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Pattern of primary and postoperative adjuvant concurrent chemoradiotherapy for treatment of uterine cervical cancer in Korea: Results of a multicenter retrospective study

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Objective: The aim of this retrospective study was to analyze and to compare the treatment outcomes of various concurrent chemoradiotherapy (CCRT) regimens for uterine cervical cancer during the past 10 years in the Republic of Korea.

Methods: Between January 1997 and December 2006 the medical records of 1,827 stage Ib–IVa cervical cancer patients from 23 institutions in Korea were retrospectively reviewed and analyzed. Of these 1,826 patients, 1,577 had complete medical records and were enrolled in the study. Patients were divided into two groups: group 1 received primary CCRT without surgery; and group 2 received adjuvant CCRT after radical hysterectomy. The survival differences between the different CCRT regimens (weekly cisplatin, monthly 5-FU+cisplatin, and monthly paclitaxel+cisplatin) were also analyzed.

Results: The median age was 54 years (range, 16–99 years). There were 1,020 patients in group 1 and 557 patients in group 2. The majority of patients in group 1 had regionally advanced stage disease (IIb–IVa), while the majority of patients in group 2 had early stage disease (Ib–IIa). In group 1, the disease-free survival (DFS) was longer in those patients who received platinum-based chemotherapy (weekly cisplatin and cisplatin+5-FU) compared to those who received paclitaxel, but there was no statistical difference in the overall survival (OS). In contrast, survival of group 2 patients was improved by the paclitaxel regimen, but without a significant difference. Significantly increased toxicities were observed in patients treated with monthly cisplatin/5-FU and paclitaxel, but the toxicities were easily managed.

Conclusion: CCRT is an effective mode of therapy for cervical cancer in Korea. Further study confirming the efficacy of various CCRT regimens is necessary.

Key words: Cervical carcinoma; Concurrent chemoradiotherapy

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Introduction

Since Marie Curie's first discovery of the radioisotope, radium, in 1896, radiotherapy has developed into an integral part of treatment for women with cancer of

the uterine cervix. While radiotherapy has been established as the primary mode of therapy, it has been shown that radiotherapy alone is accompanied by a high failure rate in patients with large-sized lesions, or in patients at risk for recurrent disease after surgical treatment. These findings have led to the development of combination radiotherapy and chemotherapy, the presently widely employed concurrent chemoradiotherapy (CCRT). In 1985, Fu et al.[1] proposed the theory that combination radiotherapy and chemotherapy resulted in a reduction in tumor size, an enhanced effect of the radiotherapy acting as a radiosensitizer, and that the systemic effect prevented distant metastasis of the cervical cancer.

With this theory as a basis, studies were initiated which investigated the therapeutic effect of CCRT in patients with squamous cancers of the head and neck, lung, and esophagus, as well as vulvar cancer in women.[2-5] Between 1999 and 2000, the results of 5 randomized prospective studies regarding the role of CCRT in cervical cancer patients were published, and all 5 studies showed that platinum-based (cisplatin) CCRT decreased local and distant metastasis rates, and thus increased survival by 30% to 50%. It was also concluded that CCRT increased survival by approximately 40% compared to radiotherapy alone.[6-10]

Thereafter, many studies have verified that CCRT is efficacious, not only in the treatment of loco-regionally advanced stage IIb–IVa cervical cancers, but also for patients with high risk factors for recurrent disease after radical hysterectomy in whom recurrence rates were decreased up to 50%.[11-13] Moreover, recent investigations have shown that CCRT using combination chemotherapy with paclitaxel/carboplatin has further enhanced treatment outcomes for patients with cervical cancer.[14-16]

The objective of the current study was to analyze the treatment results of various CCRT regimens in Korean patients with cervical cancer since its introduction in our country 10 years earlier. We also attempted to evaluate which CCRT regimen was the most effective and least toxic as either primary CCRT for stages IIb-IVa or postoperative adjuvant CCRT for stages Ib-IIa.

