Treatment Guidelines for
Uterine Body Cancer
2006 Edition

Edited by
Japan Society of Gynecologic Oncology

Translated by
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Preface

In recent years, the incidence of endometrial cancer has been steadily increasing in Japan, in all age groups of adult women. Accordingly, the Japan Society of Gynecologic Oncology (JSGO) undertook the creation of "Treatment Guidelines for Uterine Body Cancer," which followed the creation of the "Ovarian Cancer Treatment Guidelines." There are a number of outstanding issues regarding cancer of the uterine body. Evidence is scarce, and the level of evidence low, for treatment modalities for uterine body cancer such as surgery and postoperative adjuvant therapy. There are differences in the surgical procedures selected between Japan and Western countries. In Western countries, radiotherapy is the mainstay of postoperative adjuvant therapy, whereas in Japan it is more frequently chemotherapy. Evidence from Western countries cannot therefore be applied directly into recommendations for Japan. Due to the abovementioned issues, we have taken great care and spent considerable time in the descriptions and the creation of these guidelines, which are finally ready for publication.

The aim of these guidelines is to standardize the treatment of uterine body cancer. The treatments herein recommended are currently considered best practice, and consensus has been obtained among clinicians routinely involved in the investigation and treatment of uterine body cancer. Through their use, we anticipate that the quality of treatment of uterine body cancer will equalize, resulting in improvements in treatment safety and outcomes. These guidelines are provided as reference for investigation and treatment, and they are not intended to restrict the choice of treatment modalities. In actual clinical practice, the treatment method should be selected at the discretion of the clinician, using these guidelines for reference, after considering the individual case and the preferences of the patient and their family. Our aim for these guidelines does not include its use in medical practice disputes or litigation. The content of these guidelines are the responsibility of the JSGO, however, treatment results are the responsibility of the treating clinician who is directly involved in patient treatment.

In creating these guidelines, a Guidelines Formulation Committee and Evaluation Committee were established within the Guidelines Examination Committee, as was the case for the "Ovarian Cancer Treatment Guidelines." The Formulation Committee was assembled by gathering together surgeons from all over Japan who specialize in the treatment of uterine body cancer, as well as radiotherapists and gynecological oncologists. Whereas the "Ovarian Cancer Treatment Guidelines" were presented in a review format, the present guidelines are presented in a "Q&A format" in which problems in the treatment of body cancer are presented and answers provided. This format was chosen because there is only a limited body of evidence, of a low level, concerning the treatment of uterine body cancer, and treatment in Japan and Western countries differences in several important ways. The target diseases of these guidelines are primary cancer of the uterine body, atypical endometrial hyperplasia, and recurrent tumors. The 5 algorithms contained in these guidelines are mainly related to treatment of these target diseases, with each section written in a "Q&A format." The presenting problems associated with cancer of the uterine body are formulated as clinical questions (CQs). For each CQ, an exhaustive collection of literature from Japan and overseas was gathered. A structured abstract was created for each article and evaluated as evidence. After thorough evaluation, we provided comprehensively determined responses to the CQs in the form of concise recommendations. In addition, we set out the background and objectives related to the CQs, and how the recommendations were determined, in the explanation section. At the end, we added references with notation of their evidence levels. For the evidence levels

and the grades of recommendations, to maintain consistency we used the same classifications as those in the “Ovarian Cancer Treatment Guidelines”.

A draft version of the present guidelines was examined by the Guidelines Evaluation Committee and then reviewed by the JSGO. Thereafter exhaustive prolonged discussions were held by the relevant specialists at the consensus meetings, and the modified guidelines were presented to all members of the JSGO. Through this process, we received many useful suggestions. In addition, the guidelines were presented to the Japanese Gynecologic Oncology Group (JGOG), the Japan Association of Obstetricians and Gynecologists, and the Japan Society of Obstetrics and Gynecology. Opinions were gathered from these organizations as well, and their approval obtained. Final approval was obtained at the board of directors meeting of the Japan Society of Gynecologic Oncology held this summer, and we are now able to publish these guidelines.

As with the “Ovarian Cancer Treatment Guidelines,” it is our hope that the present guidelines will be utilized fully in clinical practice. We plan to revise this book every 3 years, so we would like to receive continuing critiques and advice from many people.

