. Complications associated with lymphadenectomy include damage to blood vessels and nerves during the operation; development of a deep vein thrombosis or pulmonary embolus during the postoperative period; and lymphoedema and/or pelvic lymphocyst formation. These complications can be severe and disabling, and lymphoedema and lymphocyst formation may be under-reported or under-recognised, especially in studies focusing on short-term outcomes.

Why it is important to do this review

Debate is ongoing regarding lymphadenectomy for the treatment of endometrial cancer. Lymphadenectomy may not be routinely performed, and if it is, the extent of lymphadenectomy can range from taking a few lymph nodes for sampling to performing complete pelvic and para-aortic lymphadenectomy.

The extent of disease, as assessed by preoperative imaging (such as magnetic resonance imaging (MRI)) and the grade of tumour as identified through biopsies, may influence the decision whether to undertake lymphadenectomy. The ongoing MAPPING study aims to determine whether MRI, diffusion-weighted MRI, fluorodeoxyglucose positron emission tomography (FDGPET)/computed tomography (CT) and fluoro-ethyl-choline PET/CT can identify lymph node metastasis and facilitate minimally invasive or non-invasive lymph node staging (ISRCTN84527805). Results of this study may further influence the decision to perform lymphadenectomy.

Evidence from one retrospective, non-randomised study suggested that multiple-site lymph node sampling may increase survival over procedures that do not include lymph node sampling (Kilgore 1995). In this retrospective review of 649 participants with endometrial cancer, women who underwent multiple-site lymph node sampling had improved five-year survival (extrapolated from survival curves) compared with women who underwent no pelvic node sampling (five-year survival ~90% vs ~75%; $P = 0.002$). Furthermore, one study found that patients who undergo extensive lymph node sampling may have increased survival as compared with those who have fewer lymph nodes removed (Chan 2006). This retrospective analysis of 12,333 participants with endometrioid endometrial cancer demonstrated that participants with high-risk disease (pre-2009 FIGO stage IB, grade 3 or greater) appeared to have improved five-year survival rates following extensive lymph node removal (75.3% with one node removed vs 86.8% with 20 or more nodes removed; $P = 0.001$). Another large, population-based study of 9185 women with stage I and 881 women with stage II endometrial cancer compared outcomes stratified by whether lymph node sampling had been performed (Trimble 1998). Overall investigators reported no significant differences in five-year survival for women with stage I and II disease who did or did not undergo lymph node sampling. In contrast, a retrospective study of 671 women with endometrial cancer demonstrated improve-

ment in overall survival for those at intermediate or high risk of disease recurrence among women who had undergone para-aortic lymphadenectomy in addition to pelvic lymphadenectomy compared with women treated with pelvic lymphadenectomy alone (hazard ratio (HR) 0.44, 95% confidence interval (CI) 0.30 to 0.64) (Todo 2010).

However, lymphadenectomy, similar to pelvic radiotherapy (Kong 2012), is not beneficial for most women with endometrial cancer, as most are unlikely to have lymph node involvement. Therefore, the additional surgery would make no difference to their chance of cure or need for further treatment and would benefit only a minority of women to the detriment of the majority, who would be cured by hysterectomy and BSO alone. The previous version of this review did not demonstrate that lymphadenectomy improved survival or reduced disease recurrence compared with no lymphadenectomy in women with presumed stage I disease (May 2010). However, knowledge of lymph node status does provide prognostic information and may reduce the need for adjuvant radiotherapy in women found to have negative lymph nodes (Look 2004).

As these data demonstrate, clinical controversy surrounds the role of lymphadenectomy in endometrial cancer. This procedure carries significant long-term morbidity for a large minority of patients and should be performed only if good evidence demonstrating improvements in survival and quality of life (QOL) supports its use.

This review aimed to address the value of lymphadenectomy in endometrial cancer. This included the effects of routine removal of all pelvic lymph nodes (pelvic lymphadenectomy) and effects of routine removal of para-aortic lymph nodes. This review also assessed evidence for the value of removing clinically suspicious (enlarged) lymph nodes.

OBJECTIVES

To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.

METHODS

Criteria for considering studies for this review

Types of studies

- RCTs and quasi-RCTs. We excluded cross-over trials and cluster-randomised trials.

Types of participants

Adult women diagnosed with endometrial cancer. We excluded women with other concurrent malignancies.

Types of interventions

We included the following comparisons.

- Pelvic lymphadenectomy versus no lymphadenectomy.
- Pelvic lymphadenectomy versus pelvic lymph node sampling.
- Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy.
- Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy.
- Removal of bulky pelvic lymph nodes versus no removal of lymph nodes.

Types of outcome measures

Primary outcomes

- Overall survival (OS).

Secondary outcomes

- Progression-free survival (PFS).
- QOL measured by a validated scale.
- Adverse events, for example,
 - direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection);
 - surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism), cardiac events (cardiac ischaemia and cardiac failure), cerebrovascular accident;
 - recovery: delayed discharge, unscheduled re-admission;
 - lymphoedema and lymphocyst formation; and
 - other side effects not categorised above.

Search methods for identification of studies

Electronic searches

See the [Cochrane Gynaecological Cancer Group](#) methods used in reviews.

We searched the following electronic databases.

Original review - 2010

- Cochrane Central Register of Controlled Trials (CENTRAL; 2009, Issue 2).
- MEDLINE - 1966 to June 2009.
- Embase - 1966 to June 2009.

Updated review - 2015

- Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3).
- MEDLINE - June 2009 to June 2015.
- Embase - June 2009 to June 2015.

Updated review - 2017

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 3).
- MEDLINE - June 2015 to March 2017.
- Embase - June 2015 to March 2017.

We developed a search strategy based on terms related to the review topic (for CENTRAL, MEDLINE and EMBASE search strategies, see [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#)). All relevant articles found were identified on PubMed, and, using the 'related articles' feature, we carried out a further search for newly published articles.

Searching other resources

Unpublished and grey literature

We searched metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials. We contacted the main investigators of relevant ongoing trials, along with the major co-operative trials groups active in this area, to ask for further information..

Handsearching

We handsearched the reference lists of all relevant trials obtained by this search to look for further trials.

Correspondence

We contacted authors of relevant trials to ask if they knew of additional data that may or may not have been published.

Language

We sought papers in all languages and carried out translations when necessary.

Data collection and analysis

Selection of studies

Original review - 2010

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database Endnote and removed duplicates. At least two review authors (a combination of KW, JM, and AB) independently examined the remaining references. We excluded studies that clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (JM and KW) independently assessed the eligibility of retrieved papers and resolved disagreements by discussion between them and, if necessary, with a third review author (AB). We documented reasons for exclusion.

Updated review - 2015

We downloaded all titles and abstracts retrieved by electronic searching to the reference management databases Endnote and Mendeley and removed duplicates. At least two review authors (of KW, JF, and JM) independently examined the remaining references. We excluded studies that clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (KW and JF) independently assessed the eligibility of retrieved papers and, when necessary, requested additional information from study authors. These two review authors resolved disagreements by discussion between them and, if necessary, with a third review author (JM). We documented reasons for exclusion.

Update review - 2017

We downloaded all titles and abstracts (**MEDLINE**: June 2015 to March week 4 2017 - 61 refs; **Embase**: June 2015 to 2017 week 13 - 135 refs; **Central**: Issue 3 of 12 2017 - 54 refs) to the RCT classifier for de-duplication and identification of possible RCTs. 76 unique references were identified and 20 were identified as possible clinical trials by the classifier. These 76 references were uploaded to [Covidence](#) and the 20 potential clinical trials screened independently by two reviewers (JM and JF). There were no disagreements and no additional studies were identified.

Data extraction and management

We extracted data from the included studies as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). These data consisted of characteristics of participants (inclusion criteria, age, stage, comorbidity, previous treatment, number enrolled in each arm), interventions (extent

of lymphadenectomy, number of lymph nodes removed, use of radiotherapy or chemotherapy), study quality, duration of follow-up, outcomes, any variables used to adjust HRs, and deviations from the protocol. Two review authors (a combination of JM, KW and JF) independently extracted data. When possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis. Review authors resolved differences by discussion or by appeal to a third review author (JM), if necessary.

Assessment of risk of bias in included studies

We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (assessment of blinding was restricted to blinding of outcome assessors, as generally it is not possible to blind participants and personnel to surgical interventions);
- incomplete outcome data;
- selective reporting of outcomes; and
- other possible sources of bias.

Two review authors (KW and JF) independently applied the 'risk of bias' tool and resolved differences by discussion or by appeal to a third review author (JM). We have presented results in the 'risk of bias' table, the 'risk of bias' graph and the 'risk of bias' summary section. We interpreted results of meta-analyses in the light of the 'risk of bias' assessment.

Measures of treatment effect

- For time-to-event data (overall survival, progression-free survival), we extracted the HR and its variance from trial reports; if these were not presented, we would have attempted to abstract the data required to estimate them using Parmar's methods (Parmar 1998) (e.g. number of events in each arm and log-rank P value comparing relevant outcomes in each arm, or relevant data from Kaplan-Meier survival curves).

- For dichotomous outcomes (adverse events), we extracted the number of participants in each treatment arm who experienced the outcome of interest to estimate a risk ratio (RR).

We also extracted the number of participants assessed at endpoint.

Dealing with missing data

We attempted to extract data on outcomes only for participants who were assessed at endpoint. We did not impute missing outcome data; if only imputed outcome data were reported, we contacted trial authors to request data on outcomes only among participants who were assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this.

Assessment of reporting biases

We were unable to assess reporting bias, as only three studies met our inclusion criteria.

Data synthesis

We pooled the findings of two of the three included trials in meta-analyses.

- For time-to-event data (overall survival and progression-free survival), we pooled HRs using the generic inverse variance facility of RevMan 5. We used adjusted HRs, if available; otherwise we used unadjusted results.

- For dichotomous outcomes (adverse events), we pooled RRs.

We used random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

We have presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We have created a 'Summary of findings' table based on the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and GRADEpro GDT. We used the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We downgraded the evidence from 'high' quality by one level for serious (or by two for very serious) concerns for each limitation.

Subgroup analysis and investigation of heterogeneity

We performed no subgroup analyses, as only three trials met our inclusion criteria. The two trials included in the meta-analysis showed no heterogeneity ($I^2 = 0$).

Sensitivity analysis

We performed no sensitivity analyses, as both of the studies included in the analysis were at low risk of bias.

