Supplementary. Guidelines development process in accordance with evidence-based medicine

1-1. Generation of key questions based on PICO*

Are PET/CT scans more sensitive than the CT or MRI in predicting lymph node metastasis for the treatment of cervical cancer?

| P | Cervical cancer |
| I | PET |
| C | MRI or CT |
| O | nodal metastasis or lymph node metastasis |

1-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ1

| MEDLINE | 1. "Uterine Cervical Neoplasms"[Mesh] 59998 |
| 2. "Adenocarcinoma"[Mesh:NoExp] OR "Adenocarcinoma, Clear Cell"[Mesh] OR "Adenocarcinoma, Mucinous"[Mesh] OR "Adenocarcinoma, Papillary"[Mesh] OR "Carcinoma, Endometrioid"[Mesh] OR "Carcinoma, Signet Ring Cell"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh:NoExp] OR "Carcinoma, Adenosquamous"[Mesh] OR "Carcinoma, Large Cell"[Mesh] OR "Carcinoma, Small Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh:NoExp] 242652 |
| 3. cervix[tiab] OR Cervical[tiab] OR "Signet Ring Cell"[tiab] OR Neuroendocrine[tiab] OR "Cervix Uteri"[Mesh] 237378 |
| 4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249 |
| 5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] OR Adenosquamous[tiab] OR "Squamous Carcinoma"[tiab] OR "Squamous Carcinomas"[tiab] OR "Epidermoid Carcinoma"[tiab] OR "Epidermoid Carcinomas"[tiab] 11198 |
| 6. 2 OR 4 OR 5 1798373 |
| 7. 6 AND 3 88306 |
| 8. 7 OR 2 106480 |
| 9. "Positron Emission Tomography"[tiab] OR PET[tiab] OR "Positron-Emission Tomography"[tiab] OR PET/CT[tiab] OR "Positron Emission Tomography/Computed Tomography"[tiab] 73809 |
| 10. "Positron-Emission Tomography"[Mesh] 34000 |
| 11. 9 OR 10 80815 |
| 12. 8 AND 11 1785 |
| 13. 12 NOT ('human cell'/de OR 'nonhuman'/de) 2437 |

| EMBASE | 1. uterine cervix tumor/exp 88877 |
| 2. 'adenocarcinoma' DE OR 'adenoid cystic carcinoma' EXP OR 'adenosquamous carcinoma' EXP OR 'clear cell carcinoma' EXP OR 'large cell carcinoma' EXP OR 'small cell carcinoma' EXP OR 'undifferentiated carcinoma' EXP OR 'endometrioid carcinoma' EXP OR 'signet ring carcinoma' EXP OR 'large cell neuroendocrine carcinoma' EXP 107895 |
| 3. cervix:ab,ti OR Cervical:ab,ti 235901 |
| 4. "Signet Ring Cell":ab,ti OR Neuroendocrine:ab,ti OR cancer:ab,ti OR malignant:ab,ti OR carcinoma:ab,ti OR neoplasm:ab,ti OR cancers:ab,ti OR malignancy:ab,ti OR carcinomas:ab,ti OR neoplasms:ab,ti 1749249 |
| 5. Adenocarcinoma:ab,ti OR Adenocarcinomas:ab,ti OR Adenosquamous:ab,ti OR "Squamous Carcinoma":ab,ti OR "Squamous Carcinomas":ab,ti OR "Epidermoid Carcinoma":ab,ti OR "Epidermoid Carcinomas":ab,ti 11198 |
| 6. 2 OR 4 2337031 |
| 7. 6 AND 3 93352 |
| 8. 7 OR 1 122816 |
| 9. 'positron emission tomography':ab,ti OR 'pet ct':ab,ti OR 'pet c t':ab,ti OR 'pet c t':ab,ti OR 'pet c t':ab,ti OR 'positron emission tomography':ab,ti 106793 |
| 10. 'positron emission tomography'/exp 88236 |
| 11. 9 OR 10 80815 |
| 12. 8 AND 11 2437 |
| 13. 12 NOT ('editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) 2544 |

| COCHRANE | 1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees 1771 |
| 2. MeSH descriptor: [Adenocarcinoma] this term only 2444 |
Five articles were finally selected using aforementioned method.

Figure 1. Flow chart of searching strategy for answering KQ1

1-3. Quality assessment

Two non-randomized studies were finally selected and summarized in the table.

Table 2. Study design characteristics based on the Ottawa Quality Assessment Scale
1-4. Level of evidence and grade of recommendation

Table 3. Evidence table for PET/CT in the diagnosis of primary cervical cancer

| Title | Study ID | Journal | Study Design | Setting | Study period | Intervention | Control | Age (year) | Inclusion | Results | Comment |
|-------|----------|---------|--------------|---------|--------------|--------------|---------|------------|-----------|---------|---------|
| Role of magnetic resonance imaging and positron emission tomography/computed tomography in preoperative lymph node detection of uterine cervical cancer | Chung HH, et al., 2010 | AJOG | Retrospective | Korea | 2004-2006 | PET/CT (83) | MRI (83) | 47 (44-66) | IB1-IIB | PET/CT vs MRI sensitivity 28.6% vs 64.3% (P<0.006) Specificity 83.6% vs 69.1% (P=0.057) Accuracy 65.1% vs 51.4% PPV 47.1% vs 51.4% NPV 69.7% vs 79.2% | MRI has more sensitivity than PET/CT for detecting metastatic lymph node |
| Role of 18F-FDG PET/CT in detecting pelvic lymph-node metastases in patients with early-stage uterine cervical cancer: comparison with MRI findings | Lv K, et al., 2014 | Nuclear Medicine Communications | Retrospective | China | 2008-2011 | PET/CT (87) | MRI (87) | 59 (45-73) | IA1-IIB | overall patient-based sensitivity, PPV, NPV, and accuracy of PET/CT were 100% (34/34), 87.2% (34/39), 100% (48/48), and 94.3% (82/87), corresponding MRI values were 44% (15/34), 65% (15/23), 74% (45/61), and 69% (60/87) (P<0.04) | Compared with MRI, PET/CT has higher sensitivity, PPV, NPV, and accuracy in patients with early-stage cervical cancer for detecting lymphatic metastases |

The evidence for the key question was supported by the one NRS research result.

| Outcomes | Illustrative comparative risks* (95% CI) | Pooled effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|------------------------|-------------------------------|-------------------------------|---------|
| KQ1      | Assumed risk Control | Corresponding risk | 170 (2 studies) | ⊗⊗⊗⊗ ⊗ | low* |

1-5. Meta-analysis

There is insufficient evidence that PET/CT is more sensitive than CT or MRI to predict pelvic or para-aortic lymph node metastasis. PET/CT shows discrepant results in terms of sensitivity in selected studies for meta-analysis. As per the study protocol, CT, MRI, and PET/CT have different sensitivity, specificity, negative predictive value and positive predictive value. Overall, when metastases are not identified in the CT or MRI scans or when the results are uncertain, PET/CT could be helpful in predicting pelvic or aortic lymph node metastasis. Range of effect has been suggested by figures.
1-6. Summary

[Q 1] Are PET/CT scans more sensitive than the CT or MRI in predicting lymph node metastasis for the treatment of cervical cancer?

PET/CT could be performed prior to the treatment for cervical cancer.

Level of evidence: C (low)

Strength of recommendation: 1 (strong)

1-7. References

1. Chung HH, Kang KW, Cho JY, et al. Role of magnetic resonance imaging and positron emission tomography/computed tomography in preoperative lymph node detection of uterine cervical cancer. American journal of obstetrics and gynecology. Aug 2010;203(2):156 e151-155.

2. Lv K, Guo HM, Lu YJ, Wu ZX, Zhang K, Han JK. Role of 18F-FDG PET/CT in detecting pelvic lymph-node metastases in patients with early-stage uterine cervical cancer: comparison with MRI findings. Nuclear medicine communications. Dec 2014;35(12):1204-1211.
2-1. Generation of key questions based on PICO*

**[KQ 2]** Does laparoscopic or robotic surgery have similar survival outcomes compared to open surgery for radical hysterectomy in cervical cancer stage IB-IIA?

- **P**: Cervical cancer
- **I**: Radical hysterectomy
- **C**: None
- **O**: Survival or recurrence or morbidity

2-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

| MEDLINE | EMBASE |
|----------|--------|
| 1. 'Uterine Cervical Neoplasms' [Mesh] 39998  
2. 'Adenocarcinoma' [Mesh:NoExp] OR 'Adenocarcinoma, Clear Cell'[Mesh] OR 'Adenocarcinoma, Mucinous'[Mesh] OR 'Adenocarcinoma, Papillary'[Mesh] OR 'Carcinoma, Endometroid'[Mesh] OR 'Carcinoma, Signet Ring Cell'[Mesh] OR 'Carcinoma, Neuroendocrine'[Mesh:NoExp] OR 'Carcinoma, Adenosquamous'[Mesh] OR 'Carcinoma, Large Cell'[Mesh] OR 'Carcinoma, Small Cell'[Mesh] OR 'Carcinoma, Squamous Cell'[Mesh:NoExp] 242652  
3. cervix[tiab] OR Cervical[tiab] OR 'Signet Ring Cell'[tiab] OR Neuroendocrine[tiab] OR 'Cervix Uteri'[Mesh] 237378  
4. cancer[tiab] OR malignant[tiab] OR carcino[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249  
5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] Adenosquamous[tiab] OR 'Squamous Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinoma'[tiab] OR 'Epidermoid Carcinomas'[tiab] 11198  
6. 2 OR 4 OR 5 1798373  
7. 6 AND 3 88306  
8. 7 OR 1 106480  
9. Hysterectomy[tiab] OR Hysterectomies[tiab] OR Hysterectomy[Mesh] 38216  
10. ((Surgical[tiab] OR Procedure[tiab] OR Surgery[tiab] OR resec*[tiab] OR operation[tiab] OR surgery[tiab] OR surgical[tiab] OR dissection[tiab] OR operative[tiab])) OR (Hysterectomy[tiab] OR Hysterectomies[tiab] OR Hysterectomy[Mesh]) 2049846  
11. 10 OR 9 2049846  
12. Laparoscopy[tiab] OR Laparoscopies[tiab] OR Laparoscopic[tiab] OR 'Minimally Invasive'[tiab] OR Robot*[tiab] 133968  
13. 12 OR 11 133968  
14. 14 AND 13 2698  
15. 6 AND 15 NOT ('editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) 2574 | 1. 'uterine cervix tumor'/exp 88877  
2. 'adenocarcinoma/de OR 'adenoid cystic carcinoma'/exp OR 'adenosquamous carcinoma'/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'undifferentiated carcinoma'/exp OR 'endometroid carcinoma'/exp OR 'signet ring carcinoma'/exp OR 'large cell neuroendocrine carcinoma'/exp 107895  
3. cervix:ab,ti OR Cervical:ab,ti 235901  
4. 'Neuroendocrine[tiab] OR cancer[tiab] OR malignant[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249  
5. Adenocarcinoma[ab,ti] OR Adenocarcinomas[ab,ti] OR Adenosquamous[ab,ti] OR 'Squamous Carcinoma'[ab,ti] OR 'Squamous Carcinomas'[ab,ti] OR 'Epidermoid Carcinoma'[ab,ti] OR 'Epidermoid Carcinomas'[ab,ti] 2329011  
6. 2 OR 4 2337031  
7. 6 AND 3 93352  
8. 7 OR 1 122186  
9. Hysterectomy:exp 51366  
10. 'Neuroendocrine[tiab] OR 'adenoid cystic carcinoma'/exp OR 'adenosquamous carcinoma'/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'undifferentiated carcinoma'/exp OR 'endometroid carcinoma'/exp OR 'signet ring carcinoma'/exp OR 'large cell neuroendocrine carcinoma'/exp 107895  
11. Laparoscopy:ab,ti OR Laparoscopies:ab,ti OR Laparoscopic:ab,ti OR 'Minimally Invasive'[tiab] OR Robot*[tiab] 133968  
12. 12 OR 11 133968  
13. 14 AND 13 2698  
14. 15 NOT ('editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) 2574  
15. 5 AND 14 1557 |
Four articles were finally selected using aforementioned method.

