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Practice Guideline

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The 2020 Japan Society of Gynecologic Oncology guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer

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ABSTRACT

The fifth edition of the Japan Society of Gynecologic Oncology guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer was published in 2020. The guidelines contain 6 chapters—namely, (1) overview of the guidelines; (2) epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer; (3) recurrent epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer; (4) borderline epithelial tumors of the ovary; (5) malignant germ cell tumors of the ovary; and (6) malignant sex cord-stromal tumors. Furthermore, the guidelines comprise 5 algorithms—namely, (1) initial treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer; (2) treatment for recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer; (3) initial treatment for borderline epithelial ovarian tumor; (4) treatment for malignant germ cell tumor; and (5) treatment for sex cord-stromal tumor. Major changes in the new edition include the following: (1) revision of the title to "guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer"; (2) involvement of patients and general (male/female) participants in addition to physicians, pharmacists, and nurses; (3) clinical questions (CQs) in the PICO format; (4) change in the expression of grades of recommendation and level of evidence in accordance with the GRADE system; (5) introduction of the idea of a body of evidence; (6) categorization of references according to research design; (7) performance of systematic reviews and meta-analysis for three CQs; and (8) voting for each CQ/recommendation and description of the consensus.

Keywords: Clinical Practice Guideline; Ovarian Neoplasms; Peritoneal Neoplasms; Fallopian Tube Neoplasms

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Author Contributions

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INTRODUCTION

More than 10,000 women suffer from ovarian cancer annually, and approximately 5,000 women in Japan die from ovarian cancer [1,2]. The first, second, third, and fourth editions of the Japan Society of Gynecologic Oncology (JSGO) guidelines for the treatment of ovarian cancer were published in 2004, 2007, 2010, and 2015, respectively. The fourth edition greatly changed its review style in the form of clinical questions (CQs) [3]. The Japan Society of Clinical Oncology (JSCO) Cancer Guidelines Evaluation Committee and Medical Information Network Distribution Service (MINDS) definitively evaluated the guidelines after their publication. Based on this evaluation, the contents pointed out were discussed by the exploratory committee established by the JSGO in order to improve the next revision. We draw up the guidelines while confirming this direction. The following major changes were made from previous guidelines and were added, modified, or revised in the 2020 guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer:

(1) As the World Health Organization classification of primary organ cancer was revised in 2014, the title has been renamed to “guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.” Ovarian cancer, fallopian tube cancer, and primary peritoneal cancer are integrated into the same category.
(2) Optimal patient care requires shared decision-making, and both scientific evidence and patients' diverse values are important [4]. Treatment guidelines are not only for healthcare providers but also for patients; hence, in addition to doctors, pharmacists, and nurses, the development of these guidelines has also involved patients and general (male/female) participants.
(3) Evidence-based models use a process for framing a question, locating, assessing, evaluating, and repeating, as necessary. PICO elements include ‘Problem/Patient/Population,’ ‘Intervention/Indicator,’ ‘Comparison,’ and ‘Outcome.’ CQs have been framed in PICO format [5].
(4) The expression of grades of recommendation and level of evidence has been changed in accordance with the GRADE system [6].
(5) The idea of a body of evidence has been introduced [7]. Assessment of the body of evidence is conducted for outcomes corresponding to the CQs, taking study design, risk of bias, and indirectness into account. The body of evidence determines the certainty of the level of evidence.
(6) References have been categorized according to research design.
(7) Systematic reviews and meta-analysis have been performed for three CQs (CQ03 [8], CQ05 [9], and CQ31).
(8) The committee has voted for each CQ/recommendation and description of the consensus.

An overview of the guidelines, including the preparation process, recommendation process, and conflicts of interest (COI), is presented in Chapter 1. Epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer are detailed in Chapter 2, whereas recurrent epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer are described in Chapter 3. Borderline epithelial tumors of the ovary, malignant germ cell tumors of the ovary, and malignant sex cord-stromal tumors are detailed in Chapters 4, 5, and 6, respectively.

These guidelines have primarily been designed for use by Japanese physicians and have been generated with consideration for the Japanese public health insurance system and community standards. Administration of unapproved drugs and the performance of surgical procedures

covered by the Japanese health insurance are not strongly recommended as daily clinical practices in Japan due to the high patient medical expenses and complicated procedures.

In Japan, at the time of publication of these guidelines, 1) only Olaparib was approved for use among poly(ADP-ribose) polymerase (PARP) inhibitors; 2) hormone therapies, such as aromatase inhibitors, leuprolide acetate, megestrol acetate, and tamoxifen, were not approved for treating malignant ovarian neoplasms; 3) risk-reducing salpingo-oophorectomy for *BACA1/2* variant carriers without a history of breast cancer was not approved; and 4) homologous recombination deficiency test was not approved. Notably, the related recommendations will be updated in the future.

CHAPTER 1: OVERVIEW OF GUIDELINES

1. How to use the guidelines

We describe one criterion for the selection of a better treatment method for malignant ovarian neoplasms in Japan and subsequently present evidence for the suggested approach. This does not limit treatment to that described in the guidelines. The guidelines aim to (1) define appropriate treatments for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer; (2) reduce disparities in treatment approaches among institutions; (3) improve the safety of these treatments as well as patient prognosis; (4) reduce the physical, psychological, and economic burden on patients through the use of appropriate treatments; and (5) enhance mutual understanding between medical staff and patients.

2. Intended audience

These guidelines are intended to assist practicing physicians involved in the treatment of patients with ovarian cancer, fallopian tube cancer, and primary peritoneal cancer and to help ordinary individuals, including patients and their families, to understand these aforementioned cancers.

3. Diseases addressed by these guidelines

The diseases addressed by these guidelines include malignant and borderline tumors arising from the ovary, fallopian tube cancer, and primary peritoneal cancer, as well as recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

4. Notes on using these guidelines

1) In Japan, there is both acceptable and unacceptable evidence from Europe and the United States owing to differences in the background, such as the public insurance system and approved drugs and medical technologies. Additionally, some treatments considered common in Japan differ from those in Europe and the United States. In such cases, the contents are prioritized using the current consensus in Japan.
2) Therapy is often difficult to administer under the Japanese medical care insurance system. In this regard, the guidelines follow the JSCO's Committee on Clinical Practice Guidelines for Use of Anticancer Agents.

