Retrospective Analysis of Concurrent Chemoradiation with Triweekly Cisplatin plus 5-Fluorouracil *Versus* Weekly Cisplatin in Cervical Cancer

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Abstract. *Background/Aim: Concurrent chemoradiation (CCRT) is the standard treatment for locally advanced cervical cancer. The purpose of the study was to compare the outcomes of triweekly cisplatin plus 5-fluorouracil and weekly cisplatin regimens. Patients and Methods: We retrospectively reviewed data from 91 patients with stage IB1-IVA cervical cancer. Results: Out of 91 patients, 48 received triweekly CCRT and 43 received weekly CCRT. For triweekly CCRT, patients received a median of two chemotherapy cycles and median total doses of cisplatin and 5-fluorouracil were 210 mg/body and 8,525 mg/body, respectively. For weekly CCRT, patients received a median of five chemotherapy cycles and the median total dose of cisplatin was 252 mg/body. No statistically significant differences in overall survival or progression-free survival were noted between the two groups. Conclusion: Both triweekly CCRT and weekly CCRT appear to have similar efficacy for cervical cancer patients, but the toxicities were better tolerable in weekly CCRT.*

Cervical cancer is one of the most common malignancies affecting women in developing countries, with approximately 500,000 new cases diagnosed annually (1). Approximately 12,900 new cases and 4,100 deaths are anticipated for 2015 in the United States (2). In Japan, cervical cancer incidence has increased over time, with 8,832 cases diagnosed in 1975 and 10,737 cases reported in 2010. The number of deaths has also increased from 1,583 cases in 1958 to 2,656 cases in 2013 (3). Early detection of cervical cancer and its precursors is quite effective for improving prognosis of patients with cervical cancer. Until the early 1970s, approximately 75% to 80% of cervical cancer cases in the United States were invasive at the time of diagnosis (4). However, the national screening system for detecting cervical cancer and its precursors has dramatically reduced the incidence and mortality rate of this malignancy. In contrast, patients with advanced-stage cervical cancer have a poor prognosis. While external-beam plus intra-cavitary radiotherapy (ICRT) is relatively effective for small-volume tumors, tumor control and survival decline as the bulk of pelvic disease and stage increase. Therefore, attempts to enhance the efficacy of RT in such locally advanced tumors have been made through the addition of RT-sensitizing and cytotoxic drugs [concurrent chemoradiation (CCRT)], beginning in the 1980s (5). Initially, CCRT did not result in a significant improvement in pelvic control rate or survival compared to RT-alone (6-8). Five randomized clinical trials demonstrated a significant survival benefit for patients treated with CCRT, using cisplatin-based regimens, with a 28% to 50% relative reduction in the risk of death (9-13). In addition, the results of a meta-analysis of 19 randomized clinical trials of CCRT showed that CCRT significantly improved overall (OS) as well as progression-free (PFS) survival with acceptable toxicity (14). Following these results, a US National Cancer Institute-alert in February 1999 stated that CCRT should be considered for all patients treated by RT (15).

The Gynecologic Oncology Group protocol 120 comparing weekly CCRT and monthly CCRT showed that weekly CCRT was better tolerated and that no survival differences existed between the two CCRT modalities (10). Since then, weekly CCRT has been widely used as the preferred treatment approach for locally advanced cervical cancer. The optimal chemotherapy regimen is not yet defined; however, 5-fluorouracil (5-FU) plus cisplatin every three weeks and weekly cisplatin are the most popular regimens (16). In our Institution, two CCRT regimens have been used as primary treatment for locally advanced cervical

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cancer since 1999. In the study, we retrospectively compared the tumor response, survival rates, and toxicity of patients receiving CCRT with triweekly cisplatin plus 5-FU *versus* weekly cisplatin.

