# A report for Universitätsklinikum Schleswig-Holstein/Campus Kiel on Shared Decision Making for "Cervical Cancer: minimally invasive versus open surgery"

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| CDSR | Cochrane Database of Systematic Reviews |
| CI | Confidence interval |
| CRD | Centre for Reviews and Dissemination |
| DFS | Disease-free survival |
| DVT | Deep vein thrombosis |
| ECOG | Eastern Cooperative Oncology Group |
| EQ-5D | EuroQoL-5 dimensions |
| ESMO | European Society of Medical Oncology |
| FACT-Cx | Functional Assessment of Cancer Therapy–Cervical |
| FAQ | Frequently asked question |
| FIGO | Federation of Gynecology and Obstetrics |
| GIN | Guidelines International Network |
| HR | Hazard ratio |
| HTA | Health Technology Assessment |
| kg | Kilogram |
| KSR | Kleijnen Systematic Reviews Ltd |
| LACC | Laparoscopic approach to cervical cancer |
| LRH | Laparoscopic radical hysterectomy |
| MA | Meta-analysis |
| MD | Mean difference |
| MDASI | MD Anderson Symptom Inventory |
| min | Minute |
| MINORS | Methodological Index for Non-randomised Studies |
| MIS | Minimally invasive surgery |
| ml | Millilitre |
| NA | Not applicable |
| NMA | Network meta-analysis |
| NS | Not significant |
| OR | Odds ratio |
| ORH | Open radical hysterectomy |
| OS | Overall survival |
| PE | Pulmonary embolism |
| PICOS | Participants, intervention, comparators, outcomes and study design |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROSPERO | International Prospective Register of Systematic Reviews |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RD | Risk difference |
| RR | Risk ratio |
| RRH | Robotic radical hysterectomy |
| SD | Standard deviation |
| SDM | Shared decision making |
| SF-12 | 12-item Short Form Health Survey |
| SR | Systematic reviews |
| UK | United Kingdom |
| USA | United States of America |
| UTI | Urinary tract infection |

## 1. PROJECT OBJECTIVE

A key aim of the research project "Making SDM a reality" is to create interactive websites to inform patients as part of shared decision making (SDM).

To support this, Kleijnen Systematic Reviews Ltd (KSR) have prepared an evidence report with a synthesis of the literature underpinning the supporting evidence table of treatment options.

The topic of this evidence report is the treatment of Cervical Cancer: minimally invasive versus open surgery.

In 2018, the New England Journal of Medicine published the results of a randomised controlled trial (RCT) on the laparoscopic approach to cervical cancer (LACC) reported by Ramirez et al. This non-inferiority trial evaluated the survival rate of minimally invasive surgery (MIS) versus open radical hysterectomy (ORH). In their conclusions the authors report that minimally invasive radical hysterectomy was associated with lower rates of overall survival and disease-free survival compared with ORH.[1]

Following the publication of the LACC trial, the European Society of Medical Oncology (ESMO) issued an amendment of their guidance by which radical hysterectomy performed by laparoscopy or robot-assisted surgery cannot be regarded as the preferred treatment compared with ORH for patients with FIGO (Federation of Gynecology and Obstetrics) stage IA2, IB and IIA.[2, 3] In light of this update, the available evidence from secondary publications to support or challenge the new recommendations was reviewed.

## 2. METHODS

The literature review was carried out in accordance with the methodologies recommended by Cochrane[4] and the Centre for Reviews and Dissemination (CRD)[5] following PRISMA reporting guidelines.[6, 7]

### 2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators,outcomes and study Design (PICOS), see Table 1.

Table 1: Inclusion criteria for searches

| **PICO** | |
|---|---|
| **Patients** | Patients with early stage cervical cancer |
| **Intervention treatment** | ORH |
| **Control treatment** | MIS<br>(robotic radical hysterectomy (RRH) and/or laparoscopic radical hysterectomy (LRH)) |
| **Outcomes** | • Overall survival (OS)<br>• disease-free survival (DFS)<br>• measures of surgery (e.g. operation time, blood loss, length of hospital stay)<br>• rate of intra- and post-operative complications<br>• Quality of life (QoL) |
| **Study design** | Systematic reviews (SRs), meta-analyses (MA), and literature reviews |
| **Effect modification / Subgroups** | Any indication of a specific effect modification or subgroup of patients from the evidence review, will be assessed. |
| DFS = disease-free survival; LRH = laparoscopic radical hysterectomy; MA = meta-analyses; MIS = minimally invasive surgery; ORH = open radical hysterectomy; OS = overall survival; RRH = robotic radical hysterectomy; SR = Systematic reviews | |

Titles and abstracts identified through electronic database and web searching, and subsequently full paper copies of all potentially eligible references were screened independently by two reviewers; any disagreements were resolved by discussion. No restrictions were placed on language or publication status.

In order to compare the existing (non-randomised) evidence with the LACC trial by Ramirez et al., newer reviews covering comparable outcomes were selected.

### 2.2 LITERATURE SEARCHES

In order to identify any relevant systematic reviews (SRs) and RCTs, a focused literature search was conducted using a combination of free text and database thesaurus terms. No restrictions on language or publication status were applied. Reference lists of included articles were also searched to identify additional studies.

Searches to identify relevant RCTs were conducted on the following databases from 2014 to March 2020:

- MEDLINE (Ovid): 1946-2020/03/02
- MEDLINE In-Process Citations, Medline Daily Update & Epub Ahead of Print (Ovid): up to 2020/03/02
- Embase (Ovid): 1974-2020/03/02
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/03/Iss3

Searches to identify relevant SRs were conducted on the following resources from 2014 to March-May 2020:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/03/Iss3
- KSR Evidence (KSR): up to 2020/03/03
- PROSPERO (CRD): up to 2020/05/05
- MEDLINE (Ovid): 1946-2020/05/08
- MEDLINE In-Process Citations, Medline Daily Update & Epub Ahead of Print (Ovid): up to 2020/05/08
- Embase (Ovid): 1974-2020/05/08

An example search strategy is available in Appendix 1.

### 2.3 Data extraction

Data were extracted by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

### 2.4 Quality (risk of bias) assessment

The risk of bias (methodological quality) of RCTs was assessed using the Cochrane Risk of Bias Tool for randomised clinical trials while reviews were assessed using ROBIS.[8, 9]

Risk of bias assessment was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

### 2.5 Data synthesis

Results from the LACC trial and relevant reviews were reported as a narrative synthesis with Tables and Figures.

# 3. RESULTS

## 3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

A total of 5,428 records were retrieved from the database searches. After de-duplication, 3,996 records remained. These articles were screened based on the title and abstracts; 13 were ordered for full text screening and eight were excluded. After the full text screening stage, 5 records were identified for inclusion in the review.

The flow of studies through the search and screening processes is summarised in Figure 1.

Of note, after the searches were completed, one additional reference was identified for the LACC trial, see section 3.2 and FAQ 6 for details.[10]

