Chapter 1 ■ Guideline Introduction

Ⅰ Objectives

A. To present appropriate current treatments for ovarian cancer.
B. To decrease differences in ovarian cancer treatment among various institutions.
C. To the improve the safety and results of ovarian cancer treatment in Japan.
D. To alleviate personal and financial burdens by provision of appropriate treatment.
E. To assist healthcare providers and patients to reach a mutual understanding.

Remarks

These guidelines provide one standard for better treatment selection; however, the intention of this book is not to place restrictions on treatments that are not mentioned herein.

Ⅱ Target Audience

These guidelines were developed for physicians who are involved in the routine treatment of ovarian cancer. Guidelines for people other than physicians will be developed at a later time.

Ⅲ Responsibilities

The Japan Society of Gynecologic Oncology (JSCO) is responsible only for the content of these guidelines. The final decision regarding the applicability of these guidelines to any situation must be made by the individual provider. That is, the responsibility for the results of any treatment lies directly with the person in charge of the treatment and not with the JSCO. The JSCO disclaims any responsibility for the application or use of the guidelines in any way.

Ⅳ Diseases Targeted

The diseases that are indicated in these guidelines are: (i) primary ovarian surface epithelial/stromal malignant tumors and their borderline tumors; and (ii) malignant and borderline germ cell tumors and their recurrent tumors.

Remarks

The term 'ovarian cancer' refers to epithelial malignant tumors that originate in the ovaries. However, the treatments for ovarian tumors and malignant germ cell tumors are closely related and share common characteristics. Therefore, in these guidelines, tumors other than ovarian epithelial tumors are included; hence, the guidelines are titled 'Ovarian Cancer Treatment Guidelines'.

Ⅴ Principles of Guideline Development

A. In order to create these guidelines, a Development Committee and an Evaluation Committee are to be established independently within the Ovarian Cancer Treatment Guideline Investigative Committee. These committees are to develop an original draft after thorough investigation and consideration. In addition, opinions from within and without the committees are to be included in the final draft and published after committee approval.

B. Development of the Treatment Guidelines is to be in accordance with the internationally standardized method of 'evidence-based medicine' procedures.

C. Literature and data published within Japan and overseas are to be investigated and collected as 'evidence' by May 2003.

D. The evidence collected is to be assessed for quality based on the criteria set by the Development Committee of the *Guidelines for Anticancer Agent Usage* (Japan Society of Clinical Oncology; Table 1).

E. The degrees of recommendation indicated by the guidelines are to follow the 'criteria for recommendations' established by the Development Committee of the *Guidelines for Anticancer Agent Usage* (Japan Society of Clinical Oncology; Table 2).

F. Each section generally consists of the body of text (or table) and remarks. However, if detailed explanations are necessary before recommendations can be made, these explanations are provided as notes.

G. Much of the evidence used to develop these guidelines was obtained from clinical studies in Europe and the US. However, even if the European and US evidence is of high quality, circumstances are different in Japan, making some evidence inappropriate to use in formulating the guidelines. In addition, there are methods that are in general use in Japan, but are different from the techniques used in Europe and the US. In such situations, the general consensus in Japan may take precedence over the European or US evidence, even if the quality of evidence from the West is better.

H. Literature that becomes a foundation for the development of the guidelines is to be listed in the reference section.

I. Owing to differences between the Japanese and international insurance systems, problems arise with the application of some treatments in Japan, even though the treatment may be recommended on the basis of evidence assessed to be of high quality from an international viewpoint. However, in developing the present guidelines, such problems cannot be avoided and must be recognized. Thus, information presented during the development of the *Guidelines for Anticancer Agent Usage* by the Japan Society of Clinical Oncology is to be followed as a general principle and is indicated in the notes below.

Additional Statements:

(1) Because physicians who use these guidelines are 'insurance doctors', in their medical practice they must respect the use of anticancer agents in the treatment of disease as indicated under the approved conditions.

(2) If there are discrepancies between the disease indicated in these guidelines and the approved conditions of use of particular anticancer agents, doctors are to use their discretion in applying treatments for appropriate patient conditions in their medical practice.

(3) The doses and methods of administration of anticancer agent monotherapy are to be in accordance with the approved conditions of the Japanese Pharmaceutical Affairs Law.

(4) The doses and methods of administration of anticancer agent concomitant therapy are to be within the conditions approved for each agent by the Japanese Pharmaceutical Affairs Law.

(Excerpted from the *Guidelines for Anticancer Agent Usage*,[1)2)] by the Japan Society of Clinical Oncology Guideline Development Committee.)

Ⅵ Revision

A. In line with improvements in medical treatment, revisions to these guidelines are to be made at any time.

B. The Guideline Development Committee is to compile new evidence collected after the development of the present guidelines in a database and evaluate the quality of each piece of evidence. The committee is to amend necessary sections based on that database. If the treatment application becomes inappropriate while the present guidelines are still in use, the Guideline Development Committee is to collect information and use it for the next revision.

C. The revised original draft is to be presented to the Evaluation Committee for its consideration.

D. Opinions of the Japan Society of Gynecologic Oncology, Japan Society of Clinical Oncology, Japanese Gynecologic Oncology and Chemotherapy Study Group (JGOG), Japan Association of Obstetricians and Gynecologists and affiliated scientific and research societies are to be fully incorporated.

