Chapter 5■

Treatment of Advanced and Recurrent Cancer

Overview

1) Advanced cancer

An individualized treatment strategy should be devised for each patient with stage III and IV advanced uterine body cancer. In some cases, extrauterine spread has been identified preoperatively, and in other cases spread beyond the uterus, such as to intrapelvic and intraperitoneal sites, is detected for the first time at laparotomy. Surgery for advanced uterine body cancer is sometimes performed as palliative therapy, such as to relieve an intestinal obstruction or to control hemorrhaging. Surgery may also be performed as part of a multidisciplinary strategy, to reduce the tumor mass as much as possible and provide a better outcome. Treatments used in inoperative advanced and recurrent uterine body cancer include chemotherapy, hormone therapy, and radiotherapy.

For stages III and IV uterine body cancer clinically determined to have extrauterine spread, treatment is selected based on whether cytoreduction and hysterectomy are possible. The sites of extrauterine spread of advanced uterine body cancer are the adnexae, vagina, parametrium, retroperitoneal lymph nodes, bladder, rectum, peritoneal dissemination, and distant metastasis. Depending on the case, it is important to excise the tumor as much as possible by total hysterectomy (including radical hysterectomy), vaginal resection, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomies. Pelvic clearance has been shown to be effective only in cases with local recurrence such as vaginal recurrence.[1] In advanced uterine body cancer, after achieving optimal residual tumor ($\leq$2 cm or $\leq$1 cm), the outcome can be expected to improve with adjuvant chemotherapy or radiotherapy.[2-4] However, no clinical trials have been conducted to determine the basis on which surgery, chemotherapy, and/or radiotherapy should be selected in cases where radical excision is considered impossible.

One study suggested that if the residual tumor bulk could be minimized by extended surgery, outcomes similar to cases not requiring extended surgery can be expected, regardless of the location of metastases.[5] If a patient with cancer cells only detected in pleural fluid was diagnosed as stage IVb, residual tumor could be excised optimally. However, if a patient had cancer spread beyond the pleural fluid and was diagnosed as stage IVb, then optimal excision was reportedly difficult.[3]

2) Recurrent cancer

Patterns of recurrent uterine body cancer range from local recurrence, including the vaginal stump, to distant recurrence such as lung metastases. Lesions can also range a solitary confined recurrence to multiple recurrences as in peritoneal dissemination. Chemotherapy targets mainly the latter.

Where possible, as the first step a tumorectomy is attempted for recurrent uterine body cancer, if possible. If recurrence is in the vaginal stump, the combination of tumor resection and vaginal resection or pelvic clearance is likely effective.[1] However, one cannot expect

resection to be effective against intra-abdominal recurrences other than the central pelvis and vagina.[6] Distant metastases to multiple organs such as lungs, bones, and brain are not suitable for surgery.[6] Concurrent chemotherapy or radiotherapy should always considered, regardless of the operability of recurrent and metastatic lesions.

Very few studies have addressed the usefulness of cytoreductive surgery following chemotherapy for recurrent uterine body cancer. In a retrospective study of surgery for intra-abdominal recurrences, no benefits were detected in 9 patients in terms of the survival rate or surgical success rate. These patients underwent chemotherapy for recurrent disease before referral for secondary rescue surgery.[6] However, if metastases are found only in the lung, there is a possibility that outcomes can be improved through excision of the metastases, even in patients who did not respond to chemotherapy, or if multiple lung metastases were present.[7]

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CQ28

When is surgery indicated for clinical stages III and IVa?

Recommendations

Surgery should be performed if hysterectomy and cytoreductive surgery are possible (Grade C).

Background and Objectives

We examined the benefits of surgery in patients with advanced uterine body cancer at stages III and IVa.

