Chapter 3■Postoperative Adjuvant Therapy

Overview

A. Postoperative Recurrence Risk

Surgery is the treatment of first choice for uterine body cancer. Procedures include total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissections/biopsies, and peritoneal lavage cytology. Recommendations for postoperative adjuvant therapy for uterine body cancer are based on the recurrence risk assessment for each individual patient. The important considerations in assessment of the risk of recurrence are related to cancer spread and malignancy, including surgical stage, degree of differentiation, and histological type. Treatment strategies are based on the presence or absence of risk factors for postoperative recurrence. In general, postoperative recurrence risk is determined by surgical stage,[1] histological type,[2-5] the degree of tissue differentiation,[6,7] pelvic and para-aortic metastases,[5,7-9] peritoneal cytology,[7,10] venous or lymphatic invasion,[5,11,12] and tumor size.[13] Prognostic factors used in surgical staging are myometrial invasion, cervical invasion, spread to the adnexae, spread to the serosa, spread to the cardinal ligament, vaginal wall invasion, vesical and rectal invasion, peritoneal dissemination, and distant metastases. Based on the combination of these factors, cases are classified into a low, intermediate, or high risk group.[14] (Table 1; see p. 11). A recent study[16] considered long-term outcomes of postoperative adjuvant therapy in the intermediate risk group, further subdividing it into a low-intermediate and high-intermediate risk group. Active discussion on the classification of recurrence risk can be expected in the future.

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B. Postoperative Recurrence Site

The sites of predilection for postoperative recurrence of uterine body cancer are the vaginal stump, intrapelvic sites, intraperitoneal sites, and distant organs. The recurrence rate was 15-20% for clinical stage I patients who underwent postoperative radiotherapy (N.B.: the surgical procedure for this study was total hysterectomy+bilateral salpingo-oophorectomy without lymphadenectomy). The rate of local recurrence in the vaginal stump and pelvis was 4-7%, and distant metastases were detected in 7-17%.[1] Sartori et al. analyzed a large number of cases, 1606 patients with uterine body cancer treated in 5 Italian institutions.[2] Recurrence occurred in 209 patients (13%), in whom the recurrence site was the vagina in 35 patients (16.7%), pelvis in 67 patients (32.1%), with distant metastases in 107 patients (51.2%). Many patients had recurrence within ≤2 years: ≤1 year for 94 patients (24%) and 1-2 years for 43 patients (23%). Postoperative radiotherapy reduced the pelvic recurrence rate in the high risk group of patients with uterine body cancer. However, many of these patients had distant metastases. Survival rate were not improved in the group that underwent postoperative radiotherapy.

Stewart et al. performed postoperative radiotherapy (whole abdominal irradiation) in 119 patients with stage I-III uterine body cancer. They reported recurrences in 37 patients (31%). The recurrences were in the abdomen and pelvis for 14 patients (37.8%), lungs for 8 patients {21.6%}, extraperitoneal lymph nodes for 7 patients (18.9%), vagina for 6 patients (16.2%), and other sites for 2 patients (5.4%).[3] Mundt et al. performed postoperative chemotherapy on 43 high risk uterine body cancer patients at stages I-IV. Four to six courses of chemotherapy, cisplatin and adriamycin, was performed. Recurrence was seen in 29 patients: pelvic recurrence in 17 patients (39.5%) and extrapelvic site in 23 patients (53.5%). The pelvic recurrences were in the vagina for 8 patients (18.6%), extravaginal site for 3 (7.0%), and both vaginal and extravaginal for the remaining 6 (14.0%).[4]

The GOG 122[5] trial compared groups that underwent whole abdominal irradiation and postoperative chemotherapy (AP therapy). The subjects were patients with uterine body cancer at stages III-IV. There were more recurrences at sites beyond the peritoneal cavity in the radiotherapy group than in the chemotherapy group (18.3% *vs* 9.8%). In contrast, there were fewer pelvic recurrences in the radiotherapy group than in the chemotherapy group (8.4% vs 11.3%). There was no significant difference between the 2 groups in intra-abdominal (16.3% vs 11.3%) and vaginal recurrences (5.0% vs 5.7%). For the relationship between the types of adjuvant therapies and recurrence sites, there tended to be more pelvic recurrences for adjuvant chemotherapy alone. There tended to be more distant metastases for adjuvant radiotherapy alone.

