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SPECIAL ARTICLE

Japan Society of Gynecologic Oncology guidelines 2017 for the treatment of uterine cervical cancer

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Abstract

The Japan Society of Gynecologic Oncology (JSGO) Guidelines 2017 for the Treatment of Uterine Cervical Cancer are for the purpose of providing standard treatment strategies for cervical cancer, indicating treatment methods currently considered appropriate for cervical cancer, minimizing variances in treatment methods among institutions, improving the safety of treatment and prognosis of diseases, reducing the economic and psychosomatic burden of patients by promoting performance of appropriate treatment, and enhancing mutual understanding between patients and healthcare professionals. The guidelines were prepared through consensus of the JSGO Guideline Committee, based on careful review of evidence gathered through the literature searches and in view of the medical health insurance system and actual clinical practice situations in Japan. The guidelines comprise eight chapters and five algorithms. The main features of the 2017 revision are as follows: (1) evidence was collected using a search formula and with cooperation of the Japan Library Association. The bibliographical search formula was placed at the end of the book; (2) regarding clinical questions (CQs) where evidence or clinical inspection in Japan was lacking, opinions of the Guidelines Committee were described as "proposals for future directions"; (3) cervical intraepithelial neoplasia (CIN) 3 and adenocarcinoma in situ (AIS) were treated as a cervical precancerous lesion; (4) the CQs of endoscopic surgery, radical trachelectomy, and sentinel node biopsy were newly added in Chapter 3, "primary treatment for stage IB–II cervical cancer"; and (5) the CQ about hormone replacement therapy after cancer treatment was newly established. Each recommendation is accompanied by a classification of recommendation categories based on the consensus reached by the Guideline Committee members. Here, we present the English version of the JSGO Guidelines 2017 for the Treatment of Uterine Cervical Cancer.

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

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Abbreviations

AIS	Adenocarcinoma in situ
CCRT	Concurrent chemoradiotherapy
CIN	Cervical intraepithelial neoplasia
COIs	Conflicts of interests
CQs	Clinical questions
CTV	Clinical target volume
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
Gy	Gray
HPV	Human papillomavirus
HRT	Hormone replacement therapy
HSIL	High-grade squamous intraepithelial lesion
IMRT	Intensity-modulated radiation therapy
JCOG	Japan Clinical Oncology Group
JGOG	Japanese Gynecologic Oncology Group
JSCO	Japan Society of Clinical Oncology
JSGO	Japan Society of Gynecologic Oncology
LSIL	Low-grade squamous intraepithelial lesion
Minds	Medical Information Network Distribution Service
NAC	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
PTV	Planning target volume
QOL	Quality of life
RCT	Randomized controlled trial
RTOG	Radiation Therapy Oncology Group
SIL	Squamous intraepithelial lesion
TC	Paclitaxel plus carboplatin
TP	Paclitaxel plus cisplatin
WBRT	Whole-brain radiation therapy
WHO	World Health Organization
3D-CRT	3 dimensional-conformal radiotherapy

Introduction

An estimated 10,000 new cases of cervical cancer were diagnosed in Japan in 2013, and 2700 women died of the disease. The mortality rate associated with cervical cancer in Japan decreased from the 1960s through 1990; however, the mortality has slightly increased [1].

The first edition of the Japan Society of Gynecologic Oncology (JSGO) Guidelines for the Treatment of Uterine Cervical Cancer was published in 2007 [2], and the second edition in 2011 [3]. The third edition was then revised and published 6 years later, in 2017.

After the guidelines were published, they were definitively evaluated by the Japan Society of Clinical Oncology (JSCO) Cancer Guidelines Evaluation Committee and Medical Information Network Distribution Service (Minds). Based on that evaluation, contents pointed out are discussed in the exploratory committee established by JSGO to make improvement in the next revision. We draw up guidelines while confirming the direction. In these guidelines, the preparation processes are detailed in Chapter 1, "Overview of guidelines".

The following points were added, modified, or changed in the Guidelines 2017 for the Treatment of Uterine Cervical Cancer (third version).

Matter pointed out in the guidelines evaluation, and improved

1. Chapter 1, "Overview of guidelines," details the decision process of the guidelines recommendation and appearance of conflicts of interests (COIs).
2. In formulating the guidelines, we requested the participation of not only a gynecologist, radiation oncologist, medical oncologist, and pathologist, but also of a pharmacist, nurse, and representative of a patient advocacy group.
3. We collected evidence using a search formula, with cooperation of the Japan Library Association. We placed the bibliographical search formula at the end of the book.

Matters pointed out in our committee, or contents that were added

1. Regarding clinical questions (CQs) where evidence or clinical inspection in Japan were lacking, we described opinions of the Guidelines Committee as "proposals for future directions."
2. We listed CQs, recommendations, and a recommended grade in a table at the beginning of the book.
3. We treated cervical intraepithelial neoplasia (CIN) 3 and adenocarcinoma in situ (AIS) as a cervical precancerous lesion.
4. We newly added the CQs for endoscopic surgery, radical trachelectomy, and sentinel node biopsy, in Chapter 3, "Primary treatment for stage IB–II cervical cancer."
5. We newly established the CQ about hormone replacement therapy after cancer treatment.

Chapter 1: Overview of guidelines

How to use these guidelines

The purpose of the guidelines is to indicate a set of standards that can be used to select better options in the treatment of cervical cancer in Japan, and to provide evidence on which those options are based. The guidelines are not intended to limit the therapies undescribed in this guideline. The principal

objectives of the guidelines are: (1) to indicate treatment methods currently considered appropriate for cervical cancer; (2) to minimize variances in the treatment methods among institutions; (3) to improve the safety of treatment and prognosis of the target diseases; (4) to reduce the economic and psychosomatic burdens of patients by promoting performance of appropriate treatment; and (5) to improve mutual understanding between patients and healthcare professionals.

Intended readers

The guidelines are for the use of all healthcare personnel involved in medical care for cervical cancer.

Diseases addressed by these guidelines

In the guidelines, the term "uterine cervical cancer" covers not only tumors such as cervical cancer, CIN 3, and AIS, but also recurrent cervical cancer.

How to use these guidelines

1. Each of the topics in the guidelines consists of a CQ, recommendation, background and objectives, and comments. At the end of each topic, the literature that the guideline cited is collated at the end of each CQ. The bibliographical search formula was placed at the end of the book. If a more detailed explanation is deemed necessary to recommend a treatment, the explanation is added in an additional statement.
2. Cervical cancer has few randomized controlled trials regarding treatment. Topics for which guidelines cannot be shown for treatment are presented only by an evidence level. We examined problems that must be settled in the future, reviewed experimental treatment under verification in our committee, and showed items as "proposals for future directions" after recommendation.
3. Given various different backgrounds among Western countries and Japan, we found some clinical evidence from Western countries to be unacceptable. To the contrary, some therapeutic regimens generally carried out in Japan may differ from those of Western countries. In such cases, consensus in Japan at the present has been given high priority.
4. Some treatment methods evaluated and recommended worldwide are problematic in terms of application under Japan's medical insurance system. In this regard, the present guidelines follow the Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents [4, 5].

① Based on awareness that a physician using these guidelines is "an insurance doctor," the use of anticancer drugs by practical medical care respects indication of the disease in the condition for approval.
② Regarding differences between the guidelines and indication of the disease in the condition for approval for an anticancer drug, physicians must accommodate depending on the situation of the patients and at their own discretion.
③ In the case of use of a single agent of the anticancer drug, we administer such an agent by a dose and injection method that satisfies the condition for approval set by the Pharmaceutical Affairs Act of Japan.
④ In the case of combination therapy involving an anticancer drug, we administer the medical agents as per the condition for approval condition set by the Pharmaceutical Affairs Act of Japan concerning a dose and injection method of individual anticancer drugs.

