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Review Article

Practice guidelines for management of ovarian cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement

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ABSTRACT

Since after 2006 when the first edition of practice guidelines for gynecologic oncologic cancer treatment was released, the Korean Society of Gynecologic Oncology (KSGO) has published the following editions on a regular basis to suggest the best possible standard care considering updated scientific evidence as well as medical environment including insurance coverage. The Guidelines Revision Committee was summoned to revise the second edition of KSGO practice guidelines, which was published in July 2010, and develop the third edition. The current guidelines cover strategies for diagnosis and treatment of primary and recurrent ovarian cancer. In this edition, we introduced an advanced format based on evidence-based medicine, collecting up-to-date data mainly from MEDLINE, EMBASE, and Cochrane Library CENTRAL, and conducting a meta-analysis with systematic review. Eight key questions were raised by the committee members. For every key question, recommendations were developed by the consensus meetings and provided with evidence level and strength of the recommendation.

Keywords: Ovarian Neoplasms; Practice Guideline; Consensus; General Surgery; Drug Therapy

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INTRODUCTION

Ovarian cancer is the most lethal gynecologic cancer. Any screening test or early detection of symptom was not shown to effectively reduce mortality of the disease. In addition to epithelial ovarian cancer (EOC), which consists of more than 85% of ovarian cancer, there are less common histopathologies including germ cell tumor and sex cord-stromal tumors. EOC is classified into type I and II according to origin, moleculopathologic carcinogenesis, and clinical behavior. Compared with type II cancer, less common type I cancer mostly has precursor lesions and is likely to be detected earlier. However, type II cancer tends to be diagnosed at advanced stage and accounts for most of death from ovarian cancer. Thus, majority of studies for the treatment and prevention of ovarian cancer are focused on type II cancer. Recently, it is widely accepted that type II cancer might be originated from the epithelium of fallopian tube [1]. There is accumulating evidence supporting this hypothesis which showed that opportunistic bilateral salpingectomy in benign pelvic surgery could effectively prevent the development of ovarian cancer [2,3].

It is reported that pregnancy and delivery at the young ages before 25 years old, use of oral pill, and breast-feeding might reduce 30%–60% of the development of ovarian cancer. On the contrary, nulliparity and first delivery at ≥35 years old are known to increase the risk of the disease. Germline mutation of *BRCA1* and *BRCA2* or familial history including hereditary non-polyposis colon cancer (HNPCC) also increase the risk of ovarian cancer. Thus, hereditary cancer comprised approximately 10% of ovarian cancer. Risk-reducing salpingo-oophorectomy (RRSO) in high-risk patients with *BRCA1* and *BRCA2* mutation could reduce 80% of ovarian and fallopian tube cancer. Nevertheless, the risk of primary peritoneal cancer remains the same even after RRSO.

Cancer statistics report from the Ministry of Health and Welfare which was updated in January 2015 said ovarian cancer has been slowly increasing. Annual incidence and crude incidence rate per 10^5 were 1,870 and 7.6 in 2008, 1,832 and 7.4 in 2009, 2,025 and 8.1 in 2011, and 2,167 and 8.6 in 2012. In 2012, ovarian cancer incidence ranked 10th in women cancer, which accounted for 1.9%. Regarding the age, most commonly occurs in the 50's (28.6%), followed by 40's (21.0%) and 60's (17.2%). The incidence is relatively stable. However, no significant improvement of survival outcomes in ovarian cancer between 1993–1995 and 2008–2012 (5-year survival rate, 58.7% vs. 61.9%, respectively), compared with those of breast cancer (78.0% vs. 91.3%), colon cancer (54.2% vs. 71.8%), stomach cancer (42.6% vs. 70.0%), and lung cancer (14.2% vs. 28.2%), makes the development of effective treatments for this obstinate disease urgent.

The present guidelines for ovarian cancer were updated with the recent study results based on "The Practice Guidelines for Gynecologic Cancers V2.0," which was released in 2010. Key questions from clinical situations were raised and selected in serial expert meetings of Korean Society Gynecologic Oncology (KSGO). For each question, evidence tables were created and presented with recommendation level. World Health Organization(WHO) classification of ovarian neoplasm (**Table 1**) and 2014 new International Federation of Gynecology and Obstetrics (FIGO) staging for ovarian cancer (**Table 2**) were used.

The objective of these practice guidelines is to establish standard strategies in daily practice of ovarian cancer patients based on the results of the recent publications as well as the consensus of experts as a KSGO Consensus Statement.