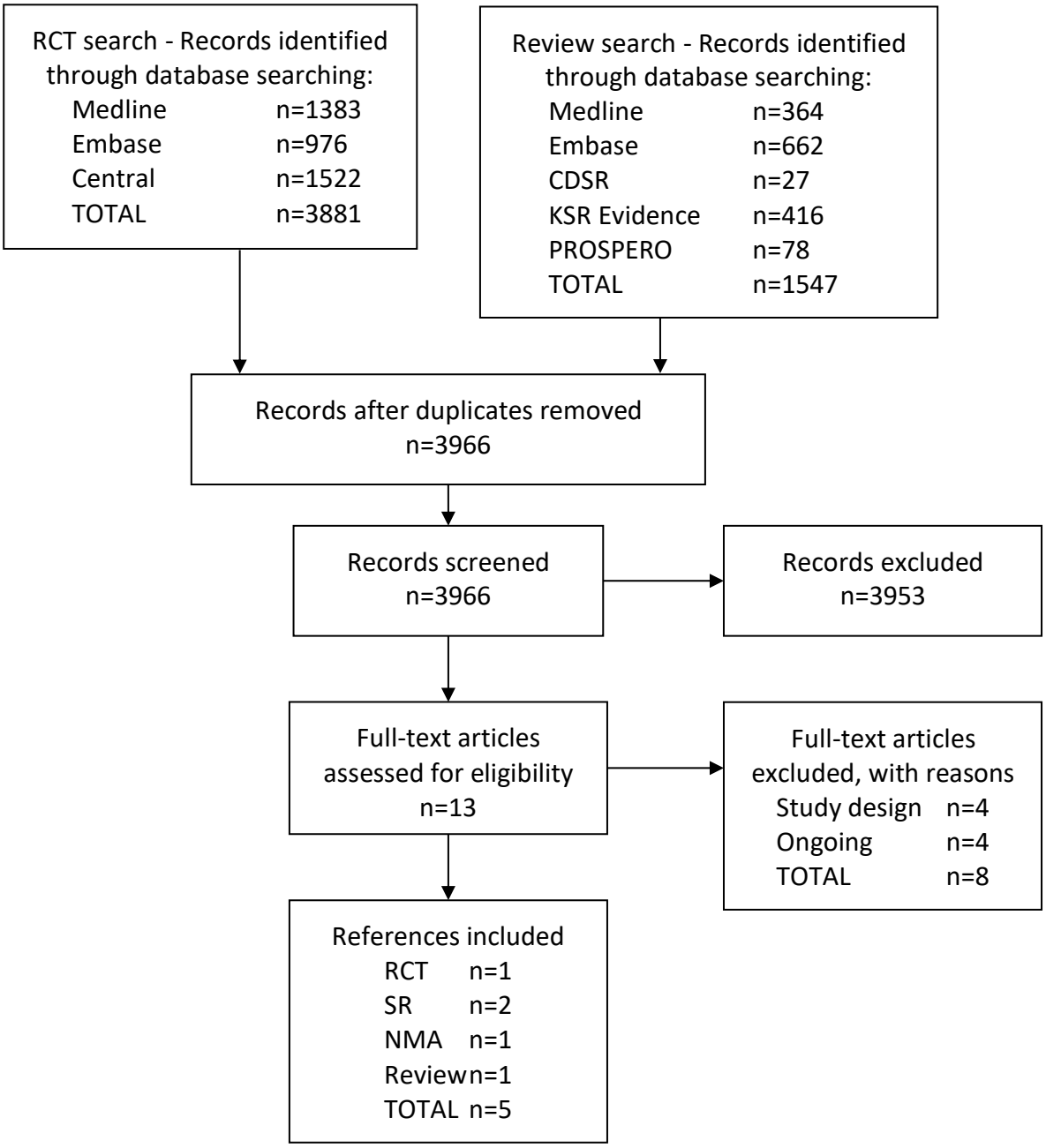
## 3.2 OVERVIEW OF THE EVIDENCE

The information identified to answer the patient questions is given below organised by question and the underpinning evidence.

This evidence report included one RCT, the Laparoscopic Approach to Cervical Cancer (LACC) trial published in November 2018,[1, 10-12] a recent literature review,[13] a recent network meta-analysis (NMA),[14, 15] and two systematic reviews.[16, 17] The primary studies that the reviews included are listed in Appendix 2.

Since no further RCTs with equivalent scope to the LACC trial were identified, the results of the LACC trial (highest evidence level in the hierarchy of individual studies) are primarily used as the basis of this evidence report. Results of the reviews of lower evidence level are reported as background information.

Figure 1: Flow chart – Selection process




CDSR = Cochrane Database of Systematic Reviews; KSR = Kleijnen Systematic Reviews; NMA = network meta-analysis; PROSPERO = International Prospective Register of Systematic Reviews; RCT = randomised controlled trial; SR = systematic review

*FAQ 1: Will the treatment prolong my life?*

The clinical evidence for the decision aid for overall survival is presented in Tables 2 and 3.

Table 2 OS from LACC trial (ITT)

| Outcome | MIS (N=319) | ORH (N=312) | MIS vs. ORH (95% CI) |
|---|---|---|---|
| **OS (%) (3-year rate)** | 93.8 | 99.0 | HR 6.00 (1.77 to 20.30)* |

Based on Figure 2A of Ramirez 2018[1]
* Hazard ratio for death from any cause
CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; LACC = laparoscopic approach to cervical cancer; MIS = minimally invasive surgery; ORH = open radical hysterectomy, OS = overall survival

Table 3 OS from reviews

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| **OS (%) (HR/RR (95% CI))** | *Meta-analyses*<br>LRH vs. ORH: HR 0.98 (95% CI NR), P=0.73; HR 0.91 (95% CI NR), P=0.76<br><br>*Prospective studies*<br>MIS vs. ORH: 91.0 vs. 78.9, P=0.026<br><br>*Epidemiological studies*<br>LRH vs. ORH: 95.2 vs. 96.4, P=0.451<br>MIS vs. ORH: 90.9 vs. 94.7, P=0.002 | *NMA*<br>RRH vs. ORH: RR 0.49 (0.28, 0.87)<br>LRH vs. ORH: RR 0.82 (0.61, 1.09)<br>RRH vs. LRH: RR 0.60 (0.33, 1.11) | *Matched studies*<br>RRH vs. LRH: 100 vs. 83.4<br>RRH vs. ORH: 97 vs. 98,<br><br>*Cohort studies*<br>RRH vs. LRH: 96.6 vs. 95.9<br>RRH vs. ORH 96.6 vs. 92.3, | NR |

CI = confidence interval, HR = hazard ratio, LRH = laparoscopic radical hysterectomy, MIS = minimally invasive surgery, NMA = network meta-analysis; NR = not reported, ORH = open radical hysterectomy, OS = overall survival, RR = risk ratio, RRH = robotic radical hysterectomy

*FAQ 2: Will the treatment prolong my disease free survival?*

The clinical evidence for the decision aid for disease free survival is presented in Tables 4 and 5.

Table 4: DFS from LACC trial

| Outcome | MIS | ORH | MIS vs. ORH (95% CI) |
|---|---|---|---|
| **Intention-to-treat (ITT)** | n=319 | n=312 | |
| DFS, % (3-year rate) | 91.2 | 97.1 | HR 3.74 (1.63 to 8.58)** |
| DFS at 4.5 years; % (95% CI) | 86.0 (79.7 to 90.4) | 96.5 (92.7 to 98.4) | -10.6 (-16.4 to -4.7)* |

Based on Figure 1, Table 3, and Supplementary Table 7 of Ramirez 2018[1]
* P=0.87, test for noninferiority
** Hazard ratio for disease recurrence or death from cervical cancer, P=0.002, test for superiority
CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; ITT = intention-to-treat; LACC = laparoscopic approach to cervical cancer; MIS = minimally invasive surgery; ORH = open radical hysterectomy

Table 5: DFS from reviews

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| **DFS HR/RR (95% CI)** | LRH vs. ORH: HR 0.97 (95% CI NR), P=0.91. | *NMA*<br>RRH vs. ORH: RR 0.92 (95% CI 0.66 to 1.27)<br>LRH vs. ORH: RR 0.90 (95% CI 0.73 to 1.11)<br>RRH vs. LRH: RR 1.02 (95% CI 0.72 to 1.44), | NR | NR |
| **DFS up to 5 years (%)** | *Prospective studies*<br>MIS vs. ORH: 92.8 vs. 81.3, P=0.03<br><br>*Epidemiological studies*<br>LRH vs. ORH: 92.8% vs. 94.4%, P=0.499 | NR | *Matched studies*<br>RRH vs. LRH: 91.3 vs. 89.9, 97 vs. 89<br>RRH vs. ORH: 90 vs. 89<br><br>*Cohort studies*<br>RRH vs. LRH: 95.6 to 100 vs. 93.5 to 100 (depending on stage), 96.4 vs. 91.9, 89.7 vs. 89.8<br>RRH vs. ORH: 89.7 vs. 84.6 | NR |

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, LACC = laparoscopic approach to cervical cancer; LRH = laparoscopic radical hysterectomy, MIS = minimally invasive surgery, NMA = network meta-analysis; NR = not reported, OR = odds ratio, OS = overall survival, RR = risk ratio, RRH = robotic radical hysterectomy

*FAQ 3: Will the treatment prevent recurrence?*

The clinical evidence for the decision aid for recurrence is presented in Tables 6 and 7.

Table 6: Recurrence from LACC trial

| Outcome | MIS | ORH | MIS vs. ORH (95% CI) |
|---|---|---|---|
| **Intention-to-treat (ITT)** | n=319 | n=312 | |
| Locoregional recurrence; n (%) | 18 (5.6) | 4 (1.3) | HR 4.26 (1.44 to 12.60) |

Based on Table 3 of Ramirez 2018[1]
CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; LACC = laparoscopic approach to cervical cancer; MIS = minimally invasive surgery; ORH = open radical hysterectomy

Table 7: Recurrence from reviews

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| **Recurrence (%) (HR/RR (95% CI)** | *Meta-analyses*<br>LRH vs. ORH: 8.77 vs. 11.93 (95% CI NR), P=0.2, 8.3 vs. 11.9 (95% CI NR), P=0.16<br><br>*Prospective studies*<br>MIS vs. ORH: 15.1 vs. 14.4 (95% CI NR), P=0.64<br><br>*Epidemiological studies*<br>LRH vs. ORH: 6.1 vs. 5.7 (95% CI NR), P=NS | NR | RRH vs. ORH: OR 0.85 (95% CI 0.58 to 1.27), 5 studies<br>RRH vs. LRH: OR 0.96 (95% CI 0.50 to 1.87), 7 studies | LRH vs. ORH: OR 0.74 (95% CI 0.49 to 1.13), 8 studies |

CI = confidence interval, HR = hazard ratio, LRH = laparoscopic radical hysterectomy, MIS = minimally invasive surgery, NR = not reported, NS = not significant; OR = odds ratio, ORH = open radical hysterectomy; RR = risk ratio, RRH = robotic radical hysterectomy

*FAQ 4: What are the intra- and postoperative complications and side effects?*

The clinical evidence for the decision aid for intra- and postoperative complications and side effects is presented in Tables 8 and 9.