Literature search

To date, the Guidelines Drafting Committee in charge of CQs collected references by a search method. However, for this revision, we asked the Japan Library Association to prepare a bibliographical search formula. We unified databases used for searching. The specific steps of the bibliographical search are as follows.

1. The Guidelines Drafting Committee chose a keyword associated with the CQ and principal articles. The person in charge for the Japan Library Association made a bibliographical search formula based on this and conducted comprehensive document retrieval. When a large number of articles were extracted, the Guidelines Drafting Committee and the library personnel changed or added to the keywords. The committee investigated extracted articles and selected around 30 as important titles.
2. We searched in literature reported in PubMed, Ichushi-Web, and the Cochrane Library for the period from January 2010 to December 2015. Even if an article was published before 2010, we adopted it in the bibliography when it was quoted in the JSGO Guidelines 2011 for the Treatment of Cervical Cancer, and was necessary for recommended decision. For articles published from January 2016 onward, we individually discussed in the Guidelines Committee as to whether they would be used in the bibliography.
3. An evidence level was shown for each reference. We clearly described whether each bibliographic item was extracted via search, quoted in this revision in a required bibliographic item, or was deemed necessary by the Guidelines Committee.

How these guidelines were developed

1. To prepare the Japan Society of Gynecologic Oncology Guidelines 2017 for the Treatment of Uterine Cervical Cancer, two independent committees, the Committee for Drafting of the Guidelines for the Treatment of Cervical Cancer and the Committee for Evaluation of the Guidelines for the Treatment of Cervical Cancer ("Drafting Committee" and "Evaluation Committee," respectively) were established within the Exploratory Committee of the Guidelines for the Treatment of Cervical Cancer established by the JSGO. The chairperson of the Guidelines Committee concurrently took on the position of chairman of the Exploratory Committee and Drafting Committee. The Evaluation Committee was composed of a nurse, pharmacists, and representatives of a patient advocacy group, as well as physicians.
2. The revision of the guidelines took place as per the following schedule.

March 6, 2015, first Exploratory Committee of the Guidelines for the Treatment of Cervical Cancer (Tokyo): Four chairpersons of the subcommittee were elected, and determined to delegate the bibliographical search to the Japan Library Association.

May 15, 2015, second Exploratory Committee of the Guidelines for the Treatment of Cervical Cancer (Tokyo): The methods of the bibliographical search were confirmed with the person in charge for the Japan Library Association. It was confirmed that the Drafting Committee members would be elected by the time of convening the first Drafting Committee, and that the CQ plans would be made in the Drafting Committee. Subsequently, the Drafting Committee members were elected in email meetings, and were officially determined.

October 29, 2015, first Drafting Committee (Kyoto): We determined the Drafting Committee and discussed the CQ plan. Subsequently, the final CQ plan was determined in email meetings.

December 4, 2015, second Drafting Committee (Tokyo): after the conducting of the bibliographical search and the bibliography item extraction were explained, we examined CQ items in each chapter and determined the person in charge of each CQ. Each member of the Drafting Committee was in charge of one or two CQs. Afterward, a bibliographical search was conducted via email between the Japan Library Association person in charge and the Drafting Committee, and the first draft was prepared.

July 7, 2016, third Drafting Committee (Yonago): recommendation levels were discussed in each subcommittee based on the first draft sent beforehand. We also discussed problems extracted from each subcommittee.

July 8, 2016, cervical cancer treatment guidelines consensus meeting (58th JSGO meeting): after explaining the revised contents of the guidelines, we commented on the revision points of each chapter. Consensus on the revision contents was obtained among the members. We heard members' opinions, and based on both the opinions at the consensus meeting and the questions at the Drafting Committee of July 7, the Drafting Committee subsequently prepared the second draft and structured abstract. Opinions on the second draft were obtained from the guidelines Evaluation Committee.

January 15, 2017, fourth Drafting Committee (Tokyo): we discussed the opinions of the Evaluation Committee. We discussed items to be studied from each chapter. Based on the results in this meeting, the chairpersons of the subcommittee and the person in charge revised the second draft and completed the third draft.

In March 2017, we placed the third draft on the homepage of JSGO and asked for public comments. We also sent it to the Japanese Society of Obstetrics and Gynecology, JSCO, the Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy, Japanese Gynecologic Oncology Group (JGOG), Japan Association of Obstetricians and Gynecologists, Japan Society of Pathology, Japanese Society for Radiation Oncology, and other relevant academic societies at the same time, and obtained opinions. We examined the opinions of the relevant organizations, as well as public comments, in an email meeting and prepared the fourth draft.

April 28–29, 2017, fifth Drafting Committee (Tokyo): we discussed the recommended contents and recommendation level of the fourth draft based on the opinions in public comments and made decisions. We also revised commentary sentences and the flowchart, and completed the final version.

Evidence level/strength of recommendations of clinical questions

1. This collected evidence was evaluated for quality using the criteria of the JSCO and its Formulation Committee

Table 1 Criteria for the evaluation of the quality of evidence (levels)

Level I: meta-analysis of multiple randomized controlled trials
Level II: randomized controlled trials or well-designed non-randomized controlled trials
Level III: well-designed quasi-experimental studies, comparative studies, correlation studies, case-comparison studies or other well-designed non-experimental descriptive studies
Level IV: reports and opinions of specialized committees or clinical experiences of authoritative persons

Table 2 Criteria for recommendation (grades)

Grade A: action is strongly recommended
Grade B: action is recommended
Grade C1: action may be considered, but scientific grounds are not yet sufficient. (Alternatively, scientific grounds are not yet sufficient, but the possibility exists that effectiveness can be expected.)
Grade C2: scientific grounds are not sufficient and application in routine treatment is not recommended
Grade D: action is not recommended
Usefulness/effectiveness is not evident, and indeed the treatment may be harmful

In addition to the question of evidence, recommendation Grade A can be applied based on judgment on the level of general common sense

on Clinical Practice Guidelines for the Use of Anticancer Agents [4, 5]. However, it was modified to allow a portion of it to fit into the guidelines (Table 1).

2. The criteria of the strengths of the recommendations in our guidelines were also determined by the recommendation criteria of the JSCO [4, 5] and the Minds Handbook on Preparation of Treatment Guidelines 2007 [6]. However, some of the content of those guidelines was modified for the purposes of the guidelines (Table 2)
3. When deciding the recommendation grade, we added the clinical factor that included an effect and a disadvantage, as well as the evidence level of the reference referring to the Minds Handbook on Preparation of Treatment Guidelines 2014 [7], and finally judged based on the agreement of the Guidelines Committee.
4. When the decision of the recommendation grade became gridlocked in a subcommittee, we conferred with the Guidelines Exploratory Committee and that subcommittee, and we ultimately determined the recommendation grade by a vote.

Disclosure of information

The guidelines are intended for wide use. Their content is published as a booklet and is available on websites of the JSGO, JSCO, and Minds.

Responsibility for treatment

The JSGO bears the responsibility for the content and descriptions of these guidelines. However, the individual user should make the final decision to use the guidelines. Thus, the physicians in charge of treatment are responsible for the treatment outcome.