![Flow chart of searching strategy for answering KQ2](image)

**2-3. Quality assessment**

The result of the evaluation of the the paper is summarized in the table below.

| Table 2. Study design characteristics |  |  |
|--------------------------------------|---|---|

Page 6
| Study ID       | Journal                  | Study design                             | SELECTION | COMPARABILITY | OUTCOME                |
|---------------|--------------------------|------------------------------------------|-----------|---------------|------------------------|
| Nam JH, et al., 2012 | Ann Oncol               | Retrospective (Matched Cohort Study)     | *         | *             | *                      |
| Bogani G, et al., 2014 | J Minim Invasive Gynecol | Prospective (Propensity-Matched Analysis) | *         | *             | *                      |
| Ditto A, et al., 2015 | Eur J Surg Oncol         | Prospective (Propensity-Matched Analysis) | *         | *             | *                      |

| Study ID       | Journal                  | Study design                             | Was the intervention independent of other changes? | Was the shape of the intervention effect pre-specified? | Was the intervention unlikely to affect data collection? | Was knowledge of the allocated interventions adequately prevented during the study? | Were incomplete outcome data adequately addressed? | Was the study free from selective outcome reporting? | Was the study free from other risks of bias? |
|---------------|--------------------------|------------------------------------------|---------------------------------------------------|------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Hong JH, et al., 2012 | Gynecol Oncol           | Retrospective                            | low                                               | low                                                  | low                                             | low                                                            | low                                              | low                                              | low                                              |

2-4. Level of evidence and grade of recommendation
Table 3. Evidence table

| Study ID          | Journal           | Study Design                                      | Setting  | Study period       | Intervention (N) | Control (N) | Age (year) | Inclusion | Results                                      | Comment                                           |
|-------------------|-------------------|--------------------------------------------------|----------|-------------------|------------------|--------------|------------|-----------|----------------------------------------------|---------------------------------------------------|
| Nam JH, et al., 2012 | Ann Oncol         | Retrospective (Matched Cohort Study)             | Korea    | October 1997 - April 2008 | LRH (263)        | RAH (263)   | Mean age 46.4 vs. 46.5 | IA2 - IIA | 5-yr RFS 92.8% vs. 94.4% (P = 0.499) 5-yr OS 95.2% vs. 96.4% (P = 0.387) | fewer postoperative complication and earlier recovery. |
| Bogani G, et al., 2014 | J Minim Invasive Gynecol | Prospective (Propensity-Matched Analysis/ Historical Control) | Italy    | May 2004 - January 2011 (Historical Control: 1995-2004) | LRH (65)        | RAH (65)    | Mean age 48.9 vs. 50.9 | IA2 - IIB | 5-yr DFS 83% vs. 80% (P=0.60) 5-yr OS 89% vs. 83% (P=0.31) | Trend toward a lower postoperative complication rate |
| Ditto A, et al., 2015 | Eur J Surg Oncol   | Prospective (Propensity-Matched Analysis)        | Italy    | February 2002 - October 2013 | LRH (60)        | RAH (60)    | Mean age 46 (29-79) vs. 45.5 (15-78) | IA2 - IBl (<2 cm) | 5-yr DFS 97% vs. 92% (P=0.29) 5-yr OS 98% vs. 95% (P=0.50) | early recovery, similar post-operative complication rate |
| Hong JH, et al., 2012 | Gynecol Oncol     | Retrospective (Single Arm)                       | Korea    | March 2003 - December 2011 | LRH (118)       |            | Mean age 49 (28-79) | IA2 - IIA | 5-yr DFS 90% 5-yr OS 89% | .                                      |

The evidence for the key question was supported by the four NRS research results.

(Level of evidence: LOW)
Table 4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-----------------------------|---------------------------------|----------|
| KQ2: Follow-up: 10 years | 75 per 1000 | 55 per 1000 (31 to 93) | RR 0.73 (0.42 to 1.25) | 776 (3 studies) | ⊕ ⊕ ⊕ ⊝ | very low |

2-5. Meta-analysis

There is no randomized trial comparing laparoscopic or robotic surgery and open surgery. Based on the meta-analysis, relative risk reduction (RRR)=27%, event rate (ER)=7.4%, optimal information size (OIS)=600, and the number of death=50 is needed to have statistically significant results. This means that larger number of the study population is needed to clarify the differentiation in the death. From several retrospective studies, treatment outcome in terms of progression-free and overall survival is comparable between two groups.

Figure 2. Result of meta-analysis

2-6. Summary

**[KQ 2]** Does laparoscopic or robotic surgery have similar survival outcomes compared to open surgery for radical hysterectomy in cervical cancer stage IB-IIA?

Laparoscopic or robotic radical hysterectomy can be performed in cervical cancer stage IB-IIA.

**Level of evidence:** D (very low)

**Strength of recommendation:** 1 (strong)
2-7. References

1. Nam JH, Park JY, Kim DY, Kim JH, Kim YM, Kim YT. Laparoscopic versus open radical hysterectomy in early-stage cervical cancer: long-term survival outcomes in a matched cohort study. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. Apr 2012;23(4):903-911.

2. Bogani G, Cromi A, Uccella S, et al. Laparoscopic versus open abdominal management of cervical cancer: long-term results from a propensity-matched analysis. Journal of minimally invasive gynecology. Sep-Oct 2014;21(5):857-862.

3. Ditto A, Martinelli F, Bogani G, et al. Implementation of laparoscopic approach for type B radical hysterectomy: a comparison with open surgical operations. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. Jan 2015;41(1):34-39.

4. Hong JH, Choi JS, Lee JH, et al. Can laparoscopic radical hysterectomy be a standard surgical modality in stage IA2-IIA cervical cancer? Gynecologic oncology. Oct 2012;127(1):102-106.
3-1. Generation of key questions based on PICO*

| KQ 3 | Does the nerve sparing radical hysterectomy have similar survival outcome compared to type III hysterectomy in early staged cervical cancer? |
|------|----------------------------------------------------------------------------------------------------------------------------------|
| P | Cervical cancer |
| I | Nerve sparing |
| C | Radical hysterectomy |
| O | Survival or recurrence or complication or morbidity |

3-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ3

**MEDLINE**

1. 'Uterine Cervical Neoplasms' [Mesh] 29998
2. 'Adenocarcinoma' [Mesh:NoExp] OR 'Adenocarcinoma, Clear Cell'[Mesh] OR 'Adenocarcinoma, Mucinous'[Mesh] OR 'Adenocarcinoma, Papillary'[Mesh] OR 'Carcinoma, Endometrioid'[Mesh] OR 'Carcinoma, Signet Ring Cell'[Mesh] OR 'Carcinoma, Neuroendocrine'[Mesh:NoExp] OR 'Carcinoma, Adenosquamous'[Mesh] OR 'Carcinoma, Large Cell'[Mesh] OR 'Carcinoma, Small Cell'[Mesh] OR 'Carcinoma, Squamous Cell'[Mesh:NoExp] 242652
3. cervix[tiab] OR Cervical[tiab] OR 'Signet Ring Cell'[tiab] OR Neuroendocrine[tiab] OR 'Cervix Uteri'[Mesh] 237378
4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249
5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] Adenosquamous[tiab] OR 'Squamous Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinomas'[tiab] 11198
6. 2 OR 4 OR 5 1798373
7. 6 AND 3 88306
8. 7 OR 1 106480
9. Hysterectomy[tiab] OR Hysterectomies[tiab] OR Hysterectomy[Mesh] 38299
10. 8 OR 9 58724
11. 10 AND Publication date from 2014/01/01 to 2015/04/06 32392

**EMBASE**

1. 'uterine cervix tumor'/exp 88877
2. 'adenocarcinoma'/de OR 'adenoid cystic carcinoma'/exp OR 'adenosquamous carcinoma'/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'small cell carcinoma'/exp OR 'undifferentiated carcinoma'/exp OR 'endometrioid carcinoma'/exp OR 'signet ring carcinoma'/exp OR 'large cell neuroendocrine carcinoma'/exp OR 'endometrioid carcinoma'/exp OR 'signet ring carcinoma'/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'small cell carcinoma'/exp OR cancer[tiab] OR malignant[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] OR Adenocarcinoma[tiab] OR 'Squamous Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Care' 89828

**COCHRANE**

1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees1771
2. MeSH descriptor: [Adenocarcinoma] this term only 2444
3. MeSH descriptor: [Carcinoma, Clear Cell] explode all trees 31
4. MeSH descriptor: [Carcinoma, Adenosquamous] explode all trees 38
5. MeSH descriptor: [Carcinoma, Endometrioid] explode all trees 32
6. MeSH descriptor: [Carcinoma, Signet Ring Cell] explode all trees 6
7. MeSH descriptor: [Carcinoma, Neuroendocrine] explode all trees 6
8. MeSH descriptor: [Carcinoma, Adenosquamous] explode all trees 38
9. MeSH descriptor: [Carcinoma, Large Cell] explode all trees 73
10. MeSH descriptor: [Carcinoma, Small Cell] explode all trees 747
11. MeSH descriptor: [Carcinoma, Neuroendocrine] this term only 3
12. MeSH descriptor: [Carcinoma, Squamous Cell] this term only 2136
13. 2-12/or 4835
14. cancer or malignant or carcinoma or neoplasm or cancers or malignancy or carcinomas or neoplasms or Adenocarcinoma or Adenocarcinomas Adenosquamous or 'Squamous Carcinoma' or 'Squamous Carcinomas' or 'Epidermoid Carcinoma' or 'Epidermoid Carcinomas':ti,ab,kw 89828
15. OR 13 or 14 89828
16. MeSH descriptor: [Cervix Uteri] explode all trees 968
17. cervix or Cervical or 'Signet Ring Cell':ti,ab,kw 10584
18. OR 16 or 17 10584
19. 18 and 15 3276
20. 19 or 13 3276
21. 20/trials 2623
Two articles were finally selected using aforementioned method.

Records identified through database searching  
- Medicine (n=329), Embase (n=734), Cochrane (n=2623)  
- Total (n=3684)

Records screened  
(n=3072)

Records excluded  
(n=3044)

Full-text articles assessed for eligibility  
(n=28)

Studies included in Guideline  
(n=2)

Figure 1. Flow chart of searching strategy for answering KQ3

3-3. Quality assessment

The result of the evaluation of the the paper is summarized in the table below.