E. The Ovarian Cancer Treatment Guideline Investigative Committee is to organize the final revised draft and obtain approval for the guidelines at the Japan Society of Gynecologic Oncology Meeting.

Ⅶ Publication

A. These guidelines are to be published as a booklet so that general and widespread use of the guidelines can be attained.

B. The guidelines are to be presented on the Society's homepage (http://www.jsgo.gr.jp/).

Table 1 Quality Assessment Criteria for Evidence Compiled

I	Meta-analyses of multiple randomized, controlled studies or evidence from multiple randomized, controlled studies.
II	Evidence from at least one randomized, controlled study or evidence from multiple well-designed, controlled studies without randomization.
III	Evidence from at least one other type of well-designed, quasi-experimental study or evidence from well-designed, non-experimental, descriptive studies, such as comparative studies, correlation studies, and case-control studies.
IV	Evidence from case series and case reports.
V	Evidence from expert committee reports or opinions and/or evidence based on the clinical experience of respected authorities.

Modified from the criteria of *Guidelines for Anticancer Agent Usage*,[1)2)] by the Japan Society of Clinical Oncology Guideline Development Committee.

Table 2 Levels of Recommendation

A	There is evidence of type I or consistent results that are types II, III, and IV from multiple studies.
B	There is evidence of types II, III, and IV, and results are generally consistent.
C	There is evidence of types II, III, and IV, and results are inconsistent.
D	There is little or no systematic empirical evidence.
E	There is no clear evidence, but the recommendation is a 'basic assumption of clinical oncology'.
F	There is no clear evidence, but the recommendation is the general consensus of the committee.

Modified from the criteria of *Guidelines for Anticancer Agent Usage*,[1)2)] by the Japan Society of Clinical Oncology Guideline Development Committee.

Chapter 2■Epithelial Ovarian Tumors

Ⅰ Introduction

There are approximately 6000 cases of ovarian cancer in Japan every year. In 1995, there were 3892 mortalities from ovarian cancer (malignant ovarian tumor) and the trend has been on the increase in recent years.[1] There are only limited subjective symptoms associated with an ovarian tumor owing to the fact that an ovary is an intraperitoneal organ. In addition, the lack of an appropriate examination for ovarian cancer contributes to nearly half the cases being detected at advanced stages III and IV.[2,3]

An improvement in the treatment results for epithelial ovarian cancer (noted subsequently as ovarian cancer) was seen following the introduction of cisplatin therapy; however, the 5-year survival rate for advanced stages III and IV is still limited to approximately 20%. Ovarian cancer is considered to have the worst prognosis among cancers of the gynecologic organ system. The introduction of paclitaxel has clearly improved the 5-year survival rate of patients with cancers of advanced stages III or IV, a fact confirmed by the National Cancer Institute Surveillance of Epidemiology and End Results (SEER)[4] (Table 3). In addition, paclitaxel + cisplatin concomitant therapy has been reported to have significantly better results (GOG111, OV-10) for a complete response rate and survival rate than previous concomitant therapy with cyclophosphamide + cisplatin.[5,6] As a result, the present standard regimen for the initial chemotherapy of ovarian cancer is a combined formulation of paclitaxel + platinum. However, the long-term survival rate is still low, with a 30% 5-year survival rate and a 10% 10-year survival rate (Fig. 1).[4,5].

As mentioned above, the results of treatment of ovarian cancer, especially in the advanced stages, are not satisfactory at the present time. It is necessary for both physicians and patients to fully realize the intractability of this disease. We await the development of a chemotherapeutic regimen that possesses a strong antitumor effect and contributes to an increase in patient survival time.

Table 3 5-Year Survival Rate According to Time Period and Disease Stage

FIGO Classification	Cases diagnosed as ovarian cancer		*P* value
	1983–1987	1988–1994	
	Treatments without paclitaxel (2194 cases)	Treatments with paclitaxel (2082 cases)	
Stage I	89.64%	92.55%	0.05
Stage II	74.31%	70.12%	NS
Stage III	29.89%	37.45%	< 0.01
Stage IV	18.05%	25.47%	< 0.01