Table 8: LACC trial - Adverse events

| **Outcome** | ***MIS (n=279)*** | ***ORH (n=257)*** | ***MIS vs. ORH (95% CI)*** |
|---|---|---|---|
| Any AE; n (%) | 164 (59) | 136 (53) | 5.9 (-2.5 to 14.3) |
| **Intraoperative AE; n (%)** | **34 (12)** | **26 (10)** | **2.1 (-3.3 to 7.4)** |
| Blood transfusion | 5 (1.8) | 12 (4.7) | -2.9 (-5.9 to 0.1) |
| Ureter injury | 5 (1.8) | 4 (1.6) | 0.2 (-1.9 to 2.4) |
| Vascular injury | 4 (1.4) | 3 (1.2) | 0.3 (-1.6 to 2.2) |
| Other | 5 (1.8) | 3 (1.2) | 0.6 (-1.4 to 2.7) |
| Bladder injury | 7 (2.5) | 2 (0.8) | 1.7 (-0.4 to 3.9) |
| Nerve injury | 6 (2.2) | 1 (0.4) | 1.8 (-0.1 to 3.6) |
| Bowel injury | 2 (0.7) | 1 (0.4) | 0.3 (-0.9 to 1.6) |
| Uterus rupture | 3 (1.1) | 0 | 1.1 (-0.7 to 2.9) |
| Vaginal laceration | 2 (0.7) | 0 | 0.7 (-0.9 to 2.4) |
| **Postoperative AE; n (%)** | **152 (54)** | **124 (48)** | **6.3 (-2.2 to 14.7)** |
| Adverse Events by organ system; n (%) | | | |
| Any urinary AE | 63 (22.6) | 46 (17.9) | 4.7 (-2.1 to 11.5) |
| Any GI AE | 44 (15.8) | 36 (14.0) | 1.8 (-4.3 to 7.8) |
| Any pulmonary AE | 5 (1.8) | 3 (1.2) | 0.6 (-1.4 to 2.7) |
| Any cardiac AE** | 2 (0.7) | 10 (3.9) | -3.2 (-5.7 to -0.6) |
| Any sepsis AE | 2 (0.7) | 2 (0.8) | -0.1 (-1.5 to 1.4) |
| Any other AE | 95 (34.1) | 86 (33.5) | 0.6 (-7.4 to 8.6) |
| Individual adverse events; n (%) | | | |
| Pain | 19 (6.8) | 24 (9.3) | -2.5 (-7.2 to 2.1) |
| Anemia | 16 (5.7) | 16 (6.2) | -0.5 (-4.5 to 3.5) |
| Delay to bladder function | 13 (4.7) | 13 (5.0) | -0.3 (-3.9 to 3.3) |
| Vaginal vault complications** | 11 (3.9) | 2 (0.8) | 3.2 (0.6 to 5.7) |
| Genitourinary fistula or stricture | 10 (3.6) | 7 (2.7) | 0.9 (-2.1 to 3.8) |
| Nausea | 8 (2.9) | 9 (3.5) | -0.6 (-3.6 to 2.3) |
| Neuropathy | 7 (2.5) | 2 (0.8) | 1.7 (-0.4 to 3.9) |
| Febrile morbidity | 6 (2.2) | 2 (0.8) | 1.4 (-0.6 to 3.4) |
| Surgical site infection | 5 (1.8) | 4 (1.6) | 0.2 (-1.9 to 2.4) |
| Wound complication** | 4 (1.4) | 16 (6.2) | -4.8 (-8.1 to -1.5) |
| Obstruction | 3 (1.1) | 1 (0.4) | 0.7 (-0.7 to 2.1) |
| Anxiety | 2 (0.7) | 3 (1.2) | -0.5 (-2.1 to 1.2) |
| Acute renal injury | 1 (0.4) | 1 (0.4) | -0.0 (-1.1 to 1.0) |
| Gastrointestinal fistula | 1 (0.4) | 0 | 0.4 (-1.1 to 1.8) |
| DVT/PE | 1 (0.4) | 0 | 0.4 (-1.1 to 1.8) |
| Lymphedema | 1 (0.4) | 2 (0.8) | -0.4 (-1.7 to 0.9) |
| Incisional or port site hernia | | 1 (0.4) | -0.4 (-1.8 to 1.0) |
| Ileus | | 2 (0.8) | -0.8 (-2.4 to 0.8) |

| Outcome | *MIS (n=279)* | *ORH (n=257)* | *MIS vs. ORH (95% CI)* |
|---|---|---|---|
| Lymphocele formation | | 3 (1.2) | -1.2 (-3.0 to 0.6) |
| Major AE; n (%) | 50 (18) | 41 (16) | 2.0 (-4.4 to 8.3) |
| Serious AE; n (%) | 39 (14) | 30 (12) | 2.3 (-3.3 to 8.0) |

Based on Table 2 and Supplemental Table 2 of Obermair et al. 2020[18]

[*] No effect estimate reported

[**] P<0.05 based on a $X^2$ Test

[***] Intraoperative and/or postoperative transfusions

AE = adverse event; CI = confidence interval; DVT = deep vein thrombosis; GI = gastrointestinal LACC = laparoscopic approach to cervical cancer; min = minute; MIS = minimally invasive surgery; PE = pulmonary embolism; ORH = open radical hysterectomy

Table 9: Intra and perioperative outcomes for the LACC trial and the reviews

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| **Estimated blood loss (ml)** | NR | NR | RRH vs. ORH: MD -322.59 (95% CI -502.75 to -142.43) 5 studies | LRH vs. ORH: MD -178.41 (95% CI -214.89 to -141.94), 13 studies |
| **Length of surgery (min)** | NR | NR | RRH vs. ORH: MD 36.07 (95% CI 5.83 to 66.31) 6 studies | LRH vs. ORH: MD 43.68 (95% CI 29.42 to 57.95), 15 studies |
| **Blood transfusion** | NR | NR | RRH vs. ORH: OR 0.19 (95% CI 0.09 to 0.39) 6 studies | LRH vs. ORH: OR 0.47 (95% CI 0.30 to 0.73), 13 studies |
| **Intraoperative complications** | NR | NR | RRH vs. ORH: OR 0.52 (95% CI 0.27 to 0.98) 5 studies | LRH vs. ORH: OR 1.14 (95% CI 0.68 to 1.93), 8 studies |
| **Postoperative complications** | NR | NR | RRH vs. ORH: OR 0.74 (95% CI 0.45 to 1.22) 7 studies | NR |
| **Length of hospital stay (days)** | NR | NR | RRH vs. open RRH: MD -2.71 (95% CI -3.74 to -1.68) 6 studies, | LRH vs. ORH: MD -3.17 (95% CI -4.06 to -2.29), 14 studies |
| **Retrieved lymph nodes (n)** | NR | NR | RRH vs. ORH: MD -3.43 (95% CI -7.74 to 0.88) 6 studies | LRH vs. ORH: MD -1.65 (95% CI -3.19 to -0.11), 8 studies |
| **DVT/PE (%) (OR (95% CI))** | NR | NR | NR | LRH vs. ORH: OR 1.31 (0.48 to 3.57), 5 studies |
| **Ileus (%) (OR (95% CI))** | NR | NR | NR | LRH vs. ORH: OR 0.34 (0.12 to 0.91), 7 studies |
| **Lymphocele/lymphedema** | NR | NR | NR | LRH vs. ORH: OR 1.46 (95% CI 0.49 to 4.36), 5 studies |
| **Duration of bladder catheterisation (days)** | NR | NR | NR | LRH vs. ORH: MD -1.69 (95% CI -2.83 to -0.55), 3 studies |
| **UTI** | NR | NR | NR | LRH vs. ORH: OR 0.58 (95% CI 0.22 to 1.57), 4 studies |
| **Ureteral/vaginal fistulas** | NR | NR | NR | LRH vs. ORH: OR 3.67 (95% CI 1.08 to 12.47), 5 studies |

CI = confidence interval; DVT = deep vein thrombosis; LACC = Laparoscopic approach to cervical cancer; LRH = laparoscopic radical hysterectomy; MD = mean difference; NR = not reported; OR = odds ratio; ORH = open radical hysterectomy; PE = pulmonary embolism; RRH = robotic radical hysterectomy; UTI = urinary tract infection

*FAQ 5: How long does the surgery take? How long do I have to stay in hospital?*

The clinical evidence for the decision aid for length of surgery and hospital stay as well as estimated blood loss and blood transfusion is presented in Table 10.

