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

[KQ 1]

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

* PICO: Population (P), Intervention / or indicator (I), Comparator (C), Outcome (O)

<table>
<thead>
<tr>
<th>[KQ 1]</th>
<th>Does systemic PLND and/or PALND improve survival outcomes for patients with early-stage EOC apparently confined to an ovary?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Clinical stage I, epithelial ovarian cancer</td>
</tr>
<tr>
<td>I</td>
<td>Systemic lymphadenectomy</td>
</tr>
<tr>
<td>C</td>
<td>No lymphadenectomy or selective lymphadenectomy</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

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 studies for answering KQ1

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>1. &quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3. &quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 231416</td>
</tr>
<tr>
<td></td>
<td>OR malignancy[tia] OR carcinomas[tia] OR neoplasms[tia] OR Adenocarcinoma[tia]</td>
</tr>
<tr>
<td></td>
<td>OR Adenocarcinomas[tia] 1776471</td>
</tr>
<tr>
<td></td>
<td>6. (&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
</tr>
<tr>
<td></td>
<td>7. 5 OR 6 1834398</td>
</tr>
<tr>
<td></td>
<td>8. 7 AND 4 75509</td>
</tr>
<tr>
<td></td>
<td>9. 8 OR 1 93357</td>
</tr>
<tr>
<td></td>
<td>10. &quot;Lymph Nodes&quot;[Mesh:NoExp] 69983</td>
</tr>
<tr>
<td></td>
<td>11. &quot;lymph node&quot;[tia] OR &quot;lymph nodes&quot;[tia] 153704</td>
</tr>
<tr>
<td></td>
<td>12. 10 OR 11 182313</td>
</tr>
<tr>
<td></td>
<td>14. 12 AND 13 56971</td>
</tr>
<tr>
<td></td>
<td>15. lymphadenectomy[tia] OR Lymphadenectomies[tia] 12721</td>
</tr>
<tr>
<td></td>
<td>16. lymph node excision&quot;[Mesh:NoExp] 25522</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>17</td>
<td>14 OR 15 OR 16 73650</td>
</tr>
<tr>
<td>18</td>
<td>9 AND 16 2144</td>
</tr>
</tbody>
</table>

**Embase**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>‘ovary cancer’/de OR ‘ovary adenocarcinoma’/exp OR ‘ovary carcinoma’/exp OR ‘ovary metastasis’/exp 75894</td>
</tr>
<tr>
<td>2</td>
<td>Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti 232073</td>
</tr>
<tr>
<td>3</td>
<td>‘ovary’/exp 139338</td>
</tr>
<tr>
<td>4</td>
<td>2 OR 3 311368</td>
</tr>
<tr>
<td>5</td>
<td>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 2292630</td>
</tr>
<tr>
<td>6</td>
<td>‘endometrioid carcinoma’/exp 2906</td>
</tr>
<tr>
<td>7</td>
<td>5 OR 6 2292749</td>
</tr>
<tr>
<td>8</td>
<td>7 AND 4 971118</td>
</tr>
<tr>
<td>9</td>
<td>8 OR 1 117046</td>
</tr>
<tr>
<td>10</td>
<td>‘lymph node’/de OR ‘paraaortic lymph node’/exp OR ‘pelvis lymph node’/exp 84500</td>
</tr>
<tr>
<td>11</td>
<td>‘lymph node’:ab,ti OR ‘lymph nodes’:ab,ti 201819</td>
</tr>
<tr>
<td>12</td>
<td>10 OR 11 224044</td>
</tr>
<tr>
<td>13</td>
<td>excision:ab,ti OR excisions:ab,ti OR resec*:ab,ti OR operation:ab,ti OR surgery:ab,ti OR surgical:ab,ti OR dissection:ab,ti OR operative:ab,ti OR dissections:ab,ti 2202600</td>
</tr>
<tr>
<td>14</td>
<td>12 AND 13 80265</td>
</tr>
<tr>
<td>15</td>
<td>lymphadenectomy:ab,ti OR Lymphadenectomies:ab,ti 17806</td>
</tr>
<tr>
<td>16</td>
<td>lymph node dissection’/exp 49870</td>
</tr>
<tr>
<td>17</td>
<td>14 OR 15 OR 16 107238</td>
</tr>
<tr>
<td>18</td>
<td>9 AND 16 3743</td>
</tr>
<tr>
<td>19</td>
<td>18 NOT (‘editorial’/it OR ‘erratum’/it OR ‘letter’/it OR ‘note’/it OR ‘short survey’/it) 3601</td>
</tr>
<tr>
<td>20</td>
<td>19 NOT (‘human cell’/de OR ‘nonhuman’/de) 3469</td>
</tr>
</tbody>
</table>

**Cochrane**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeSH descriptor: [Ovarian Neoplasms] this term only 1394</td>
</tr>
<tr>
<td>2</td>
<td>Ovarian OR Ovary OR Ovaries OR adnexa OR adnexal:ab,ti,kw 8250</td>
</tr>
<tr>
<td>3</td>
<td>MeSH descriptor: [Adnexa Uteri] explode all trees” 1169</td>
</tr>
<tr>
<td>4</td>
<td>MeSH descriptor: [Ovary] explode all trees 975 cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms OR Adenocarcinoma OR Adenocarcinomas:ab,ti,kw 89830</td>
</tr>
<tr>
<td>5</td>
<td>MeSH descriptor: [Adenocarcinoma] explode all trees 4728</td>
</tr>
<tr>
<td>6</td>
<td>MeSH descriptor: [Carcinoma, Endometrioid] explode all trees 32 1 or ((2 or 3 or 4) and (5 or 6 or 7)) 3662</td>
</tr>
<tr>
<td>7</td>
<td>8/trail 3209</td>
</tr>
</tbody>
</table>
A total of 4,354 articles were identified using aforementioned method. Five articles were finally selected.

Figure 1. Flow chart of searching strategy for answering KQ1.
1-3. Quality assessment

Finally selected 5 articles comprised 1 randomized controlled trial (RCT) and 4 non-randomized study (NRS). Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (Table 2) and Ottawa Quality Assessment Scale (Table 3) were used for assessing risk of bias, respectively.

Table 2. Quality Assessment of Diagnostic Accuracy Studies for RCT

<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>Maggioni A, 2006¹</td>
<td>low</td>
<td>low</td>
<td>unclear</td>
<td>high</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

Table 3. Ottawa Quality Assessment Scale for NRS

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Selection of the non-exposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Demonstration that outcome was not present at start of study</td>
<td>Comparability of cases and controls on the basis of the design or analysis</td>
</tr>
<tr>
<td>Chan JK, 2007²</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Suzuki S, 2008³</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Oshita T, 2013⁴</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Svolgaard O, 2014⁵</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
</tr>
</tbody>
</table>

1-4. Level of evidence and grade of recommendation

Table 4. Evidence table for systemic lymphadenectomy and survival outcomes

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study</th>
<th>Country</th>
<th>Study year</th>
<th>Population</th>
<th>Inclusion</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
</table>