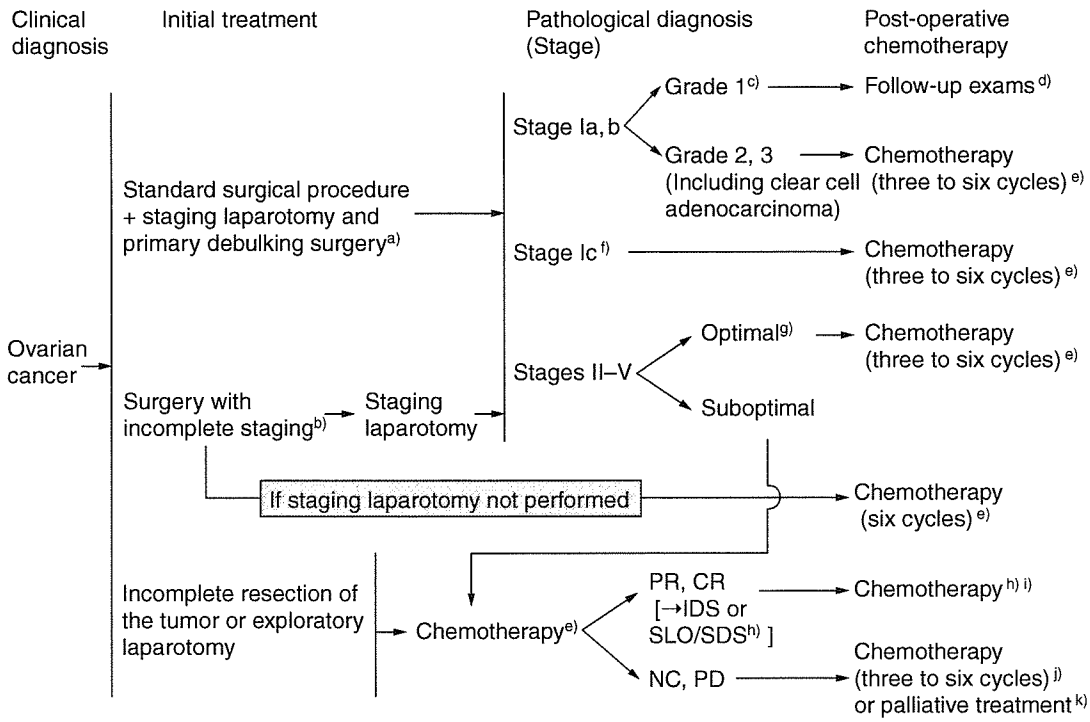
Data show the 5-year survival rate

FIGO, International Federation of Gynecology and Obstetrics; NS, not significant

Ⅱ Ovarian Cancer Treatment: Flowchart and Explanations

A. Treatment Flowchart

Modified from National Comprehensive Cancer Network (NCCN) Guidelines[1)]



CR, complete response; PR, partial response; NC, no change; PD, progressive disease; IDS, interval debulking surgery; SLO, second-look operation; SDS, secondary debulking surgery

B. Explanation of Flowchart: Selection of Treatment According to Stage

a) For an early stage cancer, an extensive systematic intraperitoneal inspection (staging laparotomy) is recommended, not only to ensure accurate staging, but also from the point of view of selecting cases in whom subsequent treatment can be omitted[2)~9)] **[II, A']**.

For an advanced cancer, in addition to the standard surgical procedure, a staging laparotomy and resection of intraperitoneal dissemination and metastasized lesions are performed. In cases where complete resection cannot be achieved, debulking surgery should be performed to minimize the lesion to an optimal size[10) 11)] **[II, A']**.

b) If close inspection was not performed at the initial surgery, reoperation (staging laparotomy) is advisable **[III, C]**.

If a reoperation is not performed, six cycles of adjuvant chemotherapy are given based on the assumption that a residual lesion remains **[III, B]**. As a general rule, it is advisable to reoperate for staging in order to omit adjuvant chemotherapy, even if a determination of stages Ia or Ib was made on the basis of findings of the initial surgery and a determination of grade 1 was made on the basis of pathological findings **[III, B]**.

Conversely, if the case is considered suboptimal because of the existence of suspected residual lesions at initial surgery, debulking surgery is performed with staging laparotomy during the reop-

eration. If reoperation is not performed, treatment should be given as for a suboptimal case [**III, A'**].

c) The degree of histological differentiation is classified as grade 1 through to grade 3, determined according to the increase in the proportion of solid growth within the adenocarcinoma as follows: grade 1, less than 5% solid growth; grade 2, 6%–50% solid growth; and grade 3, over 50% solid growth. However, FIGO,[12] the World Health Organization (WHO),[13] and GOG[14] have independently proposed their own classification systems and a standard classification system has not been established.[15) 16)] No classification system has been established for the differentiation of clear cell adenocarcinoma.

d) Presently, a follow-up examination without subsequent treatment is recommended for stages Ia and Ib, grade 1 [**II, A**]. Favorable prognoses have been reported in cases without subsequent treatment, not only for stage 1, but also stage 2, in which a thorough staging was performed and the tumor was confined to the ovary.[10) 17)~20)] Thus, the risk of recurrence is low for stages Ia and Ib.

e) Standard chemotherapy of paclitaxel + carboplatin concomitant therapy is performed [**II, A**].

f) The prognosis is considered to be worse for cases in which intraperitoneal cytological diagnosis is positive (Ic (1, 2)) or spontaneous capsular rupture(Ic (a)) has occurred[21)] than for stages I a or Ib. Conversely, opinions are divided regarding the prognostic effect of capsular rupture (Ic (b)) due to surgical manipulations. Some have reported an effect of capsular rupture on prognosis,[22)~24)] whereas others have not.[25)~27)] A standardized opinion has not been established [**III, B**].

g) In many cases, a condition is considered optimal when the largest residual tumor diameter is ≤ 1 cm after debulking surgery and suboptimal when the diameter is > 1 cm.

h) If a suboptimal case achieves clinical CR by standard chemotherapy, future chemotherapy may be omitted [**III, C**]. In the case of PR, SDS (refer to p.16) may be considered; however, subsequent chemotherapy follows salvage chemotherapy of recurrent ovarian cancer.

i) If IDS (refer to p.16) is performed, standard chemotherapy is performed. If clinical CR is achieved, maintenance chemotherapy is to be considered for some cases [**III, C**].

j) Follow with salvage chemotherapy for recurrent ovarian cancer.

k) Follow with palliative treatment for recurrent ovarian cancer.

