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Original Article

Chemoradiotherapy followed by consolidation chemotherapy involving paclitaxel and carboplatin and in FIGO stage IIIB/IVA cervical cancer patients

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ABSTRACT

Objective: To evaluate the efficacy and toxicity of paclitaxel plus carboplatin (TC)-based concurrent chemoradiotherapy (CCRT) followed by consolidation chemotherapy in the International Federation of Gynecology and Obstetrics (FIGO) stage IIIB/IVA cervical cancer patients.
Methods: We reviewed the medical records of FIGO stage IIIB/IVA cervical cancer patients (n=30) who had been intended to be treated with TC-based CCRT followed by consolidation chemotherapy (TC-CCRT-group) from April 2012–May 2016. Patients who had been treated with CCRT involving a single platinum agent (CCRT-group; n=52) or definitive radiotherapy alone (RT-group; n=74) from January 1997–September 2012 were also identified and used as historical controls. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test.
Results: Of the 30 patients included in the TC-CCRT-group, 22 patients (73.3%) completed the planned TC-based CCRT. The most frequently observed acute grade 3/4 hematological toxicities were leukopenia and neutropenia, and diarrhea was the most common acute grade 3/4 non-hematological toxicity. After a median follow-up of 35 months, 9 patients (30.0%) had developed recurrent disease. The patients' estimated 3-year progression-free survival (PFS) and overall survival (OS) rates were 67.9% and 90.8%, respectively. In comparisons with historical control groups, the survival outcomes of TC-CCRT-group was significantly superior to CCRT-group in terms of OS (p=0.011) and significantly superior to RT-group in terms of both PFS (p=0.009) and OS (p<0.001).
Conclusion: TC-based CCRT followed by consolidation chemotherapy is safe and effective. A randomized controlled study needs to be conducted to further evaluate the efficacy of this multimodal approach in this patient population.

Keywords: Uterine Cervical Neoplasms; Chemoradiotherapy; Consolidation Chemotherapy; Prognosis

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

INTRODUCTION

It is generally accepted that the ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor because the dose required to treat large tumors exceeds the toxicity limit of normal tissue [1]. As patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIB/IVA disease usually have large tumors, efforts to maximize local control and improve the survival and quality of life of cervical cancer patients are necessary.

Based on the positive results obtained in randomized controlled studies conducted in the 1990s [2-5], concurrent cisplatin combined with pelvic radiotherapy (i.e., concurrent chemoradiotherapy, CCRT) has become the standard treatment for patients with stage IB or worse cervical cancer. However, according to a report about Radiation Therapy Oncology Group (RTOG) protocol 90-01, the 5-year survival rate of patients with stage IB-IIA cervical cancer that are treated with a combination of chemotherapy and radiotherapy is 78%, whereas that for patients with stage III-IVA disease is 59% [6]. Moreover, a meta-analysis of 18 randomized trials [7] found that the absolute survival benefit of adding concurrent chemotherapy to radiotherapy was 10% in stage IA–IIA, 7% in stage IIB, and 3% in stage III–IVA disease at 5 years. Therefore, new CCRT regimens that are more effective than conventional cisplatin-based CCRT need to be developed for patients with stage IIIB/IVA cervical cancer.

One strategy that might improve the outcomes of these patients is the concurrent use of platinum-based doublet chemotherapy and pelvic radiotherapy. A recent meta-analysis showed that the concurrent administration of platinum-based doublet chemotherapy with radiotherapy was associated with improved overall survival (OS) and progression-free survival (PFS) compared with radiotherapy and concurrent cisplatin chemotherapy in patients with cervical cancer [8].

Another possible strategy is the addition of consolidation chemotherapy after definitive CCRT. A 2008 meta-analysis of randomized controlled trials strongly suggested that the addition of consolidation chemotherapy to CCRT is beneficial [7]. Currently, the efficacy of platinum-based consolidation chemotherapy after pelvic CCRT for cervical cancer is being evaluated in phase III studies in both postoperative adjuvant radiotherapy [9] and definitive radiotherapy settings, The OUTBACK Trial [10].

