

## Evidence-based guidelines for treatment of cervical cancer in Japan: Japan Society of Gynecologic Oncology (JSGO) 2007 edition

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**Abstract** Clinical practice guidelines for gynecologic cancers have been published by the National Comprehensive Cancer Network and the National Cancer Institute. Whereas these guidelines form the basis for the standard of care for gynecologic malignancies in the United States, it has proven difficult to institute them in Japan due to differences in patient characteristics, health-care delivery systems, and insurance programs. Therefore, evidence-based guidelines for treating cervical cancer specifically in

Japan have been under development. The Guidelines Formulation Committee and Evaluation Committee were independently established within the Committee for Treatment Guidelines for Cervical Cancer. Opinions from within and outside the Japan Society of Gynecologic Oncology (JSGO) were incorporated into the final draft, and the guidelines were published after approval by the JSGO. These guidelines are composed of ten chapters and comprise three algorithms. Each chapter consists of a

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clinical question, recommendations, background, objectives, explanations, and references. The objective of these guidelines is to clearly delineate the standard of care for cervical cancer treatment in Japan in order to ensure equitable care for all Japanese women diagnosed with cervical cancer.

**Keywords** Uterine cervical cancer · Clinical practice guidelines · Surgery · Chemotherapy · Irradiation

## Introduction

### Guideline objectives

Cervical cancer is the second most common cancer among women worldwide. The mortality rate of uterine cervical cancer in Japan decreased from the 1960s through 1995; however, its incidence among women between the ages of 20 and 40 has dramatically increased despite implementation of screening programs [1]. In 1999, the National Cancer Institute (NCI) issued a clinical alert that concurrent

chemoradiotherapy (CCRT) should be considered the standard of care over radiotherapy alone for women with cervical cancer. These guidelines were adopted, and CCRT is now routinely used in the United States [2]. In contrast, many stage IIb cervical cancer patients in Japan are treated by radical hysterectomy. Compared with the United States, chemotherapy agents covered by health insurance is restricted in Japan. For these reasons, clinical practice guidelines tailored for the current Japanese situation have been requested. As there is limited reliable evidence regarding the use of surgery, neoadjuvant therapy, and postoperative adjuvant therapies for cervical cancer in Japan, many clinical questions (CQs) remain unanswered. The objective of these guidelines is to clearly delineate the standard of care for cervical cancer treatment in Japan to ensure equitable care for all Japanese women diagnosed with cervical cancer.

### Basic policies in creating the guidelines

To create these guidelines, the Guidelines Formulation Committee and Evaluation Committee were independently established within the Committee for the Treatment Guidelines for Cervical Cancer. The initial draft was created after a thorough evaluation of opinions from within and outside the Japan Society of Gynecologic Oncology (JSGO) prior to incorporating them into the final draft. The guidelines were published after approval by the JSGO. These guidelines were designed in accordance with the principles of evidence-based medicine, considered internationally to be the standard method for creating clinical practice guidelines. Searches were performed of data and literature published prior to May 2005 in Japan and overseas, and evidence was collected. This collected evidence was evaluated for quality 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 1). Strengths of the recommendations in our guidelines were also 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 2).

Much of the evidence evaluated for use in the guidelines was obtained from clinical trials conducted in both Europe and the United States. Whereas the trials were all of high quality, their findings were often not applicable in Japan due to differences in patient characteristics, health-care delivery systems, and insurance programs. In addition, the most commonly used treatment methods differed between the Western countries. In the Japanese guidelines, we took this into account by having generally accepted treatment modalities take precedence over the evidence published from the United States and Europe.

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**Table 1** Evidence quality evaluation criteria (levels)

I. Evidence from meta-analyses of multiple randomized controlled trials, or evidence from multiple randomized controlled trials
II. Evidence from at least one 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, nonexperimental descriptive studies, such as comparative studies, correlation studies, and case studies
IV. Expert committee reports, or opinions and/or clinical experiences of respected authorities

**Table 2** 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

Grade for negative recommendation: When there is sufficient evidence for recommending negatively, grade A or B is used, even if it is a negative recommendation [for example: clinical question (CQ) 19]

## Algorithms

These guidelines comprise the three algorithms shown in Figs. 1, 2, and 3:

## Summary of recommendations

In general, each chapter consists of a CQ, recommendations, background, objectives, explanations, and references. This article summarizes these guidelines in a Q & A format. Recommendations from each chapter are listed below under their respective chapter titles. Background, objective, explanations, and references are available through the JSGO Web site (<http://www.jsgo.gr.jp/>.)