'Summary of findings' table

Original review - 2010

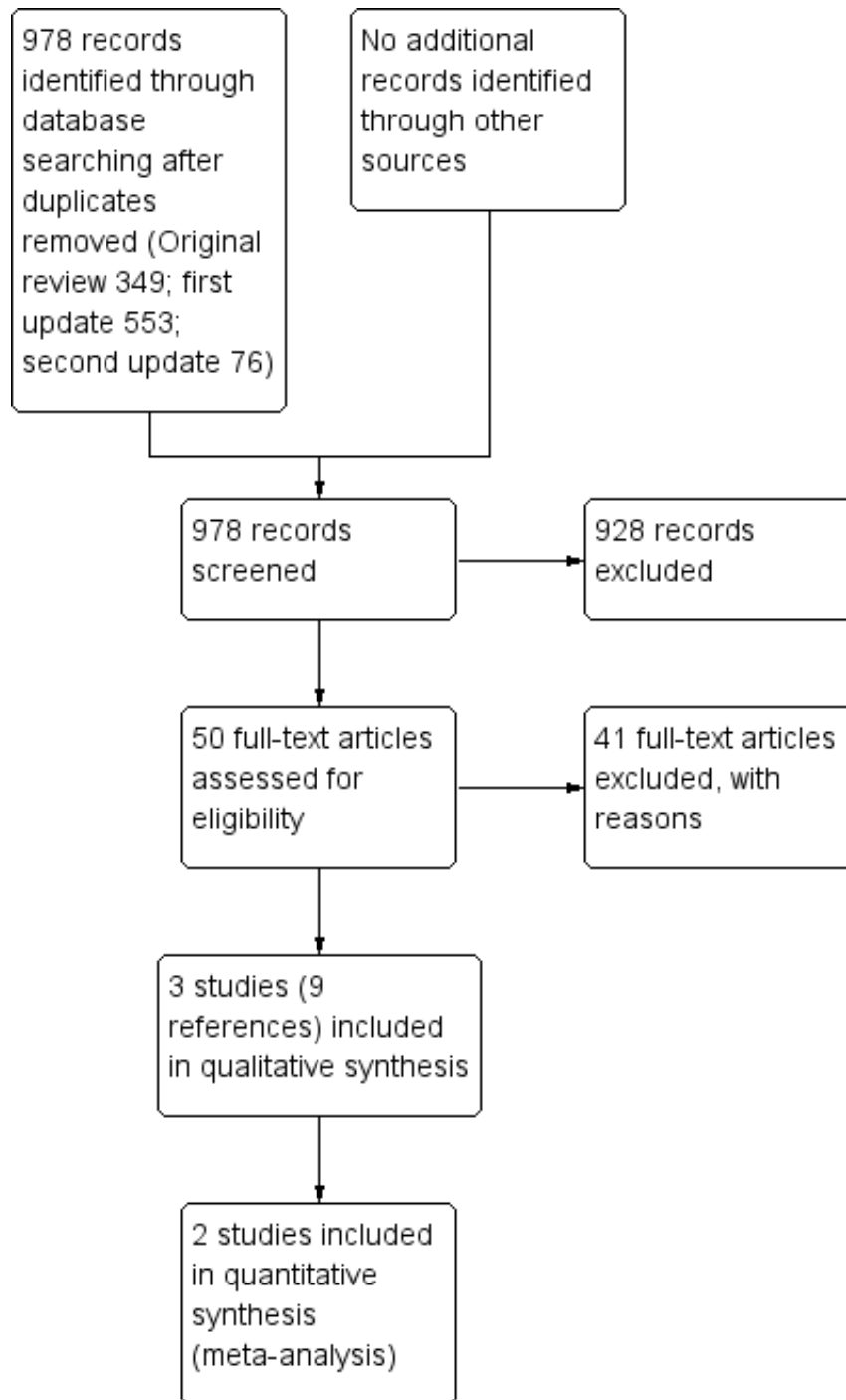
RESULTS

Description of studies

Results of the search

The search yielded 349 unique references. Three review authors independently read the abstracts of these articles and at this stage excluded articles that obviously did not meet the inclusion criteria. We retrieved 18 articles in full text and translated them into English, when appropriate; we identified updated versions of relevant studies. Through full-text screening of these 18 studies, we excluded 11 trials. However, we identified two completed RCTs that met our inclusion criteria and five references that provided preliminary results of the two included studies. See [Figure 2](#) for a study flow diagram.

Figure 2. Study flow diagram.



Updated review - 2015

The search yielded 553 additional unique references. At least two review authors (of KW, JF and JM) independently read the abstracts of these articles and excluded 521 articles that obviously did not meet the inclusion criteria. We retrieved 32 articles in full and subjected them to full-text screening. We subsequently excluded 30 of these. One additional RCT met the inclusion criteria, and one article provided additional data from a previously included RCT.

Searches of the grey literature revealed no additional relevant studies.

Therefore, in this updated version of the review, we excluded 41 of the articles reviewed in full text for the reasons given in the [Characteristics of excluded studies](#) table and included nine articles reporting results from three RCTs, as described in the [Characteristics of included studies](#) table.

Updated review - 2017

The search yielded 76 additional unique references. On screening, all articles were excluded and no articles were retrieved in full text.

Included studies

Three studies met the inclusion criteria ([Fayallah 2011](#); [Kitchener 2009](#); [Panici 2008](#)). One of these was a small RCT of 38 participants ([Fayallah 2011](#)) designed to assess the role of pretreatment detection of P53 overexpression in the selection of women with clinical stage I disease for pelvic lymphadenectomy. We excluded this study from the meta-analysis, as it was not possible to estimate hazard or risk ratios for the outcomes of interest in this review using the data provided. We contacted authors of the [Fayallah 2011](#) study via their published contact details to ask for additional information, but none has been forthcoming. We also contacted the publishers of the [Fayallah 2011](#) study to ask for further information, but we have received no response.

The two remaining included trials ([Kitchener 2009](#); [Panici 2008](#)) randomly assigned 1945 women, of whom 1923 (99%) were assessed at the end of the trial and 1851 (95%) were assessed in multivariate survival analyses using Cox models.

[Kitchener 2009](#) reported 191 (13.6%) deaths and 173 (12.3%) disease recurrences; [Panici 2008](#) reported 53 (10.3%) deaths and 78 (15.1%) disease recurrences; [Kitchener 2009](#) reported 38 (2.7%) instances of direct surgical morbidity, seven (0.5%) cases of surgery-related systemic morbidity, 12 (0.9%) cases of lymphoedema and 26 (1.8%) cases of lymphoedema; [Panici 2008](#) reported 13 (2.5%) instances of direct surgical morbidity, eight

(1.6%) cases of surgery-related systemic morbidity and 39 (7.6%) cases of lymphoedema/lymphocyst formation.

[Fayallah 2011](#) randomly assigned 38 women and reported four (10.5%) deaths; seven (18.4%) disease recurrences; five (13.2%) instances of direct surgical morbidity, one (2.6%) case of surgery-related systemic morbidity and one (2.6%) case of lymphorrhoea.

The Kitchener 2009 trial (ASTECC)

Design

Between 1998 and 2005, 1408 women with preoperative endometrial cancer thought clinically to be confined to the uterus (womb) (pre-2009 FIGO stage I) from 85 centres in four countries were randomly assigned preoperatively to standard surgery (n = 704) (total hysterectomy, bilateral salpingo-oophorectomy and palpation of para-aortic lymph nodes) or standard surgery plus systematic pelvic lymphadenectomy (n = 704) (iliac and obturator lymph nodes). Women with enlarged lymph nodes in the standard surgery arm could have these removed at the discretion of the surgeon. All operations were performed by specialist gynaecological surgeons with experience in pelvic lymphadenectomy, and the operation was performed by the same surgeon, regardless of to which arm the participant was randomly assigned. After surgery, women with early-stage disease at intermediate or high risk of recurrence were randomly assigned (independent of lymph node status) to the ASTECC radiotherapy trial, to control for adjuvant treatment.

Participants

Women were well matched between the two arms in terms of clinico-pathological features, although slightly more poor prognosis histopathological types were assigned to the lymphadenectomy arm (clear cell 10 (1%) versus 17 (2%); serous 21 (3%) versus 32 (5%)). In the lymphadenectomy arm, 58 (8%) women had no nodes removed for reasons including anaesthetic concerns, obesity, obvious late-stage disease or participant request. For those in the lymphadenectomy arm who did undergo lymphadenectomy, a median of 12 nodes (range one to 59) were removed. Thirty-five (5%) women in the standard surgery arm underwent lymph node sampling with removal of a median of two nodes (range one to 27). Lymph nodes were invaded by cancerous cells in nine participants in the standard surgery arm (27% of the 35 women who had suspicious nodes removed at the time of surgery) and in 54 (9%) of the 686 women in the lymphadenectomy arm who had lymph nodes removed.

Interventions

This study pre-dated routine use of laparoscopic surgery, and most study participants underwent open surgery. Median operating time was shorter in the standard surgery group: 60 minutes (10 to 255) for standard surgery and 90 minutes (10 to 390) for lymphadenectomy. Median hospital stay was six days (range two to 120 days) for standard surgery and six days (range two to 106 days) for lymphadenectomy. Women in the lymphadenectomy arm were more likely to have a vertical than a transverse (Pfannenstiel) abdominal incision (287 (45%) vertical incisions for standard surgery versus 384 (60%) vertical incisions for lymphadenectomy).

One-third of women in each group received adjuvant radiotherapy (standard surgery 227 (33%); lymphadenectomy 228 (33%)), and similar numbers received external beam radiotherapy plus vault brachytherapy (173 (25%) versus 165 (23%)) or brachytherapy only (54 (8%) versus 63 (9%)).

Median follow-up was 37 months (interquartile range (IQR) 24 to 58 months).

The Panici 2008 trial

Design

Over 9½ years, 514 participants with endometrial cancer clinically confined to the uterus preoperatively (pre-2009 FIGO stage I) from 31 centres (30 in Italy and 1 in Chile) were randomly assigned to undergo pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250). All eligible women had frozen section performed on the uterus to confirm the presence of endometrioid or adenosquamous carcinoma and grade of disease, and to evaluate the depth of myometrial invasion. Women without myometrial invasion (pre-2009 FIGO stage IA) and those with a well-differentiated tumour and less than 50% myometrial invasion (G1, pre-2009 FIGO stage IB) were excluded. All other women were randomly assigned intraoperatively to one of the two trial arms by a block arrangement that balanced treatment assignments at each site. Women randomly assigned to the pelvic lymphadenectomy arm had lymphatic tissue removed from the external iliac, superficial and common iliac regions. Dissection was considered appropriate only if 20 or more lymph nodes were removed for histopathological examination. Para-aortic node sampling or lymphadenectomy was performed at the discretion of the surgeon. In the no-lymphadenectomy group, no lymphatic tissue in the retroperitoneal region was removed other than bulky (> 1 cm) lymph nodes detected at gross intraoperative inspection by palpation of lymph node sites.

Participants

Women were well matched between the two arms in terms of clinico-pathological features, except for a higher proportion of

pre-2009 FIGO stage IIIC participants in the lymphadenectomy arm, following examination of lymph node status. All women allocated to the lymphadenectomy arm underwent lymphadenectomy, with a median of 26 pelvic lymph nodes removed (range 21 to 35). In the no-lymphadenectomy arm, 56 (22%) women had enlarged lymph nodes and underwent pelvic lymph node sampling or lymphadenectomy: 28 (11%) had more than 10 lymph nodes removed. Of these 56 women with bulky lymph nodes, only eight (15% of those who had lymph nodes removed) had positive lymph nodes on histological examination. Aortic lymphadenectomy was performed in 69 (26%) of the 264 women in the lymphadenectomy arm and in five (2%) of the 250 women in the no lymphadenectomy arm.

Interventions

Median operating time (180 minutes versus 120 minutes, $P < 0.001$) and hospital in-patient stay (6 days versus 5 days; P value < 0.001) were greater in the lymphadenectomy arm than in the no lymphadenectomy arm.

