SPANDIDOS PUBLICATIONS

Distribution of platinum in the female genital tract and efficacy of radiotherapy combined with transcatheter arterial infusion of cisplatin for locally advanced stage IIIb carcinoma of the uterine cervix

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Abstract. The current main treatment for locally advanced stage III/IV cervical cancer involves chemoradiotherapy. In this study, we investigated the distribution of platinum in the female genital tract by intra-arterial infusion of platinum (carboplatin 150 mg) during surgery and examined the therapeutic effects of radiotherapy with transcatheter arterial infusion (TAI) of cisplatin for locally advanced carcinoma of the uterine cervix. From January 1991, we randomly selected 26 patients with locally advanced stage IIIb cervical cancer to receive radiotherapy combined with TAI of 120 mg/body cisplatin twice a month at an interval of 4 weeks. Radiotherapy routinely involved 50 Gy of external beam irradiation to the whole pelvis and 12-24 Gy (point A dose) of intracavitary irradiation using a remote afterloading system. The mean platinum concentration in the cervical cancer was 1.77 μg/g wet tissue (wt) and high value, but the genital tract also contained the same platinum concentration. The platinum concentration in each regional lymph node was 1.10-1.48 μg/g wt, and its level of platinum was equal to that in the female genital tract. The effective histologic response rate was 88.5% (23/26). The median follow-up period was 38 months. The cumulative survival rate was 74.0%. Serious acute adverse reactions interfering with treatment were not observed. Based on these results, intra-arterial infusion of platinum produced a therapeutic effect on the primary cervical cancer site and the other parts of the female genital tract. We concluded that radiotherapy with TAI of cisplatin achieved superior therapeutic efficacy in locally advanced stage IIIb cervical cancer.

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Introduction

The morbidity and mortality associated with carcinoma of the uterine cervix have recently decreased in Japan, and the age-adjusted mortality rate has shown an approximate one-third decline over the last 30 years. However, therapy for locally advanced cervical cancer is still unsatisfactory, and approximately 2,500 patients die of cervical cancer every year (1).

Patients with locally advanced cervical cancer in clinical stages III and IV were generally managed with radiotherapy, but the combination chemotherapy selected recently and the usefulness of this treatment has been established. In addition, radiotherapy combined with hydroxyurea (2) and 5-FU (3,4) was shown to achieve a higher survival rate than radiation alone. Recently, radiation plus platinum (including cisplatin, carboplatin) has been reported to achieve even increased survival in patients with locally advanced cervical carcinoma, thus interest in concurrent chemoradiotherapy has increased (5-9). The platinum compounds are known to have an enhanced cytotoxic effect when combined with radiotherapy (10-12).

From January 1991, we randomly selected patients with locally advanced cervical cancer to receive radiotherapy combined with transcatheter arterial infusion (TAI) of cisplatin (13). In this study, we investigated the distribution of platinum in the female genital tract and the regional lymph nodes after intra-arterial platinum infusion during surgery for uterine cervical cancer, and we examined the therapeutic effects and prognosis with radiotherapy using TAI of cisplatin in a prospective follow-up study.

Materials and methods

Distribution of platinum in the female genital tract. Six patients with locally advanced cervical cancer (clinical stages

