

Practice Guideline



Clinical guidelines for ovarian cancer: the Korean Society of Gynecologic Oncology guidelines

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ABSTRACT

Since the latest practice guidelines for ovarian cancer were developed by the Korean Society of Gynecologic Oncology (KSGO) in 2021, many studies have examined the efficacy and safety of various treatments for epithelial ovarian cancer (EOC). Therefore, the need to develop recommendations for EOC treatments has been raised. This study searched the literature using 4 key items and the Population, Intervention, Comparison, and Outcome: the efficacy and safety of poly-ADP ribose polymerase inhibitors in newly diagnosed advanced EOC; the efficacy and safety of intraperitoneal plus intravenous chemotherapy in optimally debulked advanced EOC; the efficacy and safety of secondary cytoreductive surgery in platinum-sensitive recurrent ovarian cancer; and the efficacy and safety of the addition of bevacizumab to platinum-based chemotherapy in first platinum-sensitive recurrent EOC patients who received prior bevacizumab. The evidence for these recommendations, according to each key question, was evaluated using a systematic review and meta-analysis. The committee of ovarian cancer of the KSGO developed updated guidelines for treatments of EOC.

Keywords: Epithelial ovarian cancer; Survival; Poly (ADP-ribose) polymerase inhibitor; Intraperitoneal chemotherapy; Cytoreductive surgery; Bevacizumab

INTRODUCTION

Ovarian cancer is the second most common gynecologic cancer and the most common cause of death from gynecologic cancers [1,2]. Epithelial ovarian cancer (EOC) occurs in more than

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability Statement

All data used for this guideline are available in each published study included in this paper. References of all studies are listed in the appropriate section.

Author Contributions

Conceptualization: L.B., C.S.J., K.B.S., S.J.H., L.M.C., K.Y.H., L.S.W., C.C.H., E.K.J., L.J.Y.; Data curation: L.B., K.B.S.; Formal analysis: L.B., C.S.J.; Funding acquisition: K.Y.B.; Methodology: L.B., C.S.J.; Project administration: C.S.J.; Resources: L.B., S.J.H.; Supervision: S.D.H., K.Y.B.; Visualization: L.B.; Writing - original draft: L.B., C.S.J.; Writing - review & editing: L.B., C.S.J., K.B.S., S.J.H., L.M.C., K.Y.H., L.S.W., C.C.H., E.K.J., L.J.Y., S.D.H., K.Y.B.

90% of ovarian cancers, with high-grade serous carcinoma being the most common EOC subtype [2,3]. Most EOC (75%) presents as an advanced disease (stage III or IV), which shows a more than 80% response rate for the standard of care (cytoreductive surgery and platinum-based chemotherapy) [4]. On the other hand, recurrence occurs in almost 80% of advanced EOCs [5]. In most patients with advanced EOC, cancer reoccurs repeatedly with progressively shorter progression-free intervals and repeated chemotherapy. Treatment after recurrence is ineffective, with a median survival of 2 years after recurrence [2,6].

Currently, targeted therapies are included in the standard treatment of ovarian cancer. Many EOCs have homologous recombination deficiency (HRD) with or without a BRCA1/2 mutation [7]. Poly-ADP ribose polymerase (PARP) inhibitors cause double-strand breaks in DNA, which causes cancer cell death because the cancer cells cannot perform a homologous recombination [2]. Many randomized controlled trials (RCTs) have reported that PARP inhibitors improve the survival in newly diagnosed advanced EOC and platinum-sensitive recurrent EOC [8-18]. Vascular endothelial growth factor (VEGF) and angiogenesis promote the progression of ovarian cancer [19]. Bevacizumab, an anti-VEGF monoclonal antibody, inhibits angiogenesis [19]. In many RCTs, bevacizumab has improved the survival of newly diagnosed advanced EOC patients and recurrent EOC patients [20-25].

Many RCTs have reported that intraperitoneal (IP) plus intravenous (IV) chemotherapy in newly diagnosed advanced EOC improved survival compared to IV chemotherapy [26-34]. On the other hand, IP chemotherapy has not been accepted widely as the standard of care because of more adverse events, catheter complications, and inconvenience compared with IV chemotherapy [35].