Materials and Methods

The medical records of 1,827 FIGO stage Ib-IVa cervical cancer patients who received CCRT at 23 institutions in Korea between January 1997 and December 2006 were retrospectively reviewed. Two hundred fifty patients were excluded from this study because of incomplete data, leaving a total of 1,577 patients for inclusion in the study. These patients were divided into two groups: group 1 received definitive CCRT without surgery; and group 2 received surgery and adjuvant CCRT. The two groups were compared with respect to age, histologic type, FIGO stage of disease, tumor size, preoperative tumor marker (squamous cell carcinoma antigen [SCC Ag]) levels, and CCRT-related toxicities. We also analyzed differences in survival and recurrence rates, and toxicities between the following 3 types of CCRT regimens in each group: 1) weekly cisplatin, 2) monthly cisplatin/5–fluorouracil (5-FU) at 3 week intervals, 3) and a paclitaxel-based regimen. Toxicities were defined according to the GOG toxicity criteria, and recurrent disease was defined as those patients with suspected recurrent disease during follow-up by imaging studies, tumor markers, and Pap smears, and finally by histologic confirmation. Suspicious lesions on PET or CT scans, even if not confirmed by biopsy, as well as the presence of distant metastasis, were categorized as recurrent disease status.

Statistical analyses were performed using SPSS, version 12.0.1; specifically, a chi-square test, Student *t*-test, ANOVA, Kaplan-Meier survival analysis, and Cox regression analysis were used.

Results

Among the 1,577 patients enrolled in this study, 1,020 patients received definitive CCRT without surgery (group 1), and 557 patients received surgery and adjuvant CCRT (group 2). The reason for definitive CCRT without surgery for stage I patients in group 1 (7.4%) was probably attributed to factors such as stage Ib2 bulky tumors, old age, and other medical conditions which would contribute to increased morbidity.

The mean age was significantly greater in group 1 compared to group 2 (56.8 vs. 50.1 years, $P<0.001$). The histologic types, other than squamous cell carcinoma, were more prevalent in group 2 compared to group 1 (24.2% vs. 11%, $P<0.001$), and the number of patients with adenocarcinomas and adenosquamous carcinomas was higher (21.2% vs. 8.7%) in group 2. Most patients in group 1 had FIGO stage IIb or higher, and the size of the lesion and pretreatment tumor marker levels were

Table 1. Clinical characteristics according to treatment modality

	Treatment modality		*P*-value
	Primary CCRT (Group 1)	Surgery + adjuvant CCRT (Group 2)	
No. of patients	1,020	557	
Age (yr)	56.8±11.7	50.1±10.4	<0.001
Cell type, n (%)			<0.001
SCC	908 (89.0)	422 (75.8)	
AC	79 (7.7)	90 (16.2)	
ASC	10 (1.0)	28 (5.0)	
Small cell	4 (0.4)	8 (1.4)	
Others	19 (1.9)	9 (1.6)	
Stage, n (%)			<0.001
I	75 (7.4)	414 (74.3)	
IB1	49	302	
IB2	26	112	
II	292 (28.6)	143 (25.7)	
IIA	87	130	
IIB	205	13	
III	575 (56.4)	0 (0)	
IIIA	32	0	
IIIB	543	0	
IV	78 (7.6)	0 (0)	
IVA	52	0	
IVB	26	0	
Tumor size (cm)	4.4±1.7	3.7±3.5	0.001
Pretreatment SCC Ag level	15.1	6.8	<0.001
Complications (>G3), n(%)	167 (16.4)	91 (16.3)	0.986

SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous cell carcinoma.

also greater and higher in the group 1 patients (Table 1). In terms of toxicity, weekly cisplatin regimens appeared to be associated with comparatively decreased acute toxicities compared to other combination regimens, and in particular, the incidence of grade 3/4 leukopenia was significantly lower with the weekly cisplatin regimens. Recurrent disease occurred in 16.3% (257/1,577) of the patients, among whom distant metastasis was present in 42.4% (109/257). The distant failure rate was 40.4% (70/173) for the weekly cisplatin regimen, and 46.4% (39/84) for the monthly cisplatin+5FU and paclitaxel based regimens; there were no statistical differences between the CCRT regimens (Table 2).