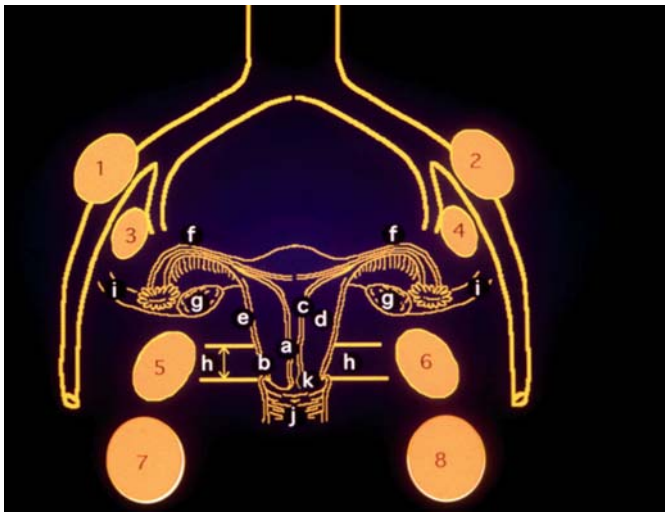

Figure 1. The regions of the female genital tract and pelvic lymph nodes. Tumor (k), cervical canal (a) and serosa (b) in the uterine cervix; endometrium (c), myometrium (d) and serosa (e) in the uterine body; both fallopian tubes (f) and ovaries (g); parametrium (h); infundibulopelvic ligament (i); and the vagina (j). The examined lymph nodes include both external iliac nodes (1,2) internal iliac nodes (3,4), obturator nodes (5,6) and suprainguinal nodes (7,8).

Table II. Radiotherapy regimen.

Stage	External irradiation (Gy)		Intracavitary irradiation (point A: Gy/fraction)
	Whole pelvis	Central shield	
I	0-30	45-50	18-30/3-5
II			
Small	0-30	45-50	18-30/3-5
Large	24-36	14-26	18-24/3-4
III			
Small-Medium[a]	30-36	14-16	18/3
Large[a]	34-40	10-14	12-24/2-4
IVA[a]	36-50	0-14	12-24/2-4
IVB[a]	Palliative		Palliative

[a]With chemotherapy (including intra-arterial infusion chemotherapy) when possible. Small, tumor slightly extending to one pelvic wall. Medium, tumor massively extending to one pelvic wall. Large, tumor extending to both pelvic walls.

Table I. Characteristics of the studied patients.

No. of cases	26
Age (mean)	26-72 (56)
Stage IIIb	26
Small	0
Medium	14
Large	12
Histology	
Squamous cell cancer	25
Keratinizing	9
Non-keratinizing	16
Special type	1
Previous surgery	
(+)	6
(-)	20
Follow-up (median)	12 months-13 years (38 months)

Ib 3, IIa 1, IIb 2) who underwent radical hysterectomy at the Department of Obstetrics and Gynecology of Hiroshima University Hospital were studied. With informed consent, intrauterine arterial carboplatin (CBDCA), 150 mg, infusion was performed for 5 min during surgery. The intra-arterial infusion consisted of 4 cases using the right uterine artery and 2 cases using the left uterine artery.

We measured the platinum concentration in the female gen ital tract, the regional lymph nodes and serum. We extirpated the genital tract at an average 3 h after intra-arterial infusion. The parts of the female genital tract that were examined are shown in Fig. 1. These included the tumor, cervical canal and serosa in the uterine cervix; endometrium, myometrium and serosa in the uterine body; both fallopian tubes and ovaries; parametrium; infundibulopelvic ligament; and vagina. Bilateral pelvic lymph nodes were removed an average of 1 h after intra-arterial infusion. The examined lymph nodes were both external iliac nodes, internal iliac nodes, obturator nodes and suprainguinal nodes.

The concentration of platinum in the tissue was measured using flameless atomic absorption spectrometry (Bristol-Myers Squibb Co., Ltd.). We also measured the total platinum concentration in serum at 15, 30, 60 and 120 min after intra-arterial infusion.

A prospective study. Of 81 patients with locally advanced cervical cancer in clinical stage II or higher who underwent radiotherapy at the Department of Obstetrics and Gynecology of Hiroshima University Hospital between January 1991 and December 2003, 26 patients with clinical stage IIIb were studied who met the following criteria and who completed their planned radiation therapy with TIA of cisplatin (Table I). All patients were fully informed of the study and gave written consent to receive radiation therapy combined with chemotherapy.

The eligibility criteria were i) no prior anticancer therapy; ii) age ≤75 years; iii) satisfactory liver, renal and bone marrow function (i.e., total bilirubin ≤3 mg/dl, GOT and GPT ≤ twice normal, creatinine ≤2 mg/dl, BUN ≤30 mg/dl, leukocyte count ≥4,000/mm^3, platelet count ≥100,000/mm^3); iv) performance status of 0-3; v) no active double cancer; vi) no history of severe disease affecting the heart, liver, kidneys or lungs; and vii) no serious complications (including infection).