Rates of adjuvant therapy (pelvic external beam, brachytherapy, chemotherapy, or combination of chemotherapy and radiotherapy) were similar between the two arms. Most participants received no adjuvant therapy (69% in the lymphadenectomy arm and 65% in the no-lymphadenectomy arm; $P = 0.07$).

Median follow-up was 49 months (IQR 27 to 79 months).

The Fayallah 2011 trial

Design

Between April 2005 and October 2008, 38 women with preoperative clinical stage I endometrial carcinoma from a single hospital were preoperatively randomly assigned to extrafascial hysterectomy, bilateral salpingo-oophorectomy with pelvic lymphadenectomy (n = 21) (iliac and obturator lymph nodes) or extrafascial hysterectomy and bilateral salpingo-oophorectomy alone (n = 17). Before surgery, immunohistochemistry was carried out on endometrial tissue for detection of P53 over-expression. After surgery, the decision to provide adjuvant radiotherapy was made at the discretion of tumour board meeting members. Women were followed up every three months with clinical assessment and ultrasound and underwent MRI every six months.

Participants

No significant difference was noted between the two arms in terms of age, medical status, surgical stage, histological type, or grade of tumour. The number of nodes removed from women in either arm was not reported.

Interventions

Operating time, route of surgery, and use of adjuvant therapy were not reported in the trial.

Mean follow-up after treatment was 21.5 months (range six to 40 months).

Outcomes reported

Both the [Panici 2008](#) trial and the [Kitchener 2009](#) trial reported overall and recurrence-free survival rates and used appropriate statistical techniques (HRs to correctly allow for censoring). Investigators adjusted for prognostic factors in the analysis of survival outcomes in each trial.

The [Fayallah 2011](#) trial reported survival rate and recurrence rate as percentages based on participants who were known to have died or were known to experience disease progression. Hazard ratios and risk ratios were not reported and could not be estimated from available data. Study authors provided no additional data.

In the trial of [Kitchener 2009](#), investigators adjusted HR for age (continuous), World Health Organization (WHO) performance status (0, 1, 2, 3, or 4), weeks between diagnosis and randomisation (six weeks or longer vs less than six weeks), surgical technique intended (open vs laparoscopic), type of incision (vertical vs Pfannenstiel vs other transverse), extent of tumour (confined vs spread), histology (endometrioid/adenocarcinoma vs other), depth of invasion (inner half vs endometrium, outer half vs endometrium), differentiation (grade 1, 2, or 3) and centre (dummy variables and centres with fewer than five women were grouped as one new centre). Seventy-one women were not included (37 standard surgery group, 34 lymphadenectomy group): 39 with no disease and 32 with differentiation not applicable (histology mixed epithelial stromal sarcoma).

In the trial of [Panici 2008](#), researchers adjusted the HR for age (65 or older, younger than 65 years), tumour grade (grade 1, 2 or 3), myometrial invasion (50% or more, less than 50%) and tumour

stage (stage I to II, stage III to IV).

A secondary analysis from the [Panici 2008](#) trial assessed survival in women who underwent lymphadenectomy compared with those who did not undergo lymphadenectomy in relation to age (older than 65 years and 65 years or younger).

For distribution of these factors at baseline in each trial by treatment arm, see the [Characteristics of included studies](#) table.

The two trials included in the analysis reported adverse events (direct surgical morbidity, surgery-related systemic morbidity, and lymphoedema or lymphocyst formation).

Excluded studies

After obtaining the full text, we excluded 41 articles for the following reasons.

- 21 studies were non-RCTs, including retrospective reviews, in which results were compared between women who underwent systematic lymphadenectomy and those who did not.
- 11 articles were reviews on the role of lymphadenectomy in endometrial cancer; none identified any RCT-level evidence.
- 9 studies were RCTs but provided no outcome information based on randomisation for lymphadenectomy.

For further details on all excluded studies, see the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

The [Panici 2008](#) and [Kitchener 2009](#) trials were at low risk of bias: They satisfied four of the criteria that we used to assess risk of bias (see [Figure 3](#) and [Figure 4](#)). The [Fayallah 2011](#) trial had an overall unclear risk of bias, as adequate information was not available concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. It was likely that the [Fayallah 2011](#) study had high risk of attrition bias, as follow-up of women was limited (see the [Characteristics of included studies](#) table).

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

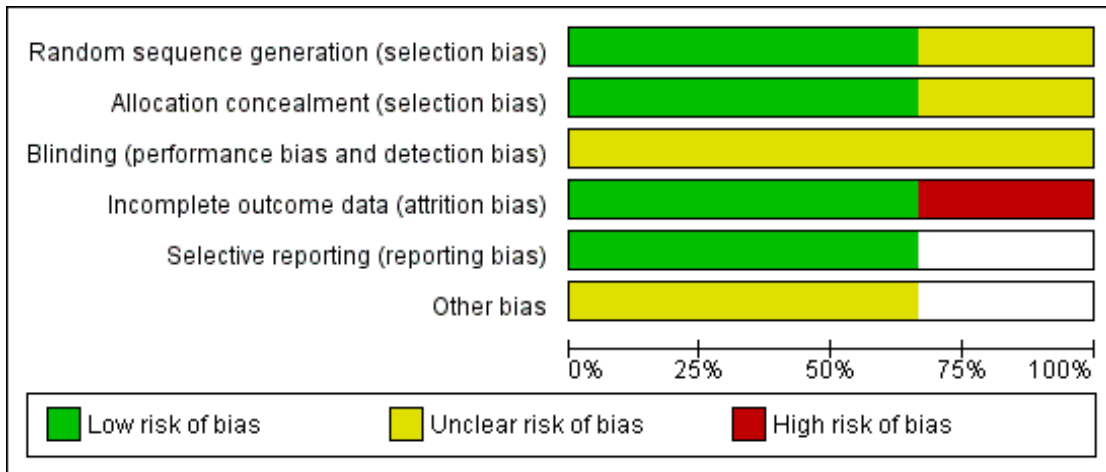


Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fayallah 2011	?	?	?	-		
Kitchener 2009	+	+	?	+	+	?
Panici 2008	+	+	?	+	+	?

The [Panici 2008](#) and [Kitchener 2009](#) trials reported the method of generation of the sequence of random numbers used to allocate women to treatment arms and concealment of this allocation sequence from participants and healthcare professionals involved in the trials. Neither trial reported whether outcome assessors were blinded. It is highly likely that both trials reported all outcomes that they assessed, but it is not clear whether any other bias may have been present. At least 95% of women who were enrolled were assessed at endpoint in both trials.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings table](#)

All meta-analyses pooled data from two trials ([Kitchener 2009](#);

[Panici 2008](#)).

Meta-analyses of survival were based on HRs that were adjusted for prognostic variables.

Overall survival

Meta-analysis, assessing 1851 women, showed no differences in risk of death among women who underwent lymphadenectomy and those who did not undergo lymphadenectomy, after adjustment for important prognostic factors including age and tumour grade (HR 1.07, 95% CI 0.81 to 1.43; [Analysis 1.1](#)). The percentage of variability in effect estimates that was due to heterogeneity rather than to sampling error (chance) was not important ($I^2 = 0\%$). The [Panici 2008](#) study reported no differences in five-year overall survival among women who underwent lymphadenectomy

and those who did not undergo lymphadenectomy in relation to age (HR 1.17, 95% CI 0.56 to 2.46 in those older than 65 years; HR 1.21, 95% CI 0.54 to 2.72 in those 65 years of age or younger), although no adjustment was made for other prognostic factors. The [Fayallah 2011](#) study also reported no differences in overall survival between those who underwent pelvic lymphadenectomy and those who did not.

Recurrence-free survival

Meta-analysis, assessing 1851 women, showed no differences in risk of disease recurrence between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy, after adjustment for important prognostic factors including age and tumour grade (HR 1.23, 95% CI 0.96 to 1.58; [Analysis 1.2](#)). The percentage of variability in effect estimates that was due to heterogeneity rather than to chance was not important ($I^2 = 0\%$).

Adverse events

Direct surgical morbidity

Meta-analysis, assessing 1922 women, showed no differences in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (RR 1.93, 95% CI 0.79 to 4.71; [Analysis 2.1](#)). The percentage of variability in effect estimates that was due to heterogeneity rather than to chance may represent moderate heterogeneity ($I^2 = 50\%$).

Surgery-related systemic morbidity

Meta-analysis of both trials, assessing 1922 women, showed that women given lymphadenectomy had higher risk of surgery-related systemic morbidity than those not given lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; [Analysis 2.3](#)). The percentage of variability in effect estimates that was due to heterogeneity rather than to chance was not important ($I^2 = 0\%$).

Lymphoedema or lymphocyst

Meta-analysis, assessing 1922 women, revealed that women given lymphadenectomy had higher risk of lymphoedema or lymphocyst formation than those not given lymphadenectomy (RR 8.39, 95% CI 4.06 to 17.33; [Analysis 2.2](#)). The percentage of variability in effect estimates that was due to heterogeneity rather than to chance was not important ($I^2 = 0\%$).

DISCUSSION

Summary of main results

We found three studies that met our inclusion criteria, but we were able to include only two of these in the meta-analysis. The two studies included in the analysis ([Kitchener 2009](#); [Panici 2008](#)) enrolled a total of 1945 women. These studies compared lymphadenectomy versus no lymphadenectomy in women with endometrial cancer that was thought on clinical grounds to be confined to the womb.

When we combined the findings from these two studies and adjusted for important prognostic factors, we found that risks of death and disease recurrence were no different among women who underwent lymphadenectomy than among those who did not (hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively). Risk of adverse events was significantly higher in women who underwent lymphadenectomy (lymphoedema and lymphocyst formation; risk ratio (RR) 8.39, 95% CI 4.06 to 17.33).

The two studies included in the meta-analysis had many strengths; HRs correctly allowed for censoring and provided information about adverse events. Both studies recruited a substantial number of women, and investigators observed a reasonably large number of events in the two survival outcomes and in the number of women with lymphoedema. Researchers reported no differences in overall or recurrence-free survival in the two groups of women, but the risk of adverse events was consistently higher among women who underwent lymphadenectomy.

Overall completeness and applicability of evidence

We found no studies that randomly assessed pelvic lymph node sampling, sentinel lymph node biopsy, pelvic and para-aortic lymphadenectomy, or removal of bulky pelvic lymph nodes.

Although we specified quality of life (QOL) as an outcome of interest, none of the trials reported this. QOL after treatment for cancer is an extremely important outcome, as treatment-related morbidity very often degrades the quality of the time that patients continue to live. This is especially important for a condition that has relatively good survival rates.

Surgical treatment of endometrial cancer varies among hospitals, and before the [Panici 2008](#) and [Kitchener 2009](#) studies were published, no clear evidence indicated whether lymphadenectomy has a role in management at early stages of the disease. However, evidence from these RCTs suggests no clear benefit of radical treatment for women with early-stage endometrial cancer.