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I. Radiotherapy

Overview

In Western countries, radiotherapy (whole-pelvis external-beam irradiation, intracavitary irradiation, and para-aortic irradiation) is frequently used as postoperative adjuvant therapy for uterine body cancer. Only 45% of gynecologic oncologists in Western countries routinely perform pelvic lymphadenectomy.[1] In Japan, pelvic lymphadenectomy is generally performed, and this difference should be considered when determining the place of postoperative radiotherapy.

According to randomized controlled trials in Western countries, pelvic recurrence rates are significantly reduced by postoperative whole-pelvis external-beam irradiation.[2-4] However, it is unclear whether survival time is prolonged. When radiotherapy is performed in combination with surgery, adverse events increase.[3-5] In particular, the incidence of adverse events increase when whole-pelvis external-beam irradiation is performed following pelvic lymphadenectomy.[6,8-10] Patients at high risk of pelvic recurrence should therefore be identified by the presence of risk factors for recurrence and therapeutic factors. Risk factors include age, myometrial invasion, the degree of tissue differentiation, lymphatic vessel invasion, and histopathological type. Therapeutic factors include whether pelvic lymphadenectomy has been performed. Following evaluation of the patient's risk of pelvic recurrence, the indications for radiotherapy should be considered carefully. A reduced rate of vaginal recurrence can be expected from postoperative whole abdominal irradiation. However, it is not clear whether whole abdominal irradiation contributes to prolongation of the overall survival time. It is uncertain in what patient subgroups para-aortic lymph node irradiation is useful. Chemotherapy is in the process of replacing whole abdominal irradiation.

Major adverse events associated with postoperative radiotherapy include small bowel obstruction, chronic diarrhea, proctitis, fistula formation, vaginal stenosis, and incomplete fracture. Late complications of external beam irradiation are mostly gastrointestinal and urinary tract disorders. Adverse events associated with whole abdominal irradiation are rectal ulcers, rectovaginal fistula, vaginal stenosis, and fibrosis of the perivaginal tissues.[5-8,11] In the Randomized Controlled Study of Postoperative Radiotherapy in Endometrial Carcinoma Trial (PORTEC), late adverse events of grades 1-4 were seen in 26% of the whole-pelvis external-beam irradiation group, compared to 4% of the non-irradiated group. The majority were grade 1: 17% in the whole-pelvis external-beam irradiation group and 4% in the non-irradiated group. Adverse events of grades 3-4 were seen only in the whole-pelvis external-beam irradiation group, with a frequency of 3% over 5 years. The majority of these were gastrointestinal disorders. Grade 1-2 urinary tract disorders were seen in 8% and 4% of the irradiated and non-irradiated group, respectively. Bone disorders were seen in 4 patients in the irradiated group. The GOG conducted a randomized controlled trial (GOG 99) on whole-pelvic external-beam irradiation after surgical staging, including detection of lymph node metastasis. The radiotherapy group experienced significantly more disorders of the gastrointestinal and urinary tracts, and hematotoxicity. Out of 190 patients in the whole-pelvis external-beam irradiation group, 6 patients developed small bowel obstruction grade 3-4.[4] The incidence of severe late adverse events associated with postoperative irradiation was 2-6% for whole-pelvis external beam irradiation after total hysterectomy + bilateral salpingo-oophorectomy, rising to 4-13% with the addition of whole abdominal irradiation. The incidence of severe late adverse events was 0-7% for whole abdominal radiotherapy alone after total hysterectomy + bilateral salpingo-oophorectomy, and 7-18% for whole-pelvis

external-beam irradiation after pelvic lymphadenectomy.[1,5-7,11] Many patients who experienced acute adverse events also went on to have late adverse events.[5,12,13] If postoperative whole-pelvis external-beam irradiation is required, ≥6 MV high energy x-ray beams and an appropriate irradiation method should be used to minimize the incidence of adverse events. Treatment of one field per day is associated with a high incidence of adverse events, and is therefore inappropriate.[9] The incidence of adverse events was lower for a 4-field box technique than a two opposed-field (AP/PA) technique.[5,6,9]