The radiotherapy regimen of our hospital is explained in Table II. Radiotherapy consisted of external beam irradiation to the whole pelvis (upper margin: above the fifth lumbar spine; lower margin: the lower two-thirds of the pubic

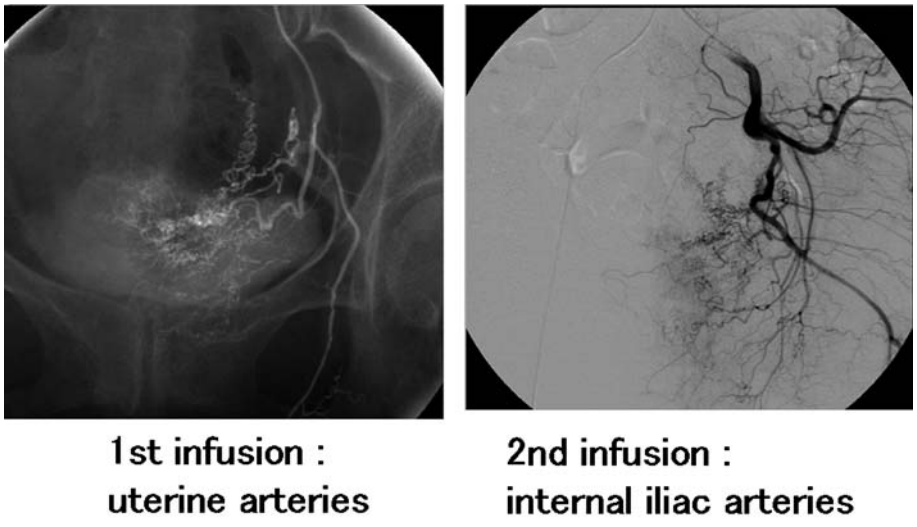

Figure 2. Intra-arterial infusion chemotherapy.

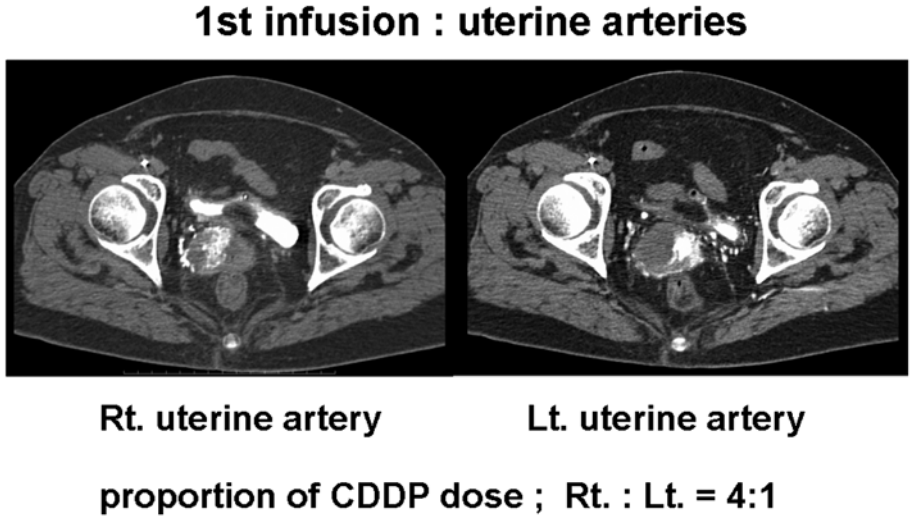

Figure 3. CT-angiography.

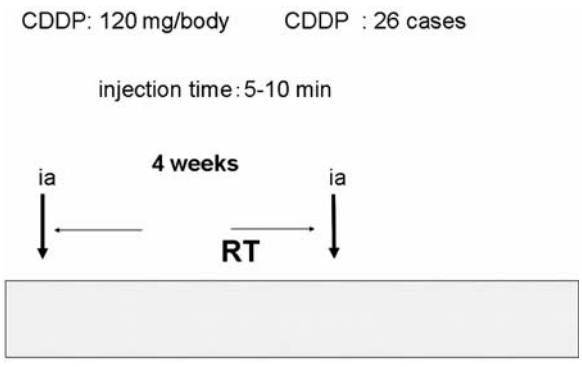

Figure 4. Transcatheter arterial infusion (TAI) and radiotherapy (RT) method.

symphysis; lateral margin: the femoral artery in the inguinal region) with 18 MV X-rays at 1.8-2.0 Gy/fraction. Radiation was administered five times weekly for a total mean dose of 50 Gy, with central shielding after 30-40 Gy of radiation, according to clinical stage and the extent of tumor growth. In addition, intracavitary brachytherapy was conducted with ^{192}Ir using a remote afterloading system (RALS) at a point A dose of 6 Gy/fraction. This was carried out two or three times in one week for a total dose of 12-24 Gy.