The 5-year disease-free survival (DFS) rates of the group 1 patients who received weekly cisplatin, monthly cisplatin+5FU, and paclitaxel-based regimens were 63.7%, 53.0%, and 42.1%, respectively; thus, the paclitaxel-based regimen had a significantly lower DFS (*P*=0.0006).

On the other hand, no statistical difference was observed in terms of overall survival (OS) between the above 3 regimens (71.1%, 74.7%, and 84.6%, respectively; *P*= 0.6888; Fig. 1). The 5-year DFS rates in group 2 patients who received weekly cisplatin, cisplatin+5FU, and the paclitaxel-based regimen were 62.7%, 72.3%, and

Table 2. Toxicity and recurrence according to chemotherapy regimen

	W-CCRT	M-CCRT		*P*-value
	Weekly CDDP (n=1,144)	FP (n=253)	TC or TP (n=180)	
Treatment modality, n (%)				<0.001
Primary CCRT	824 (72.0)	124 (49.0)	72 (40.0)	
Adjuvant CCRT	320 (28.0)	129 (51.0)	108 (60.0)	
Toxicity G3/4, n (%)	95 (8.3)	82 (32.4)	81 (45.0)	<0.001
Leukopenia	84	78	77	
Thrombocytopenia	12	19	3	
Diarrhea	9	6	7	
Nephrotoxicity	3	1	2	
Recurrence, n (%)	173 (15.1)	52 (20.6)	32 (17.8)	0.099
Central pelvic	32	7	9	
Pelvic side wall	11	5	2	
Lymph node	60	16	6	
Distant metastasis	70	24	15	

W-CCRT, weekly CCRT; M-CCRT, monthly CCRT; FP, cisplatin+5FU; TC, paclitaxel+carboplatin; TP, paclitaxel+cisplatin.

79.8%, respectively (*P*=0.1041), which suggested that while not statistically significant, there was a tendency for better outcomes after monthly cisplatin+5FU or paclitaxel+cisplatin/carboplatin regimens compared to the weekly cisplatin regimen (Fig. 2). Even though no significant difference in OS was observed between the above 3 regimens (82.7%, 93.4%, and 95.6%; *P*=0.2582), the weekly cisplatin regimen had the lowest survival rates.

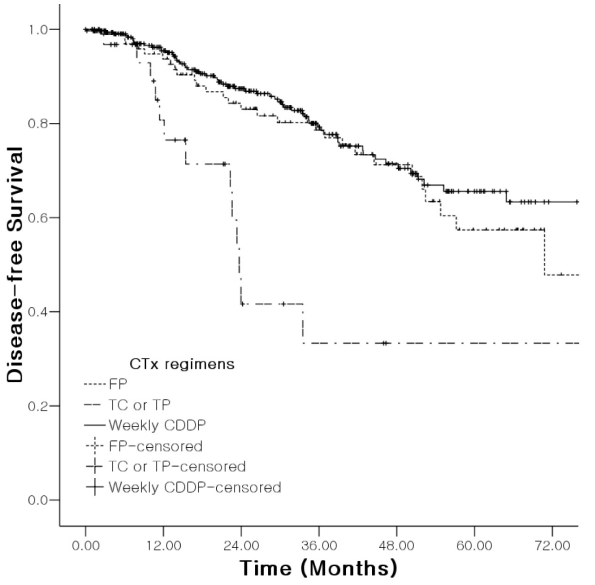
Discussion

After the publication of the randomized prospective clinical studies[6,7,9,10] which demonstrated that CCRT improved survival by 30% to 50% in patients with cervical cancer, the National Cancer Institute released an opinion that strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy for women who require radiation therapy for the treatment of cervical cancer.