Additional trials undertaken to assess lymphadenectomy for the management of endometrial cancer may test the robustness of the findings of this review, but evidence from two large included trials suggests that the true effect for the primary outcome (overall survival) may be close to the estimated effect, so it is questionable

whether additional trials are justified in this area. A higher proportion of women appeared to be disease-free in the lymphadenectomy group compared with the control group, but this finding was not statistically significant. Meta-analyses in the review found no differences between lymphadenectomy and standard surgery in risk of death (HR 1.07, 95% CI 0.81 to 1.43; [Analysis 1.1](#)) or disease recurrence (HR 1.23, 95% CI 0.96 to 1.58; [Analysis 1.2](#)), and no differences in direct surgical morbidity (RR 1.93, 95% CI 0.79 to 4.71; [Analysis 2.1](#)), but more women experienced surgery-related systemic morbidity (RR 3.72, 95% CI 1.04 to 13.27; [Analysis 2.3](#)) and lymphoedema or lymphocyst (RR 8.39, 95% CI 4.06 to 17.33; [Analysis 2.2](#)). According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach ([GRADE Working Group 2004](#)), the evidence summarised by this review is potentially adequate, and we are moderately confident in the effect estimates, but they could be substantially different (especially for recurrence-free survival and adverse event outcomes).

Quality of the evidence

Overall, the evidence appears to be of moderate quality ([GRADE Working Group 2004](#)) for all outcomes of comparisons of lymphadenectomy versus control, with the exception of the presence or absence of lymphoedema or lymphocyst, which was graded as high-quality evidence ([Summary of findings for the main comparison](#)). The quality of the evidence for primary outcomes overall and for recurrence-free survival was moderate and was mainly downgraded from high-quality evidence because of concerns regarding the degree of uncertainty in the pooled estimates, as indicated by the 95% confidence intervals and the imprecise estimates. Two trials ([Kitchener 2009](#); [Panici 2008](#)) were at low overall risk of bias, and one trial ([Fayallah 2011](#)) was at unclear risk of bias but contributed no weight to the meta-analyses and main findings of this review.

Both of the studies included in the meta-analysis ([Kitchener 2009](#); [Panici 2008](#)) had low risk of bias for concealment of the randomisation sequence from healthcare providers and participants. Inadequate concealment of allocation is often associated with overestimation of the effects of treatment ([Moher 1998](#); [Schulz 1995](#)). However, blinding of outcome assessors was not reported in either study. Evidence on overall survival therefore is more robust than that for recurrence-free survival, as blinding of outcome assessors is of less relevance for death than for disease progression.

Both trials reported the hazard ratio (HR), which is the best statistic for summarising differences in risk between two treatment groups over the duration of a trial when time to death or disease progression is 'censored' or unknown for some women, as they were still alive (or disease-free) at the end of the trial.

The two studies provided consistent evidence about all outcomes, with the exception of direct surgical morbidity, for which the trial of [Kitchener 2009](#) reported higher risk of direct surgical morbidity

for women who underwent lymphadenectomy than for those who did not, whereas the trial of [Panici 2008](#) found no differences. Both studies randomly assigned women who were thought on clinical evidence to have disease confined to the uterus. However, the timing of randomisation varied: one was randomly assigned preoperatively ([Kitchener 2009](#)), and one following examination of the uterus at the time of surgery ([Panici 2008](#)). Another difference between the two studies was the median number of lymph nodes removed: 12 (range one to 59) in the [Kitchener 2009](#) study and 26 (range 21 to 35) in the [Panici 2008](#) study. However, despite this, five-year disease-free survival rates were similar, and a predefined subgroup analysis within [Kitchener 2009](#) found a trend toward poorer survival when more lymph nodes were removed. One major difference between the studies was that [Kitchener 2009](#) included low-risk early-stage participants (49% of the standard surgery group and 42% of the lymphadenectomy group), who were specifically excluded from [Panici 2008](#), following examination of the uterus by frozen section intraoperatively. However, a predefined subgroup analysis within [Kitchener 2009](#) revealed no evidence of a difference in the relative effect of lymphadenectomy ($P = 0.55$ for overall survival; $P = 0.35$ for recurrence-free survival) when groups were stratified into low-risk early-stage disease, intermediate-risk and high-risk early-stage disease, and advanced disease. From a clinical management perspective, routine use of whole uterine frozen section is not universally available and is resource-intensive; in addition, as the two studies had similar outcomes in their high-risk groups, this is unlikely to have had a major influence on the results.

Both trials permitted removal of suspicious lymph nodes in women allocated to no lymphadenectomy, at the discretion of the surgeon. Relatively small numbers of women in the control groups of each study had lymph nodes removed (35 women in [Kitchener 2009](#); 56 women in [Panici 2008](#)), and this may cause some difficulty in interpretation of study results, but it would reflect clinical practice if lymphadenectomy was not standard treatment in the absence of suspicious lymph nodes.

Quality of life (QOL) was not reported in any of the trials, so we could not assess the quality of the evidence, which was very low for this outcome, but we could not report pertinent adverse events comprehensively.

We are moderately confident in the effect estimates in all analyses, but they could be substantially different (especially for recurrence-free survival and adverse event outcomes).

Potential biases in the review process

We conducted a comprehensive search, including a thorough search of the grey literature, and three review authors independently sifted all studies and extracted data. We restricted included studies to randomised controlled trials (RCTs), as they provide the strongest level of evidence available. Hence, we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias (i.e. studies that did not find the treatment to have been effective may not have been published). We were unable to assess this possibility, as we found only three included studies. However, as none of the studies reported differences between lymphadenectomy and no lymphadenectomy, publication bias seems unlikely.

Agreements and disagreements with other studies or reviews

A pooled HR for overall survival in the [Kitchener 2009](#) and [Panici 2008](#) studies was reported as 1.17 (95% CI 0.91 to 1.50) ([Kitchener 2009a](#)), which differs from the findings of this meta-analysis (HR 1.07, 95% CI 0.81 to 1.43), in which combined data were adjusted for prognostic factors.

Previous studies and reviews have been based on data from non-randomised studies. As discussed, some retrospective studies have demonstrated benefit from pelvic lymphadenectomy ([Chan 2006](#); [Kilgore 1995](#)), whereas other studies have not ([Trimble 1998](#); [Van Lankveld 2006](#)). Similarly, some retrospective studies have demonstrated benefit from pelvic and para-aortic lymphadenectomy compared with pelvic lymphadenectomy alone ([Todo 2010](#)), whilst others have not ([Tong 2011](#)).

One retrospective review of 649 women with endometrial cancer found that women who underwent multiple-site lymph node sampling had improved five-year survival (extrapolated from survival curves) compared with women who underwent no pelvic node sampling (five-year survival ~90% vs ~75%; $P = 0.002$) ([Kilgore 1995](#)). However, only disease-specific survival was recorded, non-endometrial cancer deaths were censored and no details were provided on participant characteristics, which are known to have a major influence on endometrial cancer survival (e.g. age, diabetes, cardiac comorbidity). Furthermore, retrospective population-based studies demonstrated no survival advantage of lymphadenectomy ([Van Lankveld 2006](#)), or showed such an advantage only for women in high-risk subgroups (high-grade (G3) stage I disease who did undergo lymph node sampling) (five-year relative survival for no node sampling 0.83 ± 0.05 ($n = 497$) versus 0.92 ± 0.04 ($n = 553$) for node sampling; $P = 0.0110$) ([Trimble 1998](#)).

AUTHORS' CONCLUSIONS

Implications for practice

This review update does not alter the conclusions of the original review ([May 2010](#)); data do not support routine use of pelvic lymphadenectomy in the treatment of endometrial cancer thought to be confined to the uterus at presentation (presumed stage I disease). We found no differences in survival between groups, and, in

relation to harmful effects of treatment, women who did not undergo lymphadenectomy showed clear benefit. We found no good quality data that assessed the role of para-aortic lymphadenectomy, or removal of grossly enlarged lymph nodes. The two trials that contributed to the meta-analyses were at low risk of bias, and the other trial was at unclear risk of bias.

Results demonstrating no benefit of routine lymphadenectomy in presumed early-stage endometrial cancer are of interest and reflect results of RCTs that have examined the role of pelvic radiotherapy in treatment of these women ([Kong 2012](#)). In addition, we found no differences in patterns of recurrence between pelvic lymphadenectomy groups and standard surgery groups in the [Kitchener 2009](#) study, which further supports the survival evidence that lymphadenectomy yields prognostic information only, rather than showing a direct therapeutic benefit. Although prognostic information is useful, these data reveal the real costs to patients associated with gathering this information and show that studies that do not look at the long-term sequelae of lymphadenectomy do not allow women to make fully informed decisions about their health care.

Implications for research

Important questions remain to be answered about the role of lymphadenectomy in endometrial cancer. However, neither this meta-analysis of pelvic lymphadenectomy in early-stage endometrial cancer nor the Cochrane review on radiotherapy for early-stage endometrial cancer ([Kong 2012](#)) supports routine adjuvant treatment to pelvic nodes for early-stage disease. The overall quality of the evidence was moderate across all outcomes (high-quality evidence for the presence or absence of lymphoedema or lymphocyst outcome) and was downgraded because of concerns over imprecision of estimates.

Studies identified in this review examined pelvic lymphadenectomy. We were not able to identify any RCTs that assessed lymph node sampling or sentinel lymph node sampling, rather than systematic lymphadenectomy. Likewise, we found no RCTs that looked at differences between pelvic and para-aortic lymph node removal. These interventions have been assessed by cohort studies but have yet to be assessed by RCTs. It is not known whether pelvic and para-aortic lymph node dissection confers any benefit over pelvic lymphadenectomy alone, and the benefit demonstrated in the SEPAL study ([Todo 2010](#)) has yet to be replicated by an RCT. It is important to note that [Kitchener 2009](#) and [Panici 2008](#) data caution against the assumption that even more surgery will result in improved survival.

The studies included in this review primarily evaluated the impact of lymphadenectomy in early-stage disease with low risk of recurrence; the role of lymphadenectomy in women with intermediate and high risk of disease recurrence has yet to be established by RCTs. Further research is underway to investigate the role of

imaging technologies in the detection of lymph node metastasis in endometrial cancer (ISRCTN84527805); findings of this research may aid future researchers in evaluating the impact of lymphadenectomy among women with intermediate and high risk of disease recurrence.

The studies included in this review did not assess use of sentinel lymph node biopsy, which has the potential to improve staging whilst minimising surgical morbidity. When lymphadenectomy or lymph node sampling is not performed, use of adjuvant therapies is based on the pathological findings derived from surgical specimens. This may lead to inappropriate use, or omission, of adjuvant therapies. Use of sentinel lymph node biopsy may have a role in surgical staging. We recommend that data should be assessed by a Cochrane Diagnostic Test Accuracy review to determine whether the sentinel lymph node approach is valid in endometrial cancer. In addition, future versions of protocols for this review should include an assessment of the role of sentinel lymph node biopsy, if this is shown to be adequately sensitive to be used in an intervention trial.