Revision

1. The Exploratory Committee of the Guidelines for the Treatment of Cervical Cancer continually revises these guidelines, applying medical advances and medical changes.
2. Newly accumulated evidence after publishing these guidelines is saved in a database.
3. Any associated information regarding clinical inconvenience occurring with the use of these guidelines is collected.
4. The Guidelines Drafting Committee and Evaluation Committee conduct revision work based on new evidence and information. Moreover, opinions from the associated academic societies, groups, or JSGO members are widely acquired.
5. After the processes described above, the Exploratory Committee of the Guidelines for the Treatment of Cervical Cancer organizes the final revisions to the guidelines, and the JSGO approves the draft.

Chapter 2: Primary treatment for cervical precancerous lesions and IA cervical cancer

Primary treatment for cervical precancerous lesions and IA cervical cancer is summarized as flow chart 1 (Fig. 1).

In the World Health Organization (WHO) histological classifications revised in 2014, classification of squamous intraepithelial lesion (SIL) was adopted, and SIL was divided into low-grade squamous intraepithelial lesion (LSIL) stemming from human papillomavirus (HPV) infection and high-grade squamous intraepithelial lesion (HSIL) as a precancerous lesion [8]. However, confusion was predicted when this SIL classification was introduced for practical medical care after quick adoption. Therefore, in the "Japanese classification of cervical cancer, pathology edition (2017)," CIN classification is left as CIN 1 (LSIL), CIN 2 (HSIL), and CIN 3 (HSIL) [9]. As described above, in these guidelines, CIN 3 is handled as a precancerous lesion of cervical squamous cancer. AIS is also treated as a precancerous lesion of cervical adenocarcinoma.

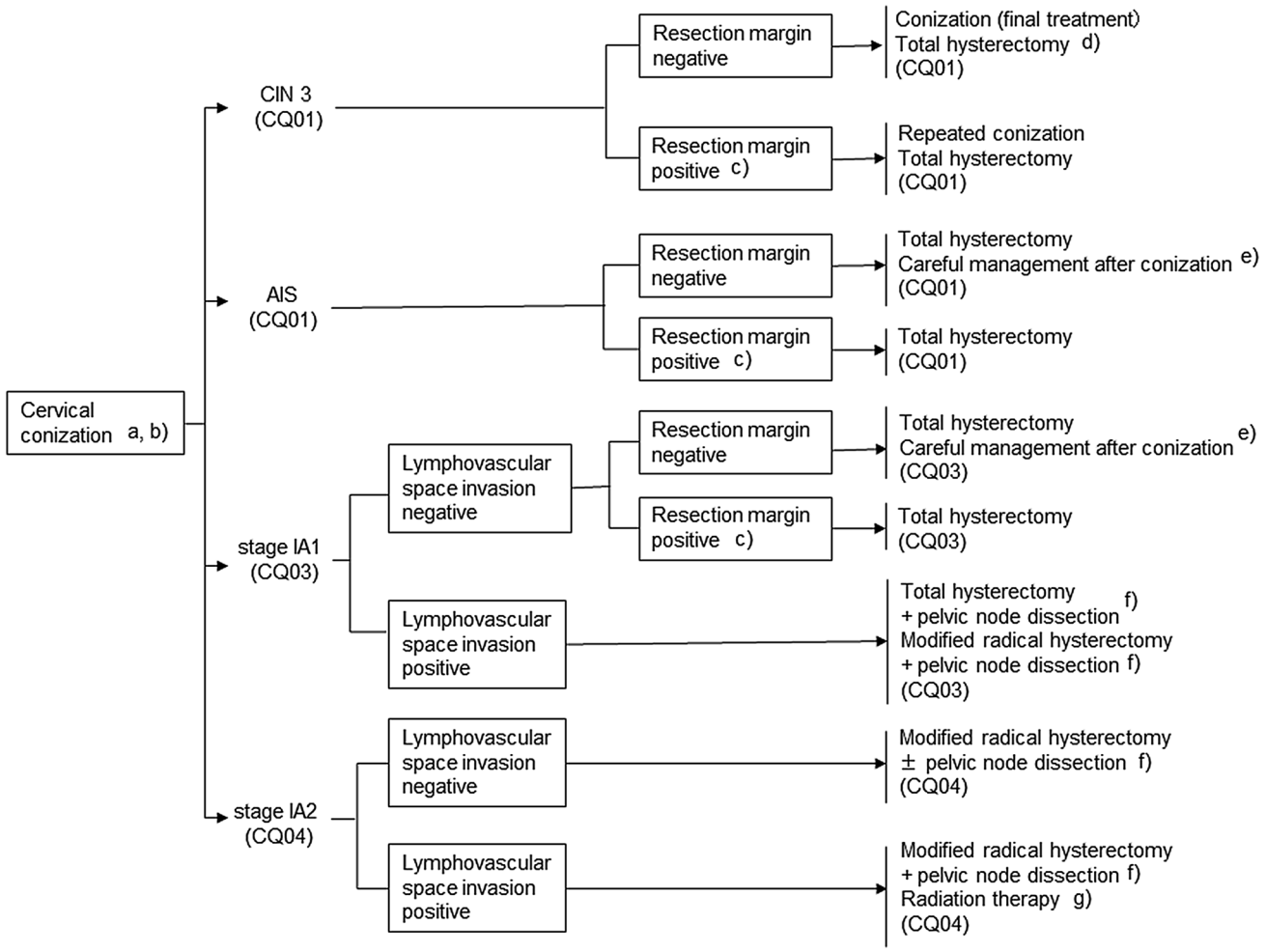

Fig. 1 Flow chart 1: primary treatment for cervical precancerous lesions (CIN 3 and adenocarcinoma in situ) and IA cervical cancer. Flow of the treatment based on a diagnosis with cervical conization. **a** The cervical conization should aim for a diagnosis or a diagnosis and treatment. If cervical curettage is positive, the patient should be treated as if they have positive margins. **b** The flow chart is based on a diagnosis with the resected specimen of the cervical conization. However, if cervical conization is difficult because of atrophy of the cervix, such as in older patients, omission of the cervical conization may be considered. However, prior to surgery, it is necessary to carefully review the cytology, colposcopy, and biopsy tissue findings; this allows for the performance of a hysterectomy suitable for the estimated lesion. **c** In the case with positive stump, a lesion should be diagnosed as more than CIN 3 (squamous lesions) or AIS (glandular lesions). **d** Hysterectomy may be considered if the patient does not wish to preserve her fertility. **e** When the patient strongly wishes to preserve her fertility, this is considered. Residual lesions are reportedly found in about 20% of cases involving negative margins. Careful inspection is required to preserve the uterus. **f** Operative procedures should be individualized according to the histopathological findings of the cervical conization specimens, namely the extent of invasion and the presence or absence of lymphovascular space invasion. **g** When surgical treatment is difficult because patients are elderly or there are medical complications, radiation therapy is also an option

CQ01. What treatments are recommended for CIN 3/AIS diagnosed by cervical conization?

Recommendations

1. Cervical conization is recommended as the final treatment for CIN 3 patients with negative resection margins (grade A).
2. Total hysterectomy is recommended for patients with AIS (grade B).
3. Repeated cervical conization or total hysterectomy is considered for CIN 3 patients with a positive resection margin (grade C1).
4. Uterus preservation is considered for AIS patients with a negative resection margin and who strongly desire fertility preservation; however, careful management is required (grade C1).

CQ02. What treatments are recommended for recurrent CIN 3 following conservative treatment?

Recommendations

1. Repeated cervical conization is recommended (grade B).
2. Total hysterectomy is also recommended in the case it is negative for invasive cancer after thorough examination (grade B).

CQ 03. What treatments are recommended for stage IA1 disease?