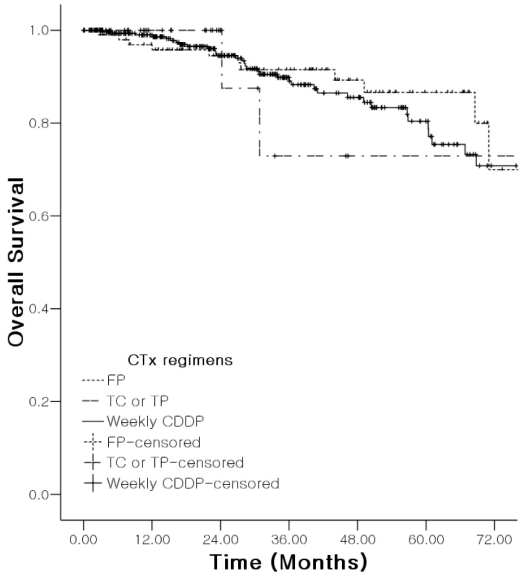
Since then, CCRT has become the mainstay treatment modality for all cervical cancer patients requiring radiotherapy, and CCRT is provided largely for the following two groups of patients: 1) primary CCRT without surgery for patients with large-sized stage Ib tumors and stage IIb–IVa locally advanced disease, and 2) postoperative adjuvant CCRT for patients at high risk of treatment failure after radical hysterectomy.

One of the first randomized prospective studies on CCRT was the Radiation Therapy Oncology Group (RTOG) #9001.[7] This study was conducted between 1986 and 1990 and enrolled patients with locally advanced disease and negative para-aortic lymph nodes; RTOG #9001 showed that administration of CCRT resulted in significantly improved DFS compared to radiotherapy alone.[7]

The next large scale study was the Gynecology Oncology Group (GOG) #120,[9] in which a comparative analysis was performed between cervical cancer patients who received weekly cisplatin, monthly cisplatin+5-FU+hydroxyurea (HFC), and hydroxyurea. The results were similar to the results of RTOG #9001, i.e., patients showed increased survival rates after cisplatin-based CCRT compared with hydroxyurea alone, and weekly cisplatin regimen was more tolerable than HFC.[9] A study of CCRT and its related toxicities in Korea showed results similar to GOG #120.[17] In the current study, the authors observed that the 5-year OS rates in group 1 patients were enhanced to a favorable 70% to 84%. Al-

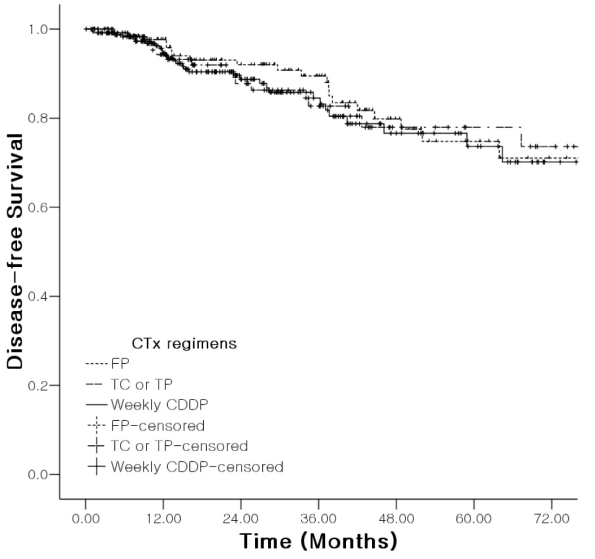


(A) Disease-free survival

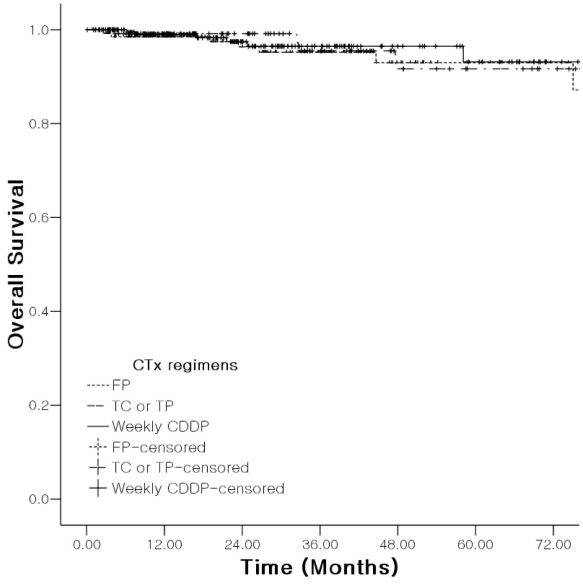


(B) Overall survival

Fig. 1. Survival of primary CCRT according to CT regimens for stages IIb~IVa.