Explanations

In advanced uterine body cancer with extrauterine spread, metastases in surgical stage III patients are detected in the peritoneum (37.0-59.0%), lymph nodes (39.3-62.0%), and ovaries (14.8%).[1,2] The 5 year disease-free survival rate was favorable at 86.2% for stage IIIa patients with positive peritoneal cytology, uterine serosal invasion, or adnexal metastases,[1] and surgery was beneficial. The 5 year disease-free survival rate was moderate at 33.9-69.5% for stage IIIc patients with lymph node metastases or parametrial invasion.[1-3] In another study, the overall survival rate was 55.8-65.0%,[2-5] indicating a poorer prognosis for stage IIIc disease compared with stage IIIa. Important independent prognostic factors for stage IIIc were residual lymph nodes with macroscopic metastases, and whether postoperative chemotherapy was performed.[6] The survival rates for patients with stage IIIc disease were improved when macroscopically metastatic positive lymph nodes was resected, and when postoperative chemotherapy was performed due to the risk of distant metastatic recurrence.[4,6] In patients with stage IIIc disease, the prognosis was poor for patients with clinically evident parametrial invasion, regardless of the treatment, with a 5 year survival rate of 0%.[7] The survival rate increased significantly when there was no residual disease after performing extended surgery, including the resection of pelvic and peritoneal metastases.[8]

We were unable to find any studies of therapeutic outcomes in patients with stage IVa disease, with invasion of the bladder and rectal mucosa. The NCCN guidelines (version 1, 2005) made the following recommendations for patients with invasion of the vagina, bladder, rectum, or parametrium: radiotherapy should be performed, and surgery might also be advisable, depending on the patient.[9] Excluding patients in whom hysterectomy is technically difficult, surgery such as hysterectomy and cytoreductive surgery should be perfomed, if possible, to improve prognosis for patients with extrauterine spread, including evidence of invasion of the parametrium.

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CQ29

What are the therapeutic benefits of cytoreductive surgery for patients with macroscopic extrapelvic and intra-abdominal spread?

Recommendations

The prognosis may be improves by cytoreductive surgery (Grade C).

Background and Objectives

The prognosis of patients with surgical stage IV disease remains poor. This is in part due to poor response rates of bulky residual lesions to radiotherapy, chemotherapy, and hormone therapy. We examined the clinical benefits of cytoreductive surgery for patients with macroscopic extrapelvic spread (surgical stage IVb).

Explanations

We reviewed the literature, including analyses of not only stage IVb, but also stage IVa. A number of reports since 1994 have indicated that outcomes are improved by cytoreduction.[1-9]

Goff et al.[1] completed debulking surgery, leaving no bulky residual tumor, in 29 of 47 stage IV patients. The median survival time was 19 months. In contrast, the mean survival time was only 8 months in 18 patients who did not undergo surgery. Similarly, McMeekin et al.[2] examined 51 stage IV patients and reported that the mean survival time was 17 months in 37 patients with residual tumor diameters of <2 cm, but only 6 months in 14 patients who did not undergo surgery. Chi et al.[3] performed surgery as the initial treatment on 55 patients with stage IV disease. The mean survival time was 31 months in patients with residual lesions of ≤2 cm, 12 months in patients with residual tumor >2 cm, and 3 months in patients with inoperable disease. They also compared prognosis between patients with preoperative lesions of >2 cm and postoperative residual lesions of ≤2 cm, and patients with preoperative tumor diameters of ≤2 cm. There was no significant difference in prognosis between the two groups, indicating that cytoreductive surgery improves outcomes. Bristow et al.[4] performed surgery as the initial treatment in 65 patients with stage IVb disease. The median survival time was 34.3 months in patients with residual tumor diameters ≤1 cm, but 11.0 months in patients with residual tumor diameters of >1 cm. Similarly, Ayhan et al.[5] found that stage IVb patients whose residual tumors were reduced to ≤1 cm had significantly better outcomes than those with larger diameters. In Japan, Eto et al.[6] conducted a study on 31 patients with stage IIIc disease and 12 with stage IVb disease. They found that in both groups, patients who underwent complete resection and without residual tumor had significantly better outcomes than those with residual tumor. In these studies, the frequency of performing optimal cytoreductive surgery was high at 44-72%. All authors except for McMeekin et al.[2] reported that significantly better outcomes were obtained in patients with optimal surgery.