Secondary cytoreductive surgery is one of the factors associated with the 5-year survival after recurrence [2,6]. Recently, 3 RCTs have reported inconsistent survival outcomes of secondary cytoreductive surgery in platinum-sensitive recurrent EOC patients predicted to have potentially resectable disease [36-38]. These results might be attributed to different criteria for potentially resectable disease in each trial.

The committee of ovarian cancer of the Korean Society of Gynecologic Oncology (KSGO) provided and updated the practice guideline for ovarian cancer in 2006, 2010, 2016 and 2021 [39-42]. Many studies have recently reported the effects of PARP inhibitors and bevacizumab on survivals in newly diagnosed advanced EOC or platinum-sensitive recurrent EOC. The survival benefit of IP plus IV chemotherapy in newly diagnosed advanced EOC has been continuously reported in recent studies. In addition, the effects of secondary cytoreductive surgery on survivals in platinum-sensitive recurrent EOC are controversial. Therefore, updated guidelines for ovarian cancer are required.

METHODS

1. Developing the recommendations

The key questions, the Population, Intervention, Comparison, and Outcome (PICO), and the scope of the guidelines were derived through meetings of the committee of ovarian cancer and the other gynecologic cancer committees to develop the KSGO guidelines (**Data S1**). The committee of ovarian cancer developed guidelines based on a systematic review of the literature and meta-analysis.

2. Strategy of literature search

The PubMed, Cochrane Library, Embase, and KoreaMed databases were searched for relevant studies in October 2022 using a combination of keywords according to each key question and its PICO (**Data S2**). Additional relevant studies not identified by these database searches were found by examining the references from the selected clinical studies and review articles.

3. Selection criteria

Two investigators selected and excluded the literature independently according to the inclusion and exclusion criteria of each key question. Discrepancies between investigators were resolved by discussion. Only studies with the most comprehensive data were selected to avoid including duplicate information when studies included overlapping groups of patients (**Data S3**).

4. Data extraction, outcomes of interest, and risk of bias

Two investigators extracted the data of interest from studies independently using the checklist of each key question. Discrepancies between investigators were resolved by discussion.

The primary outcome variable was the progression-free survival (PFS), defined as the time between randomization and disease progression or death from any cause. The overall survival (OS), the secondary outcome, was defined as the time between randomization and death from any cause. Adverse outcomes ≥ 3 were evaluated for the safety assessment.

The qualities of the included studies were appraised separately by the 2 investigators using the revised Cochrane risk of bias tool for randomized trials (RoB 2.0 version) [43]. Any discrepancies between investigators were resolved by discussion.

5. Meta-analyses

The meta-analysis was performed using Review Manager Version 5.4.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark). The p-values < 0.05 were considered significant. Random-effects models were performed using the Inverse Variance method for survival analysis. Random-effects models were also implemented in the Mantel-Haenszel method to analyze the adverse events. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for survival, and the odds ratios (ORs) were calculated for adverse events. The heterogeneities of the HRs and ORs across studies were assessed using the I^2 statistic and Cochran's Q statistic. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profiles were produced using GRADEpro GDT.

6. Quality of evidence

The guidelines of the GRADE system were used to evaluate the quality of evidence for the outcomes [44]. In this guidelines, the qualities of evidence are reported as follows: high quality, indicating that further research is unlikely to change the confidence in the estimation of effect; moderate quality, indicating that further research is likely to have a significant impact on confidence in the estimate of effect and may change the estimation; low quality, indicating further research is highly likely to have a substantial impact on confidence in the estimate of effect and is likely to change the estimation; very low quality, indicating little confidence in the estimate of effect. The GRADE guidelines involve the sequential assessment of evidence quality, evaluation of the risk–benefit balance, and subsequent appraisal of the strengths of recommendations.

Table 1. Strength of recommendation

For	Strong For Weak/Conditional For
Against	Weak/Conditional Against Strong Against

7. Strength of recommendation

The strength of a recommendation was determined using the GRADE approach (**Table 1**) [45]. In the GRADE guidelines, the strength of a recommendation is defined as the extent to which one can be confident that the desirable consequences of an intervention outweigh its undesirable consequences. In strong recommendations, all or almost all informed people would make the recommended choice for or against an intervention. In weak/conditional recommendations, most informed people would choose the recommended course of action, but a substantial number would not.