Recommendations

1. Total hysterectomy is recommended for patients who show no evidence of lymphovascular space invasion (grade B).
2. In case with lymphovascular space invasion, the addition of the pelvic lymph node dissection is considered at the same time with total hysterectomy or modified radical hysterectomy (grade C1).
3. Preservation of the uterus can be considered by performing a cervical conization in patients who strongly desire fertility preservation; however, these patients must have no lymphovascular space invasion, negative resection margins, and negative histological results from endocervical curettage (grade B).

CQ 04. What treatments are recommended for stage IA2 disease?

Recommendations

1. Modified radical hysterectomy with pelvic lymph node dissection is considered (grade C1).
2. After thorough histopathological examination of a specimen obtained by diagnostic cervical conization, omission of pelvic lymph node dissection in patients with no lymphovascular space invasion can be considered (grade C1).

Comments

Frequency of pelvic lymph node metastases in the case of stage IA2 cervical cancer is 0–10%, and that of lymphovascular space invasion is 2–30%. The risk of invasion to the parametrial tissue is very low [10]. According to a survey on surgery of stage IA2 cases in Japan, a simple total hysterectomy was performed in 17% of cases, modified radical hysterectomy including pelvic node dissection in 38%, and

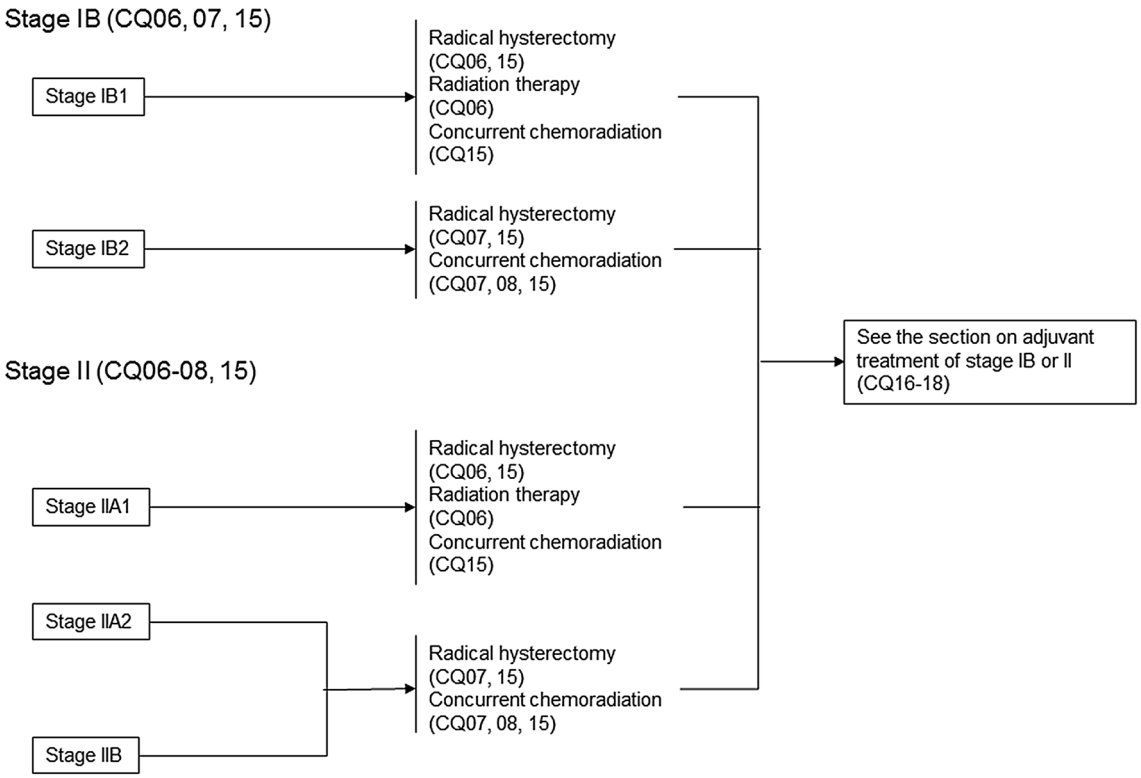

Fig. 2 Flow chart 2: primary treatment for stage IB–II cervical cancer (including squamous cell carcinoma and adenocarcinoma)

radical hysterectomy in 22% [11]. In the National Comprehensive Cancer Network (NCCN) guidelines 2016, modified radical hysterectomy with pelvic lymph node dissection was recommended for patients without fertility preservation [12].

CQ 05. What treatments are recommended if the disease is upstaged to stage IB or higher following total hysterectomy?

Recommendations

Adjuvant radiotherapy or concurrent chemoradiotherapy (CCRT) is considered (grade C1).

Chapter 3: Primary treatment for stage IB–II cervical cancer

Primary treatment for stage IB–II cervical cancer is summarized as flow chart 2 (Fig. 2).

The primary treatment of stage IB–II cervical cancer in Japan is either surgery or definitive radiotherapy including concurrent chemoradiotherapy (CCRT). For patients with stage IB or IIA disease, surgery and radiotherapy are options as per the NCCN guidelines 2016. However, for stage IIB cases the surgical option is not shown [12]. This disparity is due to differing surgical methods between Japan and Western countries. Radical hysterectomy in Western countries is basically a Wertheim operation, and cannot treat locally advanced cervical cancer. In contrast, radical hysterectomy in Japan was developed by Professor Hidekazu Okabayashi as an operative method with higher curability. Additionally, as a result of this invention—an improvement of its forerunner—it has been established as the most complete operative procedure. Okabayashi's radical hysterectomy method had the characteristics of wide extirpation of the parametrial tissue and a quite novel finding on separation of the posterior leaf of the vesico–uterine ligament. These procedures enabled the surgeon to separate the bladder with the ureter completely away from the lateral side of the cervix and vagina. Therefore, the cardinal ligament and vagina can be more extensively resected, and curability of patients with stage IIB cervical cancer increased. In other words, we need to note that radical hysterectomy in Japan differs in operative procedure and radicality from that in Western countries. However, data on treatment outcomes of the Okabayashi radical hysterectomy method in Japan are scarce; therefore, accumulation and dissemination of evidence are needed.

CQ 06. What treatments are recommended for stage IB1 and IIA1 squamous cell carcinoma?

Recommendations

1. Radical hysterectomy or radiation therapy is recommended (grade B).
2. Pelvic nerve preservation can be considered when curability is not impaired (grade C1).

Comments

In Japan, surgical treatment is chosen at a high rate as the primary treatment for stage IB1 and IIA cervical cancer. In addition to high curability by Okabayashi's radical hysterectomy method, there is a history of operative procedures to preserve functions being improved. According to a survey on surgery for stage IB1 and IIA1 cases in Japan, surgery was performed in 90% and 66% of cases, respectively, and definitive radiotherapy without surgery in 9% and 33% [11].

CQ 07. What treatments are recommended for stage IB2 and IIA2 squamous cell carcinoma?

Recommendations

Radical hysterectomy (+adjuvant therapy) or CCRT is recommended (grade B).

Comments

The primary treatment of stage IB2 or IIA2 cervical cancer is either surgery or radiotherapy. Surgical treatment including radical hysterectomy in Japan is more commonly chosen than in Western countries. According to a survey on surgery for stage IB2 and IIA2 cases in Japan in 2014, surgery was performed in 79% and 59% of cases, respectively, and definitive radiotherapy without surgery in 19% and 39% [11]. In recent years, a tendency to choose radiotherapy for this patient group is increasing in Japan. However, surgical treatment is still more commonly chosen.