Generally, radiotherapy is commenced 1-2 months after surgery. In the PORTEC trial, the median interval between surgery and commencement of postoperative radiotherapy was 42 days in the radiotherapy group. In 12% of patients, the interval exceeded 2 months. The authors did no comment on the difference in the local control rate between the two intervals.[3] We were unable to find any studies that thoroughly examined the effects of the total duration of postoperative whole-pelvis external-beam irradiation treatment on local control and other therapeutic outcomes. For whole-pelvis external-beam irradiation, 45-50 Gy is most often used in radiation monotherapy. There is typically very little variation in the dose per fraction, fractionation regimen, or total treatment time. Unlike definitive radiotherapy in uterine cervical cancer, no factors have been identified that directly affect the treatment period, such as increased acute adverse events due to concurrent chemotherapy, or differences in dosing schedules for intracavitary irradiation. The total treatment duration is approximately 5 weeks.

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CQ17

Is postoperative whole-pelvis external-beam irradiation useful?

Recommendations

Although pelvic recurrences are reduced, it is uncertain whether postoperative whole-pelvis external-beam irradiation prolongs the overall survival time (Grade C).

Background and Objectives

Randomized controlled trials in rats have shown that postoperative whole-pelvis external-beam irradiation reduces pelvic recurrences and improves progression-free survival, but not the overall survival rate. We examined the benefits of postoperative whole-pelvis external-beam irradiation.

Explanations

At less than 5%, the recurrence rate is low in the G1-G2 low risk group with ≤1/2 myometrial invasion (stages Ia-Ib). In this group, postoperative whole-pelvis external-beam irradiation is therefore unnecessary. Groups with a higher risk of recurrence show reductions in the pelvic recurrence rate using whole-pelvis external-beam irradiation. In a randomized controlled trial performed 30 years ago, the usefulness of whole-pelvis external-beam irradiation was examined in patients who underwent postoperative vaginal intracavitary irradiation. Pelvic recurrences were shown to be reduced significantly.[1]

The PORTEC trial was a large-scale trial conducted to clarify the usefulness of postoperative whole-pelvis external-beam irradiation in patients with uterine body cancer who underwent total hysterectomy and bilateral salpingo-oophorectomy (without lymph node sampling). In the 2000 study, the subjects were patients with uterine body cancer stage G1 with >1/2 myometrial invasion, all G2, or G3 with <1/2 myometrial invasion. The 5 year overall survival rate was 81% for the group that underwent whole-pelvis external-beam irradiation and 85% for the non-irradiated group. The 5 year pelvic recurrence rates were 4% and 14% in the whole-pelvis irradiated group and the non-irradiated group, respectively, significantly lower in the irradiated group.[2] Postoperative whole-pelvis external-beam irradiation was useful in controlling local recurrence, but did not improve the survival rate.

The GOG 99 trial was a randomized controlled trial in which a whole-pelvis external-beam irradiation group and a non-irradiated group were compared. Subjects were patients with stage Ib, Ic, IIa, or IIb disease who had undergone total hysterectomy and bilateral salpingo-oophorectomy as well as pelvic and para-aortic lymph node biopsies. The irradiated and non-irradiated groups had 2 year recurrence rates of 3% and 12%, 2 year intrapelvic single recurrence rates of 1.6% and 7.4%, and disease-free survival rates of 94% and 85%, respectively. Outcomes were significantly better for the irradiated group than the non-irradiated group. The improvement in the survival rate was not significant, however.[3] The GOG 99 trial focused on the following 3 factors in the intermediate risk group: G2 or G3 disease, venous or lymphatic invasion, and greater than outer 1/3 myometrial invasion. Patients in the high-intermediate risk group were defined as those with all 3 factors, or 2

factors and ≥50 years old, or 1 factor and ≥70 years old. Postoperative radiotherapy was more effective in preventing recurrence in the high-intermediate risk group. The authors concluded that postoperative radiotherapy should be limited to the high-intermediate risk group.