4
<table>
<thead>
<tr>
<th></th>
<th>design</th>
<th>Intervention</th>
<th>Control</th>
<th>criteria</th>
<th>Intervention</th>
<th>Control</th>
<th>study criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maggioni A, 2006</td>
<td>RCT</td>
<td>Systemic LND</td>
<td>LN sampling</td>
<td>Stage I-II</td>
<td>138</td>
<td>130</td>
<td>5-yr PFS: 71.3% vs. 78.3% 5-yr OS: 81.3% vs. 84.2% This study may lack power to exclude clinical effects of systemic LND on PFS and OS</td>
</tr>
<tr>
<td>Chan JK, 2007</td>
<td>Retrospective cohort</td>
<td>Systemic LND</td>
<td>LN sampling</td>
<td>Stage I</td>
<td>2,862</td>
<td>3,824</td>
<td>5-yr OS: 92.6% vs. 87.0% (p&lt;0.001) Extent of LND is an independent prognostic factors for improved survival (HR 0.72; 95% CI 0.62-0.84; p&lt;0.001). No information about LND complication (e.g. lymphedema).</td>
</tr>
<tr>
<td>Suzuki S, 2008</td>
<td>Retrospective cohort</td>
<td>Systemic LND</td>
<td>LN sampling</td>
<td>Stage I-II clear cell carcinoma</td>
<td>104</td>
<td>101</td>
<td>5-yr DFS: 79.7% vs. 73.5% (p=0.353) 5-yr OS: 84.7% vs. 85.3% (p=0.645) No information about LND complication (e.g. lymphedema). Inconsistency of adjuvant chemotherapy between groups.</td>
</tr>
<tr>
<td>Oshita T, 2013</td>
<td>Retrospective cohort</td>
<td>Systemic LND</td>
<td>No LND</td>
<td>Stage I-II</td>
<td>284</td>
<td>138</td>
<td>5-yr PFS: 83.5% vs. 80.3% (p=0.336) 5-yr OS: 89.3% vs. 86.2% (p=0.148) Longer op time, greater blood loss, lymphocyst, and leg edema in systemic LND group, but similar ileus and DVT/pulmonary embolism.</td>
</tr>
<tr>
<td>Svolgaard O, 2014</td>
<td>Retrospective cohort</td>
<td>Systemic LND</td>
<td>No LND</td>
<td>Stage I</td>
<td>216</td>
<td>411</td>
<td>5-yr OS: 85% vs. 80%; HR 1.7; 95% CI 0.9-3.0; P=0.064</td>
</tr>
</tbody>
</table>

There is only one RCT for evidence of KQ1. However, all four NRSs support consistent results. Considering RRR=0.14 and 20% risk of death in control group, OIS should be higher than 800. However, accuracy was not proved because there were only 47 deaths (evidence level: MODERATE)
Table 5. 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>OS</td>
<td>Control</td>
<td>KQ1</td>
<td>RR 0.86 (0.51 to 1.46)</td>
<td>268 (1 study)</td>
<td>☂ ☂ ☂ ☂ moderate</td>
</tr>
<tr>
<td>Follow-up: median 87.8 mo</td>
<td>192 per 1000</td>
<td>165 per 1000 (98 to 281)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-5. Meta-analysis

A meta-analysis showed that systemic PLND and/or PALND was associated with better survival outcomes than LN sampling or no LND. However, statistical significance was not found in a RCT.

Figure 2. Result of meta-analysis

1-6. Summary

[KQ 1] Does systemic PLND and/or PALND improve survival outcomes for patients with early-stage EOC apparently confined to an ovary?

Systemic PLND and/or PALND may be selectively performed for those patients with EOC apparently confined to an ovary under the physician’s discretion despite the lack of evidence for survival improvement compared with selective or omitting PLND and/or PALND.

Level of evidence: A (high)

Strength of recommendation: 2 (weak)

1-7. References


2-1. Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>KQ 2</th>
<th>Are survival outcomes from NAC followed by interval cytoreductive surgery vs. primary cytoreductive surgery comparable in patients with extensive stage IIIC-IV EOC who are not likely for optimal cytoreduction?</th>
</tr>
</thead>
</table>

P : Advanced stage epithelial ovarian cancer  
I : Neoadjuvant chemotherapy followed by interval cytoreductive surgery  
C : Primary cytoreductive surgery  
O : Overall survival or Progression-free survival

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.

Table 1. Procedure used for MEDLINE, Embase, and Cochrane to identify eligible clinical trials for answering KQ2

| MEDLINE | 1. "Ovarian Neoplasms"[Mesh:NoExp] 62383  
3. "adnexa uteri"[Mesh] OR "Ovary"[Mesh] 90365  
4. 2 OR 3 231416  
6. ("Adenocarcinoma"[Mesh]) OR "Carcinoma, Endometrioid"[Mesh] 291505  
7. 5 OR 6 1834398  
8. 7 AND 4 75509  
9. 8 OR 1 93357  
| 12. | 10 AND 11 28847 |
| 13. | 9 AND 12 1160 |

**Embase**

1. 'ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR 'ovary metastasis'/exp 75894
2. Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti 232073
3. 'ovary'/exp 139338
4. 2 OR 3 311368
5. 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 2292630
6. 'endometrioid carcinoma'/exp 2906
7. 5 OR 6 2292749
8. 7 AND 4 97118
9. 8 OR 1 117046
10. 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 Anti-cancer:ab,ti OR Chemotheraphy:ab,ti OR Chemotherapic:ab,ti OR Chemotherapies:ab,ti OR 'Chemo therapy':ab,ti OR 'Chemo-therapy':ab,ti OR 'antineoplast ic agent'/exp OR 'chemotherapy'/exp 494319
11. 'antineoplastic agent'/exp OR 'chemotherapy'/exp 1686971
12. 10 OR 11 1797961
13. neoadjuvant:ab,ti OR preoperative:ab,ti OR peri-operative:ab,ti OR 'peri operative':ab,ti OR pre-operative:ab,ti OR 'pre operative':ab,ti OR perioperative:ab,ti 335444
14. 12 AND 13 51400
15. 9 AND 14 1959
16. 15 NOT ('nonhuman'/de OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) 1885

**Cochrane**

1. MeSH descriptor: [Ovarian Neoplasms] this term only 1394
2. Ovarian OR Ovary OR Ovaries OR adnexa OR adnexal:ab,ti,kw 8250
3. MeSH descriptor: [Adnexa Uteri] explode all trees" 1169
4. MeSH descriptor: [Ovary] explode all trees 975
5. cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms OR Adenocarcinoma OR Adenocarcinomas:ab,ti,kw 89830
6. MeSH descriptor: [Adenocarcinoma] explode all trees 4728
7. MeSH descriptor: [Carcinoma, Endometrioid] explode all trees 32
8. 1 or ((2 or 3 or 4) and (5 or 6 or 7)) 3662
9. 8/trail 3209
A total of 2,335 articles were identified using aforementioned method. Seven articles were finally selected.

**Figure 1.** Flow chart of searching strategy for answering KQ2
2-3. Quality assessment

Finally selected 7 articles comprised 2 RCTs and 5 NRSs. QUADAS (Table 2) and Ottawa Quality Assessment Scale (Table 3) were used for assessing risk of bias, respectively.

Table 1. Quality Assessment of Diagnostic Accuracy Studies for RCT

<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>Ignace V, 2010¹</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>unclear</td>
<td>low</td>
</tr>
<tr>
<td>Kehoe S, 2015²</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>

Table 2. Ottawa Quality Assessment Scale for NRS

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of the exposed cohort</td>
<td>Comparability of cases and controls on the basis of the design or analysis</td>
<td>Adequacy of follow up of cohorts</td>
</tr>
<tr>
<td>Everett EN, 2006¹</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Hou JY, 2007²</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>Worley MJ Jr, 2013³</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>Glasgow MA, 2013⁶</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>Fagø-Olsen CL, 2014⁷</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
</tbody>
</table>

2-4. Level of evidence and grade of recommendation

Table 4. Evidence table for NAC followed by interval cytoreductive surgery vs. primary cytoreductive surgery
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study year (enrollment/median f/u)</th>
<th>Population</th>
<th>Inclusion Criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ignace V, 2010¹</td>
<td>RCT</td>
<td>Multicenters/ EORTC-GCG and NCIC clinical trials group</td>
<td>1998-2006/4.7 yrs</td>
<td>NAC followed by interval cytoreductive surgery</td>
<td>Primary cytoreductive surgery stage III or IV ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>322</td>
<td>Median PFS</td>
<td>12 mo vs. 12 mo (HR for PD 1.01; 90% CI 0.89-1.15)</td>
<td>For those with cytoreduction to ≤1 cm, no difference of survival outcomes between two groups. For those with metastatic tumors&lt;5cm at randomization, OS was slightly longer in the PS group than in NAC group (HR 0.64; 95% CI 0.45-0.93). Morbidity and mortality of NAC vs. PS: postop death, 0.7% vs. 2.5%; gr3 or 4 hemorrhage, 4.1% vs. 7.4%; infection, 1.7% vs. 8.1%; venous complication, 0% vs. 2.6%.</td>
</tr>
<tr>
<td>Kehoe S, 2015²</td>
<td>RCT</td>
<td>87 hospitals/UK, New Zealand (CHORUS)</td>
<td>2004-2010/4.4 yrs</td>
<td>NAC followed by interval cytoreductive surgery</td>
<td>Primary cytoreductive surgery stage III or IV ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>253</td>
<td>Median PFS</td>
<td>12 mo vs. 10.7mo (HR 0.91; 95% CI 0.76-1.09; p=0.292)</td>
<td>Gr3 or 4 postop AE (14% vs. 24%, p=0.0007) and death (&lt;1% vs. 6%, p=0.001): hemorrhage, 7% vs. 3%; infection, 3% vs. 6%; VTE, 0% vs. 2%.</td>
</tr>
<tr>
<td>Everett EN, 2006³</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>1995-2003/NA</td>
<td>NAC followed by interval</td>
<td>Primary cytoreduction Stage III-IV EOC</td>
<td>98</td>
<td>Longer PFI: PS vs. NAC (HR, 1.78; p=0.003)</td>
<td>NAC group have more stage IV (p=0.042) and gr3(p=0.025) than PS group. Optimal cytoreduction: 86%</td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Study Type</td>
<td>Country</td>
<td>Time Period</td>
<td>Primary Treatment</td>
<td>Follow-Up</td>
<td>Primary Cytoreduction</td>
<td>Stage of EOC</td>
<td>Median PFS</td>
<td>Median OS</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>---------</td>
<td>-------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>----------------------</td>
<td>--------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hou JY, 2007&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>1998-2005/NA</td>
<td>NAC followed by interval cytoreductive surgery</td>
<td></td>
<td>Primary cytoreduction</td>
<td>Stage III-IV EOC</td>
<td>37</td>
<td>109</td>
</tr>
<tr>
<td>Worley MJ Jr, 2013&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>2000-2010/NA</td>
<td>NAC followed by interval cytoreductive surgery</td>
<td></td>
<td>Primary cytoreduction</td>
<td>≥70 yrs old with stage III or IV ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>40</td>
<td>125</td>
</tr>
<tr>
<td>Glasgow MA, 2013&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>1996-2009/NA</td>
<td>NAC followed by interval cytoreductive surgery</td>
<td></td>
<td>Primary cytoreduction</td>
<td>≥70 yrs old with stage III-IV EOC</td>
<td>42</td>
<td>62</td>
</tr>
<tr>
<td>Fagö-Olsen CL, 2014&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Denmark</td>
<td>2005-2011/21mo</td>
<td>NAC followed by interval cytoreductive surgery</td>
<td></td>
<td>Primary cytoreduction</td>
<td>stage III or IV ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>335</td>
<td>990</td>
</tr>
</tbody>
</table>

There are 2 RCTs supporting the evidence of KQ2. Considering RRR=0.06, risk of death=99%, and OIS<200, NAC group can have 6% survival gain compared with primary surgery group because there were over 1,000 deaths. However, there is no statistical significance. (evidence level: HIGH)
Table 5. 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></td>
<td>Control</td>
<td>KQ2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>991 per 1000</td>
<td>988 per 1000 (980 to 993)</td>
<td>HR 0.93 (0.83 to 1.05)</td>
<td>1136</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Follow-up: median 4.4-4.7yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>high</td>
</tr>
</tbody>
</table>

2-5. Meta-analysis

A meta-analysis failed to show NAC followed by interval cytoreductive surgery could lead to survival improvement compared with primary cytoreductive surgery in patients with advanced EOC who are not likely for optimal cytoreduction.

Figure 2. Result of meta-analysis.

2-6. Summary

Are survival outcomes from NAC followed by interval cytoreductive surgery vs. primary cytoreductive surgery comparable in patients with extensive stage IIIC-IV EOC who are not likely for optimal cytoreduction?

NAC followed by interval debulking surgery may be considered for patients with extensive stage IIIC to IV EOC who are not likely for optimal cytoreduction by upfront primary surgery based on that overall survival was comparable between these patients

Level of evidence: A (high)
Strength of recommendation: 2 (weak)

2-7. References


### Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>KQ 3</th>
<th>Does weekly dose-dense paclitaxel regimen improve survival outcomes in patients with advanced EOC compared with standard therapy given every 3 weeks?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Advanced stage epithelial ovarian cancer</td>
</tr>
<tr>
<td>I</td>
<td>Dose-dense paclitaxel/carboplatin</td>
</tr>
<tr>
<td>C</td>
<td>Triweekly paclitaxel/carboplatin</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>&quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</td>
</tr>
<tr>
<td>3.</td>
<td>&quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
</tr>
<tr>
<td>4.</td>
<td>2 OR 3 231416</td>
</tr>
<tr>
<td>6.</td>
<td>(&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
</tr>
<tr>
<td>7.</td>
<td>5 OR 6 1834398</td>
</tr>
<tr>
<td>8.</td>
<td>7 AND 4 75509</td>
</tr>
<tr>
<td>9.</td>
<td>8 OR 1 93357</td>
</tr>
<tr>
<td>12.</td>
<td>10 AND 11 16482</td>
</tr>
</tbody>
</table>
14. 12 OR 13 20328
15. 9 AND 14 2137

**Embase**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>'ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR 'ovary metastasis'/exp 75894</td>
</tr>
<tr>
<td>2.</td>
<td>Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti 232073</td>
</tr>
<tr>
<td>3.</td>
<td>'ovary'/exp 139338</td>
</tr>
<tr>
<td>4.</td>
<td>2 OR 3 311368</td>
</tr>
<tr>
<td>5.</td>
<td>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 2292630</td>
</tr>
<tr>
<td>6.</td>
<td>'endometrioid carcinoma'/exp 2906</td>
</tr>
<tr>
<td>7.</td>
<td>5 OR 6 2292749</td>
</tr>
<tr>
<td>8.</td>
<td>7 AND 4 97118</td>
</tr>
<tr>
<td>9.</td>
<td>8 OR 1 117046</td>
</tr>
<tr>
<td>10.</td>
<td>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 Anti-cancer:ab,ti OR 'Anti cancer':ab,ti OR Chemotheraphy:ab,ti OR Chemotherapic:ab,ti OR Chemotherapies:ab,ti OR Chemo therapy:ab,ti OR Chemo-therapy:ab,ti 494319</td>
</tr>
<tr>
<td>11.</td>
<td>'antineoplastic agent'/exp OR 'chemotherapy'/exp 1686971</td>
</tr>
<tr>
<td>12.</td>
<td>10 OR 11 1797961</td>
</tr>
<tr>
<td>13.</td>
<td>triweekly:ab,ti OR weekly:ab,ti OR 'dose dense':ab,ti 110600</td>
</tr>
<tr>
<td>14.</td>
<td>13 AND 12 28991</td>
</tr>
<tr>
<td>15.</td>
<td>('paclitaxel'/exp OR paclitaxel:ab,ti OR Taxol:ab,ti) and ('carboplatin'/exp OR carboplatin:ab,ti OR CBDCA:ab,ti) 22333</td>
</tr>
<tr>
<td>16.</td>
<td>14 OR 15 49910</td>
</tr>
<tr>
<td>17.</td>
<td>9 AND 16 7461</td>
</tr>
<tr>
<td>18.</td>
<td>'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer* 1739043</td>
</tr>
<tr>
<td>19.</td>
<td>17 AND 18 1599</td>
</tr>
<tr>
<td>20.</td>
<td>19 NOT 'nonhuman'/de 1370</td>
</tr>
</tbody>
</table>

**Cochrane**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MeSH descriptor: [Ovarian Neoplasms] this term only 1394</td>
</tr>
<tr>
<td>2.</td>
<td>Ovarian OR Ovary OR Ovaries OR adnexa OR adnexal:ab,ti,kw 8250</td>
</tr>
</tbody>
</table>
A total of 1,884 articles were identified using aforementioned method. Three articles were finally selected.

Figure 1. Flow chart of searching strategy for answering KQ3.
3-3. **Quality assessment**

Finally selected 3 articles were all RCTs. QUADAS was used for assessing risk of bias (Table 2).

**Table 2. Quality Assessment of Diagnostic Accuracy Studies for RCT**

<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>Katsumata N, 2013¹</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>Pignata S, 2014²</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>Van der Burg MEL, 2014³</td>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

3-4. **Level of evidence and grade of recommendation**

**Table 3. Evidence table for weekly dose-dense paclitaxel regimen vs. standard triweekly regimen**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study year (enrollment/ median f/u)</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsumata N, 2013¹</td>
<td>RCT</td>
<td>Japan</td>
<td>85 centers/Japan (JGOG 3016)</td>
<td>Dose-dense (weekly P 80 mg/m² and triweekly carboplatin)</td>
<td>Conventional, epithelial ovarian, fallopian tube, or peritoneal</td>
<td>312</td>
<td>Median PFS</td>
<td>28·2 mo vs. 17.5 mo (HR 0.76; 95% CI 0.62–0.91; p=0.0037)</td>
<td>Greatest OS benefit of DD was achieved in residual ds≥1cm (51.2 mo vs. 33.5mo) and serous or other histology (not clear-cell or mucinous) (100.5mo vs. 61.2mo).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2003-2005/76.8 mo</td>
<td>Conventional, triweekly (P 180 mg/m² and carboplatin AUC 6)</td>
<td>Stage II-IV epithelial ovarian, fallopian tube, or peritoneal</td>
<td>319</td>
<td>Median OS</td>
<td>100.5 mo vs. 62.2 mo (HR 0.79; 95% CI 0.62–0.91; p=0.0037)</td>
<td>(not clear-cell or mucinous) (100.5mo vs. 61.2mo).</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Institution(s)</td>
<td>Duration</td>
<td>Dose</td>
<td>Conventional</td>
<td>Cancer</td>
<td>Median PFS</td>
<td>Estimate 2-yr OS</td>
<td>Median OS</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>----------------</td>
<td>----------</td>
<td>------</td>
<td>--------------</td>
<td>--------</td>
<td>-----------</td>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Pignata S, 2014&lt;sup&gt;2&lt;/sup&gt;</td>
<td>RCT</td>
<td>Institution(s)/Italy, France (MITO-7)</td>
<td>2008-2012/22.3 mo</td>
<td>Dose-dense, weekly (P 60 mg/m&lt;sup&gt;2&lt;/sup&gt; and carboplatin AUC 6)</td>
<td>Conventional, triweekly (P 175 mg/m&lt;sup&gt;2&lt;/sup&gt; and carboplatin AUC 6)</td>
<td>stage IC–IV epithelial ovarian, fallopian tube, or peritoneal cancer</td>
<td>413</td>
<td>409</td>
<td>95% CI 0.63–0.99; p=0.039</td>
</tr>
<tr>
<td>Van der Burg MEL, 2014&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RCT</td>
<td>Multicente rs/Netherlands</td>
<td>1999-2006/10.3 yrs</td>
<td>Dose-dense, weekly (P 90 mg/m&lt;sup&gt;2&lt;/sup&gt;, cisplatin 70 mg/m&lt;sup&gt;2&lt;/sup&gt; or carboplatin AUC 4)</td>
<td>Conventional, triweekly (P 175 mg/m&lt;sup&gt;2&lt;/sup&gt;, cisplatin 75mg/m&lt;sup&gt;2&lt;/sup&gt; or carboplatin AUC 6)</td>
<td>stage IIB–IV epithelial ovarian, fallopian tube, or peritoneal cancer</td>
<td>133</td>
<td>134</td>
<td>18.5 mo (95% CI 15.9-21.0) vs 16.4 mo (13.5–19.2); p=0.78</td>
</tr>
</tbody>
</table>

There were 3 RCTs supporting the evidence of KQ3. All 3 RCTs reported the results of PFS. However, Study of Pignata S, et al. showed inconsistent data between PFS and OS. The other two RCTs except Pignata S, et al. were used to decide the final evidence level in terms of OS. (evidence level: MODERATE)
Table 4. Estimation of GRADE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Mean difference (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>OS Follow-up: median 78 mo</td>
<td>*</td>
<td>*</td>
<td>16.64(-16.17,49.45)</td>
<td>898 (2 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
</tr>
<tr>
<td>PFS Follow-up: median 78 mo</td>
<td>*</td>
<td>*</td>
<td>3.84(-0.81,8.49)</td>
<td>1720 (3 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
</tr>
</tbody>
</table>

3-5. Meta-analysis

A meta-analysis could not find any significant difference in survival outcomes between the two groups of first-line dose-dense chemotherapy and conventional chemotherapy.

Figure 2. Result of meta-analysis.

3-6. Summary

[KQ 3] Does weekly dose-dense paclitaxel regimen improve survival outcomes in patients with advanced EOC compared with standard therapy given every 3 weeks?

Weekly dose-dense paclitaxel is associated with increased hematologic toxicity compared with standard therapy given every 3 weeks. However, weekly regimen can be considered depending on clinical judgment of gynecologic oncologist because this regimen might improve survival.

Strength of recommendation: 2 (weak)

3-7. References


4-1. Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>[KQ 4]</th>
<th>Does bevacizumab improve survival outcomes in patients with EOC as postoperative first-line therapy or second-line therapy for recurrence?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P :</td>
<td>Postoperative first-line and recurrent setting in epithelial ovarian cancer</td>
</tr>
<tr>
<td>I :</td>
<td>Chemotherapy with bevacizumab</td>
</tr>
<tr>
<td>C :</td>
<td>Chemotherapy without bevacizumab</td>
</tr>
<tr>
<td>O :</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

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 KQ4

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>1. &quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>191135</td>
</tr>
<tr>
<td></td>
<td>3. &quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 231416</td>
</tr>
<tr>
<td></td>
<td>OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] OR Adenocarcinoma[tiab]</td>
</tr>
<tr>
<td></td>
<td>OR Adenocarcinomas[tiab] 1776471</td>
</tr>
<tr>
<td></td>
<td>6. (&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
</tr>
<tr>
<td></td>
<td>7. 5 OR 6 1834398</td>
</tr>
<tr>
<td></td>
<td>8. 7 AND 4 75509</td>
</tr>
<tr>
<td></td>
<td>9. 8 OR 1 93357</td>
</tr>
<tr>
<td></td>
<td>11. 9 AND 10 455</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase</th>
<th>1. 'ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>'ovary metastasis'/exp 75894</td>
</tr>
<tr>
<td></td>
<td>2. Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti</td>
</tr>
<tr>
<td></td>
<td>232073</td>
</tr>
<tr>
<td></td>
<td>3. 'ovary'/exp 139338</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 311368</td>
</tr>
<tr>
<td></td>
<td>5. cancer:ab,ti OR malignant:ab,ti OR carcinoma:ab,ti OR neoplasm:ab,ti OR</td>
</tr>
</tbody>
</table>
cancers:ab,ti OR malignancy:ab,ti OR carcinomas:ab,ti OR neoplasms:ab,ti OR Adenocarcinoma:ab,ti OR Adenocarcinomas:ab,ti 2292630
6. 'endometrioid carcinoma'/exp 2906
7. 5 OR 6 2292749
8. 7 AND 4 97118
9. 8 OR 1 117046
10. 'bevacizumab'/exp OR bevacizumab:ab,ti OR avastin:ab,ti 35357
11. 9 AND 10 2632
12. 11 NOT ('editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) 2395
13. 12 NOT ('animal model'/de OR 'human cell'/de OR 'in vitro study'/de OR 'nonhuman'/de) 1640

Cochrane
1. MeSH descriptor: [Ovarian Neoplasms] this term only 1394
2. Ovarian OR Ovary OR Ovaries OR adnexa OR adnexal:ab,ti,kw 8250
3. MeSH descriptor: [Adnexa Uteri] explode all trees” 1169
4. MeSH descriptor: [Ovary] explode all trees 975
5. cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms OR Adenocarcinoma OR Adenocarcinomas:ab,ti,kw 89830
6. MeSH descriptor: [Adenocarcinoma] explode all trees 4728
7. MeSH descriptor: [Carcinoma, Endometrioid] explode all trees 32
8. 1 or ((2 or 3 or 4) and (5 or 6 or 7)) 3662
9. 8/trail 3209

A total of 1,756 articles were identified using aforementioned method. Four articles were finally selected.
Figure 1. Flow chart of searching strategy for answering KQ4.
4-3. Quality assessment

Finally selected 4 articles were all RCTs. QUADAS was used for assessing risk of bias (Table 2).

Table 2. Quality Assessment of Diagnostic Accuracy Studies for RCT

<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>Burger RA, 2011</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>
<tr>
<td>Perren TJ, 2011</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>Aghajanian C, 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>
<tr>
<td>Pujade-Lauraine E, 2014</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>
</tbody>
</table>

4-4. Level of evidence and grade of recommendation

Table 4. Evidence table for bevacizumab in EOC

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study year (enrollment/ median f/u)</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result [BEV-throughout vs control]</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burger RA, 2011</td>
<td>RCT</td>
<td>institutions in USA, Canada, 2005-2009/17.4 mo</td>
<td>IV TC x6 + BEV (cycle 1-6) and BEV or placebo</td>
<td>previously untreated, incompletely resectable</td>
<td>623</td>
<td>Median PFS</td>
<td>14.1mo vs. 10.3mo (HR 0.717; 95% CI 0.63-0.82; p&lt;0.001)</td>
<td>HTN requiring therapy (22.9% vs. 7.2%; p&lt;0.001); GI disruption requiring intervention</td>
<td></td>
</tr>
<tr>
<td>Perren TJ, 2011²</td>
<td>Korea, Japan (GOG218)</td>
<td>maintenance (cycles 7-22) BEV (cycle 1-6) and placebo (cycle 7-22)</td>
<td>stage III-IV epithelial ovarian, primary peritoneal, or fallopian tube cancer</td>
<td>Median OS (HR 0.915; 95% CI 0.73-1.15; p=0.45) (2.6% vs. 1.2%; NS); wound disruption (3.0% vs. 2.8%; NS). Most AE were reported during CTX phase rather than extended-therapy phase.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>263 centers from 11 countries including UK, Germany, France, Canada, Australia. (ICON7)</td>
<td>2006-2009/19.4 mo</td>
<td>IV TC x6 + BEV (cycle 5-6) and BEV additional 12 cycles or until progression</td>
<td>IV TC x6 without BEV</td>
<td>Restricted mean PFS (PFS 24.1mo vs 22.4mo (HR for progression or death 0.87; 95% CI 0.77-0.99; p=0.04) OS (HR 0.85; 95% CI 0.69-1.04; p=0.11) HTN ≥gr2 (18% vs. 2%); bleeding (38% vs. 11%); thromboembolism ≥gr3 (7% vs. 3%); GI perforation (10 vs. 3). In pts at high risk for progression, benefit was greater with BEV than without BEV at 42mo: PFS (18.1mo vs. 14.5mo; HR 0.73; 95% CI 0.60-0.93; p=0.002) and OS (36.6mo vs. 28.8mo; HR 0.64; 95% CI 0.48-0.85; p=0.002).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Time</td>
<td>Intervention</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------</td>
<td>------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aghajanian C, 2012&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RCT</td>
<td>USA (OCEANS)</td>
<td>2007-2010/24 mo</td>
<td>IV GC + BEV (6-10 cycles) then until progression</td>
<td>Median PFS 242 mo, Median OS 33.3mo vs. 35.2mo (HR 1.027; 95% CI 0.79-1.33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pujade-Lauraine E, 2014&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RCT</td>
<td>ENGOT-GCIG (AURELIA)</td>
<td>2009-2011/13.0mo vs. 13.9mo</td>
<td>CTX (PLD, wk Paclitaxel, or topotecan) plus BEV until progression</td>
<td>Median PFS 179 mo, Median OS 16.6mo vs. 13.3mo (HR 0.85; 95% CI 0.66-1.08; p&lt;0.174)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were 4 RCTs supporting the evidence of KQ4 (2 first-line; 2 second-line). For both first and second-line therapies, PFS improvement was consistently shown and thought to have high evidence level. However, OS improvement was not significant (evidence level: MODERATE).
Table 5. Estimation of GRADE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Assumed Risk</th>
<th>Corresponding risk</th>
<th>HR (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>Control</td>
<td>KQ4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary therapy OS</td>
<td>*</td>
<td>*</td>
<td></td>
<td>0.87 (0.77, 0.99)</td>
<td>2776 (2 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td></td>
</tr>
<tr>
<td>Follow-up: median 26 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary therapy PFS</td>
<td>*</td>
<td>*</td>
<td></td>
<td>0.82 (0.73, 0.92)</td>
<td>2776 (2 studies)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
</tr>
<tr>
<td>Follow-up: median 26 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence therapy OS</td>
<td></td>
<td></td>
<td>0.93 (0.77, 1.12)</td>
<td>845 (2 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence therapy PFS</td>
<td></td>
<td></td>
<td>0.48 (0.41, 0.57)</td>
<td>845 (2 studies)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4-5. Meta-analysis

A meta-analysis showed a significant PFS improvement (HR 0.82; 95% CI 0.73-0.92) when bevacizumab was used as first-line therapy. However, a long confidence interval with approaching 1 was observed as for OS data. For second-line therapy, a significant PFS improvement was also shown (HR 0.48; 95% CI 0.41-0.57). However, there was not large number of death events enough for reliable results (0.77-1.12).

![Figure 2. Result of meta-analysis for first-line treatment.](image-url)
Figure 3. Result of meta-analysis for second-line treatment.

4.6. Summary

**[KQ 4]** Does bevacizumab improve survival outcomes in patients with EOC as postoperative first-line therapy or second-line therapy for recurrence?

Bevacizumab maintenance following initial chemotherapy with paclitaxel/carboplatin/bevacizumab in patients with EOC can be recommended based on this regimen has been shown to modestly increase PFS (2A).

For recurrence therapy, bevacizumab-containing regimens can be recommended for platinum-sensitive recurrent EOC (2A) and platinum-resistant recurrent EOC with priority (level 1) based on these regimens have been shown to increase PFS.

*Level of evidence: A (high)*

*Strength of recommendation: 2 (weak)*

4.7. References


5-1. Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>KQ 5</th>
<th>Is ROMA superior to serum CA125 for differential diagnosis of adnexal tumors in terms of sensitivity and specificity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P:</td>
<td>Patients with adnexal mass</td>
</tr>
<tr>
<td>I:</td>
<td>CA125 and HE4 combination (ROMA)</td>
</tr>
<tr>
<td>C:</td>
<td>CA125</td>
</tr>
<tr>
<td>O:</td>
<td>Diagnostic sensitivity and specificity for detecting ovarian cancer</td>
</tr>
</tbody>
</table>

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 KQ5

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>1. &quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. &quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
<td></td>
</tr>
<tr>
<td>4. 2 OR 3 231416</td>
<td></td>
</tr>
<tr>
<td>OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] OR Adenocarcinoma[tiab]</td>
<td></td>
</tr>
<tr>
<td>OR Adenocarcinomas[tiab] 1776471</td>
<td></td>
</tr>
<tr>
<td>6. (&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
<td></td>
</tr>
<tr>
<td>7. 5 OR 6 1834398</td>
<td></td>
</tr>
<tr>
<td>8. 7 AND 4 75509</td>
<td></td>
</tr>
<tr>
<td>9. 8 OR 1 93357</td>
<td></td>
</tr>
<tr>
<td>11. &quot;Epididymal Secretory Proteins&quot;[Mesh]</td>
<td></td>
</tr>
<tr>
<td>12. 10 OR 11 1288</td>
<td></td>
</tr>
<tr>
<td>13. 9 AND 12 245</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase</th>
<th>1. 'ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR 'ovary metastasis'/exp 75894</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti</td>
<td>232073</td>
</tr>
<tr>
<td>3. 'ovary'/exp 139338</td>
<td></td>
</tr>
</tbody>
</table>
A total of 514 articles were identified using aforementioned method. Two articles were finally selected.
Figure 1. Flow chart of searching strategy for answering KQ5.
5-3. Quality assessment

Finally selected 2 articles were NRSs. Ottawa Quality Assessment Scale was used for assessing risk of bias (Table 2).

Table 2. Ottawa Quality Assessment Scale for NRS

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of the exposed cohort</td>
<td>Comparability of cases and controls on the basis of the design or analysis</td>
<td>Adequacy of follow up of cohorts</td>
</tr>
<tr>
<td>Moore RG, 2008¹</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>Kim YM, 2011²</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
</tbody>
</table>

5-4. Level of evidence and grade of recommendation

Table 3. Evidence table for Risk of risk of ovarian malignancy algorithm (ROMA)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study year</th>
<th>Population (intervention)</th>
<th>Population (control)</th>
<th>Inclusion Criteria</th>
<th>Number (intervention)</th>
<th>Number (control)</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore RG, 2008¹</td>
<td>Prospective cohort</td>
<td>USA</td>
<td>NA</td>
<td>CA-125+HE4</td>
<td>CA-125</td>
<td>Pelvic mass (benign and all stage ovarian cancer)</td>
<td>151</td>
<td>151</td>
<td>ROC-AUC</td>
<td>90.7% vs 86.5%, p=0.1173</td>
<td></td>
</tr>
<tr>
<td>Kim YM, 2011²</td>
<td>Prospective cohort</td>
<td>Korea</td>
<td>2009-2010</td>
<td>CA-125+HE4</td>
<td>CA-125</td>
<td>Pelvic mass (benign and all stage ovarian cancer)</td>
<td>159</td>
<td>159</td>
<td>ROC-AUC</td>
<td>99.0% vs 98.1%, p=0.4475</td>
<td></td>
</tr>
</tbody>
</table>

There was two NRSs supporting the evidence of KQ5. In both studies, the addition of HE4 to CA125, i.e., ROMA, appeared to increase AUC of ROC curves. However, direct comparison is difficult because sensitivity and specificity were provided without cut-off values. (evidence level: 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>Control</td>
<td>KQ5</td>
<td></td>
<td>NA</td>
<td>0 (2 studies)</td>
<td>⊕ ⊝ ⊝ ⊝</td>
</tr>
<tr>
<td></td>
<td>KQ5</td>
<td></td>
<td></td>
<td>very low</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. ROC curves of CA-125 alone (left) and combination of CA-125 and HE4 (ROMA) (right).

5-5. Summary

<table>
<thead>
<tr>
<th>KQ 5</th>
<th>Is ROMA superior to serum CA125 for differential diagnosis of adnexal tumors in terms of sensitivity and specificity?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROMA can be used for differential diagnosis of adnexal tumors under the clinician’s discretion based on the results that ROMA might be more sensitive and specific than CA125 alone.</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: D (very low)</td>
</tr>
<tr>
<td></td>
<td>Strength of recommendation: 2 (weak)</td>
</tr>
</tbody>
</table>

5-6. References

6-1. Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>[KQ 6]</th>
<th>Does complete staging operation improve survival outcomes in patients with serous borderline epithelial ovarian tumors?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P :</td>
<td>Borderline ovarian tumor (serous vs. mucinous)</td>
</tr>
<tr>
<td>I :</td>
<td>Full staging operation</td>
</tr>
<tr>
<td>C :</td>
<td>Incomplete staging operation</td>
</tr>
<tr>
<td>O :</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>MEDLINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</td>
</tr>
<tr>
<td>3. &quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
</tr>
<tr>
<td>4. 2 OR 3 231416</td>
</tr>
<tr>
<td>6. (&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
</tr>
<tr>
<td>7. 5 OR 6 2359068</td>
</tr>
<tr>
<td>8. 7 AND 4 85840</td>
</tr>
<tr>
<td>9. 8 OR 1 99335</td>
</tr>
<tr>
<td>11. 9 AND 10 4384</td>
</tr>
<tr>
<td>12. staging[tiab] OR &quot;Neoplasm Staging&quot;[Mesh] 158970</td>
</tr>
<tr>
<td>13. 11 AND 12 1068</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &quot;ovary tumor'/de OR ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR 'ovary metastasis'/exp 99957</td>
</tr>
<tr>
<td>2. Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti 232073</td>
</tr>
<tr>
<td>3. 'ovary'/exp 139338</td>
</tr>
</tbody>
</table>
A total of 1,821 articles were identified using aforementioned method. One article was finally selected.
6-3. Quality assessment

Finally selected article was a RCT. Ottawa Quality Assessment Scale was used for assessing risk of bias (Table 2).

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Is the case definition adequate</td>
<td>Representativeness of the cases</td>
<td>Selection of controls</td>
</tr>
<tr>
<td>Trillsch F, 2015¹</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

6-4. Level of evidence and grade of recommendation

The only selected article through PRISMA flow was not appropriate for analyzing complete staging versus incomplete staging. The article analyzed survival difference between individual staging procedures (i.e,
omentectomy, washing cytology, peritoneal biopsy), not between whether performing complete staging operation. Therefore, correction was made on PRISMA graph that there was no data which can be evidence of KQ6. A meta-analysis was not available. (evidence level; E=no evidence or difficult to analyze)

6-5. Summary

<table>
<thead>
<tr>
<th>[KQ 6]</th>
<th>Does systemic PLND and/or PALND improve survival outcomes for patients with early-stage EOC apparently confined to an ovary?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systemic PLND and/or PALND may be selectively performed for those patients with EOC apparently confined to an ovary under the physician’s discretion despite the lack of evidence for survival improvement compared with selective or omitting PLND and/or PALND.</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: A (high)</td>
</tr>
<tr>
<td></td>
<td>Strength of recommendation: 2 (weak)</td>
</tr>
</tbody>
</table>

6-6. Reference

7-1. Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>KQ 7</th>
<th>Does fertility-sparing surgery have negative impact on survival outcomes in young patients with early-stage EOC who desire to maintain their fertility?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Clinical stage I epithelial ovarian cancer</td>
</tr>
<tr>
<td>I</td>
<td>USO with comprehensive staging</td>
</tr>
<tr>
<td>C</td>
<td>Hysterectomy and BSO with comprehensive staging</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>1. &quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3. &quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 231416</td>
</tr>
<tr>
<td></td>
<td>6. (&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
</tr>
<tr>
<td></td>
<td>7. 5 OR 6 1834398</td>
</tr>
<tr>
<td></td>
<td>8. 7 AND 4 75509</td>
</tr>
<tr>
<td></td>
<td>9. 8 OR 1 93357</td>
</tr>
<tr>
<td></td>
<td>11. 9 AND 10 2407</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase</th>
<th>1. 'ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR 'ovary metastasis'/exp 75894</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti 232073</td>
</tr>
<tr>
<td></td>
<td>3. 'ovary'/exp 139338</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 311368</td>
</tr>
<tr>
<td></td>
<td>5. 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 2292630</td>
</tr>
<tr>
<td></td>
<td>6. 'endometrioid carcinoma'/exp 2906</td>
</tr>
</tbody>
</table>
A total of 567 articles were identified using aforementioned method. Three articles were finally selected.
Figure 1. Flow chart of searching strategy for answering KQ7
7-3. Quality assessment

Finally selected 3 articles were all NRSs. Ottawa Quality Assessment Scale was used for assessing risk of bias (Table 2).

Table 2. Ottawa Quality Assessment Scale for NRS

<table>
<thead>
<tr>
<th>study ID</th>
<th>Representativeness of the Exposed Cohort</th>
<th>Selection of the Non-Exposed Cohort</th>
<th>Ascertainment of Exposure</th>
<th>Demonstra-tion That Outcome of Interest Was Not Present at Start of Study</th>
<th>Compar-ability 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>Schlaerth, 2009¹</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Kajiyama, 2011²</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Ditto, 2014³</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 fertility-sparing surgery and survival outcomes

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study year (enrollment/median f/u)</th>
<th>Population</th>
<th>Inclusion Criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlaerth, 2009¹</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>1982-2002/12 2mo</td>
<td>FSS</td>
<td>Radical surgery</td>
<td>20</td>
<td>103</td>
<td>5-yr RFS</td>
<td>84% vs. 78% (p=0.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage I EOC</td>
<td></td>
<td></td>
<td>5-yr OS</td>
<td>84% vs. 82% (p=0.52)</td>
</tr>
</tbody>
</table>
Kajiyama, 2011\textsuperscript{2} Retrospective cohort Japan 1986-2007/71.6mo FSS Radical surgery Stage I mucinous ovarian cancer 41 18 5-yr DFS 90.5% vs. 94.4% (p=0.445) 5-yr OS 97.3% vs. 94.4% (p=0.180)

Ditto, 2014\textsuperscript{3} Retrospective cohort Italy 2003-2011 FSS Radical surgery Stage I EOC 18 18 Recur Median DFS 22% vs. 16%, NS 62.4mo vs. 89.1mo (p=0.422)

There were 3 NRSs supporting the evidence of KQ7. The number of event was not big enough for the minimal number by which a significance can be assessed. (evidence level: 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 Control</td>
<td>Corresponding risk KQ7</td>
<td>RR 0.74 (0.26 to 2.09)</td>
<td>182 (2 studies)</td>
<td>⊕⊝⊝⊝ very low</td>
</tr>
<tr>
<td>OS</td>
<td>Follow-up: median 71.6mo</td>
<td>165 per 1,000</td>
<td>122 per 1,000 (43 to 345)</td>
<td>RRR=26%, CE=6.5%, OIS&gt;500, Event=24</td>
<td></td>
</tr>
<tr>
<td>DFS</td>
<td>Follow-up: 76.6-122mo</td>
<td>223 per 1,000</td>
<td>172 per 1,000 (87 to 337)</td>
<td>RRR=27%, CE=22.3%, OIS=600, Event=43</td>
<td></td>
</tr>
</tbody>
</table>
7-5. Meta-analysis

A meta-analysis showed that there was no survival difference between patients with early-stage EOC who underwent fertility-sparing surgery and radical surgery.

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

7-6. Summary

**[KQ 7]** Does fertility-sparing surgery have negative impact on survival outcomes in young patients with early-stage EOC who desire to maintain their fertility?

For young patients who desire to maintain their fertility, a unilateral salpingo-oophorectomy preserving the uterus and contralateral ovary and comprehensive surgical staging may be considered for select unilateral stage I tumors because fertility-sparing surgery does not seem to damage survival outcomes.

*Level of evidence: D (very low)*

*Strength of recommendation: 2 (weak)*

7-7. References


8-1. Generation of key questions based on PICO

<table>
<thead>
<tr>
<th>[KQ 8]</th>
<th>Does PARP inhibitor maintenance therapy improve survival outcomes in patients with BRCA-associated EOC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Ovarian cancer patients with or without BRCA mutation</td>
</tr>
<tr>
<td>I</td>
<td>PARP inhibitor maintenance therapy</td>
</tr>
<tr>
<td>C</td>
<td>No PARP inhibitor maintenance therapy</td>
</tr>
<tr>
<td>O</td>
<td>Overall survival or Progression-free survival</td>
</tr>
</tbody>
</table>

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 used for MEDLINE, Embase, and Cochrane to identify eligible clinical trials for answering KQ1