Table 10: Length of surgery and hospital stay, estimated blood loss and blood transfusion

| **Outcome** | ***MIS (n=279)*** | ***ORH (n=257)*** | ***MIS vs. ORH (95% CI)*** |
|---|---|---|---|
| Length of surgery (min); geometric mean (range) | 216 (75 to 441) | 187 (61 to 425) | P<0.001* |
| Estimated blood loss (ml); geometric mean (range) | 101 (10 to 1500) | 209 (10 to 2200) | P<0.001* |
| Blood transfusion | 3.6 | 7.8 | P=0.03* |
| Length of stay (days); median (range) | 3 ( 0 to 72) | 5 (1 to 69) | P=0.002* |

Based on Table 3 of Obermair et al. 2020[18]

* No effect estimate reported

CI = confidence interval; min = minute; MIS = minimally invasive surgery; ml = millilitre, ORH = open radical hysterectomy

*FAQ 6: Will my quality of life improve?*

After conducting the systematic searches for this report, results on quality of life for the LACC trial were published.[10]

Results suggest that, six weeks after surgery, physical quality of life (physical component score) is worse than before surgery, irrespective of whether patients have undergone minimally invasive or open surgery. The physical limitations after minimally invasive surgery seems to be slightly lower than after open surgery.

Three months after surgery, quality of life seems to be as good as before sugery. No differences in physical and mental quality of life between the minimally invasive and open surgery group were identified. Detailed results are presented in Tables 11 and 12.

Table 11: Summary of change in quality of life at the early time period (6 weeks)

| Outcome | | *Baseline N; mean[†] (95% CI)* | *Early time point N; mean[†] (95% CI)* | Change (95% CI) | Difference in change (95% CI) | *P-value* |
|---|---|---|---|---|---|---|
| EQ-5D: Body state | ORH | 241; 78.3 (75.8 to 80.7) | 215; 78.4 (76.1 to 80.7) | 0.23 (-2.62 to 3.08) | 1.79 (-1.07 to 4.65) | 0.22 |
| | MIS | 245; 78.0 (75.6 to 80.3) | 219; 80.0 (78.1 to 82.0) | 2.17 (-0.32 to 4.66) | | |
| FACTO: Total score | ORH | 236; 76.9 (75.4 to 78.3) | 216; 76.7 (75.1 to 78.3) | -0.44 (-2.13 to 1.26) | 1.03 (-0.93 to 2.99) | 0.3 |
| | MIS | 244; 77.3 (75.8 to 78.8) | 219; 77.5 (76.0 to 79.1) | 0.49 (-0.96 to 1.94) | | |
| MDASI: Symptom Score | ORH | 238; 86.2 (84.4 to 88.1) | 215; 85.7 (83.7 to 87.8) | -0.51 (-2.89 to 1.87) | 0.23 (-2.40 to 2.85) | 0.86 |
| | MIS | 244; 84.5 (82.7 to 86.4) | 220; 85.5 (83.6 to 87.5) | 0.93 (-1.06 to 2.92) | | |
| MDASI: Interferences | ORH | 239; 86.8 (84.4 to 89.3) | 215; 80.4 (77.5 to 83.3) | -6.57 (-9.89 to 3.26) | 2.20 (-1.78 to 6.19) | 0.28 |
| | MIS | 244; 83.5 (80.6 to 86.4) | 219; 82.0 (79.0 to 85.0) | -1.77 (-5.18 to 1.64) | | |
| SF-12: physical component score | ORH | 230; 48.1 (47.4 to 48.9) | 207; 42.7 (41.8 to 43.6) | -5.34 (-6.47 to -4.20) | 1.92 (0.66 to 3.18) | 0.003 |
| | MIS | 240; 48.0 (47.3 to 48.8) | 213; 44.6 (43.7 to 45.4) | -3.33 (-4.34 to -2.31) | | |
| SF-12: mental component score | ORH | 230; 42.5 (41.5 to 43.6) | 207; 46.6 (45.7 to 47.5) | 4.27 (3.10 to 5.44) | -0.14 (-1.47 to 1.19) | 0.84 |
| | MIS | 240; 43.0 (42.1 to 43.9) | 213; 46.9 (45.9 to 47.9) | 3.90 (2.70 to 5.09) | | |

Based on Supplementary Table 3 of Frumovitz et al. 2020[10]
[†]All quality-of-life scores were transformed to a 0–100 scale, with higher scores indicating better quality of life.
CI = confidence interval, EQ-5D = EuroQoL-5 dimensions, FACT-Cx = Functional Assessment of Cancer Therapy–Cervical, MDASI = MD Anderson Symptom Inventory; min = minute; MIS = minimally invasive surgery; ml = millilitre, ORH = open radical hysterectomy, SF-12 = 12-item Short Form Health Survey

Table 12: Summary of change inquality of life at the late time point (3 months)

| Outcome | | *Baseline n; mean[ᵗ] (95% CI)* | *Late time point n; mean[ᵗ] (95% CI)* | Change (95% CI) | Difference in change (95% CI) | *P-value* |
|---|---|---|---|---|---|---|
| EQ-5D: Body state | ORH | 241; 78.3 (75.8 to 80.7) | 203; 81.7 (79.3 to 84.0) | 3.44 (0.52 to 6.36) | -0.40 (-3.53 to 2.72) | 0.8 |
| | MIS | 245; 78.0 (75.6 to 80.3) | 216; 80.9 (78.6 to 83.2) | 3.13 (0.39 to 5.87) | | |
| FACTO: Total score | ORH | 236; 76.9 (75.4 to 78.3) | 203; 78.6 (76.8 to 80.4) | 1.68 (-0.13 to 3.49) | 0.74 (-1.50 to 2.98) | 0.52 |
| | MIS | 244; 77.3 (75.8 to 78.8) | 216; 79.3 (77.5 to 81.0) | 2.02 (0.33 to 3.71) | | |
| MDASI: Symptom Score | ORH | 238; 86.2 (84.4 to 88.1) | 205; 85.8 (83.5 to 88.1) | -0.39 (-2.75 to 1.98) | 1.59 (-1.17 to 4.36) | 0.26 |
| | MIS | 244; 84.5 (82.7 to 86.4) | 215; 86.9 (85.0 to 88.8) | 2.39 (0.25 to 4.52) | | |
| MDASI: Interferences | ORH | 239; 86.8 (84.4 to 89.3) | 202; 85.9 (83.0 to 88.8) | -1.09 (-4.56 to 2.37) | 1.80 (-2.00 to 5.61) | 0.35 |
| | MIS | 244; 83.5 (80.6 to 86.4) | 215; 86.7 (84.1 to 89.3) | 2.91 (-0.37 to 6.20) | | |
| SF-12: physical component score | ORH | 230; 48.1 (47.4 to 48.9) | 194; 45.9 (45.1 to 46.8) | -2.11 (-3.15 to -1.07) | 0.42 (-0.74 to 1.58) | 0.48 |
| | MIS | 240; 48.0 (47.3 to 48.8) | 211; 46.4 (45.6 to 47.2) | -1.67 (-2.56 to -0.78) | | |
| SF-12: mental component score | ORH | 230; 42.5 (41.5 to 43.6) | 194; 45.6 (44.5 to 46.6) | 3.04 (1.84 to 4.24) | -0.42 (-1.80 to 0.95) | 0.55 |
| | MIS | 240; 43.0 (42.1 to 43.9) | 211; 45.2 (44.2 to 46.2) | 2.35 (1.14 to 3.55) | | |

Based on Supplementary Table 4 of Frumovitz et al. 2020[10]

[ᵗ] All quality-of-life scores were transformed to a 0–100 scale, with higher scores indicating better quality of life.

CI = confidence interval, EQ-5D = EuroQoL-5 dimensions, FACT-Cx = Functional Assessment of Cancer Therapy–Cervical, MDASI = MD Anderson Symptom Inventory; min = minute; MIS = minimally invasive surgery; ml = millilitre, ORH = open radical hysterectomy, SF-12 = 12-item Short Form Health Survey

## 3.3 ASSESSMENT OF THE CLINICAL REVIEW EVIDENCE

Details of the studies are presented in Tables 13 and 14.