Benefits of surgical treatment include the following: an evaluation of recurrent risk based on histopathological findings is possible, and individualization in post-primary treatment is made possible. Ovarian transposition allows function-preservation of the ovary. Nerve-sparing radical hysterectomies for patients with stage IB 2 or IIA cervical cancer have been reported [13, 14], but curability must be secured via the surgery.

CQ 08. What treatments are recommended for stage IIB squamous cell carcinoma?

Recommendations

Radical hysterectomy (+adjuvant therapy) or CCRT is recommended (grade B).

Comments

The primary treatment for stage IIB cervical cancer in Japan differs greatly from that in Western countries; CCRT is often chosen as the primary treatment for this cancer in the West. However, surgical treatment including radical hysterectomy has been chosen more as the primary treatment in Japan. According to a survey on the treatment of stage IIB2 cases in Japan in 2014, surgery was performed in 44% of them [11]. Additionally, patients treated with radiotherapy are increasing.

CQ 09. Is neoadjuvant chemotherapy recommended for stage IB and II squamous cell carcinoma?

Recommendations

Neoadjuvant chemotherapy can be considered depending on the extent and size of the tumor (grade C1).

Proposals for future directions

In recent years, neoadjuvant chemotherapy (NAC) has been re-evaluated and benefits including improved quality of life (QOL) have been suggested in some meta-analyses. However, evidence of improvement of prognosis has been obtained less than for standard treatment such as CCRT. There are many reports of good prognosis in NAC responders. Therefore, it would be desirable to have clinical trials taking into account individualized factors including drug selection, case selection, and optimizing injection route.

CQ 10. Is laparoscopic and robotic surgery recommended for stage IB and II cases?

Recommendations

Laparoscopic surgery and robot-assisted surgery is considered for small-sized stage IB and II cases, by gynecological oncologists who have mastered the surgical procedures, or under cooperative framework by gynecologists with certified endoscopic surgical skill and gynecological oncologists (grade C1).

Proposals for future directions

Endoscopic surgery (laparoscopic surgery and robot-assisted surgery) for cervical cancer is rapidly spreading abroad. Spread of these surgeries in Japan is comparably slow. In Japan, patients with cervical cancer must receive similar treatments to those given in foreign countries. A system and a method of education for permeation of endoscopic surgery need to be established at the same time while securing safety and intensity of treatment, for prognosis that is not inferior to those from previous, conventional treatments. However, it is important to accumulate and test data on safety and validity in Japan. It would be desirable for endoscopic surgery for cervical cancer patients to be performed as practical medical care in Japan in the near future.

CQ 11. For whom is conservative surgery indicated?

Recommendations

Radical trachelectomy can be considered as a reasonable fertility-sparing treatment option for patients with stage IA2 or IB1 cervical cancer with lesions ≤ 2 cm in diameter (grade C1).

Proposals for future directions

Cooperation of pathologists, reproductive experts, perinatologists, and neonatologists is essential for perform radical trachelectomy. Careful discussion is also necessary on the indication and practice of this surgery. At the same time, it is also important in Japan to accumulate and test data about safety and validity.

CQ 12. Is omission of pelvic lymph node dissection using sentinel lymph node biopsy recommended?

Recommendations

Sentinel lymph node biopsy should be performed in institutions where pathologists cooperate with experienced surgical teams in clinical trials. Omission of pelvic lymph node dissection in patients with negative sentinel lymph node biopsy is considered in institutions in which accuracy and safety have been fully confirmed (grade C1).

Proposals for future directions

Omission of pelvic lymph node dissection for patients with negative sentinel lymph node biopsy should be performed

under the approval of the ethical review board at the institutions where safety has been confirmed by clinical trials via a backup pelvic lymph node dissection. Whether this biopsy can become the general practice in the future should be discussed based on accumulation of data on safety and validity from each institution, verifying the outcomes in many institutions. Validation to establish the significance of extensive pathological investigation for sentinel lymph nodes is also necessary.

CQ 13. Is ovary preservation recommended in radical hysterectomy?

Recommendations

1. Ovary preservation is recommended without compromising curability if appropriate case selection is performed by considering the patient's age, histological type, or stage (grade B).
2. If the ovaries are to be preserved, ovarian transposition and fixation outside of the pelvic radiation field can be considered (grade C1).

Proposals for future directions

It is not necessarily clear for what type of case the benefits of ovarian preservation outweigh the risk. Investigation of this will be necessary in the future.

CQ14. Is para-aortic lymph node dissection/sampling relevant for stage IB and II cases?

Recommendations

Para-aortic node sampling or dissection can be considered in cases at high risk for para-aortic lymph node metastasis (grade C1).

Comments

Para-aortic lymph node metastases are one of the distant metastases of cervical cancer and are thought to have an important prognostic factor [15–17]. Performing para-aortic lymph node sampling/dissection has both diagnostic and medicinal significance. Para-aortic lymph node dissection for the purpose of diagnostic significance is not performed routinely in Japan because standard treatment is not definitively decided on regarding postoperative therapy for para-aortic node-positive cases. Para-aortic lymph node dissection is individually discussed and performed.

CQ 15. What treatments are recommended for stage IB and II adenocarcinoma?

Recommendations

1. Radical hysterectomy (+ adjuvant therapy) can be considered (grade C1).
2. CCRT can be also considered (grade C1).

Proposals for future directions

Some studies suggest surgical treatment has better outcomes than definitive radiotherapy for patients with cervical adenocarcinoma. There are no RCTs that have directly compared both and the treatment strategy is not separated by the histologic type in non-Japanese guidelines. Accumulation of evidence in Japan is necessary in the future. Additionally, gastric-type mucinous carcinoma has been reported to have a poorer prognosis than usual-type. Clinical management is not individualized and is a future problem to be considered.

Chapter 4: Postoperative therapy for stage IB–II cervical cancer

Postoperative therapy for stage IB–II cervical cancer is summarized as flow chart 3 (Fig. 3).

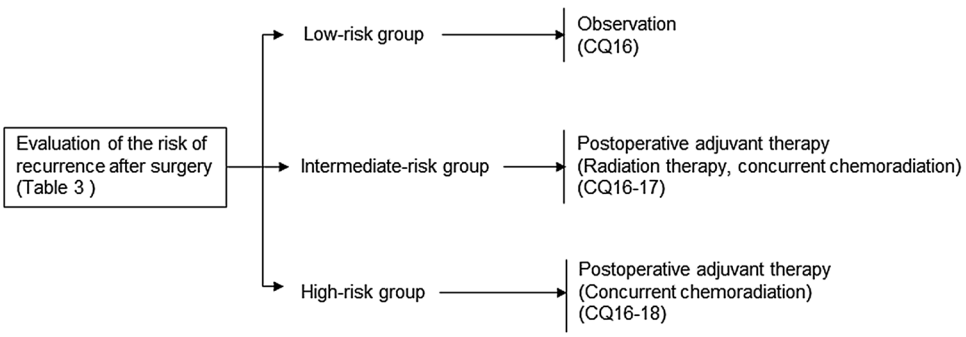

Fig. 3 Flow chart 3: postoperative therapy for stage IB–II cervical cancer (including squamous cell carcinoma and adenocarcinoma). Many discussions and reports exist on risk assessment for postoperative recurrence. Postoperative therapy must be considered according to the individual case

Table 3 Classification of risk of postoperative cervical cancer recurrence

Low-risk group: Patients who meet all the following criteria
1. Small cervical tumor
2. Negative pelvic nodes
3. Negative parametrical invasion
4. Shallow cervical stromal invasion
5. No lymphovascular space invasion
Intermediate-risk group: patients with negative pelvic nodes and negative parametrical invasion but who meet one of the following criteria
1. Large cervical tumor
2. Deep cervical stromal invasion
3. Positive lymphovascular space invasion
High-risk group: patients who meet one of the following criteria
1. Positive pelvic nodes
2. Positive parametrical invasion

Note: Various classifications and reports exist for the volume of cervical tumor, depth of cervical stromal invasion, number or area of positive pelvic lymph node metastases, and the number of risk factors for recurrence. Therefore, we judged that it was not appropriate to determine risk using the volume of cervical tumor or depth of the concrete invasion. The risk factors were described like as "shallow or deep" or "large or small." For volume of cervical tumor, many reports have adopted 4 cm as recommended by the International Federation of Gynecology and Obstetrics (FIGO) staging system. Treating positive lymphovascular space invasion is still controversial.

