

Treatment Guidelines for Cervical Cancer

2007 Edition

Edited by

Japan Society of Gynecologic Oncology

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Japan Society of Obstetrics and Gynecology
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Preface

Following the creation of the “Ovarian Cancer Treatment Guidelines”, the Japan Society of Gynecologic Oncology (JSGO) undertook the creation of the “Treatment Guidelines for Uterine Body Cancer,” published last year, and the “Uterine Cervical Cancer Treatment Guidelines.”

The standard Japanese treatment for cervical cancer, for instance stage IIb disease, is radical hysterectomy followed by radiotherapy. Radical hysterectomy was developed by our predecessors and is a highly curative surgical procedure. However, in developing these guidelines we found that treatments of cervical cancer often differ greatly from the above statement. Reliable evidence is scarce, and the level of evidence low, for treatment modalities for cervical cancer such as surgery, neoadjuvant therapies, and postoperative adjuvant therapies. There are differences in treatment between Japan and overseas. Many stage IIb cervical cancers are treated by radical hysterectomy in Japan, but definitive radiotherapy is usual in Western countries. In the past few years, concurrent chemoradiotherapy (CCRT) has been trialled mainly in Western countries. These large differences between Western countries and Japan were problematic in terms of evidence, and it therefore took 4 years to complete these guidelines.

The objective of these guidelines is to standardize the treatment of cervical cancer treatment. The treatments herein recommended are currently considered best practice, and consensus has been obtained among physicians routinely involved in the investigation and treatment of cervical cancer. Through their use, we anticipate that the quality of treatment of cervical 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, appropriate to the institution after considering the individual patient and their social background. 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 Guideline Formulation Committee and Evaluation Committee were established as for previous guidelines. The Formulation Committee was assembled by gathering together surgeons from all over Japan who specialize in the treatment of cervical cancer, as well as radiotherapists and gynecological oncologists. These guidelines are presented in a “Q&A format” in which problems in the treatment of cervical cancer are presented and answers provided. As for corpus cancer, this format was chosen because there is only a limited and low level of evidence concerning the treatment of cervical cancer and because there are differences between treatments in Japan and Western countries. The target diseases of these guidelines are primary squamous cell carcinoma and adenocarcinoma of the uterine cervix at various stages, including recurrences, and cervical cancer complicating pregnancy. The 3 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

cervical cancer 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 with their grades. 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 grades of recommendations, to maintain consistency we used the same classifications as those in the “Ovarian Cancer Treatment Guidelines” and the “Treatment Guidelines for Uterine Body Cancer”.

Page 3

A draft version of the present guidelines was examined by the Guidelines Evaluation Committee. Thereafter exhaustive prolonged discussion were held by the relevant specialists at 4 large and small consensus meetings, and the modified guidelines were presented to all members of the JSGO. Through this process, we received many useful suggestions that were incorporated into the draft guidelines. 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 JSGO held this summer, and we are now able to publish these guidelines.

As in the previously published “Ovarian Cancer Treatment Guidelines” and “Treatment Guidelines for Uterine Body Cancer,” 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 Yoshiki Inoue and Dr Naohiko Umesaki, 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 2007

Formulation Committee of the Treatment Guidelines for Cervical Cancer, Japan Society
of Gynecologic Oncology
Chairman Yasuhiro Udagawa, M.D.

Chapter 1 Overview of Guidelines

Chapter 2 Stage 0 disease

Overview

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

CQ02 What treatments are recommended for recurrence following conservative treatment?

Chapter 3 Stage Ia disease

Overview

CQ03 What treatments are recommended for stage Ia1 disease?

CQ04 What treatments are recommended for stage Ia2 disease?

CQ05 What treatments are recommended if disease up-staged to stage Ib (or more advanced) is detected following total hysterectomy?

Chapter 4 Stage Ib and II disease

Overview

I. Surgery

CQ06 What surgical procedures are recommended for stage Ib-II disease?

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

CQ08 Is ovarian preservation possible in radical hysterectomy?

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

II. Neoadjuvant chemotherapy (NAC)

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

III. Postoperative adjuvant therapy

CQ11 Is postoperative adjuvant therapy necessary?

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

CQ13 Is prophylactic para-aortic irradiation useful?

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

IV. Definitive radiotherapy

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

CQ16 What irradiation methods are recommended for definitive radiotherapy?