(A) Disease-free survival



(B) Overall survival

Fig. 2. Survival of post-op adjuvant CCRT according to CT regimens for stages Ib~IIa.

though there was no statistical difference in OS among the three CCRT regimens as primary therapy in the current study, the paclitaxel regimen had a significantly lower DFS than weekly cisplatin and monthly cisplatin+ 5-FU regimen. Therefore, we recommend that further studies focusing on the indications and determining the efficacy of paclitaxel-based CCRT regimens should be performed.

The role of CCRT as a postoperative adjuvant mode of therapy has also been well-established by previously published data.[8] Before the use of CCRT as an adjuvant therapy, the 5-year survival rate after radical hysterectomy in stage Ib–IIa was reported to be 80% to 85% in several series.[18-20] In other words, the treatment failure rate was approximately 15% to 20%. However, patients with high risk factors for postoperative recurrent disease,

such as positive pelvic lymph nodes, parametrial invasion, and tumor positive surgical margins are known to have higher failure rates.[18,21,22] In the past, patients with positive lymph nodes have been treated with radiotherapy, but at the Society of Gynecology Oncology (SGO) consensus meeting in 1980, it was concluded by Morrow et al.[23] that adjuvant radiotherapy after surgery for such patients did not increase survival. In order to answer this question, GOG study #109[8] compared the results of patients with high risk factors for recurrent disease who received postoperative radiotherapy only, to those who underwent CCRT. The results showed that survival was significantly improved in those patients who received CCRT, but with increased hematologic and gastrointestinal toxicities.[8] In the first study about CCRT in Korea, Ryu et al.[13] also showed that CCRT reduced local recurrence and increased survival in patients with high risk factors to the levels of non-high risk patients.

In 2007, the results of a multicenter study in Korea was published which retrospectively investigated the survival rates of various modes of therapy for stage Ib2 cervical cancer patients during the past 10 years in Korea.[24] This report concluded that survival rates were the best among patients who underwent postoperative adjuvant CCRT, while survival was worst in patients who received postoperative radiotherapy only. In the current study, adjuvant CCRT for cervical cancer (group 2) afforded a very favorable 5-year OS rate of 82% to 95%, and in particular, combination chemotherapy with the paclitaxel+cisplatin/carboplatin regimen resulted in a 5-year OS rate as high as 95.6%. Therefore, it was the suggestion of the authors of the current study that further prospective studies be conducted to confirm this result.

Since 2005, the Korean Gynecology Oncology Group (KGOG) has been conducting a prospective study in an attempt to ascertain the effectiveness of paclitaxel and carboplatin as a CCRT regimen for patients with high risk factors for recurrent disease after radical hysterectomy. At present, a total of 62 patients have been enrolled in that study who have been followed for a median of 21 months. Recurrent disease has been observed in 8 patients and the DFS is 87.1%, showing that paclitaxel and carboplatin is indeed effective but also with an increased incidence of acute toxicities.

We have found in this retrospective multicenter review of Korean tertiary care centers that CCRT is a widely used regimen in the treatment of patients with cervical cancer, and that it is effective. While combination chemotherapy is associated with increased toxicity, the toxicities are generally easily manageable. The weekly regimen containing cisplatin was associated with the least toxicity of all the regimens reviewed. We did not find any significant difference in DFS between the weekly and monthly chemotherapy regimens for regionally advanced stage IIb-IVa cervical cancer, but there was a tendency for improved survival in patients who received monthly chemotherapy.

One of the limitations of this study was the bias derived from the fact that radiotherapy differed from center-to-center, and surgical techniques were not standardized. Still, we conclude that some degree of uniformity pertaining to CCRT exists among the many tertiary institutions who care for cervical cancer patients in Korea, and that this study could be a basis for future prospective studies.

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Appendix

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