### Chapter 1: Overview of guidelines

### Chapter 2: Stage 0 disease

**CQ01.** What is the optimal surgical procedure for stage 0 disease?

**Recommendations:** (1) A cervical cone biopsy is recommended (grade B). (2) A total hysterectomy should be considered for patients who do not desire fertility preservation (grade C).

**CQ02.** What treatments are recommended for recurrence following conservative treatment?

**Recommendations:** (1) For recurrence following laser cone biopsy or loop electrosurgical excision procedure (LEEP), the same procedure should be repeated or a total hysterectomy considered, depending on the patient (grade B). (2) For recurrence following laser ablation or cryotherapy, either a cone biopsy or a total hysterectomy is recommended (grade B).

### Chapter 3: Stage Ia disease

**CQ03.** What treatments are recommended for stage Ia1 disease?

**Recommendations:** (1) A total hysterectomy without pelvic lymphadenectomy is recommended for patients with no evidence of vascular infiltration, lymphatic infiltration, or confluent invasion (grade B). (2) Both a modified radical hysterectomy and pelvic lymphadenectomy are sometimes performed for patients with vascular infiltration, lymphatic infiltration, or local invasion (grade C). (3) For patients who strongly desire fertility preservation, the uterus may be preserved by performing a cervical cone biopsy only in patients with no vascular or lymphatic infiltration, no local invasion, negative resection margins, and negative histological results from endocervical curettage (grade B).

**CQ04.** What treatments are recommended for stage Ia2 disease?

**Recommendation:** A modified radical hysterectomy or a more extensive procedure with lymphadenectomy is recommended for stage Ia2 disease (grade C).

**CQ05.** What treatments are recommended if the disease is up-staged to stage Ib or higher advanced disease following total hysterectomy?