Chapter 5 Stage III and IVa disease

Overview

CQ17 Which is recommended for radiotherapy of stage III and IVa disease, definitive radiotherapy or concurrent chemoradiotherapy (CCRT)?

CQ18 What regimens are recommended for concurrent chemoradiotherapy (CCRT)?

CQ19 Is chemotherapy recommended before primary treatment?

CQ20 Is surgery recommended for stage III and IVa disease?

Chapter 6 Stage IVb disease

Overview

CQ21 What treatments are recommended for stage IVb disease?

Chapter 7 Recurrent cancer

Overview

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

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

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

CQ25 Is systemic chemotherapy recommended?

CQ26 What regimens are recommended for systemic chemotherapy?

Chapter 8 Adenocarcinoma

Overview

CQ27 What treatments are recommended for stage 0 adenocarcinoma?

CQ28 What treatments are recommended for stage Ia adenocarcinoma?

CQ29 What primary treatment is recommended for invasive adenocarcinoma?

CQ30 Is neoadjuvant chemotherapy (NAC) useful?

CQ31 What postoperative adjuvant therapies are recommended for the high risk group for recurrence?

CQ32 What regimens are recommended for chemotherapy for stage IVb and recurrent adenocarcinoma?

Chapter 9 Management of Cervical Cancer Complicating Pregnancy

Overview

CQ33 How should cervical cancer complicating pregnancy be managed?

Chapter 10 Post-treatment Follow-up

Overview

CQ34 What intervals are recommended for post-treatment follow-up?

CQ35 What examinations and investigations should be performed at post-treatment follow-up?

Chapter 11 Data report

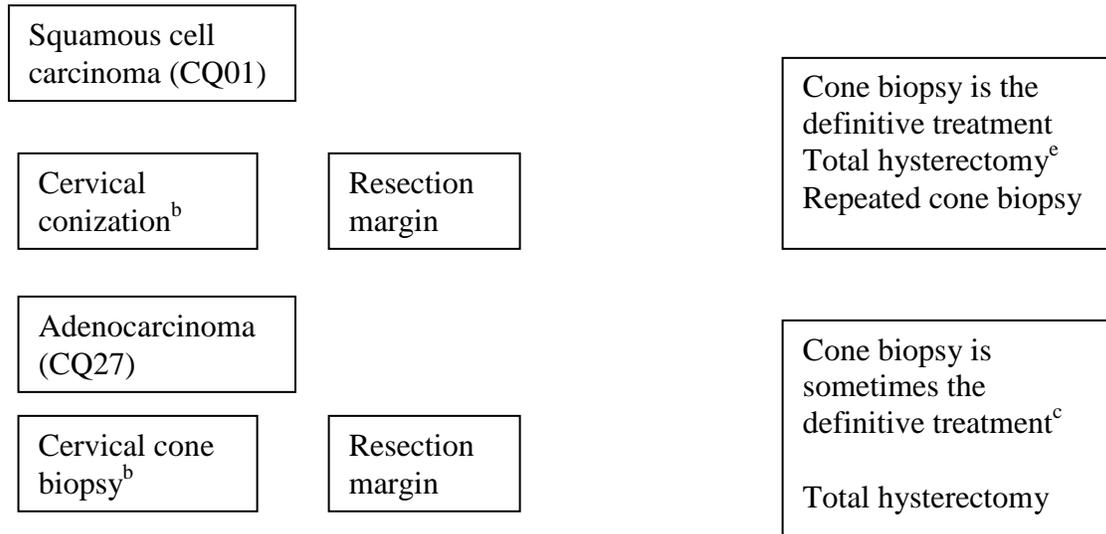
I. List of adverse events of anticancer agents