Table 1. Modified WHO classification of tumors of the ovary by the Gynecological Pathology Study Group of the KSP

A. Epithelial tumors
Serous tumors
Borderline
Serous borderline tumor
Serous borderline tumor, micropapillary variant/non-invasive low-grade serous carcinoma
Malignant
Low-grade serous carcinoma
High-grade serous carcinoma
Mucinous tumors
Borderline
Malignant
Endometrioid tumors
Borderline
Malignant
Clear cell tumors
Borderline
Malignant
Brenner tumors
Borderline
Malignant
Seromucinous tumors
Borderline
Malignant
Undifferentiated carcinoma
B. Mesenchymal tumors
Low-grade endometrioid stromal sarcoma
High-grade endometrioid stromal sarcoma
C. Mixed epithelial and mesenchymal tumors
Adenosarcoma
Carcinosarcoma
D. Sex cord-stromal tumors
Granulosa cell tumor
Adult
Juvenile
Sertoli-Leydig cell tumor
Fibrosarcoma
E. Germ cell tumors
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Non-gestational choriocarcinoma
Immature teratoma
F. Somatic-type tumors arising from a dermoid cyst
Struma ovarii, malignant
Carcinoid: Strumal carcinoid/Mucinous carcinoid
Sebaceous carcinoma
Squamous cell carcinoma
G. Miscellaneous tumors
Small cell carcinoma, hypercalcemic type
Small cell carcinoma, pulmonary type
H. Lymphoid and myeloid tumors
I. Secondary tumors

KSP, Korean Society of Pathologists; WHO, World Health Organization.

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Table 2. FIGO and TNM staging system for ovarian cancer (2014)

FIGO	TNM	Surgical-pathologic findings
I	T1	Tumor confined to ovaries
IA	T1a	Tumor limited to 1 ovary (capsule intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings
IB	T1b	Tumor limited to both ovaries (capsules intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings
IC		Tumor limited to 1 or both ovaries, with any of the following
IC1	T1c1	Surgical spill
IC2	T1c2	Capsule ruptured before surgery or tumor on ovarian surface
IC3	T1c3	Malignant cells in the ascites or peritoneal washings
II	T2	Tumor involves 1 or both ovaries with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA	T2a	Extension and/or implants on uterus and/or fallopian tubes
IIB	T2b	Extension to other pelvic intraperitoneal tissues
III		Tumor involves 1 or both ovaries, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA1	T1/T2-N1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
IIIA1(i)		Metastasis up to 10 mm in greatest dimension
IIIA1(ii)		Metastasis more than 10 mm in greatest dimension
IIIA2	T3a2-N0/N1	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	T3b-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	T3c-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
IV	Any T, any N, M1	Distant metastasis excluding peritoneal metastases
IVA	Any T, any N, M1a	Pleural effusion with positive cytology
IVB	Any T, any N, M1b	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumor, node, and metastasis.

MATERIALS AND METHODS

Methods are the same with those of practice guidelines for management of uterine corpus cancer [4] and cervical cancer [5]. Since the last version (V2.0) of the KSGO practice guidelines for gynecologic cancer management in 2010, the Guidelines Revision Committee of KSGO convened again in 2015 to revise V2.0 and make V3.0. In the committee, a comprehensive method for systematic review of relevant literature between 2010 and 2015 was adopted in order to adhere to the principles of evidence-based medicine. The process was as followed: 1) selection of key questions; 2) searching for relevant literature published after 2010 for each key question; 3) determining the level of evidence and grade of recommendation; 4) deduction of the agreements; and 5) review and approval. Key questions were chosen and edited by ovarian cancer sub-committee members considering previous ones in V2.0, the need for further clarification, and new reports after V2.0 (**Supplementary**). Data and literature published between 2010 and 2015 were searched using 3 searching engines: Cochrane Library CENRAL, MEDLINE, and Embase. Then, a meta-analysis and systematic review were conducted for determining the level of evidence. Specifically, Cochrane methodology was used for randomized controlled trials, the Newcastle-Ottawa scale for non-random studies, and the quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS-2) for diagnosis research. The level of evidence was decided as one of the 4 categories (high, moderate, low, and very low) using the methodology suggested by the grade group based on the research design, consistency among the research results, immediacy of the research subject and intervention, possibility of publishing bias, and accuracy of the research results (**Table 3**). The grade of recommendation was decided by the methodology suggested by the grade group based on the level of evidence, considering the application subject, hazard and benefit, social, and individual cost of the intervention,

Table 3. Levels of evidence and grades of recommendations

Definition	
Level of evidence	
A	High-quality evidence
B	Moderate-quality evidence
C	Low-quality evidence
D	Very low-quality evidence
E	No evidence or difficult to analyze
Grade and recommendation strength	
1	Strong recommendation
2	Weak recommendation

and patients' preference. The grade of recommendation was assigned as strong or weak recommendation (**Table 3**). The draft form and grades of recommendation were established through mutual consultation among all the members of the revision committee.