Table 13: Baseline patient characteristics of the LACC trial

| | MIS (n = 319) | ORH (n=312) |
|---|---|---|
| Age (years); mean (SD) | 46.1 (11.0) | 46.0 (10.6) |
| Body mass index (kg/m$^2$); mean (SD) | 27.2 (5.6) | 26.2 (5.3) |
| **Histology subtype; n (%)** | | |
| Squamous cell carcinoma | 214 (67.1) | 210 (67.3) |
| Adenocarcinoma | 87 (27.3) | 80 (25.6) |
| Adenosquamous carcinoma | 9 (2.8) | 6 (1.9) |
| Not reported | 9 (2.8) | 16 (5.1) |
| **Disease stage; n (%)** | | |
| IA1 | 5 (1.6) | 5 (1.6) |
| IA2 | 21 (6.6) | 20 (6.4) |
| IB1 | 293 (91.8) | 287 (92.0) |
| **ECOG performance status; n (%)** | | |
| 0 | 292 (91.5) | 289 (92.6) |
| 1 | 27 (8.5) | 23 (7.4) |
| **Surgery received; n (%)** | | |
| Minimally invasive | 289 (90.6) | 8 (2.6) |
| Open | 2 (0.6) | 274 (87.8) |
| Withdrew before surgery | 12 (3.8) | 19 (6.1) |
| Surgery was stopped | 16 (5.0) | 11 (3.5) |
| Length of hospital stay (days, median (range)) | 3 (0* to 72) | 5 (0* to 69) |

Based on Table 1 of Ramirez 2018[1]

* Length of stay was zero if patients withdrew or surgery was stopped

ECOG = Eastern Cooperative Oncology Group; kg = kilogram; LACC = laparoscopic approach to cervical cancer; MIS = minimally invasive surgery; ORH = open radical hysterectomy; SD = standard deviation

Table 14: Overview of reviews

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| **Search dates** | NR* | October 2018 | February 2018 | February 2016 |
| **Databases** | NR* | Medline and Scopus<br>No language restrictions | Pubmed, Embase, Cochrane Library and Web of Science<br>English only | Medline, Web of Knowledge, Cochrane Library and Chinese National Knowledge Infrastructure<br>No language restrictions |
| **Inclusion criteria** | | | | |
| **Population** | Cervical cancer (stage IA1 to stage IB) | Early stage cervical cancer (IA1 to IIA)<br><br>Radical trachelectomy, radical vaginal hysterectomy and neo-adjuvant chemotherapy were excluded. | Cervical cancer (IA1 to IVA)<br><br>Studies in patients with benign lesions of gynaecological malignancy other than cervical cancer were excluded. | Cervical cancer stage IA1 to IIA treated with RH with or without lymphadectomy<br><br>Radical trachelectomy, radical vaginal hysterectomy, abdominal assisted vaginal hysterectomy, and recurrent cervical cancer cases were excluded |
| **Intervention** | MIS | Radical hysterectomy with pelvic lymph dissection (LRH, RRH or ORH) | RRH | LRH |
| **Comparators** | ORH | LRH, RRH or ORH | LRH and ORH | ORH (abdominal) |
| **Outcomes** | NR* | DFS, OS | Surgical outcomes (not specified) | Intra and postoperative outcomes (listed in outcomes reported) |
| **Study designs** | NR* | Comparative observational | Prospective and retrospective cohort | Prospective and retrospective comparative |

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| **Methods** | | | | |
| **Quality assessment** | NR | NR | MINORS and Newcastle-Ottawa scale (only MINORS was reported and used to select studies for the meta-analysis, scores < 12 were excluded) | Newcastle-Ottawa scale |
| **Results** | | | | |
| **Number of studies** | 24 (MIS vs. ORH 5, LRH vs. ORH 14, RRH vs. ORH 3, LRH vs. RRH vs. ORH 2) | 21 DFS (LRH vs. ORH 19, RRH vs. ORH 8, RRH vs. LRH 8)<br>26 OS (LRH vs. ORH 15, RRH vs. ORH 8, RRH vs. LRH 6) | 25, 13 included in MA (RRH vs. ORH 4, RRH vs. LRH 6, RRH vs. LRH or ORH 3) | 23 |
| **Study designs** | MA (3), retrospective (17) and prospective (1) observational studies, epidemiological studies (3) | Comparative observational (no details) | Cohort (9 no details)<br>Matched (4 no details ) | RCT (1), prospective (2), retrospective (matched case-control 2), retrospective (18) |
| **Outcomes reported** | DFS, OS, recurrence rate | DFS, OS | DFS, OS, operation time, blood loss, transfusion, conversion, intra-operative complications, post-operative complications, length of hospital stay, retrieved lymph nodes, recurrence | Operation time, blood loss, transfusion rate, length of hospital stay, return to normal bowel activity, duration of bladder catheterisation, intestinal injury, retrieved lymph nodes, length of follow-up, recurrence, specific types of complications and injury |
| **Conclusion** | ORH to be considered standard of care. Patient to be carefully counselled before MIS (which can | MIS including LRH and RRH might be better than ORH in lowering recurrence and | RRH is safe, effective, and comparable to ORH and LRH with respect to | LRH was effective, safe, and embraced superiorities in most essential short-term and long- |

| | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| | be considered safe only for sentinel lymph node mapping in a fertility-sparing setting and could be considered after preoperative conization and for small tumours, adopting preventive surgical manoeuvres and in reference centres. | death. Further, large scale, observational studies and randomised controlled trials are required and this NMA will be updated. | outcomes in surgical trauma and postoperative recovery. | term surgical outcomes over the abdominal approach. For some terminal parameters such as 5-year survival or mortality more data are needed. |

* Literature review without reporting of systematic literature review or pre-specified inclusion criteria

DFS = disease free survival, LRH = laparoscopic radical hysterectomy, MA = meta-analysis; MINORS = Methodological Index for Non-randomised Studies; MIS = minimally invasive surgery; NMA = network meta-analysis, NR = not reported; ORH = open radical hysterectomy, OS = overall survival, RCT = randomised controlled trial; RRH = robotic radical hysterectomy

### *Risk of Bias*

The Cochrane risk of bias tool for RCTs was used to assess the quality of the LACC trial.[8] As detailed in Appendix 3, some minor issues were noted, e.g. regarding the blinding and regarding reporting of the safety population. However, overall, the trial was rated to be at low risk of bias.

The quality of the four secondary publications was assessed using the ROBIS tool (Appendix 4).[9]. The publication by Greggi et al. was a literature review, not a systematic review, so it did not follow a predefined protocol and inclusion criteria and has been rated as unclear risk of bias for each domain and overall.[13] The NMA by Purwanti et al. has not yet been published in full and the only information available was from the protocol, a conference abstract and the related poster so this was also rated as unclear risk of bias both overall and for most domains.[14, 15] However, it was rated as high risk of bias for the identification and selection of studies as only two databases were searched and only one reviewer selected the studies which increases the risk of reviewer error and bias.

The SRs by Zhang and Zhao were both rated as high risk of bias overall.[16, 17] Zhang et al. had a high risk of bias for all domains particularly as it selected studies for the meta-analysis on the basis of their score on the Methodological Index for Non-randomised Studies (MINORS) score. Only 50% of the eligible studies were included in the meta-analysis but no baseline characteristics or results were provided for the other studies.[17] Relevant studies may have been missed as the full search strategy was not reported so could not be checked and only English language studies were included. In contrast, Zhao et al. was judged to be at low risk of bias for study eligibility as the eligibility were clearly reported and there were no restrictions based on study characteristics or language.[16]

The main limitation of both SRs and Purwanti was that they were based on observational studies (there was one small Chinese RCT in Zhao).[14-17] Many of the meta-analyses in Zhang and Zhao had high levels of statistical heterogeneity which may have been due to the fact that they pooled different prospective and retrospective study designs.[16, 17] Neither review performed sensitivity or subgroup analyses, particularly by study design, to explore this heterogeneity. Details of the included study designs were not provided by Purwanti but including comparative observational studies in a network meta-analysis is a potential source of bias as there is no randomisation to balance treatment arms within each study.[14, 15]. Detailed assessments of the four secondary publications are reported in Appendix 5.

## 4. REFERENCES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[5] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

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[8] Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

[9] Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol* 2016;69:225-34.

[10] Frumovitz M, Obermair A, Coleman RL, Pareja R, Lopez A, Ribero R, et al. Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol* 2020;21(6):851-860.

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[13] Greggi S, Casella G, Scala F, Falcone F, Visconti S, Scaffa C. Surgical management of early cervical cancer: when is laparoscopic appropriate? *Curr Oncol Rep* 2020;22(1):7.