In patients with G3 and stage Ic disease, considered to have a higher risk for recurrence, the indications for whole-pelvis external-beam irradiation depend on whether pelvic lymphadenectomy is performed intraoperatively. A high proportion of these patients are positive for pelvic lymph node metastasis, reaching approximately 25% in G3 stage Ib and Ic disease.[4-6] If intraoperative pelvic lymphadenectomy is not performed, postoperative pelvis external beam irradiation is recommended since some degree of pelvis lymph node metastases is anticipated. However, even if whole-pelvis external-beam irradiation is performed on these patients, the pelvic recurrence rate is higher than in other stage I patients, and the rate of distant metastasis is also high. Therefore, whole pelvis external-beam irradiation alone is considered insufficient as adjuvant therapy.[7]

If pelvic lymphadenectomy is performed, the pattern of later recurrence differs according to whether metastases were present. In patients without lymph node metastases on histopathologically examination, the main recurrence site is the vagina. Although good local control is achieved with whole-pelvis external-beam irradiation, it is not known whether it improves the survival rate. In patients who undergo whole pelvis external beam irradiation following lymphadenectomy, the incidence of late adverse events, such as of the gastrointestinal tract, is high. If pelvic lymph node metastases are detected, systemic adjuvant therapy should be considered because there could be latent systemic metastases.

If postoperative whole pelvis external beam irradiation is performed, an acceptable level of pelvic control is achieved. When intracavitary irradiation of the vaginal stump is added, the pelvic control rate is not increased. On the other hand, the incidence of late adverse events has been shown to increase.[8-11] Therefore, the addition of stump irradiation is considered unnecessary when performing whole-pelvis external-beam irradiation.

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CQ18

Is postoperative intracavitary irradiation of the vaginal stump useful?

Recommendations

Although it may lower the vaginal recurrence rate, it is unclear whether postoperative intracavitary irradiation of the vaginal stump prolongs the overall survival time (Grade C).

Background and Objectives

The sites of predilection for postoperative recurrence are the vaginal stump and the margins of the paravaginal connective tissue. Some institutions recommend intracavitary irradiation of the postoperative vagina to prevent vaginal recurrence. We examined the benefits of postoperative intracavitary irradiation of the vaginal stump.

Explanations

In patients who underwent surgery alone, a single vaginal recurrence was seen in 3% of the low-risk group (G1-G2 with ≤1/2 myometrial invasion) and of the intermediate-risk group (G3 with a lesion confined to the mucosal surface).[1] The highest rate was 15% in the high-risk group.[2] The indications for intracavitary irradiation of the vaginal stump are patients with a certain level of recurrence with surgery monotherapy who have a high likelihood of recurrence being confined to the vagina. Generally, patients with myometrial invasion of ≤1/2 (stages Ia-Ib), and G1-G2 disease with low risk tumor, have a low risk for recurrence.[1] The NCCN guidelines state that adjuvant therapy is generally unnecessary in these patients. Analysis of risk factors for postoperative recurrence showed that the likelihood of lymph node metastasis was increased in patients with myometrial invasion of >1/2 or G3 disease.[3,4] Therefore, if lymphadenectomy is not performed, whole pelvis external beam irradiation is often performed. The PORTEC trial was a randomized controlled trial whose subjects were mainly in the intermediate risk group (G1 with >1/2 myometrial invasion; G2 (regardless of the extent of myometrial invasion); or G3 with myometrial invasion of ≤1/2). In this trial, recurrence was confined to the vagina in 73% of patients with recurrence.[5] In patients at low risk of distant metastasis and other pelvic recurrence such as lymph node metastasis, postoperative intracavitary irradiation of the vaginal stump can be expected to lower the local recurrence rate. The intermediate risk group with postoperative vaginal intracavitary irradiation had a similar control rate of stump recurrence as the group with whole pelvis external beam irradiation.[6-10] However, there have not been any randomized controlled trials comparing these two groups. In patients who underwent intraoperative lymphadenectomy or lymph node sampling, the incidence of adverse events was increased, e.g. affecting the small intestine, when postoperative whole-pelvis external-beam irradiation was performed.[9,11,12] In patients with a high risk for recurrence, such as with stage Ic disease, many are of the opinion that intracavitary irradiation alone is sufficient as adjuvant therapy, if at operation the sampled lymph nodes were negative for metastasis (pN0).[9,11-14]

For a single vaginal recurrence, it is unknown if postoperative intracavitary irradiation of the vaginal stump improves survival, since the salvage rate after recurrence is high. In a

randomized controlled trial (PORTEC trial), 79% of vaginal recurrences were controlled. Ackerman et al. indicated that two-thirds of vaginal recurrences were effectively controlled.[5,15] However, vaginal recurrences are sometimes ultimately fatal.[2,8,16] The latest PORTEC trial is being conducted to compare two treatment strategies: postoperative intracavitary irradiation of the vaginal stump, and follow-up alone with salvage therapy after confirmation of recurrence.