Additional statement: In the NCCN Clinical Practice Guidelines of cervical cancer, "resection margin positive" is treated as a risk of postoperative recurrence. However, it was excluded from postoperative recurrent risk factors in this chapter for the following reasons: (1) in the "General rules for clinical and pathological management of uterine cervical cancer, third edition" (2012) [30], treatment of the patient whose tumors were apparently persistent was defined not as a postoperative radiation case but rather as a "radiation therapy of persistence case." If a positive resection margin is included as a postoperative recurrent risk factor, consistency with the general rules for clinical and pathological management would not be ensured. This might cause unnecessary trouble in clinical practice. (2) The positive resection margin has a different meaning in Japan to in Western countries. In Japan, a positive resection margin means that CIN 3 or more lesions are persistent. In contrast, in Western countries, it generally means that the invasive tumor is persistent. Therefore, it will be inappropriate to directly draw research data from Western countries and employ this for treating Japanese patients.

Adjuvant therapy is indicated after surgery depending on histopathological findings of surgical specimens with regard to preventing recurrence [18–29]. Factors that should warrant consideration of adjuvant therapy include pelvic lymph node metastases, parametrial invasion, depth of cervical stromal invasion, tumor diameter, and lymphovascular space invasion (Table 3). Individual cases are classified into low-, intermediate-, and high-risk groups through the combination of these factors. For cases with these recurrent risk factors, radiotherapy, CCRT, or chemotherapy is added as adjuvant therapy. However, observation is appropriate for low-risk patients.

CQ 16. What is the recommended postoperative adjuvant therapy?

Recommendations

1. CCRT is recommended for patients in high-risk group (grade B).
2. Radiation therapy is recommended for patients in intermediate-risk group. However, CCRT can be considered depending on the number and extent of risk factors (grade C1).

Proposals for future directions

In Japan, many institutions treat patients with intermediate or high risk of recurrence with chemotherapy as adjuvant therapy. However, validity is not yet proven for postoperative chemotherapy. Whether chemotherapy can become an adjuvant postoperative treatment must be determined based on future evidence.

CQ17. What irradiation methods are recommended when performing postoperative adjuvant radiotherapy?

Recommendations

Whole-pelvis irradiation is recommended (grade B).

Comments

Irradiation ranges of postoperative radiation are usually considered to encompass the whole pelvis region (whole pelvis radiotherapy) [31]. The clinical target volume (CTV) of whole pelvic radiotherapy is the pelvic lymph node region, supravaginal region (from the vaginal stump to approximately 3 cm of the lower part), parametrial tissue, and paravaginal tissue. Guidelines have been already formulated in United States and Japan for the setting of CTV in postoperative whole pelvic radiotherapy [32, 33]. Three dimensional-conformal radiotherapy (3D-CRT) is a common irradiation method for planning target volume (PTV) that adds an appropriate margin to CTV from four directions, including back and forth and around. For whole pelvic radiotherapy, a dose of 45–50 Gray (Gy) (in fractions of 1.8–2.0 Gy/daily) is recommended [31, 34]. Recently, intensity-modulated radiation therapy (IMRT)

has come into use for postoperative irradiation. IMRT can reduce the radiation dose for normal tissues, such as the small intestine, rectum, bladder, or bone marrow, as compared with normal 3D-CRT. IMRT is expected to reduce complications concerning postoperative irradiation [35–39].

CQ18. For whom is prophylactic para-aortic irradiation indicated?

Recommendations

1. Prophylactic para-aortic irradiation is considered for patients diagnosed through diagnostic imaging or pathological examination as para-aortic node metastasis-positive (grade C1).
2. Prophylactic para-aortic irradiation is not recommended for patients who have no evidence of para-aortic node metastasis as seen through diagnostic imaging and have no pathological examination (grade C2).

Comments

There are few large-scale randomized controlled trials (RCTs) of prophylactic irradiation of the para-aortic lymph nodes. The main treatment is radiotherapy and is not intended for adjuvant postoperative treatment. One study showed a significantly good survival rate in its irradiation group (Radiation Therapy Oncology Group; RTOG79-20) [40]. There were no significant differences in a different report (European Organization for Research and Treatment of Cancer; EORTC) [41]. The prophylactic irradiation of the para-aortic lymph nodes region remains inconclusive in improving the survival rate.

Chapter 5: Primary therapy for stage III–IV cervical cancer

Primary treatment for stage III–IV cervical cancer is summarized as flow chart 4 (Fig. 4).

CCRT has been shown to improve survival rate in multiple RCTs in Europe and the United States involving patients with stage IB2-IVA cervical cancer. At this time, CCRT including cisplatin is one of the standard treatments for locally advanced cervical cancer [42–45].

Stage IVB cases vary depending on the condition in which an isolated metastasis is found to the situation in which complete cure cannot expected by systemic metastasis. The former receives systemic chemotherapy or surgical treatment of the metastatic lesion, and CCRT is added as local treatment when these treatments are effective. However, QOL-improvement by palliation becomes the first aim of the treatment in the latter.

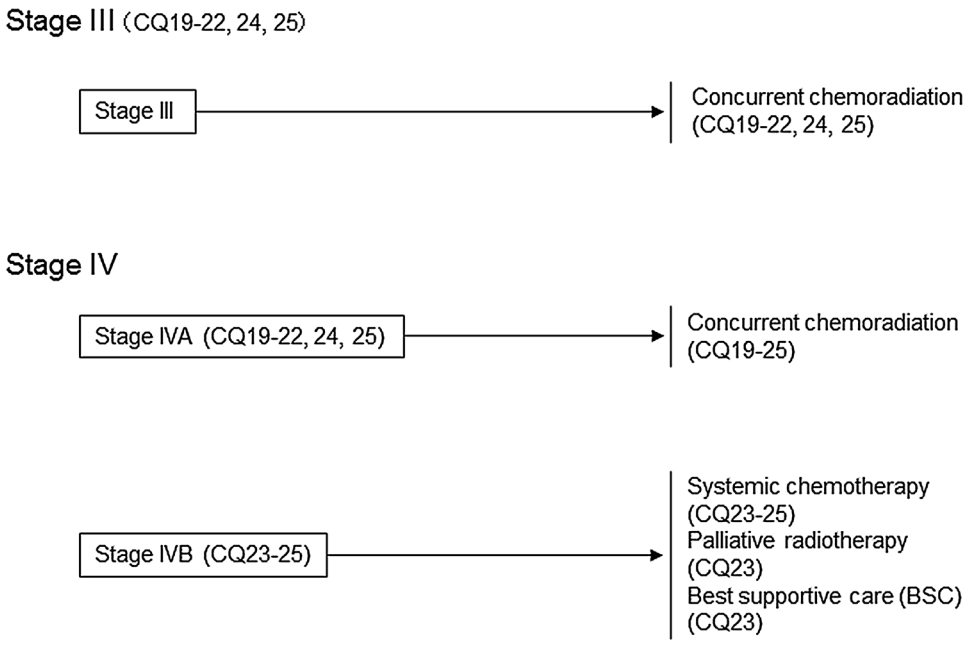

Fig. 4 Flow chart 4: primary treatment for stage III–IV cervical cancer (including squamous cell carcinoma and adenocarcinoma)

CQ 19. Which is the recommended radiotherapy for stage III and IVA disease: definitive radiotherapy or CCRT?