5. Committee members

Gynecologic oncologists, medical oncologists, radiologists, pathologists, and palliative care physicians have been involved in preparing and evaluating the draft of the guidelines. Furthermore, pharmacists, nurses, patients, and general (male/female) participants

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have cooperated as a third party from the start of setting the CQs. The chairman and vice chairman informed the external committee members about the contents and revision points of the final version of the guidelines. The external committee members participated in voting for agreements, and the patient advocacy group "Katoreanomori" participated as an evaluation committee.

6. Literature retrieval

In this revision, we requested the Japan Medical Library Association (JMLA) to prepare literature search terms for a systematic database search. The specific literature retrieval method was as follows:

1) The Formulation Committee selected an article using keywords related to the CQs, and the JMLA subsequently prepared relevant search terms and conducted a comprehensive literature search. If a large number of articles were retrieved, the keywords were changed and more were added after a review by the Formulation Committee and JMLA. The Formulation Committee examined the retrieved articles and identified approximately 20 important articles. With regard to CQ24 and CQ25, we respected the judgment of the committee member's claim to know important papers published later than those cited in the 2015 guidelines; hence, we did not use the search formula.
2) Articles published from January 2013 to December 2018 in PubMed, Japan Medical Abstract Society, and Cochrane Library were included in the search. Articles published prior to 2012 that were cited in previous editions of the guidelines and were needed for recommendations were used as references. Articles published after January 2019 were examined separately, and some were used as references.
3) Literature search items are published on the web at https://jsgo.or.jp/guideline/ransou2020_bunken.html.

7. Level of evidence and grades of recommendation

1) We referred to the 2014 MINDS practice guidelines for the determination of the level of evidence and grades of recommendation. Outcomes were set for each CQ. The body of evidence was assessed with consideration of the study design, risk of bias, and indirectness of papers selected for each outcome (**Supplementary Table 1**).
2) The level of evidence in these guidelines is determined based on factors prescribing a body of evidence and differs from the previous "level of evidence," which was based on study design (e.g., "randomized phase III"). While there exists evidence arising from a randomized phase III trial, the level of evidence may be "B (moderate)," not "A (strong)", depending on the quality of the clinical trial.
3) The Formulation Committee evaluated the grades of recommendation with consideration of not only the level of evidence, balance of benefit versus harm, and patients' values and preferences but also the community standards and insurance coverage in Japan (**Supplementary Table 2**).
4) Systematic reviews and meta-analysis were performed for each outcome corresponding to three CQs—namely, CQ03, CQ05, and CQ31. For the CQ in which quantitative evaluation (meta-analysis) was unable to be conducted, a qualitative systematic review in which logic and certainty were inferred from the context was performed.
5) Recommendation, level of evidence, and grades of recommendation were determined by the 7th Formulation Committee, and consensus was achieved by voting.
6) When consensus did not reach 75%, the recommendation was reviewed, and the grades of recommendation, level of evidence, or recommendation itself was revised. Afterward, we voted again.

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7) Opinions and points of discussion concerning the re-voted recommendations or the recommendations with consensus lower than the criteria followed the recommendations.
8) The external committee voted the recommendations in Chapter 2, and these recommendations met the criteria for consensus by the 7th Formulation Committee. Thus, the consensus in Chapter 2 shows the sum of votes by both the core and external committee members.

8. Procedure for the creation of the guidelines

To create these guidelines, the Guidelines Formulation Committee and the Guidelines Evaluation Committee were independently established within the Committee for Treatment Guidelines for Ovarian Cancer, which was formed by the JSGO's Guidelines Committee. The chair of the Guidelines Committee was concurrently the chair of the Committee for Treatment Guidelines for Ovarian Cancer and chair of the Guidelines Formulation Committee. The guidelines were revised from January 2018 to June 2020 after seven meetings by the Guidelines Formulation Committee, a consensus meeting, and a period for public comment.

9. Tips for activation of use and disclosure of information

1) Algorithms have been created to boost usefulness for the intended audience.
2) These guidelines are published as a pamphlet and on the homepages of JSGO, JSCO, and MINDS to facilitate widespread use.
3) The results of systematic reviews and meta-analysis for CQ03, CQ05, and CQ31 have been published in internationally cited journals.

10. Responsibility for treatment

The JSGO bears responsibility for the contents and descriptions provided in these guidelines. Nonetheless, the final decision to use these guidelines should be made by the individual user. Thus, the responsibility for the treatment outcomes is directly attributed to the person in charge.

11. Monitoring and revision

1) These guidelines are continuously being revised by the Committee for Treatment Guidelines for Ovarian Cancer based on medical advances and changes.
2) Evidence that is newly accumulated after the preparation of these guidelines is saved in a database.
3) Data on clinical problems occurring with the use of these guidelines are being collected.
4) The next version as a pamphlet will be published in 2025.
5) Revisions are considered by both the Guidelines Formulation Committee and the Guidelines Evaluation Committee based on new evidence and data prior to the publication of the next pamphlet, as necessary. Furthermore, opinions from academic societies, groups, and JSGO members are widely sought.
6) With the approval of the JSGO, the Committee for Treatment Guidelines for Ovarian Cancer will develop a revised version after these processes.

12. Funding

The preparation of these guidelines was funded by the JSGO only, and no assistance was provided by other organizations or companies.

13. COI

1) The Board of the Society Conflict of Interest Committee confirmed the absence of any COI. A total of 30 members (17 from the Guidelines Formulation Committee and 13 from the

Guidelines Evaluation Committee) declared COI related to their work or social activity with a company. However, none of these COI were deemed to have exceeded the acceptable range.

2) The contents of these guidelines are based on the consensus of the Guidelines Committee and are thus unaffected by any interest associated with specific groups or products.

14. Summary of recommendations

Each chapter comprises CQs, recommendations, background, objectives, explanations, and references. This article summarizes the guidelines in a question-and-answer format. Recommendations in each chapter are listed below under their respective chapter titles.

15. Algorithms

The guidelines contain the following five algorithms:

1) Initial treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (**Fig. 1**).
2) Treatment for recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (**Fig. 2**).
3) Initial treatment for borderline epithelial ovarian tumor (**Fig. 3**).
4) Treatment for malignant germ cell tumor (**Fig. 4**).
5) Treatment for sex cord-stromal tumor (**Fig. 5**).