Patients and Methods

Patients. Patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB1 to IVA cervical cancer were treated at Kyushu University Hospital from August 1999 to July 2013. All patients were previously untreated and histologically confirmed as having squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma. For the present study, clinicopathological characteristics and follow-up data were collated and retrospectively analyzed after obtaining approval by the Institutional Review Board (number 20019). All patients were required to have an Eastern Cooperative Oncology Group performance status (PS) score of 0 to 2. Additional eligibility requirements included: age ≤75 years; adequate hematological (white blood cell count ≥3,000/μl; platelet count ≥100,000/μl), hepatic (total bilirubin ≤1.5 mg/dl; aspartate aminotransferase/alanine aminotransferase ≤2.5× the upper limit of normal), renal (serum creatinine <1.5 mg/dl; blood urea nitrogen ≤20 mg/dl; creatinine clearance ≥60 ml/min), and normal electrocardiographic findings. Exclusion criteria included uncontrolled systemic disease or infection. All patients provided written informed consent before study entry.

Treatment. RT consisted of both external-beam radiotherapy (EBRT) and ICRT. In principle, EBRT was delivered as 1.8-Gy fractions to the whole pelvis by anterior-posterior and posterior-anterior parallelopposed ports or a four-field box. The center shield (4-cm width at the midline) was set up after delivering 20-30 Gy. After completion of whole-pelvis irradiation, ICRT was performed: low dose-rate ICRT (LDR-ICRT) was used until March 2003 and high dose-rate ICRT (HDR-ICRT) was adopted thereafter. Both LDR- and HDR-ICRT were performed three or four times at a frequency of once per week. HDR-ICRT was delivered with a fraction dose of 6 Gy at point A. Patients with positive para-aortic lymph nodes (PAN) also received treatment to the para-aortic field. Concurrent chemotherapy before October 2008 consisted of cisplatin (15 mg/m^2/day) and 5-FU (600 mg/m^2/day) for five consecutive days at 21-day intervals (PF group). Chemotherapy was changed to weekly cisplatin administration (40 mg/m^2/day) thereafter (P group). Agents were given as infusions with adequate hydration and antiemetics.

Based on medical history, physical examination, and blood tests, patients were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicities (17). Granulocyte colony-stimulating factor and antimicrobials were allowed for treatment of febrile neutropenia. RT was withheld or the chemotherapy dose was reduced 25% for subsequent cycles in the case of grade 4 neutropenia or thrombocytopenia or grade 3 to 4 non-hematological toxicities. In the case of an inadequate blood cell count on the first day of chemotherapy, the next cycle was delayed until blood count recovery. Tumor response was assessed after completion of treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) (18) by the same imaging modality [computed tomographic (CT) or magnetic resonance imaging (MRI)] used for baseline evaluation. Follow-up assessments were made as described previously (19).

Statistical analysis. The chi-square test was used to compare categorical data and the independent samples *t*-test was used to compare continuous data between subgroups. Time-to-event data were analyzed using the Kaplan-Meier method, and the log-rank test was used to compare survival distributions between groups. *p*-Values of less than 0.05 were considered statistically significant.

Results

Patients and treatment. The clinicopathological variables of all 91 patients are summarized in Table I. PS scores in the PF group were 0 (n=39), 1 (n=7), and 2 (n=2). In contrast, all P group patients had a PS score of 0. All patients had stage IB1 or higher disease, and the majority had stage IIIB disease (IB2, n=1; IIA2, n=2; IIB, n=7; IIIA, n=5; IIIB, n=32; and IVA, n=1 in the PF group; IB1, n=4; IB2, n=1; IIA1, n=2; IIA2, n=1; IIB, n=11; IIIA, n=1; IIIB, n=17; and IVA, n=6 in the P group). The most common histological subtype was squamous cell carcinoma (SCC), although five patients in each group had other subtypes: adenocarcinoma, n=2; carcinoma, n=2; and adenosquamous cell carcinoma, n=1 in the PF group; and adenocarcinoma, n=4; and adenosquamous cell carcinoma, n=1 in the P group. Among patients with stage I and II disease, pelvic lymph node (PLN) and PAN metastases were detected in eight and four cases by imaging study in the PF group, respectively, and in 11 and four cases, respectively, in the P group. Medical complications among patients with stage I and II disease included poorly-controlled diabetes mellitus (DM) (n=1) and deep vein thrombosis (DVT) (n=1) in the PF group; and poorly controlled DM (n=2), DVT (n=1), rheumatoid arthritis (n=1), and severe obesity (n=2) in the P group. No statistically significant differences in clinicopathological variables, except stage, were observed between the two groups (p=0.0022).