EVIDENCE

1. Key question 1: Does PARP inhibitor maintenance therapy improve survival in newly diagnosed advanced EOC patients who showed a response to chemotherapy after surgery?

Search results and characteristics and assessments of the risk of bias of the included studies

The literature search identified 3,227 potentially relevant studies, and 7 studies [8-14] that met the eligibility criteria were selected (**Data S3**). **Data S4** lists the characteristics of these studies. The PAOLA-1 trial provided 2 studies [10,11] that reported the PFS and OS individually. The SOLO1 trial also provided 2 studies [12,13] that reported the PFS and OS, respectively. **Data S5** presents the results of the risk of the bias assessments. The PFS was evaluated using 5 studies: the OS using 2 studies and adverse events of \geq grade 3 using 4 studies (**Data S6**).

Two-year PFS

The PARP inhibitors improved the PFS significantly compared with the placebo (HR=0.53; 95% CI=0.41–0.68; $p<0.00001$; I^2 , 84%; 3,071 patients; moderate-quality evidence) (**Data S6 and S7**).

Five-year OS

The OSs of the PARP inhibitors and placebo were similar (HR=0.73; 95% CI=0.44–1.20; $p=0.21$; I^2 , 86%; 1,197 patients; low-quality evidence) (**Data S6 and S7**). On the other hand, when analyzed in patients with a BRCA1/2 mutation, the PARP inhibitors improved the OS significantly compared to the placebo (HR=0.57; 95% CI=0.44–0.74; $p<0.0001$; I^2 , 0%; 2 studies; 628 patients).

Adverse events \geq grade 3

The PARP inhibitors increased adverse events of \geq grade 3 significantly compared to the placebo (OR=2.94; 95% CI=1.13–7.63; $p=0.03$; I^2 , 96%; 2,668 patients; moderate-quality evidence) (**Data S6 and S7**).

Based on the above results, the following was recommended:

PARP inhibitor maintenance therapy is recommended in newly diagnosed advanced EOC patients showing a response to chemotherapy after surgery (Strong For).

2. Key question 2: Does IP plus IV chemotherapy improve survival in optimally debulked advanced EOC patients?

Search results and characteristics and assessments of the risk of bias of the included studies

The literature search identified 1,166 potentially relevant studies; only 9 RCTs [26-34] that met the selection criteria were included (**Data S3**). **Data S4** lists the characteristics of these studies, and **Data S5** presents the results of the risk of bias assessments for each study. Walker et al. [32] reported data from the IP-Carboplatin, IP-Cisplatin, and IV-Carboplatin groups. Therefore, this study considered 2 studies: the IP-Carboplatin group vs. the IV-Carboplatin group and the IP-Cisplatin group vs. the IV-Carboplatin group. Eight studies were used to evaluate the PFS: 10 to evaluate the OS and 2 to evaluate adverse events of \geq grade 3 (**Data S6**).

Two-year PFS

IP plus IV chemotherapy improved the PFS significantly compared to IV chemotherapy (HR=0.89; 95% CI=0.82–0.96; p=0.004; I^2 , 11%; 4,144 patients; high-quality evidence) (**Data S6 and S7**).

Five-year OS

IP plus IV chemotherapy improved the OS significantly compared to the IV chemotherapy (HR=0.85; 95% CI=0.74–0.96; p=0.01; I^2 , 55%; 4,808 patients; high-quality evidence) (**Data S6 and S7**).

Adverse events \geq grade 3

The rate of adverse events of \geq grade 3 was significantly lower in the IP plus IV chemotherapy group than the IV chemotherapy group (OR=0.59; 95% CI=0.36–0.97; p=0.04; I^2 , 0%; 858 patients; high-quality evidence). When leukopenia (grade \geq 3) was analyzed, the OSs were similar in the IP plus IV chemotherapy group and the IV chemotherapy group (HR=1.39; 95% CI=0.97–2.00; p=0.08; I^2 , 82%; 5 studies; 3,439 patients) (**Data S6 and S7**).

Based on the above results, the following was recommended:

IP plus IV chemotherapy can be used in optimally debulked advanced EOC patients (Conditional for).

3. Key question 3: Does secondary cytoreductive surgery improve the survival of patients with platinum-sensitive recurrent ovarian cancer?