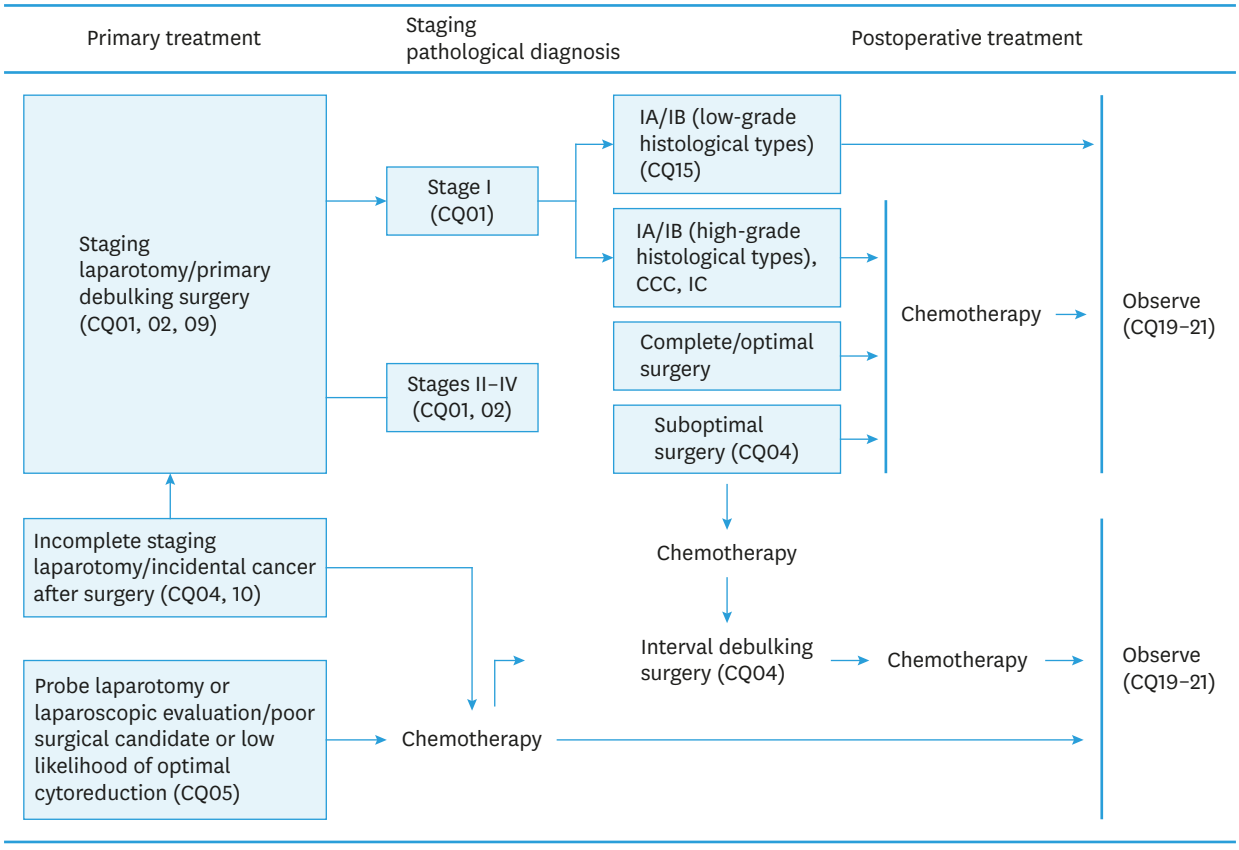

Fig. 1. Initial treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.
Complete surgery: no residual carcinoma; optimal surgery: residual tumor <1 cm; suboptimal surgery: residual tumor ≥1 cm. CQ11 and CQ14 for first-line chemotherapy, CQ12 and CQ13 for maintenance therapy, CQ17 for intraperitoneal chemotherapy, or CQ22 for hormone replacement therapy.
CCC, clear cell carcinoma; CQ, clinical question.

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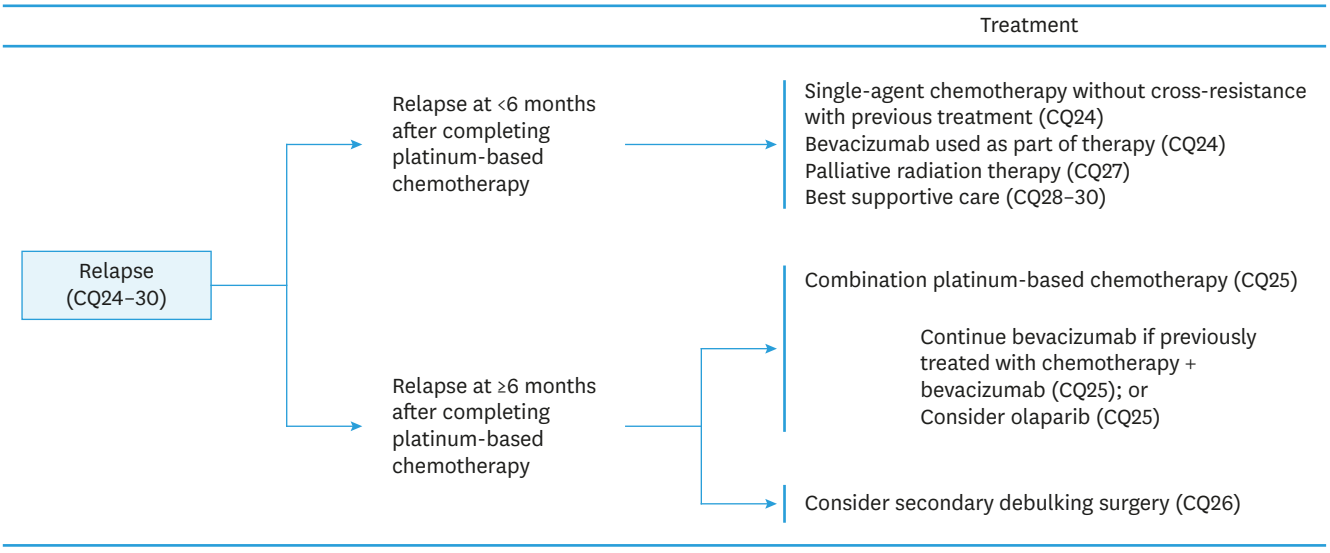

Fig. 2. Treatment for recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.
CQ, clinical question.

CHAPTER 2: EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER, AND PRIMARY PERITONEAL CANCER

1. CQ 01: For patients with stage I–IIA ovarian cancer, what staging laparotomy is recommended?

Recommendations:

1) Pelvic/para-aortic lymph node dissection (biopsy) is recommended in addition to bilateral salpingo-oophorectomy (BSO) + total hysterectomy + omentectomy (OMT) + peritoneal cytology + biopsies from sites in the abdominal cavity.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

2) When sampling from the abdominal cavity, specimens are suggested to be acquired from the surface of the pouch of Douglas, abdominal wall, diaphragm, bowel, and mesentery, in addition to the suspected lesions.