There is insufficient evidence on how to best determine the planning target volume (PTV) for intracavitary irradiation of the vaginal stump. In the low risk group, it is considered acceptable to use the upper 1/3 of the vaginal region as the PTV since recurrence is most frequent in the upper region.[2,8] However, some stage I patients have a high likelihood of recurrence, and recurrence in the inferior vagina is sometimes seen in stage II patients.[2] In stage Ib G3 and stage Ic patients, Ng et al. performed intracavitary irradiation in only the upper 2 cm of the vagina as the PTV. They performed irradiation after lymph node biopsy, observing vaginal recurrences in 10% of patients, the majority of which were in the lower 2/3 of the vagina.[9] In similar patient groups, Chadha et al.[11] and Anderson et al.[12] performed intracavitary irradiation with the whole length of the vagina as the PTV. They did not observe any vaginal recurrences. In these patients, intracavitary irradiation of only the upper vaginal region is likely insufficient. However, if the irradiated area is increased, the likelihood of adverse events from intracavitary irradiation is also increased. More evidence is needed to determine the optimum total dose of intracavitary irradiation, dose per fraction, and dose reference point.

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CQ19

Are postoperative irradiation of the para-aortic lymph node region and whole abdominal irradiation useful?

Recommendations

(1) There is insufficient evidence to state that postoperative irradiation is useful for the para-aortic lymph node region (Grade C).
(2) Postoperative whole abdominal irradiation is not recommended (Grade B).

Background and Objectives

In Japan, examinations for pelvic and para-aortic lymph node metastasis are performed intraoperatively. The para-aortic lymph node region is therefore infrequently irradiated after surgery. In addition, whole abdominal irradiation is rarely performed aggressively. Our examination of the clinical benefits of these irradiation methods was based on retrospective studies in Western countries.

Explanations

Morrow et al. examined 895 patients in clinical stages I and II who underwent pelvic and para-aortic lymph node biopsies. Para-aortic lymph node metastases were detected in only 48 patients (5.4%). Of these, other factors, such as pelvic lymph node metastases, outer 1/3 myometrial invasion, and adnexal or intraperitoneal metastases, were identified in 47 patients (98%) had.[1] Para-aortic lymph node metastasis were present in 5% of patients with the abovementioned factors associated with a poor prognosis.[2] It is highly likely that latent lesions are present in the para-aortic lymph nodes in these patients, so irradiation of the pelvic and para-aortic lymph node regions could be useful in controlling metastases. Only a few retrospective studies with small subject numbers have examined irradiation of the para-aortic lymph node region.[3-5] Even if the para-aortic region is irradiated, recurrence is often seen in sites outside of the irradiated field, such as distant metastases. Therefore, it is unclear for what patient groups irradiation of the para-aortic lymph node region might be useful.

Studies have been conducted looking at recurrences in stage III patients with extrauterine disease, and patients with highly malignant histological types such as serous adenocarcinoma and clear cell carcinoma. They found that 20-30% of such patients had extrapelvic recurrences, in intra-abdominal and distant sites.[3-7] Whole pelvic external beam irradiation alone is therefore insufficient as adjuvant therapy. Stewart et al. stated that recurrences in these patients were most frequently intra-abdominal, and they advocated whole abdominal irradiation.[8] Smith et al. also reported on the usefulness of whole abdominal irradiation.[9] However, retrospective studies indicated that intraperitoneal recurrences were seen in many patients despite the whole abdominal irradiation. In this poor prognosis group, even following irradiation to the abdominal region, many patients developed metastases in sites outside the irradiated field. Generally, in patients with extrauterine disease, 30-50% of such patients have systemic recurrences.[10] It is unclear whether extensive radiotherapy improves survival. The dose of whole abdominal irradiation is usually limited to

approximately 30 Gy after consideration of toxicity to the kidneys and gastrointestinal tract. There is insufficient evidence to say that whole abdominal irradiation is effective in controlling microscopic lesions and in preventing intra-abdominal recurrences. Chemotherapy has already been shown to be useful in stages III-IV patients.[11]

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CQ20

Are there contraindications for postoperative radiotherapy?