Serous adenocarcinoma, considered the histological type with the worst prognosis of the uterine body cancers, is characterized by extensive peritoneal dissemination. Cytoreductive surgery has been reported to be useful in this tumor.[7,8]

Cytoreductive surgery is not indicated for all advanced and recurrent cancers. For patients in whom total hysterectomy is possible, PS and complications should be thoroughly considered. The decision should then be made to perform cytoreductive surgery for peritoneal tumor, or instead to opt for chemotherapy, radiotherapy, or supportive care.

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CQ30

Are preoperative chemotherapy and preoperative radiotherapy useful?

Recommendations

(1) Preoperative chemotherapy is not recommended (Grade D).
(2) Preoperative radiotherapy is sometimes used for patients with evident cervical invasion (Grade C).

Explanations

The only studies in the literature that deal with preoperative chemotherapy for uterine body cancer are case reports and case series.[1,2] There is insufficient evidence to definitively answer this CQ.

In Western countries, preoperative radiotherapy is sometimes performed. There are some reports that a combination of preoperative radiotherapy and surgery was useful if cervical enlargement due to direct invasion was observed preoperatively.[3-5]

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CQ31

When is surgery indicated for recurrent cancer?

Recommendations

(1) Aggressive surgical resection should be considered if the lesion is operable and no other metastases are evident (Grade C).
(2) If a lung metastasis is ≤4 cm, partial resection of the lung should be considered (Grade C).

Background and Objectives

Recurrence of uterine body cancer is not limited to intrapelvic sites including the vaginal stump, but also occurs at distant sites such as peritoneal carcinomatosis, lung, liver, and lymph nodes (para-aortic and left supraclavicular lymph nodes). Many of these are multiple lesions, and surgery is therefore indicated in only a small minority of cases. In this section, we examine outcomes and complications in patients who undergo pelvic clearance and partial resection of the lung for recurrent uterine body cancer. We will then examine the indications for surgery.

Explanations

The patterns of recurrent uterine body cancer are divided into local pelvic recurrence including the vaginal stump, and distant recurrence including lung metastases.[1] For a single metastatic lesion (for instance an intrapelvic lesion), good outcomes were obtained by pelvic clearance.[2-5] Resection of a single lung metastasis also contributed positively to the prognosis.[6,7] Since pelvic clearance is very invasive surgery,[2-4] it entails considerable risk of serious perioperative complications such as intestinal and urinary fistula formation, infection, and deep vein thrombosis. In recent years, the trend is not to perform pelvic clearance. Resistance to chemotherapy can occur in recurrent lesions in postoperative radiotherapy fields, and in recurrent tumor following chemotherapy. Pelvic clearance is therefore an effective treatment method only in cases where recurrent lesions can be completely resected. Naturally, institutions need full-time gynecologists who are skilled in a variety of surgical techniques, and excellent postoperative management, including intensive care, and in addition, departments working in full cooperation. However, unlike cervical cancer, uterine body cancer has a high rate of microscopic systemic metastases, even though local recurrence is evident. This leads to a high rate of distant metastasis. Multivariate analysis shows patients with only a single vaginal recurrence to have a good prognosis.[5] For lung metastases, simultaneous recurrence at another site was reported to be unlikely if only one lung was affected, and if there were ≤5 recurrent metastases.[6] Even if a recurrence was thought to be singular, if it was over 5 cm in diameter, the presence of nearby satellite lesions was highly likely.[7] Full precautions should be taken when considering the indications for surgery .

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CQ32

Is chemotherapy useful for advanced and recurrent cancer?

Recommendations

Chemotherapy is useful for patients with incompletely excised advanced cancer (stages III and IVa), distant recurrences (stage IVb), or recurrent cancer (Grade B).

Background and Objectives

We examined the usefulness of chemotherapy for advanced and recurrent uterine body cancer.