II. Anticancer agents frequently used in uterine cervical cancer and their coverage by Japanese medical insurance

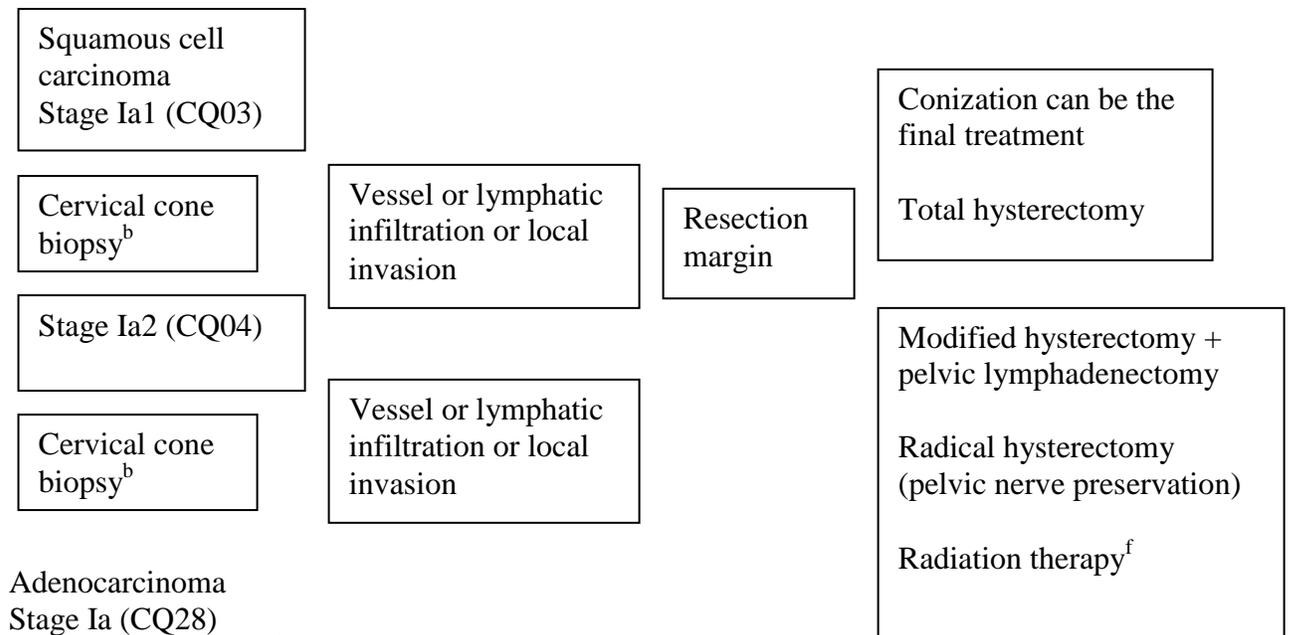
III. List of abbreviations

Flow Chart 1 Treatments for stage 0-Ia disease^a

Stage 0



Stage I



Adenocarcinoma Stage Ia (CQ28)