[14] Purwanti L, Numthavaj P, Charakorn C, Thakkinstian A. *Network meta-analysis of survival outcomes between open, laparoscopic and robotic surgery in the early stages of cervical cancer women. Poster presented at 6th Annual International Conference on New Voices in Global Health and Development 2019; 5 April 2019; Pathumthani, Thailand [PDF provided by the author]*, 2019

[15] Purwanti L, Thakkinstian A, Numthavaj P, Charakorn C. *Network meta-analysis of survival outcomes between open, laparoscopic and robotic surgery in the early stages of cervical cancer [Abstract P-30]. Presented at 6th Annual International Conference on New Voices in Global Health and Development 2019; 5 April 2019; Pathumthani, Thailand* 2019 [accessed 6.5.20]. 281p. Available from: https://fph.tu.ac.th/uploads/fph/pdf/file-news/Proceedings%20NV%202019_published%20online%202%20July%202019.pdf

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[17] Zhang S-S, Ding T, Cui Z-H, Lv Y, Jiang R-A. Efficacy of robotic radical hysterectomy for cervical cancer compared with that of open and laparoscopic surgery: a separate meta-analysis of high-quality studies. *Medicine* 2019;98(4):e14171.

[18] Obermair A, Asher R, Pareja R, Frumovitz M, Lopez A, Moretti-Marques R, et al. Incidence of adverse events in minimally invasive vs open radical hysterectomy in early cervical cancer: results of a randomized controlled trial. *Am J Obstet Gynecol* 2020;222(3):249.

## APPENDIX 1: EXAMPLE SEARCH STRATEGY

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/03/Iss3
Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/03/Iss3
Searched: 03.03.2020

#1 MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees 1990
#2 MeSH descriptor: [Cervix Uteri] explode all trees 1028
#3 (cervi* or endocervi* or ectocerv*):ti,ab,kw 21427
#4 (cancer* or tumor* or tumour* or neoplas* or malignan* or growth or adenoma* or cyst* or oncolog* or carcinom* or adenocarcinoma* or metasta* or meta-sta* or squamous or SCC or neuroendocrine or neuro-endocrine):ti,ab,kw 255122
#5 #2 or #3 21427
#6 #4 and #5 6973
#7 #1 or #6 6973
#8 MeSH descriptor: [Hysterectomy] explode all trees 1762
#9 (hysterectom* or colpohysterectom* or hysterocolpectom* or panhysterectom* or surgery or surgical* or operat*):ti,ab,kw 261325
#10 ((supervagina* or uterus or uterine) NEAR/3 (amputat* or extirpation or remov*)):ti,ab,kw 169
#11 #8 or #9 or #10 261341
#12 #7 and #11 with Cochrane Library publication date Between Jan 2014 and Apr 2020 1552

CDSR = 24
CDSR Protocols = 3
Central = 1522

## APPENDIX 2: PRIMARY STUDIES INCLUDED IN THE REVIEWS

Table 15: Primary studies included in the reviews

| Studies | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| Abu-Rustum 2003 Gynecol Oncol | | NR* | | ✓ |
| Asciutto 2015 Acta Obstet Gynecol Scand | | | ✓ | |
| Boggess 2008 Am J Obstet Gynecol | | | ✓ | |
| Cao 2015 J Laparoendoc Adv Surg Tech A | ✓ | | | |
| Chen 2012 J Sanxi Med Univ | | | | ✓ |
| Chen 2014 Int J Gynecol Cancer | | | ✓ | |
| Chiva 2019 ESGO conference | ✓ | | | |
| Choi 2012 Ann Surg Oncol | | | | ✓ |
| Chong 2013 Int J Gynecol Cancer | | | ✓ | |
| Corrado 2016 Int J Gynecol Cancer | | | ✓ | |
| Corrado 2018 Int J Gynecol Cancer | ✓ | | | |
| Cusimano 2019 Am J Obstet Gynecol | ✓ | | | |
| Dao 2012 Matern Child Health Care China | | | | ✓ |
| Desille 2013 Eur J Obstet Gynecol Reprod Biol | | | ✓ | |
| Diaz- Feijoo 2014 Gynecol Oncol | | | ✓ | |
| Ditto 2015 Eur J Surg Oncol | ✓ | | | ✓ |
| Diver 2017 J Minim Invasive Gynecol | ✓ | | ✓ | |
| Doo 2019 Gynecol Oncol | ✓ | | | |
| Estape 2009 Gynecol Oncol | | | ✓ | ✓ |
| Frumovitz 2007 Obstet Gynecol | | | | ✓ |
| Geisler 2010 Int J Gynecol CancerV | | | ✓ | |
| Ghezzi 2007 Gynecol Oncol | | | | ✓ |
| Gil-Moreno 2019 J Minim Invasive Gynecol | ✓ | | | |
| Guo 2018 Onco Targets Ther | ✓ | | | |
| Kim 2019 Cancer Res Treat | ✓ | | | |
| Kim 2019a Gynecol Oncol | ✓ | | | |
| Kim 2019b Gynecol Oncol | ✓ | | | |
| Kim JY 2015 Anticancer Res | | | ✓ | |
| Kim TH 2015 Anticancer Res | | | ✓ | |
| Ko 2008 Gynecol Oncol | | | ✓ | |
| Kong 2014 Int J Gynecol Cancer | | | | ✓ |
| Lambaudie 2010 Eur J Surg Oncol | | | ✓ | |
| Laterza 2016 Int J Gynecol Cancer | | | | ✓ |
| Lee 2011 Eur J Obstet Gynecol Reprod Biol | ✓ | | | ✓ |
| Li 2013 Shaanxi Med J | | | | ✓ |
| Lim 2019 Gynecol Minim Invasive Ther | ✓ | | | |
| Malzoni 2009 Ann Surg Oncol | ✓ | | | ✓ |
| Melamed 2018 N Eng J Med | ✓ | | | |

| Studies | Greggi 2020[13] | Purwanti 2020[14, 15] | Zhang 2019[17] | Zhao 2017[16] |
|---|---|---|---|---|
| Mendivil 2016 Surg Oncol | ✓ | | ✓ | |
| Nam 2010 Int J Gynecol Cancer | | | ✓ | |
| Nam 2012 Ann Oncol | ✓ | | | |
| Nezhat 1992 Am J Obstet Gynecol | | | ✓ | |
| Paik 2019 Gynecol Oncol | ✓ | | | |
| Park 2013 J Surg Oncol | | | | ✓ |
| Pellegrino 2017 Acta Biomed | | | ✓ | |
| Sert 2011 Gynecol Oncol | | | ✓ | ✓ |
| Sert 2016 Eur J Surg Oncol | ✓ | | ✓ | |
| Shah 2017 J Gynecol Oncol | ✓ | | | |
| Simsek 2011 Eur J Gynaecol Oncol | | | | ✓ |
| Soliman 2011 Gynecol Oncol | | | ✓ | ✓ |
| Tinelli 2011 Ann Surg Oncol | | | ✓ | |
| Toptas 2014 J Laparoendosc Adv Surg Tech A | | | | ✓ |
| Uccella 2007 Gynecol Oncol | | | | ✓ |
| Uppal 2019 J Clin Oncol | ✓ | | | |
| Vizzielli 2016 J Minim Invasive Gynecol | | | ✓ | |
| Wang 2015 BMC Cancer | ✓ | | | |
| Wright 2012 Gynecol Oncol | | | | ✓ |
| Xiong 2013 Mod Med J China | | | | ✓ |
| Yim 2014 Yonsei Med J | | | ✓ | |
| Zanagnolo 2016 Int J Gynecol Cancer | | | ✓ | |
| Zhao 2017 J Laparoendosc Adv Surg Tech A | ✓ | | | |
| Zhu 2013 Zhejiang J Trauma Surg | | | | ✓ |
| Zhu 2015 Henan J Surg | | | | ✓ |
| * Only reported in an abstract. No response by authors to request for further information<br>NR = not reported | | | | |

## APPENDIX 3: RISK OF BIAS ASSESSMENT (ROBIS) OF THE LACC TRIAL (RAMIREZ 2018)

Table 16: Risk of bias assessment (ROBIS) of the LACC trial (Ramirez 2018)