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>1. &quot;Ovarian Neoplasms&quot;[Mesh:NoExp] 62383</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3. &quot;adnexa uteri&quot;[Mesh] OR &quot;Ovary&quot;[Mesh] 90365</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 231416</td>
</tr>
<tr>
<td></td>
<td>6. (&quot;Adenocarcinoma&quot;[Mesh]) OR &quot;Carcinoma, Endometrioid&quot;[Mesh] 291505</td>
</tr>
<tr>
<td></td>
<td>7. 5 OR 6 1834398</td>
</tr>
<tr>
<td></td>
<td>8. 7 AND 4 75509</td>
</tr>
<tr>
<td></td>
<td>9. 8 OR 1 93357</td>
</tr>
<tr>
<td></td>
<td>12. 10 OR 11 16646</td>
</tr>
<tr>
<td></td>
<td>13. 9 AND 12 582</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase</th>
<th>1. 'ovary cancer'/de OR 'ovary adenocarcinoma'/exp OR 'ovary carcinoma'/exp OR 'ovary metastasis'/exp 75894</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Ovarian:ab,ti OR Ovary:ab,ti OR Ovaries:ab,ti OR adnexa:ab,ti OR adnexal:ab,ti 232073</td>
</tr>
<tr>
<td></td>
<td>3. 'ovary'/exp 139338</td>
</tr>
<tr>
<td></td>
<td>4. 2 OR 3 311368</td>
</tr>
<tr>
<td></td>
<td>5. cancer:ab,ti OR malignant:ab,ti OR carcinoma:ab,ti OR neoplasm:ab,ti OR cancers:ab,ti OR</td>
</tr>
</tbody>
</table>
A total of 1,020 articles were identified using aforementioned method. Four articles were finally selected.
Figure 1. Flow chart of searching strategy for answering KQ8.
8-3. Quality assessment

Finally selected 4 articles comprised 2 RCTs and 2 NRSs. QUADAS (Table 2) and Risk of bias for interrupted time series (ITS) studies (Table 3) were used for assessing risk of bias, respectively.

**Table 2. Quality Assessment of Diagnostic Accuracy Studies for RCT**

<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>Ledermann J, 2014</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>Oza AM, 2015</td>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

**Table 3. Risk of bias for interrupted time series (ITS) studies**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Was the intervention independent of other changes?</th>
<th>Was the shape of the intervention effect pre-specified?</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>
<tbody>
<tr>
<td>Kaufman B, 2015</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Coleman RA, 2015</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 4. Evidence table for PARP inhibitor maintenance therapy and survival outcomes**
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Country</th>
<th>Study year (enrollment/ median f/u)</th>
<th>Population</th>
<th>Inclusion Criteria</th>
<th>Number</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledermann J, 2014¹</td>
<td>Preplanned retrospective, analysis from a phase 2 RCT</td>
<td>82 sites in 16 countries including UK, USA, Germany, and Australia.</td>
<td>2008-2010/37.3mo</td>
<td>olaparib 400 mg twice daily until progression</td>
<td>Platinum sensitive recurrent serous ovarian cancer who had received ≥2 platinum-based regimens and who had a ≥PR to their most recent platinum-based regimen</td>
<td>136</td>
<td>Median</td>
<td>PFS</td>
<td>8.4mo vs. 4.8mo (HR 0.35; 95% CI 0.25-0.49; p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median OS</td>
<td>29.8mo vs. 27.8mo (HR 0.88; 95 CI 0.64-1.21; p=0.44)</td>
<td>Known BRCA status: 96% vs. 95%; gmBRCA(+): 56% vs. 50%. Greater PFS benefit in gmBRCA(+) than gmBRCA(-) (HR 0.18 [0.10-0.31] vs. 0.54 [0.34-0.85]). ≥Gr3 AE: fatigue (7% vs. 3%); anemia (5% vs. &lt;1%). Serious AE: 18% vs. 9%.</td>
</tr>
<tr>
<td>Oza AM, 2015²</td>
<td>Phase 2 RCT</td>
<td>43 sites in 12 countries</td>
<td>2010.2-2010.7/33.4mo</td>
<td>IV TC+olaparib 200mg bid 1-10days of each 21-d cycle, then olaparib 400mg bid until progression</td>
<td>Platinum sensitive recurrent, high-grade serous ovarian cancer who had received up to three previous courses of platinum-based chemotherapy</td>
<td>81</td>
<td>Median</td>
<td>PFS</td>
<td>12.2mo vs. 9.6mo (HR 0.51; 95% CI 0.34-0.77; p=0.0012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median OS</td>
<td>33.8mo vs. 37.6mo (HR 1.17; 95% CI 0.79-1.73; p=0.44)</td>
<td>Known BRCA status at entry: 19% vs. 24%. Known BRCA status at entry or retrospective tumor BRCA testing: 66%, of which 38% gmBRCA(+) (25% vs. 26%). Greatest PFS benefit was noted in gmBRCA(+) (HR 0.21 [0.08-0.55]; p=0.0015). Gr1 or 2 AE&gt;10% more common in olaparib group: alopecia, nausea, neutropenia, diarrhea, headache, pph neuropathy, dyspepsia. ≥Gr 3 AE:</td>
</tr>
<tr>
<td>Author</td>
<td>Study Type</td>
<td>Study Design</td>
<td>Country</td>
<td>Study Period</td>
<td>Treatment</td>
<td>Dose/Duration</td>
<td>AE</td>
<td>Median PFS</td>
<td>Median OS</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Kaufman B, 2015³</td>
<td>Single-arm phase 2 prospective</td>
<td>Multicenter in Israel, Australia, Germany, Spain, Sweden and USA</td>
<td>2010-2012</td>
<td>Olaparib 400mg bid until progression</td>
<td>none</td>
<td>Heavily treated, platinum-resistant advanced EOC, fallopian tube or primary peritoneal cancer with gmBRCA1 or 2(+)</td>
<td>193</td>
<td>0</td>
<td>7.0mo</td>
</tr>
<tr>
<td>Coleman RA, 2015⁴</td>
<td>Retrospective cohort</td>
<td>NRG oncology/GOG study/USA</td>
<td>2012.4-2012.11</td>
<td>Veliparib 400mg bid until progression with 1 cycle being 28 days</td>
<td>none</td>
<td>EOC, fallopian tube or primary peritoneal cancer with gmBRCA1 or 2 (+) who had received ≤3 prior cytotoxic regimens</td>
<td>50</td>
<td>0</td>
<td>8.18mo</td>
</tr>
</tbody>
</table>

There were 2 RCTs (including 1 preplanned retrospective analysis from a RCT) supporting the evidence of KQ8. Considering significant impact of gmBRCA on the effect of PARP inhibitor, prevalence of gmBRCA should not be different between two groups (PARP inhibitor use vs. non-use). However, there are quite many missing values for a prospective RCT. Double randomizations by gmBRCA and PARP inhibitor use are essential for a well-designed RCT. There is no RCT in which all gmBRCA statuses were available at the time of enrollment and used for randomization. Included NRS is a single arm phase II study. (evidence level: VERY LOW)
Table 5. 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>Assumed risk</td>
<td>Corresponding risk</td>
<td>KQ8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KQ8 PFS *</td>
<td>*</td>
<td>NA</td>
<td>0 (2 studies)</td>
<td>⊕⊕⊕⊕ ⊝ * very low</td>
<td></td>
</tr>
<tr>
<td>KQ8 OS</td>
<td>NA</td>
<td>0 (2 studies)</td>
<td>* very low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8-5. Meta-analysis

A meta-analysis showed that gmBRCA(+) patients who were treated with PARPi maintenance therapy had better PFS than placebo group (HR 0.19, [95% CI, 0.11-0.31]).

**Figure 2.** Result of meta-analysis.

8-6. Summary

**[KQ 8]** Does PARP inhibitor maintenance therapy improve survival outcomes in patients with BRCA-associated EOC?

PARP inhibitor (olaparib tablets) for maintenance therapy can be considered for patients with BRCA-associated EOC, particularly for platinum-sensitive recurrent EOC patients with germline BRCA mutation, because PARP inhibitor maintenance therapy can prolong PFS.

**Level of evidence:** D (very low) → A (for 2018 update)

**Strength of recommendation:** 1 (strong) → 2 (for 2018 update)
8-7. References