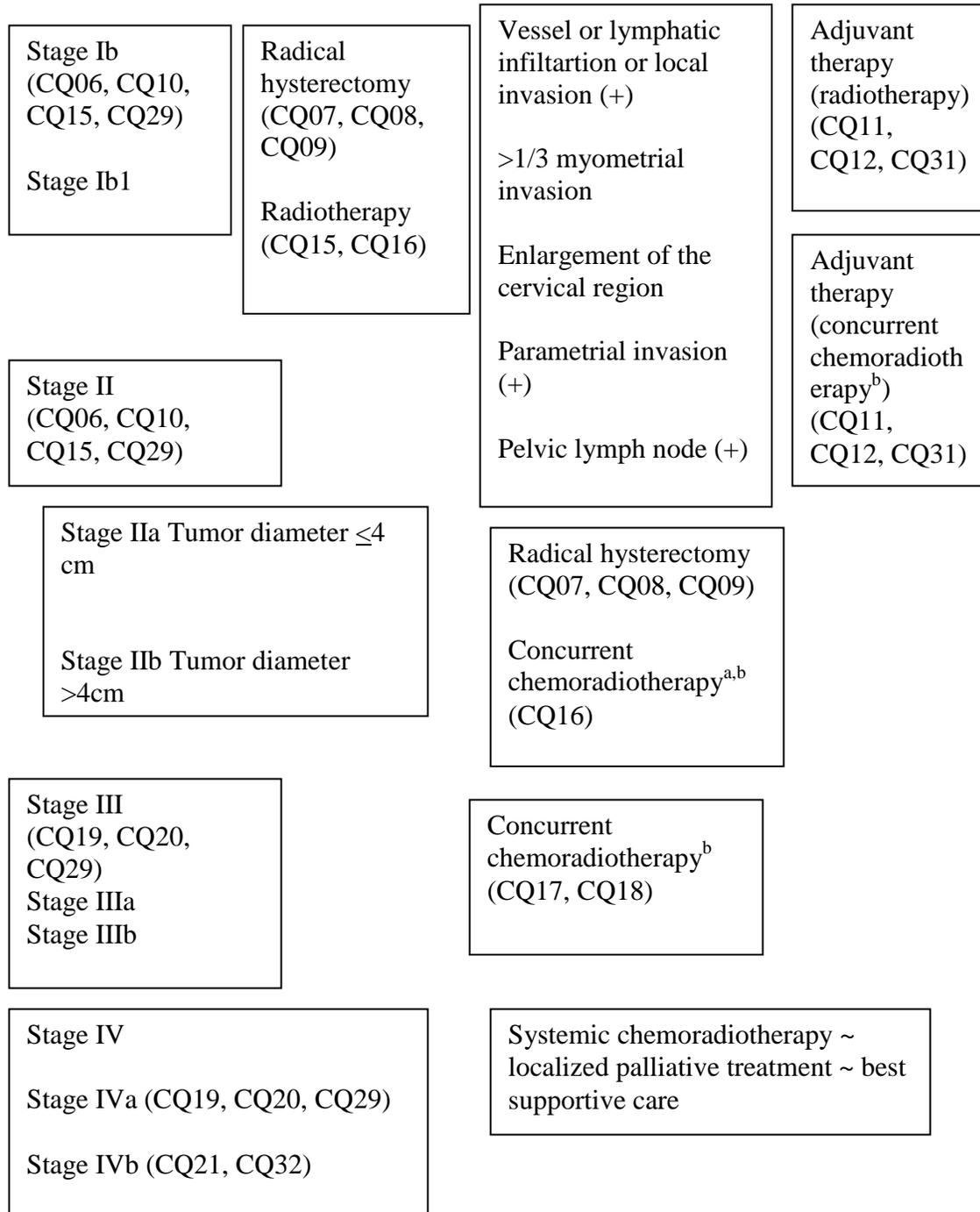
Cervical cone biopsy^b → definitive treatment: cone biopsy ~ total hysterectomy ~ radical hysterectomy (pelvic nerve preservation)

Notes:

- a) If cone biopsy is difficult, e.g. due to atrophic cervical region in the elderly, omission of cone biopsy may be considered. However, hysterectomy appropriate for the provisionally diagnosed lesion should be performed after a full examination of the preoperative cytology, colposcopy, and biopsy results.
- b) Endocervical curettage is performed at cone biopsy.
- c) Caution is required with uterine preservation, since approximately 20% of residual lesions are reportedly found in patients with negative resection margins.
- d) Surgical procedures should be individualized with consideration of the histopathological findings of the cone biopsy specimens, i.e. degree of invasion, vascular and lymphatic infiltration, and local invasion.
- e) Total hysterectomy should be considered in patients who do not desire fertility preservation.
- f) Radiotherapy is an option in the National Comprehensive Cancer Network (NCCN) treatment guidelines for cervical cancer.