For TAI, a catheter was inserted via the femoral artery using the Seldinger technique, and the tip was advanced to a level beyond the superior gluteal artery, a branch of the internal iliac artery (selective technique), or as far as the uterine artery (super-selective technique) (Fig. 2). After confirming the blood supply to the uterus by angiography, 120 mg of cisplatin (the proportion of the CDDP dose was dependent on tumor size, such as right:left = 3:1) was infused for 10 min (Fig. 3). Two infusions of cisplatin were administered, one at the start of radiotherapy and the other after four weeks of radiotherapy (Fig. 4).

To assess the response at the completion of treatment, several biopsy specimens were obtained from the cervix, and

Table III. Criteria of Oboshi and Shimosato.

Grade 0	No radiation effect found in cancer cells.
Grade 1	A slight radiotherapy (RT) effect is present but the cancer cell nest remains completely undisturbed.
Grade 2	RT effect is found in individual cancer cells: a) More than 1/4th of the cells of the specimen have a strong probability of becoming active cancer cells if the radiation is stopped at this point. b) Less than 1/4th of the cells of the specimen have a strong possibility of becoming active cancer cells if the radiation is stopped at this point.
Grade 3	Only nonviable cancer cells are present.
Grade 4	No cancer cells at all.

Table IV. Platinum concentration in each female genital tract.

Region	Mean	SD	n
	(μg/ml)		
Uterus	1.49	1.02	28
Fallopian tubes and ovaries	1.78	1.84	19
Right	2.58	2.41	9
Left	1.06	0.63	10
Vagina	1.17	0.68	5
Parametrium	1.65	2.13	9
Infundibulopelvic ligament	1.86	1.22	7

the histologic response was graded according to the criteria of Oboshi and Shimosato (Table III) (14).

After radiotherapy, periodic pelvic examination, cervical cytology, chest radiography, tests for tumor markers (SCC, CA125), CT and MRI were performed to detect recurrence or metastasis and to assess the outcome in a prospective follow-up study.

Statistical analysis. Bivariate analysis was performed using the Chi-square test or the U test, as appropriate. The cumulative survival rate was estimated by the Kaplan-Meier method. Survival was measured from the day treatment started.

Results

Distribution of platinum. The platinum concentration in each female genital tract is listed in Table IV. The mean platinum concentration in each organ was 1.49 μg/g wet tissue (wt) in the uterus, 1.78 μg/g wt in the fallopian tubes and ovaries (2.58 μg/g wt in right side, 1.06 μg/g wt in left side), and 1.17 μg/g wt in the vagina. In addition, the mean platinum concentration in the parametrium and infundibulopelvic ligament was 1.65 μg/g wt and 1.86 μg/g wt, which was nearly equal to that of the uterus and adnexa.

Table V. Mean platinum concentration in each region of the female genital tract.

Region	Mean	SD	n
	(μg/ml) (wet tissue)		
Cervix			
Tumor (k)	1.77	1.15	3
Canal (a)	0.87	0.43	5
Serosa (b)	1.33	0.29	5
Uterine body			
Endometrium (c)	1.92	0.64	5
Myometrium (d)	1.39	1.08	5
Serosa (e)	1.80	1.89	5
Fallopian tubes (f)			
Right	1.57	0.98	4
Left	0.84	0.36	5
Ovaries (g)			
Right	3.38	3.01	5
Left	1.27	0.80	5
Parametrium (h)			
Right	0.88	0.23	4
Left	2.26	2.82	5
Infundibulopelvic ligand (i)			
Right	2.12	1.62	4
Left	1.50	0.45	3
Vagina (j)	1.17	0.68	5

a-k, refer to Fig. 1.