Table 2. Study design characteristics

| Study ID | Journal | Study design | Risk of bias |
|----------|---------|--------------|--------------|
|          |         |              | Selection    |
|          |         |              | Outcome      |
|          |         |              | Comparability |
|          |         |              | Outcome      |
|          |         |              | Adequacy of Follow-Up of Cohorts |
| Rho JW et al | JGO | RCT | unclear | unclear | unclear | low | low | low | low | low | other bias |
| Ditto et al | ASO | Prospective | * | * | * | * | * | * | * | * |

3-4. Level of evidence and grade of recommendation
Table 3. Evidence table for postoperative radiotherapy

| Study ID  | Journal | Study Design       | Setting  | Study period   | Intervention (N) | Control (N) | Age (year) | Inclusion | Results                          | Comment                                                                 |
|-----------|---------|--------------------|----------|----------------|------------------|--------------|------------|-----------|----------------------------------|------------------------------------------------------------------------|
| Ditto et al | ASO   | Prospective observational study | Italy    | Jan 2001-Sep 2009 | 185              | 311          | 22-77      | Ia2-Iib   | 5yr DFS: 78.9 vs. 79.8% 5yr OS: 90.8 vs. 84.1% | Fiveyear disease-free survival estimate was 78.9% (95% confidence interval [CI] 72.0–85.7) in NSRH and 79.8% (95% CI 75.3–84.3) in RH (P = 0.519). Five-year overall survival estimate was 90.8% (95% CI 85.9–95.6) in NSRH and 84.1% (95% CI 8.0–88.3) in RH (P = 0.192). Rates of postoperative serious complications were 9.7% and 19.6% for NSRH and RH, respectively (P = 0.004). |
| Rho et al | JGO   | RCT                | Korea    | Mar 2003-Nov 2005 | 48               | 44           | Median 47.50 | Ib1-Iia   | 10yr DFS: 94.9 vs. 92.4% | Volume at residual urine, bladder complication, all parameters of urodynamic study, and international prostate symptom score deteriorated in CRH compared to NSRH |

The evidence for the key question was supported by the one RCT and 1 NRS research results. (Level of evidence: LOW)
Table 4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-----------------------------|--------------------------------|----------|
| KQ3      | 68 per 1000 (8 to 238)                 | RR 0.61 (0.11 to 3.49)   | 92 (1 study)                | ⊘◎◎◎ | low      |

3-5. Meta-analysis

Meta-analysis has been performed to investigate the survival outcome in early cervical cancer. Survival outcome after nerve sparing radical hysterectomy is similar to that of type III hysterectomy and results in decreased urinary difficulty. Based on the meta-analysis, relative risk reduction (RRR)=39%, event rate (ER)=6.8%, optimal information size (OIS)=200, and the number of death=5 is needed to have statistical analysis. One randomized trial and one non-randomized trial showed no impact of nerve sparing radical hysterectomy on survival outcome.

Figure 2. Result of meta-analysis

3-6. Summary

[KQ 3] Does the nerve sparing radical hysterectomy have similar survival outcome compared to type III hysterectomy in early staged cervical cancer?

Nerve sparing radical hysterectomy could be performed in early staged cervical cancer.

Level of evidence: C (low)

Strength of recommendation: 2 (weak)

3-7. References

1. Ditto A, Martinelli F, Mattana F, et al. Class III nerve-sparing radical hysterectomy versus standard class III radical hysterectomy: an observational study. Annals of surgical oncology. Nov 2011;18(12):3469-3478.

2. Roh JW, Lee DO, Suh DH, et al. Efficacy and oncologic safety of nerve-sparing radical hysterectomy for cervical cancer: a randomized controlled trial. Journal of gynecologic oncology. Apr 2015;26(2):90-99.
4-1. Generation of key questions based on PICO*

**[KQ 4]**

*Can we have similar survival outcome with type I hysterectomy compared to radical hysterectomy in women with cervical cancer ≤2 cm?*

| P | I | C | O |
|---|---|---|---|
| Early stage cervical cancer | Less radical hysterectomy or conization or simple trachelectomy or simple hysterectomy | Radical surgery (radical trachelectomy, radical hysterectomy) | Overall survival or Progression-free survival |

4-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

**Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ 4**

**MEDLINE**

1. "Uterine Cervical Neoplasms" [Mesh] 39998
2. "Adenocarcinoma" [Mesh:NoExp] OR "Adenocarcinoma, Clear Cell" [Mesh] OR "Adenocarcinoma, Mucinous" [Mesh] OR "Adenocarcinoma, Papillary" [Mesh] OR "Carcinoma, Endometroid" [Mesh] OR "Carcinoma, Signet Ring Cell" [Mesh] OR "Carcinoma, Neuroendocrine" [Mesh:NoExp] OR "Carcinoma, Adenosquamous" [Mesh] OR "Carcinoma, Large Cell" [Mesh] OR "Carcinoma, Small Cell" [Mesh] OR "Carcinoma, Squamous Cell" [Mesh:NoExp] 243052
3. cervix[tiab] OR Cervical[tiab] OR "Signet Ring Cell"[tiab] OR Neuroendocrine[tiab] OR "Cervix Uteri"[Mesh] 237378
4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249
5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] Adenosquamous[tiab] OR "Squamous Carcinoma"[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinoma'[tiab] OR 'Epidermoid Carcinomas'[tiab] 11198
6. 2 OR 4 OR 5 1798373
7. 6 AND 3 88306
8. 7 OR 1 106480
9. Hysterectomy[tiab] OR Hysterectomies[tiab] OR Hysterectomy[Mesh] 38177
10. 'Conization'[Mesh] OR conization[tiab] OR trachelectomy[tiab] OR Conizations[tiab] OR Conisation[tiab] OR Conisations[tiab] OR trachelectomies[tiab] 2534
11. 9 OR 10 39863
12. less[tiab] OR simple[tiab] OR "class I"[tiab] OR "type 1"[tiab] OR "class I"[tiab] OR "type I"[tiab] 1931738
13. 11 AND 12 AND 8 1230

**EMBASE**

1. 'uterine cervix tumor'/exp 88877
2. 'adenocarcinoma'/de OR 'adenoid cystic carcinoma'/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'small cell carcinoma'/exp OR 'undifferentiated carcinoma'/exp OR 'endometrioid carcinoma'/exp OR 'signet ring carcinoma'/exp OR 'large cell neuroendocrine carcinoma'/exp 107895
3. cervix:ab,ti OR Cervical:ab,ti 235901
4. 'Signet Ring Cell':ab,ti OR Neuroendocrine:ab,ti OR Cancer:ab,ti OR Malignant:ab,ti OR Carcinoma:ab,ti OR Neoplasm:ab,ti OR Cancers:ab,ti OR Malignancy:ab,ti OR Carcinomas:ab,ti OR Neoplasms:ab,ti OR Adenocarcinoma:ab,ti OR Adenocarcinomas:ab,ti OR Adenosquamous:ab,ti OR 'Squamous Carcinoma':ab,ti OR 'Squamous Carcinomas':ab,ti OR 'Epidermoid Carcinoma':ab,ti OR 'Epidermoid Carcinomas':ab,ti 11198
5. 2 OR 4 2337031
6. 3 AND 5 93352
7. 6 OR 1 122186
8. Hysterectomy/exp 51319
9. Hysterectomy:ab,ti OR Hysterectomies:ab,ti 38299
10. 8 OR 9 58724
11. Conization:ab,ti OR trachelectomy:ab,ti OR Conizations:ab,ti OR Conisation:ab,ti OR Conisations:ab,ti OR trachelectomies:ab,ti 3279
12. 'uterine cervix conization'/exp 2085
13. 11 OR 12 3871
14. 10 OR 13 61181
15. less:ab,ti OR simple:ab,ti OR 'class I':ab,ti OR 'type 1':ab,ti OR 'class I':ab,ti OR 'type I':ab,ti 1931738
16. 15 AND 14 AND 7 1754

**COCHRANE**

1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees
2. MeSH descriptor: [Adenocarcinoma] this term only
3. MeSH descriptor: [Adenocarcinoma, Clear Cell] explode all trees
4. MeSH descriptor: [Adenocarcinoma, Mucinous] explode all trees
5. MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
6. MeSH descriptor: [Carcinoma, Endometroid] explode all trees
7. MeSH descriptor: [Carcinoma, Signet Ring Cell] explode all trees
8. MeSH descriptor: [Carcinoma, Adenosquamous] explode all trees
9. MeSH descriptor: [Carcinoma, Large Cell] explode all trees
10. MeSH descriptor: [Carcinoma, Small Cell] explode all trees
11. MeSH descriptor: [Carcinoma, Neuroendocrine] this term only
12. MeSH descriptor: [Carcinoma, Squamous Cell] this term only
13. 2 OR 4 4853
One article was finally selected using aforementioned method.

Figure 1. Flow chart of searching strategy for answering KQ4

4.3. Quality assessment

The result of the evaluation of the the paper is summarized in the table below.

Table 2. Study design characteristics

| Study ID | Journal | Study design | Random sequence generation | Allocation concealment | Blinding of participants | Blinding of personnel | Blinding of outcome | Incomplete outcome data | Selective reporting | Other sources of bias |
|----------|---------|--------------|----------------------------|------------------------|-------------------------|---------------------|---------------------|----------------------|-------------------|-------------------|
| Landoni et al 2012 | EJSO | RCT | Low | High | High | High | Low | Low | Low |

4.4. Level of evidence and grade of recommendation
Table 3. Evidence table

| Study ID     | Journal | Study Design            | Setting | Study period | Intervention (N) | Control (N) | Age (year) | Inclusion                        | Results                                                                 | Comment                                                                 |
|--------------|---------|-------------------------|---------|--------------|------------------|-------------|------------|----------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------|
| Landoni et al. 2012 | EJSO    | Prospective randomized study | Italia  | 1981-1986    | Class I hysterectomy (n=62) | Class III hysterectomy (n=63) | 24-82      | cervical cancer IB-IIA, tumor <=4cm | fifteen overall survival rate 90% vs 74% (p=0.11, all cases) 76% vs 80% (p=0.88, size <=3cm) | No difference in pelvic recurrences and OS |

The evidence for the key question was supported by the one RCT research results.

(Level of evidence: VERY LOW)
Table 4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|--------------------------------------|--------------------------|-----------------------------|--------------------------------|----------|
| KQ4      | Assumed risk Correlated risk          | 90% vs 74% (p=0.11)³     | 125 (1 study)               | ⊕⊕⊕⊕ very low⁴⁵⁶⁷           |          |
| Follow-up: 5 years | See comment | See comment          |                             |                                |          |

4-5. Meta-analysis

Although based on the limited study results including one prospective randomized trial, we do not observe the definitive loss of survival outcome from type I hysterectomy compared to radical hysterectomy in women with cervical cancer ≤2cm and type I hysterectomy shows better outcome for complication. Relative risk reduction (RRR)=62%, event rate (ER)=26%, optimal information size (OIS)=100, and the number of death=22 is needed for the near future prospective study.

Figure 2. Result of meta-analysis

Specific statistics have not been suggested from the previous studies, estimated value from meta-analysis has not been described.