Flow Chart 2

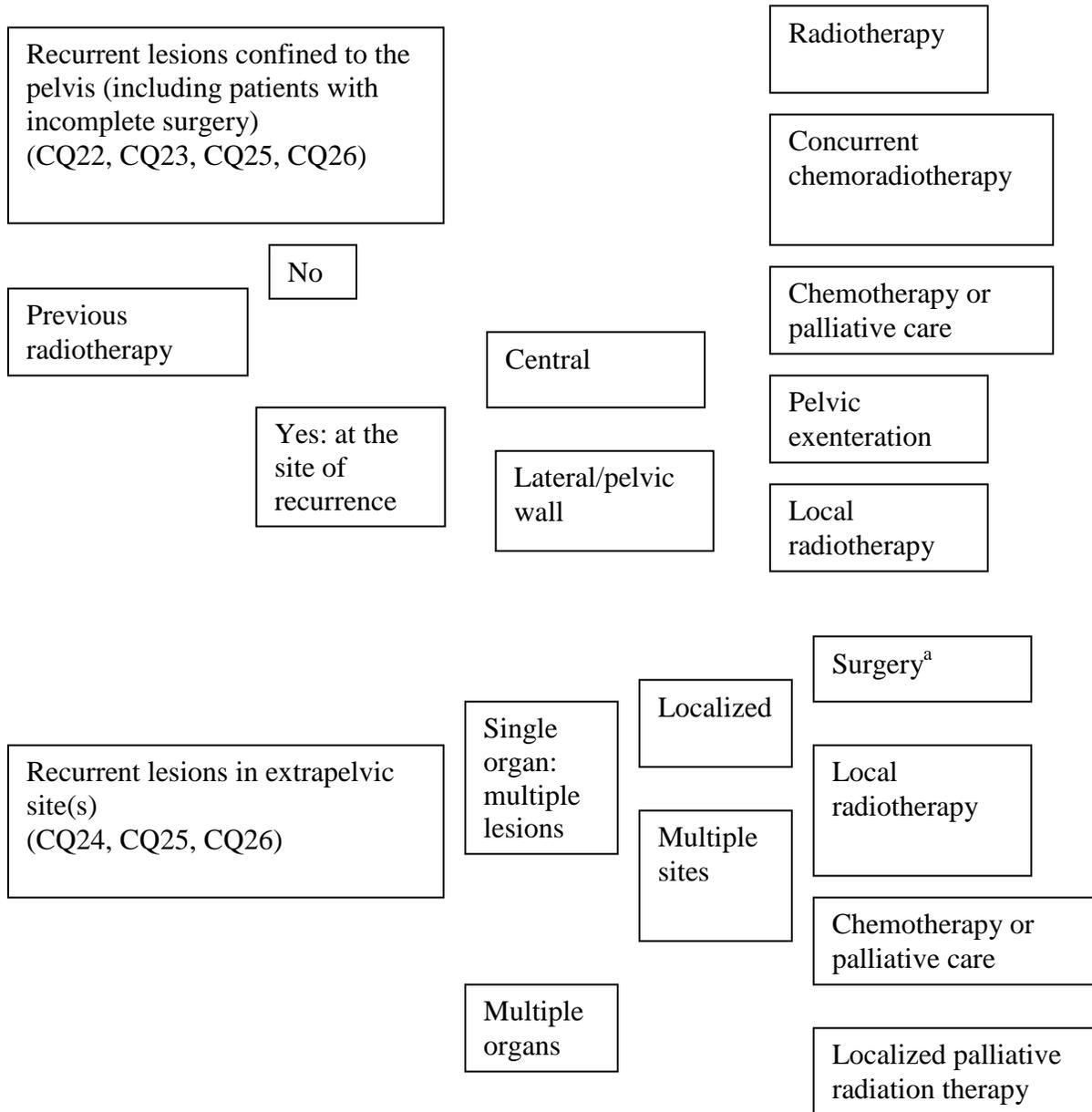
Treatment for stage Ib-V disease (including squamous cell carcinoma and adenocarcinoma)



Notes:

- a) In Japan, surgery is recommended for stages Ia and IIb. In Western countries, concurrent chemoradiotherapy is becoming the mainstream treatment for bulky tumors. Concurrent chemoradiotherapy has therefore been included as an option.
- b) Tolerability of concurrent chemoradiotherapy has not been fully verified in Japanese women. It is therefore necessary to take full precautions when performing this procedure. Definitive radiotherapy may be an option for some patients.

Flow Chart 3 Treatment of recurrent cancer



Note: ^aFor brain, adjuvant radiotherapy or radiosurgery

Notes on surgical procedures

1) Cervical cone biopsy (conization)

This involves the resection of a portion of the cervix in a cone shape, mainly as a diagnostic procedure. It can also be a treatment for dysplasia and carcinoma in situ (squamous cell carcinoma).

2) Total hysterectomy (abdominal or vaginal)

There are abdominal and vaginal approaches to this procedure. It follows the techniques of conventional total hysterectomy. However, in the presence of a cancerous lesion necessitates the removal of tissues without leaving a residual cervical area. In this case, an intrafascial method (Aldridge method) is not suitable. An extrafascial technique is used that removes some vaginal wall so that there is some distance between the outermost border of the lesion and the surgical margin.

3) Modified radical hysterectomy

This procedure, positioned between total hysterectomy and radical hysterectomy, can be summarized as follows. The anterior layer of the vesicouterine ligament is divided. The ureters are avoided and displaced laterally, and the uterus is resected by separating dividing as much as possible the anterior uterine support and vaginal wall from the cervix. This technique is called “modified radical hysterectomy”, regardless of whether or not lymphadenectomy is performed.

