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Concurrent external beam pelvic radiotherapy and weekly paclitaxel/carboplatin therapy followed by hysterectomy improves prognosis and survival of patients with non-squamous cell carcinoma of the cervix

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Summary

Purpose of investigation: The authors determined whether concurrent chemoradiotherapy (CCRT) followed by hysterectomy improves progression-free survival (PFS) and overall survival (OS) in patients with squamous cell carcinoma (SCC) and non–SCC of the cervix. *Materials and Methods:* The authors retrospectively reviewed records of 110 cervical cancer patients (FIGO Stages IB2-IVB) who underwent CCRT with paclitaxel/carboplatin. Extrafascial hysterectomy was performed for local control; primary outcomes included PFS and OS. *Results:* The sample comprising 80% SCC, 15.5% adenocarcinoma, and 4.5% other types of carcinoma patients was followed for 45.0 ± 21.0 months. The three-year PFS and OS rates were 68% *vs*. 65% ($p = 0.76$), and 88% *vs*. 72% ($p = 0.26$) for all patients with and without hysterectomy, respectively. The three-year PFS and OS rates were 64% *vs*. 38% ($p = 0.32$), and 85% *vs*. 38% ($p = 0.025$) for non-SCC patients with and without hysterectomy, respectively. *Conclusions:* Hysterectomy after CCRT with paclitaxel/carboplatin improves prognosis in patients with non-SCC of the cervix.

Key words: Cervical neoplasms; Concurrent chemoradiotherapy; Paclitaxel; Carboplatin; Survival; Hysterectomy; Surgery.

Introduction

Cervical cancer is one of the most common causes of cancer-related deaths in women. Currently, primary treatment includes radical surgery and radiotherapy. However, recent studies have shown that the curative effect of concurrent chemoradiotherapy (CCRT) is equivalent to that of radical surgery for early-stage cervical cancer and is higher than that of radiation only [1-5].

For advanced cervical cancer, CCRT only was effective. Some studies report the effectiveness of CCRT followed by hysterectomy [6-11], but not others [12, 13]. Other studies have reported that hysterectomy after CCRT was feasible [7, 9, 10, 14, 15]. In previous studies, in almost all cases, radical hysterectomy was the most commonly performed surgery [6-10].

The present authors were uncertain whether they should perform radical hysterectomy because only one study reported on residual parametrium invasion existence [11]. Simple hysterectomy might be satisfactory. In addition, they doubted that they should perform surgery for all patients with cervical cancer after CCRT. After CCRT, central recurrence was higher in non- squamous cell carcinoma (SCC) patients [16, 17]. Therefore, they speculated that an additional surgery may be necessary for non-SCC patients, but not for SCC patients.

In the past, the present authors have reported that the treatment of cervical cancer with CCRT, including paclitaxel and carboplatin, was satisfactory, with similar responses, in terms of progression-free survival (PFS) and overall survival (OS) rates, to those of previous studies [18], not only in patients with Stages IB2-IIB, but also in those with Stages III-IVB cancer. Therefore, the present retrospective study aimed at evaluating the effectiveness of hysterectomy following CCRT with paclitaxel and carboplatin in a large sample of Japanese patients with cervical cancer.

Materials and Methods

With the approval of the Jichi Medical University Institutional Review Board, the authors retrospectively reviewed the medical records of patients who received CCRT with paclitaxel and carboplatin between September 2006 and November 2013, in the Department of Gynecology at the Saitama Medical Center Jichi Medical University. The need for informed consent was waived because data were only obtained via retrospective review of records.

Indications for CCRT included patients with International Federation of Gynecology and Obstetrics (FIGO) Stages IB2-IVB cervical cancer with histopathology of SCC, adenocarcinoma, or

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Table 1. — *Patient characteristics and stages.*

Stage of patients			Patients with operation		Patient without operations	
Stage	Number		Stage	Number	Stage	Number
IB2	29(7)(2)	Others: 1 endometrioid adenocarcinoma, 1 glassy cell carcinoma	IB2	19(6)(2)	IB2	10(1)(0)
IIA1	1(0)(0)		IIA1	1(0)(0)	IIA1	0(0)(0)
IIA2	11(1)(1)	Others: 1 glassy cell carcinoma	IIA2	4(1)(1)	IIA2	7(0)(0)
IIb	38(4)(0)		IIb	14(2)(0)	IIb	24(2)(0)
IIIa	5(2)(0)		IIIa	0(0)(0)	IIIa	5(2)(0)
IIIb	11(0)(2)	Others: 1 carcinosarcoma, 1 small cell carcinoma	IIIb	3(0)(1)	IIIb	8(0)(1)
IVa	5(0)(0)		IVa	1(0(0)	IVa	4(0)(0)
IVb	10(3)(0)		IVb	2(1)(0)	IVb	8(2)(0)
Total	110 (adenocarcinoma)(others)					

Total patients			Patients with operation	Patients without operation	*p*
Age (years)	54.5 ± 11.5		51.1 ± 11.3	56.7 ± 11.2	0.012*
Tumor size (mm)	56.0 ± 16.0		52.2.0 ± 10.9	58.6 ± 18.3	0.025*
Lymph node swelling	Pelvis				
	- positive	35 (31.8%)	16	19	0.4
	- negative	75 (68.2%)	28	47	
	PAN				0.36
	- positive	12 (10.9%)	3	9	
	- negative	98 (89.1%)	41	57	
Intracavitary high dose-rate brachytherapy	Done	45 (40.9%)	2	43	0
	Not done	65 (59.1%)	42	23	
Total radiation dose	56.8 ± 7.1		57.8 ± 5.8	56.2 ± 7.9	0.26
Performed chemotherapy cycle	8.3 ± 1.7		8.5 ± 1.2	8.2 ± 1.9	0.46
PS ≥ 2			1	12	0.014*

*$p < 0.05$

others. Exclusion criteria included previous, partial treatment at another institution or a history of another malignant disease.

