# Chapter 4■ Stage Ib and II disease

## Overview

Radical hysterectomy is the recommended treatment for stage Ib and II disease. Definitive radiotherapy is an option to surgical treatment.

In Western countries, definitive radiotherapy and surgery are considered to have no difference in the disease-free survival time or overall survival time. In the U.S. National Comprehensive Cancer Network (NCCN) and National Cancer Institute (NCI) guidelines, surgery and radiotherapy are considered parallel treatment options for stage Ib and IIa disease. The abovementioned guidelines do not recommend surgery as an option for stage IIb disease. In Japan, 62% of stage IIb patients underwent surgery according to the statistics (2003) published by the Gynecologic Oncology Committee of the Japan Society of Obstetrics and Gynecology. In Japan, Okabayashi developed and promoted radical hysterectomy as a treatment with a high cure rate. Thereafter, this procedure has been modified and improved by many surgeons, resulting in the refinement of a highly optimized procedure.

Neoadjuvant chemotherapy (NAC) is sometimes performed for stage Ib and Ia lesions with a large tumor diameter, and for IIb disease to improve the prognosis. However, there is no clear evidence demonstrating an improved prognosis, and the indications and usefulness of NAC will be the topic of future studies.

Risk factors for postoperative recurrences include tumor diameter, depth of cervical stromal invasion, pelvic lymph node metastases, parametrial invasion, vascular infiltration, and lymphatic infiltration. In general, patients with these risk factors present also undergo adjuvant therapy. Radiotherapy is selected if risk factors other than positive lymph node metastases are detected in histopathological examination of excised specimens. Concurrent chemoradiotherapy (CCRT) is recommended for patients with positive lymph node metastases.

Definitive radiotherapy can be considered for stage IIb disease, and stage Ib2 or IIa disease with a tumor diameter >4 cm. In addition, definitive radiotherapy is an option for elderly patients, and patients with concurrent diseases in whom surgical treatment is difficult. If definitive radiotherapy is considered, CCRT is preferable. The tolerability of CCRT has not been sufficiently verified in Japanese women, however, so it should be applied with careful consideration.

# I. Surgery

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

**Recommendation**

Radical hysterectomy is recommended (Grade A').

Background and Objectives

Treatment strategies for cervical cancer differ greatly between Western countries and Japan. Radiotherapy is the primary treatment in Western countries, whereas radical hysterectomy is used in Japan. Radical hysterectomy has been modified and improved by our predecessors. As a result, it is now a highly optimized procedure used by many institutions. We examined surgical procedures recommended for stage Ib-II disease.

**Explanations**

Treatments for stages Ib-II uterine cervical cancer differ between countries and medical institutions. According to the 2003 annual report of uterine cervical cancer patients published by the Gynecologic Oncology Committee of the Japan Society of Obstetrics and Gynecology, surgery was selected as the primary treatment for 1410 of 1555 patients with stage Ib disease (91%), and radiotherapy in 141 patients (9%). Of 758 patients with stage IIb disease, 280 patients (37%) did not undergo surgery but rather had radiation monotherapy, or concurrent chemoradiotherapy. Surgery was performed for 468 stage IIb patients (62%), many of whom (41%) underwent surgery + radiotherapy.[6] Another study found no significant difference in outcomes between class II surgical procedures (correspond to modified radical hysterectomy) and class III surgical procedures (correspond to radical hysterectomy).[7] In Japan, radical hysterectomy is generally the treatment of choice.

In the U.S., surgery is indicated up to and including stage IIa, and stage IIb and radiotherapy for more advanced cancer.[1-3] In one study, no differences in therapeutic outcomes were reported between radical hysterectomy and radiotherapy for stage Ib and IIa disease. Grade 2 and 3 adverse events were significantly more common in the group that underwent surgery.[4] Another study reported no significant difference in therapeutic outcomes between radiotherapy and radical hysterectomy for stage Ib disease.[5] In Western countries, radiotherapy is the initial treatment of choice. In Japan, the primary treatment is surgery. Selection of surgery or radiotherapy should be determined by age, performance status (PS), and concurrent conditions.

The possibility of micro invasion should also be considered for resection of the vaginal wall in radical hysterectomy. When resected specimens from radical hysterectomy were actually measured, the mean vaginal wall resection was reported to be approximately 2 cm.[9,10] Sufficient surgical margins are necessary for curative vaginal

wall resection. Since excessive resection can lead to sexual dysfunction and urinary disorders,[10,11] depending on the patient consideration should be given to leaving some portion of the vaginal wall.

For bulky tumors of >4cm such as in stage Ib2, therapeutic outcomes were reported to improve with concurrent chemo radiotherapy (CCRT).[8] There is alck of evidence whether or not outcomes can be improved by chemotherapy prior to radical surgery (see CQ10).

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

**Recommendations**

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

Background and Objectives

We examined the merits of pelvic nerve preservation in radical hysterectomy.

**Explanations**

Bladder dysfunction is a typical postoperative complication of radical hysterectomy. Such dysfunction is usually transient, although permanent urinary disorder sometimes occurs resulting in marked impairment of patients' quality of life (QOL). Since pelvic nerve sparing surgery was first proposed,[1-3] many discussions have been held and surgical techniques improved up until the present. Many studies have reported the merits of pelvic nerve preservation.[4-10] Patients indicated for this procedure generally have stage Ib or IIa disease, although one study suggested that pelvic nerve function can be preserved in patients with stage IIb disease with only minimal parametrial invasion.[6] Although the indications for pelvic nerve sparing surgery exclude some adenocarcinomas with a poor prognosis, the evidence for this exclusion is unclear.

The results of a small number of retrospective studies on pelvic nerve-sparing surgery have consistently shown that outcomes for patients with nerve sparing surgery are comparable to the therapeutic outcome data collected by the Japan Society of Obstetrics and Gynecology.[7,8,10]

In patients in whom the pelvic nerves were spared, urinary function was significantly better than in those in whom the pelvic nerves were not spared. The following tests were used to compare urinary function: time of initiation of spontaneous urination and residual urine volume measurements,[5] urodynamic studies such as cystometrograms and uroflow pattern studies,[7-9,11] and intraoperative electrophysiological studies.[12,13]

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# CQ08
# Is ovarian preservation possible in radical hysterectomy?

## 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).

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Background and Objectives

We examined the significance of ovarian preservation in radical hysterectomy and the relationship between ovarian preservation and curativeness.

## Explanations

Oophorectomy, which is performed with radical hysterectomy, and adjuvant radiotherapy cause a loss of ovarian function, which is a serious problem for some patients. Oophorectomy greatly affects patients' overall condition, with ovarian deficiency symptoms, decreased bone mineral content, and adverse effects on the cardiovascular system. The psychological effects can also be considerable, and it is necessary to preserve the ovaries to maintain postoperative quality of life (QOL).

A significant difference in survival rates was not seen between patients in whom ovaries were preserved and those in whom they were not, indicating that the curativeness of radical hysterectomy was not compromised.[1] The rates of metastatasis by histologic type are 0-0.5% for squamous cell carcinoma and 2-14% for adenocarcinoma, significantly higher for the latter.[2-6] Ovarian preservation is therefore indicated in patients with squamous cell carcinoma. Decisions need to be made on an individual basis for patients with adenocarcinoma (see Chapter 8). Risk factors for ovarian metastasis are parametrial invasion, spread to the uterine body, vascular infiltration, and lymphatic infiltration.[5,7] These factors should be considered when performing ovarian preservation.

Important requirements for ovarian preservation are the absence of ovarian cancerous lesion or metastatic lesion. Intraoperative histological confirmation is desirable, although there is no consensus on the clinical significance of rapid intraoperative cytological diagnosis.

If the ovaries are to be preserved, ovarian transposition and fixation outside of the pelvic radiation field should be performed to avoid exposure during adjuvant radiotherapy. Sites for transposition include the paracolic gutter (lateral to the ascending colon or descending colon)[8,9] and the subcutaneous tissue of the abdomen.[10] Transposition and fixation to the abdominal subcutaneous tissue can cause swelling and pain at ovulation. Post-transposition ovarian function after transposition is generally reported to be good,[11] although the effect of adjuvant therapy is considerable. Reported rates of retention of ovarian function following radiotherapy were 41% (mean follow-up period 43 months),[12] 50% (24 months),[13] and 71% (35 months).[14] Even if ovarian fixation outside of the radiation field is performed, radiation scattering should be considered.

Accordingly, ovarian fixation should be performed at some distance from the radiation field. When the radiation dose for the transposed ovaries was ≤3 Gy, 90% of patients retained ovarian function.[14] Maximum retention of ovarian function is achieved with ovarian fixation cranially to the iliac crest. In practice, fixation to a site ≥4 cm from the radiation field is considered optimal.[15] If ovarian function declines due to adjuvant therapy, hormone replacement therapy was reported not to increase the risk of recurrence of cervical cancer.[16]

Recurrence and metastases in preserved ovaries have been reported,[17-19] so management of recurrence should address not only the pelvic region but also the transposed preserved ovaries.

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

**Recommendation**

The clinical significance of para-aortic lymphadenectomy is unknown (Grade C).

Background and Objectives

We examined the significance of performing para-aortic lymphadenectomy with radical hysterectomy.

**Explanations**

Some studies have reported the diagnostic usefulness of retroperitoneal lymphadenectomy, including para-aortic lymphadenectomy, in cervical cancer.[1-3] However, there have been no randomized controlled studies demonstrating improved outcomes with the addition of para-aortic lymphadenectomy.

Para-aortic lymph node metastasis is a prognostic factor for cervical cancer. Since the para-aortic lymph nodes are not regional lymph nodes, para-aortic lymphadenectomy is not generally added to radical hysterectomy. In the U.S., para-aortic lymph node biopsy is performed for the purpose of surgical staging.[4-6] The metastasis-positive rate for stage I disease is approximately 1-2%, and increases with increasing clinical stage. In general, the rate of metastasis is higher for patients with a large tumor diameter, and is also higher for adenocarcinoma than squamous cell carcinoma.[5]

Para-aortic lymph node metastasis usually occurs along with pelvic lymph node metastasis. Isolated metastasis to the para-aortic lymph nodes is very rare.[7,8] Many studies have indicated that if lymph node metastases are not detected in regions inferior to the inferior mesenteric artery, there will be no metastasis to the superior lymph nodes.[9,10] Therefore, evaluation of the para-aortic lymph nodes should be performed from the region inferior to the inferior mesenteric artery. The presence or absence of para-aortic lymph node enlargement should be confirmed by palpation if enlargement of the pelvic lymph nodes is detected. If the para-aortic lymph nodes are enlarged, histological diagnosis should be performed to obtain important information for further treatment and prognosis.

**【References】**

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# II. Neoadjuvant chemotherapy

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

**Recommendation**

NAC has not been shown to improve outcomes (Grade C).

Background and Objectives

Theoretically, NAC can be expected to improve outcomes for stages I and II disease, in particular for patients with poor prognosis, such as bulky stage Ib to stage II disease. NAC can be expected to reduce the tumor diameter and thereby to enable cytoreductive surgery. We examined whether NAC actually improves outcomes for stages I and II disease.

**Explanations**

The theoretical bases for expectations of improve outcomes with NAC are as follows. (1) The curativeness and safety of surgery are improved by reducing the size of the tumor. The number of patients in whom surgery is indicated is expected to increase. (2) Distant metastases are suppressed by the effectiveness of NAC against micrometastases.

The advantages of administering anticancer agents before the primary treatment such as surgery and radiotherapy are as follows. (1) Surgery and radiotherapy have not interfered with circulation to the tumor. (2) Radiotherapy has not caused bone marrow damage, leaving hematopoietic function in good condition.

The potential disadvantages of NAC are as follows. (1) If patients do not respond to NAC, the tumor may have spread further prior to commencement of the primary treatment. (2) In many cases, radiotherapy is selected if surgery is likely to be difficult. However, chemotherapy performed before radiotherapy can be detrimental to local control and survival (see CQ19). (3) It is highly likely that autologous blood donation will not be possible due to chemotherapy-induced anemia, and the patient will require blood transfusions intraoperatively and postoperatively. (4) Chemotherapy itself is toxic and can cause serious adverse reactions. (5) Since treatment can become prolonged, medical expenses may be high. (6) Delayed elimination of the primary lesion may increase patients' psychological burden. There is also the possibility of other unexpected adverse effects.

Table 4-1 lists some recently reported randomized controlled trials (RCTs) of NAC + surgery. The following trials compared NAC + surgery and surgery (including those with additional radiotherapy). Sardi et al. conducted a comparative trial with 4 groups (NAC + surgery + radiotherapy, surgery + radiotherapy, radiation monotherapy, NAC + radiotherapy).[1] They found that the NAC + surgery + radiotherapy group (7 year

survival rate 65%) enjoyed a significantly better survival rate than the surgery + radiotherapy (7 year survival rate 41%) or radiation monotherapy group (7 year survival rate 48%). The survival rate of the surgery + radiotherapy group was particularly low, however, raising the question of whether the appropriate surgery was performed. Serur et al. conducted a retrospective study of stage Ib disease. The NAC + surgery group had a better 5 year survival rate than the surgery only group, although the difference was not significant (80% and 69%, respectively).[2] Napolitano et al. recently reported a RCT which compared the results of NAC + surgery (+ radiotherapy) and surgery (+ radiotherapy) in patients with stage Ib-IIIb disease. In the subgroup analysis, NAC showed significant improvement only in the 5 year disease-free survival rate of stages Ib-IIa disease (NAC + surgery *vs* surgery: 77% *vs* 64%). However, no improvement was seen in the 5 year survival rate of patients with stage Ib-IIa disease (79% *vs* 73%), the 5 year survival rate of patients with stage IIb or more advanced disease (69% *vs* 64%), or the disease-free survival rate of patients with stages IIb or more advanced disease (56% *vs* 57%).[3]

A meta-analysis was conducted of 5 RCTs which compared NAC + surgery and radiation monotherapy for stage I and II (and some stage III) disease.[4] Although the number of subjects was small at 872, the hazard ratios for the 5 year survival rate and the 5 year disease-free survival rate were 0.65 and 0.68, respectively, with the NAC + surgery group found to have significantly better outcomes. However, the controls received radiation monotherapy, and comparisons with concurrent chemo radiotherapy (CCRT) were not performed. Benedetti et al. and Sardi et al. also conducted RCTs comparing NAC + surgery and radiotherapy, reporting that NAC + surgery improved outcomes in stages I and II patients. [5,6] Benedetti et al. performed a subgroup analysis limited to bulky cervical cancer in stages Ib2 to IIb. The 5 year survival rate (NAC + surgery *vs* radiotherapy: 65% *vs* 46%) and 5 year disease-free survival rate (60% *vs* 47%) were improved with NAC + surgery. This study was a relatively well-designed multicenter study with greater subject numbers than other studies. Their conclusions are therefore of interest, even if the data comes from a subgroup analysis. A study by Chang et al. with very similar subject types did not find NAC to be useful, however, a conclusion inconsistent with Benedetti et al.[7]

A Japanese clinical study compared surgery and radiation monotherapy performed after NAC. NAC involved arterial infusion of cisplatin and bleomycin.[8] A response to NAC was seen in 18 patients, with a 3 year survival rate of 86%. The 3 year survival rate was 43% in 7 patients who underwent post-NAC radiotherapy, and 50% in patients given radiation monotherapy. Improved outcomes were seen only in patients who responded to NAC and then underwent surgery. The overall conclusion was that NAC did not improve outcomes in comparison with radiation monotherapy.

Only a small number of comparative studies have examined CCRT. Although not an RCT, Gonzalez et al. compared NAC + surgery and radiotherapy + cisplatin chemotherapy. NAC used cisplatin and gemcitabine. The NAC + surgery group were followed up for 28 months, and the radiotherapy + cisplatin group for 24 months. Survival rates for both groups were similar.[9]

Comparison of NAC + surgery and radiation monotherapy have demonstrated the usefulness of the former. However, when NAC + surgery is compared with surgery monotherapy or CCRT, no added benefits have been demonstrated for NAC + surgery .

Haung et al. examined prognostic factors, and the indications for NAC + surgery, in patients with stage Ib-IIa disease who underwent NAC. They concluded that NAC + surgery is indicated in patients ≥35 years of age with a tumor diameter ≥5 cm.[10] Benedetti et al. found that NAC is indicated for cervical cancer of stages Ib-IIIb.[5]

Table 4-2 lists major phase II trials of NAC conducted in recent years. Most of these studies use a combination of 2 or 3 agents including cisplatin, although no consensus has been reached on NAC regimens.[11-13] In recent years, the following agents have often been used in the treatment of ovarian cancer and are being examined as regimens for NAC: carboplatin, paclitaxel, docetaxel, and irinotecan. There are expectations for good results in future studies.[11,12,14-18] Presently, the Japanese Gynecologic Oncology Group (JGOG) is conducting a phase II trial of irinotecan + nedaplatin.

Recently, an interim analysis of an RCT was released by JCOG, a multicenter clinical trial group in Japan. This involved subjects with bulky stage Ib or IIa cancers or stage IIb cancer. They compared NAC + radical hysterectomy ± radiotherapy compared with standard therapy (radical hysterectomy + radiotherapy). NAC comprised 4 courses of bleomycin, cisplatin, vincristine and mitomycin (BOMP) therapy.[19] Their report stated, "even with NAC, the survival time was highly unlikely to significantly improve in comparison with standard therapy. Furthermore, no clear reduction in surgical complications was seen." This trial was terminated, on the recommendation by the efficacy and safety evaluation committee, because subjects showed no response to treatment. Several problems have been raised concerning this trial: in particular, the response rate to BOMP therapy was lower than expected, and 4 courses of NAC, possibly an excessive number, were administered. The results of this one RCT do not completely negate the usefulness of NAC + surgery in general. However, these results are important as the first RCT which compared standard surgery performed in Japan and NAC including cisplatin.

There is no evidence that invasive NAC + surgery is better than surgery monotherapy or CCRT. Therefore, one should refrain from casually performing NAC in general practice. A new clinical trial will be required to evaluate the usefulness of NAC + surgery in stages I and II, comparing it with surgery monotherapy or CCRT. Presently, NAC is an experimental treatment that should only be performed under a clinical trial setting.

**Table 4-1 Major Randomized Controlled Trials on NAC[19]**

| Authors | Year published | No. of subjects | Clinical stage | Compared treatments | Chemotherapy regimen | Schedule | External beam radiation dose (Gy) | Intracavitary radiation dose (Gy) |
|---|---|---|---|---|---|---|---|---|
| | | | | | cisplatin<br>vincristine<br>bleomycin | every 21 days<br>3 courses | | |
| | | | | | cisplatin<br>bleomycin<br>or<br>cisplatin<br>vincristine<br>bleomycin<br>or<br>cisplatin<br>ifosfamide<br>cisplatin | every 21 days<br>2 courses<br>every 7 days<br>6 courses<br>every 7 days<br>7 courses<br>every 7 days<br>6 courses | | |
| | | | | | cisplatin<br>vincristine<br>bleomycin | every 10 days<br>3 courses | | |
| | | | | | cisplatin<br>vincristine<br>bleomycin | every 10 days<br>3 courses | | |
| | | | | | cisplatin<br>vincristine<br>bleomycin | every 10 days<br>3 courses | | |
| | | | | | cisplatin<br>vincristine<br>bleomycin | every 10 days<br>3 courses | | |
| | | | | NAC (arterial infusion) $\pm$S or $\pm$RT *vs* RT | cisplatin<br>bleomycin | every 21 days<br>2-3 courses | | |

**Table 4-2 Major Phase II Trials on NAC**

| Authors | Year published | No. of subjects | Clinical stage | Chemotherapy regimen | Response rate (%) |
|---|---|---|---|---|---|
| | | | | cisplatin+ifosfamide/every week | |
| | | | | cisplatin (arterial infusion)+vincristine+mitomycin C+peplomycin | |
| | | | | cisplatin+vincristine+bleomycin | |
| | | | | cisplatin+vincristine+bleomycin | |
| | | | | carboplatin+ ifosfamide or carboplatin+paclitaxel | |
| | | | | carboplatin+ ifosfamide+paclitaxel | |
| | | | | cisplatin+ gemcitabine | |
| | | | | cisplatin+epirubicin+paclitaxel | |
| | | | | cisplatin+vinorelbine | |
| | | | | carboplatin+paclitaxel | |
| | | | | cisplatin+ irinotecan | |
| | | | | irinotecan+mitomycin C | |

# III. Postoperative adjuvant therapy

## CQ11
## Is postoperative adjuvant therapy necessary?

**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 pelvic irradiation is considered to be postoperative adjuvant therapy, and concurrent chemoradiotherapy should also be considered for patients with positive lymph node metastases (Grade C).
(4) Presently, the usefulness of postoperative adjuvant therapy is unknown (Grade C).

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Background and Objectives

We examined postoperative adjuvant therapy for patients with advanced cervical cancer with risk factors* for recurrence.

**Explanations**

Adjuvant therapy comprises postoperative treatments performed with the objective of preventing postoperative recurrences. The subjects of adjuvant therapy are patients with high risk for recurrence. This risk is determined by the histopathological findings from surgically excised specimens at the completion of the planned surgical procedure. Efficacy has been examined for adjuvant therapies such as radiotherapy, chemotherapy, concurrent chemoradiotherapy (CCRT), and immunotherapy. Risk factors for postoperative recurrence include tumor diameter, depth of cervical stromal invasion, pelvic lymph node metastasis, parametrial invasion, vascular infiltration, and lymphatic infiltration.[1-12] Many studies have considered patients with a tumor diameter of >2 cm[13] or >4cm[14,15] as those at high risk of recurrence. In terms of cervical stromal invasion, patients with >1/3 myometrial invasion are generally placed in the high risk group for recurrence.

The efficacy of adjuvant therapy for high risk patients clearly differs depending on whether pelvic lymph node metastases are present. For high risk patients with stage Ib or IIb disease who underwent radical hysterectomy, the 5-year survival was 79-89%[16-19] for patients who received adjuvant radiotherapy and were negative for pelvic lymph node metastasis, and 37-61% for patients positive for pelvic lymph node metastasis.[20-22]

1) Patients negative for pelvic lymph node metastasis

The Gynecologic Oncology Group (GOG) 92 trial was a randomized controlled trial (RCT) in which the subjects had stage Ib disease with negative pelvic lymph nodes and at least 2 out of the following 3 risk factors for recurrence: >1/3 stromal invasion, vascular or lymphatic infiltration, and cervical enlargement. In this trial, comparisons

were performed between an untreated group and a group treated with whole pelvis irradiation as postoperative adjuvant therapy. The adjuvant radiotherapy group experienced a significantly lower recurrence rate than the untreated group.[23] A retrospective prognostic survey was conducted on 23 patients whose tumor was ≤0.5 cm from the vaginal stump at radical hysterectomy. The 5 year survival rates of the postoperative adjuvant therapy group and non-irradiated group were 81% and 29%, respectively, representing a significant difference. The recurrence rate was also significantly controlled in the radiotherapy group.[24] However, no RCT has found that survival times are prolonged by postoperative adjuvant therapy. In addition, there is no consensus on the indications for postoperative adjuvant therapy in patients following radical hysterectomy with negative surgical resection margins and negative pelvic lymph node metastasis.[25] After consideration of the present situation in Japan, if patients are pelvic lymph node negative but have other risk factors, postoperative radiotherapy to the whole pelvic space should be considered.[26]

2) Patients positive for pelvic lymph node metastasis

Conventionally, pelvic irradiation has been indicated in patients positive for pelvic lymph node metastasis. However, its efficacy has not been demonstrated.

In recent years, the Southwest Oncology Group (SWOG) in the U.S. has reported randomized controlled trial (RCT) results indicating the usefulness of concurrent chemoradiotherapy (CCRT) as postoperative adjuvant therapy. The subjects of this trial (SWOG8797) were 268 patients who underwent radical hysterectomy. They were also in stages Ia2, Ib, or IIa, with positive pelvic lymph node metastasis, positive parametrial invasion, or positive surgical margins. Comparison was made between whole pelvis irradiation only and CCRT (combination of whole pelvis irradiation and cisplatin + 5-fluorouracil, 3 week interval, 4 courses). Of the subjects of the SWOG8797 trial, over 85% had positive pelvic lymph node metastasis. This trial is considered to have demonstrated the therapeutic efficacy of CCRT in patients with positive pelvic lymph node metastasis. The results indicated significantly better overall survival times and progression-free survival times for the CCRT group in comparison to the radiation monotherapy group.[27] Other multicenter studies have reported similar results,[28] leading to high expectations for CCRT. However, the tolerability for cisplatin doses used concurrently in CCRT has not been determined for Japanese women, and the degree of late toxicity of CCRT is also unknown. In addition, the usefulness of CCRT as postoperative adjuvant therapy has not been confirmed in Japan. In such circumstances, the indications for CCRT should be considered carefully.

It is generally understood that patients with positive pelvic lymph node metastases have systemic disease. Chemotherapy is increasingly expected to replace radiotherapy, which is a local therapy, and various studies have been performed. A comparative study was performed on cervical cancer with positive pelvic lymph node metastasis. The subjects were postoperative patients with at least one of the following factors: positive for pelvic lymph node metastasis, stromal invasion >3/4, and cardinal ligament invasion. The following two treatments were compared: adjuvant chemotherapy with pepleomycin + vincristine + mitomycin C + cisplatin, and adjuvant radiotherapy performed at an affiliated institution. No significant difference was seen in the survival rate between the two treatments.[29] Another study compared survival rates in an adjuvant chemotherapy group and a historical control group in which adjuvant radiotherapy was performed to

improve the survival rate. The only risk factor examined was lymph node metastasis, and chemotherapy involved cisplatin + vinblastine + bleomycin.[30] No significant difference was seen in the survival rate between groups. Recently, a study was conducted with patients with one of the following factors: positive lymph node metastasis, cardinal ligament invasion, or positive surgical margins. They administered adjuvant chemotherapy comprising bleomycin + vincristine + mitomycin C + cisplatin. The 5 year disease-free survival rate was high at 86% for patients receiving this adjuvant therapy.[31] From these results, efficacy can be anticipated for adjuvant chemotherapy in patients positive for pelvic lymph node metastasis. However, these results were from past studies using historical controls[32] or chemotherapy alone, so adjuvant chemotherapy has not yet been established as being clearly superior.

We were only able to locate one RCT examining the usefulness of adjuvant chemotherapy for patients positive for pelvic lymph node metastasis. In this study, subjects were positive for lymph node metastasis, or for vascular or lymphatic infiltration. Comparisons were made between adjuvant chemotherapy (carboplatin+bleomycin), adjuvant radiotherapy, and follow-up without treatment. No differences were seen in the disease-free survival rate between these 3 groups.[33] In recent years, an RCT (GOG 149 trial) was conducted comparing ifosfamide + cisplatin with ifosfamide + cisplatin + bleomycin in patients with recurrent cervical cancer.[34] The results showed no additional effect of bleomycin, which is conventionally used in the treatment of cervical cancer. We can therefore conclude that the usefulness of adjuvant chemotherapy is presently unknown for cervical cancer with positive pelvic lymph nodes. A comprehensive study is needed to determine the efficacy of adjuvant chemotherapy, and in addition establish a standard therapeutic regimen.

**Notes: Positive surgical margins**

For the following reasons, patients with positive surgical margins were excluded from this discussion of adjuvant chemotherapy. (1) In the "Guidelines for the Clinical and Pathological Study of Uterine Cervical Cancer in Japan," postoperative irradiation is not indicated for cases with incomplete surgery and clear residual cancer. In the present guidelines, we will not follow the recommendations in the previous guidelines for patients with positive surgical margins. This conflict will potentially cause unwanted confusion in the clinical setting. (2) The term „positive surgical margins' has different meanings in Japan and Western countries. In Japan, „positive surgical margins' often includes residual carcinoma in situ and more advanced lesions. In Western countries, it usually means residual invasive lesions. Therefore, we considered it inappropriate to directly use data from Western countries as evidence for the present guidelines.

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

**Recommendations**

(1) Whole pelvis irradiation is recommended (Grade B).
(2) The merits of adding intracavitary irradiation are unclear (Grade C).

Background and Objectives

Radiotherapy (postoperative irradiation) is sometimes performed as adjuvant therapy following radical hysterectomy. We examined appropriate irradiation methods.

**Explanations**

Irradiation methods and radiation doses for radiotherapy (postoperative irradiation) have not been verified by clinical trial for postoperative adjuvant therapy.

The irradiation area is typically the whole pelvic region.[1] A dose of 45-50 Gy with 1.8-2.0 Gy per fraction is used for external irradiation (whole pelvis irradiation). However, various studies have failed to confirm a clear dose response. Doses of ≥50 Gy carry a high risk of small intestinal complications, and should not be used.[2] There have been a small number of studies of small pelvic field irradiation for patients negative for pelvic lymph node metastasis.[3,4] Hong et al. compared whole pelvis irradiation and low pelvis irradiation in patients with stage Ib and IIa disease. Their subjects were negative for pelvis lymph node metastasis, but had other risk factors for recurrence. No difference was seen in the 5 year disease-specific survival rate between the two treatments.[3] It is desirable to use ≥6 MV energy for external irradiation when considering the dose reduction to the small intestines and the skin. If energy lower than this level needs to be used, the two opposed-field (AP/PA) technique should be avoided. The 4-field box radiotherapy technique should instead be used, in which case attention should be paid to the posterior border of the lateral radiation field, so that the entire region containing the sacral lymph nodes and lymph nodes within the cardinal ligaments is included.[5] In Japan, a center splitter is sometimes used in the whole pelvis radiation field for postoperative irradiation.[6] However, its benefits are unclear.

The benefits of intracavitary irradiation are also unclear. Kim et al. performed postoperative irradiation using intracavitary radiation monotherapy in patients with stage Ib disease. Recurrence occurred in 0/2 patients with positive resection margins near the vaginal stump. Recurrence was seen in 5/5 patients with positive parametrial margins. The distribution of doses of intracavitary radiation was suggested to be the likely cause of these results. The authors stated that postoperative intracavitary irradiation monotherapy is not recommended except for very specific cases (vaginal stump CIS patients).[7] A study of the combination of external and intracavitary irradiation did not obtain consistent

therapeutic outcomes.[8] The benefits and disadvantages of adding intracavitary irradiation have yet to be clearly identified, as is the case with prophylactic postoperative irradiation to the para-aortic region.[9-12]

Hong et al. examined factors involved in the onset of complications.[3] The radiation field (whole pelvis/low-pelvis irradiation) was an independent predictive factor for small intestinal complications, and the dosage (>50 Gy/<50Gy) and irradiation method (two opposed-field (AP/PA) technique/4-field box technique) were independent predictive factors for leg edema.[3] Yamazaki et al. compared the two opposed-field (AP/PA) technique and an irregularly-shaped 4-field box technique using CT simulation. The latter technique yielded significantly lower incidences of grade 2 to 3 complications: intestinal complications (18% *vs* 3%) and leg edema (29% *vs* 3%).[13]

In recent years, rapid strides have been made in radiotherapy techniques . For instance, intensity modulated radiotherapy (IMRT) has a significantly lower incidence of late intestinal complications compared to conventional whole pelvis irradiation (4-field box technique).[14]

# CQ13
# Is prophylactic para-aortic irradiation useful?

**Recommendation**

The usefulness of prophylactic para-aortic irradiation is unclear (Grade C).

Background and Objectives

The reported incidence of latent metastases to the para-aortic lymph nodes is 6-21% in stage I and II disease. The risk is related to tumor diameter and the presence or absence of pelvic lymph node metastases.[1] Prophylactic para-aortic irradiation is theoretically reasonable for patients who meet certain criteria. We examined the clinical usefulness of prophylactic para-aortic irradiation.

**Explanations**

There have been two large-scale randomized controlled trials (RCTs) on prophylactic para-aortic irradiation.[2,3] Neither study was limited to adjuvant therapy.