**Recommendation:** Adjuvant radiotherapy is recommended (grade C).

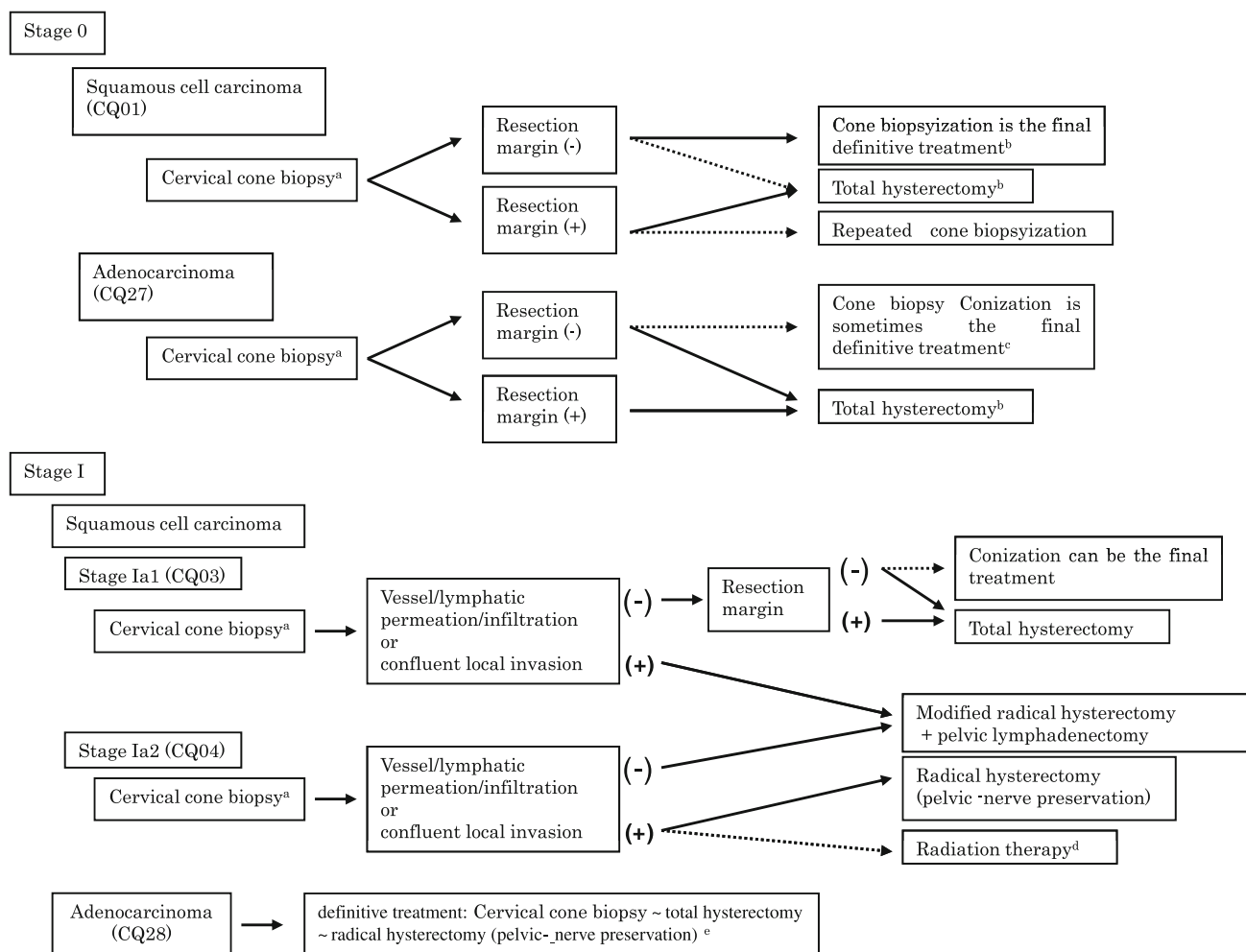
### Chapter 4: Stage Ib and stage II disease

**CQ06.** What surgical procedures are recommended for stage Ib–II disease?

**Recommendation:** A radical hysterectomy is recommended (grade A').

**CQ07.** What is the significance of pelvic nerve preservation in radical hysterectomy?

**Recommendation:** Pelvic nerve preservation is significant to the extent that it does not decrease the curativeness of radical hysterectomy (grade B).



**Fig. 1** Treatment for stage 0–Ia disease. For the diagnosis of stage 0–Ia disease, the cone biopsy may be omitted in technically challenging cases, including postmenopausal atrophy. However, hysterectomy appropriate for the provisionally diagnosed lesion should be performed after a complete evaluation of the preoperative cytology, colposcopy, and biopsy results. **a** Endocervical curettage should be performed at the time of cone biopsy. **b** Total hysterectomy should be considered in patients who do not desire fertility

preservation. **c** Caution is required with uterine preservation, as residual lesions are reportedly found in approximately 20% of patients with negative resection margins. **d** Radiotherapy is an option in the National Comprehensive Cancer Network (NCCN) treatment guidelines for cervical cancer. **e** Surgical procedures should be individualized considering the histopathological findings of the cone biopsy specimens, i.e., degree of invasion, vascular and lymphatic infiltration, and local invasion

**CQ08.** Is ovarian preservation possible in a radical hysterectomy?

**Recommendation:** NAC has not been shown to improve outcomes (grade C).

**Recommendations:** (1) Ovarian preservation is possible without compromising curativeness if appropriate case selection is performed (grade B). (2) If the ovaries are to be preserved, ovarian transposition and fixation outside of the pelvic radiation field should be performed (grade C).