Finally, we would like to express our deep gratitude to the doctors in the Guidelines Formulation Committee, including Committee Vice Chairman Dr. Nobuo Yaegashi and Subcommittee Chairmen Dr. Masamichi Hiura and Dr. Noriaki Sakuragi, for their commitment and tremendous unstinting efforts. We would also like to thank the staff of the editing department of Kanehara Shuppan for their efforts, and the people at the office of the Japan Society of Gynecologic Oncology for overseeing the collection and organization of large volumes of manuscripts.

September 2006

Formulation Committee of the Uterine Body Cancer Treatment Guidelines,
Japan Society of Gynecologic Oncology

Chairman Yasuhiro Udagawa, M.D.

Chapter 4 ■Post-treatment Follow-up

Overview

CQ24 What intervals are recommended for post-treatment follow-up?
CQ25 Is determination of serum CA125 and CA19-9 levels useful in post-treatment follow-up?
CQ26 Are pelvic examination and vaginal vault smears useful in post-treatment follow-up?
CQ27 Are plain chest radiography and other diagnostic imaging methods useful in post-treatment follow-up?

Chapter 5■Treatment of Advanced and Recurrent Cancer

Overview

CQ28 When is surgery indicated for clinical stages III and IVa?
CQ29 What are the therapeutic benefits of cytoreductive surgery for patients with macroscopic extrapelvic and intra-abdominal spread?
CQ30 Are preoperative chemotherapy and radiotherapy useful?
CQ31 When is surgery indicated for recurrent cancer?
CQ32 Is chemotherapy useful for advanced and recurrent cancer?
CQ33 Which regimens are recommended for chemotherapy in advanced and recurrent cancer?
CQ34 Is radiotherapy useful for recurrent and inoperable advanced cancer?
CQ35 Is progesterone therapy useful for advanced and recurrent cancer?

Chapter 6 ■Fertility-Preserving Treatment

Overview

CQ36 Is progesterone therapy useful for patients with well-differentiated endometrioid adenocarcinoma who request fertility preservation?
CQ37 What treatments are recommended for recurrent cases of well-differentiated endometrioid adenocarcinoma after fertility preservation therapy?
CQ38 What are the adverse effects of progesterone therapy and their associated risk factors?
CQ39 Is induction of ovulation safe in fertility-preserved patients?
CQ40 What intervals are recommended for follow-up after fertility-preserving treatment? What examinations and investigations should be performed?