The Radiation Therapy Oncology Group (RTOG) compared pelvic irradiation with pelvic irradiation + para-aortic lymph node irradiation. The subjects were patients with stage Ib or IIa disease with tumor diameters ≥4 cm and patients with stage IIb disease. The 10 year survival rate was significantly better in the group receiving the latter treatment (44% *vs* 55%).[2] The European Organisation for Research and Treatment of Cancer (EORTC) conducted an RCT with patients with stage Ib and IIb disease. One group received pelvic irradiation and the other pelvic irradiation + para-aortic irradiation. Subjects were negative for para-aortic lymph node metastasis and positive for pelvis lymph node metastasis on lymphangiography or pathological examination. Overall, no significant differences were seen in survival rates, local control rates or distant metastasis rates between the two groups. However, when subgroup analysis was performed on patients with local control, the distant metastasis rate (hazard ratio: 2.4) and para-aortic lymph node metastasis rate (hazard ratio: 2.8) were significantly lower in the prophylactic para-aortic irradiation group.[3] It is not known whether prophylactic para-aortic irradiation improves survival. However, there may be significant benefits if its use is limited to patients with a high risk of recurrence in the para-aortic lymph nodes and with good preospects for local control.

Examination of the cumulative 10 year complication rate in the abovementioned RTOG study indicated that the incidence of late complications tended to be higher (8% *vs* 4%) in the group with para-aortic irradiation.[2] In the EORTC study, the incidence of serious late gastrointestinal complications of grade 3 or 4 was 2.3-fold in the group with para-aortic irradiation.[3] The irradiation method should therefore be selected paying careful attention to late complications if irradiation is performed in the para-aortic lymph node region.

The National Comprehensive Cancer Network (NCCN) and National Cancer Institute (NCI) guidelines do not clearly recommend the use of prophylactic para-aortic irradiation as adjuvant therapy.[4,5]

# 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).

Background and Objectives

We examined the usefulness of maintenance therapy after radical surgery in patients at high risk of recurrence. The maintenance therapies examined were oral anticancer agents and immunotherapy.

**Explanations**

1) Oral anticancer agents

The Japanese Gynecologic Oncology Group (JGOG) performed a randomized controlled trial (RCT) on an untreated group and a group postoperatively administered oral 5-fluorouracil. The subjects were patients with stage Ib to IIb disease. Among patients who underwent surgery + radiotherapy and were negative for pelvic lymph node metastasis, those administered oral 5-fluorouracil enjoyed a significantly better 5 year survival rate.[1] However, this result was derived from a subgroup analysis, and has not been reproduced in any other similar trials. Following publication of the JGOG study, the usefulness of concurrent chemo radiotherapy (CCRT) with cisplatin was demonstrated, but it is not clear whether these results can be applied as is to clinical practice.

2) Immunotherapy

The efficacy of immunotherapy as maintenance therapy after radical surgery has not been demonstrated. RCTs have found that outcomes are improved using sizofiran. However, the subjects were patients with stage II and III disease in whom radiation monotherapy was administered as the initial treatment.[2-4] According to these studies, improved outcomes were seen in patients with stage II disease, but not with stage III disease.

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

**Recommendations**

(1) No clear differences have been demonstrated in pelvic recurrence rates or survival rate between surgery (± radiotherapy) and radiotherapy, and definitive radiotherapy can reasonable be selected (Grade B).
(2) The use of concurrent chemo radiotherapy (CCRT) can also be considered for patients with stage IIb disease or a tumor diameter >4 cm (Grade B).

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Background and Objectives
We examined the applicability of definitive radiotherapy for stage I and II disease.

**Explanations**

The U.S. National Comprehensive Cancer Network (NCCN) and National Cancer Institute (NCI) guidelines state that surgery and radiotherapy are parallel treatment options for patients with stage Ib-IIa disease with tumor diameters of ≤4 cm. An Italian randomized controlled trial compared surgery and definitive radiotherapy for stage Ib and IIa disease.[1] In this trial, no significant differences were found between surgery (± radiotherapy) and definitive radiotherapy in the 5 year disease-free survival rate (74% for both treatments) or 5 year survival rate (83% for both treatments). Significantly more complications (grade 2 or 3) were seen with surgery than with radiotherapy (28% *vs* 12%). This study also showed that definitive radiotherapy is indicated for patients with stage Ib or IIa disease and relatively small tumor diameters. However, in this Italian trial, the surgery group also included many patients in whom surgery was incomplete or with parametrial invasion, and it should be noted that there have been criticisms due to the inclusion of such patients and the frequent use of postoperative irradiation.

In the abovementioned U.S. guidelines, surgery was not an option for patients with stage IIb disease, or stage Ib or IIa disease with tumor diameters >4 cm. In such cases, CCRT was recommended.[2,3] It highly likely that adjuvant therapy will be required in such cases. If postoperative irradiation is performed as adjuvant therapy, late adverse events could increase. If CCRT is used, further increases in the frequencies of adverse events are expected. Accordingly, in the U.S., not surgery but definitive radiotherapy, particularly CCRT, is the usual initial treatment. In Japan, there is a lack of data on the tolerability of CCRT, and late adverse events.

There have been no randomized controlled trials (RCTs) comparing surgery and definitive radiotherapy in patients with stage IIb disease. In this patient group, there are problems in staging through evaluation of parametrial invasion.[4] Comparisons of retrospective analyses between institutions are very difficult.

From the above, definitive radiotherapy is a valid treatment for stage I and II disease based on the literature. Historically in Japan, radical hysterectomy has been

performed aggressively for stage I and II disease, limiting the application of definitive radiotherapy.[5] In clinical practice, the use of definitive radiotherapy should be carefully considered.