After debates in a public hearing with all members of the KSGO and invited representatives of related academic societies, a tentative version of the guidelines was re-evaluated and supplemented. For an internal and external review, the KSGO sent the final version of the guidelines to related organizations, including the Korean Society for Radiation Oncology (KOSRO), Korean Society of Pathologists (KSP), Korean Cancer Study Group (KCSG), Korean Society of Urogenital Radiology (KSUR), Korean Society of Nuclear Medicine (KSNM), Korean Society of Obstetrics and Gynecology (KSOG), and Korean Gynecologic Oncology Group (KGOG). Subsequent to these reviews, there were no objections or requests for revision. Finally, recommendations of the 2 key questions (4 and 8) were reupdated on the basis of high-level evidence that released after a public hearing. Those updated recommendations were added to this manuscript through the consensus between all ovarian cancer sub-committee members of the Guidelines Revision Committee of KSGO.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

1. Epithelial ovarian cancer

1) Diagnosis

(1) Pelvic mass suspicious of ovarian cancer

Diagnostic tests for patients with pelvic mass (or ascites) or abdominal distension suspicious of cancer of ovary but not likely other sites include history, physical exam, and tumor markers. Serum cancer antigen (CA) 125 is firstly recommended. CA19-9 or carcinoembryonic antigen (CEA) may also be evaluated as clinically indicated. Serum alpha-fetoprotein (α-FP) and β-human chorionic gonadotropin (β-hCG) are the options for germ cell tumor. Risk of ovarian malignancy algorithm (ROMA), the combination of human epididymis protein 4 (HE4) and CA125 values, was reported to be more sensitive and specific than CA125 alone for diagnosis of ovarian cancer, for which the level of evidence, however, is low and can be used under the clinician's discretion (strength of recommendation and level of evidence 2D, evidence **Table 5 in Supplementary**). In addition to basic laboratory tests, including blood cell count, chemistry, and urinalysis, and electrocardiography, some imaging tests, such as chest X-ray, pelvic ultrasound, pelvis-abdomen-chest computed tomography (CT), magnetic resonance imaging (MRI), and positive emission tomography, are also among the options as clinically indicated. Genetic counseling is considered for the patients who have family history of ovarian and/or breast cancer. Endoscopic examinations for gastrointestinal tract are recommended in order to exclude metastasis from other sites.

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(2) Diagnosis of ovarian cancer after surgery
For the patients who were diagnosed as ovarian cancer after surgery and did not undergo comprehensive surgical staging with maximal cytoreduction or such information is not available at the time of transfer, all diagnostic tests should be taken as noted above. Every pathology should also be reviewed.

2) Primary treatment
(1) Pelvic mass suspicious of ovarian cancer
Primary treatment includes surgical staging with maximal cytoreduction followed by adjuvant chemotherapy. Open surgery with midline incision should be performed at surgeries for staging, primary debulking, interval cytoreduction after neoadjuvant chemotherapy (NAC), or secondary cytoreduction after recurrence. However, minimally invasive surgery (MIS) such as laparoscopic operation can be selectively considered for newly diagnosed cases confined to ovary and pelvic cavity only when experienced gynecologic oncologists are available (strength of recommendation and level of evidence 2D). Nonetheless, conversion to open surgery from MIS should be performed for the cases in which maximal cytoreduction is not likely achievable by MIS. MIS is also useful in confirming the feasibility of optimal cytoreduction with no residual tumor in newly diagnosed or recurrent ovarian cancer. Peritoneal lavage should be performed for cytologic examinations immediately after entering the abdomen even though there is no significant amount of ascites. Frozen biopsy during the operation can be of great help to decide treatment plan. All the peritoneal surfaces should be examined, and any peritoneal surface suspicious for harboring metastasis should be excised and biopsied. When there is no suspicious lesion, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm. Diaphragm scraping for Papanicolaou smear is an acceptable alternative of excisional diaphragm biopsy. Procedures for comprehensive staging operation include hysterectomy, bilateral salpingo-oophorectomy (BSO), omentectomy, pelvic and paraaortic lymph node dissection (PLND and PALND), multiple peritoneal biopsy, and maximum cytoreduction as well as peritoneal cytologic examination. Every effort should be made during BSO and hysterectomy to keep an encapsulated mass intact during removal. For selected patients desiring to maintain fertility, unilateral salpingo-oophorectomy preserving the uterus and contralateral ovary may be considered for unilateral stage I tumors (stage IA and IC, but not stage IB) (strength of recommendation and level of evidence 2D, evidence **Table 7 in Supplementary**). PALND should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels. Preferred method of PLND is bilateral removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve. 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 (strength of recommendation and level of evidence 2B, evidence **Table 1 in Supplementary**).

In general, maximum cytoreduction is strongly recommended in stage II, III, and IV disease. Every effort should be made during a primary cytoreduction to removal all gross disease since this offers superior survival outcomes although residual disease <1 cm defines optimal cytoreduction [6]. However, NAC followed by interval debulking surgery may be considered for patients with extensive stage IIIC to IV disease who are not likely for optimal cytoreduction by upfront primary surgery (strength of recommendation and level of evidence