4-6. Summary

| [KQ 4] | Can we have similar survival outcome with type I hysterectomy compared to radical hysterectomy in women with cervical cancer ≤2 cm? |
|--------|----------------------------------------------------------------------------------------------------------------------------------|
|        | Type I hysterectomy might be performed in a case of higher estimation of postoperative complication based on the clinical decision. |
|        | Level of evidence: D (very low)                                                                                                 |
|        | Strength of recommendation: 2 (weak)                                                                                           |

4-7. References

1. Landoni F, Maneo A, Zapardiel I, Zanagnolo V, Mangioni C. Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. Mar 2012;38(3):203-209.
5-1. Generation of key questions based on PICO*

| KQ 5 | Does intensity modulated radiotherapy (IMRT) result in less complications compared to standard radiotherapy in women with cervical cancer? |
|------|----------------------------------------------------------------------------------------------------------------------------------|
| P    | Cervical cancer                                                                                                                  |
| I    | Intensity modulated radiation therapy                                                                                             |
| C    | Radiation therapy                                                                                                                |
| O    | Toxicity                                                                                                                         |

5-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ 5

MEDLINE
1. 'Uterine Cervical Neoplasms' [Mesh] 39998
2. 'Adenocarcinoma'[Mesh:NoExp] OR 'Adenocarcinoma, Clear Cell'[Mesh] OR 'Adenocarcinoma, Mucoepidermoid'[Mesh] OR 'Adenocarcinoma, Papillary'[Mesh] OR 'Adenocarcinoma, Adenosquamous'[Mesh] OR 'Carcinoma, Signet Ring Cell'[Mesh] OR 'Carcinoma, Neuroendocrine'[Mesh:NoExp] OR 'Carcinoma, Adenosquamous'[Mesh] OR 'Carcinoma, Large Cell'[Mesh] OR 'Carcinoma, Small Cell'[Mesh] OR 'Carcinoma, Squamous Cell'[Mesh:NoExp] 242652
3. cervix[tiab] OR Cervical[tiab] OR 'Signet Ring Cell'[tiab] OR Neuroendocrine[tiab] OR 'Cervix Uteri'[Mesh] 237378
4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249
5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] Adenosquamous[tiab] OR 'Squamous Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinoma'[tiab] OR 'Epidermoid Carcinomas'[tiab] 11198
6. 2 OR 4 OR 5 1798373
7. 6 AND 3 88306
8. 7 OR 1 106593
9. 'Radiotherapy, Conformal'[Mesh] OR IMRT[tiab] 12609
10. (Radiotherapies[tiab] OR Radiotherapy[tiab] OR 'Radiation Therapy'[tiab] OR 'Radiation Therapies'[tiab]) AND ('Intensity Modulated'[tiab] OR 'Volumetric-Modulated'[tiab] OR 'Intensity-Modulated'[tiab] OR 'Volumetric-Modulated'[tiab] OR 'Helical Tomotherapy'[tiab] OR 'Helical Tomotherapies'[tiab] OR 'Conformal'[tiab] OR 'Target Organ Alignment'[tiab]) 10549
11. 9 R 10 15355
12. 8AND 11 535

EMBASE
1. 'uterine cervix tumor'/exp 8887
2. 'adenocarcinoma'/de OR 'adenoid cystic carcinoma'/exp OR 'adenosquamous carcinoma'/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'small cell carcinoma'/exp OR 'undifferentiated carcinoma'/exp OR 'endometrioid carcinoma'/exp OR 'signet ring carcinoma'/exp OR 'large cell neuroendocrine carcinoma'/exp 107895
3. cervix:ab,ti OR Cervical:ab,ti 235901
4. 'Signet Ring Cell':ab,ti OR Neuroendocrine:ab,ti OR carcinoma:ab,ti OR malignancy:ab,ti OR cancers:ab,ti OR 'Squamous Carcinoma':ab,ti OR 'Squamous Carcinomas':ab,ti OR 'Epidermoid Carcinoma':ab,ti OR 'Epidermoid Carcinomas':ab,ti 89828
5. 2 OR 4 2337031
6. 3 AND 5 93352
7. 6 OR 1 122186
8. 'intensity modulated radiation therapy'/exp OR IMRT[ab,ti] 16767
9. (Radiotherapies[ab,ti] OR Radiotherapy[ab,ti] OR 'Radiation Therapy'[ab,ti] OR 'Radiation Therapies'[ab,ti]) AND ('Intensity Modulated'[ab,ti] OR 'Volumetric-Modulated'[ab,ti] OR 'Intensity-Modulated'[ab,ti] OR 'Volumetric-Modulated'[ab,ti] OR 'Helical Tomotherapy'[ab,ti] OR 'Helical Tomotherapies'[ab,ti] OR 'Conformal'[ab,ti] OR 'Target Organ Alignment'[ab,ti]) 16414
10. 8 OR 9 23587
11. 7 AND 10 1074

COCHRANE
1. MeSH descriptor: 'Uterine Cervical Neoplasms' explode all trees1771
2. MeSH descriptor: 'Adenocarcinoma' this term only 2444
3. MeSH descriptor: 'Adenocarcinoma, Clear Cell' explode all trees 31
4. MeSH descriptor: 'Adenocarcinoma, Mucoepidermoid' explode all trees 69
5. MeSH descriptor: 'Adenocarcinoma, Papillary' explode all trees 23
6. MeSH descriptor: 'Carcinoma, Endometrioid' explode all trees 32
7. MeSH descriptor: 'Carcinoma, Signet Ring Cell' explode all trees 6
8. MeSH descriptor: 'Carcinoma, Adenosquamous' explode all trees 38
9. MeSH descriptor: 'Carcinoma, Large Cell' explode all trees 73
10. MeSH descriptor: 'Carcinoma, Small Cell' explode all trees 747
11. MeSH descriptor: 'Carcinoma, Neuroendocrine' this term only 3
12. MeSH descriptor: 'Cervix Uteri' this term only 2136
13. 2-12OR 4835
14. cancer or malignant or carcinoma or neoplasm or cancers or malignancy or carcinomas or neoplasms or 'Adenocarcinoma' or 'Adenocarcinomas' Adenosquamous or 'Squamous Carcinoma' or 'Squamous Carcinomas' or 'Epidermoid Carcinoma' or 'Epidermoid Carcinomas' ti,ab,kw 89828
15. 13 or 14 89828
16. MeSH descriptor: [Cervix Uteri] explode all trees 968
Three articles were finally selected using aforementioned method.

![Flow chart of searching strategy for answering KQ5](image)

**Figure 1. Flow chart of searching strategy for answering KQ5**

### 5.3. Quality assessment

The result of the evaluation of the the paper is summarized in the table below.

| Table 2. Study design characteristics |
### 5-4. Level of evidence and grade of recommendation

#### Table 3. Evidence table

| Study ID    | Journal | Study design | Setting       | Study period          | Intervention (N) | Control (N) | Age (year) | Inclusion | Results                          | Comment                        |
|-------------|---------|--------------|---------------|-----------------------|------------------|-------------|------------|-----------|----------------------------------|--------------------------------|
| Gandhi AK, et al., 2013 | DROBP | Nonblinded, parallel RCT | India | 2010-2012 | IMRT (22) | CRT (22) | 45-50 | High | Less acute grade 2 & 3 GI toxicity Grade 2, 31.8 vs. 63.6% Grade 3, 4.5 vs. 27.3% Less chronic grade 3 GI toxicity Grade 3, 13.6 vs. 50% | No difference in PFS & OS |
| Chen LA, et al., 2015 | GO | Retrospective | USA | IMRT, 2008-2012 & 3D-CRT, 2005-2007 | IMRT (46) | CRT (34) | 58-60 | High | Less late overall toxicity Grade 2, 15 vs. 50% Grade 3, 3 vs. 22% | No difference in PFS & OS |
| Liang JA, et al., 2014 | DCC | Prospective for IMRT & Retrospective for CRT | Taiwan | IMRT, 2007-2011 & CRT, 2002-2007 | IMRT (52) | CRT (47) | 51 | High | Grade 2 & 3 late toxicity, 15.6% & 6.2% | Toxicity profile was available for prospective cohort |

Three non-randomized prospective studies support primary use of IMRT for cervical cancer. Toxicity has been reduced with similar survival outcomes. (Level of evidence: LOW)

#### Table 4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-----------------------------|---------------------------------|----------|
| KQ5      | 500 per 1000 (10 to 635)                | RR 0.17 (0.02 to 1.27)   | 44                          | ☯ ☯ ☯ ☯                        | low 5/9  |

There is risk of bias related randomization and allocation concealment for the previous results. Relative risk reduction (RRR)=83%, event rate (ER)=50%, optimal information size (OIS)=50, and the number of death=7 is needed for the near future prospective study.

### 5-5. Meta-analysis

Figure 2. Result of meta-analysis
Summary

**[KQ 5]** Does intensity modulated radiotherapy (IMRT) result in less complications compared to standard radiotherapy in women with cervical cancer?

IMRT could be used as primary treatment for cervical cancer, based on the similar treatment outcome in terms of recurrence and survival with fewer complication rate.

**Level of evidence:** C (low)

**Strength of recommendation:** 2 (weak)

References

1. Gandhi AK, Sharma DN, Rath GK, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. International journal of radiation oncology, biology, physics. Nov 1 2013;87(3):542-548.
2. Chen LA, Kim J, Boucher K, et al. Toxicity and cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for postoperative treatment of gynecologic cancers. Gynecologic oncology. Mar 2015;136(3):521-528.
3. Liang JA, Chen SW, Hung YC, et al. Low-dose, prophylactic, extended-field, intensity-modulated radiotherapy plus concurrent weekly cisplatin for patients with stage IB2-IIIB cervical cancer, positive pelvic lymph nodes, and negative para-aortic lymph nodes. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. Jun 2014;24(5):901-907.
6-1. Generation of key questions based on PICO*

[KQ 6] Does radical hysterectomy result in similar survival outcome like concurrent chemoradiotherapy in cervical cancer stage IB2 and IIA2?

P: Cervical cancer
I: Radical hysterectomy
C: Concurrent chemoradiation or Radiation
O: Survival or complication

6-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ6

**MEDLINE**

1. 'uterine cervical Neoplasms'[Mesh] 39998
2. 'Adenocarcinoma'[Mesh:NoExp] OR 'Adenocarcinoma, Clear Cell'[Mesh] OR 'Adenocarcinoma, Mucinous'[Mesh] OR 'Adenocarcinoma, Papillary'[Mesh] OR 'Adenocarcinoma, Endometroid'[Mesh] OR 'Carcinoma, Signet Ring Cell'[Mesh] OR 'Carcinoma, Neuroendocrine'[Mesh:NoExp] OR 'Carcinoma, Adenosquamous'[Mesh] OR 'Carcinoma, Large Cell'[Mesh] OR 'Carcinoma, Small Cell'[Mesh] OR 'Carcinoma, Squamous Cell'[Mesh:NoExp] 242652
3. cervix[tiab] OR Cervical[tiab] OR 'Signet Ring Cell'[tiab] OR Neuroendocrine[tiab] OR 'Cervix Uteri'[Mesh] 237737
4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249
5. 'Squamous Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinoma'[tiab] OR 'Epidermoid Carcinomas'[tiab] 11198
6. 2 OR 4 OR 5 1798373
7. 6 AND 3 88306
8. 7 OR 1 106593
9. 'Radiotherapy, Conformal'[Mesh] OR IMRT[tiab] 12609
10. (Radiotherapies[tiab] OR Radiotherapy[tiab] OR 'Radiation Therapy'[tiab] OR 'Radiation Therapies'[tiab]) AND ('Intensity Modulated'[tiab] OR 'V olumetric-Modulated'[tiab] OR 'Intensity-Modulated'[tiab]) OR 'Helical Tomotherapy'[tiab] OR 'Helical Tomotherapies'[tiab] OR 'Conformal'[tiab] OR 'Target Organ Alignment'[tiab] 10549
11. 9 R 10 15355
12. 8 AND 11 535