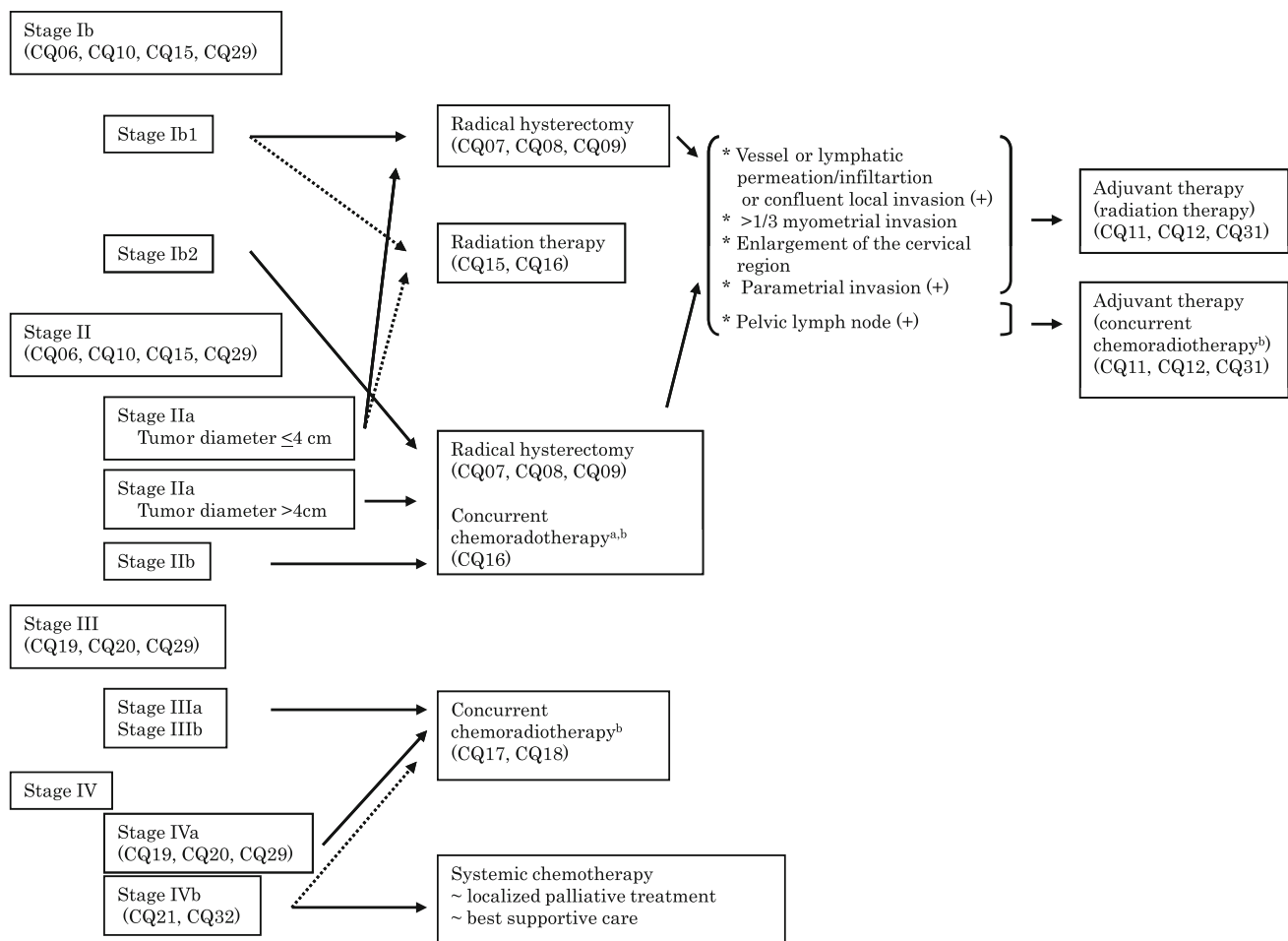
**CQ11.** Is postoperative adjuvant therapy necessary?