Ⅲ Surgical Treatments

A. Indications for Surgery

First, whether a mass is tumorous or non-tumorous must be determined when the presence of ovarian mass is confirmed clinically on the basis of pelvic examinations or ultrasonography. In many cases, determination of a non-tumorous mass can be accomplished by diagnostic imaging and changes in the size of the mass during the menstrual cycle can be monitored. If the mass is determined to be tumorous, indications for surgery are considered. Differential diagnosis of malignancy or a benign tumor becomes important when considering indications for surgery. In any situation, when a tumor cannot be determined as being either malignant or benign, it is advisable to refer the patient to a tertiary medical institution where a rapid, intraoperative, pathological examination can be performed **[IV, A']**.

Remarks

1. With regard to tumor size, a patient in her reproductive years can be monitored by follow-up examinations for a tumor diameter up to 6–7 cm. However, a standard of 5 cm is appropriate for a post-menopausal patient.[1)~5)]
2. If tumor enlargement is observed during the course of periodic examinations, surgery should be considered.
3. Other characteristics of the tumor, in addition to size, should be determined using diagnostic imaging, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging[6)~8)] (MRI; advisable to be performed with contrast media). It is important to determine the presence of multilocularity, solid areas, ascites, and bilaterality from the diagnostic image.
4. Tumor marker values (Table 4) should be used as a reference to comprehensively determine whether the tumor is malignant or benign.[9) 10)]

Table 4 Histogenesis of an Ovarian Tumor and Selection of Tumor Markers

Core protein associated antigens	CA125, CA130, CA602
Sialyl Tn antigens	CA546, CA72-4, STN
Sialyl Lewis antigens	CA19-9, SLX
Embryonic protein	CEA
Others	GAT
Germ cell tumor	AFP, hCG, SCC, LDH
Sex cord stromal tumor	Estrogen, androgen, inhibin-A*

For a surface epithelial/stromal tumor, a combination of different types of markers is recommended.
*Not covered by insurance.
CA, carbohydrate antingen; STN, Sialyl Tn antigen; SLX, Sialyl Lewisx-i antigen; CEA, carcinoembryonic antigen; GAT, galactosyltransferase; AFP, α-fetoprotein; hCG, human chorionic gonadotrophin; SCC, squamous cell carcinoma; LDH, lactate dehydrogenase.

B. Objectives of Surgery

1. To make a definitive diagnosis of ovarian tumor and to determine whether the tumor is malignant or benign.
2. To determine the histological type and stage (surgical staging), if the tumor is malignant.
3. To completely resect or maximally resect the lesion (maximum debulking).
4. To obtain information for subsequent treatment.

The evidence level and the strength of the recommendations for the above points are **[III, A']**.

Remarks

Important clinical pathological prognostic factors for ovarian cancer are: (i) patient factors;[1)~6)] (ii) tumor factors; and (iii) treatment factors related to surgery and chemotherapy. Detailed examination of these factors has been undertaken with multivariate analyses. These factors are closely related to the surgical objectives. The following is a list of known prognostic factors for ovarian cancer.

Prognostic Factors for Ovarian Cancer

1. Among the factors relating to the tumor itself, stage is the most important factor that correlates with prognosis.[7)~10)]
2. Among the treatment factors relating to surgery, the degree of surgical completeness is especially important. Specifically, the post-operative diameter of the residual tumor affects the response to chemotherapy, patient quality of life (QOL), and mean survival time.[11)~16)] In many reports, surgery is considered optimal when the diameter of residual tumor is ≤ 1 cm.[17)]
3. Prognosis is poor for cases in which there is lymph node metastasis. However, prognosis is better in cases in which retroperitoneal lymph node dissection is performed and determination of stage IIIc is made solely on the basis of lymph node metastasis than when the determination is made on the basis of intraperitoneal dissemination.[15) 18)~22)]
4. In terms of histological type, mucinous adenocarcinoma and clear cell adenocarcinoma have low sensitivity to chemotherapy and a poor prognosis compared with other histological types.[11) 23)~28)]
5. The degree of histological differentiation (grade) is also an important prognostic factor and the lower the differentiation, the worse the prognosis. The degree of histological differentiation has particularly important significance in the prognosis of stage I tumors.[25) 26) 29) 30)]
6. The amount of ascites and the tumor mass at the start of treatment are significant prognostic factors for stage I tumors.[31)]

C. Definitions of Terms Relating to Surgical Procedures

Standard surgical procedures	Bilateral adnexectomy, hysterectomy, greater omentectomy
Staging laparotomy	Surgery that includes procedures necessary for the determination of stage
Exploratory laparotomy	Surgery that is limited to biopsy and minimal staging when tumorectomy of the primary lesion is difficult
Cytoreductive surgery	Total tumorectomy, including procedures for the maximal reduction of tumor mass
Primary debulking surgery	Total tumorectomy or maximal reduction of tumor mass at initial surgery
IDS (early stage tumor mass or size-reduction surgery)	Tumorectomy performed on the residual tumor after two to three cycles of chemotherapy have been effective 1. IDS performed after cytoreduction by neoadjuvant chemotherapy 2. IDS performed after cytoreduction by chemotherapy of the residual tumor remaining after initial surgery.
SDS (secondary tumor mass or size-reduction surgery)	Tumorectomy of the residual or recurrent tumor detected after initial planned chemotherapy 1. In cases where initial surgery was not performed 2. In cases where initial surgery was complete 3. In cases where residual tumor was present at the initial surgery
SLO	Surgery to determine the efficacy of post-operative chemotherapy and the time for its discontinuation in cases of clinical remission after initial surgery; tumorectomy of recurrence that is detected in this surgery is called SLO/SDS.