Chemotherapy consisting of paclitaxel plus carboplatin (TC) has been shown to be effective in patients with advanced or recurrent cervical cancer. In a recent randomized phase III study, TC was demonstrated to be comparably effective to and less toxic than cisplatin plus paclitaxel in patients with stage IVB or recurrent cervical cancer [11]. Moreover, as both paclitaxel plus carboplatin have been shown to act as radiosensitizers [12,13], the use of TC concurrently with pelvic radiotherapy and/or as a consolidation chemotherapy might be appropriate in patients with stage IIIB/IVA cervical cancer.

We have recently reported that pelvic TC-based CCRT followed by consolidation chemotherapy in the adjuvant setting is safe and highly effective in women with surgically treated early-stage cervical cancer [14]. However, in the setting of definitive radiotherapy, although several clinical trials have been conducted [15-20], there is limited information available regarding the efficacy and toxicity of TC-based chemoradiotherapy followed by consolidation chemotherapy.

JOURNAL OF GYNECOLOGIC ONCOLOGY

With an aim to improve the prognosis of FIGO stage IIIB/IVA cervical cancer patients, we retrospectively investigated whether pelvic TC-based chemoradiotherapy followed by consolidation chemotherapy achieves better outcomes than pelvic CCRT involving a single platinum agent or definitive radiotherapy alone.

MATERIALS AND METHODS

1. Patients and methods

Permission to proceed with the data acquisition and analysis was obtained from the institutional review board of Osaka University Hospital. A list of FIGO stage IIIB/IVA cervical cancer patients who had been treated with definitive radiotherapy from January 1997–May 2016 was generated from our institutional tumor registries. Through a chart review, patients who were intended to be treated with TC-based CCRT followed by consolidation chemotherapy (TC-CCRT-group; n=30) were identified. Of the 30 patients in TC-CCRT-group, 25 were treated in the context of our institutional phase II study, which is registered with the University Hospital Medical Information Network (UMIN, Registration No.: UMIN000017232).

2. Radiotherapy

The external beam radiotherapy (EBRT) was delivered with CT-based treatment planning, with a dose of 2 Gy per fraction, five times per week as reported previously [21]. The clinical target volume (CTV) included the gross disease, cervix, parametria, uterus, upper part of vagina, and regional lymph nodes (common, presacral, internal, and external iliacs). The initial 30–40 Gy was delivered to the whole pelvis with a 4-field box and then pelvic irradiation with a 4 cm-width of central shield being ensued reducing organ at risk exposure. Total pelvic side wall dose was 50 Gy in 25 fractions.

After adequate tumor regression, high-dose-rate intracavitary brachytherapy (HDR-ICBT) was performed once a week during the course of the EBRT with a midline block field. ICBT was administered to the patients using the microSelectron digital (HDR-V3) brachytherapy afterloader (Elekta Inc., Atlanta, GA, USA) with Fletcher-type (Fletcher-Williamson Asia Pacific) metal applicators (Elekta Inc.) comprising one curved central tandem applicator and two non-shielded ovoid applicators. A planning CT scan was obtained before the delivery of each fraction. The high-risk CTV and organs at risk were contoured on the planning CT according to the GEC-ESTRO guidelines using Oncentra® (Electa Inc.).

The ICBT dose was prescribed at point A, which was defined as 2 cm above the cervical os marker and 2 cm perpendicular to the uterine axis along the plane of the uterus. The planned total dose of HDR-ICBT was 27.2 Gy in 4 fractions. After standard loading of source dwell positions and weighting with a fraction dose at point A in all patients, dwell times were then manually modified to maximize coverage of the high-risk CTV while reducing dose to the organs at risk. Patients in whom it was found that it was unlikely that ICBT would be able to irradiate the whole tumor volume were treated with interstitial brachytherapy (ISBT), as described previously [22]. EBRT was skipped on the days on which HDR-ICBT or HDR-ISBT was performed.

3. Chemotherapies

1) Concurrent chemotherapy

Chemotherapy consisting of paclitaxel (35 mg/m^2) and carboplatin (area under the curve

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[AUC]: 2.0, Calvert's formula) was infused once a week prior to the EBRT (**Fig. 1A**). The doses of paclitaxel and carboplatin were chosen based on the findings of our previous phase I study of TC-based CCRT for patients with uterine cervical cancer [23]. Paclitaxel was administered as a 60-minute continuous infusion, and carboplatin was administered as a 30-minute infusion after the paclitaxel.

