Chapter 5■ Stage III and IVa disease

Overview

Concurrent chemoradiotherapy (CCRT) is recommended for stage III and IVa disease. Recommended regimen for the chemotherapy portion generally include cisplatin. However, there is a lack of evidence supporting specific administration methods.

Radical hysterectomy or extended radical hysterectomy is sometimes performed for stage III disease in addition to chemotherapy. However, there is no clear evidence that these treatments improve outcomes compared to radiation monotherapy. Disease can be inoperable even after NAC. In such cases, radiotherapy is generally administered following chemotherapy. In this patient group, outcomes were significantly worse than with radiation monotherapy, in terms of local control rates and the survival rates. Accordingly, NAC is not recommended.

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

Recommendation

CCRT is favored over radiation monotherapy (Grade B).

Background and Objectives

We examined the usefulness of CCRT for stage III and IVa disease.

Explanations

Multiple large-scale randomized control trials (RCTs)[1-5] and meta-analyses[6-8] have been conducted on the usefulness of CCRT in locally advanced uterine cervical cancer. In these RCTs, progression-free survival and overall survival rates were significantly better in the CCRT group.[1-3] Based on these results, the U.S. National Cancer Institute (NCI) recommended in February 1999: "CCRT should be considered in uterine cervical cancer patients who require radiotherapy." The Cochrane Collaboration conducted a meta-analysis of RCTs performed in the period 1981-2000.[6] CCRT was shown to significantly improve the progression-free survival rate (odds ratio 0.61) and the overall survival rates (odds ratio 0.71). In addition, CCRT reduced the local recurrence rate (odds ratio 0.61) and the distant recurrence rate (odds ratio 0.57). A Canadian group (the Cancer Care Ontario Practice Guidelines Initiative Gynecology Disease Site Group) conducted a systematic review of 8 RCTs using cisplatin.[7] CCRT was shown to decrease mortality (relative risk 0.74). Based on the above findings, the National Comprehensive Cancer Network (NCCN) and NCI strongly recommend CCRT as the standard treatment for stage III and IVa disease.[8,9]

On the other hand, there are arguments against the use of CCRT. First, the studies on which the NCI based its recommendation differ from the Japan clinical situation in the following ways: eligibility criteria (exclusion of subjects positive for para-aortic lymph node metastasis) and radiation treatment methods (total dose, use of center splitter, total treatment time, and intracavitary irradiation dose rate). Therefore, the NCI recommendations are not necessarily directly applicable to Japan. In a Canadian RCT , subjects positive for para-aortic lymph node metastasis were not excluded. No significant difference was seen in the survival rate between the CCRT group and the radiation monotherapy group.[4] This result also supported the above argument against CCRT, but the problem with this Canadian RCT was small number of subjects. Therefore, the usefulness of CCRT cannot be denied using this RCT alone.[10] We should also consider differences in radiotherapy methods. In general, a high dose rate (HDR) is standard in Japan, although there is a lack of evidence supporting its use. Although several studies have examined CCRT using HDR, most are retrospective studies.[11-13] There is also a problem regarding the use of a center splitter. A center splitter was not used in any of the

abovementioned RCTs except RTOG 9001. In contrast, in Japan, a center splitter is often inserted from the time the irradiation dose reaches 30-40 Gy for advanced cancer, in which CCRT is indicated. In CCRT performed in Japan for primary cervical cancer, only intracavitary irradiation is used concurrently with chemotherapy in the midcourse of treatment. We should therefore recognize differences between the methods used in the abovementioned RCTs and the methods used in Japan. The American Brachytherapy Society (ABS) recommended not to use chemotherapy concurrently with HDR because of the increased risk of late complications.[14] In a Japanese study, 20 of 40 patients received chemotherapy concurrently with HDR radiotherapy, with only 1 patient developing late complications of ≥grade 3.[13] In a study that became the basis for the ABS recommendations, HDR was administered at a very high dose, 10 Gy per fraction for a total of 3 fractions.[11] The high incidence of late complications was likely due to the excessive radiation doses, and not from chemotherapy. In any case, prospective trials are needed in Japan to examine the efficacy and safety of radiotherapy in the form of CCRT (HDR, center splitter use).

Secondly, there is insufficient evidence on the usefulness of CCRT when limited to stage III and IVa Disease. In the RTOG 9001 trial, subgroup analyses were performed according to clinical stage. Survival rates for stage III and IVa disease were not significantly improved by CCRT.[1] Eifel et al. later published the final results of this RCT, reporting that progression-free survival times were significantly improved in stage III and IVa disease (radiotherapy *vs* CCRT: 37% *vs* 54%). However, no significant difference was seen in the overall survival rate (45% *vs* 59%, P=0.07).[5] In other RCTs, subgroup analysis was not performed by stage. In a meta-analysis by the Cochrane Collaboration, if the proportion of subjects with stage I and II disease was large (≥70%), survival rates was improved greatly by CCRT.[6]

Kirwan et al. performed a systematic review of the toxicity of CCRT. They found a significant increase in acute toxicity, in terms of upper gastrointestinal disorders and hematological toxicity (leukocytopenia and thrombocytopenia). Insufficient data for late toxicity led them to defer any conclusions.[15]

From the results of systematic reviews and meta-analyses, there is a very high level of evidence for the usefulness of CCRT against locally advanced cervical cancer. However, there is a lack of Japanese clinical data, and overall evidence is limited to stage III and IVa disease, leaving it unclear whether there is an increase in late complications. Caution should be taken in the application of CCRT in clinical practice.[16]

CQ18
What regimens are recommended for concurrent chemo radiotherapy (CCRT)?

Recommendation

Regimens which include cisplatin are recommended (Grade A).

Background and Objectives

We examined appropriate chemotherapy regimens for CCRT.

Explanations

Multiple randomized controlled trials (RCTs)[1-5] and meta-analyses[6,7] have demonstrated the efficacy of CCRT in the treatment of locally advanced cervical cancer. As indicated in the meta-analyses, comparison of the merits and disadvantages of different regimens was difficult due to clinical and statistical heterogeneity of RCTs. Akthough various regimens were used in RCTs performed in the past (Table 5-1), they can be divided into 2 major groups by the use or non-use of cisplatin.

1) Regimens containing cisplatin

These include cisplatin monotherapy and cisplatin + 5-fluorouracil. The Gynecologic Oncology Group (GOG) 120 trial,[2] the GOG 123 trial,[2,4] and the National Cancer Institute (NCI) Canadian trial[8] were RCTs which used cisplatin monotherapy (40 mg/m^2/week, 6 courses). In the first two trials, survival rates were improved by cisplatin, but not in the last trial. In the GOG 123 trial, a preventative effect was not observed for distant metastasis. Two GOG clinical trials (GOG 120 and GOG 85 trials)[2,3] and the RTOG 9001 trial[1,5] were RCTs which used cisplatin + 5-fluorouracil. Survival rates were improved in all 3 studies. In the RTOG 9001 trial, distant metastases were also significantly reduced. The GOG 120 trial compared cisplatin monotherapy and cisplatin + 5-fluorouracil. No differences in long-term outcomes were seen between the two regimens, although the incidence of grade 3 and 4 acute adverse events (in particular hematologic toxicity) were significantly higher for cisplatin + 5-fluorouracil. Based on studies such as these, cisplatin monotherapy (40 mg/m^2/week, 6 courses) is the standard treatment in further U.S. clinical trials presently being conducted (GOG, RTOG) and in clinical practice.

In Japan, a phase I trial was conducted on cisplatin monotherapy used in CCRT. They reported that only 1 out of 6 patients developed dose-limiting toxicity (DLT) at a cisplatin dosage of 40 mg/m^2/week. As in the U.S., the recommended dose was 40 mg/m^2/week.[9] Another study reported DLT in 5 out of 5 patients at 40 mg/m^2/week, and their recommended dose was 30 mg/m^2/week.[10] Comparisons are difficult since the criteria for DLT differed in these studies, although both reported a marked neutropenia. Multicenter prospective clinical trials are needed to examine safety and efficacy.

Another regimen, cisplatin 20 mg/m^2 x 5 days (21-day interval), is still under investigation, and the results of a phase II trial have not yet been released.[11]

2) Regimens without cisplatin

In an RCT, CCRT with 5-fluorouracil monotherapy failed to demonstrate superiority to radiotherapy alone.[12] In another RCT, the local control rate was not improved by chemoradiotherapy using epirubicin, although distant metastases were significantly reduced, resulting in a significant improvement in the survival rate.[13] There have also 2 RCTs conducted with mitomycin C. Both RCTs reported superior results for CCRT compared to radiation monotherapy.[14,15] However, there were problems in the design of these studies, reducing their reliability.