Treatment summaries for each group are presented in Table II. Although all patients completed scheduled RT, the numbers of chemotherapy cycles were different depending on adverse effects. EBRT for PAN metastases was given at a median of 46 Gy (range=32-46 Gy). ICRT was performed for 15 patients by LDR and 31 patients by HDR in the PF group, while 42 patients in the P group patients received ICRT by HDR. The median dose of pelvic EBRT and ICRT was not statistically significantly different between the two groups (p=0.2425). The median dose of cisplatin and 5-FU administered per day in the PF group was 22 mg (range=18-27 mg) and 880 mg (range=720-1,100 mg), resulting in total doses of 210 mg (range=75-270 mg) and 8,525 mg (range=3,000-11,000 mg), respectively. Patients of the P group received 60 mg of cisplatin (range=45-75 mg) as the median dose per day and 252 mg (range=60-420 mg) as the median total dose.

Treatment response and survival. Treatment responses and recurrences in each group are summarized in Table III. Although patients in the P group had a significantly shorter

Table I. *Clinicopathological variables for patients with cervical cancer.*

Clinicopathological variable	PF (n=48)	P (n=43)	*p*-Value
Age, years*	54.5 (20-75)	60.0 (29-75)	0.3259
Stage			0.0022
I	1	5	
II	9	14	
III	37	18	
IV	1	6	
Histological subtype			0.8536
Squamous cell carcinoma	43	38	
Other	5	5	
Parametrial involvement			0.7782
Positive	41	35	
Negative	7	8	
Pelvic lymph node metastasis			0.9118
Positive	24	21	
Negative	24	22	
Para-aortic lymph node metastasis			0.6130
Positive	12	8	
Negative	36	35	

*Values are presented as the median (range). PF: Concurrent chemoradiation with cisplatin and 5-fluorouracil; P: concurrent chemoradiation with cisplatin alone.

Table II. *Summary of treatment in each group.*

Variable	PF (n=48)	P (n=43)
Radiotherapy*		
Dose of pelvic EBRT, Gy	45.0 (39.6-55)	48.6 (43.2-65)
Dose of ICRT, Gy	24 (12-24)	24 (6-24)
Chemotherapy		
Number of cycles	2 (1-4)	5 (1-6)
Total dose of cisplatin, mg	210 (75-270)	252 (60-420)
Total dose of 5-FU, mg	8,525 (3,000-11,000)	NA

*Values are presented as the median (range). PF: Concurrent chemoradiation with cisplatin and 5-fluorouracil (5-FU); P: concurrent chemoradiation with cisplatin alone; EBRT: external-beam radiotherapy; ICRT: intracavitary brachytherapy; NA: not applicable.

Table III. *Treatment response and recurrence in each group.*

Variable	PF (n=48)	P (n=43)	*p*-Value
Follow-up period, months*	77.9 (3.0-166.4)	20.5 (4.0-62.1)	<0.0001
Response			0.1730
No resistance** and no recurrence	25	29	
Resistance	2	3	
Recurrence	21	11	
Site of recurrence			0.2661
Inside irradiation field only	8	7	
Outside irradiation field only	8	2	
Both areas	5	2	

*Values are presented as the median (range). **Resistance: Progression or persistent disease. PF: Concurrent chemoradiation with cisplatin and 5-fluorouracil; P: concurrent chemoradiation with cisplatin alone.

Table IV. *Treatment response by histological subtype.*

Variable	SCC	Other	*p*-Value
PF Group			0.2423
No resistance and no recurrence	23	2	
Resistance	1	1	
Recurrence	19	2	
P Group			0.1971
No resistance and no recurrence	27	2	
Resistance	2	1	
Recurrence	9	2	

PF: Concurrent chemoradiation with cisplatin and 5-fluorouracil; P: concurrent chemoradiation with cisplatin alone; SCC: squamous cell carcinoma.

follow-up period than those in the PF group ($p<0.0001$), responses and patterns of recurrence were not significantly different between the two groups. Treatment responses by histological subtype are shown in Table IV. Both the PF and P groups showed no statistically significant differences in treatment response between SCC and other histological subtypes.