Search results and characteristics and assessments of the risk of bias of the included studies

The literature search identified 2,301 potentially relevant studies, but only 3 RCTs [36-38] that met the selection criteria were eventually included (**Data S3**). **Data S4** lists the characteristics of these studies, and **Data S5** presents the results of risk of bias assessments for each study. Three studies were used to evaluate the PFS and OS (**Data S6**).

Two-year PFS

The PFS was significantly improved in the group of secondary cytoreductive surgery followed by platinum-based chemotherapy than in the platinum-based chemotherapy-alone group

(HR=0.58; 95% CI=0.39–0.87; p=0.008; I², 89%; 1,249 patients; moderate-quality evidence) (**Data S6** and **S7**).

Five-year OS

The OSs were similar in the secondary cytoreductive surgery group followed by the platinum-based chemotherapy and the platinum-based chemotherapy alone group (HR=0.93; 95% CI=0.66–1.32; p=0.68; I², 76%; 1,249 patients; low-quality evidence) (**Data S6** and **S7**).

Adverse events ≥ grade 3

Meta-analysis could not be performed because there were no adequate data. Shi et al. [38] reported that the adverse events of ≥ grade 3 during platinum-based chemotherapy occurred in 25% and 20% in the groups with and without secondary cytoreductive surgery, respectively. Moreover, surgical complications of ≥ grade 3 at 30 days after secondary cytoreductive surgery occurred in 5%. There were no deaths 60 days after receiving the assigned treatment and no treatment-related deaths (**Data S4**).

Based on the above results, the following was recommended:

Secondary cytoreductive surgery is recommended in patients with platinum-sensitive recurrent ovarian cancer who are predicted to have potentially resectable disease (Strong For).

4. Key question 4: Does bevacizumab/platinum-based chemotherapy followed by bevacizumab maintenance therapy improve survival in patients with platinum-sensitive recurrent ovarian cancer who had previously received first-line platinum-based chemotherapy, including bevacizumab?

Search results and characteristics and assessments of the risk of bias of the included studies

The literature search identified 474 potentially relevant studies, but only one RCT [25] met the selection criteria (**Data S3**). **Data S4** lists the characteristics of these studies, and **Data S5** presents the results of risk of bias assessments for each study. One study was used to evaluate the PFS and OS (**Data S6**). The heterogeneities of the HRs were not assessed because only one study was included in meta-analyses.

Two-year PFS

The PFS was improved significantly in the group of platinum-based chemotherapy with bevacizumab followed by maintenance therapy than in the group of the platinum-based chemotherapy without bevacizumab (HR=0.52; 95% CI=0.41–0.65; p<0.00001; 406 patients; high-quality evidence) (**Data S6** and **S7**).

Five-year OS

The OSs were similar in the groups of the platinum-based chemotherapy with and without bevacizumab (HR=1.01; 95% CI=0.73–1.39; p=0.96; 406 patients; moderate-quality evidence) (**Data S6** and **S7**).

Adverse events ≥ grade 3

Meta-analysis cannot be performed because there were no adequate data. Adverse events of ≥ grade 3 occurred in 79% and 69% of the groups of the platinum-based chemotherapy with and without bevacizumab, respectively. Treatment-related deaths occurred in <1% and 1% of these groups.

The following was recommended based on the above results:

Platinum-based chemotherapy plus bevacizumab can be used in patients with platinum-sensitive recurrent ovarian cancer who had previously received first-line platinum-based chemotherapy including bevacizumab (Weak/Conditional for).

DISCUSSION

The presented recommendations for the treatments of EOC patients were based on evidence supported by a systematic review and meta-analysis. The critical RCTs reported recently were included in the meta-analyses.

Recently, 5 phase 3 RCTs [8-10,12,14] showed that PARP inhibitor maintenance therapy improved the PFS in a BRCA mutation cohort, BRCA wild cohort, HRD cohort, homologous-recombination proficiency (HRP) cohort, and the overall population of newly diagnosed advanced EOC patients with a complete or partial response to platinum-based chemotherapy. On the other hand, only 2 phase 3 RCTs [11,13] reported that the PARP inhibitor improved the OS in a BRCA mutation cohort and a HRD cohort but not in a HRP cohort and overall population. In this meta-analysis, including these studies, the PARP inhibitor improved the PFS significantly but not the OS in the overall population. On the other hand, PARP inhibitors improved the OS in a BRCA mutation cohort. The effects of the PARP inhibitor on OS require clarification based on further research. Nevertheless, in this meta-analysis, PARP inhibitors increased adverse events of \geq grade 3 significantly. Although PARP inhibitors are associated with a high risk of serious adverse events, the survival benefit of PARP inhibitors has greater clinical significance than adverse events because of the poor prognosis of advanced EOC. Therefore, the current guidelines recommend PARP inhibitors in newly diagnosed advanced EOC patients who show a response to platinum-based chemotherapy after primary surgery.