The mean platinum concentration in each region of the female genital tract is shown in Table V. In the uterine cervix, the mean platinum concentration in the tumor was 1.77 μg/g wt, with a higher concentration compared to 0.87 μg/g wt in the cervical canal and 1.33 μg/g wt in the cervical serosa. In the uterine body, the mean platinum concentration was 1.92 μg/g wt in the endometrium, 1.39 μg/g wt in the myometrium and 1.80 μg/g wt in the uterine body serosa. In the fallopian tubes and ovaries, the mean platinum concentration on the right side was higher, but there was no significant difference between the right and left side. From these results, the uterine cervix and the other female genital organs showed the same platinum concentration.

The platinum concentration in each regional lymph node is shown in Table VI. The mean platinum concentration was 1.10-1.48 μg/g wt, and the level of platinum in the lymph nodes was equal to that in the female genital tract. The level of the total serum platinum concentration is shown in Table VII, which was at the maximum level at 30 min and gradually decreased thereafter.

A prospective study. Table I shows the clinicopathological characteristics of 26 patients with regard to age, clinical stage and tumor extension and histologic type. The mean age was 56 years. The effective response rate showing changes of

Platinum concentration in each regional lymph node.

Regional lymph node	Mean (μg/ml) (wet tissue)	SD	n
External iliac	1.48	1.52	10
Right (1)	2.03	1.97	5
Left (2)	0.93	0.75	5
Internal iliac	1.46	1.39	10
Right (3)	1.61	1.74	6
Left (4)	0.59	0.82	4
Obturator	1.10	1.26	12
Right (5)	1.61	1.67	6
Left (6)	0.59	0.33	6
Suprainguinale	1.16	1.00	10
Right (7)	0.97	1.16	6
Left (8)	1.45	0.81	4

1-8, refer to Fig. 1.

Table VII. Total serum platinum concentration.

Time after TIA (min)	Mean (μg/ml)	SD	n
15	1.648	1.138	4
30	1.873	1.014	6
60	1.203	0.683	6
120	1.045	0.249	5

grade 3 and 4 according to the criteria of Oboshi and Shimosato was 88.5% (23/26).

The mean follow-up period was 38 months (32 months-13 years). The local control rate was 87.0% (Fig. 5). The cumulative survival and survival by tumor size for all patients are shown in Figs. 6 and 7. As shown in Fig. 6 the cumulative survival rate for patients with clinical stage IIIb lesions was 74.0%.

Comparison of the results for the cumulative patient survival rate and tumor size showed no significant differences for medium and large tumors (Fig. 7) (p=0.268). Regarding the TAI of cisplatin, there was no difference in outcome between selective and super-selective techniques (13).

Table VIII shows the acute adverse reactions of the patients (NCL-ITC). Although grade 3 myelosuppression occurred frequently, serious acute adverse reactions interfering with treatment were not observed.

Initial recurrence in stage III lesions is shown in Table IX. Two patients had local recurrence; one patient with cervical recurrence and the other with vaginal recurrence. Nine patients had distant metastasis; six with para-aortic lymph node metastasis, one with lung and bone metastasis, one with lung and lymph node metastasis, and one with liver metastasis.

Late complications of the patients (NCI-CTC) are indicated in Table X. The rate of grade 2 involvements of the bladder, rectum and small bowel were 8, 17 and 8%, respectively.

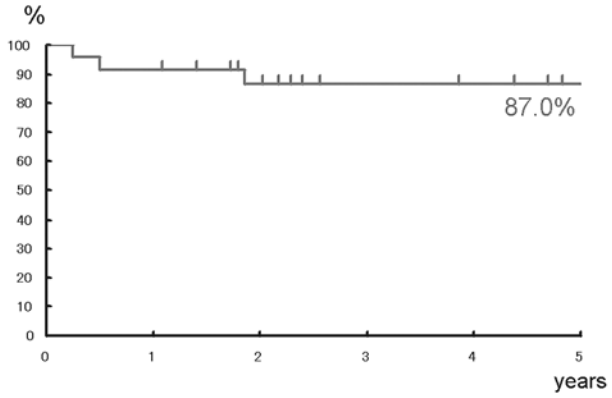

Figure 5. Local control rate.