**CQ09.** What is the therapeutic significance of a para-aortic lymphadenectomy performed with radical hysterectomy?

**Recommendations:** (1) Postoperative adjuvant therapy is recommended for patients with positive pelvic lymph node metastasis (grade A'). (2) Postoperative adjuvant therapy should be considered for patients with high risk factors for recurrence other than positive pelvic lymph node metastases (grade C). (3) Whole-pelvis irradiation is considered to be a postoperative adjuvant therapy, and CCRT should also be considered for patients with positive lymph node metastases (grade C). (4) Presently, the usefulness of postoperative adjuvant chemotherapy is unknown (grade C).

**Recommendation:** The clinical significance of para-aortic lymphadenectomy is unknown (grade C).

**CQ10.** Is neoadjuvant chemotherapy (NAC) useful in stage I and II disease?



**Fig. 2** Treatment for stage Ib–V disease (including squamous cell carcinoma and adenocarcinoma). **a** In Japan, surgery is recommended for stages Ib to IIb. In the United States and Europe, concurrent chemoradiotherapy (CCRT) is becoming the mainstream treatment

for bulky tumors and has therefore been included as an option. **b** Tolerability of CCRT has not been fully verified in Japanese women and should be used cautiously until more evidence is available. Definitive radiotherapy may be an option for some patients

**CQ12.** What irradiation methods are recommended when performing postoperative adjuvant radiotherapy for the high-recurrence-risk group?

**Recommendations:** (1) Whole-pelvis irradiation is recommended (grade B). (2) The merits of adding intracavitary irradiation are unclear (grade C).

**CQ13.** Is prophylactic para-aortic irradiation useful?

**Recommendation:** The usefulness of prophylactic para-aortic irradiation is unclear (grade C).

**CQ14.** Are oral anticancer drugs and immunotherapy useful as maintenance therapies?

**Recommendations:** (1) The usefulness of oral anticancer agents is unclear (grade C). (2) The usefulness of immunotherapy has not been fully verified (grade D).

**CQ15.** Is definitive radiotherapy recommended for stage I and II disease?

**Recommendations:** (1) No clear differences have been demonstrated in the pelvic recurrence rate or survival rate between surgery ( $\pm$  radiotherapy) and radiotherapy, and definitive radiotherapy can reasonably be selected (grade B). (2) The use of CCRT can also be considered for patients with stage IIb disease or a tumor diameter >4 cm (grade B).

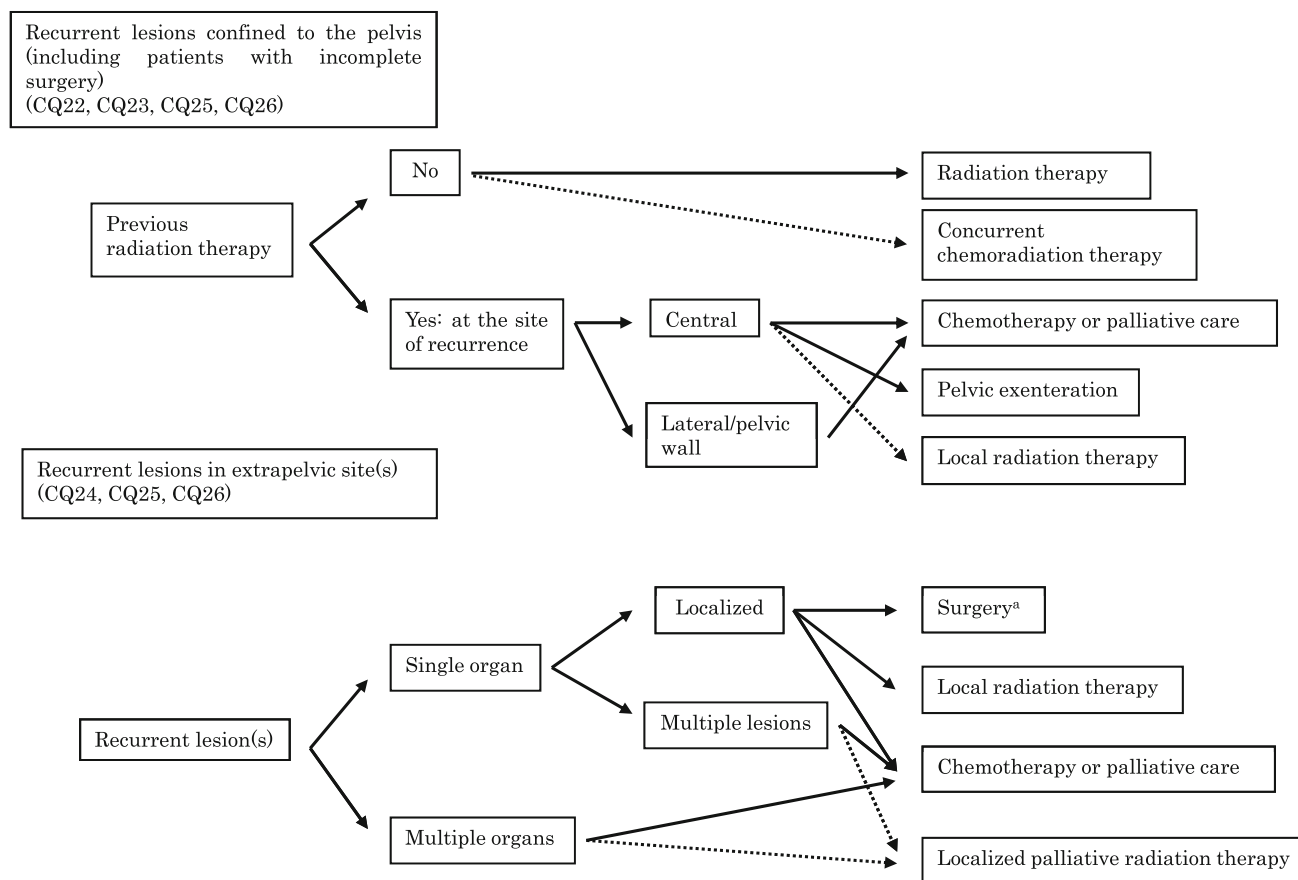
**CQ16.** What irradiation methods are recommended for definitive radiotherapy?