Cytoreduction is intended for the removal of malignant tumor cells and can be performed (i) via anticancer agents and radiation therapy; or (ii) via surgery

Debulking is intended for cytoreduction in cases where complete tumorectomy was not achieved by surgery; it involves limited surgery to reduce tumor size in order to increase the therapeutic effect of chemotherapy and radiation therapy

IDS, interval debulking surgery; SLO, second-look operation; SDS, secondary debulking surgery

Remarks

In these guidelines, the standard surgical procedures are those that are essential to achieve the surgical objectives. The terms 'cytoreduction' and 'debulking'[1) 2)] are used to mean primary and secondary tumor mass or size reduction. However, these definitions are not always in general use. In order to avoid confusion, it is important to use terms consistently. Therefore, the terms used in these guidelines have been defined.

D. Specific Surgical Procedures [IV, A']

Procedures included in standard surgery	Bilateral salpigo-oophorectomy, hysterectomy, greater omentectomy
Procedures included in staging laparotomy	Peritoneal cytological diagnosis, intraperitoneal biopsies, retroperitoneal (pelvic, para-aortic) lymph node dissection (or biopsy)
Procedure included in cytoreductive surgery	Resection of disseminated intraperitoneal lesions

Remarks

1. Greater omentectomy.[1)~5)]
   (1) Partial omentectomy: resection below the transverse colon.
   (2) Subtotal omentectomy: resection directly below the gastroepiploic vessels.
   (3) Total omentectomy: resection of the gastroepiploic vessels.
      a. No visible dissemination/metastasis (stages I and II): partial resection is acceptable. Because the frequency of metastasis to the greater omentum is reported to be approximately 10%, its examination is important.
      b. Dissemination/metastasis is suspected by visual inspection: subtotal omentectomy or total omentectomy is advisable. In some cases, this helps in the reduction of tumor size.
      c. Not optimal debulking (optimal debulking: 1 cm or less residual tumor); partial resection is acceptable[6)]
2. Peritoneal cytological diagnosis: a standard examination necessary for stage classification.
   (1) If ascites is present, collect a sufficient amount.
   (2) If ascites is not present, wash the entire intraperitoneal area using an adequate amount of physiological saline solution (200 mL or more) and collect the wash.
   (3) It is advisable to obtain exfoliative cytological diagnosis of tissues of the pelvic peritoneum, peritoneum in the right and left iliac fossa, and the undersurfaces of the diaphragm.
3. Retroperitoneal (pelvic, para-aortic) lymph node dissection or biopsy, extending from the pelvic lymph nodes to the para-aortic lymph nodes at the height of the renal veins.
   (1) The diagnostic significance of retroperitoneal (pelvic, para-aortic) lymph node dissection or biopsy in obtaining an accurate assessment of stage has been established.
   (2) There are no reports from clinical controlled studies indicating that retroperitoneal lymph node dissection contributes to prognostic improvement and its therapeutic efficacy is unknown.[7)~9)]
4. Intraperitoneal biopsies.[1) 2) 5) 10) 11)] A thorough examination of the pouch of Douglas, parietal peritoneum, surfaces of the diaphragm, the intestinal tract and mesenteric surfaces should be performed. Biopsies of suspicious lesions are advisable for an accurate diagnosis of stage.
5. Resection of the disseminated lesion. In some cases, peritoneal resection and/or partial resection of the intestinal tract are performed for the resection of dissemination/metastasis.
   (1) Resection of dissemination/metastasis.
   (2) Peritonectomy: resection of disseminated lesions with the peritoneum of the vesiscouterine pouch, iliac fossa, paracolic gutters, and/or the undersurface of the diaphragm.
   (3) Partial resection of intestinal tracts: partial resection should be considered as a proactive approach in cases where there is an invasion of the rectum at the pouch of Douglas, invasion of the sigmoid colon, and/or invasive adhesion of the small intestines.

6. Appendectomy.[12)~15)]
   (1) Detection of an abnormality by visual inspection: resection.
   (2) No abnormalities detected by visual inspection: significance of resection has not been established.

Additional Statements:

Metastatic rates to retroperitoneal lymph nodes (pelvic, para-aortic) in early stage cancer[16)~29)] are given in Table 5.

(1) The metastatic rate to lymph nodes was 5%–25% (mean~14%) for stage I cases in which systematic pelvic/para-aortic lymph node dissections were performed.
(2) The metastatic rates to retroperitoneal lymph nodes according to substages were 11.7% (stage Ia) and 11.5% (stage Ic). There were no significant differences in metastatic rates between these substages.
(3) Metastasis to contralateral lymph nodes: frequency is low.
(4) The frequency of retroperitoneal lymph node metastasis according to histological type and degree of differentiation was investigated and a high frequency was observed for a histological type of serous adenocarcinoma; a high frequency of retroperitoneal lymph node metastasis was observed in cases with a low degree of differentiation.