2) Consolidation chemotherapy
The patients were scheduled to begin consolidation chemotherapy within 3–5 weeks of the completion of the CCRT. Three cycles of paclitaxel (175 mg/m^2 in 3 hours) and carboplatin (AUC: 5.0, Calvert's formula, in 30 minutes) were administered every 3–4 weeks [24].

4. Toxicity assessment

The patients were assessed for toxicities every week during treatment. Complications that occurred within 90 days of the start of the primary treatment were considered to be acute complications, and those that occurred more than 90 days after the start of treatment were considered to be late complications. The severity of acute complications was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Late complications were graded according to the RTOG Late Radiation Morbidity Scoring Scheme [25].

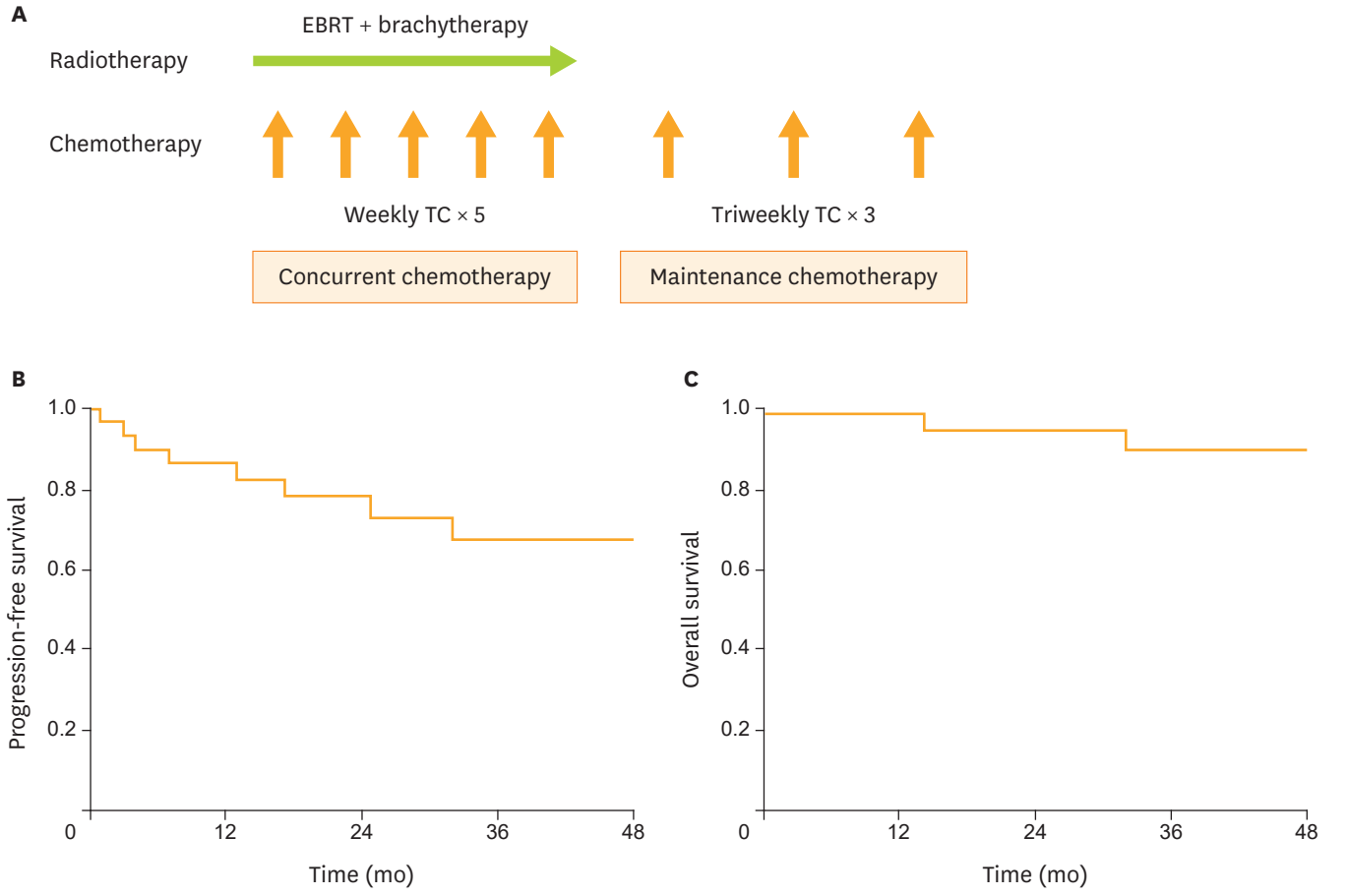

Fig. 1. TC-based CCRT followed by consolidation chemotherapy. (A) Treatment schedule; (B) Kaplan-Meier estimates of PFS (all patients); and (C) Kaplan-Meier estimates of OS (all patients).

CCRT, concurrent chemoradiotherapy; EBRT, external beam radiation therapy; OS, overall survival; PFS, progression-free survival; TC, paclitaxel plus carboplatin.

5. Response evaluation

We evaluated the tumor response at one month after the completion of TC-based CCRT. The response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors. A complete response (CR) was defined as the disappearance of all target and non-target lesions and the absence of new lesions. A partial response (PR) was defined as at least a 30% reduction in the sum of the longest dimensions of the target lesions. Progressive disease (PD) was defined as a 20% increase in the sum of the longest dimensions of the target lesions or the development of new lesions. Stable disease (SD) implies that none of the above apply.

6. Follow-up

Once treatment ended, the patients were followed-up regularly by both gynecological oncologists and radiation oncologists, as reported previously [26]. When recurrence was suspected, a biopsy was taken for confirmation whenever possible. The median duration of the follow-up period was 35 months.

7. Control patients