Adverse events of radiotherapy include reduced ovarian function, sexual dysfunction, and bladder and rectal dysfunction.[6,7] Since the proportion of young patients is relatively high for stages I and II, it is necessary to consider not only therapeutic outcomes, but also post-treatment quality of life (QOL) in treating these patients.

## 【References】

(5) Gynecologic Oncology Committee Report. 2001 Report on uterine cervical cancer patients. Acta Obstetrica et Gynaecologica Japonica 2004;56:1-115. (Level IV) (in Japanese)

(7) Sakurai H, Takahashi M, Suzuki Y, et al. Changes in sex life after radiotherapy for uterine cervical cancer. J Jpn Soc Ther Radiol Oncol 2003; 15:187-191 (Level III) (in Japanese)

# CQ16
# What irradiation methods are recommended for definitive radiotherapy?

**Recommendations**

A combination of external irradiation (whole pelvis irradiation) and intracavitary irradiation is recommended (Grade A').

Background and Objectives

We examined appropriate irradiation methods for definitive radiotherapy in stage I and II disease.

**Explanations**

A retrospective analysis of the Pattern of Care Study (PCS) in the U.S. examined definitive radiotherapy with and without intracavitary irradiation. Significant differences were seen in the pelvic control rate and survival rate between the two methods.[1] Although not verified in clinical trials, the standard definitive radiotherapy treatment can be considered to be external irradiation with intracavitary irradiation.[2-4]

The irradiation site (clinical target volume) of external irradiation is normally the whole pelvic region. The benefits and disadvantages have yet to be identified for prophylactic irradiation to the para-aortic lymph node region.[5,6]

There have been two Japanese randomized controlled clinical trials of the dose rates of intracavitary irradiation.[7,8] The results of both trials indicated no difference in the local control rate between low dose rate (LDR) and high dose rate (HDR) groups. In one trial, the HDR group experienced a significantly higher incidence of late complications than the LDR group.[7] In a number of retrospective analyses, the incidence of complications from HDR were within tolerable levels.[9,10] Therefore, there are few problems with the use of HDR in the clinical setting. In using LDR radiotherapy, radiation exposure to medical staff, and increased patient discomfort due to long-term treatment need to be considered. Where possible, HDR radiotherapy should be used.

Since treatment schedules and doses differ greatly between Japan and the U.S., caustion is neede in applying overseas data. In Japan, HDR intracavitary irradiation is used in most institutions. Treatment schedules are used that comply with the *Guidelines for the Clinical and Pathological Study of Uterine Cervical Cancer in Japan*[2] (Table 4-3). Characteristic of Japanese treatment schedules are the following: a center splitter is inserted in the midcourse of external irradiation (whole pelvis irradiation), and a low dose of intracavitary irradiation is used, particularly for advanced cancer. Several retrospective analysis have confirmed the safety and efficacy of Japanese treatment schedules,[9] engendering confidence in the safety of treating patients in accordance with the abovementioned guidelines. In the U.S., LDR intracavitary irradiation is used widely.[11] Recommendations of LDR are based on retrospective analyses of the dose-effect relationship. The recommended total dose from external irradiation and intracavitary

irradiation (LDR) at point A is a minimum of 80 Gy in patients with a small tumor diameter and a minimum of 85 Gy in patients with a large tumor diameter.[3] In the U.S., HDR treatment schedules are based on the biologically equivalent dose of the LDR recommended dose. This schedule is recommended by the American Brachytherapy Society (ABS).[12]

The dose to the primary lesion in the cervical region is higher in the U.S. HDR treatment schedule in the Japanese schedule. However, there is very little clinical data to support the U.S. treatment schedule, and in particular, its safety is unknown. We therefore consider it inappropriate to apply this schedule in Japanese patients.

Interstitial irradiation is administered to patients with extensive parametrial invasion, and patients in whom local control is considered difficult using conventional intracavitary irradiation. Relatively good results have been reported using interstitial irradiation in such cases,[13] but many complications have also been reported.[14] Intensity modulated radiotherapy (IMRT) has recently been applied in cervical cancer, and appears to have reduced acute toxicity and a lower incidence of late adverse events.[15]

The total treatment time has been indicated as an important therapeutic factor affecting treatment outcomes.[16,17] The ABS recommends limiting the total treatment time to ≤8 weeks.[12] Treatment should be completed as soon as possible, avoiding unnecessary rest periods.

Maintenance of the hemoglobin concentration above a certain level has been reported improve outcomes.[18] The possibility of anemia should be considered during radiotherapy.

**Table 4-3 Standard radiotherapy schedules for uterine cervical cancer**

| Stage (size of cancer) | External irradiation | | Intracavitary irradiation HDR (Point A dose) |
|---|---|---|---|
| | Whole pelvis | Center splitter | |
| I | | | 29 Gy/5 fractions |
| II (small) | | | 29 Gy/5 fractions |
| II (large) | | | 23 Gy/4 fractions |
| III (small-medium) | | | 23 Gy/4 fractions |
| III (large) | | | 15-20 Gy/3-4 fractions |
| IVa | | | 15-20 Gy/3-4 fractions |

HDR: high dose rate
Extracted and modified from reference 2.

**【References】**

(2) *Guidelines for the Clinical and Pathological Study of Uterine Cervical Cancer in Japan*. October, 1997 (revision, 2nd ed.) (guidelines) (in Japanese)