Patient prognoses were evaluated with respect to OS and PFS. OS of patients at all disease stages and those with stage III and IV disease are shown in Figure 1. The median OS periods for all stages were 77.9 and 20.5 months in the PF and P groups, respectively; the difference between the two groups was not statistically significant ($p=0.2108$). OS among patients with stage III and IV disease was also not significantly different between the two groups ($p=0.5657$); the median OS in the PF and P groups was 84.7 and 20.8 months, respectively. The median PFS for patients at all disease stages was 45.6 and 16.4 months in the PF and P groups, respectively; this difference was not statistically significant ($p=0.8718$) (Figure 2). Among patients with stage III and IV disease, no significant difference in PFS was revealed between the two groups ($p=0.4211$); due to median PFS was 64.9 *versus* 17.0 months in the PF and P groups, respectively.

Adverse effects. Acute grade 3 or 4 toxicities are shown in Table V. Major acute toxicities included hematological and gastrointestinal toxicities. No remarkable alopecia was observed, nor did cisplatin-induced neurotoxicity or ototoxicity occur. Although hyponatremia due to renal tubular injury was observed, no irreversible adverse effects, such as

Table V. *Acute grade 3/4 toxicities experienced by patients with cervical cancer.*

Adverse effect	PF (n=48)	P (n=43)	*p*-Value
Hematological toxicity			0.9754
Leukopenia	12 (25)*	12 (27)	
Neutropenia	5 (10)	4 (9)	
Anemia	5 (10)	3 (6)	
Thrombocytopenia	2 (4)	1 (2)	
Non-hematological toxicity			0.8151
Appetite loss	0 (0)	1 (2)	
Nausea	5 (10)	2 (4)	
Vomiting	1 (2)	1 (2)	
Diarrhea	5 (10)	2 (4)	
Liver dysfunction	0 (0)	3 (6)	
Hyponatremia due to renal tubular injury	3 (6)	2 (4)	
Dermatitis	1 (2)	2 (4)	
Discontinuation of chemotherapy	8 (16)	4 (9)	0.3633

*Numbers in parenthesis indicate the occurrence percentage. PF: Concurrent chemoradiation with cisplatin and 5-fluorouracil; P: concurrent chemoradiation with cisplatin alone.

Table VI. *Late grade 3/4 toxicities experienced by patients with cervical cancer.*

Adverse effect	PF (n=48)	P (n=43)	*p*-Value
Non-hematological toxicity			0.0297
Enterocolitis	4 (8)*	2 (4)	
Bowel obstruction	2 (4)	0 (0)	
Cystitis	1 (2)	0 (0)	
Rectovaginal fistula	2 (4)	0 (0)	
Lymph edema	1 (2)	0 (0)	

*Numbers in parenthesis indicate the percentage occurrence. PF: Concurrent chemoradiation with cisplatin and 5-fluorouracil; P: concurrent chemoradiation with cisplatin alone.

persistent electrolyte imbalance and bone marrow failure, were noted in either group. Two patients in the P group developed herpes zoster during CCRT. Discontinuation of chemotherapy occurred in eight and four patients in the PF and P groups, respectively. No statistically significant difference in acute toxicities or chemotherapy discontinuation was observed between the two groups.

The types and frequencies of grade 3 or 4 late adverse effects are shown in Table VI. Most gastrointestinal and genitourinary toxicities were controlled with supportive care. Although the follow-up period of the P group was shorter than that of the PF group, the frequencies of late adverse effects were significantly higher in the PF group than in the P group (p=0.0297).