A non-randomized group of patients with FIGO stage IIIB/IVA cervical cancer patients who had been treated with CCRT involving a single platinum agent (CCRT-group; n=52) or definitive radiotherapy alone (RT-group; n=74) from January 1997–September 2012 were also identified and used as historical controls. The clinicopathological characteristics of these patients are presented in **Supplementary Table 1**. Of these, 30 patients in CCRT-group and 21 patients in RT-group were included in our previous clinical studies [21,27]. At our institutions, nedaplatin is employed as a radiosensitizing agent for patients with cervical cancer [21,27-30]. In CCRT-group, weekly nedaplatin (40 mg/m^2) was administered intravenously during the course of pelvic radiotherapy. The radiotherapy administered to the control patients was same as the radiotherapy employed in patients in TC-CCRT-group.

8. Statistical analysis

The differences between the two groups with respect to categorical variables such as FIGO stage, performance status (PS), histology, pelvic nodal status, and hydronephrosis were assessed with Fisher's exact test. Continuous variables such as age, maximum tumor diameter, and pretreatment hemoglobin level were analyzed with Student's t test or Mann-Whitney U test. PFS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. PFS was defined as the time interval between the start of treatment and the detection of recurrence. OS was defined as the time from the start of treatment to the date of death or to the date of censoring. All statistical analyses were two-tailed, and p-values of less than 0.05 were considered statistically significant. MedCalc (MedCalc Software, Mariakerke, Belgium) was used for all analyses.

RESULTS

1. Patients

Thirty patients were treated with TC-based CCRT followed by consolidation chemotherapy between April 2012 and March 2016. All of the patients exhibited the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS) of 0. The clinicopathological characteristics of the enrolled patients are presented in **Table 1**. The patients' median age was 53 years (range: 30–68). Twenty-nine patients had FIGO stage IIIB disease and one had FIGO stage IVA disease. Twenty-four patients had tumors that displayed squamous cell carcinoma

Table 1. Patient characteristics

Variables		TC-CCRT	
		No.	%
Age (yr)	Median (range)	53	(30–68)
	≤50	13	43.3
	51–74	17	56.7
FIGO stage	IIIB	29	96.7
	IVA	1	3.3
PS	0–1	30	100.0
	≥2	0	0.0
Histology	SCC	24	80.0
	Non-SCC	6	20.0
Pelvic nodal status*	Yes	23	76.7
	No	7	23.3
Hydronephrosis	Yes	5	16.7
	No	25	83.3
Maximum tumor diameter (mm)†	Median (range)	60	(40–76)
	≤40	2	6.7
	41–60	17	56.7
	≥61	11	36.7
Pretreatment hemoglobin level (mg/dL)‡	Mean (range)	12.1	(7.2–14.7)
	≤10.0	4	13.3
	>10.0	26	86.7