Table 5 Frequency of Lymph Node Metastasis for Stage pT1 Ovarian Cancer (Systematic PALA + PLA)

Reference	Year of publication	No. cases	Positive metastatic rate (%)	Positive rate according to substage (%)		
				Ia	Ib	Ic
DiRe[17)]	1989	128	12.5			
Pickel[10)]	1989	28	25.0	25.0	20.0	
Burghardt[20)]	1991	37	24.0			
Benedetti[18)]	1993	35	14.0			
Petru[21)]	1994	40	23.0			
Onda[22)]	1996	33	21.0			
Baiocchi[30)]	1998	242	13.2	12.0	14.7	13.6
Kanazawa[31)]	1999	44	11.4			
Sakuragi[28)]	2000	78	5.1	3.2	6.4	
Suzuki[29)]	2000	47	10.6	5.6	13.8	
Total		712	14.1	11.7 (29/247)		11.5 (13/113)

PALA, para-aortic lymphadenectomy, PLA: pelvic lymphadenectomy.

E. Cytoreductive Surgery Performed Depending on the Outcome of Chemotherapy

1. IDS: early tumor mass or size-reduction surgery
   The usefulness of IDS in lengthening the survival time is not necessarily clear[1) 2)~4)] **[II, C]**.
2. SDS: secondary tumor mass or size-reduction surgery
   If an optimal debulking is performed, prognostic improvement is possible. The most important aspect is the degree of completeness of SDS; that is, the reduction of the residual tumor diameter to a microscopic size[5)~12)] **[III, B]**.

Additional Statements:

(1) Two randomized controlled studies:

a. EORTC[13)]
   The evaluation of IDS effectiveness was reported for 425 cases classified as stages IIb–IV with residual lesions of > 1 cm at initial surgery. In this study, there were improvements in both the overall survival (OS) and progression-free survival (PFS) in cases of advanced ovarian cancer that were responsive to three cycles of cyclophosphamide + cisplatin. If the lesion is responsive to chemotherapy and if optimal debulking is possible, then improvement in the prognosis can be expected.

b. GOG152[3)]
   The usefulness of IDS was investigated by examining PFS and OS in 550 cases of stages III and IV ovarian cancer with suboptimal debulking at initial surgery. There were no significant differences in PFS and OS between the group that continued chemotherapy after paclitaxel + cisplatin and the IDS group.

The reason for these two contradictory results is that the EORTC study had many cases in stage IV with a large residual tumor diameter after initial surgery. The GOG study is different from the EORTC study in two ways: (i) the residual tumor diameter was small owing to a higher rate of prior maximum primary cytoreduction; and (ii) the chemotherapeutic regimen itself. Specifically, in the EORTC study, the initial diameter of the residual tumor was large; therefore, there may have been a greater contribution of IDS to the prognostic improvement after chemotherapy.

(2) Considerations for performing SDS.[5)~11) 14)]

a. Complete resection is presumed to be possible for a local recurrence.[10)]
b. The disease-free interval (DFI) or the progression-free interval (PFI) is > 6 months after the initial treatment.

F. Second-Look Operation (SLO)

1. Diagnostic significance:
   A useful measure for the early detection of recurrence **[III, B]**.
2. Effect on prognosis
   Many opinions consider the effect of SLO on prognosis questionable **[III, B]**.
3. SLO/SDS
   There is no consensus regarding whether debulking by SLO/SDS improves prognosis. There are reports indicating no effects of debulking by SLO/SDS on prognosis,[1)~8)] as well as reports of improvement in cases where debulking reduced the tumor to a microscopic size[9)~18)] **[III, C]**.

Remarks

The recommendation from the National Institutes of Health (NIH) indicates that SLO is a good method for most accurately assessing the state of disease, but there is a lack of any scientific evidence supporting its diagnostic and therapeutic significance. Therefore, at the present time, SLO can only be considered a research protocol and is not indicated for all cases.

In order to prevent confusion in the present guidelines, we define 'second-look operation' as a surgical procedure performed to determine the efficacy of post-operative chemotherapy and the time for its discontinuation in cases of clinical remission after the initial surgery (p.16). In addition, 'SLO/SDS' is defined as a surgery to resect a recurrence that is detected during the SLO procedure.

Additional Statements:

The following summarizes the opinions that question the effects of SLO on prognosis.

(1) The mean SLO positive rate in the early stages of cancer (I/II) is 13.2% and a very high rate of 59.8% has been reported in cases of advanced stages of cancer (III/IV).[2)~5) 12)~15) 18)~26) 31) 32)]

(2) The recurrence rate for SLO negative cases in the early stages of cancer is 20% (range 15%–62%)[3) 7) 11) 18) 20) 21)] and a high recurrence rate of 39% has been reported for cases in the advanced stages of cancer (range 17%–71%).[5) 7) 14) 15) 22) 24) 25) 27)~30)]

(3) There is no effective treatment for patients with a positive SLO and no obvious prognostic improvement has been seen after SLO.[1)~3)]

G. Endoscopic Surgery

1. The NIH consensus statement[1] indicates that endoscopic surgery cannot be considered safe and effective because of its insufficiencies. At least at the present time, endoscopic surgery is not considered a standard surgical procedure that can replace laparotomy **[IV, E]**.
2. However, endoscopic surgery may possibly replace laparotomy for the diagnosis of intraperitoneal lesions **[III, D]**.

Remarks

The following is a list of disadvantages of endoscopic surgery compared with laparotomy.

1. There is a possibility of being unable to accurately stage the ovarian cancer owing to difficulties in performing a detailed peritoneal examination.
2. There is a possibility of capsular rupture during surgical manipulations.
3. The only way to remove the tumor from the body is by aspiration. This is equivalent to iatrogenic capsular rupture, resulting in 'up-staging'.
4. There is a report of tocar port-site metastases.[2]
5. The possibility of an increase in tumor cells owing to pneumoperitoneum has been indicated.[3) 4)]

H. Surgical Procedures for Conservative Surgery in Cases in Whom the Preservation of Fertility is Desired [III, C]

Procedures included in the standard surgical procedures	Unilateral salpingo-oophorectomy, greater omentectomy
Procedures included in staging laparotomy	Peritoneal cytological diagnosis, biopsy of the contralateral ovary, intraperitoneal biopsies, retro-peritoneal (pelvic, para-aortic) lymph node dissection or biopsy

Remarks

1. Objective: preservation of fertility, determination of stage, and complete resection of the lesion.
2. Selection of surgical procedures: because the specifics of surgical procedures will be different for each case, it is necessary to obtain thorough informed consent. In stage Ia and well-differentiated or borderline tumors, pathological determination by rapid intraoperative pathology may be difficult, and resection of only the main lesion may be performed. Then, it is necessary to re-examine the surgical procedures for reoperation after confirming the results from permanent tissue sections.
3. Indications:
   (1) Clinical conditions for considering conservative surgery:
      a. The patient herself has a strong desire to have a child.
      b. The patient and her family have a deep understanding of the disease.
      c. Thorough informed consent can be obtained.
      d. Strict and long-term follow up is possible.
   (2) Pathologically necessary conditions for conservative surgery:
      a. Stage Ia with well-differentiated or borderline tumor,[1)~8)] except for clear cell adenocarcinoma.[9)]
      b. It has been reported that there is no difference in the prognosis of intraoperative capsular rupture for stage Ic [Ic (b) stages] and stage Ia.[10)]
      c. There is no consensus for cases of moderately differentiated tumor.[11)]
   (3) Adjuvant chemotherapy: presently, there is no consensus for cases that do not require adjuvant chemotherapy. However, NCCN and NIH recommend follow-up examination with no subsequent treatments for well-differentiated stages Ia and Ib.

Additional Statements:

Surgical Procedures:

(1) Intraperitoneal cytological diagnosis, unilateral adnexectomy, partial omentectomy.
Refer to the section on Specific Surgical Procedures.

(2) Biopsy of the contralateral ovary.[11)~14)]
a. Perform a biopsy of the contralateral ovary if an abnormality is detected by visual inspection.
b. The biopsy may be omitted if no abnormality is detected by visual inspection.
However, because it has been reported that the metastatic rate of the visually normal contralateral ovary is 12%,[14)] a prudent response is advisable.

(3) Retroperitoneal lymph node (pelvic･para-aortic) dissection or biopsy.
The diagnostic significance of the procedures has been established, but the therapeutic significance has not. With regard to the therapeutic significance of retroperitoneal lymph node (pelvic･para-aortic) dissection or biopsy, the only reports available are from a small number of cases; there is no firm evidence from any prospective randomized controlled study to support the omission of retroperitoneal lymph node dissection. However, retroperitoneal lymph node metastasis is very rare in well-differentiated stage Ia cases.[15)~18)] If there are no detectable swollen lymph nodes after careful palpation, many opinions suggest omitting retroperitoneal lymph node dissection.

Ⅳ Chemotherapy

A. Classification of Chemotherapy According to Objectives

Chemotherapy is effective against epithelial ovarian cancer. In general, many cases are of advanced cancer and recurrence is frequently seen, even in cases of early stage cancer. Therefore, many patients end up undergoing chemotherapy.

The classifications according to the objectives of chemotherapy and its timing are listed below:

Postoperative chemotherapy	
Remission-induction therapy	The objective is to achieve the absence (remission) of all lesions in cases with assessable or measurable lesions after the initial surgery.
Adjuvant chemotherapy	The objective is to improve the results of curative resection for cases with complete resection or optimal reduction of lesions during the initial surgery.
Pre-operative chemotherapy	
Neoadjuvant chemotherapy	The objective is to improve the curative resection rate and neoadjuvant chemotherapy is given before the initial surgery or after the exploratory laparotomy with a premise of performing IDS.
Maintenance chemotherapy	The objective is the long-term maintenance of remission. 1. Maintenance chemotherapy performed after achieving remission by remission-induction therapy (consolidation therapy). 2. Limited maintenance chemotherapy performed after adjuvant chemotherapy.
Salvage chemotherapy	Secondary chemotherapy, including experimental chemotherapy for cases that are resistant to standard chemotherapy.