2A, evidence **Table 2 in Supplementary**). Tissue or cytologic diagnosis should be obtained by fine-needle aspiration, biopsy, or paracentesis before initiation of NAC. Overall survival was comparable between these patients, however, patients receiving NAC with interval debulking surgery had fewer complications [7,8]. Among patients with metastatic tumors <5 cm in diameter at randomization, overall survival was slightly longer in the primary surgery group than NAC group (hazard ratio [HR]=0.64; 95% confidence interval [CI]=0.45–0.93) [8]. Therefore, NAC could be considered for women who has peritoneal carcinomatosis including metastatic tumors ≥5 cm and are not likely to have optimal cytoreduction. For ovarian cancer involving pelvis and upper abdomen, omentum and lymph nodes suspicious of any tumor involvement should be completely removed along with performing washing cytology at pelvis and abdomen. In addition, multi-visceral resection including bowel resection, appendectomy (in case of mucinous carcinoma), diaphragm stripping and peritonectomy, splenectomy, partial cystectomy, ureteroneocystostomy, partial liver resection, partial gastrectomy, cholecystectomy, distal pancreatectomy and so on can be performed. Some of the patients who have residual tumor <1 cm after surgery could considered for postoperative intraperitoneal (IP) chemotherapy. Catheter for IP chemotherapy should be inserted during the primary surgery. Complete staging operation should be performed by gynecologic oncologists, and it is also recommended in this guideline.

(2) Cancer diagnosis only after surgery

For women with incomplete previous surgery and/or staging, treatment guidelines are as following. First, for patients who were thought to have stage IA or IB, grade 1 tumor, complete staging operation should be performed because no additional treatment is needed if stage IA or IB, grade 1 tumor is confirmed. Second, staging operation with cytoreduction is recommended for patients with suspected residual disease that is considered optimally resectable. Third, for patients who have more advanced cancer than stage IA or IB, grade 1 tumor but without residual tumor, chemotherapy or complete staging operation can be considered. Patients with stage IA or IB, grade 2 tumor might be followed up without chemotherapy. Fourth, for patients with stage II to IV disease who have residual disease that is considered unresectable, consider completion surgery after 3–6 cycles of chemotherapy based on the clinical judgment of the gynecologic oncologist. Postoperative chemotherapy may also be recommended depending on the surgical results. Patients with stage II–IV tumor but no residual tumor can receive 6–8 cycles of chemotherapy.

3) Postoperative adjuvant chemotherapy

Most patients with EOC receive postoperative systemic chemotherapy. However, observation without adjuvant chemotherapy is recommended for patients with surgically staged IA or IB, grade 1 tumor, because survival is greater than 90% for this group with surgery alone. Patients with stage IA or IB, grade 2 tumor can be followed up without adjuvant treatment or receive 3–6 cycles of taxane/platinum-based chemotherapy. However, patients with stage IA or IB, grade 3 (including clear cell carcinoma) and stage IC irrespective of grade should be treated with 3–6 cycles of adjuvant taxane/platinum-based chemotherapy. For patients with advanced-stage disease (stages II–IV), 6–8 cycles of intravenous taxane/platinum-based chemotherapy is standard of care. For patients who underwent incomplete surgery, interval cytoreductive surgery can be selectively performed according to resectability and tumor response to chemotherapy after 3–6 cycles of chemotherapy (including NAC). IP chemotherapy regimen is recommended for patients with stage III–IV cancer with optimally debulked (<1 cm residual) disease (strength of recommendation and level of evidence 2A). Weekly dose-dense paclitaxel is associated with increased hematologic toxicity, such as anemia and neutropenia, nausea and

vomiting, and peripheral neuropathy 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 and level of evidence 2B, evidence **Table 3 in Supplementary**). Of the 3 randomized studies included in the meta-analysis for deciding level of evidence, the study of Katsumata et al. [9] was the only study that reported the significant survival improvement of dose-dense regimen. Although the meta-analysis failed to show the significant survival improvement of dose-dense regimen compared with standard triweekly regimen, strength of recommendation and level of evidence 2B was decided considering expert opinion of gynecologic oncologists that weekly dose-dense regimen could improve survival outcomes based on the completeness of the study of Katsumata et al. [9]. After a public hearing where strength of recommendation and level of evidence was decided, evidence was updated with robust results from randomized trials of dose-dense regimen including ICON8 [10] and GOG262 [11], in both of which weekly paclitaxel, as compared with triweekly paclitaxel, did not prolong progression-free survival (PFS) among patients with EOC. However, ovarian cancer sub-committee members of the Guidelines Revision Committee of KSGO decided to maintain current recommendation level 2B. Regimens of primary adjuvant chemotherapy are listed up in **Table 4**.

All of chemotherapy regimens have different toxicity profiles. Regimen and route of administration should be decided based on medical conditions, toxicity, and performance status and so on. Docetaxel/carboplatin regimen is associated with increased risk of neutropenia. The intravenous paclitaxel/carboplatin regimen is associated with sensory peripheral neuropathy. For patients with diabetes who are susceptible to neurotoxicity, docetaxel/carboplatin regimen could be primarily considered. IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, and neurotoxicity. In the initial studies [12-14], only 42% of women were able to complete all 6 treatment cycles of the IP regimen because of toxicity. Patients with poor performance status, comorbidities, stage IV disease, or advanced age (>65 years) may not tolerate the IP regimen. In addition, high-dose chemotherapy using peripheral blood stem cell transplantation (PBST) is recommended to use only in the setting of clinical trial, because PBST did not show any survival improvement yet.