4) Radical hysterectomy

This is the usual surgical procedure for cervical cancer. The regional lymph nodes are dissected. The paravesical space and pararectal space are expanded, and each of the anterior, middle, and posterior uterine supports is separated and severed. The fatty tissues of the middle uterine support are resected, and the vessels are bundled. The cardinal ligament is severed near the pelvic wall, and the anterior layer of the vesicouterine ligament is separated and severed. The ureters are detached and displaced laterally, and the posterior layer is separated and severed. The rectovaginal ligament and ligament in the rectal space are severed. Then paravaginal connective tissue and a portion of the vaginal wall (at least 3 cm) are then adequately excised. Lymph node dissection is characteristic of this surgical procedure, and should be performed as extensively and thoroughly as possible. The lymph nodes that are dissected are the so-called “regional lymph nodes,” which include nodes in the cardinal ligaments, internal iliac nodes, obturator nodes, external iliac nodes, sacral nodes, common iliac nodes, and suprainguinal nodes.

5) Extended radical hysterectomy

In this procedure, the internal iliac vessels, inferior gluteal vessels, and internal pudendal vessels are severed, and the root of the cardinal ligaments are excised, including the pelvic wall attachment sites (cardinal ligament excision). This procedure is

used in some patients with clinical stage IIIb disease. It is also used in stage IIb disease if local invasion has reached near the pelvic wall.

6) Pelvic exenteration (total, anterior or posterior)

This procedure involves the excision of the female internal genitalia, as well as other pelvic organs including the bladder and rectum. There are anterior, posterior, and total exenteration methods. If cancer has reached the bladder or rectum, this procedure is rarely indicated since distant metastases are usually present in such cases.

(Excerpt from the “*Guidelines for the Clinical and Pathological Study of Uterine Cervical Cancer in Japan,*” 1997; revision, 2nd ed.)

Comparison of Terminologies

Japan Society of Obstetrics and Gynecology

(1) Para-aortic lymph nodes (inferior border of the left renal vein to the root of the inferior mesenteric artery) (#326 b1)

(1) Para-aortic lymph nodes (root of the inferior mesenteric artery to the aortic bifurcation) (#326 b2)

(Not applicable)

(7) Sacral lymph nodes (#412)

(2) Common iliac lymph nodes (#413)

(3) External iliac lymph nodes (#403)

(4) Suprainguinal lymph nodes (#401)

(5) Internal iliac lymph nodes (#411)

(6) Obturator lymph nodes (#410)

(8) Parametrial lymph nodes (#405)

(9) Inguinal lymph nodes (#401a)

Japan Society of Clinical Oncology

Para-abdominal aortic lymph nodes (inferior border of the left renal vein to the root of the inferior mesenteric artery)

Para-abdominal aortic lymph nodes (root of the inferior mesenteric artery to the aortic bifurcation)

Lymph nodes at the aortic bifurcation

Median sacral lymph nodes

Lateral sacral lymph nodes

Common iliac lymph nodes

External iliac lymph nodes

Suprafemoral lymph nodes

Internal iliac lymph nodes

Obturator lymph nodes

Parametrial lymph nodes

Inguinal lymph nodes

The names of structures established in the “Guidelines for Clinical and Pathological Management of Cervical Cancer; October 1997 (revised, 2nd ed.)” (Japan Society of Obstetrics and Gynecology, Japanese Society of Pathology, and Japan Radiological Society, editors; 1997)¹ are considered the names commonly proposed for various organs and established in the “Guidelines and Statements on Cancer: Japan Society of Clinical Oncology” (Japan Society of Clinical Oncology: Joint Committee on Cancer Treatment, editors; 1991).² The use of numbers for lymph nodes was eliminated in the “Japan Society of Clinical Oncology: Classification of Regional Lymph Nodes in Japan” (Japan Society Clinical Oncology, editors; 2002).³

Figure 1 “Guidelines for Clinical and Pathological Management of Cervical Cancer; October 1997 (revised, 2nd edition)” (1997, Kanehara & Co.)¹

	Ureter
	Obturator nerve
	Structures (1)-(9) are described in Table 4.
a. Classification of para-aortic lymph nodes and their borders	b. Lymph nodes related to uterine cervical cancer treatment and their names

Figure 2 “Japan Society of Clinical Oncology: Classification of Regional Lymph Nodes in Japan” (2002, Kanehara & Co.)³