Discussion

This retrospective study revealed no statistically significant difference in patient prognosis between the PF and P groups, although significant differences in stage and follow-up period were noted. Thus far, two other studies have previously compared the efficacy and adverse effects associated with these two regimens (10, 20). Table VII summarizes these results, including those of the current study. The dose of 5-FU administered during PF treatment was smaller in the present study than in other studies, and grade 3 and 4 acute hematological toxicities were more often observed in the P group in the current study. Toita *et al*. reported the results of a multi-institutional phase II study (JGOG1066) to assess the feasibility and acute toxicity of CCRT with HDR-ICBT plus weekly cisplatin (40 mg/m^2) for Japanese patients with cervical cancer (21). The present study included 71 patients with FIGO stage III-IVA disease. Sixty-five patients (92%) received the planned five courses of chemotherapy, and RT was completed per protocol in sixty-eight patients (96%). The following grade 3 or 4 acute adverse events were observed: neutropenia, n=31 (44%); anemia, n=10 (14%); diarrhea, n=4 (6%); and anorexia, n=3 (4%). The 2-year PFS and pelvic disease progression-free rate were 66% and 73%, respectively (22). The 2-year cumulative late complication rates were 24% for all grades. No fatal toxicities were observed. The authors concluded that CCRT with HDR-ICBT plus weekly cisplatin is feasible and could be safely administered to Japanese patients with cervical cancer.

No significant differences in recurrence patterns were observed between the PF and P groups in the present study. Recurrences were also detected outside the RT field. Hong reported that although CCRT has been strongly recommended for women with cervical cancer requiring RT, some subsets of patients, particularly those with stage IB1 disease and elderly patients with stage IB2 and II disease, can achieve good treatment outcomes from RT alone. In contrast, the author claimed that more intensive combination chemotherapy regimens should be developed for patients who have a high risk of distant relapse (23). Green *et al*. performed a systematic review of randomized controlled trials done between 1981 and 2000 (17 published, two unpublished) of CCRT (14). The most striking finding was the highly significant reduction in distant metastases; this reduction suggests that the drugs used could act as systemic cytotoxic agents. Hirakawa *et al*. identified a positive serum SCC levels immediately after treatment as a factor predictive of distant recurrence in patients with locally advanced SCC treated with CCRT (24).

New strategies are considered to improve the prognosis of patients with a high risk of recurrence. Mabuchi *et al*. retrospectively reviewed whether nedaplatin-based CCRT using HDR-ICBT is superior to RT alone in patients with

Table VII. *Reports on the treatment results of concurrent chemoradiation comparing cisplatin (CDDP) plus 5-fluorouracil (5-FU) and cisplatin alone.*

Authors	Year	Study type	Stage	Chemotherapy	No. of cases	OS, % (at year)	PFS, % (at year)	Acute toxicity* (%)		Late toxicity* (%)
								H	non-H	
Rose *et al*. (10)	1999	RCT	II-IVA	CDDP (50 mg/m^2, day 1) + 5-FU (1,000 mg/m^2, days 1-4) + hydroxyurea	173	67 (2.5)	64 (2)	47	20	NM
				CDDP (40 mg/m^2)	176	66 (2.5)	67 (2)	22	15	NM
Kong *et al*. (19)	2012	Retro-spective	IIB-IVA	CDDP (70 mg/m^2, day 1) + 5-FU (1,000 mg/m^2, days 2-5)**	103	73 (5)	74 (5)	21	35	NS
				CDDP (40 mg/m^2)	152	78 (5)	64 (5)	7	14	NS
Current study	2014	Retro-spective	IB1-IVA	CDDP (15 mg/m^2, days 1-5) + 5-FU (600 mg/m^2, days 1-5)	48	71 (5)	55 (5)	50	29	20
				CDDP (40 mg/m^2)	43	85 (2)	62 (2)	46	25	4

*Grade 3 or 4 toxicities. **One or two cycles of chemotherapy were added as consolidation after completion of two cycles of concurrent chemoradiation. OS: Overall survival; PFS: progression-free survival; H: hematological; non-H: non-hematological; RCT: randomized clinical trial; NM; not mentioned; NS: no serious event.