**Recommendations:** A combination of both external irradiation (whole-pelvis irradiation) and intracavitary irradiation is recommended (grade A').

**Chapter 5: Stage III and IVa disease**

**CQ17.** Which is recommended for radiotherapy of stage III and IVa disease: definitive radiotherapy or CCRT?

**Recommendation:** CCRT is favored over radiation monotherapy (grade B).



**Fig. 3** Treatment of recurrent cancer. <sup>a</sup>Adjuvant radiotherapy or radiosurgery is recommended if the recurrent lesion is located in the brain

CQ18. What regimens are recommended for CCRT?

Recommendation: Regimens that include cisplatin are recommended (grade A).

CQ19. Is chemotherapy recommended before primary treatment?

Recommendation: Chemotherapy is not recommended before radiotherapy (grade B).

CQ20. Is surgery recommended for stage III and IVa disease?

Recommendation: Surgery is not recommended (grade A').

#### Chapter 6: Stage IVb disease

CQ21. What treatments are recommended for stage IVb disease?

Recommendations: (1) Systemic chemotherapy is recommended for patients with a good performance status and preserved organ function (grade C). (2) Surgery, radiotherapy, chemotherapy, or a combination of these

treatments should be selected for patients with distant metastatic lesions, such as resectable lung metastases, or with lymph node metastases only (grade C). (3) If there are severe symptoms accompanying oncological complications, priority is placed on palliative radiotherapy to the causal lesion (grade B).

#### Chapter 7: Recurrent cancer

CQ22. What treatment methods are recommended for recurrence confined to the pelvis if radiotherapy has not been previously performed?

Recommendations: (1) Radiotherapy is recommended (grade B). (2) CCRT can be an option (grade C).

CQ23. What treatments are recommended for recurrence within the radiation field?

Recommendations: (1) Chemotherapy and palliative treatment for symptomatic relief are the general rule for treatment (grade C). (2) For central recurrence in the vaginal stump, localized radiotherapy or pelvic

exenteration should be considered after a thorough preoperative evaluation (grade C).

**CQ24.** What treatments are recommended for recurrence outside the radiation field, or extrapelvic recurrence if radiotherapy has not been previously performed?