**EMBASE**

1. 'uterine cervix tumor/exp 8887
2. 'adenocarcinoma/de OR 'adenoid cystic carcinoma/exp OR 'adenosquamous carcinoma/exp OR 'clear cell carcinoma/exp OR 'large cell carcinoma/exp OR 'small cell carcinoma/exp OR 'undifferentiated carcinoma/exp OR 'endometrioid carcinoma/exp OR 'signet ring carcinoma/exp OR 'large cell neuroendocrine carcinoma/exp 107895
3. cervix,ab,ti OR Cervical,ab,ti 235901
4. 'Signet Ring Cell',ab,ti OR Neuroendocrine,ab,ti OR cancer,ab,ti OR malignant,ab,ti OR neoplasms,ab,ti OR cancers,ab,ti OR malignancy,ab,ti OR carcinomas,ab,ti OR neoplasms,ab,ti OR Adenocarcinoma,ab,ti OR Adenosquamous,ab,ti OR 'Squamous Carcinoma',ab,ti OR 'Squamous Carcinomas',ab,ti OR 'Epidermoid Carcinoma',ab,ti OR 'Epidermoid Carcinomas',ab,ti 2326011
5. 2 OR 4 2337031
6. 3 AND 5 93352
7. 6 OR 1 122186
8. 'Intensity modulated radiation therapy/exp OR IMRT,ab,ti 16767
9. (Radiotherapies,ab,ti OR Radiotherapy,ab,ti OR 'Radiation Therapy',ab,ti OR 'Radiation Therapies',ab,ti) AND ('Intensity Modulated',ab,ti OR 'V olumetric-Modulated',ab,ti OR 'Intensity-Modulated',ab,ti OR 'V olumetric-Modulated',ab,ti OR 'Helical Tomotherapy',ab,ti OR 'Helical Tomotherapies',ab,ti OR 'Conformal',ab,ti OR 'Target Organ Alignment',ab,ti) 16414
10. 8 OR 9 23587
11. 7 AND 10 1074

**COCHRANE**

1. 'uterine cervical Neoplasms' explode all trees 1771
2. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees 2444
3. MeSH descriptor: Adenocarcinoma, Clear Cell] explode all trees 31
4. MeSH descriptor: Adenocarcinoma, Mucinous] explode all trees 69
5. MeSH descriptor: Adenocarcinoma, Papillary] explode all trees 23
6. MeSH descriptor: Carcinoma, Endometrioid] explode all trees 32
7. MeSH descriptor: Carcinoma, Signet Ring Cell] explode all trees 38
8. MeSH descriptor: Carcinoma, Adenosquamous] explode all trees 38
9. MeSH descriptor: Carcinoma, Large Cell] explode all trees 73
10. MeSH descriptor: Carcinoma, Small Cell] explode all trees 747
11. MeSH descriptor: Carcinoma, Neuroendocrine] this term only 3
12. MeSH descriptor: Carcinoma, Squamous Cell] this term only 2136
13. 2 OR 12 4855
14. cancer or malignant or carcinoma or neoplasm or cancers or malignancy or carcinomas or neoplasms or 'Adenocarcinoma' or 'Adenosquamous Carcinoma' or 'Squamous Carcinoma' or 'Epidermoid Carcinoma' or 'Epithelial Carcinoma' 15. 13 or 14 89828
16. MeSH descriptor: [Cervix Uteri] explode all trees 968
One randomized trial result and 4 non-randomized studies were finally selected using aforementioned method.

![Flow chart of searching strategy for answering KQ6](chart.png)

**Figure 1. Flow chart of searching strategy for answering KQ6**

### 6-3. Quality assessment

The result of the evaluation of the the paper is summarized in the table below.

Table 2. Study design characteristics
### Study ID | Journal | Study design | Random sequence generation | Allocation concealment | Blinding of participants | Blinding of personnel | Blinding of outcome | Incomplete outcome data | Selective reporting | Other sources of bias |
|------------|---------|--------------|----------------------------|------------------------|-------------------------|----------------------|---------------------|-----------------------|------------------|------------------|
| Landoni F., et al., 1997 | Lancet | RCT | Low | Low | High | High | High | Low | Low | Low |

### Study ID | Journal | Study design | SELECTION | COMPARABILITY | OUTCOME |
|-------------|---------|--------------|------------|--------------|---------|
| H-S Ryu, et al. 2007 | Int J Gynecol Cancer | Retrospective multicenter | Low | Low | Low |
| Jeong-Yeol Park, et al., 2013 | JGO | Retrospective two centers | High | Low | Low |
| Alleyene-Mike K., et al., 2013 | Int J Gynecol Cancer | Retrospective single center | High | Low | Low |
| Zivanovic O., et al., 2008 | Gynecol Oncol | Retrospective single center | High | Low | Low |

### 6-4. Level of evidence and grade of recommendation
Table 3. Evidence table

| Study ID          | Journal                  | Study Design   | Setting       | Study period | Intervention (N) | Control (N) | Age (year) | Inclusion | Results                                  | Comment                                       |
|-------------------|--------------------------|----------------|---------------|--------------|-----------------|--------------|------------|-----------|------------------------------------------|-----------------------------------------------|
| Landoni F, et al., 1997 | Lancet                  | RCT            | Italy         | 1986-1991    | RH (Ib2 or Ila2, n=55) | RT (Ib2 or Ila2, n=54) | 46 vs. 50 | Ib or Ila | 5Yr OS : RH 70% vs. RT 72%  
5Yr DFS : RH 63% vs. RT 57% | No significant differences in OS & DFS |
| H-S Ryu, et al. 2007 | Int J Gynecol Cancer     | Retrospective multicenter | Korea         | 1995-2005    | RH (n=103)      | CRT (n=51)   | 50         | IB2       | 5Yr OS : RH 89% vs. CRT | Not significant difference in OS |
| Jeong-Yeol Park, et al, 2012 | JGO                     | Retrospective two centers | Korea         | 2001-2010    | RH+adj Tx (n=147) | CRT (n=68)   | 47 vs. 54 | IB2, IIA2 | 5Yr RFS : 77% vs. 66%  
5Yr OS : 78% vs. 67% | Not significant differences in RFS and OS |
| Alleyene-Mike K. et al., 2013 | Int J Gynecol Cancer     | Retrospective single center | South Africa | 1993-2008    | RH (n=25)       | RT/CRT (n=53) | 45.6      | IB2       | 5 Yrs OSR : 88% vs. 62.5% | Significant difference in OS (p=0.03) |
| Zivanovic O., et al., 2008 | Gynecol Oncol           | Retrospective single center | USA           | 1982-2006    | RH (n=27)       | RT/CRT (n=20) | 42 vs. 43 | IB2       | 3 Yr PFS : 52% vs. 55%  
3Yr OS : 72% vs. 55% | No significant differences in PFS & OS |

The evidence for the key question was supported by one RCT and four NRS research results.
(Level of evidence: LOW)
Table 4. Estimation of GRADE

| Outcomes       | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------------|----------------------------------------|--------------------------|-----------------------------|--------------------------------|----------|
|                | Assumed risk                           | Corresponding risk       |                             |                                |          |
| KQ6            | 280 per 1000 (162 to 568)              | 305 per 1000 (162 to 568)| RR 1.09 (0.58 to 2.03)     | 96 (1 study)                   | ⊕⊕⊝⊝     |

6-5. Meta-analysis

Similar survival outcome has been observed between radical hysterectomy with selective adjuvant treatment and primary concurrent chemoradiotherapy in cervical cancer stage IB2 and IIA2. Although the result of one randomized trial is not consistent to that of 4 non-randomized study, decrease of survival has not been observed in primary surgical group.

Figure 2. Result of meta-analysis

6-6. Summary

**[KQ 6]** Does radical hysterectomy result in similar survival outcome like concurrent chemoradiotherapy in cervical cancer stage IB2 and IIA2?

Radical hysterectomy and concurrent chemoradiotherapy could be selectively used considering the clinical situation of patients.

*Level of evidence:* C (low)

*Strength of recommendation:* 2 (weak)

6-7. References

1. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. Aug 23 1997;350(9077):535-540.
2. Ryu HS, Kang SB, Kim KT, Chang KH, Kim JW, Kim JH. Efficacy of different types of treatment in FIGO stage IB2 cervical cancer in Korea: results of a multicenter retrospective Korean study (KGOG-1005).
3. Park JY, Kim DY, Kim JH, et al. Comparison of outcomes between radical hysterectomy followed by tailored adjuvant therapy versus primary chemoradiation therapy in IB2 and IIA2 cervical cancer. Journal of gynecologic oncology. Oct 2012;23(4):226-234.

4. Alleyne-Mike K, van Wijk L, Hunter A. A retrospective review of patients with stage IB2 cervical cancer treated with radical radiation versus radical surgery as a primary modality. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. Sep 2013;23(7):1287-1294.

5. Zivanovic O, Alektiar KM, Sonoda Y, et al. Treatment patterns of FIGO Stage IB2 cervical cancer: a single-institution experience of radical hysterectomy with individualized postoperative therapy and definitive radiation therapy. Gynecologic oncology. Nov 2008;111(2):265-270.
7-1. Generation of key questions based on PICO*

| [KQ 7] | Does simple trachelectomy or conization have similar survival outcome with radical hysterectomy in cervical cancer stage Ia1 with lymphovascular space invasion? |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| P      | Cervical cancer                                                                                                                             |
| I      | Fertility sparing or trachelectomy or conization                                                                                           |
| C      | None                                                                                                                                 |
| O      | Recurrence or survival                                                                                                                     |

7-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ7

| MEDLINE                                                                 |
|------------------------------------------------------------------------|
| 1.  "Uterine Cervical Neoplasms"[Mesh] 59998                           |
| 2.  "Adenocarcinoma"[Mesh:NoExp] OR "Adenocarcinoma, Clear Cell"[Mesh] OR "Adenocarcinoma, Mucinous"[Mesh] OR "Adenocarcinoma, Papillary"[Mesh] OR "Carcinoma, Endometrioid"[Mesh] OR "Carcinoma, Signet Ring Cell"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh:NoExp] OR "Carcinoma, Adenosquamous"[Mesh] OR "Carcinoma, Large Cell"[Mesh] OR "Carcinoma, Small Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh:NoExp] 242652 |
| 3. cervix[tab] OR Cervical[tab] OR "Signet Ring Cell"[tab] OR Neuroendocrine[tab] OR "Cervix Uteri"[Mesh] 237378 |
| 4. cancer[tab] OR malignant[tab] OR carcinoma[tab] OR neoplasm[tab] OR cancers[tab] OR malignancy[tab] OR carcinomas[tab] OR neoplasms[tab] 1749249 |
| 5. Adenocarcinoma[tab] OR Adenocarcinomas[tab] Adenosquamous[tab] OR "Squamous Carcinoma"[tab] OR "Squamous Carcinomas"[tab] OR "Epidermoid Carcinoma"[tab] OR "Epidermoid Carcinomas"[tab] 11198 |
| 6. 2 OR 4 OR 5 1798373                                               |
| 7. 6 AND 3 88306                                                    |
| 8. 7 OR 1 106480                                                   |
| 9. "Conization"[Mesh] OR conization[tab] OR trachelectomy[tab] OR Conizations[tab] OR Conisation[tab] OR Conisations[tab] OR trachelectomies[tab] 2534 |
| 10. 8 AND 9 2074                                                   |

| EMBASE                                                                 |
|------------------------------------------------------------------------|
| 1. uterine cervix tumor/exp 98877                                      |
| 2.  'adenocarcinoma'/'de OR 'adenoid cystic carcinoma'/'exp OR 'adenosquamous carcinoma'/'exp OR 'clear cell carcinoma'/'exp OR 'large cell carcinoma'/'exp OR 'small cell carcinoma'/'exp OR 'undifferentiated carcinoma'/'exp OR 'endometrioid carcinoma'/'exp OR 'signet ring carcinoma'/'exp OR 'large cell neuroendocrine carcinoma'/'exp 107895 |
| 3. cervix:ab,t OR Cervical:ab,t 2359011                                    |
| 4. "Signet Ring Cell"'ab,t OR Neuroendocrine'ab,t OR cancer'ab,t OR malignant'ab,t OR carcinoma'ab,t OR neoplasms'ab,t OR cancers'ab,t OR malignancy'ab,t OR carcinomas'ab,t OR neoplasms'ab,t OR Adenocarcinoma'ab,t OR Adenocarcinomas'ab,t OR Adenosquamous'ab,t OR "Squamous Carcinoma"'ab,t OR "Squamous Carcinomas"'ab,t OR "Epidermoid Carc 5 |
8. conization:ab,ti OR trachelectomy:ab,ti OR Conizations:ab,ti OR Conisation:ab,ti OR Conisations:ab,ti OR trachelectomies:ab,ti 3279
9. 'uterine cervix conization'/exp 2085
10. 11 OR 12 3871
11. 7 AND 10 3096
12. NOT ('editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) 2960
13. NOT 'nonhuman'/de 2920