Grade 2 (↑); level of evidence: C; consensus: 100%

2. CQ 02: For patients thought to have stage IIB or higher ovarian cancer, is primary debulking surgery (PDS) recommended as the initial treatment?

Recommendations:

1) Maximal debulking surgery is recommended to achieve complete resection (i.e., no gross residual tumor).

Grade 1 (↑↑); level of evidence: A; consensus: 100%

2) The procedures are recommended to be performed in a JSGO-designated training facility or an institute with a full-time JSGO-certified gynecologic oncologist where multidisciplinary treatment can be implemented in cooperation with surgeons, urologists, oncologists, etc.

Grade 1 (↑↑); level of evidence: C; consensus: 94%

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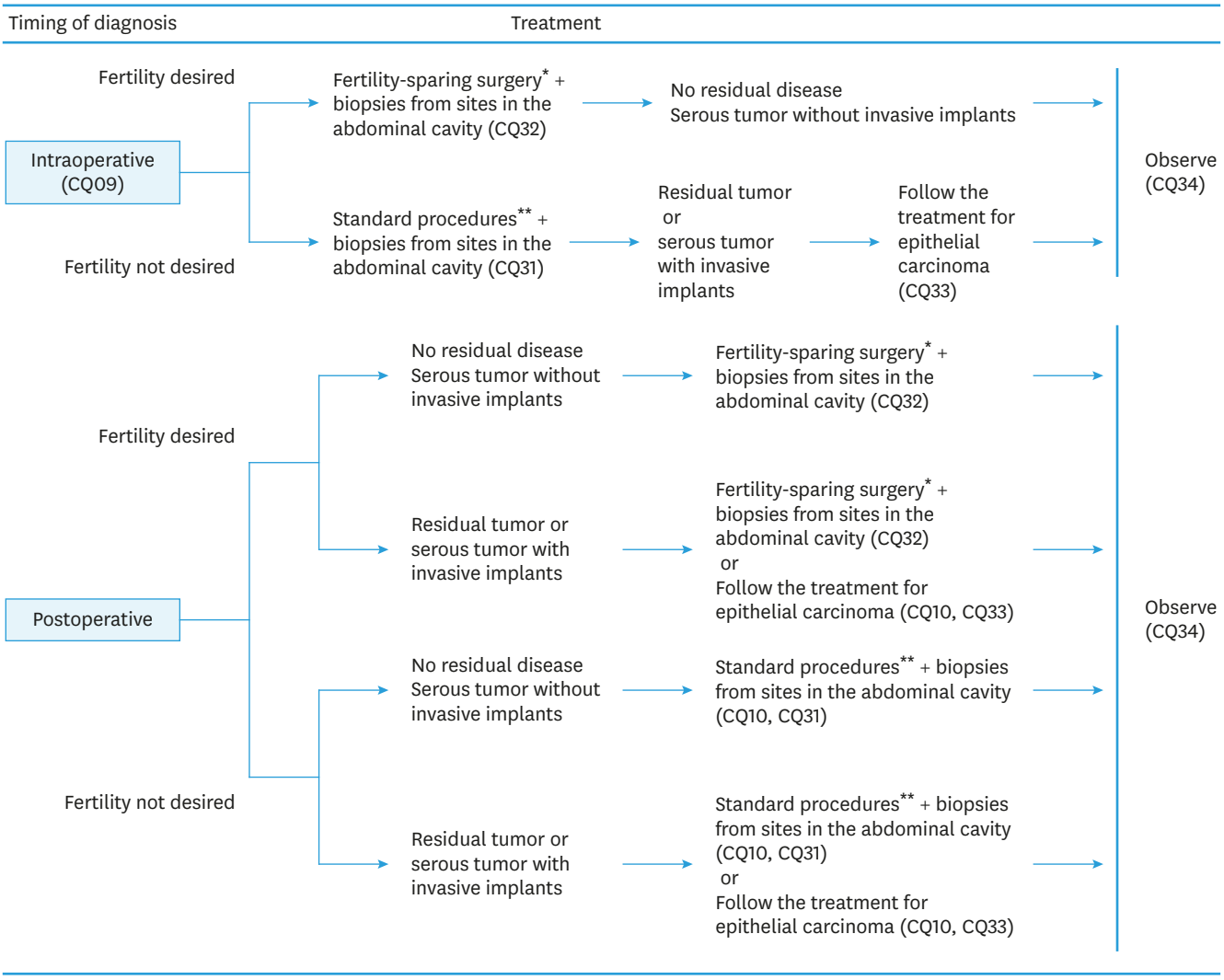

Fig. 3. Initial treatment for borderline epithelial ovarian tumor.
BSO, bilateral salpingo-oophorectomy; CQ, clinical question; OMT, omentectomy; USO, unilateral salpingo-oophorectomy.
*Fertility-sparing surgery: USO (affected side) + OMT + peritoneal cytology. **Standard procedures: BSO + hysterectomy + OMT + peritoneal cytology.

3. CQ 03: For patients thought to have stage IIB or higher ovarian cancer, is pelvic or para-aortic lymphadenectomy recommended as a primary surgery?

Recommendations:

1) Pelvic or para-aortic lymph node dissection is suggested to be not performed if no lymph node metastasis is clinically detected on imaging or by intraoperative palpation and visual inspection.