Studies conducted to determine the role of adjuvant treatment in early-stage cancer have highlighted that, for most women, simple surgery alone is sufficient to provide cure. Further research is needed to allow more individualised treatment strategies, ensur-

ing that women with later-stage or more aggressive cancers receive appropriate treatment, whilst not exposing women with a good prognosis to potentially serious lifelong side effects. In addition, the impact of any intervention on quality of life must be examined in future studies, particularly for cancer types with good survival rates.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Fayallah 2011

Methods	Single-centre RCT randomly assigning participants from a university hospital in Egypt	
Participants	<p>38 women with histologically proven endometrial carcinoma thought to be International Federation of Gynecology and Obstetrics stage I</p> <p>Women recruited between April 2005 and October 2008 were randomly assigned pre-operatively to undergo extra fascial hysterectomy, bilateral salpingo-oophorectomy with pelvic lymphadenectomy (iliac and obturator lymph nodes) (n = 21) or extrafascial hysterectomy and bilateral salpingo-oophorectomy alone (n = 17). Before surgery, immunohistochemistry was carried out on endometrial tissue for detection of P53 overexpression. A total of 30 (79%) women had FIGO surgical stage I disease, four (11%) had stage II and four (11%) stage III disease. Depth of invasion was as follows: endometrium only 6 (16%); inner half of myometrium 17 (45%); and outer half of myometrium or further 15 (39%). Histological cell types were as follows: endometrioid 29 (80%); adenocarcinoma NOS 4 (11%); and papillary serous 5 (13%). Tumour grade was as follows: 14 (37%) had tumour grade 1; 16 (42%) grade 2; and 8 (21%) grade 3</p> <p>No significant difference was noted between arms in terms of age, medical status, surgical stage, histological type, or grade of tumour. The number of nodes removed from participants in either arm was not reported, although the overall number of nodes removed on each pelvic side was reported as ranging from 6 to 14</p> <p>After surgery, adjuvant radiotherapy was provided at the discretion of tumour board members. Women were followed up every 3 months with clinical assessment and ultrasound and underwent an MRI every 6 months</p>	
Interventions	<p>Intervention</p> <p>Extrafascial hysterectomy with bilateral salpingo-oophorectomy combined with pelvic lymphadenectomy involving common iliac, external iliac and obturator lymph node dissection</p> <p>Comparison</p> <p>Extrafascial hysterectomy with bilateral salpingo-oophorectomy alone</p>	
Outcomes	<p>Overall survival</p> <p>Recurrence rate</p>	
Notes	<p>Mean duration of follow-up was 21.5 months (range 6 to 40)</p> <p>Outcomes of overall survival and recurrence rate were based on the number of participants known to have died or in whom the disease was known to have progressed, rather than knowledge of survival and recurrence status among study participants</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Mean follow-up duration from treatment was 21.5 months (range 6 to 40 months) ; no other information regarding attrition was given

Kitchener 2009

Methods	Multi-centre RCT randomly assigning participants from 85 centres in 4 countries (UK, South Africa, Poland, and New Zealand)
Participants	<p>1408 women with histologically proven endometrial carcinoma thought preoperatively to be confined to the corpus</p> <p>Median age at the time of randomisation was 63 years (range 36 to 89) for standard surgery and 63 years (range 34 to 93) for lymphadenectomy</p> <p>Time from diagnosis to random assignment was ≤ 6 weeks for 576 (82%) women in the standard surgery group vs 588 (84%) in the lymphadenectomy arm and > 6 weeks for 128 (18%) women in the standard surgery group vs 116 (16%) in the lymphadenectomy arm</p> <p>1057 participants (75%) had WHO performance status 0; 295 (21%) had status 1; 45 (3%) status 2; 9 (1%) status 3; and 2 (0%) status 4, similarly spread between the 2 groups</p> <p>650 (92%) women underwent open surgery and 54 (8%) underwent laparoscopic surgery in the standard surgery group vs 659 (94%) open and 45 (6%) laparoscopic in the lymphadenectomy group</p> <p>Baseline characteristics below excluded participants whose pathology details did not confirm endometrial cancer: 39 women (21 standard surgery group, 18 lymphadenectomy group) who had no other tumour in the surgical specimen; atypical hyperplasia; or cervical, ovarian, or colorectal cancer</p> <p>Tumour was confined to the corpus uteri in 1091 (80%) women and spread beyond the corpus in 274 (20%) women: 553 (81%) standard surgery; 538 (79%) lymphadenectomy</p> <p>Depth of invasion was as follows for standard surgery: endometrium only 96 (14%); inner half of myometrium 369 (55%); outer half of myometrium 212 (31%); unknown 6 (0.9%)</p> <p>Depth of invasion was as follows for lymphadenectomy: endometrium only 89 (13%); inner half of myometrium 310 (46%); outer half of myometrium 274 (41%); unknown 13 (1.9%)</p> <p>FIGO staging (pre-2009): Stage IIIC was not included, and women with positive lymph nodes were classified irrespective of nodal status. In the standard surgery group, 553 participants (81%) were stage I according to FIGO, 86 (13%) were stage II and 38 (5.6%) were stage III or IV. FIGO stage was unknown in 6 (0.9%) participants. In the lymphadenectomy group, 532 participants (78%) were stage I according to FIGO, 91 (13%) were stage II and 52 (7.5%) were stage III or IV. FIGO stage was unknown in 11 (1.6%) participants</p>

	<p>Histological cell types were as follows for standard surgery vs lymphadenectomy: endometrioid 545 (80%) vs 541 (79%); adenocarcinoma NOS 46 (7%) vs 37 (5%); clear cell 10 (1%) vs 17 (2%); serous 21 (3%) vs 32 (5%); squamous 6 (1%) vs 5 (1%); mucinous 1 (< 1%) vs 4 (1%); mixed epithelial stromal 7 (1%) vs 8 (1%); sarcoma 10 (1%) vs 9 (1%); other epithelial 4 (1%) vs 6 (1%); mixed epithelial 31 (5%) vs 25 (4%); unknown 2 (0.5%) in both groups</p> <p>Tumour grade was as follows for standard surgery vs lymphadenectomy: 225 women (33%) vs 213 (31%) had tumour grade 1; 300 (44%) vs 290 (43%) grade 2; 139 (20%) vs 158 (23%) grade 3; and in 19 (3%) vs 25 (4%) women, tumour grade was unknown or was not applicable</p> <p>Of the 1403 women who completed surgery, surgical technique used in the standard surgery group was as follows: laparoscopic 42 (6%); vertical incision 287 (45%); Pfannenstiel incision 311 (49%); other transverse 43 (7%); unknown 6. Surgical technique used in the lymphadenectomy group was as follows: laparoscopic 45 (6%); vertical incision 384 (60%); Pfannenstiel incision 208 (32%); other transverse 49 (8%); unknown 7. Five women (2 standard surgery; 3 lymphadenectomy) did not undergo completed surgery</p>				
Interventions	<p>Intervention Lymphadenectomy: Women in the lymphadenectomy group had standard surgery plus a systematic dissection of the iliac and obturator nodes. If the nodes could not be dissected thoroughly because of obesity or anaesthetic concerns, sampling of suspect nodes was recommended and para-aortic node sampling was done at the discretion of the surgeon</p> <p>Comparison Standard surgery: Women in the standard surgery group had a hysterectomy and BSO, peritoneal washings and palpation of para-aortic nodes. Nodes that were suspicious could be sampled if the surgeon believed this to be in the woman's best interest</p>				
Outcomes	<p>Overall survival Recurrence-free survival Surgical complications</p>				
Notes	<p>Median duration of follow-up was 37 months (IQR 24 to 58 months) Specialist gynaecological surgeons who were experienced in pelvic lymphadenectomy undertook all surgical procedures</p> <p>69 women in the lymphadenectomy group received a different intervention from the intervention to which they were assigned: 3 women had no surgery, 2 had subtotal hysterectomy, 6 women were given unknown intervention and 58 (8%) had no nodes taken</p> <p>In the standard surgery group, 2 had no surgery, 6 had subtotal hysterectomy, 11 were given unknown intervention and 35 (5%) had nodes taken</p> <p>No adjuvant radiotherapy was received by 471 (67%) in the standard surgery group and by 469 (67%) in the lymphadenectomy group</p>				
<i>Risk of bias</i>					
Bias	<table border="1"> <thead> <tr> <th data-bbox="624 1701 1027 1757">Authors' judgement</th> <th data-bbox="1027 1701 1439 1757">Support for judgement</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	Authors' judgement	Support for judgement		
Authors' judgement	Support for judgement				

Kitchener 2009 (Continued)

Random sequence generation (selection bias)	Low risk	“We used a method of minimisation. Stratification factors were centre, WHO performance status (0-1 <i>versus</i> 2 to 4), time since diagnosis (<= 6 weeks <i>versus</i> > 6 weeks), and planned surgical approach (open <i>versus</i> laparoscopic)” Minimisation is a method that attempts to randomly assign while at the same time balancing groups for several prognostic variables, so the method of sequence generation was adequate in this trial
Allocation concealment (selection bias)	Low risk	“Randomisation was done by a telephone call to the Medical Research Council Clinical Trials Unit (MRC CTU)”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	For multivariate Cox model: % analysed: 1337/1408 (95%)
Selective reporting (reporting bias)	Low risk	All important survival and adverse event outcomes have been reported. Survival outcomes have been analysed using appropriate statistical techniques to account for censoring
Other bias	Unclear risk	Information was insufficient for assessment of whether an important risk of bias existed

Panici 2008

Methods	Multicentre RCT randomly assigning participants from Italy and Chile
Participants	Women with preoperative International Federation of Gynecology and Obstetrics stage I endometrial carcinoma Median age at time of random assignment was 62 years (IQR 56 to 68); standard surgery 63 (IQR 55 to 68); lymphadenectomy 63 (IQR 56 to 68) 386 participants (75%) were stage I according to FIGO (standard surgery 195 (78%) ; lymphadenectomy 191 (72%)); 43 (8%) were stage II (standard surgery 21 (8%) ; lymphadenectomy 22(8%)); 71 (14%) were stage III (standard surgery 27 (11%); lymphadenectomy 44 (17%)); and 6 (1%) were stage IV (standard surgery 3 (1%); lymphadenectomy 3 (1%)). FIGO stage was unknown in 8 (2%) participants (2 in each group) Histological cell types were similar between the 2 groups and were as follows: endometrioid 474 (92%); adenosquamous 33 (6.4%); clear cell 1 (0%); serous 3 (0.6%); mullerian

	<p>mixed malignant tumour 2 (0.4); tumour not found 1 (0%) 38 women (7%) had tumour grade 1 (standard surgery 19 (8%); lymphadenectomy 19 (7%)); 298 (58%) grade 2 (standard surgery 148 (59%); lymphadenectomy 150 (57%)); 169 grade 3 (33%) (standard surgery 78 (31%); lymphadenectomy 91 (35%)); and in 9 (2%) women, tumour grade was unknown (standard surgery 5 (2%); lymphadenectomy 4 (1.5%))</p>	
Interventions	<p>For both lymphadenectomy and no-lymphadenectomy arms, primary surgery included standard hysterectomy with bilateral salpingo-oophorectomy</p> <p>Intervention Lymphadenectomy group underwent external/common iliac and superficial obturator node dissection. Systematic/para-aortic lymphadenectomy was performed at surgeon's discretion</p> <p>Comparison Removal of bulky (> 1 cm) nodes at surgeon's discretion in no lymphadenectomy arm</p>	
Outcomes	<p>Overall survival Disease-free survival (defined as time from random assignment to earliest occurrence of relapse or death from any cause) Severe intraoperative complications Postoperative complications</p>	
Notes	<p>Median duration of follow-up was 49 months (IQR 27 to 79 months) 38 women in the lymphadenectomy group had fewer than 20 nodes resected In the standard surgery group, 56 women (22%) underwent lymph node sampling/removal, and 17 had 20 or more pelvic lymph nodes resected Para-aortic lymphadenectomy was performed in 69 (26%) of the 264 participants in the lymphadenectomy group and in 5 (2%) in the standard surgery group Adjuvant treatment (chemotherapy and radiotherapy) did not vary significantly between the 2 arms (no adjuvant therapy in 182 (69%) of the lymphadenectomy group and in 162 (65%) of the standard surgery group) (P = 0.07)</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to one of the two trial arms by a block arrangement that balanced the treatment assignment within each site"
Allocation concealment (selection bias)	Low risk	"Intraoperative random assignment was performed centrally by telephone at the Mario Negri Institute, Milan"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported

Panici 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	For all outcomes: % analysed: 514/537 (96%) By treatment arm: Intervention: 264/273 (97%) Comparison: 250/264 (95%)
Selective reporting (reporting bias)	Low risk	All important survival and adverse event outcomes have been reported. Survival outcomes have been analysed using appropriate statistical techniques to account for censoring
Other bias	Unclear risk	Information was insufficient for assessment of whether an important risk of bias existed

BSO - IQR - interquartile range
FIGO - International Federation of Gynaecology and Obstetrics
MRI - Magnetic resonance imaging
NOS - Not otherwise stated
RCT - Randomised controlled trial
WHO - World Health Organization

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Angoli 2013	Retrospective review; comparison of lymphadenectomy vs no lymphadenectomy; quality of life assessment
Ansari 2013	Systematic review and meta analysis - no additional RCT evidence found
Babilonti 1989	Retrospective review; comparison of lymphadenectomy vs no lymphadenectomy; examination of short-term complications
Barton 2009	Narrative review article only - no additional RCT evidence found
Bogani 2014	Narrative review article - no additional RCT evidence found
Chan 2006	Retrospective case review
Crosbie 2012	Incorrect comparator - analysis by body mass index only
Fujimoto 2009	Narrative evaluation of RCT only; no primary data

(Continued)

Gao 2013	Retrospective case review
Havrilesky 2013	Review of study methods only
Hofstetter 2014	Retrospective case review
Huh 2008	All participants underwent lymph node dissection. Study randomly assigned processing of samples
Kang 2009	Retrospective study - no lymphadenectomy randomly assigned
Kim 2012	Systematic review - no additional RCT evidence found
Kitchener 2011	No additional information by relevant comparator
Kitchener 2013	Narrative review article - no additional RCT evidence found
Kyrgiou 2013	Incorrect interventional comparator
Kyrgiou 2013a	Incorrect interventional comparator
Lamela 2013	Incorrect interventional comparator
Look 2004	Systematic review - no additional RCT evidence found
Mannel 1989	Retrospective study - no lymphadenectomy randomly assigned
Mariani 2000	Retrospective study
Mosgaard 2013	Incorrect study intervention
Nahhas 1980	Retrospective review of treatment of individuals with stage II endometrial cancer with no randomisation
Obermair 2012	Incorrect study intervention
Poll-Franse 2012	Retrospective non-randomised study assessing health-related quality of life
Puente 2011	Retrospective non-randomised study
Quinn 1993	Randomised controlled trial of progesterone therapy for high-risk endometrial cancer - no surgical randomisation. Comparison of outcomes of 238 women who underwent pelvic lymphadenectomy vs 774 women who did not under pelvic lymphadenectomy. Women who underwent lymphadenectomy were younger and showed less myometrial invasion. Longer overall survival in women with lymphadenectomy. No differences in patterns of recurrence
Rodolakis 2012	Retrospective non-randomised study
Rossi 2013	Incorrect study design

(Continued)

Rossi 2014	Incorrect study intervention
Rubin 1990	Retrospective non-randomised study
Salvesen 2001	Systematic review of role of lymphadenectomy in gynaecological malignancies - no RCT or endometrial cancer found
Schulz 1986	RCT of adjuvant hormonal therapy after surgery for endometrial cancer
Shan 2013	Incorrect study design
Tinelli 2009	Narrative review article - no additional RCT evidence found
Tong 2011	Retrospective case review
Trovik 2013	Incorrect study intervention
Turkler 2013	Retrospective non-randomised study
Watari 2014	Narrative review article - no additional RCT evidence found
Zapico 2013	Incorrect study intervention

DATA AND ANALYSES

Comparison 1. Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2	1851	Hazard Ratio (Random, 95% CI)	1.07 [0.81, 1.43]
2 Recurrence-free survival	2	1851	Hazard Ratio (Random, 95% CI)	1.23 [0.96, 1.58]

Comparison 2. Adverse events

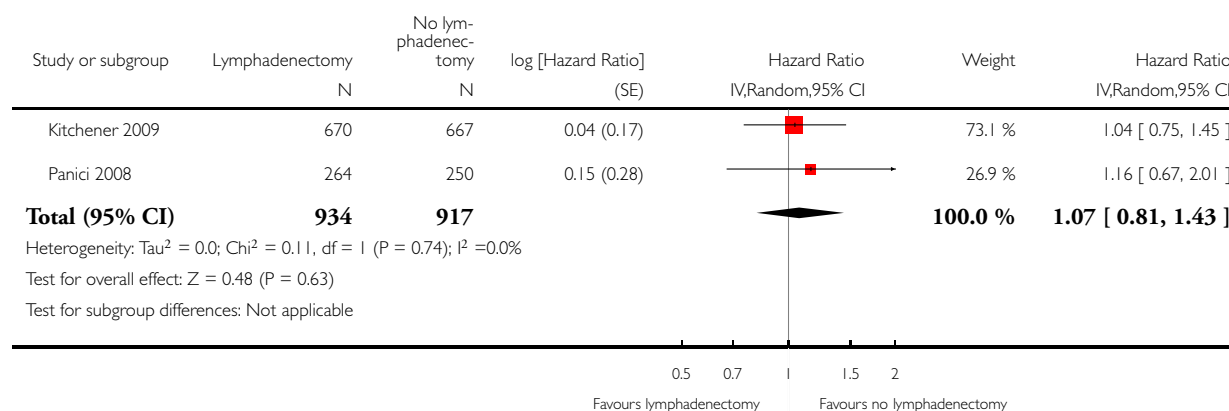
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Direct surgical morbidity	2	1922	Risk Ratio (IV, Random, 95% CI)	1.93 [0.79, 4.71]
2 Lymphoedema or lymphocyst	2	1922	Risk Ratio (IV, Random, 95% CI)	8.39 [4.06, 17.33]
3 Surgery-related systemic morbidity	2	1922	Risk Ratio (IV, Random, 95% CI)	3.72 [1.04, 13.27]

Analysis 1.1. Comparison 1 Survival, Outcome 1 Overall survival.

Review: Lymphadenectomy for the management of endometrial cancer

Comparison: 1 Survival

Outcome: 1 Overall survival

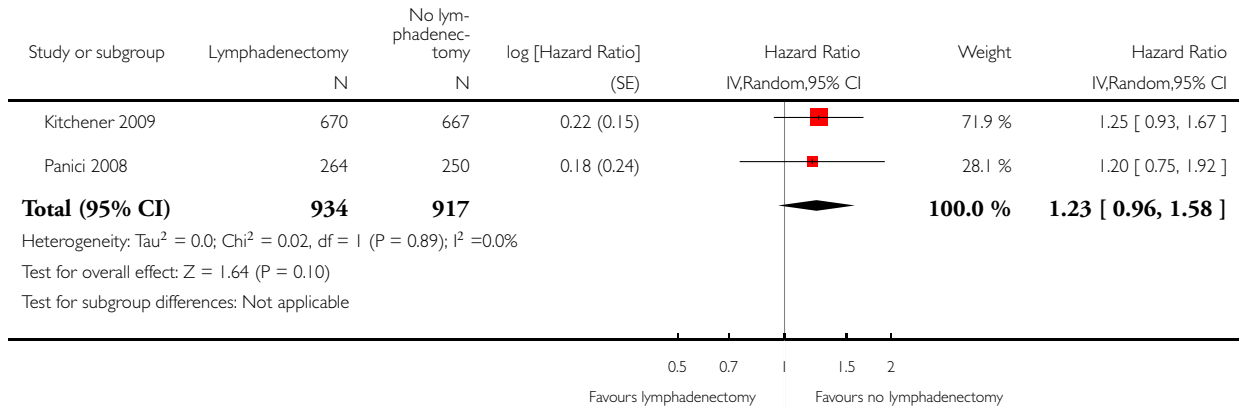


Analysis 1.2. Comparison 1 Survival, Outcome 2 Recurrence-free survival.

Review: Lymphadenectomy for the management of endometrial cancer

Comparison: 1 Survival

Outcome: 2 Recurrence-free survival

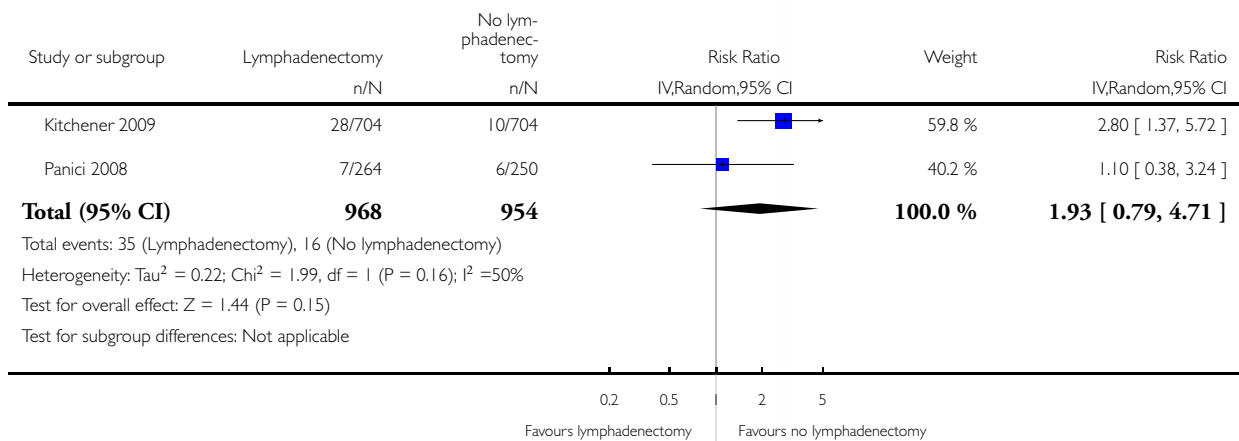


Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Direct surgical morbidity.