### COCHRANE

1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees 1771
2. MeSH descriptor: [Adenocarcinoma] this term only 2444
3. MeSH descriptor: [Adenocarcinoma, Clear Cell] explode all trees 31
4. MeSH descriptor: [Adenocarcinoma, Mucinous] explode all trees 69
5. MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees 23
6. MeSH descriptor: [Carcinoma, Endometrioid] explode all trees 32
7. MeSH descriptor: [Carcinoma, Signet Ring Cell] explode all trees 6
8. MeSH descriptor: [Carcinoma, Adenosquamous] explode all trees 38
9. MeSH descriptor: [Carcinoma, Large Cell] explode all trees 73
10. MeSH descriptor: [Carcinoma, Small Cell] explode all trees 747
11. MeSH descriptor: [Carcinoma, Neuroendocrine] this term only 3
12. MeSH descriptor: [Carcinoma, Squamous Cell] this term only 2136
13. 2-12/or 4835
14. cancer or malignant or carcinoma or neoplasm or cancers or malignancy or carcinomas or neoplasms or Adenocarcinoma or Adenocarcinomas Adenosquamous or "Squamous Carcinoma" or "Squamous Carcinomas" or "Epidermoid Carcinoma" or "Epidermoid Carcinomas":ti,ab,kw 89828
15. 13 or 14 89828
16. MeSH descriptor: [Cervix Uteri] explode all trees 968
17. cervix or Cervical or "Signet Ring Cell":ti,ab,kw 10584
18. 16 or 17 10584
19. 18 and 15 3276
20. 19 or 1 3276
21. 20/trials 2623

One article was finally selected using aforementioned method.
Figure 1. Flow chart of searching strategy for answering KQ7

7.3. Quality assessment
The result of the evaluation of the paper is summarized in the table below.

Table 2. Study design characteristics

| Study ID       | Journal          | Study design | Risk of bias       |
|----------------|------------------|--------------|--------------------|
|                |                  |              | Selection          |
|                |                  |              | Comparability      |
|                |                  |              | Outcome            |
| Bekkers, et al, 2002 | IJGC            | Retrospective| *                  |
| Lee, et al, 2009 | Acta Obstetricia et Gynecologica | Retrospective| *                  |

| Study ID       | Journal          | Study design | Risk of bias       |
|----------------|------------------|--------------|--------------------|
|                |                  |              | Selection          |
|                |                  |              | Comparability      |
|                |                  |              | Outcome            |
| Plante, et al, 2013 | IJGC            | Prospective  | Low                |
| Yudianty, et al, 2014 | IJGC            | Retrospective| Low                |

7-4. Level of evidence and grade of recommendation

Table 3. Evidence table
| Study ID        | Journal | Study Design | Setting      | Study period | Intervention (N) | Control (N) | Age (year) | Inclusion     | Results                                                                 | Comment                                      |
|-----------------|---------|--------------|--------------|--------------|------------------|-------------|------------|---------------|-------------------------------------------------------------------------|----------------------------------------------|
| Bekkers, et al, 2002 | IJGC    | Retrospective | Netherlands | 1981-1999   | Cone (5)          | Hysterectomy (4) | 34 (44)    | IA1 with LVSI | No recurrences were noted with a median of 6 years                      | No difference in recurrence rate             |
| Lee, et al, 2009  | Acta Obstetricia et Gynecologica | Retrospective | Korea       | 1997-2006   | Cone (9)          | Hysterectomy (20) | 35 (48)    | IA1 with LVSI | No recurrences were noted with a mean of 34 months                       | No difference in recurrence rate             |
| Plante, et al, 2013 | IJGC    | Prospective | Canada       | 2007-2012   | simple vaginal trachelectomy+PLND (16) | NA          | 30 (22-44) | IA1 with LVSI, IA2, IB1 | No recurrences were noted with a median of 27 months (range, 1-65 months) | single arm study                             |
| Andikyan, et al, 2014 | IJGC    | Retrospective | USA          | 2005-2012   | Cone+sentinel LND (10) | NA          | 28 (20-31) | IA1 with LVSI, IB1 | No recurrences were noted with a median follow-up of 17 months (range, 1-83 months) | single arm study                             |

The evidence for the key question was supported by the four NRS research results.

(Level of evidence: VERY LOW)
Table 4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|-------------------------|----------------------------|-------------------------------|----------|
| KQ7 Follow-up: 5-6 years | See comment | See comment | Not estimable | 61 (2 studies) | ⊕⊕⊕⊕ very low

7-5. Meta-analysis
From the 2 comparison studies and 2 non-comparison studies, similar survival outcomes have been identified in total 61 patients.

7-6. Summary

| [KQ 7] | Does simple trachelectomy or conization have similar survival outcome with radical hysterectomy in cervical cancer stage Ia1 with lymphovascular space invasion? |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|        | Simple trachelectomy and conization could be performed for women with cervical cancer IA1 with lymphovascular space invasion, based on the similar survival outcomes from the radical hysterectomy. |
|        | **Level of evidence:** D (very low)  
**Strength of recommendation:** 2 (weak) |

7-7. References

1. Bekkers RL, Keyser KG, Bulten J, et al. The value of loop electrosurgical conization in the treatment of stage IA1 microinvasive carcinoma of the uterine cervix. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. Sep-Oct 2002;12(5):485-489.
2. Lee SW, Kim YM, Son WS, et al. The efficacy of conservative management after conization in patients with stage IA1 microinvasive cervical carcinoma. *Acta obstetricia et gynecologica Scandinavica.* 2009;88(2):209-215.
3. Plante M, Gregoire J, Renaud MC, et al. Simple vaginal trachelectomy in early-stage low-risk cervical cancer: a pilot study of 16 cases and review of the literature. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* Jun 2013;23(5):916-922.
4. Andikyan V, Khoury-Collado F, Denesopolis J, et al. Cervical conization and sentinel lymph node mapping in the treatment of stage I cervical cancer: is less enough? *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* Jan 2014;24(1):113-117.
8-1. Generation of key questions based on PICO*

| KQ 8 | Does addition of adjuvant chemotherapy after concurrent chemoradiotherapy improve survivals in patients with locally advanced cervical cancer? |

**P**: Locally advanced cervical cancer  
**I**: Adjuvant chemotherapy  
**C**: Concurrent chemoradiation  
**O**: Survival or complication

8-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

**MEDLINE**
1. "Uterine Cervical Neoplasms" [Mesh] 39998  
2. "Adenocarcinoma"[Mesh] OR "Adenocarcinoma, Clear Cell"[Mesh] OR "Adenocarcinoma, Mucinous"[Mesh] OR "Adenocarcinoma, Papillary"[Mesh] OR "Carcinoma, Endometrioid"[Mesh] OR "Carcinoma, Signet Ring Cell"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh:NoExp] OR "Carcinoma, Adenosquamous"[Mesh] OR "Carcinoma, Large Cell"[Mesh] OR "Carcinoma, Small Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh:NoExp] 242652  
3. cervix[tab] OR Cervical[tab] OR "Signet Ring Cell"[tab] OR "Cervix Uteri"[Mesh] 237379  
4. cancer[tab] OR malignant[tab] OR carcinoma[tab] OR neoplasm[tab] OR cancers[tab] OR malignancy[tab] OR carcinomas[tab] OR neoplasms[tab] 1749249  
5. Adenocarcinoma[tab] OR Adenocarcinomas[tab] OR Adenosquamous[tab] OR "Squamous Carcinoma"[tab] OR "Squamous Carcinomas"[tab] OR "Epidermoid Carcinoma"[tab] OR "Epidermoid Carcinomas"[tab] 11198  
6. 2 OR 3 OR 4 1798373  
7. 6 AND 3 88306  
8. 7 OR 1 106593  
9. ((Antineoplastic[tiab] OR Antineoplastics[tiab] OR "Anti neoplastic"[tiab] OR "Anti-neoplastic"[tiab] OR Antineoplastically[tiab] OR Chemotherapeutic[tiab] OR Anticancer[tiab] OR Chemotherapy[tiab] OR Anti-cancer[tiab] OR 'Anti cancer'[tiab] OR Chemotherapy[tiab] OR Chemotherapies[tiab] OR "Chemotherapy"[tiab] OR "Chemo-therapy"[tiab]) OR (("Antineoplastic Agents"[Mesh]) OR "Antineoplastic Agents"[Pharmacological Action]) OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh]) 1103984  
10. Chemoradiotherapies[tiab] OR Radiochemotherapy[tiab] OR Radiochemotherapies[tiab] OR Chemoradiotherapy[tiab] OR Chemoradiation[tiab] 28690  
11. 8 AND 9 AND 10 1180

**EMBASE**
1. uterine cervix tumor/exp 88877  
2. adenocarcinoma/de OR adenoid cystic carcinoma/exp OR 'adenosquamous carcinoma/exp OR 'clear cell carcinoma/exp OR 'large cell carcinoma/exp OR small cell carcinoma/exp OR 'undiifferentiated carcinoma/exp OR 'endometrioid carcinoma/exp OR 'signet ring carcinoma/exp OR 'large cell neuroendocrine carcinoma/exp 107895  
3. cervix;ab,ti OR Cervical;ab,ti 235901  
4. "Signet Ring Cell";ab,ti OR "Neuroendocrine";ab,ti OR cancer;ab,ti OR malignant;ab,ti OR carcinoma;ab,ti OR neoplasm;ab,ti OR cancers;ab,ti OR malignancy;ab,ti OR carcinomas;ab,ti OR neoplasms;ab,ti OR Adenocarcinoma;ab,ti OR Adenocarcinomas;ab,ti OR Adenosquamous;ab,ti OR Squamous Carcinoma;ab,ti OR Squamous Carcinomas;ab,ti OR 'Epidermoid Carcinoma';ab,ti OR 'Epidermoid Carcinomas';ab,ti 2329011  
5. 2 OR 4 2337031  
6. 3 AND 5 93352  
7. 6 OR 1 122186  
8. Antineoplastic;ab,ti OR Antineoplastics;ab,ti OR 'Anti neoplastic';ab,ti OR 'Anti-neoplastic';ab,ti OR Antineoplastically;ab,ti OR Chemotherapeutic;ab,ti OR Anticancer;ab,ti OR Chemotherapy;ab,ti OR Anticancer;ab,ti OR 'Anti cancer';ab,ti OR Chemotherapy[tiab] OR Chemotherapies[tiab] OR 'Chemo-therapy'[tiab] OR 'Chemotherapy'[tiab] OR (("Antineoplastic Agents"[Mesh]) OR "Antineoplastic Agents"[Pharmacological Action]) OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh]) 1103984  
9. antineoplastic agent/exp OR 'chemotherapy'/exp 1690617  
10. 8 OR 9 1801763  
11. chemoradiotherapy[tiab] OR Radiochemotherapy[tiab] OR Radiochemotherapies[tiab] OR Chemoradiotherapy[tiab] OR Chemoradiation[tiab] 28690  
12. chemoradiotherapy/de 16316  
13. 11 OR 12 32824  
14. 7 AND 10 AND 13 3007  
15. 14 NOT 'nonhuman'/de 2945  
16. 15 NOT (editorial/it OR letter/it OR 'note/it' OR 'short survey/it') 2844