Grade 2 (↓); level of evidence: B; consensus: 95%

2) When lymph node metastasis is clinically detected on diagnostic imaging or by intraoperative palpation and visual inspection, pelvic or para-aortic lymph node dissection or removal of swollen lymph nodes is recommended if complete resection can be achieved.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

4. CQ 04: For patients with residual disease after PDS, is interval debulking surgery (IDS) recommended?

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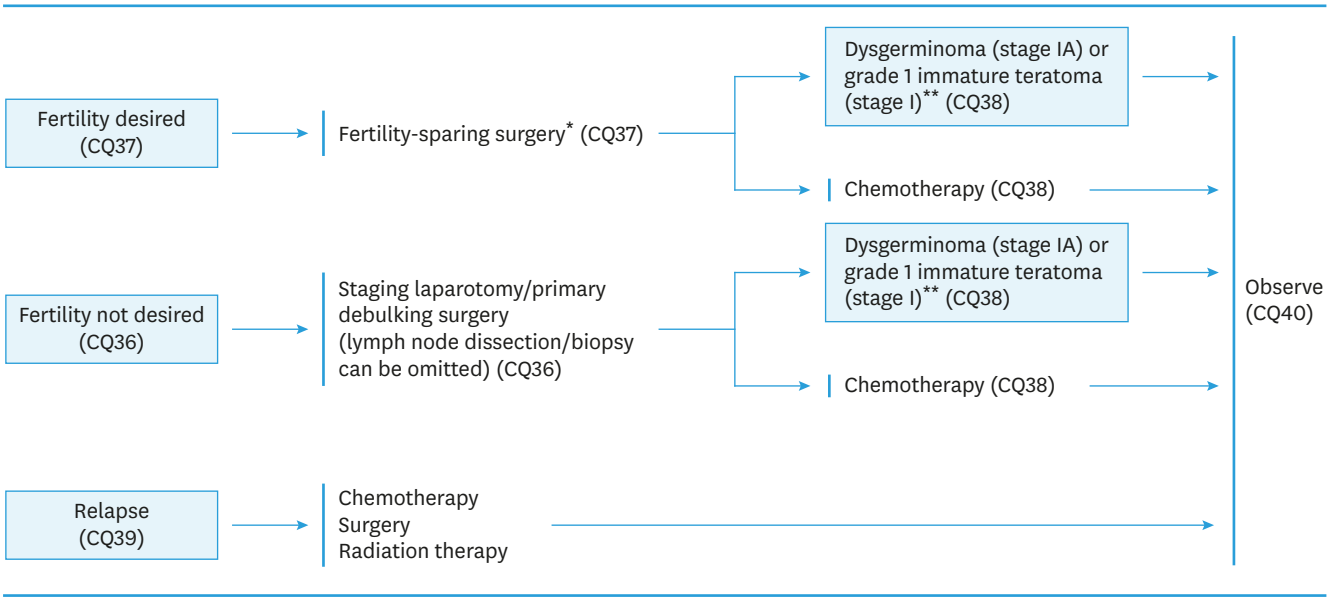

Fig. 4. Treatment for malignant germ cell tumor.
CQ, clinical question; OMT, omentectomy; USO, unilateral salpingo-oophorectomy.
*Fertility-sparing surgery: USO (affected side) + OMT + peritoneal cytology + careful examination of the abdominal cavity. **For those aged <15 years with immature teratoma, regardless of grade or whether complete resection was achieved, observation without chemotherapy is recommended (CQ38).

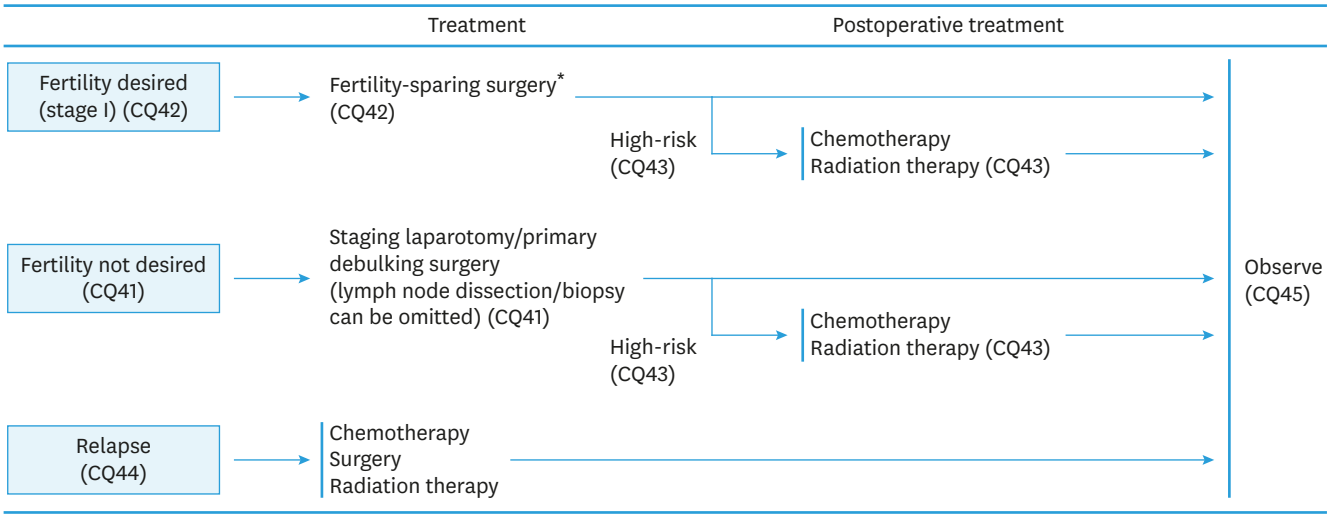

Fig. 5. Treatment for sex cord-stromal tumor.
OMT, omentectomy; USO, unilateral salpingo-oophorectomy.
*Fertility-sparing surgery: USO (affected side) + OMT + peritoneal cytology + careful examination of the abdominal cavity.

Recommendation:

IDS is suggested.

Grade 2 (↑); level of evidence: C; consensus: 95%

5. CQ 05: For patients with advanced-stage ovarian cancer, are neoadjuvant chemotherapy (NAC) and IDS recommended, as compared to PDS?

Recommendation:

NAC + IDS is recommended for advanced-stage ovarian cancer when optimal surgery is

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expected to be difficult or impossible to achieve.
Grade 1 (↑↑); level of evidence: B; consensus: 100%

6. CQ 06: For patients who desires that their fertility will be preserved, is fertility-sparing surgery recommended?

Recommendations:

1) In addition to unilateral salpingo-oophorectomy (USO) (affected side) + OMT + peritoneal cytology, intraperitoneal examination is recommended to be performed as a basic surgical procedure for fertility preservation.
Grade 1 (↑↑); level of evidence: B; consensus: 100%
2) Biopsy of the contralateral ovary, biopsy (dissection) of pelvic or para-aortic lymph nodes, and biopsy from sites in the abdominal cavity are suggested as staging laparotomy, depending on the case.
Grade 2 (↑); level of evidence: C; consensus: 100%
3) Fertility-sparing treatment is recommended for stage IA non-clear cell carcinoma (CCC) with low histological grade.
Grade 1 (↑↑); level of evidence: B; consensus: 100%
4) Fertility-sparing treatment is suggested for non-CCC patients (stage IC1 confined to one side of the ovary and low histological grade) or patients with CCC (stage IA).
Grade 2 (↑); level of evidence: C; consensus: 100%
5) Adjuvant chemotherapy is recommended in the same manner as when standard surgical procedures are performed.
Grade 1 (↑↑); level of evidence: B; consensus: 100%