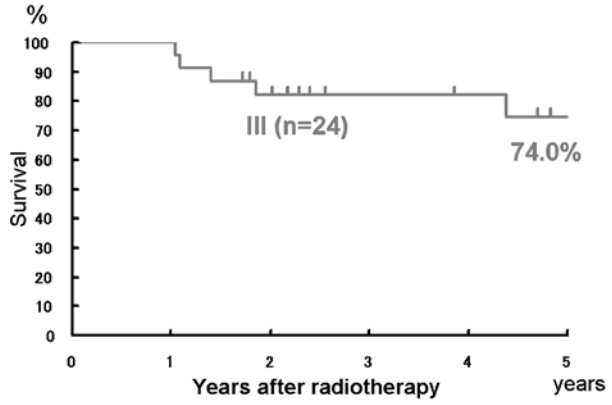

Figure 6. Cumulative patient survival.

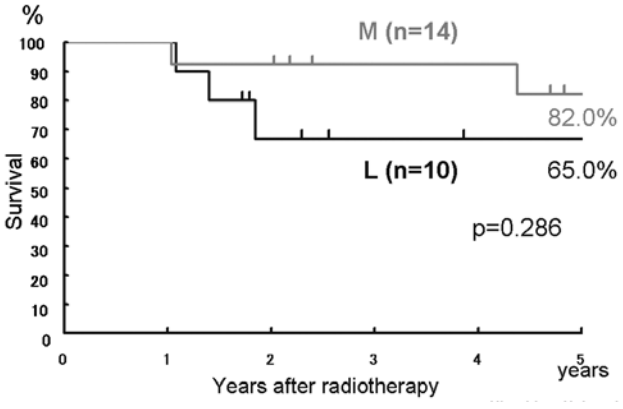

Figure 7. Cumulative patient survival by tumor size. M, medium; L, large.

Discussion

In Japan, radiotherapy is a first-line treatment for cervical cancer in clinical stages III and IV, as well as stage I and II disease in elderly patients and patients with complications. However, the age-adjusted mortality rate has remained the same during the last 10 years (1). This is due to the lack of marked improvement in the treatment of locally advanced cancer over the last 20 years. The five-year survival rate of

Table VIII. Acute adverse reactions (NCI-CTC).

Grade	0	1	2	3	4
Hematologic (% patients)					
Anemia	5	35	50	10	0
Leukopenia	0	35	35	30	0
Thrombocytopenia	95	0	5	0	0
Gastrointestinal					
Nausea	45	30	20	5	0
Fever	55	30	15	0	0
Neurological	0	5	0	0	0

Table IX. Initial recurrence[a] (1991-2003).

	Local	Distant	Local + Distant
	1[a] (cervix)	6 (PAN)	1[c]
	1 (vagina)	1 (liver)	
		1 (lung + bone)	
		1 (LN[b] + lung)	
Total	2 (8%)	9 (38%)	1 (4%)

[a]Including one local uncontrolled case. [b]PAN, mediastinal lymph node (LN); virchow LN. [c]Peritonitis ca. (cervix, pancreas, head).

Table X. Late complications (NCI-CTC).

	n	%
Bladder		
Grade 2	2/24	8
3	0/24	0
Rectum		
Grade 2	4/24	17
3	0/24	0
Small bowel		
Grade 2	2/24	8
3	1/24	4
Bone		
Grade 1 (iliac and pubic bone fracture)	1/24	4

patients with locally advanced cervical cancer at 164 Japanese institutions was as follows (5): 61.8% for stage II disease, 38.1% for stage III disease and 12.8% for stage IV disease in 1972 versus 63.5% for stage II, 39.7% for stage III and 13.1% for stage IV in 1989, showing little difference between the two periods. Thus, marked improvement in the treatment of locally advanced cervical carcinoma is needed.

In our hospital, radiotherapy for advanced cervical cancer without distant metastasis is routinely 50 Gy of external beam irradiation to the whole pelvis and 12-24 Gy (point A dose) of intracavitary irradiation using an RALS. Most cervical cancer is thought to be in a state of remission after radiotherapy. However, since the disease can recur in some patients achieving remission, clinically undetectable cancer cells must remain viable. Our previous study showed that the five-year survival rate of 445 patients with locally advanced cervical carcinoma treated with radiotherapy alone between 1971 and 1984 was 64.4% for stage II, 40.2% for stage III, and 19.4% for stage IV.