腹部大動脈周囲リンパ節	Para-abdominal aortic lymph nodes	胸管	Thoracic duct
b2 群 大脈前リンパ節	b2 Group Precaval lymph nodes	上腸間膜動脈	Superior mesenteric artery
大脈外側リンパ節	Laterocaval lymph nodes	腹部大動脈周囲リンパ節	Para-abdominal aortic lymph nodes
大動脈分岐部リンパ節	Lymph nodes at the aortic bifurcation	a2 群 大動脈後リンパ節	a2 Group Retroaortic lymph node
正中仙骨リンパ節	Median sacral lymph nodes	大動脈外側リンパ節	Latero-aortic lymph node
総腸骨リンパ節	Common iliac lymph nodes	b1 群 大脈後リンパ節	b1 Group Retrocaval lymph nodes
外腸骨リンパ節	External iliac lymph nodes	大動脈外側リンパ節	Latero-aortic lymph nodes
閉鎖神経	Obturator nerve	腹部大動脈周囲リンパ節	Para-abdominal aortic lymph nodes
閉鎖リンパ節	Obturator lymph nodes	大動脈前リンパ節	Preaortic lymph nodes
子宮円索	Round ligament of the uterus	大動脈前リンパ節	Preaortic lymph nodes
基靭帯リンパ節	Parametrial lymph nodes	下腸間膜動脈	Inferior mesenteric artery
		卵巣動脈	Ovarian artery
		閉鎖リンパ節	Obturator lymph nodes
		大腿上リンパ節	Suprafemoral lymph nodes
		鼠径靭帯	Inguinal ligament
		深鼠径リンパ節	Deep inguinal

			lymph nodes
		浅鼠径リンパ節	Superficial inguinal lymph nodes
		臍動脈索	Medial umbilical ligament

References

(1) Guidelines for Clinical and Pathological Management of Uterine Body Cancer (revised, 2nd ed.) Japan Society of Obstetrics and Gynecology, Japanese Society of Pathology, and Japan Radiological Society, editors. Kanehara & Co., Tokyo, October 1997 (guidelines) (in Japanese)

(2) Guidelines and statements on cancer: Japan Society of Clinical Oncology. Japan Society of Clinical Oncology: Joint Committee on Cancer Treatment, editors; 1991 (guidelines) (in Japanese)

(3) Japan Society of Clinical Oncology: Classification of Regional Lymph Nodes in Japan. Society of Clinical Oncology, editor. Kanehara & Co., Tokyo, 2002 (guidelines) (in Japanese)

Chapter 1 ■ Overview of Guidelines

I. Objectives

- A. To describe treatment methods presently considered appropriate for cervical cancer
- B. To reduce the differences in treatment levels of cervical cancer between institutions
- C. To improve safety and outcomes for treatment of cervical 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 standards and evidence is shown to aid in the selection of treatment of cervical 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 cervical 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 the content of these guidelines. The final decision of whether or not to apply these guidelines should be made by the user, so the clinician directly in charge of treatment is responsible for the results of treatment.

IV. Target Diseases

The target diseases of these guidelines are primary cancers and dysplastic lesions of the uterine cervix, and recurrent tumors.

V. Basic Policies 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 Cervical 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 1-1).

Page 16

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 1-2).

F. In general, each section consists of 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, treatment methods used commonly in Japan can differ from methods used in Western countries. In such a situation, 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 physicians” and must respect the indicated diseases in the approval conditions for use of anticancer agents 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 patients’ condition, at the clinician’s discretion.
3. When using an anticancer agent 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)
5. For important categories, delays in publication allowed data published on or after May 2005 to be cited in the references of these guidelines.

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 will be fully incorporated in the revisions: Japan Society of Obstetrics and Gynecology (JSOG), Japan Society of Clinical Oncology, Japanese Gynecologic Oncology Group (JGOG), and Japan Association of Obstetricians and Gynecologists.

Page 17

- E. The Committee for Treatment Guidelines for Cervical Cancer will produce a final revised draft, and revisions will be made after approval by the Japan Society of Gynecologic Oncology.

VII. Publication

- A. These guidelines are to 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 1-1 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 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 1-2 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

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 recommending negatively, Grade A or B is used even if it is a negative recommendation (for example: CQ19).