FIGO, International Federation of Gynecology and Obstetrics; PS, performance status; SCC, squamous cell carcinoma; TC-CCRT, paclitaxel plus carboplatin-based concurrent chemoradiotherapy followed by consolidation chemotherapy.
*Nodal status was examined using positron emission tomography/computed tomography (PET-CT); †The maximal tumor diameter was measured three-dimensionally based on T2-weighted images. The longest diameter was used as the maximal tumor diameter; ‡Pretreatment hemoglobin level just before the initiation of radiotherapy.

(SCC) histology, and 6 had tumors that exhibited non-SCC histology. Twenty-three patients had radiologic evidence of pelvic lymph node metastases. Although hydronephrosis was observed in 5 patients, none of these patients had renal dysfunction; i.e., an elevated serum creatinine or blood urea nitrogen level. Most patients had massive tumors (median tumor diameter: 60 mm, range: 40–76). The patients' mean hemoglobin concentration before treatment was 12.1 g/dL (range: 7.2–14.7 g/dL).

2. Treatment outcomes

During the course of the pelvic EBRT, all of the patients received concurrent weekly carboplatin at a dose of AUC=2 and paclitaxel at a dose of 35 mg/m^2/week. The median number of courses of concurrent chemotherapy administered was 5, and 22 out of 30 patients (73.3%) received more than 5 courses of concurrent chemotherapy (**Table 2**). The median duration of radiotherapy was 43 days (range: 41–52). After the completion of the TC-based CCRT, 21 patients (70.0%) received consolidation chemotherapy (median: 3 courses). The remaining 9 patients (30.0%) did not receive consolidation chemotherapy due to the following reasons: refusal in 6 patients and side effect associated with TC-based CCRT in 3 patients. Twenty-four patients (80.0%) achieved a CR, and 6 patients (20.0%) achieved a PR. Five out of 6 patients who achieved PR were subsequently treated with radical hysterectomy.

At the time of this analysis, 9 patients (30.0%) had developed recurrent lesions. Most of the recurrent lesions developed at extra-pelvic sites: local recurrence in 2 patients, local plus distant recurrence in 2 patients, and distant recurrence in 5 patients. Currently, 28 patients are alive (26 are alive without disease and 2 are alive with disease) after a median follow-up period of 35 months (**Fig. 1B, C**). The patients' estimated 3-year PFS and OS rates were 67.9% and 90.8%, respectively.

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Table 2. Treatment outcomes

Variables		No. of patients (%)
Course of TC administered during CCRT	Median (range)	5 (2–7)
	1	0 (0.0)
	2–4	8 (26.7)
	5–6	22 (73.3)
Duration of radiotherapy (day)	Median (range)	43 (41–52)
Course of consolidation TC administered	Median (range)	3 (0–3)
	0	9 (30.0)
	1–2	2 (6.7)
	3	19 (63.3)
Local control	CR	24 (80.0)
	PR	6 (20.0)
	SD	0 (0.0)
	PD	0 (0.0)
Patients with recurrence	Total	9 (30.0)
Site of recurrence	Local*	2
	Local*+Distant†	2
	PALN	2
	Distant†	2
	PALN+Distant†	1
Patients with death		2 (6.7)

CCRT, concurrent chemoradiotherapy; CR, complete response; PALN, para-aortic lymph nodes; PD, progressive disease; PR, partial response; SD, stable disease; TC, paclitaxel plus carboplatin.

*Recurrence in uterus; †Recurrences in distant organs excluding PALN.