stage IIIB cervical cancer (25). Nephrotoxicity caused by weekly cisplatin during CCRT may limit the use of this agent for patients with stage IIIB disease with impaired renal function due to ureteral obstruction. Nedaplatin, a derivative of cisplatin, was developed with the aim of producing a treatment with lower renal toxicity but similar efficacy to that of cisplatin (26). CCRT with weekly nedaplatin (median dose=35 mg/m^2) was shown to be significantly superior to RT alone with respect to PFS and OS. The frequency of acute grade 3 or 4 toxicities was significantly higher in CCRT than in RT; however, no statistically significant differences were observed concerning severe late toxicity. Nedaplatin-based CCRT has been suggested to be safe and to significantly improve prognosis of stage IIIB patients. Choi *et al*. retrospectively compared the efficacy and toxicity of consolidation chemotherapy after CCRT and CCRT alone in patients with stage IIB-IVA disease (27). Consolidation chemotherapy consisted of three additional cycles of chemotherapy with cisplatin at 60 mg/m^2 (day 1) and 5-FU 1,000 mg/m^2 per day (days 1-5) given every three weeks. Distant relapse with or without locoregional/lymphogenous recurrence occurred more frequently with CCRT alone than with CCRT with consolidation chemotherapy. CCRT with consolidation chemotherapy also resulted in significantly better OS compared to CCRT alone. The authors claimed that consolidation chemotherapy after CCRT may improve survival and reduce distant recurrence without additional toxicity compared to CCRT alone. Ushijima *et al*. retrospectively evaluated the efficacy of CCRT using EBRT and HDR-ICRT with daily low-dose cisplatin (cisplatin at 5 mg/m^2/day five days per week) for stage IB2-IVA cervical cancer (28). The 5-year OS rates were 71% and 46% in stage I-II and stage III-IVA, respectively. Hematological toxicities, the most frequent acute toxicities, were relatively severe (*e.g.* grade 3 or 4 neutropenia occurred in 37% of patients) compared to rates observed in previous studies (29), and late gastrointestinal toxicities occurred in 13% of patients. CCRT using daily low-dose cisplatin was suggested to be tolerable and to induce a favorable initial response.

In the present study, neither the PF nor the P group showed a statistically significant difference in treatment response between SCC and other histological subtypes. In contrast, the incidence of adenocarcinoma has been reported to increase and be less sensitive to RT and chemotherapy than SCC (30). Thus, improvement in the therapeutic outcomes in patients with adenocarcinoma is urgently required. Shim *et al*. developed a nomogram for predicting the probability of 5-year survival after CCRT (31). Multivariate regression analysis revealed that histology (non-SCC) was one of the independent predictors for OS. Nagai *et al*. retrospectively analyzed the clinical data of patients with stage IIB-IVA adenocarcinoma who were treated with RT alone or CCRT (32). CCRT using cisplatin (50 mg/m^2 every three weeks) plus paclitaxel (50 mg/m^2 weekly) achieved much better local control and OS than CCRT using cisplatin alone (20 mg/m^2 for five days every three weeks) or RT alone. Tang *et al*.