3) Cochrane Collaboration meta-analysis

Subgroup analysis was conducted of the use of cisplatin as an anticancer agent. Significant improvement was seen in the disease-free survival rate regardless of whether cisplatin was used or not (with cisplatin: odds ratio 0.63, without cisplatin: odds ratio 0.57).[6] The U.S. National Comprehensive Cancer Network (NCCN) and (NCI) guidelines recommend a regimen containing cisplatin, but do not specify details such as the administration method.[16,17]

Table 5-1 Randomized controlled trials on concurrent chemo radiotherapy (CCRT) in cervical cancer

Authors	Year published	Subjects	Regimen	Improvement in survival rate
(regimens with cisplatin)				
		IIb, IIIb (>4 cm, marked parametrial invasion)	cisplatin 50 mg/m^2 + vincristine 1 mg/m^2 + bleomycin 25 mg/m^2 x 2 x (4 courses)	
			1) cisplatin 40 mg/m^2/wk x (6 courses) 2) cisplatin 50 mg/m^2, 5FU 4 g/m^2 x (2 courses) hydroxyurea 2 g/m^2 (2 times/wk), 1-6 weeks	
			cisplatin 50 mg/m^2, 5FU 4 g/m^2 x (2 courses)	
			cisplatin 40 mg/m^2/wk x (6 courses)	

		Ib-IIa (>5 cm/pelvic lymph nodes) IIb-IVa	cisplatin 75 mg/m^2, 5FU 4 g/m^2 x (3 courses)	
		Ib-IIa (>5 cm/pelvic lymph nodes) IIb-IVa	cisplatin 40 mg/m^2/wk x (5 courses)	
(regimens without cisplatin)				
			5FU 4 g/m^2 x (2 courses)	
			epirubicin 60 mg/m^2 x (1 course) + adjuvant (5 courses)	
			mitomycin C 15 mg/m^2 x (2 courses)	Significant tendency

【References】

(9) Oono T, Kato S, Tsuji H. Phase I trial of radiotherapy combined with weekly cisplatin for locally advanced cervical cancer. Journal of the Japan Society of Gynecologic Oncology 2005; 23:564-71. (Level III) (in Japanese)

CQ19
Is chemotherapy recommended before primary treatment?

Recommendation

Chemotherapy is not recommended before radiotherapy (Grade B).

Background and Objectives

Presently, concurrent chemoradiotherapy is considered the standard treatment for stages III and IVa. After cytoreductive chemotherapy, radiotherapy or surgery are the possible primary treatments. We examined the usefulness of chemotherapy before primary treatment for locally advanced cancer at stage III and IV.

Explanations

1) Chemotherapy followed by radiotherapy

Numerous randomized controlled trials (RCTs) were conducted in the 1980s and early 1990s on the usefulness of neoadjuvant chemotherapy (NAC) followed by radiotherapy. Many of these trials did not show significant differences in survival rates between radiation monotherapy and radiotherapy after chemotherapy.[1,2] Some studies found that pelvic control rates and survival rates were significantly worse in the group which received chemotherapy.[3,4] A systematic review was conducted of clinical trials on radiotherapy after NAC for cervical cancer, examining studies published between 1970 and 1996. NAC performed before radiotherapy had no beneficial effects on local control rates or survival rates.[5] The English Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-Analysis Collaboration (NCCCM) examined trials which completed their case registration between 1975 and 2002. A meta-analysis of RCTs was performed, examining whether chemotherapy should be performed before definitive radiotherapy.[6,7] It examined RCTs comparing a group with radiation monotherapy and a group with radiotherapy after chemotherapy. No improvement was seen in overall survival time, disease-free survival time, local recurrence, or distant metastasis with the addition of chemotherapy before radiotherapy. In the same study, subgroup analyses were performed on the interval between administration of chemotherapy, and on cisplatin doses. The results indicated that the survival rate was better in the NAC group if the interval between administrations was $\leq$14 days and the cisplatin dose $\geq$25 mg/m^2/week. In contrast, the survival rate was worse in the NAC group if the interval between administrations was $\geq$15 days or the cisplatin dose <25 mg/m^2/week. This indicates that the chemotherapy cycle and cisplatin dose can affect the outcome. However, this subgroup analysis included 3 RCTs from the same group in the total of 7 RCTs analyzed. Therefore, the analysis results could have been greatly influenced by the results from this one group, and caution is required in interpreting their findings.