Review: Lymphadenectomy for the management of endometrial cancer

Comparison: 2 Adverse events

Outcome: 1 Direct surgical morbidity

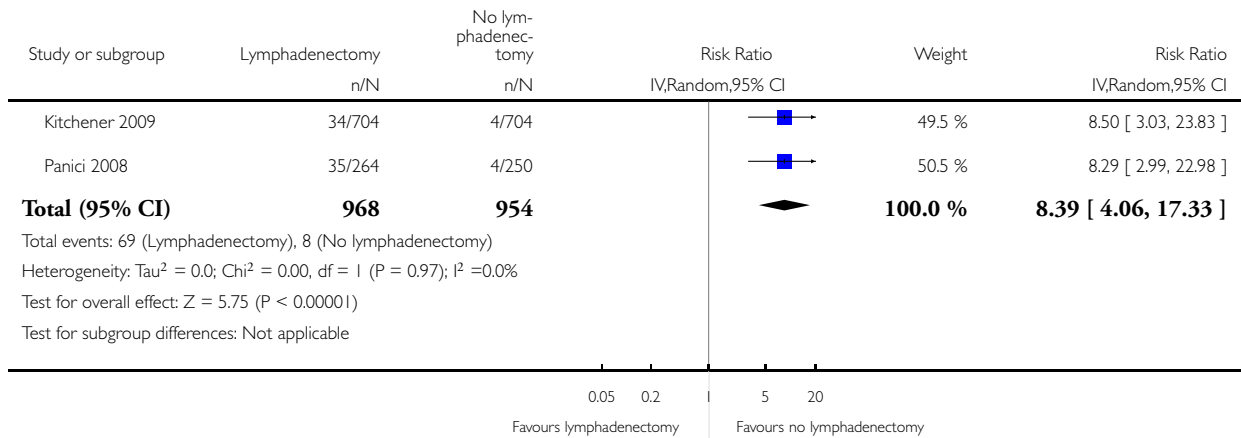


Analysis 2.2. Comparison 2 Adverse events, Outcome 2 Lymphoedema or lymphocyst.

Review: Lymphadenectomy for the management of endometrial cancer

Comparison: 2 Adverse events

Outcome: 2 Lymphoedema or lymphocyst

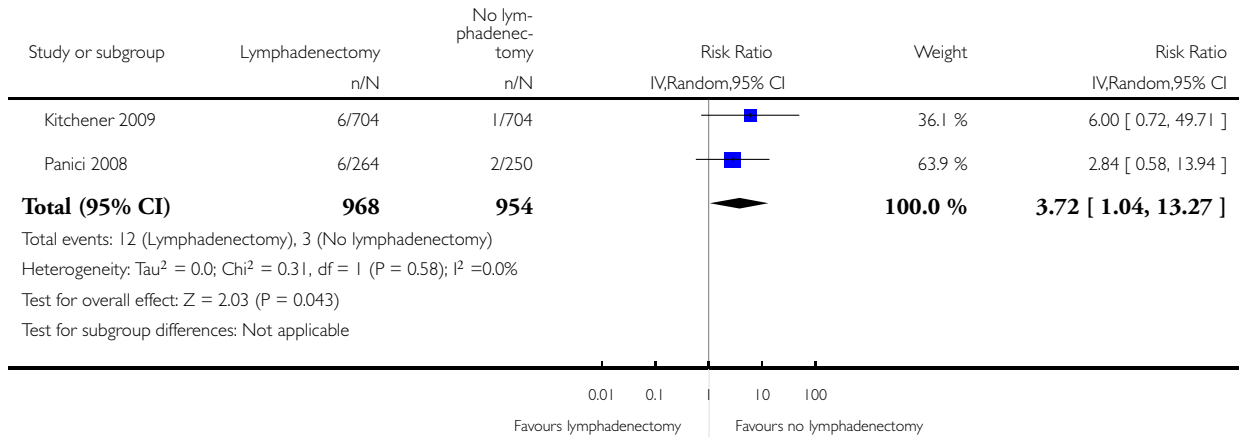


Analysis 2.3. Comparison 2 Adverse events, Outcome 3 Surgery-related systemic morbidity.

Review: Lymphadenectomy for the management of endometrial cancer

Comparison: 2 Adverse events

Outcome: 3 Surgery-related systemic morbidity



ADDITIONAL TABLES

Table 1. Pre-2009 FIGO staging

Stage	Extent of disease
I	Tumour limited to uterine body
IA	Limited to endometrium
IB	< 1/2 myometrial depth invaded
IC	> 1/2 myometrial depth invaded
II	Tumour limited to uterine body and cervix
IIA	Endocervical invasion only
IIB	Invasion into cervical stroma
III	Extension to uterine serosa, peritoneal cavity and/or lymph nodes
IIIA	Extension to uterine serosa, adnexae or positive peritoneal fluid (ascites or washings)

Table 1. Pre-2009 FIGO staging (Continued)

	IIIB	Extension to vagina
	IIIC	Pelvic or para-aortic lymph nodes involved
IV		Extension beyond true pelvis and/or involvement of bladder/bowel mucosa
	IVA	Extension to adjacent organs
	IVB	Distant metastases or positive inguinal lymph nodes

Table 2. FIGO staging (2009)

Stage	Extent of disease
1	Tumour confined to corpus uteri
	IA No or less than half myometrial invasion
	IB Invasion equal to or greater than half of the myometrium
II	Tumour invasion into cervical stroma but not extending beyond uterus
III	Local and/or regional spread of tumour
	IIIA Tumour invasion into serosa of corpus uteri and/or adnexae
	IIIB Vaginal and/or parametrial involvement
	IIIC Metastases to pelvic and/or para-aortic lymph nodes
	IIIC1 Positive pelvic nodes
	IIIC2 Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
	Stage IV tumour invasion into bladder and/or bowel mucosa, and/or distant metastases
	IVA Tumour invasion into bladder and/or bowel mucosa
	IVB Distant metastases, including intra-abdominal metastasis and/or inguinal nodes

Pelvic washings/cytology should be recorded separately and now does not change the stage.

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Lymph Node Excision explode all trees
- #2 lymphadenectom*
- #3 (lymph NEAR node) NEAR/5 excision*
- #4 (lymph NEAR node) NEAR/5 dissection*
- #5 (lymph NEAR node) NEAR/5 surg*
- #6 (lymph NEAR node) NEAR/5 removal
- #7 (lymph NEAR node) NEAR/5 clearance
- #8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
- #9 MeSH descriptor Endometrial Neoplasms explode all trees
- #10 endometr* NEAR/5 neoplas*
- #11 endometr* NEAR/5 carcinom*
- #12 endometr* NEAR/5 malignan*
- #13 endometr* NEAR/5 cancer*
- #14 endometr* NEAR/5 tumor*
- #15 endometr* NEAR/5 tumour*
- #16 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
- #17 (#8 AND #16)

Appendix 2. MEDLINE search strategy

- 1 exp Lymph Node Excision/
- 2 (lymph adj node adj5 (excision* or dissection* or surg* or removal or clearance)).mp.
- 3 lymphadenectom*.mp.
- 4 1 or 2 or 3
- 5 exp Endometrial Neoplasms/
- 6 (endometr* adj5 (neoplas* or carcinom* or malignan* or cancer* or tumor* or tumour*)).mp.
- 7 5 or 6
- 8 randomized controlled trial.pt.
- 9 controlled clinical trial.pt.
- 10 randomized.ab.
- 11 randomly.ab.
- 12 trial.ab.
- 13 groups.ab.
- 14 8 or 9 or 10 or 11 or 12 or 13
- 15 4 and 7 and 14

Key:

mp=title, original title, abstract, name of substance word, subject heading word, pt=publication type, ab=abstract

Appendix 3. EMBASE search strategy

- 1 exp lymphadenectomy/
- 2 (lymph adj node adj5 (excision* or dissection* or surg* or removal or clearance)).mp.
- 3 lymphadenectom*.mp.
- 4 1 or 2 or 3
- 5 exp endometrium tumor/
- 6 (endometr* adj5 (neoplas* or carcinom* or malignan* or cancer* or tumor* or tumour*)).mp.
- 7 5 or 6
- 8 exp controlled clinical trial/
- 9 randomized.ab.
- 10 randomly.ab.
- 11 trial.ab.
- 12 groups.ab.
- 13 8 or 9 or 10 or 11 or 12
- 14 4 and 7 and 13

Key

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name, ab=abstract

Appendix 4. Data abstraction form

Lymphadenectomy for the management of endometrial cancer

Paper ID:

Reviewer:

THE DATA COLLECTION CHECKLIST

April 2009

DATA COLLECTION

Once potentially relevant studies have been identified for a review, the following data should be extracted independently by two reviewers.

Please record your name and the Study ID (first author and year of publication) in the space provided on this page and on any page(s) that may be separated from the main checklist (e.g. Results section).

For all items, review authors should mark an X against the appropriate response in each case. In addition, it will be helpful if you cut and paste relevant supporting text and state its original location in the paper (page/column/paragraph). This facilitates later comparisons of extracted data. Any other comments can also be recorded in the right-hand side boxes.

Data that are missing or 'UNCLEAR' in a published report should be marked clearly on the data collection form.

Items on the data extraction sheet that clearly are not applicable to the study in question should be marked accordingly (i.e. N/A).

After data extraction, review authors should compare their completed data extraction sheets and attempt to reach agreement for each item on the checklist before submitting their completed data records.

SCOPE OF REVIEW: INCLUSION/EXCLUSION CRITERIA

Inclusion criteria	Yes/No/Unclear	Relevant supporting text and location (page/column/paragraph)
Were participants adult women diagnosed with endometrial cancer?		
Did the trial include at least 1 of the following comparisons? <ul style="list-style-type: none"> ● Pelvic lymphadenectomy vs no lymphadenectomy ● Pelvic lymphadenectomy vs pelvic 		

(Continued)

lymph node sampling <ul style="list-style-type: none"> • Pelvic and para-aortic lymphadenectomy vs no lymphadenectomy <ul style="list-style-type: none"> • Pelvic and para-aortic lymphadenectomy vs pelvic lymphadenectomy <ul style="list-style-type: none"> • Removal of bulky pelvic lymph nodes vs no removal of lymph nodes 		
Was the type of study design as described by the authors: Randomised controlled trial (RCT) Quasi-randomised controlled trial (quasi-RCT)		
Exclusion criteria		
Did the trial not include women with other concurrent malignancies?		
Was the trial not cluster-randomised, or was it not a cross-over trial?		
<i>If any of the inclusion criteria are not satisfied and the answer to any of the questions above is "NO", the study should be excluded from the review. COLLECT NO FURTHER DATA</i>		

STUDY DETAILS	Relevant supporting text and location (page/column/paragraph)	
Country: If multi-centre, please give details Please state UNCLEAR if information is not available		
Setting:		
Duration: Indicate N/A as appropriate		
Median length of follow-up:		
Mean length of follow-up:		

(Continued)

Min length of follow-up:		
Max length of follow-up:		
Additional information:		

	Baseline characteristics of participants	Relevant supporting text and location (page/column/paragraph)
Age	Mean = Years SD = Median = Years Range:	
FIGO stage	Number (%) stage I: Number (%) stage II: Number (%) stage III: Number (%) stage IV: Number (%) unknown:	
Grade	Number (%) grade I: Number (%) grade II: Number (%) grade III: Number (%) unknown:	
Comorbidities		
Previous treatment		
Additional information		