4) Recommendations after primary treatment

Patients without complete remission (i.e., progression, persistent disease, or stable disease) after initial treatment should be treated with second-line approaches. Observation with follow-up is recommended for patients who have complete remission. Maintenance therapy is an option based on the results from GOG178 of 3 vs. 12 months of further paclitaxel

Table 4. Regimens of primary adjuvant chemotherapy

Preferred regimens
1. Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks × 6 cycles.
2. Dose-dense paclitaxel 80 mg/m^2 IV over 1 hour Days 1, 8, and 15 followed by carboplatin AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks × 6 cycles.
3. Paclitaxel 60 mg/m^2 IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes. Weekly for 18 weeks.
4. Docetaxel 60–75 mg/m^2 IV over 1 hour followed by carboplatin AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks × 6 cycles.
5. Bevacizumab-containing regimens per ICON-7 and GOG218:
Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin AUC 5–6 IV over 1 hour, and bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1. Repeat every 3 weeks × 5–6 cycles. Continue bevacizumab for up to 12 additional cycles. (category 3) or Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks × 6 cycles. Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV over 30–90 minutes every 3 weeks for up to 22 cycles.
Alternative regimens
Paclitaxel 135 mg/m^2 IV continuous infusion over 3 or 24 hours Day 1; cisplatin 75–100 mg/m^2 IP Day 2 after IV paclitaxel; paclitaxel 60 mg/m^2 IP Day 8. Repeat every 3 weeks × 6 cycles.

AUC, area under the receiver operating characteristic curve; IP, intraperitoneal.

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(135–175 mg/m^2 every 4 weeks for 12 cycles) after initial chemotherapy. The results of this trial suggested that patients receiving 12 months of therapy sustained a PFS advantage (28 vs. 21 months) (strength of recommendation and level of evidence 2C). In addition, use of 12–22 cycles of maintenance bevacizumab has been shown to modestly increase PFS when administered following initial chemotherapy with paclitaxel/carboplatin/bevacizumab (strength of recommendation and level of evidence 2A, evidence **Table 4 in Supplementary**). Second-look operation can be selectively considered for the patients who were thought to achieve maximal debulking to resection of all visible disease, because there is no evidence that second-look operation lead to survival advantage (strength of recommendation and level of evidence E). Patients with residual disease in the second-look operation are thought to have a partial remission and recommended to have treatment for recurrent ovarian cancer.

5) Follow-up recommendations

After the completion of primary surgery and chemotherapy in patients with all stages of ovarian cancer, the standard recommendation is observation with follow-up to monitor for recurrent disease. Patients are recommended to visit for follow-up including history taking and physical examination every 2–4 months for the first 2 years, then 3–6 months for 3 years, then annually after 5 years. Blood test including CBC and chemistry profile and chest X-ray can be monitored as indicated. Chest/abdominal/pelvic CT, MRI, positron emission tomography (PET)/CT, or PET may also be ordered if clinically indicated. If the CA125 level was initially elevated, then measurement of a CA125 level or other tumor markers is recommended for every visit. Disease progression is typically defined using Gynecologic Cancer InterGroup (GCIG) criteria (**Table 5**) [15]. Indication of genetic counseling and clinical genetic testing on women with peritoneal, ovarian, and fallopian tubal cancers and their families were released at KSGO position statement in 2016 [16].

6) Treatment of recurrent disease

Recurrent disease may be identified clinically, biochemically (i.e., elevated CA125 levels), with abnormal findings on imaging and/or biopsy. However, patients can be found to have an increasing CA125 level (during routine monitoring and follow-up) but no signs or symptoms of recurrent disease. After the documentation of an increased CA125 level (i.e., biochemical relapse), the median time for a clinical relapse is 2–6 months. Currently, there is no consensus on the time when the treatment for recurrence should be started. However, data suggest that immediate treatment for this biochemical relapse is not beneficial. After biochemical relapse, recommended options include enrollment in a clinical trial, delaying treatment (i.e., observation) until clinical symptoms arise (strength of recommendation and level of evidence 2D), or immediate treatment (strength of recommendation and level of evidence 2D).

Table 5. Definition of progression after first-line therapy in ovarian cancer proposed by gynecologic cancer intergroup [15]

Characteristic	Patients group (definitions below)		
	A	B	C
Measurable/nonmeasurable disease	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) or Any new lesions (measurable or nonmeasurable) Date PD: date of documentation of increase or new lesions		
CA125	CA125 ≥2 × UNL documented 2 occasions* Date PD: first date of the CA125 elevation to ≥2 × UNL	CA125 ≥2 × nadir value on 2 occasions* Date PD: first date of the CA125 elevation to ≥2 × nadir value	As for A

Patients group: A, patients with elevated CA125 pretreatment and normalization of CA125 (up to 60% of all new patients); B, patients with elevated CA125 pretreatment, which never normalizes (up to 30% of all new patients); C, patients with CA125 in normal range pretreatment (up to 10% of all new patients). CA125, cancer antigen 125; PD, progressive disease; RECIST, response evaluation criteria in solid tumors; UNL, upper normal limit.
*Repeat CA125 anytime, but normally not less than 1 week after the first elevated level. CA125 level sampled within 4 weeks after surgery, paracentesis, or administration of mouse antibodies should not be taken into account.