Recommendations

CCRT is recommended (grade B).

CQ 20. What CCRT regimens are recommended for stage III and IVA disease?

Recommendations

Regimens that include cisplatin are recommended (grade A).

CQ 21. Is chemotherapy recommended prior to principal treatment for stage III and IVA disease?

Recommendations

1. Chemotherapy is not recommended before radiotherapy (grade D).
2. Chemotherapy is not recommended before surgery (grade C2).

CQ 22. Is surgery recommended for stage III and IVA disease?

Recommendations

Surgery is not recommended (grade C2).

CQ23. What treatments are recommended for stage IVB disease?

Recommendations

1. Systemic chemotherapy can be considered for patients with a good performance status and preserved organ function (grade C1).
2. When systemic chemotherapy is given, combination with bevacizumab is recommended (grade B).
3. If the patient has severe symptoms accompanying oncological complications, palliative radiotherapy of the causal lesion is recommended (grade B).

Comments

A chemotherapy regimen that uses cisplatin or carboplatin together with paclitaxel was reported to be relatively effective [46, 47]. For metastatic or recurrent cervical cancer, the Japan Clinical Oncology Group (JCOG) 0505 randomized phase III study of either conventional paclitaxel plus cisplatin (TP) or paclitaxel plus carboplatin (TC) was conducted. Non-inferiority of TC was shown with regard to overall survival [48].

CQ 24. What treatments are recommended for stage III or IV adenocarcinoma?

Recommendations

1. CCRT is recommended for stage III or IVA adenocarcinoma (grade B).
2. A platinum-containing drug, either as monotherapy or as part of combination chemotherapy, can also be considered for patients with stage IVB adenocarcinoma with preserved organ function (grade C1).

CQ 25. What treatments are recommended for cases with T3 or T4 in the TNM staging system and that have positive para-aortic lymph node metastasis?

Recommendations

CCRT with extended-field radiotherapy is considered after discussing age, general status, organ function, previous history, and estimated adverse events (Grade C1).

Comments

Diagnostic images in the advanced cervical cancer stage are recommended for evaluating local extension or distant metastasis of the tumor [30]. Diagnostic images are also considered useful for evaluating for the presence or absence of lymphadenopathy. The imaging study is also recommended to evaluate this presence or absence of lymphadenopathy in the NCCN guidelines 2016. In those guidelines, extraperitoneal or laparoscopic lymph node dissection is considered when an enlarged para-aortic lymph node is found in the imaging study [12]. Extremely few institutions in Japan evaluate the presence or absence of para-aortic lymph node metastases in surgical staging. In most Japanese institutions, that presence or absence of lymph node metastasis is diagnosed using an imaging study (CT, MRI, and PET/CT).

Chapter 6: Therapies for relapsed cervical cancer

Therapy for relapsed cervical cancer is summarized as flow chart 5 (Fig. 5).

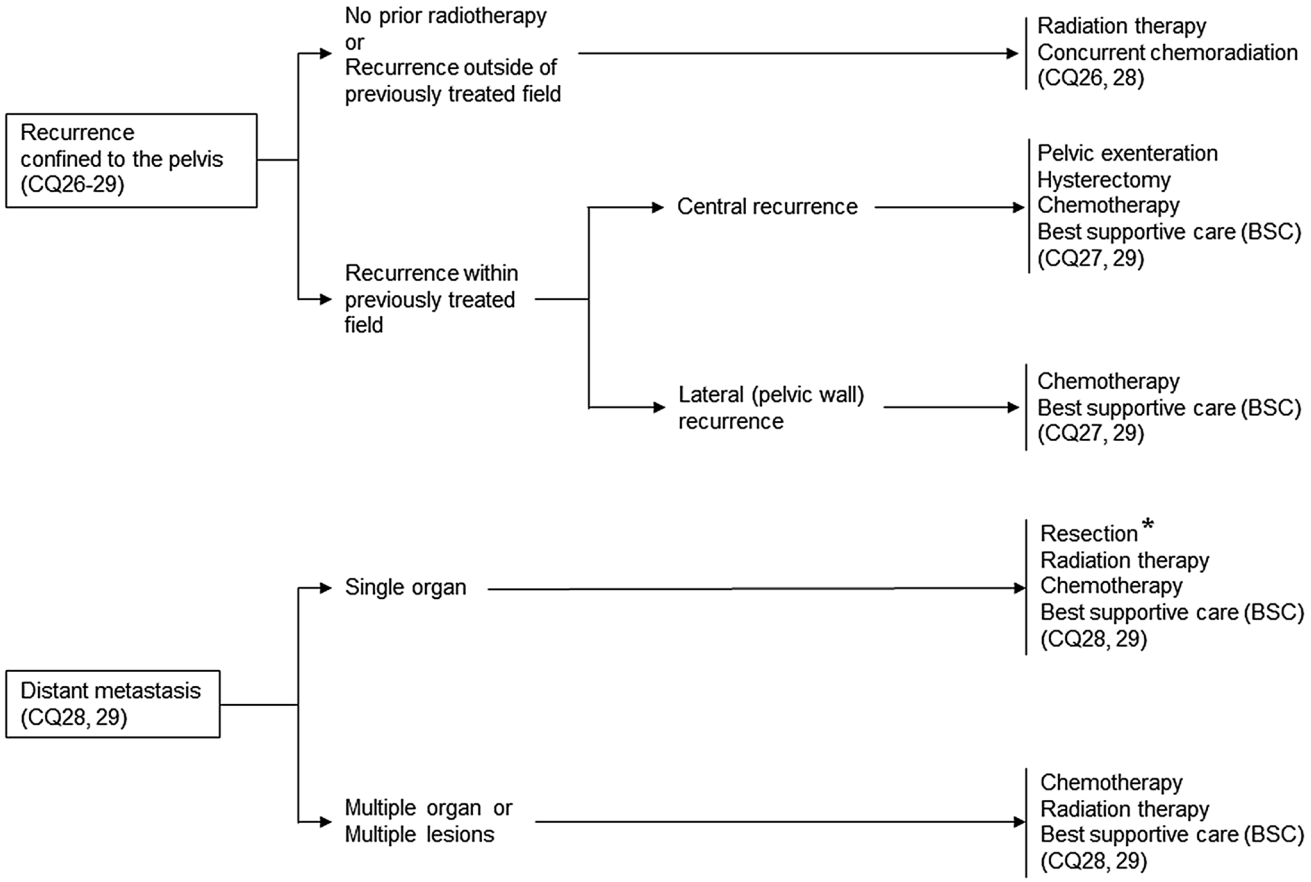

Fig. 5 Flow chart 5: therapy for relapsed cervical cancer (including squamous cell carcinoma and adenocarcinoma). *The therapeutic strategy will differ according to the metastasized organ or by the number of lesions

Treatment strategies for recurrent cervical cancer vary greatly depending on the site of recurrence, presence of past irradiation, age, or general condition. Therefore, individualization is important. Apart from that concern, for cases that have residual diseases after incomplete surgery, the same treatments in this chapter are recommended as radiotherapy for the residual recurrence [49–51].