Chapter 7 ■Atypical Endometrial Hyperplasia

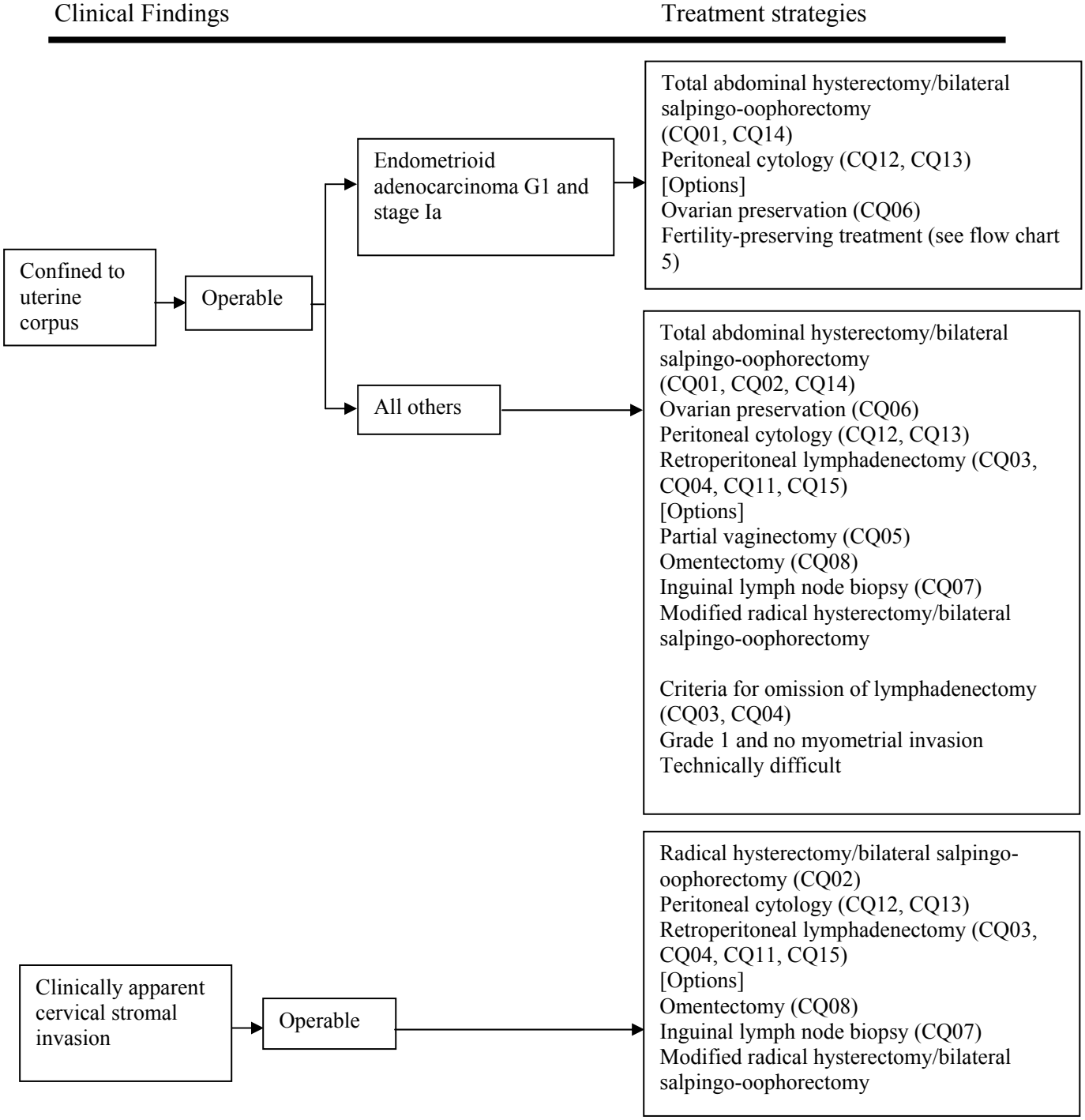
Overview

CQ41 If fertility-preserving treatment is to be performed for atypical endometrial hyperplasia:
(1) Is progesterone therapy useful?
(2) What intervals are recommended for follow-up, and what examinations and investigations should be performed?

Chapter 8 ■Data Report

Flow Chart 1

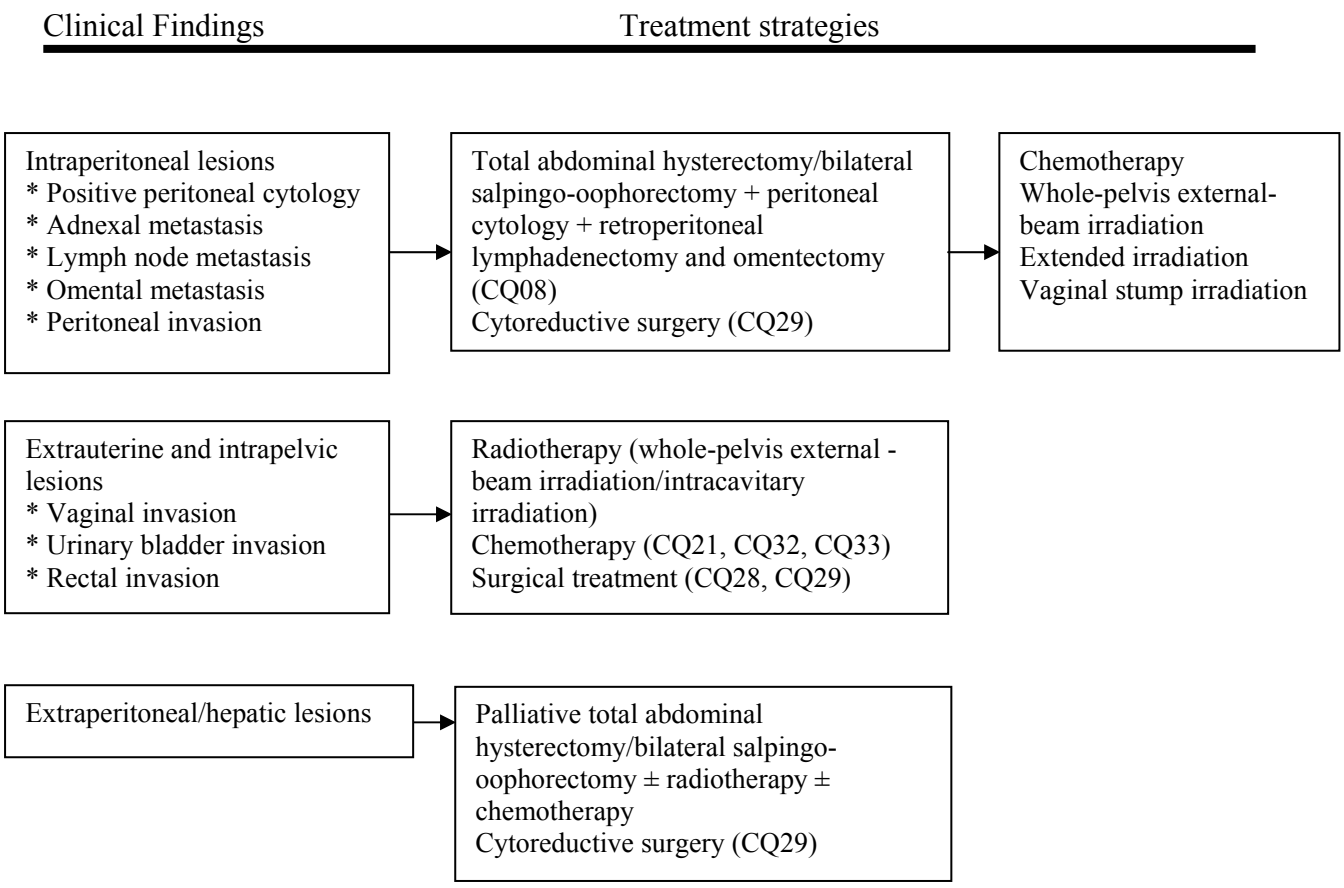
Initial Treatment: Clinical Stages I and II



* Radiotherapy or chemotherapy is performed for inoperable patients.
* Staging is based on the clinical findings.
* CQ: Clinical question

Flow Chart 2

Initial Treatment: Clinical Stages III and IV

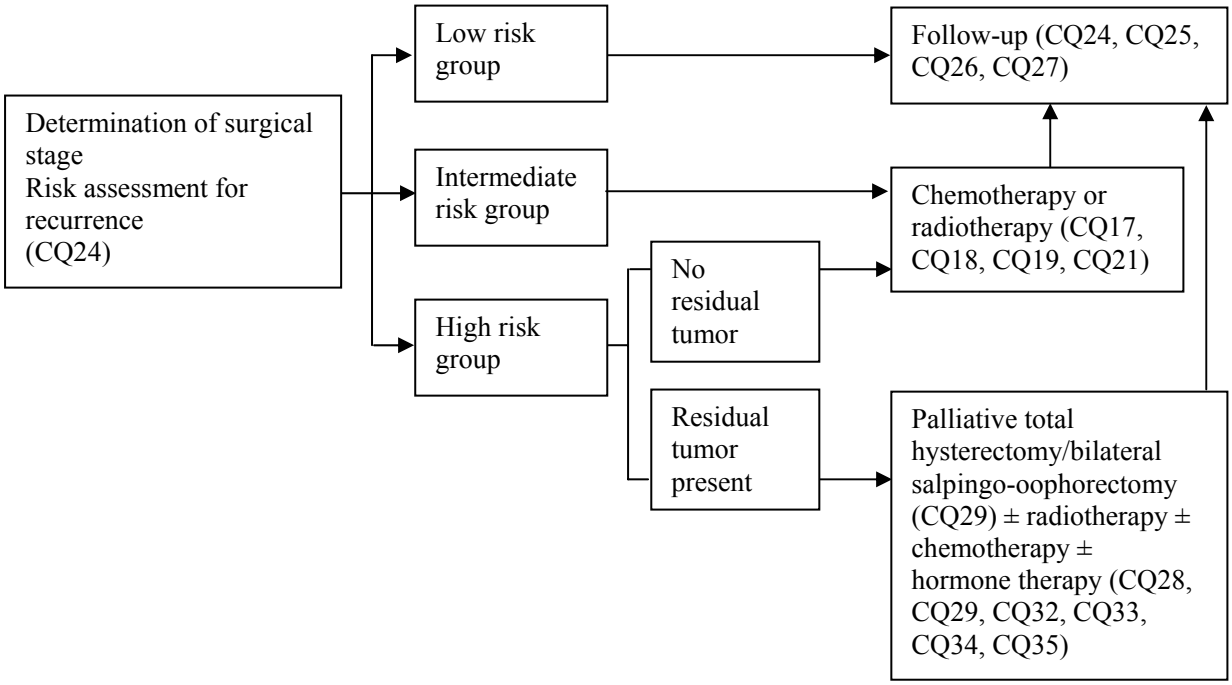


* Patients with extraperitoneal/hepatic lesions can present with symptoms such as hemorrhage. Accordingly, palliative total abdominal hysterectomy is sometimes performed.

Flow Chart 3

Treatment after Surgery for Uterine Body Cancer

Postoperative histopathological findings | Treatment strategies



* Patients with positive peritoneal cytology are classified as stage IIIa in the surgical staging. However, if there are no other predictive factors associated with a poor prognosis other than positive peritoneal cytology, or there are no findings of extrauterine spread, it has been reported that positive peritoneal cytology is not a predictive factor associated with a poor prognosis (CQ12). If there are predictive factors associated with a poor prognosis, other than positive peritoneal cytology or spread to an extrauterine site, in addition to positive peritoneal cytology, the risk for distant metastatic recurrence, including intraperitoneal recurrence, is increased. Positive peritoneal cytology is therefore a factor for poor prognosis. Other prognostic factors are evaluated, and then the appropriate postoperative treatment is selected.

* Radiotherapy or chemotherapy are often performed as adjuvant therapy for the high risk group. However, there is insufficient evidence for their utility, and there is a need for clinical trials with patient participation. See CQ17, CQ18, CQ19, and CQ21.

Table 1：Classification of Postoperative Recurrence Risk of Uterine Body Cancer (see p 56)

Low risk group:
Endometrioid adenocarcinoma G1 or G2 and ≤1/2 myometrial invasion
No cervical invasion
Negative peritoneal cytology
No venous or lymphatic invasion
No distant metastasis

Intermediate risk group:
Endometrioid adenocarcinoma G3 and ≤1/2 myometrial invasion
Endometrioid adenocarcinoma and >1/2 myometrial invasion
Cervical invasion
Positive peritoneal cytology (see CQ12)
Venous or lymphatic invasion
Serous adenocarcinoma, clear cell adenocarcinoma, or undifferentiated carcinoma
No distant metastasis

High risk group:
Spread to the uterine adnexae, serosa, or cardinal ligament
Invasion of the vaginal wall
Pelvic or para-aortic lymph node metastasis
Vesical or rectal invasion
Peritoneal dissemination
Distant metastasis

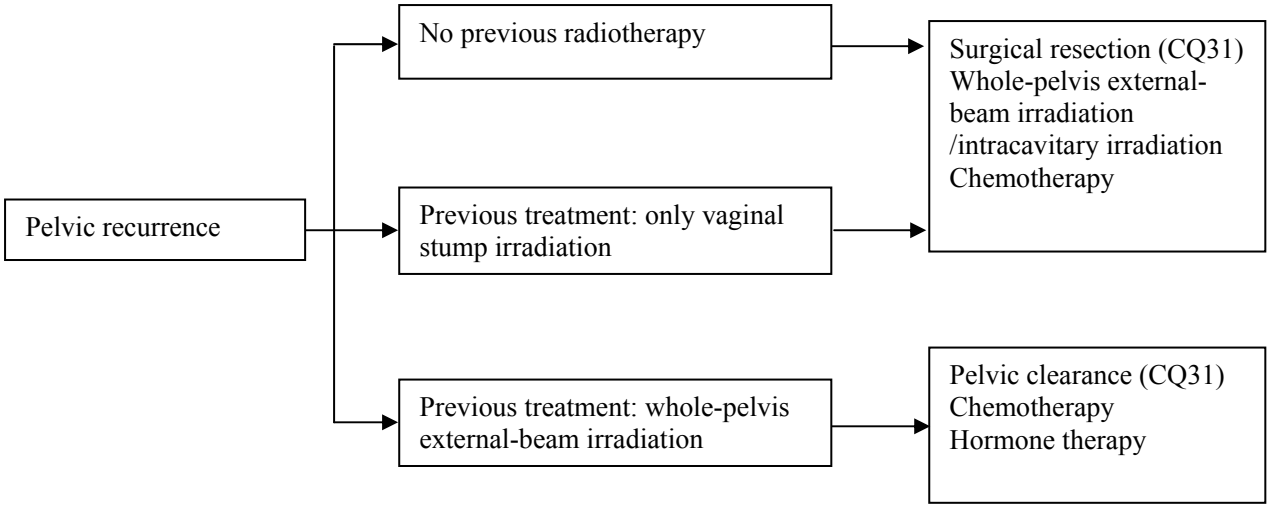
Extracted from reference 1 (with some modifications)

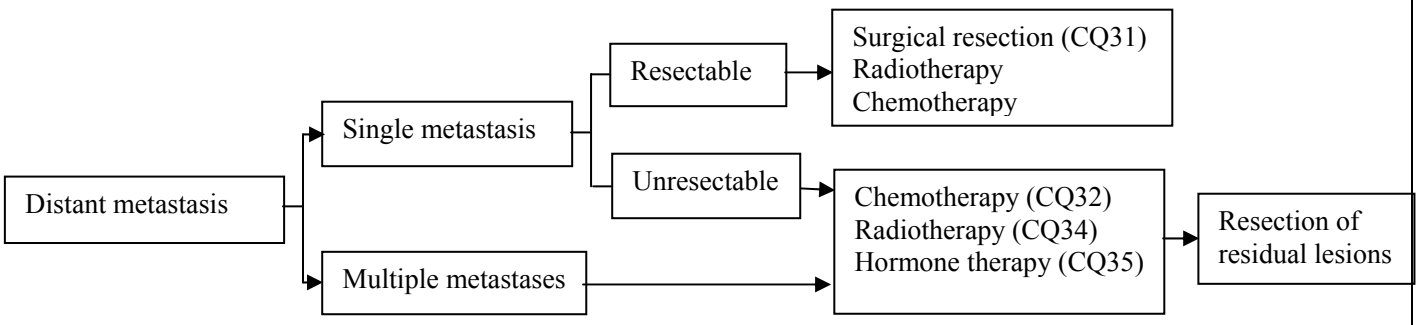
1) Lurain JR. Uterine cancer. In: Berek JS ed. Novak's Gynecology 13th ed. Philadelphia: Lippincott Williams & Wilkins, 2002, pp 1143-7. (Level III)

Flow Chart 4

Treatment of Recurrent Cancer

Clinical Findings | Treatment strategies



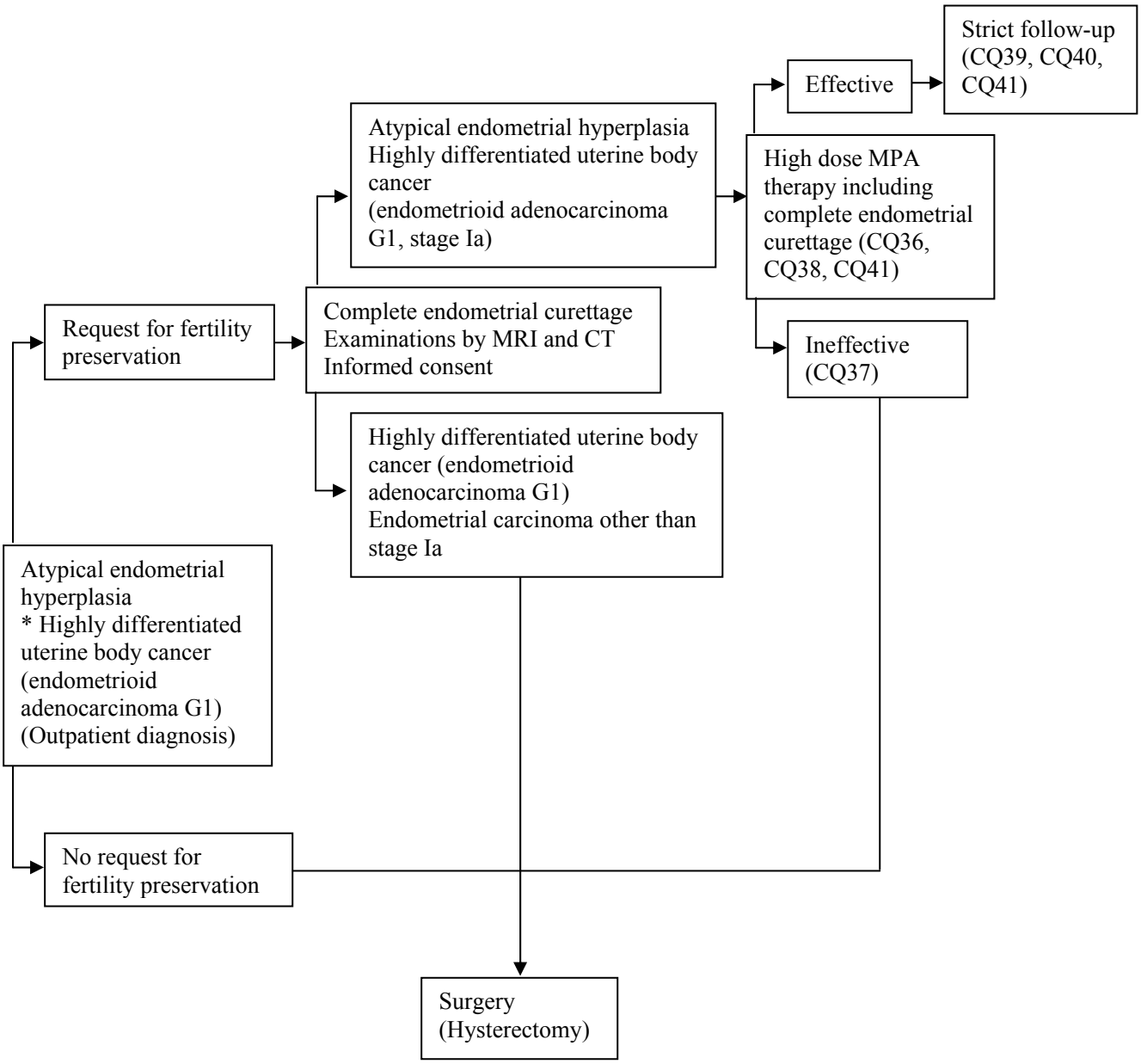


* Surgical resection is sometimes performed for patients with multiple metastases if resectable.

Flow Chart 5

Strategies for Fertility-Preserving Treatment
Atypical Endometrial Hyperplasia and Highly Differentiated Uterine Body Cancer (Endometrioid Adenocarcinoma G1)

Clinicopathological Findings | Treatment strategies



Chapter 1 ■Overview of Guidelines

I. Objectives

A. To describe treatment methods presently considered appropriate for uterine body cancer
B. To reduce the differences in treatment levels of uterine body cancer between institutions
C. To improve safety and outcomes for treatment of uterine body cancer in Japan
D. To reduce the personal and financial burden on patients by performing appropriate treatment
E. To help establish mutual understanding between health care providers and patients

Comments:

In these guidelines, one set of standard treatments is shown to aid in the selection of treatment for uterine body cancer. However, the purpose of these guidelines is not to restrict the use of treatments not mentioned in this book.

II. Targets

The targets of these guidelines are medical practitioners who are routinely involved in the investigation and treatment of uterine body cancer.

III. Responsibility

A number of associated organizations provided support in the creation of these guidelines. However, the Japan Society of Gynecologic Oncology assumes the responsibility for content of these guidelines. The final decision of whether to apply these guidelines should be made by the user, i.e. the clinician directly in charge of treatment who is responsible for the results of treatment.

IV. Target Diseases

The target diseases of these guidelines are primary cancer of the uterine body, atypical endometrial hyperplasia, and recurrent tumors.

V. Basic Policy in Creating the Guidelines

A. To create these guidelines, the Guidelines Formulation Committee and Evaluation Committee were independently established within the Committee for Treatment Guidelines for Uterine Body Cancer. The initial draft was created after a thorough evaluation. Opinions from within and without the Japan Society of Gynecologic Oncology were incorporated into the final draft. The guidelines were published after their approval by the Japan Society of Gynecologic Oncology.
B. These guidelines were created in accordance with the principles of “Evidence-Based Medicine”, considered to be the international standard method for creating clinical practice guidelines.
C. Searches were performed of data and literature published up until May 2005 in Japan and overseas, and evidence was collected.

D. The quality of the collected evidence was evaluated using the criteria of the Japan Society of Clinical Oncology and its Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents (Table 2).

E. The strength of the recommendations in our guidelines was determined by the "recommendation criteria" of the Japan Society of Clinical Oncology and its Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents (Table 3).

F. In general, each section comprises a CQ (clinical question), recommendations, background, objectives, explanations, and references.

G. Much of the evidence was obtained from clinical trials in Western countries, and our guidelines also used much overseas evidence. However, even if the evidence is of a high quality in Western countries, it is difficult to apply it in Japan as is, due to differences in backgrounds between Japan and Western countries. In addition, methods used commonly in Japan can differ from methods used in Western countries. In case of a conflict, the general consensus in Japan sometimes took priority, even if evidence of as high quality as that from overseas was not available.

H. Even if a treatment method was recommended based on evidence which was evaluated to be of high quality from a global viewpoint, there may be problems in its application under the Japanese medical insurance system. This type of problem could not be avoided in creating our guidelines. In principle, we applied the basic understanding of this problem gained at the time of creating the "Clinical Practice Guidelines for the Use of Anticancer Agents" of the Japan Society of Clinical Oncology (see notes).

Notes

1. Clinicians using these guidelines must be cognizant of their position as "health insurance medical practitioners", and must respect the indicated diseases in the approval conditions for use of anticancer drugs in their medical practice.
2. In medical practice, if there are differences between our guidelines and the indicated diseases in the approval conditions for anticancer agents, the clinician should treat their patients in accordance with the patient's condition, at the clinician's discretion.
3. When using an anticancer drug as monotherapy, the dosage and method of administration must satisfy the approval conditions established by the Japanese Pharmaceutical Affairs Law.
4. When using a combination of anticancer agents, the dosage and method of administration of each anticancer agent must satisfy the approval conditions established by the Japanese Pharmaceutical Affairs Law.

   (Excerpt from the "Clinical Practice Guidelines for the Use of Anticancer Agents" of the Japan Society of Clinical Oncology)

VI. Revision

A. These guidelines will be revised as needed in accordance with advances in medical science.

B. The Guidelines Formulation Committee will collect evidence newly reported after the production of the present guidelines, create a database, and evaluate the quality of each piece of evidence. Necessary revisions will be made based on this database. If adverse events occur during the use of the present guidelines, the Guidelines Formulation Committee will collect this information and include it in the next revision.

C. The revised draft will be presented to the Guidelines Evaluation Committee for examination.

D. The opinions of the following associated academic societies and study groups will be fully incorporated in the revisions: Japan Society of Obstetrics and Gynecology, Japan Society of Clinical Oncology, Japanese Gynecologic Oncology Group (JGOG), and Japan Association of Obstetricians and Gynecologists.

E. The Committee for Treatment Guidelines for Uterine Body Cancer will produce a final revised draft, and revisions will be made after approval at the annual meeting of the Japan Society of Gynecologic Oncology.

VII. Publication

A. These guidelines will be published in booklet form to gain widespread use.
B. These guidelines are also published on the website of the Japan Society of Gynecologic Oncology.

Table 2. Evidence Quality Evaluation Criteria (Levels of Evidence)

Ⅰ	Evidence from meta-analyses of multiple randomized controlled trials, or evidence from multiple randomized controlled trials
Ⅱ	Evidence from at least 1 randomized controlled trial, or evidence from multiple well-designed controlled studies without randomization
Ⅲ	Evidence obtained from at least one other type of well-designed quasi-experimental study, or evidence obtained from well-designed, non experimental descriptive studies, such as comparative studies, correlation studies, and case studies
Ⅳ	Expert committee reports or opinions and/or clinical experiences of respected authorities

Excerpt from the criteria of the Japan Society of Clinical Oncology Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents (modified in parts)

Table 3. Recommendation Criteria (Grades)

A	Evidence of Type I or consistent findings from multiple studies of Type II, III, or IV
B	Evidence of Type II, III, or IV and generally consistent findings
C	Evidence of Type II, III, or IV but inconsistent findings
D	Little or no systematic empirical evidence

A'. No clear evidence found but considered "common knowledge in clinical oncology"
E. No clear evidence found, but consensus of the committee

Excerpt from the criteria of the Japan Society of Clinical Oncology Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents

Note: Grade for negative recommendation
When there is sufficient evidence for a negative recommendation, Grade A or B is used even if it is a negative recommendation (for example: CQ12, CQ19, CQ23).