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Treatment of recurrent disease is generally as follows depending on time interval between the completion of previous treatment and recurrence:

1) Enrollment in a clinical trial or treatment for recurrent disease can be considered for progressive/stable/persistent disease during or after primary adjuvant chemotherapy.

2) Options for patients with platinum-resistant disease with recurrence less than 6 months after the completion of chemotherapy or for those with stage II–IV disease who have a partial response (including confirmation of cancer at the second-look operation) after primary chemotherapy include clinical trial and recurrent therapy. For platinum-resistant disease, single non-platinum-based agents or regimens are preferred. Response rate of the following agents for recurrent cancer appears to be similar: topotecan, 20% [17]; gemcitabine, 19% [18]; liposomal doxorubicin, 26% [19]; oral etoposide, 27% [20]; belotecan (CKD-602), 20% [21]; docetaxel, 22% [22]; irinotecan, 29% [23]; and weekly paclitaxel, 21% [24]. Other potentially active agents include vinorelbine, cyclophosphamide, melphalan, etc. The response rate for single-agent bevacizumab is about 20% [25]. On the base of the study results (AURELIA trial) that combination targeted therapy regimens with bevacizumab and one of paclitaxel/topotecan/liposomal doxorubicin could significantly improve PFS, these combinations can be recommended even though bevacizumab may cause hypertension, proteinuria, or intestinal perforation (strength of recommendation 1).

3) For patients with platinum-sensitive disease (i.e., complete remission and relapse ≥6 months after completing prior chemotherapy), preferred combinations include carboplatin/paclitaxel [26], carboplatin/liposomal doxorubicin (especially for partially platinum-sensitive which recur between 6 months and 1 year after completing prior chemotherapy) [27], carboplatin/gemcitabine/bevacizumab (strength of recommendation and level of evidence 2A, evidence **Table 4 in Supplementary**) [28], carboplatin/weekly paclitaxel [9], carboplatin/docetaxel [29], carboplatin/gemcitabine [30], or cisplatin/gemcitabine [30]. Based on a recent phase 3 randomized trial (GOG213) [31], ovarian cancer sub-committee members of the Guidelines Revision Committee of KSGO decided to add carboplatin/paclitaxel/bevacizumab as a potentially active regimen for patients with platinum-sensitive recurrent ovarian cancer (strength of recommendation and level of evidence 2A). Enrollment to a clinical trial is also strongly considered to this group of patients. For patients with platinum-sensitive disease who cannot tolerate combination therapy, the preferred single agent is carboplatin, cisplatin, or oxaliplatin [32]. Based on a recent phase 3 randomized trial (SOLO2/ENGOT-Ov21) [33], ovarian cancer sub-committee members of the Guidelines Revision Committee of KSGO decided to level up the recommendation for KQ8 from 1D to 2A: single-agent olaparib tablets for maintenance therapy can be considered if platinum-sensitive disease with partial or complete response following 2 or more lines of platinum-based therapy (strength of recommendation and level of evidence 2A, evidence **Table 8 in Supplementary**). SOLO2/ENGOT-Ov21 showed that the median PFS was significantly longer in women receiving olaparib than in those receiving placebo (19.1 months, 95% CI=16.3–25.7] vs. 5.5 months, 95% CI=0.22–0.41; p<0.001). Serious adverse events including anemia (19% vs. 2%), fatigue or asthenia (4% vs. 2%), and neutropenia (5% vs. 4%) were more frequently observed in olaparib maintenance group than placebo group. For another 2018 update on olaparib, ovarian cancer sub-committee members added a footnote that olaparib single therapy can be considered for patients with deleterious germline *BRCA*-mutated advanced ovarian cancer (platinum-sensitive or resistant) who have been treated with ≥3 lines of chemotherapy (strength of recommendation and level of evidence 2D) [34].

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4) Secondary cytoreductive surgery can be considered for patients who recur after a long disease-free interval ≥6 months and lesions are localized and small (strength of recommendation and level of evidence 2D, version 2.0) [35]. After secondary cytoreductive surgery, combination chemotherapy mentioned above including carboplatin/paclitaxel, carboplatin/gemcitabine, or carboplatin/liposomal doxorubicin or other recurrence therapy can be considered.

5) Patients who cannot tolerate or fail to chemotherapy can be considered for tamoxifen and other hormonally active agents, including letrozole, anastrozole, leuprolide acetate, or megestrol acetate (level of evidence D), localized radiation therapy (RT) can also provide effective palliation (evidence level E).