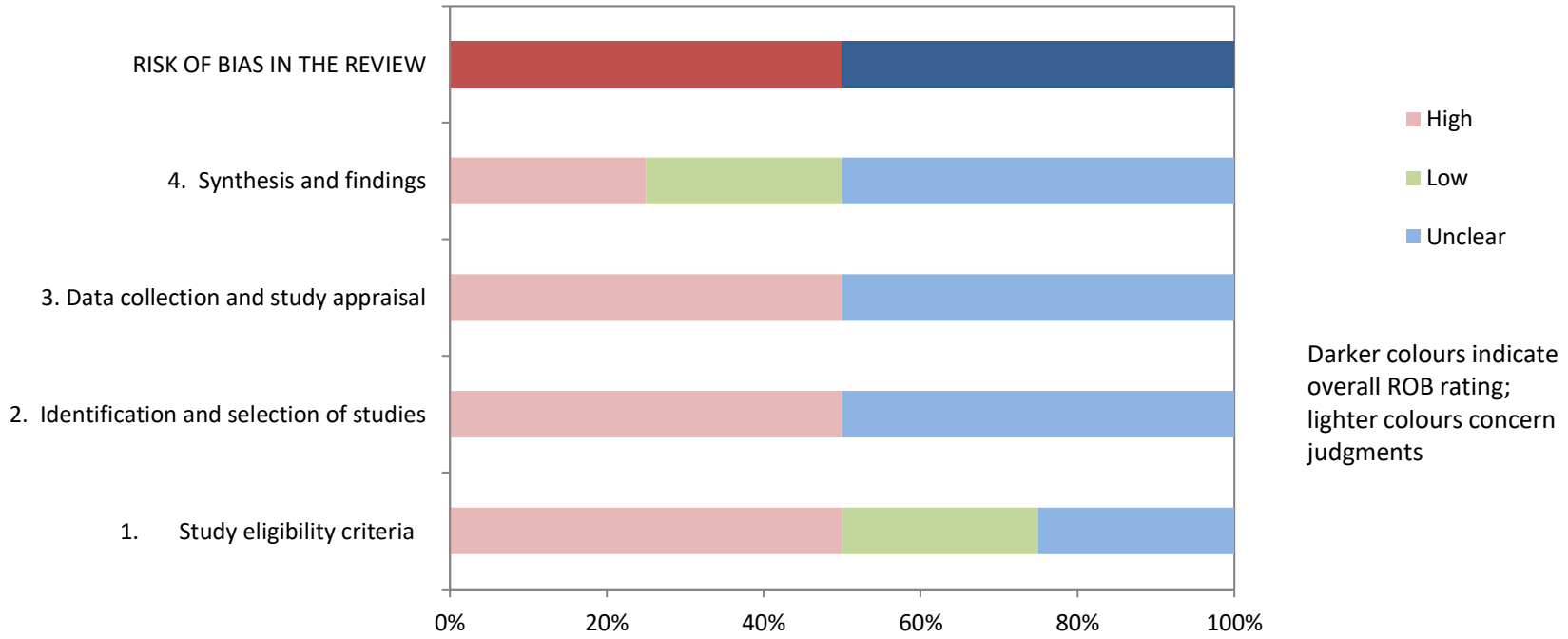
| **Unique ID** | #265 | **Study ID** | Ramirez 2018 | **Assessors** | GW/RW |
|---|---|---|---|---|---|
| **Ref or Label** | N Engl J Med 2018;379:1895-904 | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | Minimally invasive hysterectomy | **Comparator** | Abdominal radical hysterectomy | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Rate of disease-free survival at 4.5 years (percentage of participants reporting so). Non-inferiority is set at -7.2 points. Analysis is two-sided | **Results** | Absolute difference = -10.6 (95% CI -16.4 to -4.7, p=0.74 for superiority and p = 0.87 for noninferiority) | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Randomised; minimization.<br>Randomisation was performed with a web-based system. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | No, baseline characteristics appeared to be balanced between groups |
| | **Risk of bias judgement** | **Low** | **No evidence of issues in the randomisation process** |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | Y | Yes, surgery not possible to blind |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | Y | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context? | PY | Some patients did not receive their randomised surgery (30 MIS and 38 ORH patients), 31 withdrew prior to |

| | | | |
|---|---|---|---|
| | | | surgery, 27 had surgery aborted and 10 switched surgery groups. |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | N | The primary outcome is a long-term outcome measured objectively (DFS) and unlikely to be affected by changes to surgery |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | Intention-to-treat |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Some concerns** | **Due to the lack of blinding and the fact that more patients swapped to MIS than to ORH** |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | All randomised patients were included in the ITT population. However, it is unclear why 15% of randomised participants were not included in the safety population. |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | **No evidence of issues regarding missing outcome data in the ITT population. Some concern regarding the safety population.** |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | N | Disease-free survival was defined as the time from randomization to disease recurrence or death from cervical cancer. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Outcomes were evaluated the same way in both groups and recurrences were assessed by an independent committee |

| | | | |
|---|---|---|---|
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | Y | Surgical intervention |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | PY | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | PN | |
| | **Risk of bias judgement** | **Low** | **Unlikely that measurement of outcome was an issue** |
| Bias in selection of the reported result | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | Y | Protocol was available and analyses followed a prespecified analysis plan |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | Definition of the outcome was unambiguous. |
| | 5.3 ... multiple eligible analyses of the data? | N | The statistical analysis plan was written before unblinding of the trial results to the trial management. |
| | Risk of bias judgement | Low | No evidence of issues regarding selective outcome reporting |
| Overall bias | Risk of bias judgement | Low | The potential biases in the methods of this trial can be regarded to be of no impact to the findings. |

## APPENDIX 4: RISK OF BIAS ASSESSMENT OF IDENTIFIED REVIEWS




Based on Whiting et al. 2016[9]
ROB = risk of bias

## APPENDIX 5: FULL ROBIS ASSESSMENTS FOR EACH REVIEW

Table 17: Full ROBIS assessments for each review

| **Greggi 2020** | | | |
|---|---|---|---|
| **Domain 1: Study eligibility criteria** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? | | No information | Unclear risk<br><br>This is a literature review not a systematic review so the review questions and eligibility criteria were not stated |
| 1.2 Were the eligibility criteria appropriate for the review question? | | No information | |
| 1.3 Were eligibility criteria unambiguous? | | No information | |
| 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate? | | No information | |
| 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate? | | No information | |
| **Domain 2: Identification and selection of studies** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports? | | No information | Unclear risk |
| 2.2 Were methods additional to database searching used to identify relevant reports? | | No information | |
| 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | | No information | |

| Greggi 2020 | | | |
|---|---|---|---|
| 2.4 Were restrictions based on date, publication format, or language appropriate? | | No information | |
| 2.5 Were efforts made to minimise errors in selection of studies? | | No information | |
| **Domain 3: Data collection and study appraisal** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 3.1 Were efforts made to minimise error in data collection? | | No information | Unclear risk |
| 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | | No information | |
| 3.3 Were all relevant study results collected for use in the synthesis? | | No information | |
| 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | | No information | |
| 3.5 Were efforts made to minimise error in risk of bias assessment? | | No information | |
| **Domain 4: Synthesis and findings** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 4.1 Did the synthesis include all studies that it should? | | No information | Unclear risk<br><br>As this was a literature review which did not follow predefined inclusion criteria it is not possible to judge whether all relevant studies were included in the synthesis |
| 4.2 Were all predefined analyses followed or departures explained? | | No information | |
| 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | A narrative synthesis was presented which was appropriate | Probably yes | |

| Greggi 2020 | | | |
|---|---|---|---|
| 4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis? | | No information | |
| 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | | No information | |
| 4.6 Were biases in primary studies minimal or addressed in the synthesis? | | No information | |
| **OVERALL RATING OF RISK OF BIAS** | | | |
| **Question** | **Evidence** | **Rating** | |
| Did the interpretation of findings address all of the concerns identified in domains 1 to 4? | | No information | |
| Was the relevance of identified studies to the review's research question appropriately considered? | | No information | |
| Did the reviewers avoid emphasizing results on the basis of their statistical significance? | | No information | |
| **UNCLEAR RISK OF BIAS**<br>This was a literature review and so did not use systematic review methods so many methodological aspects were not relevant or unclear | | | |

| Purwanti 2019 | | | |
|---|---|---|---|
| **Domain 1: Study eligibility criteria** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? | The protocol was published on PRISMA | Probably Yes | Unclear risk<br><br>Abstract and poster only with limited information |
| 1.2 Were the eligibility criteria appropriate for the review question? | Based on the protocol, the eligibility criteria seem appropriate | Probably Yes | |
| 1.3 Were eligibility criteria unambiguous? | Full details of eligible outcomes were not reported | No information | |
| 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate? | No details | No information | |
| 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate? | The exclusion criteria suggest possible language restrictions (languages which the reviewers could not translate) but there were no further details | No information | |
| **Domain 2: Identification and selection of studies** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports? | Pubmed and SCOPUS were searched but no further details were provided. | Probably No | High risk<br><br>Two databases were searched, and selection was performed by one reviewer. |
| 2.2 Were methods additional to database searching used to identify relevant reports? | No details | No information | |
| 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | No details | No information | |
| 2.4 Were restrictions based on date, publication format, or language appropriate? | Searches were not restricted by language. | Probably Yes | |
| 2.5 Were efforts made to minimise errors in selection of studies? | Study selection was performed by one reviewer. | No | |
| **Domain 3: Data collection and study appraisal** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 3.1 Were efforts made to minimise error in data collection? | Data extraction was conducted independently by three reviewers | Yes | Unclear risk |