Recommendations

(1) Absolute contraindication: previous radiotherapy to the pelvic region (Grade A)
(2) Relative contraindications: concurrent rheumatic diseases, such as scleroderma or systemic lupus erythematosus (Grade B)
(3) Patients in whom caution should be exercised concerning adverse events: concurrent inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease (Grade B)

Background and Objectives

Patients with a history of irradiation to the pelvic region are not suitable for postoperative irradiation. We examined whether concurrent rheumatic disease or inflammatory bowel disease are contraindications for postoperative irradiation.

Explanations

If there is a history of irradiation to the pelvic region, such as for rectal cancer, external beam irradiation is contraindicated to the pelvic region, since the normal tissue tolerance dose will be exceeded for the gastrointestinal tract. If intracavitary radiation monotherapy is planned, past radiotherapy records should be obtained and carefully examined to determine whether the projected radiation doses would be within the allowable limits for organs such as the bladder and rectum.

Radiation has been reported to increase adverse events in patients with concurrent rheumatic diseases,[1] although another study did not find an increased rate of adverse events in similar patients.[2] Morris and Powell retrospectively examined 209 cancer patients with rheumatic diseases and investigated acute and late adverse events following radiotherapy. Compared with rheumatoid arthritis patients, those with rheumatic diseases other than rheumatoid arthritis experienced a significantly higher incidence of late adverse events ≥grade 3, mainly involving the skin and mucosa (5 years: 6% *vs* 21%). They concluded that radiotherapy should be avoided in this group.[3] Following radiotherapy for breast cancer and nasopharyngeal cancer, adverse events mainly affecting the skin and mucosa were reported to increase for patients with rheumatic diseases other than rheumatoid arthritis.[4,5] In controlled studies, patients with and without concurrent rheumatic diseases were compared with a control group. No significant differences in acute or late adverse events were seen in patients with or without concurrent rheumatic diseases in comparison with the control group.[6,7] Activity of the rheumatic disease at the time of irradiation, and duration of disease, did not affect the incidence of adverse events.[2,6] More studies are required to determine whether adverse events are increased during or after radiotherapy in patients with rheumatic diseases.

Patients with concurrent inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, experienced high incidences of severe acute adverse events necessitating a

rest period from radiotherapy, and late adverse events requiring surgical treatment.[8,9] These retrospective studies were conducted with only small subject numbers, so it is unclear whether adverse events are increased by whole-pelvis external-beam irradiation in patients with concurrent inflammatory bowel disease. If these patients require postoperative radiotherapy, it is necessary to modify the radiation field to minimize intestinal exposure.

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II. Chemotherapy and Hormone Therapy

Overview

Postoperative recurrence sites for uterine body cancer are divided into intrapelvic and extrapelvic sites (distant metastases and intra-abdominal recurrence). Postoperative whole pelvis external irradiation is therefore limited in its ability to improve survival. Systemic chemotherapy can be expected to achieve more favorable outcomes than whole pelvis external irradiation. Clinical trials are needed to provide evidence to determine the usefulness of chemotherapy. Some non-comparative trials have found that postoperative chemotherapy prolongs survival. Burke et al. of the M. D. Anderson Cancer Center used CAP therapy (6 courses) in 62 high risk patients (G2 with ≥1/3 myometrial invasion; G3 with myometrial invasion, inoperable extrauterine spread; serous or clear cell adenocarcinoma). The 3 year survival rate was 46% in patients with extrauterine spread, and 83% in patients with no extrauterine spread, demonstrating high survival rates in high risk patients with cancer confined to the uterus.[1] However, distant recurrences could not be controlled in patients with extrauterine spread. Aoki et al. performed postoperative CAP therapy in 61 patients in stage III, achieving a 5 year survival rate of 79%.[2]

Since extrapelvic recurrence is common in patients with extrauterine spread, whole abdominal irradiation is routinely performed postoperatively in some U.S. institutions. The GOG conducted a phase II trial on whole abdominal irradiation, confirming its safety and some degree of efficacy. A phase III trial was conducted with whole abdominal irradiation and AP (adriamycin and cisplatin) therapy, demonstrating efficacy against advanced uterine body cancer.[3] The results of this trial supported the usefulness of postoperative chemotherapy for advanced uterine body cancer. The trial results will be described in more detail in CQ21 and CQ22. There is insufficient evidence on the usefulness of chemotherapy in the intermediate risk group without extrauterine spread.