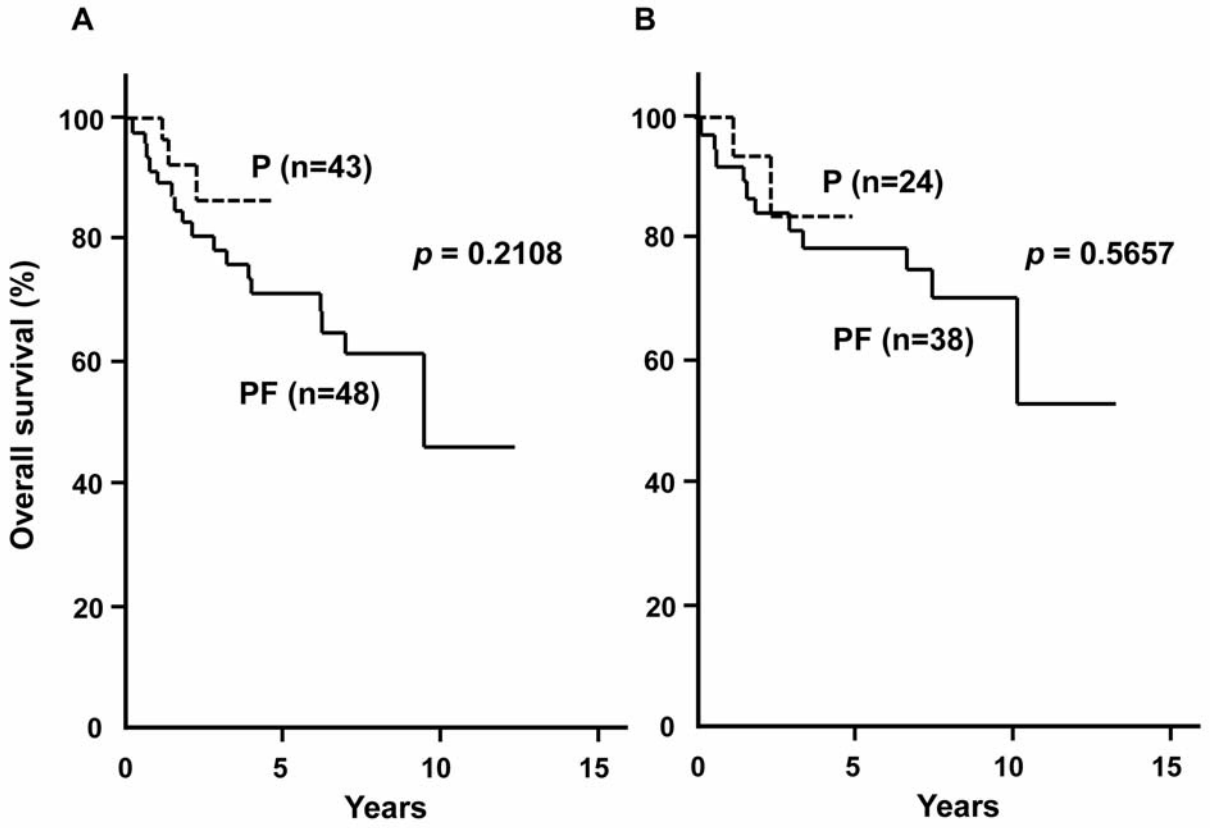

Figure 1. *Overall survival according to the type of concurrent chemoradiation (CCRT). A: The median survival time of patients with all disease stages was 77.9 and 20.5 months for treatment by CCRT with cisplatin and 5-fluorouracil (PF) and cisplatin alone (P), respectively (p=0.2108). B: The median survival time of patients with stage III or IV disease was 84.7 and 20.8 months for treatment by CCRT with PF and P, respectively (p=0.5657).*

compared CCRT and chemotherapy with CCRT alone for stage IIB-IVA adenocarcinoma in a randomized trial (33). A cisplatin dose of 40 mg/m^2 was administered for CCRT. Chemotherapy consisted of one cycle of neoadjuvant chemotherapy with paclitaxel (135 mg/m^2) and cisplatin (75 mg/m^2) before CCRT, and two cycles of consolidation chemotherapy with the same agents after CCRT. Patients who received CCRT with chemotherapy had significantly longer disease-free survival, cumulative survival, and long-term local tumor control. Shibata *et al*. retrospectively evaluated the efficacy of preoperative CCRT in patients with stage IB2-IVB adenocarcinoma (34). On post-surgical pathological examination, five (26%) and 13 (68%) patients out of a total 19 patients experienced a complete response and partial response, respectively. This report demonstrated that preoperative CCRT improved the survival of patients with locally advanced adenocarcinoma with manageable toxicities.

To the best of our knowledge using a MEDLINE search (search terms: cervical cancer and CCRT), this is the first report to compare the outcomes of triweekly and weekly CCRT for Japanese patients with cervical cancer. The current study has the following limitations. Firstly, anticancer agents used in CCRT historically changed during the study period. Secondly, the retrospective design, single-institution data, lack of randomization, and small number of patients may contribute to potential biases. Thirdly, we cannot exclude the possibility that other factors, such as comorbidities, might have significantly influenced survival. Fourthly, the incidence of late toxicity, particularly in the P group, requires further investigation. Although both triweekly CCRT with cisplatin plus 5-FU and weekly CCRT with cisplatin alone seem to have similar efficacy as initial treatment for cervical cancer, the toxicities were better tolerated in weekly CCRT. Because CCRT should be optimized to reduce the incidence of refractory or recurrent disease, further multi-center randomized clinical trials with newer chemotherapeutic agents are required to evaluate the efficacy and quality of life after treatment.

