Chapter 7■ Recurrent Cancer

Overview

Treatment strategies for recurrent cancer differ greatly according to the recurrence site (local recurrence or distant recurrence), whether previous radiotherapy was performed, age, and performance status. Individualization of the treatment strategy is therefore essential. Patients with evident residual cancer following incomplete surgery are treated as residual recurrences and undergo radiotherapy, similar to the subjects of this chapter.

In general, radiotherapy is the main option for patients with pelvic recurrence, or solitary localized recurrences outside the radiation field, after previous radiotherapy.

Chemotherapy is the main option for patients with recurrence within the radiation field, or metastases to multiple organs, following previous radiotherapy.

Surgery can be considered for a solitary distant metastasis or local recurrence.

Palliative treatment should in some cases be considered after a comprehensive assessment of the effectiveness of radiotherapy and/or chemotherapy, the patient's performance status, and the degree of cancer spread.

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

Recommendations

(1) Radiotherapy is recommended (Grade B).
(2) Concurrent chemoradiotherapy (CCRT) can be an option (Grade C).

Background and Objectives

We examined treatment selection and outcomes for pelvic recurrence in patients in whom radiotherapy has not been previously performed.

Explanations

In cases of postoperative pelvic recurrence where radiotherapy has not been previously performed, radiotherapy (external radiation monotherapy or concurrently with intracavitary irradiation) results in a 5 year survival rate of 33-74%.[1-4] In particular, good local control rates and disease-free survival rates were obtained in disease confined to the vaginal wall, central recurrence in the vaginal stump, and recurrence with relatively small tumor size (≤3 cm).[1-3]

A phase II trial using CCRT yielded response rates and disease-free survival rates similar to or better than those from radiation monotherapy used as historical controls. Several RCTs have compared radiation monotherapy and CCRT as the initial treatment for cervical cancer in stages Ib2-IVa. Their results indicate superior results for CCRT (see CQ17). [5-8] Therefore, a CCRT regimen with cisplatin is an option for pelvic recurrence in patients in whom radiotherapy has not been previously performed.

Regardless of whether chemotherapy is given concurrently, outcomes were poor for pelvic wall recurrence.[1-3,5-8] Treatment should be aggressive for these cases. In addition, surgery should be considered for patients with central recurrence in the vaginal stump, or fistulas (e.g. vesicovaginal or rectovaginal fistula).

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

Recommendations

(1) Chemotherapy and palliative treatment for symptomatic relief are the general rule for treatment (Grade C).
(2) For central recurrence in the vaginal stump, localized radiotherapy or pelvic exenteration should be considered after a thorough preoperative evaluation (Grade C).

Background and Objectives

We examined treatment selection, outcomes, and complications for intractable recurrence inside the radiation field.

Explanations

Surgery (e.g. pelvic exenteration, which is described later) or re-irradiation is indicated for local recurrence with a history of previous irradiation,. However, elimination of recurrent lesions is difficult in many cases, and patient quality of life (QOL) can decline markedly due to surgical invasiveness and complications. The possible benefits and disadvantages should therefore be considered fully, and the feasibility of implementing certain procedures at the particular institution must also be taken into account. Chemotherapy should be considered for improving QOL by relieving symptoms. However, response rates to chemotherapy for recurrence inside the radiation field are reported to be lower than for recurrence outside the radiation field.[1,2] From the above, if chemotherapy is selected, it is necessary to obtain informed consent from the patient after explaining that palliative therapy is also a reasonable option (for details see CQ25).

The following is a discussion on surgical procedures and re-irradiation.

1) Surgery

(1) Pelvic exenteration

The reported 5 year survival rate following pelvic exenteration for local pelvic recurrence, particularly central recurrence in the vaginal stump, is 32%-67%. It is the treatment that yields the best long-term outcomes.[3-8] An analysis of patients who underwent pelvic exenteration demonstrated good outcomes in those with a small tumor diameter (≤3 cm), central recurrence not reaching the pelvic wall, ≥1 year disease-free survival following initial treatment, and completely resectable lesions.[4,8,10,11] Pelvic exenteration is indicated in patients who fit these criteria. For patients with recurrent disease confined to the vesicovaginal space or rectovaginal space, anterior exenteration and posterior exenteration can be applied, respectively.

The incidence of cardiovascular, respiratory, urinary tract, and gastrointestinal complications is 45-65% following pelvic exenteration. The perioperative mortality rate is relatively high at 2-14%.[3-9] In recent years, the incidence of complications and the

mortality rate have both decreased, due to improvements in surgical techniques and perioperative management, modifications of reconstructive methods (urinary tract, vagina, and pelvic floor), and improved rehabilitation programs. However, it is necessary to thoroughly examine the indications for pelvic exenteration at each institution. It is essential to gain cooperation between departments, obtain thorough informed consent from patients and their families, and provide social and psychological counseling.

(2) Laterally extended endopelvic resection (LEER)

Pelvic exenteration is not indicated for recurrences from the lateral resection margin to the pelvic wall, and these cases also have a poor prognosis. Recently, studies have examined laterally extended endopelvic resection (LEER) and combined operative and radiotherapeutic treatment (CORT), which concurrently uses interstitial irradiation. LEER involves extensive resection of areas including the internal iliac vascular system, and the internal obturator, coccygeal, iliococcygeal and pubococcygeal muscles. The 5 year survival rates for LEER and CORT are reported as 44% and 46%, respectively.[12,13] The indications for these procedures have stricter criteria than for pelvic exenteration, and they have not yet gained general acceptance.

2) Re-implementation of radiotherapy

Re-irradiation is not the first choice treatment for recurrence outside the radiation field. The local control rate and 5 year survival rate are 64-92%[14,15] and 4-40%,[15,16,18] respectively, using external irradiation monotherapy, intracavitary or interstitial irradiation monotherapy, or a combination. The incidence of urinary and gastrointestinal adverse reactions is high at 38%-66%.[14,16,18] In some studies, treatment mainly with interstitial irradiation was selected for some patient types, in whom pelvic exenteration could not be performed for various reasons, such as concurrent diseases. These included patients with recurrence confined to the vaginal wall, central recurrence in the vaginal stump, recurrence with a relatively small tumor size, or late recurrence with ≥5 year disease-free survival time.[16-18] However, the results of these studies are not generally applicable because of unclear inclusion criteria , and problems related to irradiation techniques. The use of re-irradiation as palliative treatment should be considered carefully.

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

Recommendations

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

Background and Objectives

We examined treatments for metastases to the following frequently affected sites of extrapelvic recurrences or recurrences outside the radiation field: lung, brain, para-aortic lymph nodes, and bone.

Explanations

1) Lung metastases

Long-term survival rates of 30-50% have been reported, when metastases were confined to the lung and surgically excised in cases with: ≤3 metastatic lesions, maximum diameter of 3 cm, and histologic type of squamous cell carcinoma.[1-3] Body stereotactic radiotherapy (body SRT) is now sometimes used for cases with solitary or ≤2 metastases,.[4,5] However, its usefulness has yet to be confirmed. In the majority of patients, extrapulmonary recurrences or metastases are also present, and chemotherapy is sometimes indicated in these patients. The response rate for lung metastases using chemotherapy with platinum-based drugs is relatively good at 68%, although the 5 year survival rate is poor at 2%.[6] A more effective salvage therapy is needed.

2) Para-aortic lymph node metastases

A Japanese multicenter trial recently compared radiation monotherapy and a combination of radiotherapy and chemotherapy for patients with para-aortic lymph node metastasis only. The 5 year survival rate was approximately 30% for both treatments.[7] Other studies have reported a very poor prognosis for patients with neuralgia, lower limb edema, or hydronephrosis.[8-10]

The reported 3 year and 5 year survival rates for concurrent chemoradiotherapy (CCRT) are 19%[11] and >50%,[9,10] respectively. Better outcomes were reported for asymptomatic patients with ≥2-year disease-free time. However, both these studies had small subject numbers. In many patients with para-aortic lymph node metastases,

recurrence or metastasis also occurs at other sites. The use of chemotherapy should therefore be considered in these patients.

3) Brain metastases

Whole brain radiotherapy (WBRT) is performed as supportive therapy for solid cancer brain metastases. The median survival time using WBRT is short at only 3-6 months. Two randomized controlled trials (RCT) compared surgery + WBRT and WBRT alone in subjects with solitary and excisable metastatic lesions. Survival times were prolonged using surgery + WBRT.[12,13] Another study contradicted this result, however.[14] Accordingly, a consensus has not been reached on this matter.

In recent years, surgery-replacing treatments have been introduced: stereotactic radiosurgery (SRS) using a linear accelerator (Linac) system or gamma knife, and stereotactic radiotherapy (SRT), in which fractionated irradiation is performed. An RCT compared WBRT monotherapy and WBRT + SRS in subjects with 1-3 unexcisable metastatic lesions. WBRT + SRS was shown to be superior, and could therefore become a treatment option.[15,16] These RCTs were performed on a wide variety of cancers, and the applicability of their results to cervical cancer is uncertain.

There is still insufficient evidence to recommend chemotherapy for brain metastases, although there are some responders when WBRT is used concurrently.

4) Boney metastases

Radiotherapy is considered to provide the most effective pain relief for localized painful bone metastases. A review of RCT results related to pain relief found no difference between short and long course fractionated treatments.[17]

CQ25
Is systemic chemotherapy recommended?

Recommendations

Systemic chemotherapy is recommended in patients with disease difficult to control by surgery or radiotherapy, and patients with a good performance status and preserved organ function (Grade B).

Background and Objectives

If metastases or recurrent lesions can be controlled by surgical resection or radiotherapy, a radical cure and long-term survival is possible. Local therapy is recommended for such lesions. In some patients with multiple recurrences or distant metastases to multiple organs, complete control of lesions cannot be expected with local therapy. There are also patients with local recurrences within the radiation field of previous radiotherapy. In these patients, systemic chemotherapy is indicated as a treatment that can control such lesions. The indications for chemotherapy have broadened with the development of new agents and advances in adjuvant therapies. In this section, we will examine the usefulness of systemic chemotherapy for recurrent cancer in which radical surgery or radiotherapy is not feasible.

Explanations

Overall, the median 1 year and 3 year survival times of patients with recurrent cervical cancer are approximately 6%.[1] Among these patients, the prognosis is particularly poor for those in whom radical surgery or radiotherapy is not indicated. Systemic chemotherapy is not curative, as with many solid cancers. The first goal of treatment is the relief of symptoms and improvement of quality of life (QOL), and then some prolongation of overall survival times can be expected.

A randomized controlled trial (RCT) comparing chemotherapy with supportive palliative care would be needed to demonstrate the usefulness of chemotherapy, which can be highly toxic. However, no such trial has yet been conducted,[2] and logically, will probably not be performed in the future. Therefore, systemic chemotherapy cannot be said to be the standard therapy for patients with recurrences when surgery and radiotherapy are not expected to be curative. Following the development of various agents, such as cisplatin, and advancements in supportive therapy using granulocyte colony-stimulating factor (G-CSF) and antiemetic drugs, a number of patients have been enrolled in clinical trials of systemic chemotherapy. These patients are potentially the subjects of this CQ. Although the results of these trials are not consistent, in some retrospective studies response rates were significantly higher for patients with lung metastases who had not previously undergone radiotherapy.[3,4]

Predictive factors for the efficacy of chemotherapy include age,[3] a good performance status (PS) at the time of treatment, and a long interval between the initial occurrence and recurrence.[5]

From the above findings, the possibility of lesion control by surgery and radiotherapy should first be ruled out when considering systemic chemotherapy for patients with recurrence. The decision should be based on a comprehensive review of the patient's age, PS, organ function, history of radiotherapy to the lesion, and disease-free interval. Before commencing systemic chemotherapy, the patient should be informed that it is unknown whether such treatment prolongs the survival time compared to best supportive care (BSC). The patient should also be informed that palliative care is a reasonable option, and then systemic chemotherapy administered if the patients desires it.