ASSESSMENT OF RISK OF BIAS

Sequence generation	Tick one row	Relevant supporting text and location (page/column/paragraph)
Was the allocation sequence adequately generated? Describe in sufficient detail the method used to generate the allocation sequence to allow assessment of whether it should produce comparable groups		

(Continued)

Yes e.g. a computer-generated random sequence or a table of random numbers		
No e.g. non-randomised or quasi-randomised (participants allocated on basis of date of birth, clinic ID number or surname)		
Unclear insufficient information about the sequence generation		
ALLOCATION CONCEALMENT Was the randomisation sequence for allocating participants to different arms of the trial adequately concealed, to prevent both participants and clinicians providing treatment from predicting in advance to which arm of the trial a women would be assigned?		
Yes e.g. when the allocation sequence could not be foretold		
No e.g. allocation sequence could be foretold by participants, investigators or treatment providers		
Unclear e.g. if use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed		
BLINDING OF OUTCOME ASSESSORS Were the clinicians who assessed disease progression at the end of follow-up prevented from knowing to which arm of the trial the women were assigned?		
Yes Outcome assessors were blinded		
No No blinding or incomplete blinding of outcome assessors		
Unclear Information was insufficient to permit judgement of 'yes' or 'no'		

LOSS TO FOLLOW-UP	Enter numbers below	Relevant supporting text and location (page/column/paragraph)
<p>How many participants were enrolled in each treatment arm?</p> <p>group: Intervention</p> <p>group: Comparison</p>		
<p>How many participants were assessed at the end of follow-up in each treatment arm?</p> <p>group: Intervention</p> <p>group: Comparison</p>		
<p>What % of participants were lost to follow-up?</p> <p>group: Intervention</p> <p>Comparison group:</p> <p>Overall:</p>		
Now code satisfactory level of loss-to-follow-up as Yes/No/Unclear:	Tick one row below	
Yes: if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms		
No: if more than 20% of participants were lost to follow-up or reasons for loss to follow-up were different in different treatment arms		
Unclear: If loss to follow-up was not reported		
Selective reporting of outcomes: Are reports of the study free of the suggestion of selective outcome reporting?		
Yes e.g. if review reports all outcomes specified in the protocol		
No		
Unclear		

(Continued)

Other potential threats to validity: Was the study apparently free of other problems that could put it at high risk of bias?		
Yes		
No		
Unclear		

CHARACTERISTICS OF THE INTERVENTIONS

Describe the intervention(s) for each study group. Report this in the words of the paper and give specific details if they are provided e.g. type of surgeon (gynaecologist, gynaecologist, general surgeon) and experience of surgeon, etc.	Location of text (page/column/paragraph)
Intervention details:	
Comparison details:	
Did any women receive a different intervention from the one to which they were assigned? Yes/No/Unclear	
If the answer to the question above is YES, record any reported changes in assigned treatment	
Intervention:	
Comparison:	
If women received treatments different from those to which they were assigned, were outcomes reported in the groups to which they were assigned?	

(Continued)

Yes/No/Unclear		
OUTCOMES		
Overall survival		
If the following were reported, record the value	Value	Relevant supporting text and location (page/column/paragraph)
Unadjusted hazard ratio (HR) Was the comparison group the reference group for the estimate of the HR?	Yes/No/Unclear	
95% confidence on unadjusted HR Lower 95% confidence limit Upper 95% confidence limit		
Adjusted hazard ratio (HR) Was the comparison group the reference group for the estimate of the HR? List the factors for which the HR was adjusted:	Yes/No/Unclear	
95% confidence on adjusted HR Lower 95% confidence limit Upper 95% confidence limit		
If an HR was reported, record the number of women in each treatment arm on whom the estimated HR was based: Number of women in intervention arm: Number of women in comparison arm:		
If an HR was reported, and if the study was based on a prespecified protocol for assigning women to intervention group or comparison group, was the HR based on an intention-to-treat (ITT) analysis? i.e. were women analysed in the groups to which they were assigned, regardless of which treatment they received?	Yes/No/Unclear	
SE(HR)		
SE(ln(HR))		

(Continued)

Var(HR)		
Var(ln(HR))		
Kaplan-Meier plots	Yes/No	
Minimum follow-up time		
Maximum follow-up time		
Log rank P value		
Was Cox regression reported?	Yes/No	
Cox P value		

OUTCOMES		
Progression-free survival		
If the following were reported, record the value	Value	Relevant supporting text and location (page/column/paragraph)
Unadjusted hazard ratio (HR) Was the comparison group the reference group for the estimate of the HR?	Yes/No/Unclear	
95% confidence on unadjusted HR Lower 95% confidence limit Upper 95% confidence limit		
Adjusted hazard ratio (HR) Was the comparison group the reference group for the estimate of the HR? List the factors for which the HR was adjusted:	Yes/No/Unclear	
95% confidence on adjusted HR Lower 95% confidence limit Upper 95% confidence limit		
If an HR was reported, record the number of women in each treatment arm on whom the estimated HR was based Number of women in intervention arm: Number of women in comparison arm:		

(Continued)

If an HR was reported, and if the study was based on a prespecified protocol for assigning women to intervention group or comparison group, was the HR based on an intention-to-treat (ITT) analysis? i.e. were women analysed in the groups to which they were assigned, regardless of which treatment they received?	Yes/No/Unclear	
SE(HR)		
SE(ln(HR))		
Var(HR)		
Var(ln(HR))		
Kaplan-Meier plots	Yes/No	
Minimum follow-up time		
Maximum follow-up time		
Log rank P value		
Was Cox regression reported?	Yes/No	
Cox P value		

	Intervention group	Comparison group	Location of text (page/column/paragraph)
Total number of women enrolled in study			
For women enrolled in comparison of intervention/comparison treatment			
Number of women enrolled			
Number (%) of women who died			
Number of women whose vital status was known			

(Continued)

Time point at which death was recorded e.g. 1 year/5 years/end of study/not reported			
Median time to death:			
Mean (SD) time to death:			

	Intervention group	Comparison group	Location of text (page/column/paragraph)
Number (%) of women with disease progression			
Number of women whose disease was assessed			
Time point at which disease progression was recorded e.g. 1 year/5 years/end of study/not reported			
Median time to disease progression:			
Mean (SD) time to disease progression:			

Quality of life outcome	Response	Relevant supporting text and location (page/column/paragraph)
State 'not reported' if not given		
Validated scale Yes/No		
Name of scale		
Intervention group: Mean QOL at end of follow-up SD of QOL at end of follow-up Number of women assessed for QOL at end of follow-up		
Comparison group: Mean QOL at end of follow-up SD of QOL at end of follow-up Number of women assessed for QOL at		

(Continued)

end of follow-up		
Adverse events	Number	
	Intervention group	Comparison group
		Location of text (page/column/paragraph)
<p>Direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel or colon), presence and complications of adhesions, febrile morbidity, intestinal obstruction, haematoma, local infection) List below the specific types and numbers of adverse events reported</p>		
<p>Surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism), cardiac events (cardiac ischaemias and cardiac failure), cerebrovascular accident) List below the specific types and numbers of adverse events reported</p>		
<p>Recovery: delayed discharge, unscheduled re-admission List below the specific types and numbers of adverse events reported</p>		
<p>Lymphoedema and lymphocyst formation List below the specific types and numbers of adverse events reported</p>		
<p>Other side effects not categorised above List below the severity of bleeding and numbers of adverse events reported</p>		
Does the number of adverse events reported above refer to the number of women who experienced adverse events or to the number of episodes of adverse events?	Number of women/Number of episodes	

WHAT'S NEW

Last assessed as up-to-date: 30 March 2017.

Date	Event	Description
2 October 2017	Amended	Author contact details amended.
25 September 2017	New search has been performed	New search March 2017 - no new studies identified.
25 September 2017	New citation required but conclusions have not changed	Review revised but conclusions not changed.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 1, 2010

Date	Event	Description
29 June 2015	New citation required but conclusions have not changed	Review updated
23 June 2015	New search has been performed	New study identified. Results unchanged as no data available to be added to the meta-analysis

CONTRIBUTIONS OF AUTHORS

JF and JM contributed equally to the review update. The protocol was originally developed by JM, KW, HD, and AB. JF, KW, AB, and JM sifted references, and KW, JF, and AB extracted data, which were checked by JM. AB, JF, and JM co-wrote the results and conclusions of the review with input from KW.

DECLARATIONS OF INTEREST

Jonathan Frost - none known

Katie Webster - none known

Jo Morrision - none known

Andrew Bryant - none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.
NHS Cochrane Collaboration programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to methods described in the protocol, we used the GRADE approach to define the quality of the evidence and the extent to which we can be confident that an estimate of effect or association is free from bias.

In the most recent update of the review in 2017, as the first step of screening, we applied the machine learning classifier (RCT model) available in the Cochrane Register of Studies ([CRS-web](#); [Wallace 2017](#)). The classifier assigns a probability (from 0 to 100) to each citation for being a true RCT. For citations that are assigned a probability score of less than 10, the machine learning classifier currently has a specificity/recall of 99.987% (James Thomas, personal communication). For citations assigned a score from 10 to 100, we screened them independently and in duplicate using [Covidence](#) on-line software (Covidence).

The following methods were specified in the protocol but were not implemented, as we found only three trials that met our inclusion criteria, only two of which could be included in the meta-analysis. Both trials included in the meta-analysis reported HRs, so we did not need to estimate RRs. Neither trial reported continuous outcomes such as quality of life and neither included multiple treatment groups. Both trials were at low risk of bias, so we did not conduct sensitivity analysis around quality. However, the methods specified below may be required when this review is next updated.

Measures of treatment effect

- If it is not possible to estimate the HR, we will abstract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed, to estimate a risk ratio (RR).
- For continuous outcomes (QOL measures), we will abstract the final value and the standard deviation of the outcome of interest in each treatment arm at the end of follow-up for each study, if available.

For dichotomous and continuous data, we will extract the number of participants assessed at endpoint.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analyses of the primary outcome to assess the potential for small-study effects such as publication bias. If these plots suggest that treatment effects may not be sampled from a symmetrical distribution, as assumed by the random-effects model, we will perform further meta-analyses using the fixed-effect model.

Data synthesis

- For continuous outcomes (e.g. QOL measures), we will pool mean differences between treatment arms at the end of follow-up, if all trials measured outcomes on the same scale; otherwise we will pool standardised mean differences.

If any trials include multiple treatment groups, we will divide the 'shared' comparison group into single treatment groups, and we will treat comparisons between treatment groups and the split comparison group as independent comparisons.

If possible, we will synthesise studies making different comparisons by using the subgroup methods of [Bucher 1997](#).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses by grouping the trials by:

- early-stage disease low-risk participants (stage IA-B, G1 or G2) versus high-risk participants (stage IB, G3 or stage IC or higher, any grade); or
- no obvious lymph node enlargement versus lymph node enlargement.

We will consider factors such as age, stage, type of intervention, length of follow-up, and adjusted/unadjusted analysis when interpreting any heterogeneity.

Sensitivity analysis

We will perform sensitivity analyses that exclude studies at high risk of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Disease-Free Survival; Endometrial Neoplasms [*surgery]; Lymph Node Excision [*adverse effects]; Lymphatic Metastasis; Lymphedema [etiology]; Lymphocele [etiology]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans