Supplementary 1.

Guidelines development process in accordance with evidence-based medicine

<table>
<thead>
<tr>
<th>KQ</th>
<th>Is the survival rate similar between laparoscopic staging surgery and open surgery in early-stage endometrial cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Early-stage endometrial carcinoma</td>
</tr>
<tr>
<td>I</td>
<td>Laparoscopic hysterectomy</td>
</tr>
<tr>
<td>C</td>
<td>Total abdominal hysterectomy</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or progression-free survival</td>
</tr>
</tbody>
</table>

*PICO: Population (P), Intervention or Indicator (I), Comparator (C), Outcome (O).

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>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. 1 OR 2</td>
<td>3. 1 OR 2</td>
</tr>
<tr>
<td>7. 5 OR 6</td>
<td>7. 5 OR 6</td>
</tr>
<tr>
<td>10. 4 OR 9</td>
<td>10. 7 AND 9</td>
</tr>
<tr>
<td>11. 10 AND 7</td>
<td>11. 11 OR 14</td>
</tr>
<tr>
<td>12. 3 OR 8 OR 11</td>
<td>12. AND 15</td>
</tr>
</tbody>
</table>
A total of 2,834 papers were searched using the aforementioned method from January 2010 to December 2014. Inclusion and exclusion criteria were applied to these papers, as shown in Figure 1, and five papers were finally selected.

Figure 1. Flow chart of searching strategy for answering KQ1.

1-3. Quality assessment
All of the finally-selected papers concerned randomized controlled clinical research, and, to evaluate the appropriateness of the study design, Cochrane Collaboration’s tool for assessing risk of bias was used. The results of the evaluation of the risk of bias in five papers are summarized in Table 2.

Table 2. Study design characteristics based on the QUADAS tool
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu, 2013</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Walker, 2012</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Malzoni, 2009</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zullo, 2009</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Tozzi, 2005</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
1-4. Level of evidence and grade of recommendation

Table 3. Evidence table for laparoscopy

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study period</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Results (5-year OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu, 2013</td>
<td>RCT</td>
<td>China</td>
<td>Median F/U: 68 months</td>
<td>Laparoscopy</td>
<td>All stages</td>
<td>151</td>
<td>121</td>
<td>96% vs. 91%</td>
</tr>
<tr>
<td>Walker, 2012</td>
<td>RCT</td>
<td>USA (LAP2)</td>
<td>Median F/U: 59.3 months</td>
<td>Laparoscopy</td>
<td>Clinical stages I–IIA</td>
<td>1,696</td>
<td>920</td>
<td>89.8% vs. 89.8%</td>
</tr>
<tr>
<td>Malzoni, 2009</td>
<td>RCT</td>
<td>Italy</td>
<td>Nov 2001–Jan 2006</td>
<td>Laparoscopy</td>
<td>Clinical stage I</td>
<td>81</td>
<td>78</td>
<td>93.2% vs. 91.1%</td>
</tr>
<tr>
<td>Zullo, 2009</td>
<td>RCT</td>
<td>USA</td>
<td>Mar 2001–Dec 2003</td>
<td>Laparoscopy</td>
<td>Clinical stage I</td>
<td>40</td>
<td>38</td>
<td>82.5% vs. 84.2%</td>
</tr>
<tr>
<td>Tozzi, 2005</td>
<td>RCT</td>
<td>Germany</td>
<td>Median F/U: 44 months</td>
<td>Laparoscopy</td>
<td>All stages</td>
<td>63</td>
<td>59</td>
<td>82.7% vs. 86.5%</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; F/U, follow-up; OS, overall survival.

The evidence for the key question was supported by the results of five randomized controlled trials. According to the research result, survival rates were not different for laparoscopic staging surgery compared with laparotomy in early-stage endometrial cancer, and therefore laparoscopic staging surgery may be conducted. (Level of evidence: high)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1, Follow-up: 5 years</td>
<td>126 per 1000</td>
<td>126 per 1000 (104–152)</td>
<td>RR 1.00 (0.83–1.21)</td>
<td>3247 (5 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
</tbody>
</table>
1-5. Meta-analysis

For this recommendation, a meta-analysis was conducted to identify differences in survival rates according to surgical method in early-stage endometrial cancer patients. There was no difference in 5-year survival rates between the group that underwent laparoscopic staging surgery and the group that underwent open surgery (relative risk: 1.00; 95% confidence interval: 0.83–1.21).

![Figure 2. Result of meta-analysis. RR, relative risk; CI, confidence interval.]

1-6. Summary

**[KQ 1]** Is the survival rate similar between laparoscopic staging surgery and open surgery in early-stage endometrial cancer?

Laparoscopic staging surgery is recommended for the surgical staging of early-stage endometrial cancer.

Level of evidence: A (high)

Strength of recommendation: 1 (strong)

1-7. References


2-1. Generation of key questions based on PICO*

<table>
<thead>
<tr>
<th>KQ 2</th>
<th>Does ovarian preservation affect survival in patients with early-stage endometrial cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Early-stage endometrial carcinoma</td>
</tr>
<tr>
<td>I</td>
<td>Ovarian preservation (or ovarian saving)</td>
</tr>
<tr>
<td>C</td>
<td>Bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or progression-free survival</td>
</tr>
</tbody>
</table>

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).

2-2. Medical literature search and study identification

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

Table 1. Procedure to identify eligible clinical trials for answering KQ2

|         | 3. 1 OR 2
|         | 4. ("Uterus"[Mesh:NoExp] OR "Endometrium"[Mesh])
|         | 5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab]
|         | 7. 5 OR 6
|         | 8. "Carcinoma, Endometrioid"[Mesh]
|         | 10. 4 OR 9
|         | 11. 10 AND 7
|         | 12. 3 OR 8 OR 11
|         | 14. ("Organ Sparing Treatments"[Mesh] OR "Ovarietomy"[Mesh])
|         | 17. 13–16 OR 8 OR 12 AND 17
|         | 18. 12 NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term]))
|         | 19. 18 NOT "review"[Publication Type] OR "review literature as topic"[MeSH Terms]
|         | 20. 19 AND Publication date from 2010/01/01 to 2014/12/31
| EMBASE | 1. "endometrium tumor"/de OR "endometrium cancer"/de OR "endometrium carcinoma/"exp OR "uterus tumor"/de OR "uterus cancer"/de OR "uterus carcinoma/"exp
|         | 3. 1 OR 2
|         | 4. "uterus"/de OR "endometrium"/exp OR "uterus cavity"/exp
|         | 5. Adenocarcinoma[ab,ti] OR Adenocarcinomas[ab,ti]
|         | 6. "adenocarcinoma"/de
|         | 7. 5 OR 6
|         | 9. 8 OR 4
|         | 10. 7 AND 9
|         | 11. "endometrioid carcinoma"/exp
|         | 12. 3 OR 10 OR 11
|         | 13. "organ preservation"/de OR "fertility preservation"/exp OR "conservative treatment"/de OR "ovarian preservation"/exp OR "ovaricectomy"/exp
|         | 16. 13–15 OR 8
|         | 17. 12 AND 16
|         | 18. 17 NOT ("article in press"/it OR "conference review"/it OR "editorial"/it OR "letter"/it OR "note"/it OR "review"/it OR "short survey"/it)
|         | 19. 18 NOT "animal cell"/de OR "animal experiment"/de OR "animal model"/de OR "animal tissue"/de OR "human cell"/de OR "human tissue"/de OR "in vitro study"/de OR "nonhuman/"de)
| Cochrane | 1. (Endometrial OR Endometroid OR Endometrium OR Uterus OR Uterine) AND (cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms):ti,ab,kw
|         | 2. MeSH descriptor: [Endometrioid Neoplasms] explode all trees
|         | 3. MeSH descriptor: [Uterine Neoplasms] this term only
|         | 4. 1–3 OR 5
|         | 5. MeSH descriptor: [Uterus] this term only
|         | 6. MeSH descriptor: [Endometrium] explode all trees
A total of 1,702 papers were searched using the aforementioned method from January 2010 to December 2014. Inclusion and exclusion criteria were applied to these papers as shown in Figure 1, and three papers were finally selected.

**2-3. Quality assessment**

All three ultimately selected papers were nonrandomized studies (NRSs), and to evaluate the appropriateness of the study design, the Newcastle-Ottawa Quality Assessment Scale technique was used. The results of the evaluation of the three papers are summarized in the table below.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the nonexposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at start of study</th>
<th>Comparability of cohorts on the basis of the design or analysis</th>
<th>Assessment of outcome</th>
<th>Was follow-up long enough for outcomes to occur?</th>
<th>Adequacy of follow-up of cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, 2013</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Sun, 2013</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Wright, 2009</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Figure 1. Flow chart of searching strategy for answering KQ2
2-4. **Level of evidence and grade of recommendation**

Table 3. Evidence table for ovarian preservation

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study period</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result (5-year OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2013</td>
<td>Retrospective cohort</td>
<td>Korea</td>
<td>1997–2008</td>
<td>Ovarian preservation</td>
<td>Bilateral salpingo-oophorectomy</td>
<td>Stage I-II EC, premenopausal women</td>
<td>176</td>
<td>319</td>
</tr>
<tr>
<td>Sun, 2013</td>
<td>Retrospective cohort</td>
<td>China</td>
<td>2000–2010</td>
<td>Ovarian preservation</td>
<td>Bilateral salpingo-oophorectomy</td>
<td>Early-stage EC (&lt;45 years)</td>
<td>34</td>
<td>169</td>
</tr>
<tr>
<td>Wright, 2009</td>
<td>Retrospective cohort</td>
<td>SEER dataset</td>
<td>1988–2004</td>
<td>Ovarian preservation</td>
<td>Bilateral salpingo-oophorectomy</td>
<td>Stage I EC (&lt;45 years)</td>
<td>402</td>
<td>2,867</td>
</tr>
</tbody>
</table>

OS, overall survival; EC, endometrial carcinoma; HR, hazard ratio; CI, confidence interval.

The evidence for the key question was supported by the three NRS research results. There was no difference in survival rates between those whose ovary was removed and those whose ovary was not removed if the tumor was confined to the uterine corpus and there was no finding of distant metastasis. Therefore, women ≤45 years old who want preservation of their ovary may selectively undergo ovary preservation. Because there is no randomized controlled trial verifying the results, the level of evidence is low. (Level of evidence: low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KQ2, Follow-up: 5 years</td>
<td>See comment</td>
<td>See comment</td>
<td>0.83 (0.47–1.47)</td>
<td>3,967 (3 studies)</td>
<td>⊕⊕⊕⊕ low</td>
</tr>
</tbody>
</table>
2-5. Meta-analysis

For this recommendation, a meta-analysis was conducted to identify differences in survival rates when the ovary was preserved and not preserved in patients with early-stage endometrial cancer. The death rate in the group with ovary preservation was 0.83 times the rate in the group without ovary preservation (hazard ratio: 0.83; 95% confidence interval: 0.47–1.47).

![Figure 2. Result of meta-analysis. SE, standard error; CI, confidence interval.]

2-6. Summary

[KQ 2] Does ovarian preservation affect survival in patients with early-stage endometrial cancer?

Ovarian preservation is recommended at the time of hysterectomy for young women with early-stage endometrial cancer that is confined to the uterus without evidence of extrauterine spread.

Level of evidence: C (low)

Strength of recommendation: 2 (weak)

2-7. References


3-1. Generation of key questions based on PICO*

Is progestin therapy for fertility-sparing treatment effective for young women with early-stage endometrial cancer?

P : Endometrial carcinoma
I : Progestin-based therapy
C : Total hysterectomy ± bilateral salpingo-oophorectomy / or <NONE>
O : Response rate or pregnancy outcome

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).

3-2. Medical literature search and study identification

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

Table 1. Procedure to identify eligible clinical trials for answering KQ3

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (&quot;Endometrial Neoplasms [Mesh]) OR &quot;Uterine Neoplasms [Mesh:NoExp]</td>
<td>1. (&quot;Endometrium tumor/de OR &quot;endometrium cancer/de OR &quot;uterus tumor/de OR &quot;uterus cancer/de OR &quot;uterus carcinoma&quot;/exp OR &quot;uterus tumor&quot;/de OR &quot;uterus cancer&quot;/de OR &quot;uterus carcinoma&quot;/exp</td>
</tr>
<tr>
<td>2. (Endometrial/ab,t OR Endometrioid/ab,t OR Endometrium/ab,t OR Uterus/ab,t OR Uterine/ab,t) AND (cancer/ab,t OR malignan/ab,t OR carcinoma/ab,t OR neoplasm/ab,t OR cancers/ab,t OR malignancy/ab,t OR carcinomas/ab,t OR neoplasms/ab,t)</td>
<td>2. (Endometrial:ab,t OR Endometrioid:ab,t OR Endometrium:ab,t OR Uterus:ab,t OR Uterine:ab,t) AND (cancer:ab,t OR malignan:ab,t OR carcinoma:ab,t OR neoplasm:ab,t OR cancers:ab,t OR malignancy:ab,t OR carcinomas:ab,t OR neoplasms:ab,t)</td>
</tr>
<tr>
<td>3. I OR 2</td>
<td>3. I OR 2</td>
</tr>
<tr>
<td>5. Adenocarcinoma/ab,t OR Adenocarcinomas/ab,t</td>
<td>5. Adenocarcinoma:ab,t OR Adenocarcinomas:ab,t</td>
</tr>
<tr>
<td>7. 5 OR 6</td>
<td>7. 5 OR 6</td>
</tr>
<tr>
<td>9. (Endometrial/ab,t OR Endometrioid/ab,t OR Endometrium/ab,t OR Uterus/ab,t OR Uterine/ab,t)</td>
<td>9. (Endometrial:ab,t OR Endometrioid:ab,t OR Endometrium:ab,t OR Uterus:ab,t OR Uterine:ab,t)</td>
</tr>
<tr>
<td>10. 4 OR 9</td>
<td>10. 4 OR 9</td>
</tr>
<tr>
<td>11. 10 AND 7</td>
<td>11. 10 AND 7</td>
</tr>
<tr>
<td>12. 3 OR 8 OR 11</td>
<td>12. 3 OR 8 OR 11</td>
</tr>
<tr>
<td>13. Desogestrel/ab,t OR Dydrogesterone/ab,t OR Progestrone/ab,t OR Pregnenedione/ab,t OR Megestrol/ab,t OR Gestagens/ab,t OR Progestagens/ab,t</td>
<td>13. Desogestrel:ab,t OR Dydrogesterone:ab,t OR Progestrone:ab,t OR Pregnenedione:ab,t OR Megestrol:ab,t OR Gestagens:ab,t OR Progestagens:ab,t</td>
</tr>
<tr>
<td>14. (Progestational/ab,t OR Gestagenic/ab,t OR Progestagenic/ab,t OR Progestin/ab,t OR Gestagen/ab,t OR Progestagens/ab,t) AND (Agents/ab,t OR Hormones/ab,t OR Compounds/ab,t OR drug/ab,t OR Agent/ab,t OR Hormone/ab,t OR Compound/ab,t)</td>
<td>14. (Progestational:ab,t OR Gestagenic:ab,t OR Progestagenic:ab,t OR Progestin:ab,t OR Gestagen:ab,t OR Progestagens:ab,t) AND (Agents:ab,t OR Hormones:ab,t OR Compounds:ab,t OR drug:ab,t OR Agent:ab,t OR Hormone:ab,t OR Compound:ab,t)</td>
</tr>
<tr>
<td>15. Fertility[ab,t] AND (Preservations[ab,t] OR Preservation[ab,t])</td>
<td>15. Fertility[ab,t] AND (Preservations:ab,t OR Preservation:ab,t)</td>
</tr>
<tr>
<td>17. 13–16OR</td>
<td>17. 13–16OR</td>
</tr>
<tr>
<td>18. 12 AND 17</td>
<td>18. 12 AND 17</td>
</tr>
<tr>
<td>19. 18 NOT (&quot;review&quot;[Publication Type] OR &quot;review literature as topic&quot;[MeSH Terms])</td>
<td>19. 18 NOT (&quot;review&quot;[Publication Type] OR &quot;review literature as topic&quot;[MeSH Terms])</td>
</tr>
<tr>
<td>20. 19 NOT (&quot;animal cell&quot;/de OR &quot;animal experiment&quot;/de OR &quot;animal model&quot;/de OR &quot;animal tissue&quot;/de OR &quot;human cell&quot;/de OR &quot;in vitro study&quot;/de OR &quot;nonhuman&quot;/de)</td>
<td>20. 19 NOT (&quot;animal cell&quot;/de OR &quot;animal experiment&quot;/de OR &quot;animal model&quot;/de OR &quot;animal tissue&quot;/de OR &quot;human cell&quot;/de OR &quot;in vitro study&quot;/de OR &quot;nonhuman&quot;/de)</td>
</tr>
</tbody>
</table>

Cochrane

1. ("Endometrial Neoplasms OR Endometrioid OR Endometrium OR Uterus OR Uterine) AND (cancer OR malignan:OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms):ti,ab,kw
2. MeSH descriptor: "Endometrial Neoplasms" explode all trees
3. MeSH descriptor: "Uterine Neoplasms" this term only
A total of 6,969 papers were searched using the aforementioned method until December 2014. Inclusion and exclusion criteria were applied to these papers as shown in Figure 1, and three papers were finally selected.

3-3. Quality assessment

The three finally selected papers were all nonrandomized studies (NRSs), and, to assess the appropriateness of their design, the suggested risk of bias criteria for Effective Practice and Organization of Care (EPOC) reviews was examined. The results of the evaluation of the three papers are summarized in Table 2.

Table 2. Study design characteristics

<table>
<thead>
<tr>
<th>study ID</th>
<th>Was the intervention independent of other changes?</th>
<th>Was the shape of the intervention effect prospecified?</th>
<th>Was the intervention unlikely to affect data collection?</th>
<th>Was knowledge of the allocated interventions adequately prevented during the study?</th>
<th>Were incomplete outcome data adequately addressed?</th>
<th>Was the study free from selective outcome reporting?</th>
<th>Was the study free from other risks of bias?</th>
</tr>
</thead>
</table>

Figure 1. Flow chart of searching strategy for answering KQ3.
<table>
<thead>
<tr>
<th>Study</th>
<th>Low</th>
<th>Low</th>
<th>Low</th>
<th>Unclear</th>
<th>Unclear</th>
<th>Low</th>
<th>( - )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park, 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ushijima, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3-4. Level of evidence and grade of recommendation

Table 3. Evidence table for progestin-based therapy

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Population</th>
<th>Number (age, year)</th>
<th>Inclusion criteria</th>
<th>Outcome type</th>
<th>Type of treatment</th>
<th>Result CR rate</th>
<th>Recurrence rate</th>
<th>5-year recurrence-free survival</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2014</td>
<td>Retrospective cohort</td>
<td>Taiwan</td>
<td>Progestin-based therapy (no hysterectomy)</td>
<td>37 (-)</td>
<td>Grade 1 endometrioid EC at presumed stage IA</td>
<td>CR rate, recurrence-free survival</td>
<td>MA, 160 mg/d</td>
<td>81.1% (30/37), lasting &gt; 6 months</td>
<td>50.0% (15/30), median PFI: 20.0 months</td>
<td>51.0%</td>
<td>11 attempted pregnancies, 8 pregnancies (2 abortions, 2 ectopic, 1 preterm, 3 full-term)</td>
</tr>
<tr>
<td>Park, 2013</td>
<td>Retrospective cohort</td>
<td>Korea (KGOG)</td>
<td>Progestin-based therapy (no hysterectomy)</td>
<td>148 (&lt;40)</td>
<td>Stage IA, grade 1 EC</td>
<td>CR rate, recurrence-free survival</td>
<td>Daily oral MPA or MA</td>
<td>115/148 (77.7%)</td>
<td>30.4% (35/115), after median F/U of 66 months</td>
<td>68% (95% CI: 58.5%–76.9%)</td>
<td>44 pregnancies</td>
</tr>
<tr>
<td>Ushijima, 2007</td>
<td>Prospective cohort</td>
<td>Japan (Japan GCSG)</td>
<td>Progestin-based therapy (no hysterectomy)</td>
<td>28 (&lt;40)</td>
<td>EC at presumed stage IA</td>
<td>CR rate, Pregnancy rate</td>
<td>Daily 600 mg MPA with low-dose aspirin (26 week)</td>
<td>54.5% (12/22), at 26 week. 63.6% (14/22) at additional 3–6 months</td>
<td>57.1% (8/14), median PFI: 34.6 months</td>
<td>(-)</td>
<td>4 pregnancy (1 abortion, 3 full-term)</td>
</tr>
</tbody>
</table>

EC, endometrial carcinoma; MA, megestrol acetate; MPA, medroxyprogesterone acetate; F/U, follow-up; CI, confidence interval.

The evidence for the key question was supported by the three NRSs. According to the study results, the lesion was confined to the endometrium. The outcome of progestin-based therapy in grade 1 endometrioid carcinoma patients was that tumor response and recurrence and survival rates were clinically allowable, and, therefore, if a patient strongly desires pregnancy, progestin therapy may be used without performing a hysterectomy for preservation of fertility. Because there was no randomized controlled trial to verify the results and the three NRSs were studies of a single group, the level of evidence is very low. (Level of evidence: very low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ3 Follow-up: 5 years</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>213 (3 studies)</td>
<td>⊕⊕⊕⊕ very low</td>
</tr>
</tbody>
</table>
3-5. Summary

<table>
<thead>
<tr>
<th>KQ 2</th>
<th>Is progestin therapy for fertility-sparing treatment effective for young women with early-stage endometrial cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fertility-sparing treatment through progestin-based therapy is recommended in early-stage endometrial cancer if the tumor is grade 1 endometrioid adenocarcinoma and limited to the endometrium if the patient strongly desires pregnancy.</td>
</tr>
<tr>
<td>Level of evidence: D (very low)</td>
<td></td>
</tr>
<tr>
<td>Strength of recommendation: 1 (strong)</td>
<td></td>
</tr>
</tbody>
</table>

3-6. References

4-1. Generation of key questions based on PICO*

**[KQ 4]**

**Does adjuvant radiotherapy improve survival in patients with stage IB/grade 3 endometrial cancer with risk factors after surgery?**

| P : Stage IB, grade 3 endometrial carcinoma |
| I : Pelvic RT and/or vaginal brachytherapy (±chemotherapy) |
| C : Observation |
| O : Overall survival or progression-free survival |

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).*

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 to identify eligible clinical trials for answering KQ4

| MEDLINE | 1. *(Endometrial Neoplasms [Mesh]) OR "Uterine Neoplasms [Mesh:NoExp]*
| 3. 1 OR 2
| 4. *("Uterus"[Mesh:NoExp]) OR "Endometrium"[Mesh]
| 5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab]
| 6. *"Adenocarcinoma"[Mesh:NoExp]*
| 7. 5 OR 6
| 8. "Carcinoma, Endometrioid"[Mesh]
| 10. 4 OR 9
| 11. 10 AND 7
| 12. 3 OR 8 OR 11
| 14. *(Radiotherapy [Mesh:NoExp])
| 15. 13 OR 14
| 16. 12 AND 15
| 17. 16 NOT "review"[Publication Type] OR "review literature as topic"[MeSH Terms]

| EMBASE | 1. "endometrium tumor /de OR "endometrium cancer /de OR "endometrium carcinoma /exp OR "uterus tumor /de OR "uterus cancer /de OR "uterus carcinoma"/exp"
| 3. 1 OR 2
| 4. *("uterus"/de OR "endometrium"/exp OR "uterus cavity"/exp"
| 5. Adenocarcinoma[ab,ti] OR Adenocarcinomas[ab,ti]
| 6. "adenocarcinoma"/de
| 7. 5 OR 6
| 9. 8 OR 4
| 10. 7 AND 9
| 11. "endometrium carcinoma"/exp
| 12. 3 OR 10 OR 11
| 13. stereotactic[ab,ti] OR radiotherapy[ab,ti] OR Radiotherapies[ab,ti]
| 14. *(radiotherapy)/de
| 15. 13 OR 14
| 16. 12 AND 15
| 17. 16 NOT *(article in press"/it OR "conference review"/it OR "editorial"/it OR "erratum"/it OR "letter"/it OR "note"/it OR "review"/it OR "short survey"/it)
| 18. 17 NOT *("human cell"/de OR "human tissue"/de OR "in vitro study"/de)

| Cochrane | 1. *(Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine) AND (cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms):ti,ab,kw
| 2. MeSH descriptor: [Endometrial Neoplasms] explode all trees
| 3. MeSH descriptor: [Uterine Neoplasms] this term only
| 4. 1–3/or
| 5. MeSH descriptor: [Uterus] this term only
| 6. MeSH descriptor: [Endometrium] explode all trees
| 7. Adenocarcinoma or Adenocarcinomas:ti,ab,kw
| 8. MeSH descriptor: [Adenocarcinoma] this term only
| 9. 7 or 8
| 10. MeSH descriptor: (Carcinoma, Endometrioid) explode all trees
| 11. Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine
| 12. 11 or 5 or 6
| 13. 12 and 9
| 14. 13/trial

A total of 7,425 papers were searched using the aforementioned method until December 2014. Inclusion and exclusion criteria were applied to these papers as shown in Figure 1, and four papers were finally selected.
4.3. Quality assessment

The finally-selected four papers included three randomized controlled trials (RCTs) and one nonrandomized study (NRS). To assess the appropriateness of the study design, the Cochrane Collaboration’s tool for assessing risk of bias and the Newcastle-Ottawa Quality Assessment Scale were used. The results of evaluating the four papers are summarized in Table 2.

Table 2. Study design characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake, 2009</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Soderini, 2003</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Aalders, 1980</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Chino, 2012</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>
### 4-4. Level of evidence and grade of recommendation

Table 3. Evidence table for postoperative radiotherapy

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
<td>5-year DFS</td>
<td>5-year OS</td>
</tr>
<tr>
<td>Chino, 2012</td>
<td>Retrospective cohort</td>
<td>SEER dataset</td>
<td>RT (VB and/or WPRT)</td>
<td>Observation</td>
<td>1,218</td>
<td>723</td>
<td>66.9% vs. 57.2%</td>
</tr>
<tr>
<td>Blake, 2009</td>
<td>NRS (only selected group from RCT)</td>
<td>Multicenter Study (ASTEC/EN.5)</td>
<td>Pelvic RT</td>
<td>Observation</td>
<td>89</td>
<td>113</td>
<td>96.6% vs. 93.8%</td>
</tr>
<tr>
<td>Soderini, 2003</td>
<td>RCT</td>
<td>Argentinean high-risk trial</td>
<td>Pelvic RT</td>
<td>Observation</td>
<td>63</td>
<td>60</td>
<td>87.3% vs. 78.3%</td>
</tr>
<tr>
<td>Aalders, 1980</td>
<td>RCT</td>
<td>Norwegian Radium Hospital trial</td>
<td>Pelvic RT</td>
<td>Observation</td>
<td>44</td>
<td>51</td>
<td>81.8% vs. 68.6%</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results; RT, radiation therapy; WPRT, whole pelvic RT; EC, endometrial carcinoma; RCT, randomized controlled trial; G3, grade 3.

The evidence for the key question was supported by the results of the two RCTs and two NRSs (one study [Blake P, 2009] was an RCT, but, because it extracted necessary subjects, the principle of randomness was compromised; as a result, it was reclassified as an NRS). However, the two RCTs did not present the survival rates until the present, and, therefore, a large-scale retrospective cohort research result presenting the survival rates was adopted. According to the study results, in patients with stage IB and grade 3 who had a risk of recurrence after uterine endometrial cancer surgery, the group who received pelvic radiation therapy and intravaginal radiation therapy as additional therapies exhibited higher survival rates than the follow-up group. Therefore, additional postoperative treatment based on pelvic radiation therapy and intravaginal radiation therapy is considered necessary. However, the results were based on one NRS, and, therefore, it is difficult to evaluate the research results consistently. Hence, the level of evidence is very low. (Level of evidence: very low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ4</td>
<td>Assumed risk Control</td>
<td>Corresponding risk</td>
<td>RR 0.77 (0.69–0.87)</td>
<td>1941 (1 study)</td>
<td>⊗ ⊗ ⊗ ⊗ very low</td>
</tr>
<tr>
<td>Follow-up: 5 years</td>
<td>427 per 1000</td>
<td>329 per 1000 (295–372)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4-5. Meta-analysis

For this recommendation, a meta-analysis was conducted to verify the need of radiation therapy as an additional treatment method for stage IB, grade 3 patients who had postoperative risk factors. In the two RCTs, there was no significant difference in progression-free survival rates between groups receiving radiation therapy and groups not receiving radiation therapy (hazard ratio: 0.58; 95% confidence interval: 0.34–1.01). However, there is no result of survival rates in the RCTs, and the lack of statistical significance of the progression-free survival rates is attributable to the insufficient number of patients. There was improvement in survival rates in the well-designed NRS, supporting the need of radiation therapy.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT: DFS</td>
<td>8</td>
<td>44</td>
<td>16</td>
<td>53.8%</td>
</tr>
<tr>
<td>Soeremen A, 2003</td>
<td>6</td>
<td>63</td>
<td>13</td>
<td>60.46%</td>
</tr>
<tr>
<td>Subtotal (65% CI)</td>
<td>107</td>
<td>111</td>
<td>100.00%</td>
<td>0.58 [0.34, 1.01]</td>
</tr>
<tr>
<td>Total events</td>
<td>16</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau^2 = 0.00; Chi^2 = 0.00, df = 1 (P = 0.98); P = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.03 (P = 0.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRS: DFS</th>
<th>3</th>
<th>80</th>
<th>7</th>
<th>113</th>
<th>100.00%</th>
<th>0.54 [0.34, 1.04]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (65% CI)</td>
<td>80</td>
<td>113</td>
<td>100.00%</td>
<td>0.54 [0.34, 1.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.50 (P = 0.27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRS: OS</th>
<th>403</th>
<th>1210</th>
<th>309</th>
<th>723</th>
<th>100.00%</th>
<th>0.77 [0.69, 0.87]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (65% CI)</td>
<td>403</td>
<td>723</td>
<td>100.00%</td>
<td>0.77 [0.69, 0.87]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>403</td>
<td>309</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.32 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Results of meta-analysis.

4-6. Summary

**[KQ 4]** Does adjuvant radiotherapy improve survival in patients with stage IB/grade 3 endometrial cancer with risk factors after surgery?

Pelvic RT and/or vaginal brachytherapy with (or without) chemotherapy is recommended as the adjuvant treatment in patients with stage IB, grade 3 endometrial cancers with risk factors after surgery.

Level of evidence: D (very low)
Strength of recommendation: 2 (weak)

4-7. References

5-1. Generation of key questions based on PICO*

| P | Advanced endometrial carcinoma |
| I | Sequential or concurrent chemoradiotherapy |
| C | Radiotherapy alone or chemotherapy alone / or <NONE> |
| O | Overall survival or progression-free survival |

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).

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 to identify eligible clinical trials for answering KQ4

| MEDLINE | 1. ('Endometrial Neoplasms' [Mesh]) OR 'Uterine Neoplasms' [Mesh:NoExp]  
|         | 2. ('Endometrium'/ti OR Endometrioid'/ti OR Endometrium'/ti OR Uterus'/ti OR Uterine'/ti) AND  
|         | ('cancer'/ti OR 'malignant'/ti OR 'carcinoma'/ti OR 'neoplasm'/ti OR 'cancers'/ti OR 'cancers'/ti OR 'malignancy'/ti OR 'carcinomas'/ti OR 'neoplasms'/ti) AND  
|         | ('Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine' AND 'cancer' OR 'malignant' OR 'carcinoma' OR 'neoplasm')  
|         | 3. 1 OR 2  
|         | 4. ('Uterus'[^Mesh:NoExp]) OR 'Endometrium'[^Mesh]  
|         | 5. Adenocarcinoma'/ti OR Adenocarcinomas'/ti  
|         | 6. 'Adenocarcinoma'[^Mesh:NoExp]  
|         | 7. 5 OR 6  
|         | 8. 'Carcinoma, Endometrioid'[^Mesh]  
|         | 9. ('Endometrium'/ti OR Endometrioid'/ti OR Endometrium'/ti OR Uterus'/ti OR Uterine'/ti) AND  
|         | ('cancer'/ti OR 'malignant'/ti OR 'carcinoma'/ti OR 'neoplasm'/ti OR 'cancers'/ti OR 'cancers'/ti OR 'malignancy'/ti OR 'carcinomas'/ti OR 'neoplasms'/ti) AND  
|         | ('Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine' AND 'cancer' OR 'malignant' OR 'carcinoma' OR 'neoplasm')  
|         | 10. 4 OR 9  
|         | 11. 10 AND 7  
|         | 12. 3 OR 8 OR 11  
|         | 13. stereotactic'/ti OR radiotherapy'/ti OR Radiotherapies'/ti  
|         | 14. 'Radiotherapy'[^Mesh:NoExp]  
|         | 15. 13 OR 14  
|         | 16. 12 AND 15  
|         | 17. 16 NOT 'review'/[Publication Type] OR 'review literature as topic'[^Mesh Terms] |

| EMBASE | 1. 'endometrium tumor'/de OR 'endometrium cancer'/de OR 'endometrium carcinoma'/exp OR 'uterus tumor'/de OR 'uterus cancer'/de OR 'uterus carcinoma'/exp  
|        | 2. ('Endometrial'/ab OR Endometrioid'/ab OR Endometrium'/ab OR Uterus'/ab OR Uterine'/ab) AND  
|        | ('cancer'/ti OR 'malignant'/ti OR 'carcinoma'/ti OR 'neoplasm'/ti OR 'cancers'/ti OR 'cancers'/ti OR 'malignancy'/ti OR 'carcinomas'/ti OR 'neoplasms'/ti) AND  
|        | ('Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine' AND 'cancer' OR 'malignant' OR 'carcinoma' OR 'neoplasm')  
|        | 3. 1 OR 2  
|        | 4. 'uterus'/de OR 'endometrium'/exp OR 'uterus cavity'/exp  
|        | 5. Adenocarcinoma'/ab OR Adenocarcinomas'/ab  
|        | 6. 'Adenocarcinoma'/de  
|        | 7. 5 OR 6  
|        | 8. Endometrial'/ab OR Endometrioid'/ab OR Endometrium'/ab OR Uterus'/ab OR Uterine'/ab  
|        | 9. 8 OR 4  
|        | 10. 7 AND 9  
|        | 11. 'endometrium carcinoma'/exp  
|        | 12. 3 OR 10 OR 11  
|        | 13. stereotactic'/ab OR radiotherapy'/ab OR Radiotherapies'/ab  
|        | 14. 'radiotherapy'/de  
|        | 15. 13 OR 14  
|        | 16. 12 AND 15  
|        | 17. 16 NOT ('article in press'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) OR 'in vitro study'/de  
|        | 18. 17 NOT ('human cell'/de OR 'human tissue'/de OR 'human study'/de) |

| Cochrane | 1. ('Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine') AND (cancer OR malignant OR 'carcinoma' OR 'neoplasm' OR 'cancers' OR 'malignancy') OR ('carcinomas' OR 'neoplasms')/ti,ab,kw  
|         | 2. MeSH descriptor: 'Endometrial Neoplasms' explode all trees  
|         | 3. MeSH descriptor: 'Uterine Neoplasms' this term only  
|         | 4. 1–3/or  
|         | 5. MeSH descriptor: 'Uterus' this term only  
|         | 6. MeSH descriptor: 'Endometrium' explode all trees  
|         | 7. Adenocarcinoma or Adenocarcinomas/ti,ab,kw  
|         | 8. MeSH descriptor: 'Adenocarcinoma' this term only  
|         | 9. 7 or 8  
|         | 10. MeSH descriptor: ['Carcinoma, Endometrioid'] explode all trees  
|         | 11. Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine  
|         | 12. 11 or 5 or 6  
|         | 13. 12 and 9  
|         | 14. 13/ftarr|

A total of 7,425 papers were searched using the aforementioned method until December 2014. Inclusion, and exclusion criteria were applied to these papers, as shown in Figure 1; finally, four papers were selected.
Figure 1. Flow chart of searching strategy for answering KQ5.

5.3. Quality assessment

The finally selected papers were composed of one randomized controlled trial (RCT) and three nonrandomized studies (NRSs). To evaluate the appropriateness of their study designs, the Cochrane Collaboration’s tool for assessing risk of bias and the suggested risk of bias criteria for Effective Practice and Organization of Care (EPOC) reviews were used for the randomized studies and the before-and-after study without subjects, respectively. Table 2 summarizes the results of evaluating the four papers.

Table 2. Study design characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Random sequence generation</th>
<th>Allocation conceal-ment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogberg, 2010</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Marichetti, 2011</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td></td>
<td>Low</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>Nakayama, 2010</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td></td>
<td>Low</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>Secord, 2007</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td></td>
<td>Low</td>
<td>(-)</td>
<td></td>
</tr>
</tbody>
</table>
5-4. Level of evidence and grade of recommendation

Table 3. Evidence table for postoperative chemotherapy and radiotherapy

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Population Intervention</th>
<th>Inclusion criteria</th>
<th>Number Intervention</th>
<th>Outcome</th>
<th>Type of treatment</th>
<th>Result</th>
<th>Study</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marchetti, 2011</td>
<td>Prospective cohort (phase II)</td>
<td>USA</td>
<td>Sequential CTx and RT</td>
<td>EBRT</td>
<td>Stage III</td>
<td>19</td>
<td>PFS, TAP #3 + EBRT</td>
<td>HR: 0.2 (0.04–1.08)</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>Hogberg, 2010</td>
<td>RCT</td>
<td>MaNGO ILIAD-III</td>
<td>Sequential CT-RT</td>
<td>EBRT</td>
<td>Stage IIIB, IIIA–C</td>
<td>80</td>
<td>5-year PFS, 5-year OS</td>
<td>AP#3 + pelvic RT (+/-) PAoLN, Brachy CAP#6 + RT</td>
<td>HR: 0.61 (0.33–1.12) 5-year PFS: 77.5% vs. 65.8% HR: 0.74 (0.36–1.52) 5-year OS: 82.5% vs. 77.6% HR: 0.31 (0.10–1.01)</td>
<td></td>
</tr>
<tr>
<td>Nakayama, 2010</td>
<td>Retrospective cohort</td>
<td>Japan</td>
<td>Sequential CTx and RT</td>
<td>WPRT</td>
<td>Stage III–IV</td>
<td>26</td>
<td>PFS, OS</td>
<td>HR: 0.41 (0.12–1.42)</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>Secord, 2007</td>
<td>Retrospective cohort</td>
<td>Multicenter, USA</td>
<td>Concurrent CTx and RT</td>
<td>RT or CTx</td>
<td>Stage III–IV</td>
<td>83</td>
<td>PFS, OS</td>
<td>TAP#6 with RT 1) vs RT, HR: 0.56 (0.34–0.92); 2) vs CTx HR: 0.43 (0.20–0.89)</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) vs CTx, HR: 0.50 (0.29–0.86) 2) vs CTx, HR: 0.54 (0.30–0.77)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; CTx, chemotherapy; RT, radiation therapy; HR, hazard ratio.

The evidence for the key question was supported by the results of one RCT and two NRSs evaluating radiation therapy and one NRS evaluating radiation therapy or chemotherapy. Survival rates and progression-free survival rates improved when a combination of chemotherapy and radiation therapy was performed, compared with chemotherapy only in one NRS. According to the RCT evaluating radiation therapy, the improvement in survival rates was not statistically significant, but analysis of the three NRSs showed that a combination of chemotherapy and radiation therapy was effective for improving survival rates and progression-free survival rates. The effect of additional chemotherapy in the radiation therapy group was statistically significant in the RCT and NRSs, but, given that the size of such effects was similar, it is estimated that the difference in the effects between the two groups was not proved because of the small number of RCT subjects. Therefore, it is thought that, despite the low level of evidence, a concurrent or sequential combination of radiation therapy and chemotherapy may be performed based on chemotherapy in patients with stage III and IV endometrial cancer. (Level of evidence: low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ5</td>
<td>Assumed risk 224 per 1000</td>
<td>HR 0.74 (0.36–1.52)</td>
<td>156 (1 study)</td>
<td>⊗ ⊗ ⊗ low</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up: 5 years
5.5. Meta-analysis

For this recommendation, a meta-analysis was carried out to verify the effect of postoperative chemoradiation therapy in endometrial cancer patients. There was no statistical difference between the two groups when chemoradiation therapy was conducted in the one RCT group compared with the group that received radiation therapy only (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.36–1.52), but the lack of statistical significance was because the evaluation was of only one RCT and the combination of chemotherapy and radiation therapy is supported by the well-designed NRS. In other words, in the NRS that compared the group that received chemotherapy only, the HR was 0.54 (95% CI: 0.30–0.97), and in the NRS that compared the group that received radiation therapy only, the HR was 0.46 (95% CI: 0.28–0.75). The improvement in survival rates with a combination of chemotherapy and radiation therapy was significant.

![Figure 2. Result of meta-analysis.](image-url)
5-6. Summary

<table>
<thead>
<tr>
<th>[KQ 5]</th>
<th>Is adjuvant treatment with concurrent chemoradiotherapy or sequential chemotherapy and radiotherapy effective in patients with advanced-stage endometrial cancers?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined chemotherapy and radiotherapy in a concurrent or sequential approach is recommended for patients with advanced-stage endometrial cancers after surgery.</td>
<td></td>
</tr>
<tr>
<td>Level of evidence: C (low)</td>
<td></td>
</tr>
<tr>
<td>Strength of recommendation: 2 (weak)</td>
<td></td>
</tr>
</tbody>
</table>

5-7. References


6-1. Generation of key questions based on PICO*

**[KQ 6]** Does paclitaxel/carboplatin therapy show a similar survival rate compared with doxorubicin combination therapy in patients with advanced and recurrent endometrial cancers?

P : Advanced, recurrent endometrial carcinoma  
I : Paclitaxel-carboplatin  
C : Cisplatin/doxorubicin  
O : Overall survival or progression-free survival or toxicity

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).

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 to identify eligible clinical trials for answering KQ4

| MEDLINE | 1. (“Endometrial Neoplasms”[Mesh]) OR “Uterine Neoplasms”[Mesh:NoExp]  
| | 3. 1 OR 2  
| | 4. (“Uterus”[Mesh:NoExp]) OR “Endometrium”[Mesh]  
| | 5. Adenocarcinoma[tiab] OR Adenocarcinomas[tiab]  
| | 6. “Adenocarcinoma”[Mesh:NoExp]  
| | 7. 5 OR 6  
| | 8. “Carcinoma, Endometrioid”[Mesh]  
| | 10. 4 OR 9  
| | 11. 10 AND 7  
| | 12. 3 OR 8 OR 11  
| | 13. (“Paclitaxel”[tiab] OR “Doxorubicin”[tiab])  
| | 14. (“Paclitaxel”[Mesh]) OR “Doxorubicin”[Mesh]  
| | 15. 13 OR 14  
| | 16. 12 AND 15  
| | 17. 16 NOT (“review”[Publication Type] OR “review literature as topic”[Mesh Terms])  

| EMBASE | 1. “endometrium tumor”/de OR “endometrium cancer”/de OR “endometrium cancer”/exp OR “uterus tumor”/de OR “uterus cancer”/de OR “uterus carcinoma”/exp  
| | 2. (Endometrial:ab,ti OR Endometrioid:ab,ti OR Endometrium:ab,ti OR Uterus:ab,ti OR Uterine:ab,ti) AND (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)  
| | 3. 1 OR 2  
| | 4. “uterus”/de OR “endometrium”/exp OR “uterus cavity”/exp  
| | 5. Adenocarcinoma:ab,ti OR Adenocarcinomas:ab,ti  
| | 6. “adenocarcinoma”/de  
| | 7. 5 OR 6  
| | 8. Endometrial:ab,ti OR Endometrioid:ab,ti OR Endometrium:ab,ti OR Uterus:ab,ti OR Uterine:ab,ti  
| | 9. 8 OR 4  
| | 10. 7 AND 9  
| | 11. “endometrium cancer”/exp  
| | 12. 3 OR 10 OR 11  
| | 13. “Paclitaxel”:ab,ti OR “Doxorubicin”:ab,ti  
| | 14. “paclitaxel”/exp OR “doxorubicin”/exp  
| | 15. 13 OR 14  
| | 16. 15 AND 12  
| | 17. 16 NOT (“article in press”/it OR “conference review”/it OR “editorial”/it OR “erratum”/it OR “letter”/it OR “note”/it OR “review”/it OR “short survey”/it)  
| | 18. 17 NOT (“animal experiment”/de OR “animal model”/de OR “human cell”/de OR “human tissue”/de OR “in vitro study”/de OR “nonhuman”/de)  

| Cochrane | 1. (Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine) AND (cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms):ti,ab,kw  
| | 2. MeSH descriptor: [Endometrial Neoplasms] explode all trees  
| | 3. MeSH descriptor: [Uterine Neoplasms] this term only  
| | 4. 1–3/for  
| | 5. MeSH descriptor: [Uterus] this term only  
| | 6. MeSH descriptor: [Endometrium] explode all trees  
| | 7. Adenocarcinoma or Adenocarcinomas:ti,ab,kw  
| | 8. MeSH descriptor: [Adenocarcinoma] this term only  
| | 9. 7 OR 8  
| | 10. MeSH descriptor: [Carcinoma, Endometrioid] explode all trees  
| | 11. Endometrial OR Endometrioid OR Endometrium OR Uterus OR Uterine  
| | 12. 11 OR 5 OR 6  
| | 13. 12 AND 9  
| | 14. 13/trial  

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A total of 3,105 papers were searched using the aforementioned method until December 2014. Inclusion and exclusion criteria were applied to these papers, as shown in Figure 1, and one paper was finally selected.

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

6-3. Quality assessment
The one finally selected paper was an RCT. To evaluate the appropriateness of its study design, the Cochrane Collaboration’s tool for assessing risk of bias technique was used.

Table 2. Study design characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller, 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
6-4. **Level of evidence and grade of recommendation**

Table 3. Evidence table for carboplatin/paclitaxel

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller, 2012</td>
<td>RCT</td>
<td>GOG209 (interim analysis)</td>
<td>642 TC, 663 TAP</td>
<td>Metastatic or recurrent EC</td>
<td>PFS, OS</td>
<td>Median PFS: 14.0 vs. 14.0 months (HR: 1.03)</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; EC, endometrial carcinoma; HR, hazard ratio.

The evidence for the key question was supported by the one RCT study. The paclitaxel/carboplatin group showed no difference in survival rates compared with the paclitaxel/doxorubicin/cisplatin group and exhibited excellent results in terms of treatment toxicity. Therefore, as chemotherapy for patients with progressive and recurrent endometrial cancer, paclitaxel/carboplatin therapy is preferentially recommended. (Level of evidence: low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Median OS</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk Corresponding risk Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KQ6</td>
<td>Follow-up: 5 years</td>
<td>32.0 vs 38.0</td>
<td>1,305 (1 study)</td>
<td>🟢🟢🟢🟢 low</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; OS, overall survival.

6-5. **Summary**

**[KQ 4] Does paclitaxel/carboplatin therapy show a similar survival rate compared with doxorubicin combination therapy in patients with advanced and recurrent endometrial cancers?**

The combination of paclitaxel and carboplatin is recommended in patients with advanced and recurrent endometrial cancer. This is supported by the preliminary results of a randomized trial showing similar efficacy and less toxicity compared with cisplatin/doxorubicin/paclitaxel.

Level of evidence: C (low)

Strength of recommendation: 1 (strong)

6-6. **References**

7-1. Generation of key questions based on PICO*

**[KQ 7]** Does power morcellation affect survival in patients with uterine sarcoma?

- **P**: Leiomyosarcoma
- **I**: Power morcellation
- **C**: En bloc resection as hysterectomy or myomectomy
- **O**: Overall survival or Progression-free survival

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).

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>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
<th>Cochrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. leiomyosarcoma[tiab] OR Leiomyosarcomas[tiab]</td>
<td>1. leiomyosarcoma:ab,ti OR Leiomyosarcomas:ab,ti</td>
<td>1. leiomyosarcoma or Leiomyosarcomas</td>
</tr>
<tr>
<td>5. (“Uterus”[Mesh:NoExp]) OR “Endometrium”[Mesh]</td>
<td>5. “uterus”/de OR “endometrium”/exp OR “uterus cavity”/exp</td>
<td>5. 3 or 4</td>
</tr>
<tr>
<td>7. 5 OR 6</td>
<td>7 OR 6</td>
<td>7. 9 and 5</td>
</tr>
<tr>
<td>8. 7 AND (3 OR 4)</td>
<td>8 OR 1 OR 2</td>
<td>8. 10 OR 11</td>
</tr>
</tbody>
</table>

A total of 567 papers were searched using the aforementioned method until December 2014. Inclusion and exclusion criteria were applied to these papers, as shown in Figure 1, and three papers were finally selected.
Figure 1. Flow chart of searching strategy for answering KQ7

7-3. **Quality assessment**

The three finally-selected papers were all NRSs, and, to assess the appropriateness of the study design, the Newcastle-Ottawa Quality Assessment Scale technique was used. The evaluation results of the three papers are summarized in Table 2.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the nonexposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at start of study</th>
<th>Comparability of cohorts on the basis of the design or analysis</th>
<th>Assessment of outcome</th>
<th>Was follow-up long enough for outcomes to occur?</th>
<th>Adequacy of follow-up of cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>George, 2014</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Park, 2011</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Perri, 2009</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>
7-4. Level of evidence and grade of recommendation

Table 3. Evidence table for ovarian preservation

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
<th>5-year OS</th>
<th>HR or OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>George, 2014</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>Morcellation</td>
<td>No morcellation</td>
<td>Uterine leiomyosarcoma</td>
<td>19</td>
<td>39</td>
<td>5-year OS 57.9% vs. 66.7%</td>
<td>HR (for recurrence): 3.18 (1.5–6.8)</td>
</tr>
<tr>
<td>Perri, 2009</td>
<td>Retrospective cohort</td>
<td>Israel</td>
<td>Morcellation</td>
<td>No morcellation</td>
<td>Uterine leiomyosarcoma</td>
<td>16</td>
<td>21</td>
<td>5-year OS 37.5% vs. 61.9%</td>
<td>HR (for survival, TAH vs. morcellation): 0.36 (0.13–0.98)</td>
</tr>
<tr>
<td>Park, 2011</td>
<td>Retrospective cohort</td>
<td>Korea</td>
<td>Morcellation</td>
<td>No morcellation</td>
<td>Uterine leiomyosarcoma</td>
<td>25</td>
<td>31</td>
<td>5-year OS 56.0% vs. 83.9%</td>
<td>OR (for survival): 3.11 (1.07–9.06)</td>
</tr>
</tbody>
</table>

OS, overall survival; HR, hazard ratio; OR, odds ratio.

The evidence for the key question is supported by the three NRS results. Laparoscopic power morcellation decreased the survival rates of uterine sarcoma patients. Therefore, power morcellation through laparoscopic surgery should be avoided when uterine sarcoma is suspected before a surgery. Because there is no RCT verifying the results and the conditions of relative risk reduction at 34%, optimal information size at 200, and event number at 55 are required to examine the effects on survival rates, and, therefore, the level of evidence is very low under the present conditions. (Level of evidence: very low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% No. of the evidence Comments</th>
<th>ILR 1.66 (1.08–2.53) 151 (3 studies)</th>
<th>(grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ7 Follow-up: 5 years</td>
<td>286 per 1000 474 per 1000 (309–723)</td>
<td>RR 1.66 (1.08–2.53) 151 (3 studies)</td>
<td>⊘ ⊘ ⊘ very low</td>
<td></td>
</tr>
</tbody>
</table>

30
7-5. Meta-analysis

For this recommendation, a meta-analysis was conducted to verify the effects of power morcellation on survival rates in uterine sarcoma patients. Significant differences were found between groups undergoing power morcellation and those that did not (hazard ratio: 1.66; 95% confidence interval: 1.08–2.53).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M-H</td>
<td>Random</td>
</tr>
<tr>
<td>George S, 2014</td>
<td>0</td>
<td>19</td>
<td>1.2</td>
<td>20</td>
<td>37.9%</td>
<td>1.23</td>
</tr>
<tr>
<td>Park JY, 2011</td>
<td>11</td>
<td>24</td>
<td>5</td>
<td>21</td>
<td>24.4%</td>
<td>2.73</td>
</tr>
<tr>
<td>Perri T, 2003</td>
<td>10</td>
<td>16</td>
<td>0</td>
<td>21</td>
<td>40.7%</td>
<td>1.84</td>
</tr>
<tr>
<td>Total (65% CI)</td>
<td>60</td>
<td>91</td>
<td>100.0%</td>
<td>1.66</td>
<td>[1.08, 2.53]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Chi² = 1.77, df = 2 (P = 0.41), I² = 0%
Total for overall effect: Z = 2.33 (P = 0.02)

Figure 2. Results of meta-analysis.

7-6. Summary

[KQ 7] **Does power morcellation affect survival in patients with uterine sarcoma?**

In patients suspected to have uterine sarcoma, power morcellation should be avoided through laparoscopic surgery because power morcellation has been found to decrease the survival of patients with uterine sarcoma.

Level of evidence: D (very low)

Strength of recommendation: I (strong)

7-7. References

8-1. Generation of key questions based on PICO*

<table>
<thead>
<tr>
<th>KQ 8</th>
<th>Does pazopanib therapy improve survival in recurrent uterine LMS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Leiomyosarcoma (progressing despite previous standard chemotherapy)</td>
</tr>
<tr>
<td>I</td>
<td>Pazopanib</td>
</tr>
<tr>
<td>C</td>
<td>Placebo</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

*PICO: Population (P), Intervention or indicator (I), Comparator ©, Outcome (O).

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.

Table 1. Procedure to identify eligible clinical trials for answering KQ1

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
<th>Cochrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. leiomyosarcoma[tiab] OR Leiomyosarcomas[tiab]</td>
<td>1. leiomyosarcoma:ab,ti OR Leiomyosarcomas:ab,ti</td>
<td>1. leiomyosarcoma or Leiomyosarcomas</td>
</tr>
<tr>
<td>5. (“Uterus”[Mesh:NoExp]) OR “Endometrium”[Mesh]</td>
<td>5. “uterus”/de OR “endometrium”/exp OR “uterus cavity”/exp</td>
<td>5. 3 or 4</td>
</tr>
<tr>
<td>7. 5 OR 6</td>
<td>7. 5 OR 6</td>
<td>7. MeSH descriptor: [Endometrium] explode all trees</td>
</tr>
<tr>
<td>8. 7 AND (3 OR 4)</td>
<td>8. 7 AND (3 OR 4)</td>
<td>8. Endometrial or Endometrioid or Endometrium or Uterus or Uterine:ab,kw</td>
</tr>
<tr>
<td>9. 8 OR 1 OR 2</td>
<td>9. 8 OR 1 OR 2</td>
<td>9. 6–8/or</td>
</tr>
<tr>
<td>11. 9 AND 10</td>
<td>11. 9 AND 10</td>
<td>11. 10 and 5</td>
</tr>
</tbody>
</table>

A total of 320 papers were searched using the aforementioned method until December 2014. Inclusion and exclusion criteria were applied to these papers as shown in Figure 1, and one paper was finally selected.
8-3. Quality assessment

The finally-selected paper was an RCT, and, to evaluate the appropriateness of the study design, the Cochrane Collaboration’s tool for assessing risk of bias technique was used. The evaluation of the results is summarized in Table 2.

Table 2. Study design characteristics based on the QUADAS tool

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Graaf, 2012</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
---

### 8-4. Level of evidence and grade of recommendation

Table 3. Evidence table for pazopanib

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design (only selected group from RCT)</th>
<th>Country</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Graaf,</td>
<td>Multicenter study (PALETTE)</td>
<td></td>
<td>Pazopanib</td>
<td>Angiogenesis inhibitor-naive, metastatic soft-tissue sarcoma, progressing despite</td>
<td>115</td>
<td>PFS</td>
<td>36.5% vs. 12.0% HR (UtLMS vs. other sarcoma): 0.88 (0.63–1.21)</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td>Placebo</td>
<td>previous standard chemotherapy (UtLMS)</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS, progression-free survival; HR, hazard ratio; NRS, nonrandomized study; RCT, randomized controlled trial.

The evidence for the key question was supported by one NRS, which was an RCT, but, because the necessary subjects were extracted, which compromises the principle of randomness, it was reclassified as an NRS. In leiomyosarcoma patients, the group that used pazopanib exhibited higher progression-free survival rates than the placebo group. Therefore, in patients with recurrent leiomyosarcoma that fail to respond to previous standard chemotherapy, pazopanib, a target treatment agent, may be used as monotherapy. Because there was a single RCT, the level of evidence is very low. (Level of evidence: very low)

Table 4. Estimation of grade

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (grade)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KQ8</td>
<td>880 per 1000</td>
<td>783 per 1000 (726–839)</td>
<td>HR 0.72 (0.61–0.86)</td>
<td>165 (1 study)</td>
<td>⊗⊗⊗⊗ ⊗ low</td>
</tr>
<tr>
<td>Follow-up: 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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1. Very low

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8-5. Meta-analysis

For this recommendation, a meta-analysis was conducted to verify the effect of pazopanib in patients with metastatic, recurrent uterine LMS. There were significant differences in progression-free survival rates of the group that was administered pazopanib compared with the group that was administered placebo (risk ratio: 0.72; 95% confidence interval: 0.61–0.86).

![Figure 2. Results of meta-analysis.](image)

8-6. Summary

**[KQ 8]** Does pazopanib therapy improve survival in recurrent uterine LMS?

- In patients with metastatic and recurrent LMS that previously failed to respond to standard chemotherapy, pazopanib is recommended as monotherapy.
- Level of evidence: D (very low)
- Strength of recommendation: 1 (strong)

8-7. References