7. CQ 07: For patients with ovarian cancer, is laparoscopic surgery instead of laparotomy recommended?

Recommendation:

Laparoscopic surgery is suggested to be not performed at the moment.
Grade 2 (↓); level of evidence: C; consensus: 100%

8. CQ 08: For patients thought to have peritoneal dissemination, is diagnostic laparoscopy recommended?

Recommendation:

Diagnostic laparoscopy is suggested for the purpose of predicting complete surgery, staging, or collecting tissues.
Grade 2 (↑); level of evidence: B; consensus: 100%

9. CQ 09: Is intraoperative pathology consultation recommended to determine operative procedures?

Recommendation:

Intraoperative pathology consultation is recommended in order to determine the surgical procedures when the malignancy of a lesion is difficult to judge based on preoperative and/or intraoperative findings.
Grade 1 (↑↑); level of evidence: B; consensus: 100%

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10. CQ 10: For patients with incidental ovarian cancer after surgery, what treatment is recommended?

Recommendations:

1) Staging laparotomy is recommended.
Grade 1 (↑↑); level of evidence: B; consensus: 100%
2) IDS after chemotherapy is recommended for patients with advanced-stage ovarian cancer, in whom optimal surgery is difficult or impossible to achieve.
Grade 1 (↑↑); level of evidence: B; consensus: 100%

11. CQ 11: For chemotherapy-naïve patients, what is the recommended regimen?

Recommendations:

1) Conventional paclitaxel plus carboplatin (TC) therapy is recommended.
Grade 1 (↑↑); level of evidence: A; consensus: 100%
2) Dose-dense TC therapy is suggested.
Grade 2 (↑); level of evidence: B; consensus: 38%*
*Rate for grade 1. The grade of recommendation for the second one was initially proposed as grade 1 because dose-dense TC therapy was superior to conventional TC therapy in the JGOG 3016 trial with respect to overall survival among Japanese patients. However, the ICON8 trial denied the superiority of dose-dense TC therapy, and committee consensus did not reach 75% (i.e., agreement criteria). Thus, the grade of recommendation was judged to be grade 2 (final consensus: 89%).
3) A combination of TC and bevacizumab followed by bevacizumab maintenance therapy is recommended for patients with stage III/IV disease.
Grade 1 (↑↑); level of evidence: B; consensus: 89%**
**There existed an opinion that the grade of recommendation should be scored as grade 2 instead, considering the adverse effects of bevacizumab and PARP inhibitors in *BRCA* variant carriers. In these guidelines, we defined "variant" as pathogenic or likely a pathogenic variant.

12. CQ 12: For patients with complete remission (CR) after chemotherapy following primary surgery, is maintenance therapy recommended?

Recommendations:

1) Maintenance therapy is suggested to be not administered.
Grade 1 (↓↓); level of evidence: B; consensus: 100%
2) Maintenance therapy with bevacizumab is recommended for patients with stage III/IV disease after CR is achieved by first-line chemotherapy with bevacizumab.
Grade 1 (↑↑); level of evidence: B; consensus: 100%
3) Olaparib is recommended for patients with stage III/IV disease who carry BRCA1/2 variants after CR is achieved by first-line chemotherapy.
Grade 1 (↑↑); level of evidence: B; consensus: 100%

13. CQ 13: For patients with persistent disease after first-line chemotherapy following primary surgery, is further treatment recommended?

Recommendations:

1) Bevacizumab is recommended except for patients exhibiting disease progression after first-line chemotherapy with bevacizumab.

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Grade 1 (↑↑); level of evidence: B; consensus: 95%

2) Olaparib is recommended for patients with BRCA1/2 variants when first-line chemotherapy results in partial response.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

3) For patients who fail to respond to first-line chemotherapy and those exhibiting tumor progression, another treatment (i.e., second-line chemotherapy or radiation therapy), participation in clinical trials, or best supportive care is suggested.

Grade 2 (↑); level of evidence: C; consensus: 95%

14. CQ 14: For patients in whom TC therapy is considered inappropriate, what regimen is recommended?

Recommendations:

1) Docetaxel plus carboplatin or pegylated liposomal doxorubicin plus carboplatin is recommended.

Grade 1 (↑↑); level of evidence: B; consensus: 95%

2) For patients in whom docetaxel plus carboplatin or pegylated liposomal doxorubicin plus carboplatin is difficult to administer, weekly TC is suggested.

Grade 2 (↑); level of evidence: C; consensus: 100%

3) For patients in whom combination chemotherapy is inappropriate to be provided, carboplatin monotherapy is suggested.

Grade 2 (↑); level of evidence: C; consensus: 100%

15. CQ 15: For patients with stage I ovarian cancer, is the omission of postoperative chemotherapy recommended?

Recommendation:

Omission of adjuvant chemotherapy is suggested for non-CCC patients with low grade and stage IA or IB, as defined by staging laparotomy.

Grade 2 (↑); level of evidence: B; consensus: 94%

16. CQ 16: Is it recommended to choose a different chemotherapy regimen depending on the histological* type of ovarian cancer?

Recommendation:

It is suggested that chemotherapy regimen should not be altered based on histology.

Grade 2 (↓); level of evidence: B; consensus: 84%

*There is no evidence of a regimen that has superiority over TC therapy as a treatment for clear cell carcinomas and mucinous carcinomas, which are more likely to resist platinum-based chemotherapy than high-grade serous carcinomas and endometrioid carcinomas.

17. CQ 17: For patients with advanced-stage ovarian cancer, is intraperitoneal chemotherapy recommended as first-line chemotherapy?

Recommendations:

1) Intraperitoneal chemotherapy is suggested to be administered in an appropriate facility with provision of adequate informed consent concerning risks and benefits.

Grade 2 (↑); level of evidence: B; consensus: 94%

2) Hyperthermic intraperitoneal chemotherapy is suggested to be provided in a clinical trial.

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Grade 2 (↑); level of evidence: B; consensus: 94%

18. CQ 18: When hypersensitivity reaction (HSR) occurs during drug administration, is re-administration of the same or similar drug possible?

Recommendations:

1) For patients with mild HSR to non-platinum agents, careful re-administration of the same drug is suggested following confirmation of symptom loss after stopping the administration.