3. Toxicities

Overall, the TC-based CCRT was well tolerated. As shown in **Table 3**, the most frequently observed grade 3–4 acute toxicities were hematological toxicities such as leukopenia and neutropenia. None of the patients developed thrombocytopenia. Grade 3–4 acute hematological and non-hematological toxicities were observed in 18 patients (60.0%) and 5 patients (16.7%), respectively. Grade 3–4 late toxicities occurred in 6 patients (20.0%): a vesicovaginal fistula in one patient, rectal bleeding in 3 patients, and hydronephrosis in

Table 3. Grade 3–4 toxicities

Type of toxicity			No. of patients (%)
Acute toxicity	Patients with hematologic toxicities	Total	18 (60.0)
		Leukopenia	6
		Neutropenia	0
		Leukopenia+Neutropenia	10
		Anemia	0
		Thrombocytopenia	1
		Febrile Neutropenia+Thrombocytopenia+Anemia	1
	Patients with non-hematologic toxicities	Total	5 (16.7)
		Nausea/vomiting	0
		Diarrhea	3
		Bowel obstruction	0
		Fatigue	1
		Lymph edema	0
		Infection	1
		Neuropathy	0
Late toxicity	Patients with late toxicities	Total	6 (20.0)
		Rectovaginal fistula	0
		Vesicovaginal fistula	1
		Hematuria	0
		Rectal bleeding	3
		Bowel obstruction	0
		Hydronephrosis	2

2 patients. Both vesicovaginal fistula and hydronephrosis were developed in patients who underwent radical hysterectomy for the persistent disease.

4. Comparisons with historical controls

We identified patients with stage IIIB/IVA cervical cancer who had received CCRT involving a single platinum agent (n=52) or radiotherapy alone (n=74) through a chart review and used them as historical controls (**Supplementary Table 1**). As shown in **Fig. 2**, TC-based CCRT followed by consolidation chemotherapy resulted in significantly improved survival compared with CCRT using single platinum agent (log-rank: PFS, p=0.100; OS, p=0.011) or radiotherapy alone (log-rank: PFS, p=0.009; OS, p<0.001).

DISCUSSION

In the current study, we have found that pelvic TC-based CCRT follow by consolidation chemotherapy was well tolerated and resulted in encouraging locoregional control and survival. The patients' estimated 3-year PFS and OS rates were 67.9% and 90.8%, respectively. Comparisons with historical control groups should always be treated with caution, as patients had not been randomly assigned into each group. However, although pelvic node metastasis, a strong poor prognostic factor, was more frequently observed in patients in TC-CCRT-group than in those in CCRT-group or RT-group (**Supplementary Table 1**), TC-based CCRT followed by consolidation chemotherapy was significantly superior to conventional CCRT involving a single platinum agent or definitive RT alone, which were previously employed at our institution (**Fig. 2**).

Concurrent cisplatin and pelvic radiotherapy has been the standard treatment for cervical cancer. A problem that can arise during the treatment of stage IIIB/IVA disease using cisplatin-based CCRT is hydronephrosis due to ureteral obstruction. It has previously been reported that the presence of hydronephrosis is an important indicator of a poor prognosis [31]. The