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|---|---|---|---|
| **Purwanti 2019** | | | |
| 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | No details | No information | There was no information about the included studies |
| 3.3 Were all relevant study results collected for use in the synthesis? | No details | No information | |
| 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Risk of bias was assessed with the Newcastle Ottawa tool. | Probably Yes | |
| 3.5 Were efforts made to minimise error in risk of bias assessment? | No details | No information | |
| **Domain 4: Synthesis and findings** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 4.1 Did the synthesis include all studies that it should? | No details | No information | Unclear risk<br><br>There were no details about the included or results of pairwise meta-analyses and heterogeneity assessments |
| 4.2 Were all predefined analyses followed or departures explained? | No details | No information | |
| 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | Possibly not given that it contained observational studies but there were no further details | No information | |
| 4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis? | The protocol mentions assessment of heterogeneity and subgroup analyses, but no results were reported | No information | |
| 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | The protocol mentions publication bias tests, but no results were reported | No information | |
| 4.6 Were biases in primary studies minimal or addressed in the synthesis? | No details | No information | |

| Purwanti 2019 | | |
|---|---|---|
| **OVERALL RATING OF RISK OF BIAS** | | |
| **Question** | **Evidence** | **Rating** |
| Did the interpretation of findings address all of the concerns identified in domains 1 to 4? | No discussion as only an abstract/poster but the authors did acknowledge the limitations of including observational studies. | No |
| Was the relevance of identified studies to the review's research question appropriately considered? | | No |
| Did the reviewers avoid emphasizing results on the basis of their statistical significance? | | Yes |
| **UNCLEAR RISK OF BIAS**<br>This review was reported as an abstract and poster with limited information | | |

| Zhang 2019 | | | |
|---|---|---|---|
| **Domain 1: Study eligibility criteria** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? | No protocol was reported but the eligibility criteria were clear | Probably Yes | High risk<br><br>Outcomes were not clearly defined, and studies were selected for further analysis based on their quality score |
| 1.2 Were the eligibility criteria appropriate for the review question? | The eligibility criteria were appropriate | Probably Yes | |
| 1.3 Were eligibility criteria unambiguous? | Outcomes were not defined only described as "interested surgical outcomes" | No | |
| 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate? | Inclusion was also based on study quality (< 12 points on the MINORS scale were excluded) | Probably No | |
| 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate? | All restrictions were relevant for the review question | Probably Yes | |
| **Domain 2: Identification and selection of studies** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports? | PubMed, Embase, the Cochrane Library, and Web of Science were searched. | Probably Yes | High risk |

| | | | |
|---|---|---|---|
| **Zhang 2019** | | | |
| 2.2 Were methods additional to database searching used to identify relevant reports? | References of the included studies were searched. | Yes | The full search strategy was not reported and only studies published in English were included. |
| 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | Only keywords were reported, not the full search strategy | No information | |
| 2.4 Were restrictions based on date, publication format, or language appropriate? | Only studies published in English were included | Probably No | |
| 2.5 Were efforts made to minimise errors in selection of studies? | Two reviewers independently performed study selection | Yes | |
| **Domain 3: Data collection and study appraisal** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 3.1 Were efforts made to minimise error in data collection? | Two reviewers performed the data collection. | Probably Yes | High risk<br><br>There was a lack of detail about the study participants and there were no study characteristics or results reported for the 13 studies excluded from the meta-analysis. |
| 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | Details of patient age and surgical stage were not reported. No data were reported for the 13 studies not included in the meta-analysis. | No | |
| 3.3 Were all relevant study results collected for use in the synthesis? | All relevant study results appear to have been included | Probably Yes | |
| 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Risk of bias was assessed using two different tools, MINORS for inclusion screening and the Newcastle-Ottawa tool (although these results were not reported) | Probably Yes | |
| 3.5 Were efforts made to minimise error in risk of bias assessment? | Two investigators conducted the risk of bias assessment. | Probably Yes | |
| **Domain 4: Synthesis and findings** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 4.1 Did the synthesis include all studies that it should? | Intra- and postoperative outcomes were pooled in a meta-analysis, but overall and disease-free survival were presented in a narrative synthesis which was appropriate as the outcomes were reported in different ways | Probably Yes | High risk<br><br>Different study designs were pooled, statistical heterogeneity was |

| | | | |
|---|---|---|---|
| **Zhang 2019** | | | |
| 4.2 Were all predefined analyses followed or departures explained? | The analyses followed those specified in the methods | Probably Yes | high and not explored through further analyses. |
| 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | Different study designs were pooled (prospective and retrospective) which is not appropriate | Probably No | |
| 4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis? | Statistical heterogeneity was high for many analyses which was not explored. | No | |
| 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | No sensitivity analyses or funnel plots were provided | No | |
| 4.6 Were biases in primary studies minimal or addressed in the synthesis? | Biases were not addressed in the synthesis. | No | |
| **OVERALL RATING OF RISK OF BIAS** | | | |
| **Question** | **Evidence** | **Rating** | |
| Did the interpretation of findings address all of the concerns identified in domains 1 to 4? | The authors acknowledged heterogeneity but no other limitations of the review. | No | |
| Was the relevance of identified studies to the review's research question appropriately considered? | | Probably No | |
| Did the reviewers avoid emphasizing results on the basis of their statistical significance? | Only half the studies were included in the meta-analysis, no details and results were reported for the other studies | No | |
| **HIGH RISK OF BIAS**<br>Methodological issues appear evident in the conduct of this review for all domains. Critically authors disregard the different stages of cervical carcinoma and the role that this variable may play in the clinical outcomes. | | | |

| Zhao 2017 | | | |
|---|---|---|---|
| **Domain 1: Study eligibility criteria** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? | No protocol was reported but the eligibility criteria were reported | Probably Yes | Low risk<br><br>The definition of the eligibility criteria appears appropriate and there were no restrictions |
| 1.2 Were the eligibility criteria appropriate for the review question? | Population, interventions, outcomes, and study designs were specified | Probably Yes | |
| 1.3 Were eligibility criteria unambiguous? | Eligibility criteria were clear | Probably Yes | |
| 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate? | Publications not reporting specified outcomes were excluded | Yes | |
| 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate? | No restrictions are reported. | Yes | |
| **Domain 2: Identification and selection of studies** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports? | Medline, Web of Knowledge (WOK), Cochrane Library and Chinese National Knowledge Infrastructure (CNKI). | Probably Yes | High risk<br><br>The search strategy does not appear sufficiently sensitive. |
| 2.2 Were methods additional to database searching used to identify relevant reports? | References of the included studies were searched. | Yes | |
| 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | The search strategy was limited and did not allow for truncation. | Probably No | |
| 2.4 Were restrictions based on date, publication format, or language appropriate? | No language restrictions were reported | Probably Yes | |
| 2.5 Were efforts made to minimise errors in selection of studies? | Two reviewers independently performed study selection. | Yes | |
| **Domain 3: Data collection and study appraisal** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 3.1 Were efforts made to minimise error in data collection? | Data extraction was performed independently by two reviewers | Yes | High risk |

| Zhao 2017 | | | |
|---|---|---|---|
| 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | There was a lack of information about the included studies, particularly age and cancer stage. | Probably No | There was a lack of information about the study characteristics. |
| 3.3 Were all relevant study results collected for use in the synthesis? | Relevant results appear to have been collected | Probably Yes | |
| 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Risk of bias was assessed with the Newcastle Ottawa tool. | Probably Yes | |
| 3.5 Were efforts made to minimise error in risk of bias assessment? | Two investigators conducted the risk of bias assessment. | Yes | |
| **Domain 4: Synthesis and findings** | | | |
| **Question** | **Evidence** | **Rating** | **Overall domain rating** |
| 4.1 Did the synthesis include all studies that it should? | All relevant studies appear to have been included in the synthesis | Probably Yes | High risk<br><br>Different study designs were pooled, statistical heterogeneity was high and not explored through further analyses. |
| 4.2 Were all predefined analyses followed or departures explained? | Authors appear to adhere to the planned analysis methods | Yes | |
| 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | Different study designs were pooled (prospective and retrospective) which is not appropriate | Probably No | |
| 4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis? | Statistical heterogeneity was high for some outcomes and this was not explored. | No | |
| 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | No sensitivity analyses or funnel plots were provided | No | |
| 4.6 Were biases in primary studies minimal or addressed in the synthesis? | Biases were not addressed in the synthesis. | No | |

| Zhao 2017 | | |
|---|---|---|
| **OVERALL RATING OF RISK OF BIAS** | | |
| **Question** | **Evidence** | **Rating** |
| Did the interpretation of findings address all of the concerns identified in domains 1 to 4? | The authors acknowledged possible publication bias, limitations with study designs and heterogeneity. | No |
| Was the relevance of identified studies to the review's research question appropriately considered? | | Probably yes |
| Did the reviewers avoid emphasizing results on the basis of their statistical significance? | | Probably yes |
| **HIGH RISK OF BIAS**<br>The search strategy was limited so some studies may have been missed. There was a lack of detail about the included studies and the results of the meta-analysis may not be reliable due to the pooling of prospective and retrospective studies and high levels of statistical heterogeneity. | | |