Mean survival times of 9 months have been achieved in some phase III trials with patients who are potentially the subjects of this CQ. However, subjects enrolled into these trials had relatively good PS and organ function. Therefore, the reported outcomes cannot be simply used to predict outcomes in the subjects of this CQ. All possible care should be taken in providing comprehensive information to patients with recurrent cervical cancer before obtaining informed consent for systemic chemotherapy.

CQ26
What regimens are recommended for systemic chemotherapy?

Recommendations

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

Background and Objectives

For patients with recurrent cancer in which surgery or radiotherapy is not anticipated to be curative, systemic chemotherapy can be expected to be useful in relieving symptoms and prolonging life. The efficacy and safety of various agents have been examined. Drugs shown to be efficacious underwent phase III trials to determine their usefulness in prolonging life expectancy. In this section, we will examine drugs suitable for treating recurrent cancer, based on the results of these clinical trials.

Explanations

Presently, the objectives of chemotherapy for recurrent cancer are relief of symptoms and the resulting improvement of quality of life (QOL). Despite expectations of prolonging life, as mentioned in the previous section, chemotherapy has not been demonstrated to prolong overall survival times. In selecting the agent(s), a high response rate of chemotherapy is of course desirable, although one must be cautious of impaired QOL due to toxicity. Therefore, the trend has been to monotherapy using less toxic agents.

Table 7-1 shows the response rates for various anticancer agents as monotherapy. Cisplatin has been studied most often, with response rates of 20-30%.[1] It has been the key drug for over 20 years. In 1985, the Gynecologic Oncology Group (GOG) announced the results of a randomized controlled trial (RCT) on the dosagee and dosing schedule of cisplatin monotherapy, as shown in Table 7-2. Increases in the cisplatin dosage only increased toxicity and did not improve outcomes, and fractionated administration did not reduce toxicity. The standard dosage for cisplatin was established as 50 mg/m^2 once every 3 weeks for either monotherapy or combination therapy.[2] The median overall survival time was short at approximately 7 months using cisplatin monotherapy. Expectations of improved outcomes have been placed on multiple drug therapy, possibly outweighing the increased risk of toxicity. RCTs have been conducted on patients with stage IVb and recurrent disease, mainly by the GOG. Table 7-2 shows descriptions of these RCTs, and their results.

Ifosfamide has the second highest response rate, following cisplatin. In 1997, the results of an RCT on the additive effect of ifosfamide were published. The response rate was significantly improved, and the progression-free survival time significantly prolonged, in the ifosfamide + cisplatin (IP regimen) group. However, no significant

difference was seen in the overall survival time. The IP therapy group showed significantly more toxicity: leukocytopenia, renal toxicity, upper gastrointestinal symptoms, and central and peripheral neuropathy. In addition, IP therapy was more useful in patients with better performance status (PS) and in older patients.[3] The benefits of IP therapy were questionable in improving the response rate and the progression-free survival time.

Next, the GOG expected to improve the overall survival time by adding bleomycin to IP therapy. Instead, they found no significant improvement in the response rate, progression-free survival time, or overall survival time. Only toxicity increased, disproving any additive effect for bleomycin.[12] In Japan, regimens including bleomycin, such as BOMP and BIP, had been widely used, until the above findings provided the evidence to discontinue the use of bleomycin in the treatment of recurrent cervical cancer.

The response rate to paclitaxel monotherapy is 17%.[4] In a phase II trial of a combination of paclitaxel and cisplatin (TP regimen), 91% of subjects had a history of previous radiotherapy. However, the response rate was high at 46%, and TP therapy became a promising treatment.[5] In an RCT comparing cisplatin monotherapy and TP therapy, TP therapy had an increased response rate and significantly improved progression-free survival time, similar to IP therapy. However, no significant difference was seen in the overall survival time between TP therapy and cisplatin monotherapy. Unlike IP therapy, potentially fatal toxicity was not seen with TP therapy, and a decline in QOL due to combination therapy was avoided.[6] Based on this result, the GOG is presently conducting a clinical trial of TP therapy in a standard treatment group of patients with stage IVb and recurrent disease. Much of the evidence for recurrent cancer has arisen from GOG trials. The treatment considered standard by the GOG, TP therapy, is accordingly the most commonly recommended chemotherapy regimen for patients with recurrence or metastases. In Japan, medical insurance does not cover paclitaxel in the treatment of cervical cancer, and the Japan Society of Gynecologic Oncology is in the process of applying for extension of the indications for paclitaxel.