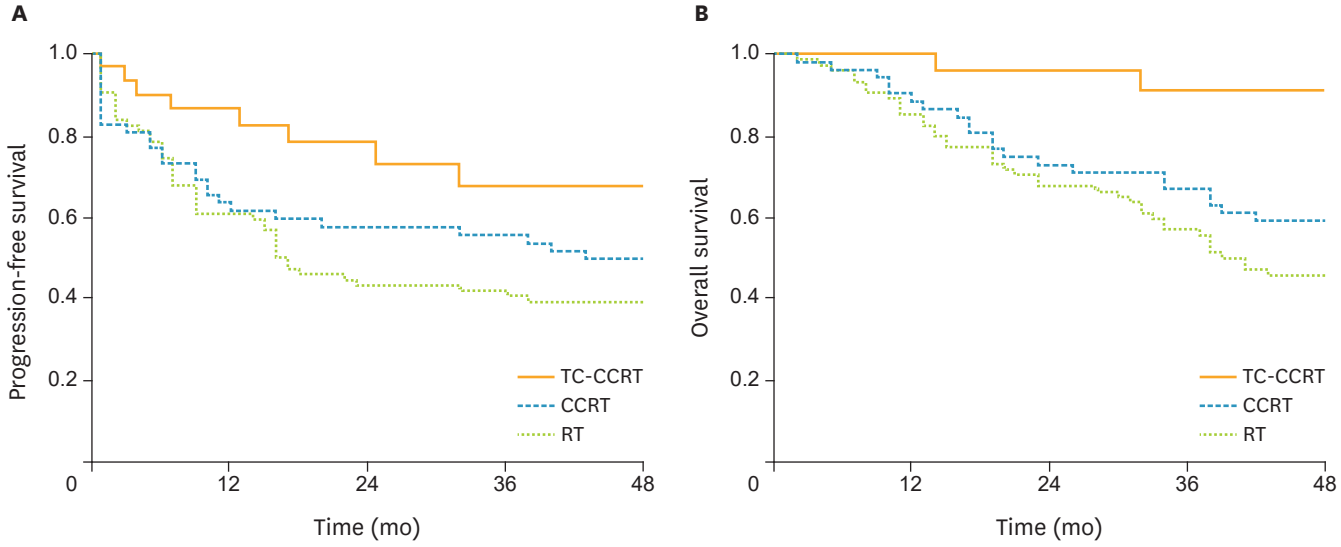

Fig. 2. Survival estimates according to treatment type. (A) Kaplan-Meier estimates of PFS according to treatment type (log-rank: TC-CCRT vs. RT, p=0.009; TC-CCRT vs. CCRT, p=0.100; CCRT vs. RT, p=0.180); (B) Kaplan-Meier estimates of OS according to treatment type (log-rank: TC-CCRT vs. RT, p<0.001; TC-CCRT vs. CCRT, p=0.011; CCRT vs. RT, p=0.066).

CCRT, concurrent chemoradiotherapy; OS, overall survival; PFS, progression-free survival; RT, definitive radiotherapy alone; TC, paclitaxel plus carboplatin.

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precise incidence of ureteral obstruction is unknown, but it is reported to be 7% among all cases of invasive cervical cancer, and 55.8% among patients with stage III–IV disease [31]. Although the weekly administration of cisplatin during radiotherapy has been generally tolerated, its nephrotoxicity might limit its use in stage IIIB/IVA cervical cancer patients, especially those with impaired renal function due to ureteral obstruction. According to a report by Cetina et al. [32] only 67% of cervical cancer patients are able to receive the entire planned dose of weekly cisplatin (40 mg/m^2) during pelvic EBRT, indicating the need for the development of less toxic regimens. A recent phase III trial demonstrated that CCRT involving cisplatin and gemcitabine followed by adjuvant cisplatin and gemcitabine is significantly superior to CCRT involving weekly cisplatin alone with regard to PFS and OS [33]. However, cisplatin/gemcitabine CCRT caused significant toxicities in other studies [34,35].

As shown in **Table 4**, the use of TC as radiosensitizing agents in locally advanced cervical cancer has been evaluated in several clinical trials. De Vos et al. [15] investigated the feasibility of combining weekly paclitaxel (60 mg/m^2) and weekly carboplatin (AUC: 2) with

Table 4. Summary of studies of definitive concurrent chemoradiotherapy using paclitaxel-carboplatin in patients with cervical cancer

Author [ref.]	Year	Phase	Radiotherapy	Eligibility	No. of patients	PTX (mg/m^2)	CBDCA (AUC)	Schedule	Consolidation chemotherapy	Tolerability	Follow-up (median, mo)	Outcome
de Vos et al. [15]	2004	Phase I	Pelvic EBRT+ICBT	IB2-IVA	8	60	2	Weekly	No	Tolerable	26	Recurrence rate was 12.5%
Rao et al. [16]	2005	Phase I	Pelvic EBRT+ICBT	IB2-IVA	15	50	1.5 to 3	Weekly	No	MTD was PTX (50 mg/m^2) +CBDCA (AUC 2.5)	17	Recurrence rate was 20% 2-year DFS was 80% 2-Year OS was 86%
Higgins et al. [18]	2007	Phase II	Pelvic EBRT+ICBT	IB1-IVA	22	40	2	Weekly	No	Tolerable	23	Recurrence rate was 31.8% 3-year PFS was 70% 3-Year OS was 65%
Lee et al. [17]	2007	Retrospective	Pelvic EBRT+ICBT	IB-IVB	33	135	4.5	4 weekly	No	Tolerable	27	Recurrence rate was 15.1% 3-year DFS was 75% 3-Year OS was 86%
Addeo et al. [19]	2008	Phase I	Pelvic EBRT+ICBT	IB2-IVA	9	30	5 and 6	Twice weekly	No	CBDCA (AUC6) was Tolerable	NA	NA
Kim et al. [20]	2012	Phase II	Pelvic EBRT+ICBT	IIB-IVA	18	135	5	3 weekly	Yes	Tolerable	35	Recurrence rate was 44.4% 3-year PFS was 51.9% 3-Year OS was 60%
Current study	2016	Retrospective	Pelvic EBRT+ICBT	IIIB-IVA	25	35	2	Weekly	Yes	Tolerable	35	Recurrence rate was 30.0% 3-year PFS was 67.9% 3-Year OS was 90.8%