Conflicts of Interest

The Authors have no conflicts of interest with respect to the information presented in this article.

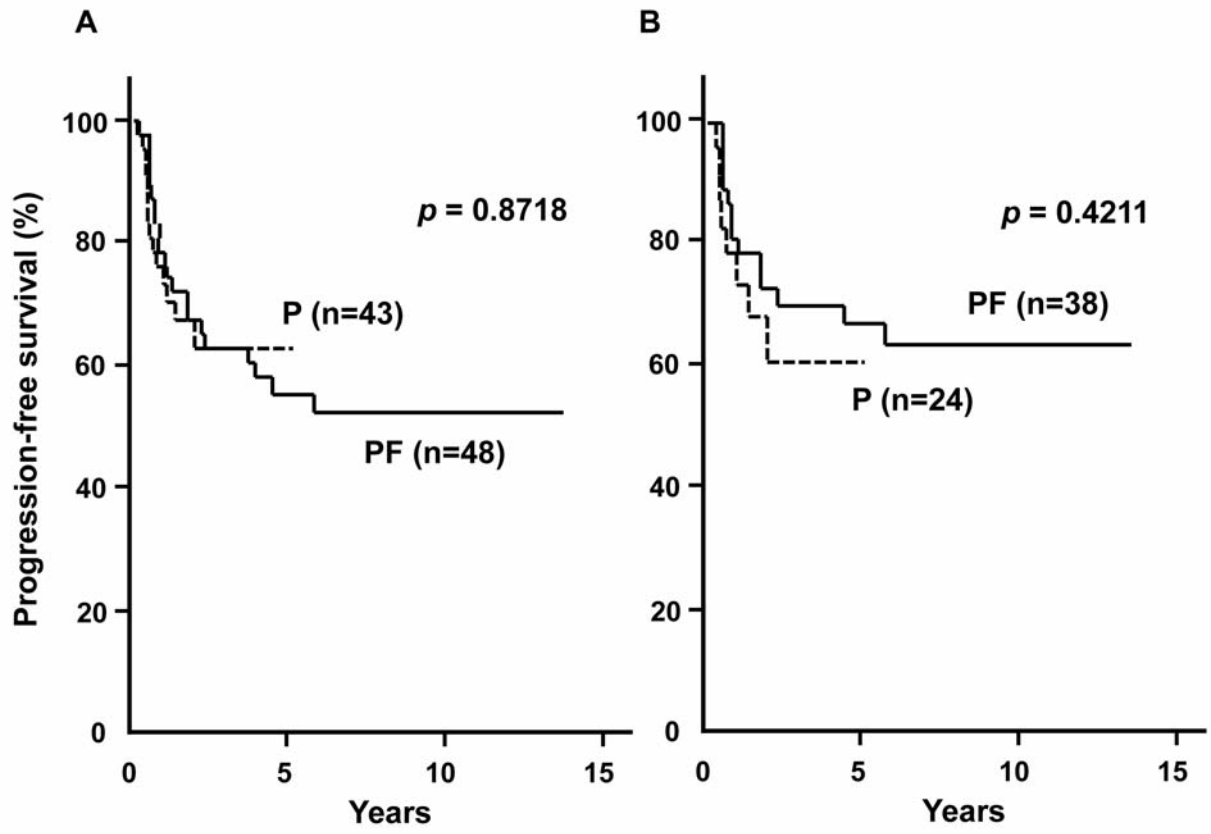

Figure 2. *Progression-free survival according to the type of concurrent chemoradiation (CCRT). A: The median survival time of patients with all disease stages was 45.6 and 16.4 months for treatment by CCRT with cisplatin and 5-fluorouracil (PF) and cisplatin alone (P), respectively (p=0.8718). B: The median survival time of patients with stage III or IV disease was 64.9 and 17.0 months for treatment by CCRT with PF and P, respectively (p=0.4211).*

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