**COCHRANE**
1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees 771  
2. MeSH descriptor: Adenocarcinoma this term only 2444  
3. MeSH descriptor: Adenocarcinoma, Clear Cell explode all trees 31  
4. MeSH descriptor: Adenocarcinoma, Mucinous explode all trees 69  
5. MeSH descriptor: Adenocarcinoma, Papillary explode all trees 23  
6. MeSH descriptor: [Carcinoma, Endometrioid] explode all trees 32  
7. MeSH descriptor: [Carcinoma, Signet Ring Cell] explode all trees 6
8. MeSH descriptor: [Carcinoma, Adenosquamous] explode all trees 38
9. MeSH descriptor: [Carcinoma, Large Cell] explode all trees 73
10. MeSH descriptor: [Carcinoma, Small Cell] explode all trees 747
11. MeSH descriptor: [Carcinoma, Neuroendocrine] this term only 2136
12. MeSH descriptor: [Carcinoma, Squamous Cell] this term only 3
13. 2-12/or 4833
14. cancer or malignant or carcinoma or neoplasm or cancers or malignancy or carcinomas or neoplasms or Adenocarcinoma or Adenocarcinomas Adenosquamous or “Squamous Carcinoma” or “Squamous Carcinomas” or “Epidermoid Carcinoma” or “Epidermoid Carcinomas” “ti,ab,kw 89828
15. 13 or 14 89828
16. MeSH descriptor: [Cervix Uteri] explode all trees 968
17. cervix or Cervical or “Signet Ring Cell” “ti,ab,kw 10584
18. 16 or 17 10584
19. 18 and 15 3276
20. 19 or 1.3276
21. 20/trials 2623

One article was finally selected using aforementioned method.

Figure 1. Flow chart of searching strategy for answering KQ8

8-3. Quality assessment

The result of the evaluation of the paper is summarized in the table below.

Table 2. Study design characteristics

| Study ID | Journal | Study design | Random sequence generation | Allocation concealment | Blinding of participants | Blinding of personnel | Blinding of outcome | Incomplete outcome data | Selective reporting | Other sources of bias |
|----------|---------|--------------|----------------------------|------------------------|-------------------------|----------------------|----------------------|-----------------------|---------------------|---------------------|
| Duenas-Gonzalez A et al. 2011 | JCO | BCT | Low | Low | High | High | Low | Low | Low | Low |
| Chatterjee K et al. 2013 | EJC | BCT | Unclear | Unclear | High | High | Unclear | Low | Low | Low |
8-4. Level of evidence and grade of recommendation
Table 3. Evidence table

| Study ID          | Journal | Study Design | Setting                                      | Study period               | Intervention (N) | Control (N) | Age (year) | Inclusion | Results                                                                 | Comment                                                                 |
|-------------------|---------|--------------|----------------------------------------------|----------------------------|------------------|-------------|------------|-----------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Chatterjee K et al. 2013 | EJC     | RCT          | India                                       | June 2008 and July 2009  | (40) wddp + FP (2 cycles) | (40) wddp   | IB to IIIB |           | Control vs. Intervention DFS 63.88% vs. 67.56% [P = 0.8079] OS 80.55% vs. 83.78% [P = 0.7676] | Toxicity profiles had no significant difference.                       |
| Duenas-Gonzalez A et al. 2011 | JCO     | RCT          | Argentina, Bosnia and Herzegovina, India, Mexico, Pakistan, Panama, Peru, and Thailand | May 2002 to March 2004   | (259) GP + GP (2 cycles)       | (256) wddp  | 46 (18-70) | IIB to IVA | Intervention vs. Control PFS at 3 years 74.4% (68.0% to 79.8%) vs. (P=.029) Overall PFS (P=.0227; HR, 0.68; 0.49 to 0.95) Overall OS (P=.0224; HR,0.68; 0.49 to 0.86) |                                                                        |

The evidence for the key question was supported by the two RCT research results.

(Level of evidence: LOW)
Table 4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-----------------------------|-------------------------------|----------|
| KQ9      | 324 per 1000 (175 to 409)               | RR 0.82 (0.54 to 1.26)   | 595 (2 studies)             | ⊕⊕⊕⊕                | low [12,13] |
| Follow-up: 3~ years | 266 per 1000                           |                          |                             |                               |          |

8-5. Meta-analysis

Although statistical heterogeneity is not significant ($I^2=23\%$) from the 2 randomized trials, estimated direction of effect is the opposite each other. Addition of adjuvant chemotherapy after concurrent chemoradiotherapy in patients with locally advanced cervical cancer has not been supported from the previous studies

RRR=18\%, ER=32\%. OIS=800, Number of death=172

Figure 2. Result of meta-analysis

8-6. Summary

[KQ 8] Does addition of adjuvant chemotherapy after concurrent chemoradiotherapy improve survivals in patients with locally advanced cervical cancer?

The addition of adjuvant chemotherapy after concurrent chemoradiotherapy has not been recommended.

Level of evidence: C (low)

Strength of recommendation: 2 (weak)

8-7. References

1. Duenas-Gonzalez A, Zarba JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 1 2011;29(13):1678-1685.
9-1. Generation of key questions based on PICO*

| KQ 9 | Does PET/CT improve the accuracy of diagnosis of recurrence compared to CT or MRI in cervical cancer? |
|------|------------------------------------------------------------------------------------------------------|
| P    | Cervical cancer                                                                                     |
| I    | PET/CT                                                                                              |
| C    | CT or MRI                                                                                           |
| O    | Recurrence                                                                                         |

9-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ9

| MEDLINE                                      | EMBASE                                                                 |
|----------------------------------------------|------------------------------------------------------------------------|
| 1. "Uterine Cervical Neoplasms"[Mesh] 59998  | 1. 'uterine cervix tumor'/exp 88877                                    |
| 2. 'Adenocarcinoma'/Mesh:NoExp OR 'Adenocarcinoma, Clear Cell'/Mesh OR 'Adenocarcinoma, Mucinous'/Mesh OR 'Adenocarcinoma, Papillary'/Mesh OR 'Carcinoma, Endometrioid'/Mesh OR 'Carcinoma, Signet Ring Cell'/Mesh OR 'Carcinoma, Neuroendocrine'/Mesh:NoExp OR 'Carcinoma, Adenosquamous'/Mesh OR 'Carcinoma, Large Cell'/Mesh OR 'Carcinoma, Small Cell'/Mesh OR 'Carcinoma, Squamous Cell'/Mesh:NoExp 242652 | 2. 'adenocarcinoma/de OR 'adenoid cystic carcinoma/exp OR 'adenosquamous carcinoma/exp OR 'clear cell carcinoma/exp OR 'large cell carcinoma/exp OR 'small cell carcinoma/exp OR 'undifferentiated carcinoma/exp |
| 3. cervix[tiab] OR Cervical[tiab] OR 'Signet Ring Cell'[tiab] OR Neuroendocrine[tiab] OR 'Cervix Uteri'[Mesh] 237378 | 3. OR 2 OR 4 OR 5 1798373 |
| 4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasms[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 237378 | 4. OR 2 OR 4 OR 5 1798373 |
| 5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] OR Adenosquamous[tiab] OR 'Squamous Carcinoma'[tiab] OR 'Squamous Carcinomas'[tiab] OR 'Epidermoid Carcinoma'[tiab] OR 'Epidermoid Carcinomas'[tiab] 11198 | 5. OR 2 OR 4 OR 5 1798373 |
| 6. 2 OR 4 OR 5 1798373 | 6. OR 2 OR 4 OR 5 1798373 |
| 7. 6 AND 3 88306 | 7. 6 AND 3 88306 |
| 8. 7 OR 1 106480 | 8. 7 OR 1 106480 |
| 9. "Positron Emission Tomography'[tiab] OR PET[tiab] OR "Positron-Emission Tomography'[tiab] OR PET/CT[tiab] OR "Positron Emission Tomography/Computed Tomography'[tiab] 73809 | 9. OR 4 OR 10 80815 |
| 10. "Positron-Emission Tomography'[Mesh] 34000 | 10. OR 4 OR 10 80815 |
| 11. 9 OR 10 80815 | 11. OR 9 OR 10 80815 |
| 12. 8 AND 11 1785 | 12. 8 AND 11 1785 |
| 13. 12 NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term])) 1775 | 13. 12 NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term])) 1775 |
One article was finally selected using aforementioned method.
Figure 1. Flow chart of searching strategy for answering KQ9

9.3. Quality assessment
The result of the evaluation of the the paper is summarized in the table below.

Table 2. Study design characteristics
9-4. Level of evidence and grade of recommendation

Table 3. Evidence table
| Title                                                                 | Study ID            | Journal          | Study Design        | Setting         | Study period     | Intervention (N) | Control (N)     | Age (year) | Inclusion                        | Results                                                                 |
|----------------------------------------------------------------------|---------------------|------------------|---------------------|-----------------|------------------|------------------|----------------|------------|----------------------------------|---------------------------------------------------------------------|
| Performance of FDG-PET/CT for diagnosis of recurrent uterine cervical cancer | Kitajima et al., 2008 | Eur Radiol       | Prospective         | Japan (52 patients) | April 2005 - June 2006 | PET/CT (52)     | PET (52)       | 37—78 years; mean 58 years | recurrent uterine cervical cancer | Sensitivity, specificity, and accuracy of PET/CT were 92.0% (23/25), 92.6% (25/27), and 92.3% (48/52). Sensitivity, specificity, and accuracy of PET were 80.0% (20/25), 77.8% (21/27), and 78.8% (41/52). Recurrence: 25 (48%) |
| Lee M et al (2011) Usefulness of F-18 FDG PET/CT in assessment of recurrence of cervical cancer after surgery | Lee et al., 2011    | Nucl Med Mol Imaging | Retrospective      | Korea           | June 2006 and August 2009 | PET/CT 51      | .              | 54 (28–76) | recurrent uterine cervical cancer | Sensitivity, 97.3% specificity, 71.4% PPV, 90% NPV, 90.6% Recurrence: 37 (72.5%) |
| Ryu SY et al (2003) Detection of early recurrence with 18F-FDG PET in patients with cervical cancer | Ryu et al., 2003    | JNM              | Retrospective       | Korea           | September 1997 to March 2000 | PET 249        | .              | 51 (31–78) | recurrent uterine cervical cancer | The sensitivity and specificity of 18F-FDG PET for detection of early recurrence were 90.3% and 76.1%, respectively. Recurrence: 26 (11.2%) |
| Yen TC et al (2004) Defining the priority of using 18F-FDG PET for recurrent cervical cancer | Yen et al., 2004    | JNM              | Prospective         | Taiwan          | February 1, 2001, and January 31, 2003 | PET 55         | .              | 51 (25–86) | recurrent uterine cervical cancer | Sensitivity, 89.4 [81.3–94.8] specificity, 98.2 [96.6–99.2] PPV, 91.3 [88.6–96.2] NPV, 91.3 [86.6–96.2] 97.8 [96.0–98.9] All 55 patients had recurrent disease. Sensitivity/specificity - evaluated based on the region by region |

The evidence for the key question was supported by the four NRS research results.