Explanations

Adriamycin is the key drug for chemotherapy in uterine body cancer. The reported response rate for adriamycin monotherapy is 17-26%. The response rate for cisplatin monotherapy is 25%, and 28% for carboplatin monotherapy.[1] AP (adriamycin + cisplatin) therapy[2] and CAP (cyclophosphamide + adriamycin + cisplatin) therapy[3] have been used since the 1980s. However, the EORTC and GOG randomized controlled trials showed that AP therapy gave results superior to adriamycin monotherapy for advanced and recurrent uterine body cancer.[4,5] Since approximately 1996, paclitaxel has been used as chemotherapy for advanced and recurrent uterine body cancer, just as in ovarian cancer. The response rate for paclitaxel monotherapy was 35.7% in 30 subjects with advanced and recurrent uterine body cancer in a phase II trial.[6] A response rate of 27.3% was achieved in 44 subjects with uterine body cancer with no response to, or recurrence after, previous chemotherapy.[7] Following this good response rate using paclitaxel, the randomized controlled trial GOG 177 was conducted, in which subjects were administered either paclitaxel monotherapy, AP therapy (adriamycin 60 mg/m^2 and cisplatin 50 mg/m^2), or TAP therapy (paclitaxel + adriamycin + cisplatin) and G-CSF. Response rates, progression-free survival time, and overall survival time were all significantly better with TAP therapy. However, the toxicity of TAP therapy, in particular causing peripheral neuropathy, was higher than that with AP therapy.[8] In addition, the GOG separated subjects with advanced and recurrent uterine body cancer. Subjects with resistant serous adenocarcinoma were also considered separately. In a subsequent phase II trial, subjects were administered a combination of paclitaxel and carboplatin (TC therapy).[9] Radiotherapy is used in combination with chemotherapy for advanced uterine body cancer, with favorable response rates of 50-78%. TC therapy is therefore a strong candidate for chemotherapy for advanced and recurrent uterine body cancer. One case report stated that weekly administration of paclitaxel was effective in 3 patients with serous adenocarcinoma resistant to TC therapy, or recurrent disease.[10]

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CQ33

Which regimens are recommended for chemotherapy in advanced and recurrent cancer?

Recommendations

Platinum-based drugs in combination with anthracyclines or taxanes are recommended (Grade B).

Background and Objectives

We specifically examined chemotherapy regimens recommended for advanced and recurrent uterine body cancer.

Explanations

Adriamycin is the key drug for chemotherapy in uterine body cancer. The reported response rate for adriamycin monotherapy against advanced and recurrent uterine body cancer was 17-26%.[1-4] The reported response rates were 43%[4] and 60%[5] when cisplatin was used in combination with adriamycin (AP therapy). The response rate for CAP therapy, a combination of cyclophosphamide, adriamycin and cisplatin, was 47%.[6] For adriamycin monotherapy, a dosage of 60 mg/m^2 was administered every 4 weeks. For AP therapy, dosages of adriamycin 60 mg/m^2 and cisplatin 50 mg/m^2 were administered every 4 weeks. For CAP therapy, dosages of cyclophosphamide 500 mg/m^2 for, adriamycin 50 mg/m^2 , and cisplatin 50 mg/m^2 were administered every 3 weeks. In 30 patients with recurrent uterine body cancer in the GOG phase II trial, the response rate for paclitaxel monotherapy was 35.7%[7] using 250 mg/m^2 infused over 24 hours every 3 weeks. In 44 patients with no response to previous chemotherapy or with recurrence of uterine body cancer, the response rate was 27.3%[8] using 175-200 mg/m^2 of paclitaxel over 3 hours every 3 weeks. In a phase II trial on advanced and recurrent uterine body cancer in Japan, the response rate was 30.4% using 210 mg/m^2 paclitaxel administered over 3 hours.[9] In another phase II trial in Japan, the response rate was 31%[10] for docetaxel monotherapy at a dosage of 70 mg/m^2. In another phase II trial, a combination of paclitaxel and carboplatin (TC therapy) was used for advanced and recurrent uterine body cancer at the following dosages: paclitaxel 175 mg/m^2 administered over 3 hours and carboplatin AUC5-7 were administered every 3 weeks . The response rate was very favorable at 50-78%.[11]