Grade 2 (↑); level of evidence: C; consensus: 63%*

*Rate for grade 1

2) For patients with mild HSR to platinum agents, desensitization therapy for the same drug or alternation with other platinum agents is suggested after the establishment of a system that can immediately cope with serious complications, including cardiopulmonary arrest.

Grade 2 (↑); level of evidence: C; consensus: 89%

3) For patients with severe HSR to chemotherapy, non-administration of the same or similar drug is recommended.

Grade 1 (↓↓); level of evidence: B; consensus: 100%

19. CQ 19: What are the recommended intervals for post-treatment surveillance?

Recommendation:

The following intervals are suggested after the start of initial treatment:

Years 1–2: an interval of 1–3 months

Years 3–5: an interval of 3–6 months

Year 6 onward: an interval of 1 year

Grade 2 (↑); level of evidence: C; consensus: 94%

20. CQ 20: Are medical interview, pelvic examination, serum tumor marker measurement, and diagnostic imaging during ovarian cancer follow-up recommended?

Recommendations:

1) Medical interview, pelvic examination, and transvaginal ultrasonography are recommended during every patient's visit.

Grade 1 (↑↑); level of evidence: C; consensus: 94%

2) Serum tumor marker measurement and computed tomography are recommended to be conducted, as necessary.

Grade 1 (↑↑); level of evidence: C; consensus: 100%

21. CQ 21: For asymptomatic patients with elevation in serum cancer antigen 125 (CA125) level during ovarian cancer follow-up, is an intervention recommended?

Recommendation:

It is suggested not to intervene based only on an elevation in the serum level of CA125, a tumor marker.

Grade 2 (↓); level of evidence: B; consensus: 95%

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22. CQ 22: Is hormone replacement therapy (HRT) recommended during treatment or ovarian cancer follow-up?

Recommendation:

HRT is recommended for patients exhibiting symptoms or those aged <45 years.

Grade 1 (↑↑); level of evidence: B; consensus: 59%*

*Consensus for the recommendation "early intervention just after oophorectomy, Grade 2 (↑)" was initially 38%. Despite various opinions as to when to start the HRT, the committee members agreed that it did not worsen the prognosis. After adding age as a factor, the physicians' consensus reached 82%. The final consensus, including the opinions of the external committee members, was 59%.

23. CQ 23: For carriers of *BRCA1/2* variants who have not developed breast cancer, is risk-reducing salpingo-oophorectomy recommended?

Recommendation:

Following the review and approval by the ethics committee, the performance of risk-reducing salpingo-oophorectomy by gynecologic oncologists in cooperation with clinical geneticists in a facility where genetic counseling and pathologists' cooperation are available is recommended.

Grade 1 (↑↑); level of evidence: A; consensus: 100%

CHAPTER 3: RECURRENT EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER, AND PRIMARY PERITONEAL CANCER

1. CQ 24: For patients with platinum-resistant recurrence, what is the recommended chemotherapy regimen?

Recommendations:

1) A single agent without cross-resistance to previous treatment is suggested.

Grade 2 (↑); level of evidence: B; consensus: 100%

2) The addition of bevacizumab to a cytotoxic agent is suggested.

Grade 2 (↑); level of evidence: B; consensus: 100%

2. CQ 25: For patients with platinum-sensitive recurrence, what is the recommended chemotherapy regimen?

1) Combination chemotherapy with a platinum agent is recommended.

Grade 1 (↑↑); level of evidence: A; consensus: 100%

2) The addition of bevacizumab to the combination chemotherapy followed by bevacizumab maintenance therapy is recommended.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

3) Olaparib is recommended for patients with BRCA1/2 variants after tumor regression by platinum-based chemotherapy.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

4) Olaparib is suggested for patients identified to have no variants after BRCA testing as well as those with or without BRCA1/2 variants after tumor regression due to platinum-based

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chemotherapy.
Grade 2 (↑); level of evidence: B; consensus: 85%

3. CQ 26: For patients with recurrence, is surgery recommended?

Recommendations:

1) For patients with platinum-sensitive recurrence, secondary debulking surgery is suggested to be performed when it is thought that the lesion can possibly be resected completely.
Grade 2 (↑); level of evidence: C; consensus: 100%
2) For patients with platinum-resistant recurrence, surgery is suggested to be not performed, except for the purpose of symptom relief or in cases with resectable solitary lesion.
Grade 2 (↓); level of evidence: C; consensus: 92%

4. CQ 27: For patients with unresectable recurrence, is radiation therapy recommended?

Recommendations:

1) Radiation therapy is suggested for the purpose of pain relief or hemostasis.
Grade 2 (↑); level of evidence: B; consensus: 100%
2) Radiation therapy for brain metastasis is suggested to relieve the symptoms and improve the prognosis.
Grade 2 (↑); level of evidence: B; consensus: 92%

5. CQ 28: For patients with ovarian cancer who have an ileus, is surgery or medication recommended?

Recommendations:

1) A surgical solution accounting for eligibility and risk of surgery is suggested for physical obstruction to improve emesis and vomiting.
Grade 2 (↑); level of evidence: C; consensus: 100%
2) Corticosteroids, octreotide, or both are suggested to relieve emesis and vomiting.
Grade 2 (↑); level of evidence: C; consensus: 100%

6. CQ 29: For patients with massive ascites, is medication or ascites drainage recommended?

Recommendation:

Diuretic agent, ascites drainage, or concentrated ascites reinfusion therapy with consideration of patients' condition is suggested for symptom relief.
Grade 2 (↑); level of evidence: C; consensus: 92%

7. CQ 30: For patients being considered for chemotherapy beyond third-line chemotherapy, is further chemotherapy recommended?

Recommendation:

After adequate discussion with the patients and careful assessment of their condition, the administration of chemotherapy with different regimens is suggested if they are judged to be less disadvantageous owing to their adverse effects.
Grade 2 (↑); level of evidence: C; consensus: 100%

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CHAPTER 4: BORDERLINE EPITHELIAL TUMORS OF THE OVARY

1. CQ 31: For patients with incidental borderline tumor of the ovary after USO, is additional surgery recommended?

Recommendation:

BSO + total hysterectomy + OMT + peritoneal cytology + biopsies from sites in the abdominal cavity are suggested.

Grade 2 (↑); level of evidence: C; consensus: 100%

2. CQ 32: For patients with incidental borderline tumor of the ovary after ovarian tumor enucleation, what is the recommended type of fertility-sparing surgery?

Recommendation:

In addition to USO (affected side) + OMT + peritoneal cytology, biopsies from sites in the abdominal cavity are suggested.

Grade 2 (↑); level of evidence: C; consensus: 100%

3. CQ 33: For patients with borderline epithelial tumor of the ovary, is postoperative chemotherapy recommended?

Recommendations:

1) Combination chemotherapy with taxane and platinum agents is suggested for patients with serous tumor accompanied by invasive implantation in the peritoneum.

Grade 2 (↑); level of evidence: C; consensus: 100%

2) Chemotherapy is recommended not to be performed for patients without invasive implantation in the peritoneum.

Grade 1 (↓↓); level of evidence: B; consensus: 100%

3) Combination chemotherapy with taxane and platinum agents is suggested for patients with residual disease, irrespective of histological type.

Grade 2 (↑); level of evidence: C; consensus: 100%

4. CQ 34: For patients with borderline epithelial tumor of the ovary, is a long-term follow-up recommended?

Recommendation:

A long-term follow-up of >5 years is suggested.

Grade 2 (↑); level of evidence: C; consensus: 92%

5. CQ 35: For patients with recurrent borderline epithelial tumor of the ovary, is surgery recommended?

Recommendation:

Surgery is suggested for the purpose of complete resection and pathological diagnosis.

Grade 2 (↑); level of evidence: C; consensus: 100%

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CHAPTER 5: MALIGNANT GERM CELL TUMORS OF THE OVARY

1. CQ 36: For patients with malignant germ cell tumor of the ovary, is debulking surgery recommended?

Recommendation:

Surgery similar to that for epithelial ovarian cancer is recommended. Nonetheless, lymph node dissection (biopsy) can be omitted.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

2. CQ 37: For patients with malignant germ cell tumor of the ovary who require fertility preservation, is fertility-sparing surgery recommended?

Recommendation:

Fertility-sparing surgery is recommended irrespective of stage.

Grade 1 (↑↑); level of evidence: B; consensus: 85%

3. CQ 38: For patients with malignant germ cell tumor of the ovary, is postoperative chemotherapy recommended?

Recommendations:

1) Combination chemotherapy with bleomycin, etoposide, and cisplatin is recommended.

Grade 1 (↑↑); level of evidence: A; consensus: 100%

2) It is suggested that chemotherapy should not be performed for patients with stage IA dysgerminoma or stage I immature teratoma (grade 1) under strict follow-up.

Grade 2 (↓); level of evidence: B; consensus: 100%

4. CQ 39: For patients with recurrent malignant germ cell tumor of the ovary after primary chemotherapy, is surgery, chemotherapy, or radiation therapy recommended?

Recommendations:

1) Chemotherapy is recommended.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

2) Tumor resection is suggested.

Grade 2 (↑); level of evidence: C; consensus: 100%

3) Radiation therapy is suggested for patients who are resistant to chemotherapy or are not eligible for surgery.

Grade 2 (↑); level of evidence: C; consensus: 100%

5. CQ 40: In patients with malignant germ cell tumor of the ovary after chemotherapy, what should we pay attention to during follow-up?

Recommendations:

1) Note the occurrence of ovarian dysfunction.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

2) Note the secondary carcinogenesis caused by etoposide.

Grade 1 (↑↑); level of evidence: B; consensus: 92%

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CHAPTER 6: MALIGNANT SEX CORD-STROMAL TUMORS

1. CQ 41: For patients with sex cord-stromal tumor of the ovary, what is the recommended type of surgery?

Recommendation:

Surgery similar to that for epithelial ovarian cancer is recommended. Nonetheless, lymph node dissection (biopsy) can be omitted.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

2. CQ 42: For patients with sex cord-stromal tumor of the ovary who require fertility preservation, is fertility-sparing surgery recommended?

Recommendations:

1) Fertility-sparing surgery is suggested for stage I patients.

Grade 2 (↑); level of evidence: B; consensus: 69%*

*The strength of recommendation was initially proposed as grade 1; however, there was an opinion that the criteria for fertility preservation as well as malignant germ cell tumors cannot be treated in the same way. Malignant sex cord-stromal tumors contain high-grade granulosa cell tumors and poorly differentiated Sertoli–Leydig cell tumors; thus, fertility-sparing surgery cannot be recommended for these. The consensus for grade 1 was 69% and did not hence reach 75% (i.e., agreement criteria). The grade of recommendation was determined as grade 2.

2) Fertility-sparing surgery for patients with sex cord-stromal tumor is the same as that for patients with epithelial ovarian cancer. Specifically, USO (affected side) + OMT + peritoneal cytology + biopsies from sites in the abdominal cavity are suggested for patients with sex cord-stromal tumor.

Grade 2 (↑); level of evidence: B; consensus: 92%

3. CQ 43: For patients with sex cord-stromal tumor of the ovary, is postoperative chemotherapy or radiation therapy recommended?

Recommendations:

1) Platinum-based chemotherapy is recommended for patients at high risk for recurrence or those with residual disease.

Grade 1 (↑↑); level of evidence: B; consensus: 100%

2) Postoperative radiation therapy is suggested for patients with localized residual lesion.

Grade 2 (↑); level of evidence: B; consensus: 85%

4. CQ 44: For patients with recurrent sex cord-stromal tumor of the ovary after primary chemotherapy, is drug therapy, surgery, or radiation therapy recommended?

Recommendations:

1) Surgery or radiation therapy is suggested for patients with localized residual lesion.

Grade 2 (↑); level of evidence: C; consensus: 58%*

*The grade of recommendation for the above was initially grade 1. There was an opinion that radiation therapy is often performed as palliative care and cannot be in the same row as surgery. Furthermore, references on the recurrence of sex cord-stromal tumors were few.

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Thus, consensus did not reach 75% (i.e., agreement criteria). The grade of recommendation was judged as grade 2.
2) Drug therapy-is recommended for patients who are not eligible for surgery.
Grade 1 (↑↑); level of evidence: C; consensus: 83%

5. CQ 45: In patients with sex cord-stromal tumor of the ovary, what should we pay attention to during follow-up?

Recommendation:

A similar manner to that for epithelial ovarian cancer is recommended. For granulosa cell tumors, a long follow-up period of at least 10 years after treatment is recommended.
Grade 1 (↑↑); level of evidence: B; consensus: 100%

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Certainty ratings for outcomes to determine grades of recommendation

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Supplementary Table 2

Strength of recommendation

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