(Level of evidence: LOW)
Table 9-4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|----------------------------|--------------------------------|----------|
| KQ10     | Assumed risk                           | Corresponding risk       | Not estimable              | ⊕⊕⊝                            | low^1^   |
| Follow-up: 1-3 years | See comment | See comment             | (4 studies)               |                               |          |

9-5. Meta-analysis

Statistical analysis for the diagnostic accuracy of CT, MRI and PET/CT has not been performed due to heterogeneity of the statistical analysis from each study. From the review of each study, PET/CT could be used to identify the recurrence of cervical cancer when recurrence is not identified or recurrence is suspicious with conventional image. And PET/CT might be used to confirm the field of recurrence.

Figure 2. Result of meta-analysis

PET/CT_KQ10

Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
------|----|----|----|----|---------------------|---------------------|---------------------|---------------------|
Kitajima et al., 2008 | 23 | 2  | 26 | 75 | 0.92 [0.74, 0.99] | 0.93 [0.76, 0.99] | 0.93 [0.76, 0.99] | 0.93 [0.76, 0.99] |
Lee et al., 2011 | 36 | 4  | 1  | 10 | 0.97 [0.86, 1.00] | 0.71 [0.42, 0.92] | 0.71 [0.42, 0.92] | 0.71 [0.42, 0.92] |

PET_KQ10

Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
------|----|----|----|----|---------------------|---------------------|---------------------|---------------------|
Ryu et al., 2003 | 25 | 5  | 3  | 168 | 0.89 [0.72, 0.88] | 0.76 [0.60, 0.84] | 0.76 [0.60, 0.84] | 0.76 [0.60, 0.84] |
Yen et al., 2004 | 84 | 8  | 10 | 448 | 0.89 [0.81, 0.95] | 0.90 [0.97, 0.99] | 0.90 [0.97, 0.99] | 0.90 [0.97, 0.99] |

9-6. Summary

[**KQ 9**] Does PET/CT improve the accuracy of diagnosis of recurrence compared to CT or MRI in cervical cancer?

**Recommendation:** PET/CT could be performed clinically if diagnosis of recurrent cervical cancer with CT/MRI is uncertain or PET/CT is needed to confirm the field of recurrence.

**Level of evidence:** C (low)

**Strength of recommendation:** 1 (strong)

9-7. References

1. Kitajima K, Murakami K, Yamasaki E, Domeki Y, Kaji Y, Sugimura K. Performance of FDG-PET/CT for diagnosis of recurrent uterine cervical cancer. European radiology. Oct 2008;18(10):2040-2047.

2. Lee M, Lee Y, Hwang KH, Choe W, Park CY. Usefulness of F-18 FDG PET/CT in Assessment of Recurrence of Cervical Cancer After Treatment. Nuclear medicine and molecular imaging. Jun 2011;45(2):111-116.

3. Ryu SY, Kim MH, Choi SC, Choi CW, Lee KH. Detection of early recurrence with 18F-FDG PET in patients with cervical cancer. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. Mar 2003;44(3):347-352.
4. Yen TC, See LC, Chang TC, et al. Defining the priority of using 18F-FDG PET for recurrent cervical cancer. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. Oct 2004;45(10):1632-1639.
10-1. Generation of key questions based on PICO*

| KQ 10 | Does addition of bevacizumab to conventional chemotherapy improve survival in patients with recurrent or persistent cervical cancer? |
|-------|---------------------------------------------------------------------------------------------------------------------------------|
| P     | Cervical cancer                                                                                                                  |
| I     | Bevacizumab                                                                                                                     |
| C     | Chemotherapy                                                                                                                     |
| O     | Survival                                                                                                                         |

10-2. Medical literature search and study identification

PubMed, EMBASE, and Cochrane were used for the literature search, and the search formula is as follows.

Table 1. Procedure used for MEDLINE, EMBASE, and COCHRANE to identify eligible clinical trials for answering KQ10

**MEDLINE**

1. "Uterine Cervical Neoplasms"[Mesh] 59998
2. "Adenocarcinoma"[Mesh:NoExp] OR "Adenocarcinoma, Clear Cell"[Mesh] OR "Adenocarcinoma, Mucinous"[Mesh] OR "Adenocarcinoma, Papillary"[Mesh] OR "Carcinoma, Endometroid"[Mesh] OR "Carcinoma, Signet Ring Cell"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh:NoExp] OR "Carcinoma, Adenosquamous"[Mesh] OR "Carcinoma, Large Cell"[Mesh] OR "Carcinoma, Small Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh:NoExp] 242652
3. cervix[tiab] OR Cervical[tiab] OR "Signet Ring Cell"[tiab] OR Neuroendocrine[tiab] OR "Cervix Uteri"[Mesh] 237378
4. cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] 1749249
5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] OR Adenosquamous[tiab] OR "Squamous Carcinoma"[tiab] OR "Squamous Carcinomas"[tiab] OR "Epidermoid Carcinoma"[tiab] OR "Epidermoid Carcinomas"[tiab] 11198
6. 2 OR 4 OR 5 1798373
7. 6 AND 3 88306
8. 7 OR 1 106593
9. "bevacizumab" [Supplementary Concept] OR "Angiogenesis Inhibitors" [Pharmacological Action] OR bevacizumab[tiab] 45022
10. 8 AND 9 327

**EMBASE**

1. 'uterine cervix tumor'/exp 88777
2. adenocarcinoma/de OR adenoid cystic carcinoma/exp OR adenosquamous carcinoma/exp OR 'clear cell carcinoma'/exp OR 'large cell carcinoma'/exp OR 'small cell carcinoma'/exp OR 'undifferentiated carcinoma'/exp OR 'endometrioid carcinoma/exp OR 'signet ring carcinoma'/exp OR 'large cell neuroendocrine carcinoma'/exp 107895
3. cervix:ab,ti OR Cervical:ab,ti 235901
4. 'Signet Ring Cell':ab,ti OR Neuroendocrine:ab,ti OR cancer:ab,ti OR malignant:ab,ti OR carcinoma:ab,ti OR neoplasm:ab,ti OR cancers:ab,ti OR malignancy:ab,ti OR carcinomas:ab,ti OR neoplasms:ab,ti 2329011
5. 2 OR 4 2337031
6. 3 AND 5 93152
7. 6 OR 1 122186
8. bevacizumab:ab,ti OR 'bevacizumab'/exp OR 'angiogenesis inhibitor'/exp 92825
9. 7 AND 8 10531
10. 9 NOT (animal model/de OR 'animal tissue'/de OR 'in vitro study'/de OR nonhuman/de) 667

**COCHRANE**

1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees1771
2. MeSH descriptor: Adenocarcinoma this term only 2444
3. MeSH descriptor: Adenocarcinoma, Clear Cell explode all trees 31
4. MeSH descriptor: Adenocarcinoma, Mucinous explode all trees 69
5. MeSH descriptor: Adenocarcinoma, Papillary explode all trees 23
6. MeSH descriptor: Carcinoma, Endometroid explode all trees 32
7. MeSH descriptor: Carcinoma, Signet Ring Cell explode all trees 6
8. MeSH descriptor: Carcinoma, Adenosquamous explode all trees 38
9. MeSH descriptor: Carcinoma, Large Cell explode all trees 73
10. MeSH descriptor: Carcinoma, Small Cell explode all trees 747
11. MeSH descriptor: Carcinoma, Neuroendocrine this term only 3
12. MeSH descriptor: Carcinoma, Squamous Cell this term only 2136
13. 2-12/or 4835
14. cancer or malignant or carcinoma or neoplasm or cancers or malignancy or carcinomas or neoplasms or Adenocarcinoma or Adenocarcinomas Adenosquamous or "Squamous Carcinoma" or "Squamous Carcinomas" or "Epidermoid Carcinoma" or "Epidermoid Carcinomas":ti,ab,kw 89828
15. 13 or 14 89828
One article was finally selected using aforementioned method.

Figure 1. Flow chart of searching strategy for answering KQ10

10-3. Quality assessment

The result of the evaluation of the the paper is summarized in the table below.

Table 2. Study design characteristics

| Study ID | Journal | Study design | Risk of bias |
|----------|---------|--------------|--------------|
|          |         |              | selection bias | performance bias | detection bias | attrition bias | reporting bias | other bias |
| Tewari K, et al, 2014 | NEJM | RCT, 2x2 factorial design | low | unclear | unclear | unclear | low | low | low |

10-4. Level of evidence and grade of recommendation
## Table 3. Evidence table

| Study ID                  | Journal  | Study Design | Setting               | Study period          | Intervention                                           | Control                                  | Age (year) | Inclusion                                | Results                                                                 |
|---------------------------|----------|--------------|-----------------------|-----------------------|--------------------------------------------------------|------------------------------------------|------------|------------------------------------------|-------------------------------------------------------------------------|
| Krishnansu S. Tewari, et al 2014 | NEJM     | RCT          | USA and Spain         | April 2009 - Dec 2012 | cisplatin 50 mg/BSA + paclitaxel 135 or 175 mg/m2 or topotecan 0.75 mg/m2 on days 1 to 3 + paclitaxel 175 mg/m2 on day 1, and bevacizumab 15mg/kg | cisplatin 50 mg/BSA + paclitaxel 135 or 175 mg/m2 or topotecan 0.75 mg/m2 on days 1 to 3 + paclitaxel 175 mg/m2 on day 1 | 48 (20-85) | metastatic, persistent, and recurrent cervical carcinoma | the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% confidence interval, 0.54 to 0.95; P=0.004 in a one-sided test) |
Table 10-4. Estimation of GRADE

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-------------------------------|--------------------------------|----------|
| Control  | KQ10 622 per 1000 499 per 1000 (409 to 603) | HR 0.71 (0.54 to 0.95)   | 452 (1 study)                | ⊕⊕⊕⊝ moderate14,15             |          |

14 One randomized trial
15 RRR=29%, ER=62.2%, OIS=150, number of deaths=271

10-5. Meta-analysis

One randomized trial suggests that addition of bevacizumab improve survival outcome (HR, 0.29) (Level of evidence: moderate)

Figure 2. Result of meta-analysis

10-6. Summary

[KQ 10] Does addition of bevacizumab to conventional chemotherapy improve survival in patients with recurrent or persistent cervical cancer?

Bevacizumab could be used for recurrent or persistent cervical cancer to improve survival outcomes.

Level of evidence: B (moderate)

Strength of recommendation: 1 (strong)

10-7. References

1. Tewari KS, Sill MW, Long HJ, 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. The New England journal of medicine. Feb 20 2014;370(8):734-743.