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CQ21

Has efficacy been established for postoperative adjuvant chemotherapy?

Recommendations

(1) Postoperative chemotherapy is not recommended for low risk patients (Grade C).
(2) Postoperative chemotherapy may be as effective as, or more effective than, radiotherapy for intermediate risk patients (Grade C).
(3) Postoperative chemotherapy is recommended for high risk patients with postoperative residual tumor of ≤2 cm (Grade B).

Background and Objectives

Adjuvant radiotherapy is considered the standard treatment for patients classified as intermediate or high risk for postoperative recurrence. We examined the usefulness of postoperative chemotherapy based on the results of recent clinical trials.

Explanations

A small number of randomized controlled trials have examined the benefits of chemotherapy as postoperative adjuvant therapy. The U.S. GOG conducted the GOG 34 trial which examined subjects with one or more risk factors for recurrence: postoperative lymph node metastases, ≥50% myometrial invasion, cervical involvement, or adnexal invasion. This study compared two groups of subjects. After radiotherapy, the first group (92 subjects) was administered 60 mg/m^2 of adriamycin (ADM) every 3 weeks up to a total dose of 500 mg/m^2. The second group of patients was not administered adriamycin (89 subjects).[1] The registration rate was very low in this trial, with only 181 subjects registered over a 9 year period. There were also 43 ineligible subjects, and 25 subjects allocated to the adriamycin group were not administered adriamycin. The results showed no differences in the recurrence rate or survival rate between the groups. Since the detectability was low, this trial alone could not determine whether chemotherapy was effective.

A subsequent randomized controlled trial, GOG 122, was conducted with stage III/IV subjects with no postoperative residual tumor ≥2 cm. Whole abdominal irradiation was the control arm, and it was compared with AP therapy (cisplatin 50 mg/m^2 + adriamycin 60 mg/m^2).[2] AP therapy produced good progression-free survival (hazard ratio: 0.81, 95% CI: 0.63-1.05), as wells as better overall survival time (hazard ratio: 0.71, 95% CI: 0.54-0.94). However, since the allowable limit for the total dose of adriamycin is 420 mg/m^2, the eighth course was cisplatin alone. There were 8 treatment-related deaths out of 96 patients administered AP therapy, and 5 treatment-related deaths out of 126 patients receiving whole abdominal irradiation. Careful attention must be paid to toxicity.

The JGOG 2033 trial was a randomized controlled trial conducted in Japan. Subjects with intermediate or high risk were randomly allocated into a postoperative whole pelvis external beam irradiation group or a CAP chemotherapy group. The 5 year survival was

similar in both groups: 85.9% for the radiotherapy group (186 subjects) and 87.1% for the chemotherapy group (188 subjects).[3]

Patients indicated for postoperative adjuvant chemotherapy are those with factors associated with a poor prognosis (e.g. pelvic or para-aortic lymph node metastases, cervical invasion, adnexal invasion, deep myometrial invasion, G3, and serous or clear cell adenocarcinoma histological types).[4,5] Randomized controlled studies of subjects with stage III and IV disease have shown that postoperative chemotherapy is more useful than radiotherapy. Further studies are needed to examine the usefulness of postoperative chemotherapy in stage I and II patients with deep myometrial invasion, G3 disease, or serous and clear cell adenocarcinoma histological types.

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CQ22

Which drugs are recommended for postoperative adjuvant chemotherapy?

Recommendations

(1) Regimens including anthracyclines and platinum-based drugs are recommended (Grade B).
(2) Taxanes can also be used in combination with the above, although there is insufficient evidence to recommend them (Grade C).

Background and Objectives

The following anticancer drugs have reported response rates of over 20% when used as monotherapy: cisplatin (CDDP), carboplatin (CBDCA), adriamycin (ADM), epirubicin (EPI), paclitaxel (PTX), and 5-fluorouracil (5-FU).[1-3] The results of recent clinical trials were used to examine the usefulness of postoperative chemotherapy and to investigate what combination of drugs are recommended.