Previous RCTs reported that IP plus IV chemotherapy improved the survival in newly diagnosed advanced EOC patients with optimally or suboptimally debulked disease (**Data S4**) [26-30]. These reports were continued in recent RCTs (**Data S4**) [31-34]. In South Korea, however, IP plus IV chemotherapy has rarely been performed because of the disadvantages of IP chemotherapy. The current guidelines handle this issue to encourage using IP plus IV chemotherapy. In this meta-analysis, including 9 RCTs, IP plus IV chemotherapy improved the PFS and OS significantly compared to IV chemotherapy. Moreover, IP plus IV chemotherapy was associated with a lower rate of adverse events of \geq grade 3 (2 RCTs analysis) and a similar rate of leukopenia of \geq grade 3 (5 RCTs analysis) compared to IV chemotherapy. Although the significance of analysis is limited to the few studies included a meta-analysis of adverse events of \geq grade 3 provided high-quality evidence. Based on the meta-analyses, the current guideline recommends IP plus IV chemotherapy in optimally debulked advanced EOC patients.

Secondary cytoreductive surgery and a favorable response to second-line chemotherapy are factors associated with 5-year survival after recurrence [2,6]. The response rates to second-line chemotherapy in platinum-sensitive recurrent EOC patients are 30%–70% [46]. Therefore, secondary cytoreductive surgery may help extend survival. Recently, 3 phase 3 RCTs [36-38] reported different survival outcomes of secondary cytoreductive surgery in first platinum-sensitive recurrent EOC patients who are predicted to have potentially resectable disease (**Data S4**). Although inconsistent survivals of the studies might be attributed to

different eligibility criteria, the effects of secondary cytoreductive surgery on survivals need to be clarified. In this meta-analysis, including these 3 RCTs, secondary cytoreductive surgery significantly improved the PFS but not the OS. On the other hand, one RCT [38] reported similar rates of adverse events of \geq grade 3 between the patients with and without secondary cytoreductive surgery. Moreover, secondary cytoreductive surgery was associated with a low rate of surgical complications of \geq grade 3 [38]. Therefore, the current guidelines recommend secondary cytoreductive surgery in platinum-sensitive recurrent EOC patients who are predicted to have potentially resectable disease.

The previous phase 3 RCT [20] reported a prolonged PFS by adding bevacizumab to platinum-based chemotherapy in the first platinum-sensitive recurrent EOC patients not previously treated with bevacizumab. Recently, one phase 3 RCT [25] reported that adding bevacizumab to platinum-based chemotherapy improved the PFS significantly but not the OS in the first platinum-sensitive recurrent EOC patients previously treated with bevacizumab. In this RCT, the rates of adverse events of \geq grade 3 and treatment-related death were similar in the patients with and without bevacizumab (**Data S4**). The survival outcomes of this RCT were identical to those of the meta-analyses, including only this RCT. Although only one study provided evidence, the survival benefit of adding bevacizumab to platinum-based chemotherapy has clinical significance based on the poor prognosis of recurrent EOC. Therefore, the current guidelines recommend the addition of bevacizumab to platinum-based chemotherapy in platinum-sensitive recurrent EOC patients who had previously received first-line platinum-based chemotherapy, including bevacizumab.

The present recommendation will be updated once further studies on the 4 key questions are published. These recommendations will be distributed to all members of the KSGO and members of the relevant association who use it for patient care.

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SUPPLEMENTARY MATERIALS

Data S1

The Population, Intervention, Comparison, and Outcome (PICO) for key questions

[Click here to view](#)

Data S2

Search strategy

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Data S3

Flow chart of study selection

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Data S4

Characteristics of the included studies

[Click here to view](#)**Data S5**

Risk of bias

[Click here to view](#)**Data S6**

Meta-analysis

[Click here to view](#)**Data S7**

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profiles

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