The GOG 177 randomized controlled trial examined two chemotherapy regimens: AP therapy (adriamycin 60 mg/m^2 + cisplatin 50 mg/m^2) and TAP therapy (paclitaxel 160 mg/m^2 + adriamycin 45 mg/m^2 + and cisplatin 50 mg/m^2) – with G-CSF. Response rates, progression-free survival time, and overall survival time were all significantly better with TAP therapy. However, the toxicity of TAP therapy, in particular causing peripheral neuropathy, was higher than that with AP therapy.[12] Commonly used regimens combine a platinum-based drug with adriamycin and paclitaxel. In addition to AP and CAP therapies, TC therapy is considered a valid option for chemotherapy for advanced and recurrent uterine body cancer.

Since the majority of the above trials were conducted in Western countries, dosages may not be directly applicable to Japanese patients. We have accordingly made no dosage recommendations in these guidelines.

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CQ34

Is radiotherapy useful for recurrent and inoperable advanced cancer?

Recommendations

(1) Radiotherapy is useful in recurrence in the vaginal stump (Grade B).
(2) Radiotherapy is useful as treatment for symptoms associated with cancer (Grade B).
(3) Radiotherapy can be expected to show efficacy as palliative treatment (Grade B).

Background and Objectives

Radiotherapy is not only performed as postoperative adjuvant therapy for uterine body cancer, but also frequently as treatment for advanced and recurrent uterine body cancer. We examined the indications for, and efficacy of, radiotherapy. In addition to radical treatment, radiotherapy is performed as palliative treatment for various types of advanced cancer and their distant metastases. We also examined the benefits of radiotherapy as palliative care for advanced body cancer.

Explanations

Uterine body cancer very rarely metastasizes to the brain, at a frequency of 0.3%. Complete remission has been achieved using a combination of stereotactic radiosurgery and chemotherapy for multiple brain metastases.[1] We were unable to find any studies of the efficacy of radiotherapy in inoperable uterine body cancer in a large number of cases. Landgren et al. stated that the 5 year survival after radiotherapy was 26% in a study on 26 patients with inoperable advanced uterine body cancer.[2] Radiotherapy is also useful as palliative care for vaginal hemorrhage and pain control. No randomized controlled trials have been conducted comparing the efficacy of chemotherapy and radiotherapy in inoperable advanced or recurrent uterine body cancer.

The randomized controlled trial PORTEC examined salvage rates for vaginal recurrence after uterine body cancer surgery, using intracavitary irradiation, pelvic external beam irradiation, or a combination of both. The salvage rate was 79% in this trial.[3] Ackerman et al. reported a salvage rate of 2/3.[4] A single center study was conducted at M. D. Anderson Cancer Center involving 91 patients with a single vaginal recurrence. They achieved favorable results, with 2 year and 5 year local control rates of 82% and 75%, respectively, and an overall survival rate of 43%.[5] For optimum symptomatic relief, a course of radiotherapy should be short in duration, with few adverse effects, and long-lasting palliative effect. It should also entail only a few treatments, and represent only a small physical and economic burden on the patient. In general, a lower total dose than that used in definitive radiotherapy is administered by increasing the dose per fraction and decreasing the frequency of treatments. For palliative irradiation for the purpose of symptomatic relief, a total dose of approximately 30-40 Gy is generally administered over 10-20 fractions. However, massive doses are sometimes used over a small number of fractions with 5-10 Gy per fraction. No optimal

dosing schedule has been established. For uterine body cancer, radiotherapy is mainly for terminal-stage palliative care, such as for hemorrhage and pain due to intrapelvic tumor spread, or pain due to bony metastases.