**Recommendations:** (1) Treatment should be individualized based on patient performance status (PS), sites of recurrences and metastases, number and size of recurrent lesions, and disease-free time since initial treatment (grade A'). (2) For localized recurrent lesions ( $\leq 2-3$  lesions) with no recurrence or metastases in other sites, surgery or radiotherapy is indicated depending on the site (grade C). (3) Systemic chemotherapy is sometimes indicated for patients with multiple recurrences or recurrences in multiple organs (grade C). (4) Radiotherapy can be useful as supportive therapy depending on the recurrence site (grade B).

**CQ25.** Is systemic chemotherapy recommended?

**Recommendation:** Systemic chemotherapy is recommended for patients with disease difficult to control by surgery or radiotherapy, and patients with a good performance status and preserved organ function (grade B).

**CQ26.** What regimens are recommended for systemic chemotherapy?

**Recommendations:** (1) Cisplatin as monotherapy, or as part of a two-drug combination chemotherapy, is recommended (grade A). (2) A platinum-based agent other than cisplatin, as monotherapy or as part of a two-drug combination chemotherapy, can also be considered (grade B).

## Chapter 8: Adenocarcinoma

**CQ27.** What treatments are recommended for stage 0 adenocarcinoma?

**Recommendations:** (1) A total hysterectomy is recommended (grade B). (2) In patients who desire to have children, uterus preservation can be considered with cervical cone biopsy only and with careful management (grade C).

**CQ28.** What treatments are recommended for stage Ia adenocarcinoma?

**Recommendations:** (1) In cases with deep invasion, a radical hysterectomy or modified radical hysterectomy with pelvic lymphadenectomy is recommended (grade C). (2) In cases with shallow invasion, a hysterectomy without pelvic lymphadenectomy (total hysterectomy or modified radical hysterectomy) may be performed (grade C). (3) If the patient strongly desires fertility preservation, with

careful case selection, a cervical cone biopsy can be performed to preserve the uterus (grade C).

**CQ29.** What primary treatments are recommended for invasive adenocarcinoma?

**Recommendations:** (1) In principle, surgery is recommended for stage I and II disease (grade B). (2) Definitive radiotherapy or CCRT is recommended for stage III and IVa disease (grade B).

**CQ30.** Is NAC useful?

**Recommendation:** NAC cannot be recommended, as its usefulness has not been determined (grade C).

**CQ31.** What postoperative adjuvant therapies are recommended for the group with a high risk of recurrence?

**Recommendation:** Whole-pelvis irradiation is recommended, while also considering use of CCRT (grade C).

**CQ32.** What regimens are recommended for chemotherapy against stage IVb or recurrent carcinoma?

**Recommendation:** A platinum-based agent, as monotherapy or in combination, is recommended (grade C).

## Chapter 9: Management of cervical cancer complicating pregnancy

**CQ33.** How should cervical cancer complicating a pregnancy be managed?

**Recommendations:** (1) Cone biopsy may be delayed until after delivery as long as microinvasive or more advanced lesions are not suspected based on the results of cytology, colposcopy, or biopsy (grade C). (2) If stage Ia disease is suspected, a cervical cone biopsy should be performed to determine the diagnosis. If the cone biopsy result shows that uterine preservation is possible, cone biopsy can be the final treatment (grade B). (3) If a hysterectomy is necessary for stage Ia1 or higher disease, treatment and its timing should be tailored to the individual (grade B).

## Chapter 10: Posttreatment follow-up

**CQ34.** What intervals are recommended for posttreatment follow-up?

**Recommendation:** The following intervals are for standard follow-up (grade E):

For the first 1–3 years: every 1–3 months

For the 4th and 5th years: every 6 months

For  $\geq 6$ th year: every 12 months

**CQ35.** What investigations and examinations should be performed during posttreatment follow-up?

**Recommendation:** It is desirable to perform a physical examination (including pelvic and rectal examination), cervical cytology, chest radiography, measurement of tumor markers, and computerized tomography (CT) or magnetic resonance imaging (MRI) scanning (grade E).

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