Japan Society of Gynecologic Oncology Guidelines 2015 for Treatment of Ovarian Cancer including Primary Peritoneal Cancer and Fallopian Tube Cancer

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Abstract

The Guideline for Treatment of Ovarian Cancer including Primary Peritoneal Cancer and Fallopian Tube Cancer Version 2015 (4th edition) was edited and published by the Japan Society of Gynecologic Oncology. This guideline contains seven chapters and six flow charts. The major changes in this new edition are as follows: (1) The format has been changed from review to clinical questions (CQ), and the guidelines for optimal clinical practice in Japan are now shown as 41 CQs and answers. (2) The “flow charts" have been improved and placed near the beginning of the guideline. (3) The "basic points", including tumor staging, histological classification, surgical procedures, chemotherapy, and palliative care, have been described before the chapter. (4) FIGO surgical staging of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer was revised in 2014. Accordingly, this guideline has been revised to be compliant with the new version of this classifications. (5) Procedures for examination and management of hereditary breast and ovarian cancer (HBOC) have been described. (6) Information on molecular targeting therapy has been added. (7) Guidelines for treatment of recurrent cancer based on tumor markers alone have been described, as well as guidelines for providing hormone replacement therapy (HRT) after treatment.

Keywords: Guideline, Ovarian Cancer, Primary Peritoneal Cancer, Fallopian Tube Cancer, Japan Society of Gynecologic Oncology

Introduction

The number of patients with ovarian cancer is increasing in Japan and there were reported to be 8,631 patients in 2007 [1)]. Deaths due to ovarian cancer are also increasing and 4,705 patients died of this disease in 2011 [1)]. Ovarian cancer is the most common cause of death among malignant tumors of the female genital tract. Tumor stage is thought to be an important prognostic factor, with stage III and IV cancer having a poor prognosis [2)]. Since the ovary is a pelvic organ, an ovarian tumor may not cause any early symptoms, so approximately 40–50% of patients with ovarian cancer have stage III or IV disease (with a poor prognosis) at the time of first presentation [3)]. Thus, an important challenge is to improve the outcome of treatment in patients with advanced ovarian cancer.

In order to improve the prognosis of ovarian cancer and reduce regional differences of its management in Japan, the 1st edition of the Guideline for Treatment of Ovarian Cancer was edited and published by the Japan Society of Gynecologic Oncology in 2004. It has since been revised several times, and the 4th edition was published in April 2015. The new guideline has seven chapters and six flow charts. The major changes in this new edition are as follows:

(1) The format has been changed from a review format to a clinical question (CQ) format, so the guidelines for optimal clinical practice in Japan are now shown as 41 CQs and answers.

(2) The "flow charts" have been improved and have all been placed near the beginning of this guideline.

(3) As "basic points", descriptions of staging, histological classification, surgical procedures, chemotherapy, and palliative care have been included before the chapter.

(4) FIGO surgical staging of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer was revised in 2014. Therefore, this guideline has been revised to be compliant with the revised version of this classification.

(5) Procedures for examination and management of hereditary breast and ovarian cancer (HBOC) have been described.

(6) Information on molecular targeting therapy has been added.

(7) Guidelines for treatment of recurrent cancer based on tumor markers alone and for providing hormone replacement therapy (HRT) after treatment have been described.

Chapter 1 Overview

The aims of this guideline are to describe current optimal treatment for ovarian cancer (epithelial tumors, germ cell tumors, and sex cord stromal tumors), primary peritoneal cancer, and fallopian tube cancer, to reduce differences of management between medical institutions, to improve the safety of therapy and the prognosis, to reduce the burden (physical, mental, and economic) on patients by promoting optimal treatment, and to improve communication between patients and healthcare professionals.

Much of the evidence adopted in this guideline was obtained from clinical studies performed in Europe, the USA, and Japan. However, some evidence from Europe and the USA does not apply in Japan because of differences in background factors between Europe/USA and Japan. Conversely, some treatments used widely in Japan are uncommon in Europe and the USA. In such cases, the current consensus for disease management in Japan is prioritized in this guideline.

This guideline was created according to the principles of "evidence-based medicine", which is a standard method for producing clinical practice guidelines. The quality of evidence was evaluated by using the criteria shown in Table 1 [1, 2]. In addition, the grade of each recommendation in the guideline was determined by using the criteria set out in Table 2 [1–3].

Chapter 2 Epithelial ovarian cancer

Treatment of epithelial ovarian cancer is summarized as Flow chart 1 (Figure 1).

CQ 01

What is the optimal surgical procedure for ovarian cancer when the tumor seems to be localized to

the ovary?

Recommendations

(1) In addition to bilateral salpingo-oophorectomy + total hysterectomy + omentectomy, peritoneal cytology + pelvic / para-aortic lymph node dissection (biopsy) + biopsies from sites in the abdominal cavity are recommended (Grade B).

(2) When biopsies are obtained from sites in the abdominal cavity, sampling from the following sites should be considered: pouch of Douglas, parietal peritoneum, surface of the diaphragm, intestinal tract, mesentery, and suspected lesions (Grade C1).

CQ 02

What is the optimal surgical procedure for ovarian cancer that is thought to be stage II or more advanced stage preoperatively?

Recommendations

Maximal debulking surgery to accomplish complete resection (no gross residual tumor) is strongly recommended (Grade A).

CQ 03

Is interval debulking surgery (IDS) recommended for advanced ovarian cancer if primary debulking surgery (PDS) had a suboptimal outcome?

Recommendations

As a treatment option, IDS should be considered during chemotherapy for patients with advanced cancer if previous surgery had a suboptimal outcome (Grade C1)

CQ 04

What is the optimal management if a patient wishes to preserve fertility?

Recommendations

(1) Detailed informed consent about preservation of fertility is necessary (Grade A).

(2) As the basic operative procedure to preserve fertility, affected-side salpingo-oophorectomy + omentectomy + peritoneal cytology is recommended (Grade B).

(3) In addition to above-mentioned basic procedure, biopsy of the contralateral ovary, biopsy (dissection) of the pelvic / para-aortic lymph nodes, and biopsies from sites in the abdominal cavity should be considered as part of staging laparotomy (Grade C1).

CQ 05

Is risk-reducing salpingo-oophorectomy (RRSO) recommended for patients with the BRCA1 or BRCA2 gene mutation?

Recommendations

It is recommended that RRSO only be performed by a gynecologic oncologist who is a member of the Japan Society of Gynecologic Oncology in cooperation with a clinical geneticist at a medical facility with an established genetic counseling system and cooperative pathologists, after review and approval by the institutional ethics committee (Grade B).

CQ 06

Is laparoscope-assisted surgery possible?

Recommendations

(1) Currently, laparoscope-assisted surgery is not recognized as a standard procedure that can be substituted for laparotomy (Grade C2).

(2) However, in patients with advanced cancer, laparoscope-assisted surgery may be substituted for

laparotomy to observe the abdominal cavity and collect tissue samples (Grade C1).

CQ 07

For which patients is intraoperative rapid pathological examination recommended?

Recommendations

For patients in whom judgment among benign / borderline malignancy / malignancy is difficult based on preoperative evaluation and intraoperative findings, intraoperative rapid pathological examination is recommended for selecting the optimal surgical procedure (Grade B).

CQ 08

What is the recommended management of a patient in whom ovarian cancer is diagnosed after surgery?

Recommendations

Staging laparotomy (re-laparotomy) is recommended (Grade B).

CQ 09

What chemotherapy regimen is recommended as first-line therapy?

Recommendations

(1) Paclitaxel + carboplatin (conventional TC therapy) is strongly recommended (Grade A).

(2) Dose-dense TC therapy is also recommended (Grade B).

CQ 10

What chemotherapy regimens other than TC therapy are recommended as first-line therapy?

Recommendations

(1) Docetaxel + carboplatin (DC therapy) is recommended (Grade B).

(2) Cisplatin monotherapy or carboplatin monotherapy can be considered (Grade C1).

CQ 11

Which patients do not need postoperative chemotherapy?

Recommendations

It can be omitted for patients with stage I A / I B, Grade 1 disease confirmed by staging laparotomy (Grade B).

CQ 12

Should first-line chemotherapy be selected by considering tumor histology?

Recommendations

This is not recommended because there is insufficient evidence to show that standard treatment should be changed depending on tumor histology (Grade C2).

CQ 13

Is intraperitoneal chemotherapy recommended as the first-line therapy?

Recommendations

Intraperitoneal chemotherapy should be considered for patients with advanced cancer who have undergone optimal surgery (Grade C1).

CQ 14

Are neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) recommended for

advanced ovarian cancer if optimal surgery is thought to be impossible?

Recommendations

For patients with advanced cancer in whom it is thought that primary surgery will not result in an optimal outcome, preoperative chemotherapy and debulking surgery (NAC + IDS) are recommended as a treatment option (Grade B).

CQ 15

Is maintenance chemotherapy recommended after complete remission is achieved?

Recommendations

It is not recommended, because usefulness of maintenance chemotherapy has not been demonstrated (Grade C2).

CQ 16

What management approach is recommended if complete remission is not achieved by initial treatment?

Recommendations

Additional treatment (second-line chemotherapy and radiotherapy), participation in a clinical trial, or best supportive care (BSC) should be considered (Grade C1).

CQ 17

What is the recommended management of serious adverse events associated with chemotherapy?

Recommendations

Hypersensitivity reactions (HSR)

(1) Premedication should be provided because taxanes, such as paclitaxel, are associated with a risk of HSR (Grade A).

(2) When carboplatin causes HSR, premedication alone cannot reduce the risk of recurrence. Therefore, switching to another drug or desensitization therapy should be considered (Grade C1).

Gastrointestinal symptoms (nausea, diarrhea)

(1) For nausea, refer to the relevant guideline [7], and provide adequate antiemetic therapy (Grade A).

(2) For mild diarrhea, antidiarrheal agents should be administered orally. For severe diarrhea complicated by other symptoms, early aggressive treatment should be performed, such as fluid replacement and administration of an antibacterial agent (Grade A).

Myelosuppression / febrile neutropenia

Refer to the relevant guideline [8], and provide adequate treatment with an antibacterial agent and/or a granulocyte- colony stimulating factor (G-CSF) preparation (Grade A).

CQ 18

Are any molecular targeting drugs recommended as first-line therapy or as treatment for recurrence?

Recommendations

Bevacizumab should be considered in combination with chemotherapy and as subsequent maintenance therapy. However, careful patient selection and appropriate monitoring for adverse events are required when bevacizumab is used (Grade C1).

CQ 19

What is the optimal follow-up interval after treatment?

Recommendations

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

The above-mentioned intervals are only intended as a guide (Grade C1).

CQ 20

What examinations / tests should be performed for follow-up after treatment?

Recommendations

(1) Taking a history and performing and pelvic examination at every visit should be considered (Grade C1).

(2) Measurement of CA125, transvaginal ultrasonography, or CT scanning should be considered as required (Grade C1).

CQ 21

Is intervention for recurrence recommended if the patient only has elevation of CA125 without any symptoms?

Recommendations

Early intervention in response to elevation of CA125 alone is not necessarily recommended (Grade C2).

CQ 22

Is hormone replacement therapy (HRT) recommended?

Recommendations

After informing the patient about its merits and demerits, hormone replacement therapy (HRT)

should be considered carefully for individual patients (Grade C1).

Chapter 3 Borderline epithelial ovarian tumors

Treatment of borderline epithelial ovarian tumors is summarized as Flow chart 2 (Figure 2).

CQ 23

What is the optimal surgical procedure for borderline epithelial ovarian tumors?

Recommendations

(1) In addition to bilateral salpingo-oophorectomy + total hysterectomy + omentectomy + peritoneal cytology, detailed intra-abdominal examination is recommended (Grade B).

(2) If suspected peritoneal lesions are found by intra-abdominal examination, removing such lesions should be considered, or taking peritoneal biopsies from several sites should be considered if there are no suspected peritoneal lesions (Grade C1).

(3) For patients who wish to preserve fertility, in addition to salpingo-oophorectomy on the affected side + omentectomy + peritoneal cytology, detailed intra-abdominal examination should be considered (Grade C1).

CQ 24

What are the indications for chemotherapy and the recommended regimens?

Recommendations

For patients with gross residual tumor and patients with invasive peritoneal implants, performing postoperative chemotherapy with platinum agents and taxanes according to the treatment regimens for ovarian cancer should be considered (Grade C1).

CQ 25

What is important for follow-up after treatment of a borderline epithelial ovarian tumor?

Recommendations

In patients with borderline epithelial tumors, long-term follow-up for at least 10 years after treatment should be considered (Grade C1).

Chapter 4 Recurrent epithelial ovarian cancer

Treatment of recurrent ovarian cancer is summarized as Flow chart 3 (Figure 3).

CQ 26

What chemotherapy regimen is recommended for recurrence after a disease-free interval (DFI) of < 6 months?

Recommendations

Monotherapy that avoids cross-resistance to previous treatment is recommended (Grade B).

CQ 27

What chemotherapy regimen is recommended for recurrence after a disease-free interval (DFI) of ≥ 6 months?

Recommendations

Combination therapy including a platinum agent is strongly recommended (Grade A).

CQ 28

What are the indications and strategy for secondary debulking surgery (SDS) in patients with

recurrence?

Recommendations

(1) Whether or not SDS is worth performing should be carefully determined by evaluating the timing of recurrence, the primary surgical procedure, the site of recurrence, the number of lesions, and the performance status (PS) of the patient in a comprehensive manner (Grade C1).

(2) When SDS is performed, the objective should be complete resection of the tumor when possible (Grade C1).

CQ 29

What are the indications for radiation therapy in patients with recurrence?

Recommendations

(1) Radiation therapy should be considered in order to relieve symptoms, such as pain and bleeding (Grade C1).

(2) Radiation therapy should be considered for brain metastasis, not only to relieve symptoms, but also to prolong survival (Grade C1).

CQ 30

What is the recommended management strategy for intestinal obstruction and accumulation of ascites?

Recommendations

Intestinal obstruction

(1) Administration of octreotide is strongly recommended for nausea / vomiting (Grade A).

(2) Correcting physical obstruction by palliative surgery is recommended for relieving nausea / vomiting (Grade B).

(3) Administration of corticosteroids should be considered to relieve nausea / vomiting (Grade C1).

Accumulation of ascites

(1) In patients with terminal cancer whose life expectancy is estimated to be 1–2 months or less, the volume of infusion solution should be limited to ≤ 1,000 mL/day if the patient has pain due to accumulation of ascites (Grade C1).

(2) Taking the underlying pathological state into consideration, administration of diuretics, drainage of ascitic fluid (paracentesis), creation of a peritoneovenous shunt, and cell-free and concentrated ascites reinfusion therapy (CART) should be considered for relieving pain due to accumulation of ascites (Grade C1).

Chapter 5 Primary peritoneal cancer / Fallopian tube cancer

Treatment of primary peritoneal cancer or fallopian tube cancer is summarized as Flow chart 4 (Figure 4).

CQ 31

What is the optimal surgical procedure for primary peritoneal cancer?

Recommendations

Maximal debulking surgery to accomplish complete resection (no gross residual tumor) should be considered (Grade C1).

CQ 32

What chemotherapy regimen is recommended for primary peritoneal cancer?

Recommendations

(1) Either conventional TC therapy or dose-dense TC therapy should be considered (Grade C1).

(2) Neoadjuvant chemotherapy (NAC) should also be considered (Grade C1).

CQ 33

What is the optimal surgical procedure for fallopian tube cancer?

Recommendations

(1) According to the procedure for treating ovarian cancer, bilateral salpingo-oophorectomy + total hysterectomy + omentectomy are recommended together with peritoneal cytology + pelvic / para-aortic lymph node dissection (biopsy) + biopsies from sites in the abdominal cavity (Grade B).

(2) Maximal debulking surgery to accomplish complete resection (no gross residual tumor) is recommended for patients with advanced cancer (Grade B).

CQ 34

What chemotherapy regimen is recommended for fallopian tube cancer?

Recommendations

Conventional TC therapy or dose-dense TC therapy should be considered (Grade C1).

Chapter 6 Malignant ovarian germ cell tumors

Treatment of malignant ovarian germ cell tumors is summarized as Flow chart 5 (Figure 5).

CQ 35

What is the optimal surgical procedure for malignant ovarian germ cell tumors?

Recommendations

(1) For patients who wish to preserve fertility, in addition to salpingo-oophorectomy on the affected

side + omentectomy + peritoneal cytology, detailed intra-abdominal examination is recommended (Grade B).

(2) For patients who do not require preservation of fertility, according to the procedure for treating ovarian cancer, bilateral salpingo-oophorectomy + total hysterectomy + omentectomy are recommended together with peritoneal cytology, pelvic / para-aortic lymph node dissection (biopsy), and biopsies from sites in the abdominal cavity. However, lymph node dissection (biopsy) can be omitted (Grade B).

(3) For patients with advanced cancer, maximal debulking surgery to accomplish complete resection (no gross residual tumor) is recommended. However, lymph node dissection (biopsy) can be omitted (Grade B).

CQ 36

What postoperative treatment is recommended for malignant ovarian germ cell tumors?

Recommendations

Chemotherapy using bleomycin, etoposide, and cisplatin (BEP therapy) is strongly recommended (Grade A).

CQ 37

What treatment is recommended for recurrence of malignant ovarian germ cell tumors after first-line chemotherapy?

Recommendations

(1) Combination chemotherapy using cisplatin, such as a triple-drug combination of cisplatin with two other drugs (from among ifosfamide, etoposide, vinblastine, and/or paclitaxel), should be considered (Grade C1).

(2) Secondary debulking surgery (SDS) can be considered for some patients (Grade C1).

CQ 38

What should be kept in mind during follow-up after treatment of malignant ovarian germ cell tumors?

Recommendations

(1)You should be mindful that ovarian dysfunction may occur (Grade C1).

(2) When etoposide has been administered, you should consider that secondary cancer may occur (Grade C1).

Chapter 7 Malignant sex cord -stromal tumors

Treatment of malignant sex cord -stromal tumors is summarized as Flow chart 6 (Figure 6).

CQ 39

What is the optimal surgical procedure for malignant sex cord-stromal tumors?

Recommendations

(1) According to the procedure for treating ovarian cancer, bilateral salpingo-oophorectomy + total hysterectomy + omentectomy are recommended together with peritoneal cytology, pelvic / para-aortic lymph node dissection (biopsy), and biopsies from sites in the abdominal cavity. However, lymph node dissection (biopsy) can be omitted (Grade C1).

(2) For patients who wish to preserve fertility, in addition to affected-side salpingo-oophorectomy + omentectomy + peritoneal cytology, detailed intra-abdominal examination should be considered (Grade C1).

CQ 40

What postoperative treatment is recommended for malignant sex cord-stromal tumors?

Recommendations

(1) With regard to chemotherapy, a platinum-containing regimen should be considered (Grade C1).

(2) Radiotherapy should also be considered (Grade C1).

CQ 41

What is important during follow-up after treatment of malignant sex cord-stromal tumors?

Recommendations

Management should be performed according to the protocol for ovarian cancer. Additionally, long-term follow-up for at least 10 years after treatment should be considered for granulosa cell tumors (Grade C1).

Acknowledgments

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Guideline for Treatment of Ovarian Cancer including Primary Peritoneal Cancer and Fallopian Tube Cancer 2015 (4th edition)

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Table 1. Criteria for evaluating the quality of evidence (levels of evidence)

Level I	Evidence from meta-analyses of multiple randomized controlled trials
Level II	Evidence from randomized controlled trials, or evidence from well-designed nonrandomized controlled trials
Level III	Evidence from well-designed quasi-experimental studies, or evidence from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
Level IV	Expert committee reports and opinions, or clinical experiences of respected authorities

Table 2. Grading of recommendations

Grade A	The proposed treatment is strongly recommended. In principle, there is at least one source of Level I evidence showing efficacy of the treatment.
Grade B	The proposed treatment is recommended. In principle, there is at least one source of Level II evidence showing efficacy of the treatment.
Grade C1	The proposed treatment may be considered. However, there is not enough scientific evidence. (Or the treatment may have efficacy, although sufficient scientific evidence has not been obtained.) There are multiple sources of Level III evidence showing efficacy of the treatment and the outcomes are roughly consistent.
Grade C2	There is not enough scientific evidence, and the treatment is not recommended in routine clinical practice.
Grade D	The treatment is not recommended (usefulness or efficacy have not been shown, and the treatment may rather be harmful).

611 Figure legends

612

613 Figure 1. Flow chart 1 Treatment of epithelial ovarian cancer

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615 Figure 2. Flow chart 2 Treatment of borderline epithelial ovarian tumors

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617 Figure 3. Flow chart 3 Treatment of recurrent epithelial ovarian cancer

618

619 Figure 4. Flow chart 4 Treatment of primary peritoneal cancer and fallopian tube cancer

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621 Figure 5. Flow chart 5 Treatment of malignant germ cell tumors

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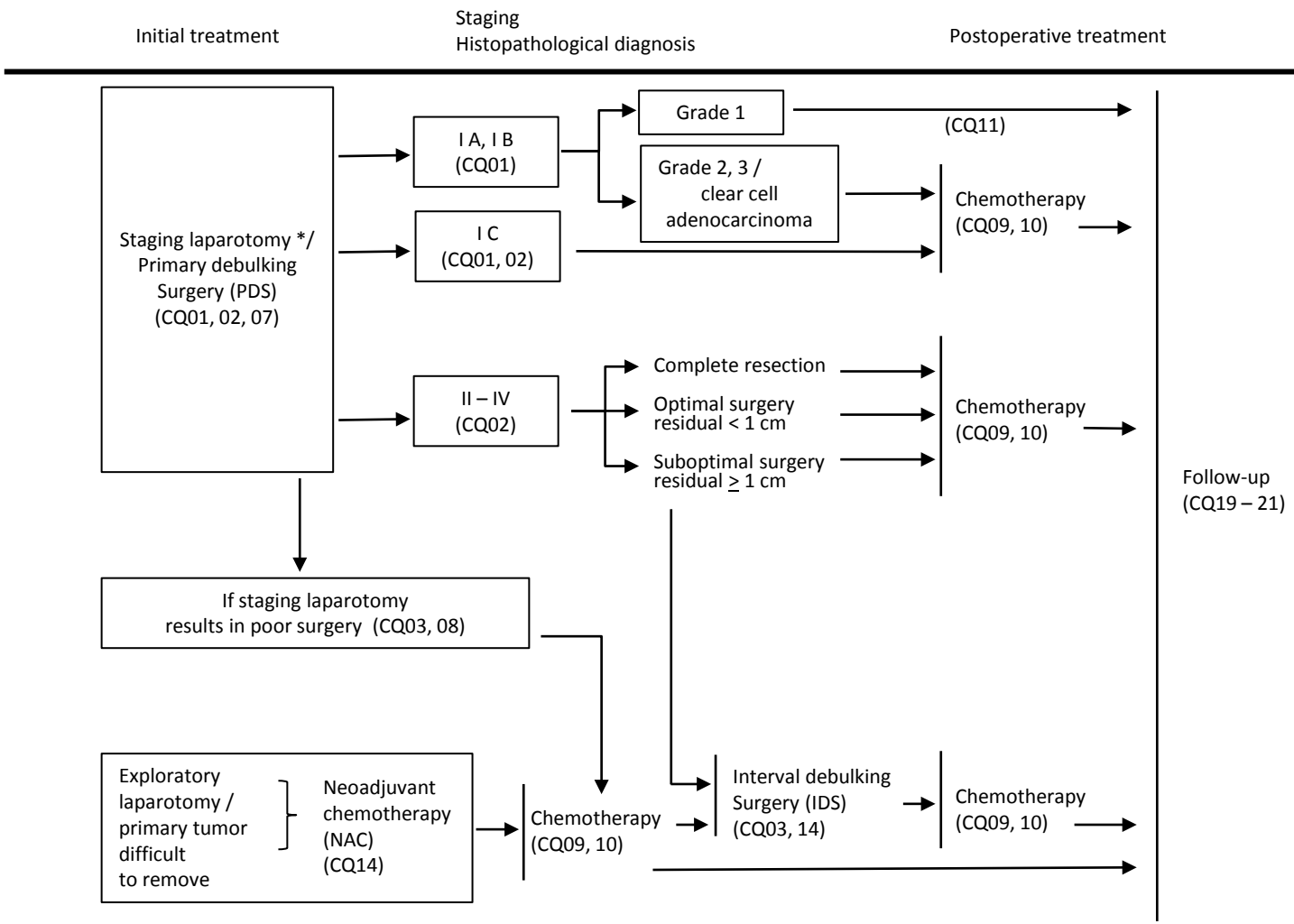
623 Figure 6. Flow chart 6 Treatment of malignant sex cord-stromal tumors

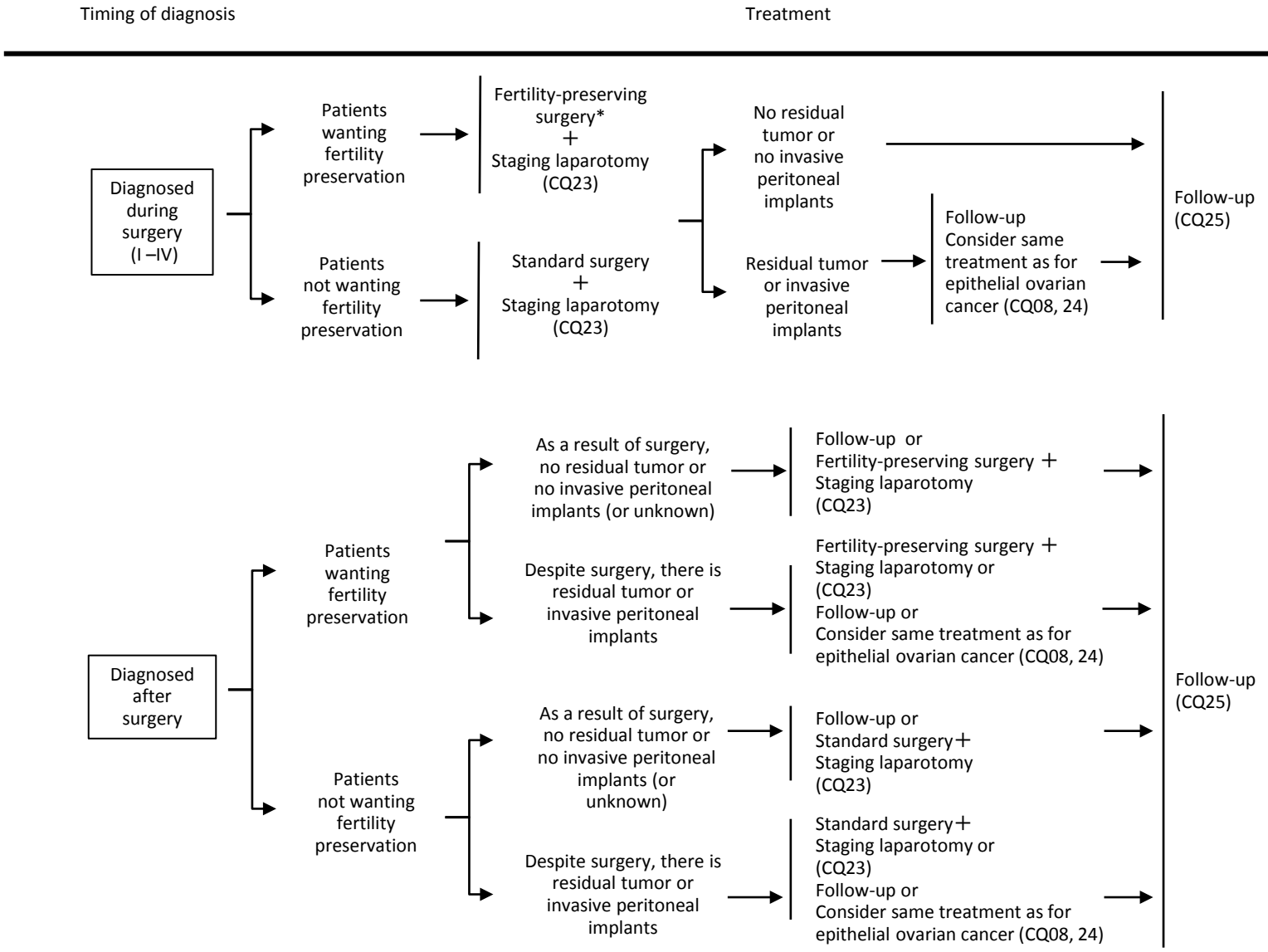
Flow chart 1
Treatment of epithelial ovarian cancer



* Staging laparotomy: bilateral salpingo-oophorectomy + total hysterectomy + omentectomy + peritoneal cytology + pelvic / para-aortic lymph node dissection (biopsy) + biopsies from sites in the abdominal cavity

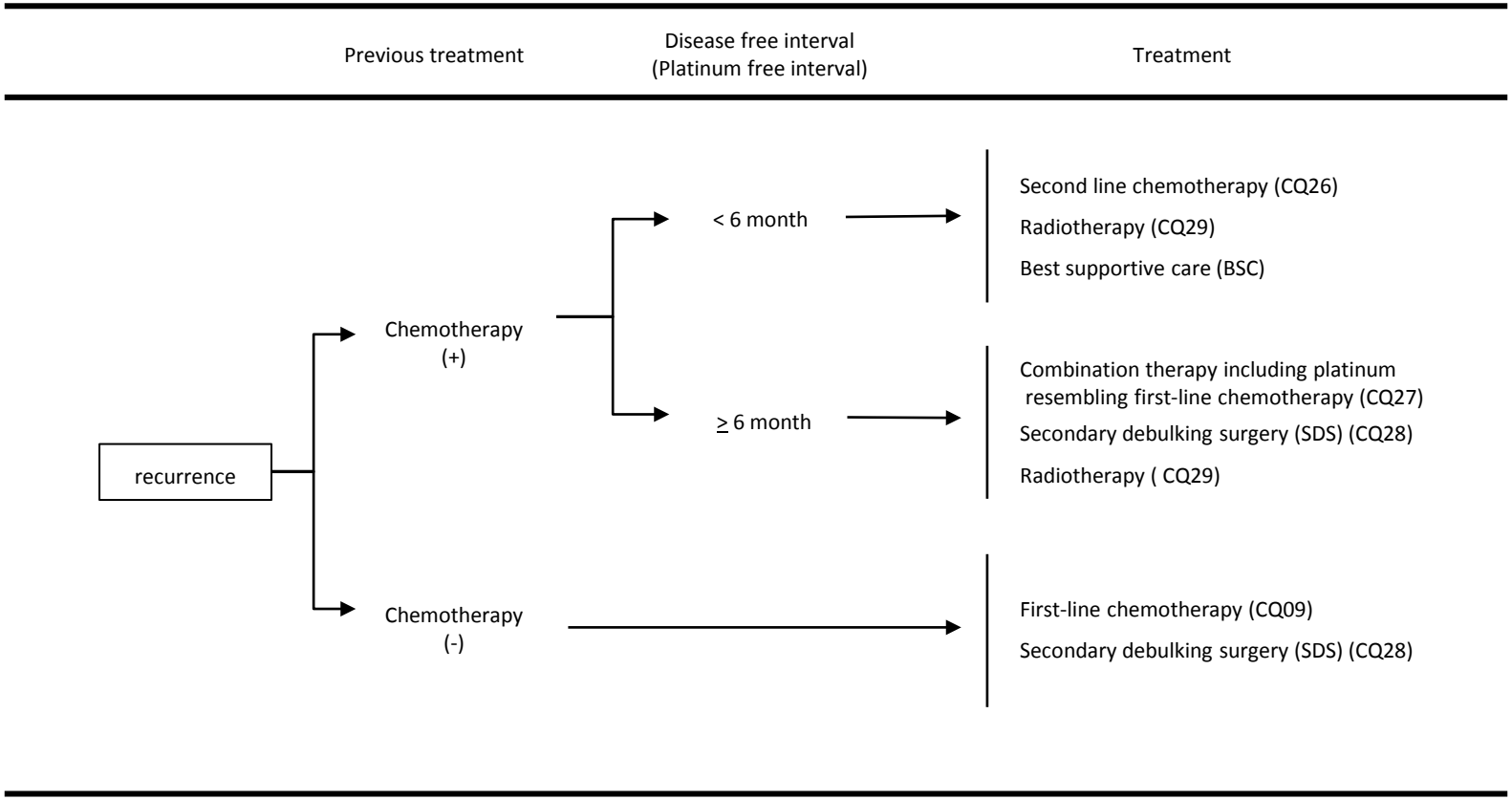
Flow chart 2

Treatment of borderline epithelial ovarian tumors

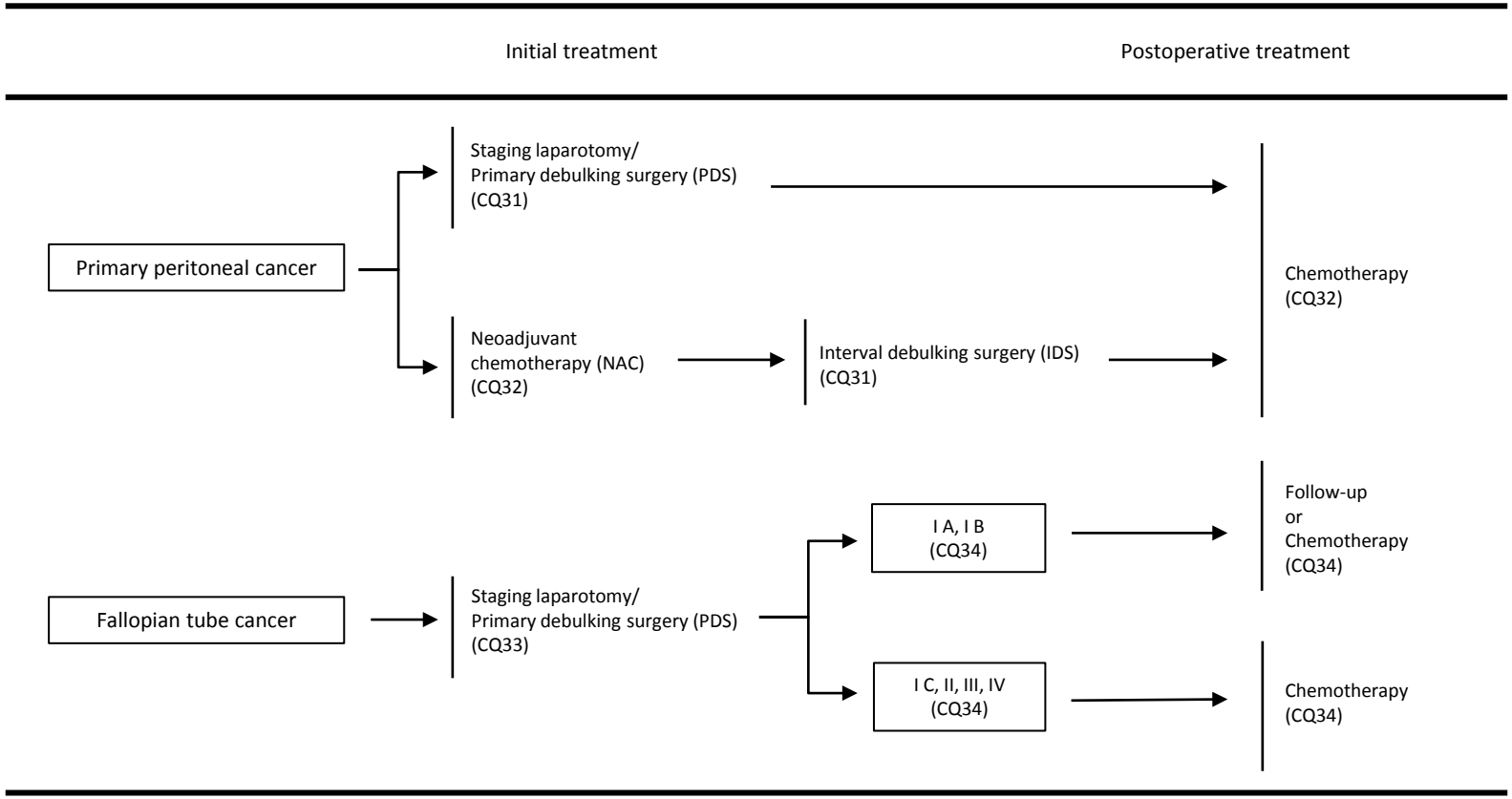


* Fertility-preserving surgery : affected-side salpingo-oophorectomy + omentectomy + peritoneal cytology + detailed intra-abdominal examination

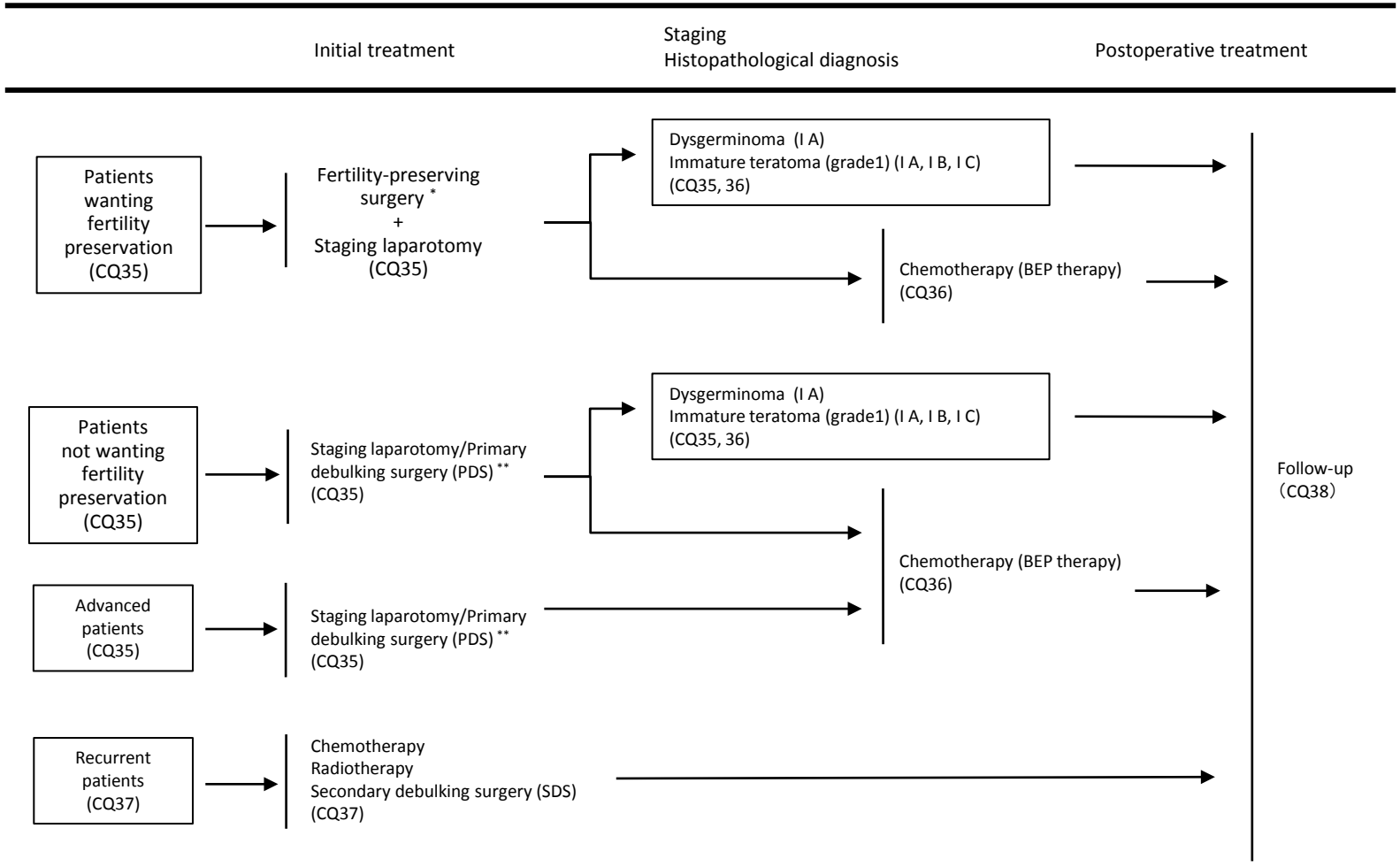
Flow chart 3
Treatment of recurrent epithelial ovarian cancer



Flow chart 4
Treatment of primary peritoneal cancer and fallopian tube cancer

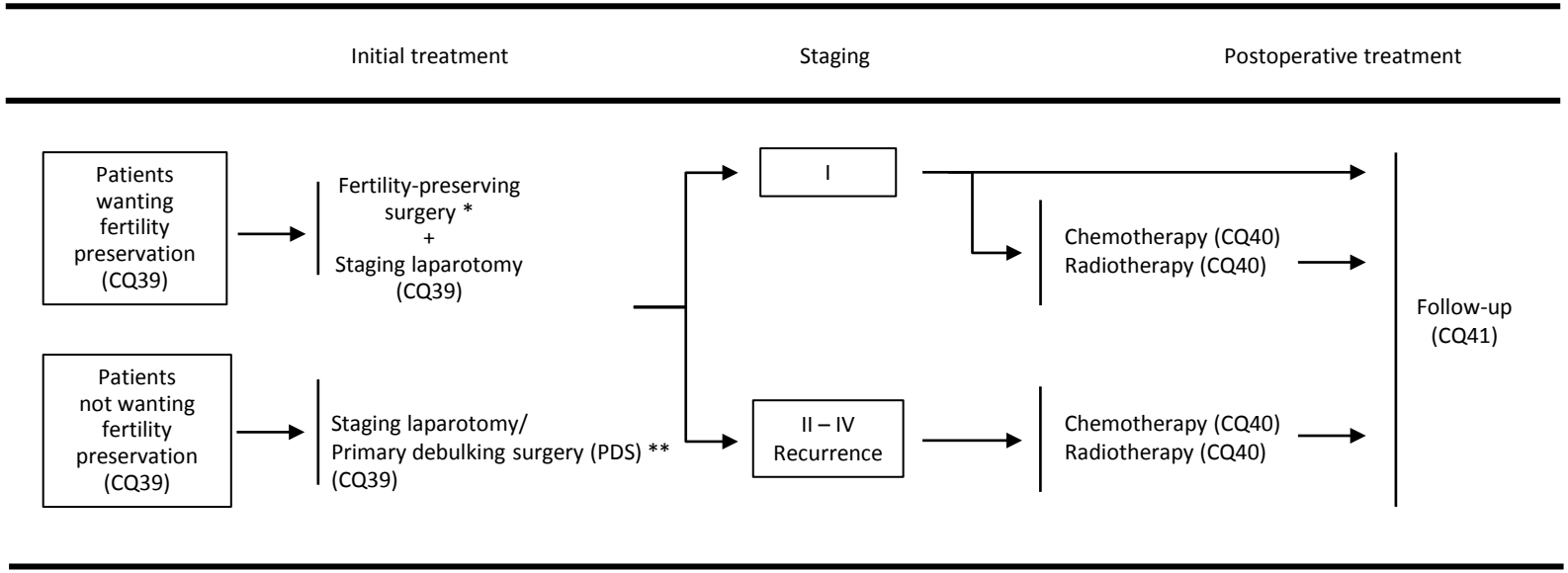


Flow chart 5
Treatment of malignant germ cell tumors



* Fertility-preserving surgery : affected-side salpingo-oophorectomy + omentectomy + peritoneal cytology + detailed intra-abdominal examination
** Lymph node dissection (biopsy) can be omitted.

Flow chart 6
Treatment of malignant sex-cord stromal tumors



* Fertility-preserving surgery : affected-side salpingo-oophorectomy + omentectomy + peritoneal cytology + detailed intra-abdominal examination
** Lymph node dissection (biopsy) can be omitted.