Regardless of which regimen is selected initially, reevaluation should follow after 2–4 cycles of chemotherapy (depending on the agent) to determine if patients benefited from chemotherapy. Patients who primarily progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit may not benefit from additional therapy. Decisions to offer supportive care, additional therapy, or clinical trials should be made on a highly individual basis.

2. Borderline epithelial ovarian tumor (low malignant potential)

1) Diagnosis and treatment

A borderline epithelial tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion and with a clinically indolent behavior and good prognosis with 5-year survival greater than 80%. In contrast to patients with frankly invasive ovarian carcinoma, women with borderline epithelial tumors tend to be younger and are often diagnosed with stage I disease. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants can be identified microscopically by the pathologist. Some clinicians feel that the appearance of invasive implants on the peritoneal surfaces in patients with borderline epithelial tumors portends a less favorable prognosis; therefore, postoperative chemotherapy can be considered for these patients. However, the benefit of chemotherapy is controversial in patients with borderline epithelial tumors. Especially for the patients without microscopically demonstrable invasive implants, observation is recommended option because the benefit of postoperative chemotherapy has not demonstrated.

Treatment of borderline epithelial tumors generally depends on the histologic and clinical characteristics, the age of the patients, stage, and whether invasive implants are present.

(1) Patients with a borderline epithelial tumor who desire to maintain their fertility may undergo surgery limited to a unilateral salpingo-oophorectomy with resection of residual disease. However, if the patient does not desire fertility-sparing surgery, standard ovarian cancer staging operation (total abdominal hysterectomy, BSO, and debulking as needed) and resection of residual disease are recommended. There is not enough evidence of whether complete staging operation may lead to better survival compared with incomplete staging operation in serous borderline epithelial tumors (evidence level E, evidence **Table 6 in Supplementary**). Observation without postoperative adjuvant therapy is recommended for patients without invasive implants or only with noninvasive implants after surgery [36]. For patients with invasive implants after surgery, observation or adjuvant chemotherapy with the same regimens used for EOC can be considered (strength of recommendation and level of evidence 2C).

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(2) Pathologic reevaluation is recommended if borderline epithelial tumor is diagnosed at previously performed surgery. If complete staging operation was performed, adjuvant treatment is recommended as mentioned above. If patients with known borderline epithelial tumors were incompletely staged at the time of their initial surgery, recommendations depend on whether residual tumor is present. If residual tumor is suspected, patients who want to preserve their fertility should have fertility-sparing surgery and resection of residual disease (for patients with invasive implants) or observation without further treatment (for patients without invasive implants or unknown). If residual tumor is not suspected, patients can be followed up without any further treatment even after initial incomplete staging operation.

2) Follow-up and recurrence treatment

After the completion of primary treatment, patients should be monitored for recurrent disease. Recommended schedule for follow-up visit includes history taking and physical examination every 2–4 months for the first 2 years, then 3–6 months for 3 years, then annually after 5 years. Blood test including CBC and chemistry profile and chest X-ray can be monitored as indicated. Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary. Chest/abdominal/pelvic CT, MRI, PET/CT or PET may also be ordered if clinically indicated. If the CA125 level was initially elevated, then measurement of a CA125 level or other tumor markers is recommended for every visit.

At the time of clinical relapse, surgical evaluation and debulking are recommended if appropriate. Patients who have invasive implants or low-grade invasive carcinoma after surgery may be treated using the same recommendations as for low-grade serous EOC (strength of recommendation and level of evidence 2C); those with high-grade invasive implants may be treated using the same recommendations as for EOC. Observation is recommended for those with noninvasive disease.

3. Less common ovarian histopathologies (LCOH)

The LCOH include carcinosarcomas (malignant mixed Müllerian tumors [MMMTs]), malignant germ cell tumors, and malignant sex cord-stromal tumors. LCOH is rare and different from EOC in terms of biologic behavior and treatment strategy. Many of LCOH occur in girls, adolescents, and younger women who are often diagnosed with stage I disease. Therefore, fertility-sparing surgery is often considered for those desiring fertility preservation. MIS sometimes can be used [37].

1) Recommended workup

Diagnosis of LCOH is often not made until after surgery for s suspicious pelvic mass. Therefore, the workup for LCOH is the same as for other types of ovarian cancer (ultrasound, CT, MRI, and/or PET, etc.) except that tumor markers are measured and other testing is done to determine the specific histopathology. Tumor markers may include CA125, inhibin, β-hCG, α-FP, lactic dehydrogenase (LDH), and CEA. An intraoperative frozen section evaluation is recommended for women who would like to maintain their fertility. Fertility-sparing surgery may be performed if the intraoperative frozen section results are positive for apparent early-stage tumors and/or low-risk tumors (i.e., malignant germ cell tumors or clinical stage I sex cord-stromal tumors) [38]. Patients who do not desire fertility preservation; those who have a clinical stage II–IV EOC; those with a clinical stage II–IV sex cord-stromal tumor; or those with carcinosarcoma should undergo comprehensive surgical staging as per the ovarian cancer guidelines. The recommended initial surgical recommendation for patients who were pathologically diagnosed at

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the previous operation depends on the specific histologic diagnosis and the surgical completeness of the previous operation.