Chemotherapy followed by radiotherapy is presently not recommended on a worldwide basis.[8] In the National Comprehensive Cancer Network (NCCN) and National

Cancer Institute (NCI) guidelines, it is not included as a treatment option.[9,10] In Japan, chemotherapy followed by radiotherapy is not recommended.

2) Chemotherapy followed by surgery

Benedetti et al. conducted an RCT on the usefulness of neoadjuvant chemotherapy followed by surgery. They compared NAC + surgery and radiation monotherapy for stages Ib2-III.[11] They performed subgroup analysis of stage III disease, finding no difference between the two treatment methods. In an RCT, Sardi et al. compared NAC + surgery, NAC + radiotherapy, and radiation monotherapy for stage IIIb disease. No improvements were seen in the overall survival time or disease-free survival time for NAC + surgery or NAC+ radiotherapy in comparison with radiation monotherapy.[12] NAC cannot be recommended based on these trial results alone, because of the small subject numbers for this trial, and concurrent chemo radiotherapy (CCRT), the present standard treatment for stage III and IVa disease, was not used as a control. Furthermore, if there is no response to chemotherapy, it can be difficult to perform surgery thereafter, and radiotherapy is often selected instead. In this case, survival rates are reported to be lower than if radiotherapy was selected initially.[3,4]

In clinical practice, chemotherapy is not recommended before radical treatments such as radiotherapy and surgery for stage III and IVa disease. If chemotherapy followed by radical treatment is performed for stage III and IVa disease in a clinical trial, the abovementioned points should be considered. A thorough explanation should then be given before informed consent is obtained, and utmost care should be taken treating patients with chemotherapy followed by radical treatment in a clinical trial.

CQ20
Is surgery recommended for stage III and IVa disease?

Recommendation

Surgery is not recommended (Grade A').

Background and Objectives

For advanced cancer at ≥stage III, pelvic exenteration is performed, or surgery is sometimes performed after cytoreduction using radiotherapy or chemotherapy. We examined the significance of surgery for stages III and IVa.

Explanations

Generally, surgery is not indicated as a standard treatment for advanced cancer at ≥stage III.[1-3] Therefore, if surgery is considered for stage III or IVa disease, pelvic exenteration is performed, or surgery is performed after cytoreductive chemotherapy or radiotherapy.[4] Total hysterectomy, modified hysterectomy, radical hysterectomy, extended radical hysterectomy, pelvic exenteration, and laterally extended endopelvic resection (LEER) are surgical techniques used to remove the uterus.[5] With advances in chemotherapy and radiotherapy, the significance of these surgical procedures is also changing.

In reports on outcomes of stage III disease, radical hysterectomy following neoadjuvant chemotherapy (NAC) is the most often used of the above procedure. Benedetti et al. performed a randomized controlled trial of NAC + surgery and radiation monotherapy in patients with stage Ib2-III disease.[4] Overall outcomes were significantly better for the NAC + surgery group. However, a subgroup analysis limited to stage III disease found no difference between the two treatments. If there is no response to chemotherapy, it can be difficult to perform surgery thereafter, and radiotherapy is often selected instead. In this case, survival rates are reported to be lower than if radiotherapy was selected initially.

Recently, a randomized controlled trial compared concurrent chemo radiotherapy (CCRT) (pelvic irradiation + cisplatin + 5-fluorouracil) and irradiation of the pelvic and para-aortic lymph nodes only for cervical cancer of stages IIb-IVa. Survival rates were significantly prolonged with CCRT in comparison with radiation monotherapy.[6] The following are comparisons of the results of this study[6] and the results of the abovementioned study by Benedetti et al.[4] For CCRT, the 5 year survival rate and 5 year disease-free survival rate were 59% and 54%, respectively. For NAC + radical surgery, these rates were 42% and 42%, respectively. A direct comparison of results from different reports may not be appropriate. Even these indirect data indicated that CCRT should be recommended as the standard treatment for advanced cancer at ≥stage IIIa.

A study was conducted of extended radical hysterectomy following NAC.[7] However, subject numbers were limited, and long-term outcomes have yet to be announced.

【References】

(1) Kobayashi T. Cervical cancer surgery. Nanzando: Tokyo, 1961 (Level IV). (in Japanese)
(7) Sato K, Sakamoto H. Extended radical hysterectomy. Medical View 2000 (Level IV) (in Japanese)