B. Standard Remission-Induction Therapy and Adjuvant Chemotherapy

The standard chemotherapy for ovarian cancer is taxane and platinum concomitant therapy, typically paclitaxel and carboplatin concomitant therapy (TJ therapy) **[I, A]**.

TJ therapy
Paclitaxel 175–180 mg/m^2, i.v., Day 1 (infused over 3 h)
Carboplatin AUC = 5–6, i.v., Day 1 (infused over 1–2 h)
Every 3–4 weeks up to a total of three to six cycles*

*Refer to the Treatment Flowchart for the appropriate number of cycles.
AUC, area under the concentration–time curve (see below).

Remarks

Changes in standard remission-induction therapy and adjuvant chemotherapy.

1. After 1980, cisplatin was introduced into chemotherapy, and the usefulness of concomitant therapy with cyclophosphamide + doxorubicin + cisplatin (CAP) was established (GOG47[1]). Then, a comparative study of CAP and CP showed that there was no significant difference in the prognosis between the two types of therapy, but there were more adverse side-effects associated with CAP.[2] Therefore, treatment without doxorubicin, CP therapy, became the standard chemotherapy.[1) 2)]
2. Comparative studies of TP therapy (paclitaxel + cisplatin) and CP therapy showed that TP therapy was significantly better in terms of complete response rate and survival rate than CP therapy. With these benefits, TP therapy was established as a standard chemotherapy (Table 6).[3) 4)]
3. When comparing therapies with the platinum agents carboplatin and cisplatin, the antitumor effects are equivalent[5] but, in many cases, carboplatin is the therapy of choice owing to its lower toxicity and greater convenience.
   For example, clinical studies comparing TJ therapy and TP therapy showed no difference in their efficacy rate but, because of the lower toxicity associated with TJ therapy, this therapy became the main therapy[6)~8)] (Tables 7–9). A phase I study is currently being conducted in Japan investigating TJ therapy for Japanese patients.[9)~11)]
4. From the above, at present the first choice of standard chemotherapy as an initial therapy is paclitaxel (175–180 mg/m^2) + carboplatin (AUC 5–6) administered every 3–4 weeks for a total of six cycles. The administration of the paclitaxel dose is recommended to be accomplished over a period of 3 h.[12)]

Additional Statements:

(1) Paclitaxel is administered through an in-line filter with a membrane pore size of less than 0.22 μm. A drip infusion set that contains the plasticizer di (2-ethylhexyl) phthalate (DEHP) in areas that will come in direct contact with the paclitaxel solution should be avoided.

(2) The term 'AUC' above is used to refer to the area under the concentration–time curve. Refer to p.30 for the established doses of carboplatin.

5. The GOG157 study[13) 14)] examined the use of adjuvant chemotherapy for early stage cancer. The GOG157 study is a prospective phase III randomized, controlled study with subjects in stages Ic and II, poor differentiation or clear cell adenocarcinoma stages Ia and Ib. After complete surgery, subjects received three or six cycles of TJ therapy and the 5-year recurrence rates were compared between groups. The 5-year recurrence rates were found to be 27% and 19% for patients receiving three and six cycles of TJ therapy, respectively. Although the latter rate had decreased to approximately two-thirds of the former, the difference was not statistically significant. However, recently, two large-scale randomized, controlled studies (ICON1, EORTC-ACTION)[15)~17)] reported that adjuvant chemotherapy was useful against early stage cancer. Prospective phase III randomized, controlled studies were conducted with a patient group that received platinum-based adjuvant chemotherapy and another group receiving no adjuvant chemotherapy. The results showed significantly improved survival rates in the group receiving a platinum-based adjuvant chemotherapy agent compared with the group not receiving adjuvant chemotherapy.

   However, in the subgroups that received accurate staging, there was no difference in the prognosis between patients receiving platinum-based adjuvant chemotherapy and those not receiving adjuvant chemotherapy. To clarify this point, it is necessary to reconduct a randomized, controlled study with accurate staging.

Table 6 Cyclophosphamide + Cisplatin (CP Therapy) Versus Paclitaxel + Cisplatin (TP Therapy)

Authors (study)	Cases	Chemotherapeutic agents		Results
McGuire[3)] (GOG111)	Stage III–IV, 410 cases; residual tumor diameter > 1 cm	Cyclophosphamide cisplatin every 3 weeks ×6	750 mg/m^2, 75 mg/m^2	pCR: 31% PFS: 13 months OS: 24 monoths
		Paclitaxel cisplatin every 3 weeks ×6	135 mg/m^2 per 24 h, 75 mg/m^2	pCR: 51% PFS: 18 months OS: 38 months
Piccart[4)] (OV-10)	Stage IIb–IV, 680 cases	Cyclophosphamide cisplatin every 3 weeks ×6	750 mg/m^2, 75 mg/m^2	cCR: 27.3% PFS: 11.5 months OS: 25.8 months
		Paclitaxel cisplatin every 3 weeks ×6	175 mg/m^2 over 3 h, 75 mg/m^2	cCR: 40.7% PFS: 15.5 months OS: 35.6 months

pCR, pathological complete response; cCR, clinical complete response; PFS, progression-free survival; OS, overall survival.