2) Diagnosis and treatment

(1) Malignant germ cell tumor

Workup for diagnosis of malignant germ cell tumor basic test, CA125, inhibin, β-hCG, α-FP, LDH, ultrasound, CT, MRI, and/or PET, and, if necessary, pulmonary function test can be performed (strength of recommendation and level of evidence 1C). For patients who do not want to maintain their fertility, complete staging operation is recommended. Fertility-sparing surgery is recommended for those desire fertility preservation, regardless of stage. After appropriate treatment, 5-year survival is more than 85%. Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations; completion surgery should be considered after finishing childbearing.

After comprehensive surgical staging, observation with monitoring is recommended for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma. If patients have had incomplete surgical staging, observation with monitoring or complete surgical staging operation can be considered depending on the type of tumor, the results of imaging and tumor marker testing, the age of the patient, and whether the patient desires fertility preservation (strength of recommendation and level of evidence 2C). In children or adolescents with early-stage germ cell tumors, comprehensive staging may be omitted [39,40]. For patients without evidence of residual tumor, observation with surveillance is the recommended option. However, combination chemotherapy with bleomycin/etoposide/cisplatin (BEP) is considered for patients with residual disease. If considering the use of bleomycin, pulmonary function tests are recommended. If bleomycin is contraindicated because of any medical conditions, vincristine/dactinomycin/cyclophosphamide (VAC) combination could be used (strength of recommendation and level of evidence 1C).

Postoperative chemotherapy for 3–4 cycles with BEP is recommended for any stage embryonal tumors or endodermal sinus tumors, stage II–IV dysgerminoma, or stage I, grade 2–3, or stage II–IV immature teratoma. In select patients with stage IB–III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be considered. Patients achieving a complete clinical response after chemotherapy should be observed clinically every 2–4 months with α-FP and β-hCG levels (if initially elevated) for 2 years.

For patients having radiographic evidence of residual tumor after surgery and chemotherapy, but with normal α-FP and β-hCG, consider surgical resection of the tumor or observation with monitoring. For those with definitive residual disease and with persistently elevated α-FP and/or β-hCG after first-line chemotherapy, recommendations include paclitaxel/ifosfamide/cisplatin (TIP) or high-dose chemotherapy. Other regimens include VAC, etoposide/ifosfamide/cisplatin (VIP), cisplatin/etoposide, vinblastine/ifosfamide/cisplatin (VeIP), docetaxel, paclitaxel, or RT.

(2) Sex cord-stromal tumor

Patients with stage IA or IC sex cord-stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery. Otherwise, complete staging is recommended for all other patients. Observation is recommended for those with surgical findings of low-risk stage I tumor. For patients with high-risk stage I tumors (tumor rupture, stage IC, poorly differentiated tumor, and tumor size >10–15 cm), postoperative recommendations include

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observation or consideration of platinum-based chemotherapy (strength of recommendation and level of evidence 2C). For patients with stage II–IV tumors, recommended options include RT for limited disease or platinum-based chemotherapy (BEP or paclitaxel/carboplatin regimens are preferred) (strength of recommendation and level of evidence 2C). For patients with stage II–IV tumors who subsequently have a clinical relapse, options include: a clinical trial, cytotoxic recurrence therapy (including docetaxel, paclitaxel, paclitaxel/ifosfamide, paclitaxel/carboplatin, and VAC), hormone recurrence therapy (aromatase inhibitors, leuprolide, and tamoxifen), secondary cytoreductive surgery, and palliative localized RT.

(3) Carcinosarcoma

After complete surgical staging, several postoperative chemotherapy regimens are recommended for patients with stage I–IV carcinosarcoma. Patients with stage I–IV carcinosarcoma or recurrence may be treated using the same primary chemotherapy regimens that are recommended for EOC.

SUMMARY OF RECOMMENDATION AND CONCLUSIONS

The following recommendations and conclusions are based on 4 levels of evidence (A, high; B, moderate; C, low; D, very low) and 2 strengths of recommendation (1, strong; 2, weak).

1. 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 **(2B)**.

2. NAC followed by interval debulking surgery may be considered for patients with extensive stage IIIC–IV EOC who are not likely for optimal cytoreduction by upfront primary surgery based on that overall survival was comparable between these patients **(2A)**.

3. 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 **(2B)**.

4. 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.

5. 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 **(2D)**.

6. Evidence level of whether complete staging operation may lead to better survival compared with incomplete staging operation in serous borderline epithelial tumors cannot be appropriately decided **(E)**.

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7. 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 **(2D)**.

8. Poly(ADP-ribose) polymerase (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 **(1D) (for 2018 update, 2A)**.

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SUPPLEMENTARY MATERIAL

Supplementary

Guideline development process in accordance with the evidence-based medicine.

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