In Europe and North America, the drugs used in combination with radiotherapy for cervical cancer are hydroxyurea (2), 5-FU (3,4), mitomycin, and cisplatin (5-9), with modes of action that are thought to include i) direct cytotoxicity, ii) tumor cell cycle synchronization, and iii) inhibition of the repair of radiation damage (16). The platinum compounds (including cisplatin) are known to have an enhanced cytotoxic effect when combined with radiotherapy (10-12).

Recently, chemoradiotherapy using platinum compounds has been employed to treat locally advanced cervical cancer and has demonstrated therapeutic efficacy. Five large randomized clinical trials demonstrated a significant survival benefit for patients treated with concurrent chemoradiotherapy using a cisplatin-based regimen, with a 28-50% relative reduction in the risk of death. Rose *et al* (7) compared the results of radiotherapy for locally advanced cervical cancer between i) cisplatin alone; ii) cisplatin, fluorouracil and hydroxyurea; and iii) hydroxyurea alone, and found that cisplatin produced an increase in the overall survival rate when compared with hydroxyurea alone. Morris *et al* (6) randomly administered radiotherapy alone (whole pelvis plus para-aortic irradiation) or radiotherapy combined with fluorouracil and cisplatin to patients with locally advanced cervical cancer and noted that overall survival significantly improved in the group receiving radiation therapy with chemotherapy (73%) when compared with the group administered radiation alone (58%) (p=0.004). Thus, chemoradiotherapy is a useful treatment and cisplatin is a key drug for chemoradiotherapy. However, the efficacy of concurrent chemoradiotherapy was not observed in patients with stage III and IV cancer, and no statistically significant difference was found in the five-year survival rates.

In the present study, we performed radiotherapy combined with TAI of cisplatin in patients with locally advanced cervical cancer who met the criteria for eligibility, and followed them to assess the results. The advantage of TIA from the pharmacokinetics was the attainment of a high concentration of platinum directly into the region of the tumor. The effect of TIA is expected in areas with little circulating blood volume. In general, the blood flow to the pelvic internal organs is less than 1/10 of the cardiac output at rest, and so the region of the female genital organs is selected due to the hemodynamics for the use of TIA (17).

The study of the distribution of platinum concentration in the female genital tract revealed that the mean platinum concentration in the region of cervical cancer was high (1.77 μg/g wt of the female genital tract), and the other female

act sites including the endometrium, ovaries and tubes contained the same platinum concentration. In addition, the platinum concentration in each regional lymph node was equal to that in the female genital tract. The level of total serum platinum concentration was maximum at 30 min and gradually decreased thereafter. From these results, we suggest that TIA of platinum enhances the cytotoxic effect compared to intravenous injection of platinum and produced a therapeutic effect on the primary region of uterine cancer and the other female genital tract.

In the present study involving radiotherapy combined with TAI of cisplatin, the local response rate according to the criteria of Oboshi and Shimosato was 87.5% (23/26), and the local control rate was 87.0%, indicating that this treatment was successful. The cumulative patient survival rate of radiotherapy combined with TIA of cisplatin improved compared to treatment with radiotherapy alone. The cumulative survival rate for patients with IIIb lesions was 74.0%, and the rate was significantly higher than the 40.4% treated with radiotherapy alone. Acute adverse reactions and late complications in patients were not observed.

However, among the patients with tumors showing changes of grade 4 according to the criteria of Oboshi and Shimosato, the disease recurred locally in three patients, and metastasis occurred in the lungs and liver reducing the survival rate. Improvement in therapeutic effects for locally advanced cervical cancer requires better local control and prevention of distant metastasis.

In conclusion, locally advanced cervical cancer is responsive to chemoradiotherapy. However, to improve the therapeutic effects, it is important to establish the regimen, dose, schedule and timing of radiotherapy. Therefore, further studies are required to determine the dosage and administration method for such a multi-agent regimen.

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