CQ 26. 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 also be considered (grade C1).

CQ27. What treatments are recommended for recurrence within the radiation field?

Recommendations

1. Palliative treatment for symptom relief can be considered (grade C1).
2. Chemotherapy can also be considered for symptom relief (grade C1).
3. Pelvic exenteration or hysterectomy can also be considered for central recurrence in the vaginal stump or uterine cervix (grade C1).
4. Re-irradiation is not recommended (grade C2).

CQ 28. What treatments are recommended for recurrence outside the radiation field or for extrapelvic recurrence if radiotherapy has not been previously performed?

Recommendations

Para-aortic lymph node metastasis

Radiation therapy or CCRT can be considered for metastasis confined to para-aortic lymph node metastasis (grade C1).

Brain metastasis

1. Stereotaxic radiosurgery along with whole-brain radiation therapy (WBRT) or tumor resection along with WBRT is recommended for solitary brain metastases (grade B).
2. Stereotaxic radiosurgery with WBRT, or WBRT alone, is recommended for metastases at two–four sites (grade B).
3. WBRT is recommended for five or more metastases (grade B).

Bone metastasis

1. Single-fraction or multi-fraction radiotherapy is recommended for pain relief (grade B).
2. Bisphosphonates are recommended for symptom relief (grade B).
3. Strontium chloride can be considered for multiple bone metastases if medical therapy is ineffective (grade C1).

Lung metastasis

Resection or stereotactic body radiotherapy can be considered for one–three localized metastases (grade C1).

CQ 29. What systemic chemotherapy regimens are recommended to treat recurrent disease?

Recommendations

1. A platinum-containing drug as either monotherapy or part of two-drug combination chemotherapy is recommended (grade B).
2. Regimens containing bevacizumab are recommended (grade B).
3. A platinum-containing drug as either monotherapy or part of two-drug combination chemotherapy is preferable for recurrent adenocarcinoma (grade C1).

Comments

QOL is also as important as the response rate in chemotherapy for recurrent cervical cancer. Less-toxic monotherapy has been considered as an option. Breadth of the drug selection within the Japanese insurance has recently broadened regarding application of paclitaxel or topotecan. Development of more effective and less toxic treatments is being pushed forward by the introduction of molecularly targeted drugs, including bevacizumab.

RCTs of TC therapy and TP therapy were performed in JCOG (JCOG0505). In this trial, non-inferiority of TC therapy was examined, and this non-inferiority was shown to be significant. Survival was longer with TP group among patients who had not received prior cisplatin. At the same time, TC therapy showed a good prognosis in patients with prior platinum administration [48]. Considering cisplatin is already used in CCRT or adjuvant postoperative treatment as an initial treatment for many cervical cancer patients, TC therapy is one of the regimens that should be considered for recurrence.

Nedaplatin developed in Japan is one of the platinum-containing drugs, and the response rate with the single agent for cervical cancer is high, at 34–41% [52, 53]. Clinical trial results with combination therapy with irinotecan or paclitaxel have also been reported. Nedaplatin is a useful drug for cases with renal dysfunction [54, 55].

Chapter 7: Management of cervical cancer during pregnancy

The frequency of cervical cytological abnormalities in the pregnant woman is presumed as approximately 1–5% [56]. CIN 3 or microinvasive cancer are common, and the frequency of invasive cancers is reported as 1–12 per 10,000 pregnancies [57–59]. Recently in Japan, the peak of the maternal age and the onset of cervical cancer tend to overlap because cervical cancer patients are becoming younger and women are marrying later in life. Therefore, cervical cytological abnormality during pregnancy is often experienced. It is not rare to be diagnosed with cervical cancer by screening cytodiagnosis during pregnancy.

CQ 30. What treatments are recommended for CIN 3/AIS disease during pregnancy?

Recommendations

1. Cervical conization should be delayed until after delivery as long as the diagnosis is CIN 3 disease, based on consistent cytology, colposcopy, or biopsy analysis results (grade B).
2. If an AIS is suspected via punch biopsy, a cervical conization is considered to determine the diagnosis during pregnancy (grade C1).

CQ 31. What treatments are recommended for women suspected of having stage IA disease during pregnancy?

Recommendations

If stage IA is suspected, a cervical conization is recommended to determine the diagnosis during pregnancy (grade B).

Comments

As a result of cervical conization, the pregnancy can continue when the lesion is stage IA1 squamous carcinoma, with no invasive lesion on the stump, and no lymphovascular space invasion. A spontaneous vaginal delivery is possible if there are no obstetrical abnormalities [49]. The possibility of uterine preservation needs to be individually examined in the following cases: (1) stage IA1 squamous cancer with positive micro invasive cancer on the stump, (2) stage IA2 squamous cancer, and (3) stage IA1 or IA2 adenocarcinoma.

CQ32. What treatments are recommended for stage IB / II invasive cancer during pregnancy?

Recommendations

1. Standard treatment after delivery can be considered if the diagnosis made during the gestational period indicates the fetus can survive outside the uterus (grade C1).
2. Therapeutic strategy should be discussed individually if the diagnosis made during the gestational period indicates the fetus cannot survive outside the uterus. Staging or gestational weeks need to be taken into consideration (grade C1).
3. Standard treatment after prompt termination of the pregnancy is considered in cases with positive lymph-node metastasis or advanced cases with stage II–IV disease (Grade C1).
4. Administration of chemotherapeutic drugs is not recommended during the first trimester because these can cross the placenta to the fetus (Grade D).

Chapter 8: Surveillance after treatment for cervical cancer

There are no reliable clinical studies about surveillance after treatment of cervical cancer, and no consensus of views [60]. Previously, surveillance was aimed at prompt therapy and improved prognosis by early detection of recurrence. At the same time, attention needs to be paid to whether adverse effects of treatment affect QOL [61]. Generally, approximately 75% of recurrence occurs within 3 years after initial treatment, and the surveillance of this period is particularly important [62]. However, in survivors of cervical cancer for 5 years or longer, complications with treatment led to impaired QOL [63–65]. Long-term observation is therefore necessary. Menopause with treatment leads to decreased QOL because cervical cancer patients in particular are younger than those with other gynecologic cancers.

CQ 33. What intervals are recommended for post-treatment surveillance?

Recommendations

The following intervals are recommended for standard surveillance (grade C1):

For the first 1–2 years: every 1–3 months.
3rd year: every 3–6 months.
4th and 5th years: every 6 months.
6th year onward: every 12 months.

CQ 34. What investigations and examinations should be performed during post-treatment surveillance?

Recommendations

1. Physical examination (including pelvic and rectal examination), cytological examination, blood test, biochemical examination, measurement of tumor markers, and diagnostic imaging should be considered (grade C1).
2. Any complications associated with surgery, radiotherapy, or chemotherapy should be noted (grade C1).

CQ 35. Is hormone replacement therapy (HRT) after cancer treatment recommended?

Recommendations

HRT, after informing the patient about its advantages and disadvantages, should be considered for individual patients (Grade C1).

Proposals for future directions

For younger patients who acquire surgical menopause after cervical cancer treatment, it is clear that disadvantages are substantial when HRT is foregone. Describing these

recommendations in this CQ was unavoidable because there is little evidence that HRT does not raise recurrent risk. However, in the "Hormone replacement therapy guidelines 2017 version," HRT was strongly recommended for patients who acquire surgical menopause after cervical cancer treatment. New evidence needs to be accumulated in the future on whether HRT is associated with the prognosis.

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