Another RCT compared cisplatin monotherapy with topotecan + cisplatin combination therapy of. The combination therapy group had a better response rate, progression-free survival time, and overall survival time. Although these findings are not final results, this report is the first to show a significantly better overall survival time with a combination therapy than with cisplatin monotherapy. There was a high incidence in the combination therapy group of neutropenia of ≥grade 3 (70% *vs* 1%), as well as other adverse reactions such as anemia, neutropenic fever, nausea, vomiting, and electrolyte abnormalities.[8] At present, topotecan + cisplatin therapy should not be used in Japan due to the high toxicity of this combination therapy, and its unapproved status.

Irinotecan is a topoisomerase I inhibitor like topotecan. Irinotecan is a drug that was developed in Japan, and has been evaluated in many trials in this country. It is one of the few anticancer drugs covered by Japanese insurance for cervical cancer. The response rate is good at 59% for cisplatin + irinotecan combination therapy, with a manageable level of toxicity.[10] In this study, only 21% of subjects had a history of previous radiotherapy. This may have contributed to the high response rate and low incidence of adverse reactions. Nevertheless, this combination therapy is considered to be one of the most effective treatments administrable with Japanese insurance coverage.

Hydronephrosis and hydroureter are commonly seen in patients with advanced and recurrent cancer, and often cause postrenal renal failure. In such cases, use of cisplatin is difficult since it requires diuresis before and after administration to prevent renal toxicity. Carboplatin is a platinum-based drug similar to cisplatin. However, its renal toxicity is lower, and its dosage can easily be adjusted in accordance with the patient's renal function. In patients with stage IVb and recurrent cancer, the response rate to carboplatin monotherapy is not very good at 15%.[12,13] A combination of carboplatin and paclitaxel yielded a good response rate at 60% in a retrospective study.[14] In a Japanese phase II trial, the response rate to carboplatin + cisplatin was 59%, with a mean progression-free survival time of 4.9 months, and mean overall survival time of 9.4 months. In addition, no serious adverse events were reported.[15]

Nedaplatin is another platinum-based drug that was developed in Japan. The response rate to nedaplatin monotherapy is high at 34%-41% for cervical cancer.[16,17] Although there has been little evaluation performed overseas, Japanese clinical trials have examined combinations of nedaplatin with other agents such as irinotecan. Nedaplatin is considered a useful alternative for patients with renal dysfunction.[18]

A Japanese study examined the combination of irinotecan and mitomycin, a regimen without a platinum-based drug. The response rate was good at 51%.[19] In the absence of any results from RCTs, its usefulness has yet to be determined.

Table 7-1 Response rates (%) of monotherapy for cervical cancer

Cisplatin[1]	Carboplatin[12]	Nedaplatin[16,17]	Ifosfamide[1]	Paclitaxel[4]	Irinotecan[9]	Topotecan[7]

Table 7-2 Randomized controlled trials of chemotherapy for stage IVb or recurrent cancer

	Response rate (%)	Progression-free survival time (months)	Overall survival time (months)	Reference
Cisplatin				
Cisplatin *vs* Cisplatin + ifosfamide (IP)				
Ifosfamide + cisplatin (IP) Bleomycin + ifosfamide + cisplatin (BIP)				
Cisplatin *vs* Cisplatin + paclitaxel (TP)				
Cisplatin *vs* Cisplatin + topotecan				

【Reference】

(15) The 57th Annual Meeting of Japan Society of Obstetrics and Gynecology 2005;420(S234) (Level III)