Explanations

The GOG 34 study was a randomized controlled trial with 181 subjects with clinical stages I and II (occult) and at least one risk factor for recurrence out of myometrial invasion of >1/2, pelvic or para-aortic lymph node metastases, cervical invasion, and adnexal metastases. Subjects were allocated to a group administered postoperative radiotherapy and adriamycin 60 mg/m^2 (up to a total dose of 500 mg/m^2) and a group administered radiotherapy only. Radiotherapy was whole-pelvis external-beam irradiation in all cases, with the addition of para-aortic irradiation if para-aortic lymph node metastases were present. The trial results did not demonstrate any benefits from the addition of chemotherapy.[4]

The GOG 122 study was a randomized controlled trial of advanced uterine body cancer in stages III and IV. Subjects were allocated to a group administered postoperative whole abdominal irradiation or a group administered AP therapy (adriamycin 60 mg/m^2 + cisplatin 50 mg/m^2 every 3 weeks; 8 courses in total). AP therapy was shown to improve outcomes.[5] This was the first time that the usefulness of chemotherapy as postoperative adjuvant therapy was demonstrated for uterine body cancer, and this treatment became a standard therapy. In the GOG 122 trial, 27% of subjects receiving AP therapy had to discontinue mid-treatment, 17% due to adverse reactions. The number of subjects who completed the treatment was small. In a subsequent clinical trial of postoperative adjuvant therapy (GOG 184), the dosages and number of courses for AP therapy were established as adriamycin 45 mg/m^2 + cisplatin 50 mg/m^2 every 3 weeks for a total of 6 courses. Chemotherapy regimen dosages given here are derived from clinical trials in Western countries. Caution is required in applying these dosage regimens in Japanese patients.

The GOG 184 trial is a randomized controlled trial, presently being conducted, in which paclitaxel was introduced after postoperative adjuvant therapy (in addition to postoperative radiotherapy, AP therapy vs TAP therapy).[6]

In 2005, a national survey was conducted by the Japanese Gynecologic Oncology Group (JGOG). In over half of the institutions surveyed, the first choice treatment was a

combination of paclitaxel and carboplatin (TC). Reported response rates using TC have been high at 87%,[8] 63%,[9] and 78%[10] for advanced and recurrent uterine body cancer. Although TC therapy is one option for postoperative adjuvant therapy for the intermediate to high risk group, there is still insufficient evidence to recommend its use as postoperative adjuvant therapy.

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CQ23

Is hormone therapy effective as postoperative adjuvant therapy?

Recommendations

Postoperative hormone therapy is not recommended (Grade A).

Background and Objectives

Since the 1970s, hormone therapy, using agents such as medroxyprogesterone acetate (MPA) and tamoxifen, has been used as postoperative adjuvant therapy. Some reports in recent years indicate that hormone therapy has little effect on survival rates. We examined the efficacy of hormone therapy as postoperative adjuvant therapy.

Explanations

Lewis et al. used depo-MPA in 956 patients, their results showing no difference in the survival rate between the depo-MPA and placebo groups.[1] Studies from England[2] and Norway[3] have showed that little improvement in survival rates with progesterone therapy. In the 1990s, an Italian study[4] also showed no effect on survival.

In Japan, the Japan Gynecologic Oncology Group conducted a secondary study of chemotherapy for uterine body cancer.[5] It found that postoperative MPA therapy is not useful as adjuvant therapy. In a study conducted in Australia and other countries, postoperative MPA adjuvant therapy was performed in over 1,000 patients, and showed little effect on outcomes.[6] In recent years, a comparison of MPA and tamoxifen found that tamoxifen had little effect as adjuvant hormone therapy, but was possibly useful for patients with complications.[7]

The 2003 Cochrane database of systematic reviews[8] summarized the above reports, evaluating the efficacy of progesterone in preventing postoperative recurrence of uterine body cancer. In 6 clinical trials, progesterone was administered postoperatively for uterine body cancer in a randomized manner. Survival rates, causes of death, and recurrences were evaluated in 4,351 patients with uterine body cancer from these trials (3 trials were for stage I only and the other 3 trials included advanced cancer). In 5 trials, survival rates were not improved by postoperative progesterone therapy (odd ratio: 1.05, 95% CI: 0.88-1.24). Deaths and recurrences tended to decrease with progesterone therapy for uterine body cancer. However, there was a high frequency of deaths not related to uterine body cancer for patients who received progesterone therapy.

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