Whole pelvis external beam irradiation for advanced uterine body cancer usually involves the administration of 10 Gy per fraction with a rest period of 3-4 weeks, repeated 2-3 times. After ≥2 fractions, vaginal hemorrhage was controlled in 90% of the patients and pain relief was achieved in ≥60% of patients.[6-8] However, local adverse reactions are seen following radiotherapy. For patients surviving ≥1 year, late adverse events became a problem in the gastrointestinal tract when the dose per fraction was increased.[7,9] The Radiotherapy Oncology Group reduced the dose per fraction from 10 Gy to 3.7 Gy for palliative irradiation and performed irradiation twice per day, demonstrating that adverse events were decreased.[10] In one study, surgery performed after radiotherapy did not significantly improve the 5 year survival rate compared to radiation monotherapy in inoperable uterine body cancer.[11] However, another study did show an improved survival rate.[12]

In general, radiotherapy for bone metastasis relieved pain in 80-90% of patients.[13,14] In addition, osteogenesis was observed in 65-85% of osteolytic bone metastatic sites. The area of irradiation varies with each patient, ranging from localized irradiation confined to a single metastatic site to hemibody irradiation for multiple bone metastases. The dosages and fractionation regimen for local irradiation can range from 8 Gy to 30-40 Gy per fraction over 10-20 fractions. The pain relieving effect is similar for both methods. The dosing schedule is determined for each patient depending on a variety of factors including the patient's condition and the number of treatment facilities.

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CQ35

Is progesterone therapy useful for advanced and recurrent cancer?

Recommendations

Progesterone therapy is recommended for patients with endometrioid adenocarcinoma G1 and advanced or recurrent uterine body cancer positive for progesterone receptors (Grade C).

Background and Objectives

Excessive stimulation from long-term estrogen use is closely associated with the onset and growth of uterine body cancer. Accordingly, hormone therapy has been performed for a long time, although many question its usefulness. We investigated the indications for, and efficacy of, hormone therapy based on an examination of recent studies. In addition, we examined the benefits of combining chemotherapy with progesterone therapy for advanced and recurrent uterine body cancer.

Explanations

Estrogen and progesterone-receptor positive tumors respond best to progesterone therapy. A study was conducted with 115 patients with advanced uterine body cancer who underwent progesterone therapy. The response rate to progesterone therapy was 75% (42 of 56 patients) for patients with progesterone-receptor positive tumors. The response rate was only 7% (4 of 59 patients) for progesterone-receptor negative tumors.[1] In another study, 20% of uterine body cancer cases which did not respond to standard progesterone therapy responded to tamoxifen.[2]

The GOG examined the effective dose of medroxyprogesterone acetate (MPA) for advanced and recurrent uterine body cancer.[3] In the group administered MPA 200 mg/day, the complete response rate was 17% and the partial response rate 8%, yielding a total of 25% for the response rate. In a group administered 1000 mg/day, the complete response rate was 9% and the partial response rate 6%, yielding a total of 15% for the response rate. The disease-free survival time was 3.2 months for the low dosage group and 2.5 months for the high dosage group. The survival time was 11.1 months for the low dosage group and 7.0 months for the high dosage group. PS, age, degree of tissue differentiation, and progesterone receptor levels are associated with responsiveness to progesterone therapy. Oral MPA was effective against uterine body cancer, and the response rate was particularly high in well differentiated and progesterone-receptor positive tumors. Dosages of 1,000 mg/day did not give superior results to 200 mg/day. The optimum dosage of MPA was therefore 200 mg/day.

The mainstay of chemotherapy for advanced and recurrent uterine body cancer has been mainly CAP or AP therapy, with the goal of producing synergistic effects by combining anticancer agents, which have also showed efficacy as monotherapy. However, the reported response rates for these combination therapies have been 31-63%, with an average of 46%. These results cannot be called satisfactory. When various hormone therapies are added to these combination chemotherapies for uterine body cancer, the response rate is still only 27-60%, so there is insufficient evidence to recommend the addition of hormone therapies.[4-7]

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