AUC, area under the curve; CBDCA, carboplatin; DFS, disease free survival; EBRT, external beam radiation therapy; ICBT, intracavitary brachytherapy; MTD, maximum tolerated dose; NA, not available; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel.

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pelvic radiation as a primary treatment for cervical cancer. However, they found that this regimen was poorly tolerated; grade 3 diarrhea occurred in half of the patients. Rao et al. [16] performed a dose escalation trial of weekly TC and concurrent pelvic radiotherapy and found that the maximum tolerable dose was 50 mg/m^2 for paclitaxel and an AUC of 2.5 for carboplatin. Addeo et al. [19] demonstrated in their phase I study that twice weekly paclitaxel (30 mg/m^2) and carboplatin (AUC: 6) can be tolerated. The doses of concurrent paclitaxel and carboplatin employed in the current study (carboplatin: AUC: 2; paclitaxel: 35 mg/m^2), which were based on the findings of our previous phase I study [23], were lower than those used in the abovementioned studies. Differences in ethnicity or body mass index between the reports might explain this. So far, including ours, two studies have evaluated the efficacy of TC-based CCRT followed by consolidation chemotherapy. Kim et al. [20] employed a 3 weekly schedule in stage IIB–IVA patients and reported 3-year PFS and OS rates of 51.9% and 60.0%, respectively. In contrast, although we included cases of more advanced disease (stage IIIB/IVA), we achieved better oncological outcomes; i.e., 3-year PFS and OS rates of 67.9% and 90.8%, respectively. This survival difference between the two studies might indicate that the weekly administration of TC concurrently with pelvic radiotherapy is better than the use of a 3-weekly schedule in this patient population.

One concern regarding the use of more intensive CCRT involving platinum-based doublet chemotherapy is that it may cause excessive toxicity. In the current study, 22 patients (73.3%) were able to receive 5–6 courses of concurrent TC during pelvic EBRT without any treatment modification. Neutropenia was the most frequently observed grade 3/4 hematological toxicity. Although diarrhea was found to be a dose-limiting toxicity in previous phase I studies of TC-based CCRT [15,19], none of the patients in the current study developed grade 4 diarrhea, indicating the safety of this treatment regimen.

The limitations of our study need to be addressed. First, although 25 out of 30 patients were treated in the context of our institutional phase II study and the clinical data of these patients were collected prospectively, this study is the retrospective analysis. Thus, potential biases cannot be excluded: a selection bias might have been introduced by the physicians when they chose the salvage treatments. In addition, the accuracy of diagnosis of stage IIIB/IVA disease might have been influenced by the training background of physicians. Second, this study involves a relatively small sample size and a relatively short follow-up period. Third, as the survival comparison with historical controls in the current study cover a long study period, changes in the choice of treatments for recurrent disease, the pretreatment work-up and diagnostic procedures, and improvements in radiotherapy procedures might have affected the patients' survival. Lastly, although the current study has shown that TC-based CCRT followed by consolidation chemotherapy displays promising activity, it remains uncertain to what extent the observed survival benefit is attributable to the chemoradiotherapy phase or the consolidation chemotherapy phase. Thus, larger prospective studies, especially in the randomized setting, are necessary.

In summary, pelvic TC-based CCRT followed by consolidation chemotherapy is effective and exhibits an acceptable toxicity profile in FIGO stage IIIB/IVA cervical cancer patients; i.e., it resulted in estimated 3-year PFS and OS rates of 67.9% and 90.8% after a median follow-up period of 35 months, respectively. This multimodal treatment might represent a new treatment strategy for FIGO stage IIIB/IVA cervical cancer. A randomized controlled study needs to be conducted to further verify the efficacy of this approach in patients with stage IIIB/IVA cervical cancer.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1
Patient characteristics

Click here to view

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