The following data were collected: age, histopathology, Stage, Eastern Cooperative Oncology Group performance status (PS), tumor size, number of chemotherapy cycles, toxicities, operating time, and bleeding, which was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) guideline (version 1.1). PFS and OS were determined as the primary outcomes. PFS was defined as the interval from the date of diagnosis to the time of recurrence, disease progression, or death. PFS data were right-censored at the time of the last evaluation for patients lost to follow-up. OS was defined as the time from diagnosis to the date of death and right-censored at the date of the last follow-up visit for patients who were alive at the end of the study.

Clinical staging was evaluated using pelvic and bimanual rectal examinations. Tumor diameter was calculated using magnetic resonance imaging (MRI). Metastatic survey was conducted by physical examination, chest radiography, cystoscopy, proctoscopy, and computed tomography (CT).

All patients received concurrent weekly paclitaxel, carboplatin, and radiation therapy as primary treatment in the present institution. Radiation treatment was administered by external beam pelvic radiotherapy using the four-field box technique (anteroposterior, posteroanterior, and two lateral fields) within one week, approximately, following chemotherapy, when possible. The schedule for radiation is typically fully booked; therefore, the number of chemotherapy cycles prior to radiation was not restricted to avoid delayed treatment for the cancer patients. A total dose of 45–60 Gy was administered in daily fractions of 1.8–2.0 Gy, five days per week. At 20–30 Gy, a center split was performed. If patients were administered high dose-rate brachytherapy, two to four fractions of intracavitary high dose-rate brachytherapy were administered in weekly fractions of five to six Gy each to point A, based on the external os of the uterus, overlap with the external beam, and tumor volume. The total brachytherapy dose was 12–24 Gy [18].

The paclitaxel and carboplatin doses were administered at the treating physician's discretion. Paclitaxel was administered at a weekly dose of 60–70 mg/m^2, with 70 mg/m^2 likely administered to patients with good PS and general condition. Carboplatin was administered based on the area under the curve (2) [18]. Chemotherapy was administered six to nine times during or after irradiation; before each cycle, ≥ 1,000 neutrophils and ≥ 100,000 blood platelets were obtained using growth factors in patients with neutropenia or leukopenia, respectively, at the treating physician's discretion. Patients with hemoglobin levels < 10 g/dl received a red blood cell transfusion before further treatment.

Additional surgery was performed eight to 12 weeks after the completion of chemoradiation therapy. Patients were informed that the effectiveness of surgery in improving chances of OS was not known; however, the authors performed extrafascial hysterectomy (Piver I: simple hysterectomy) for local control. If patients opted for hysterectomy, the surgery was performed. Pelvic lymphadenectomy and a para-aortic lymphadenectomy were not carried out. Prior to surgery, patients were re-evaluated by clinical examination, and systematic post-chemoradiation imaging was performed using CT and MRI. The resection was classified based on per-operative and pathological data i.e., whether residual cancer was present or absent. If there was evidence of the involvement of cervical margins or peri-cervical structures, unresectable positive lymph nodes (pelvic or para-aortic), peritoneal carcinomatosis, or distant metastasis discovered at surgery, surgery was not performed.

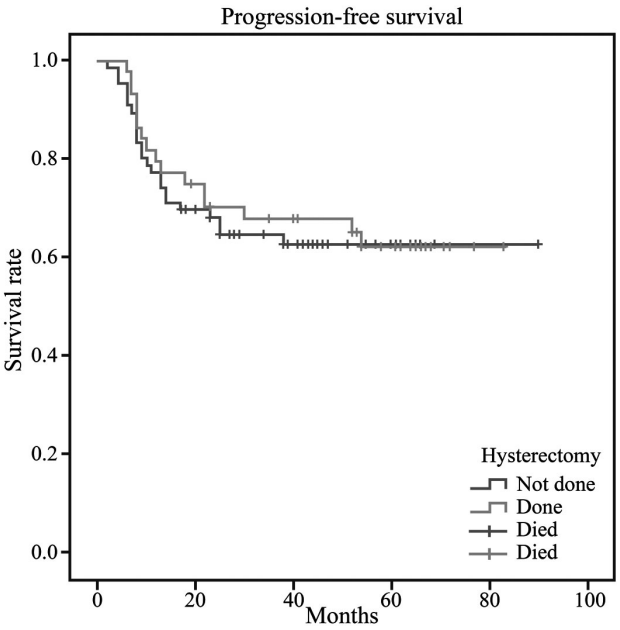

Figure 1. — Kaplan-Meier estimates of progression-free survival in patients with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin with or without hysterectomy.

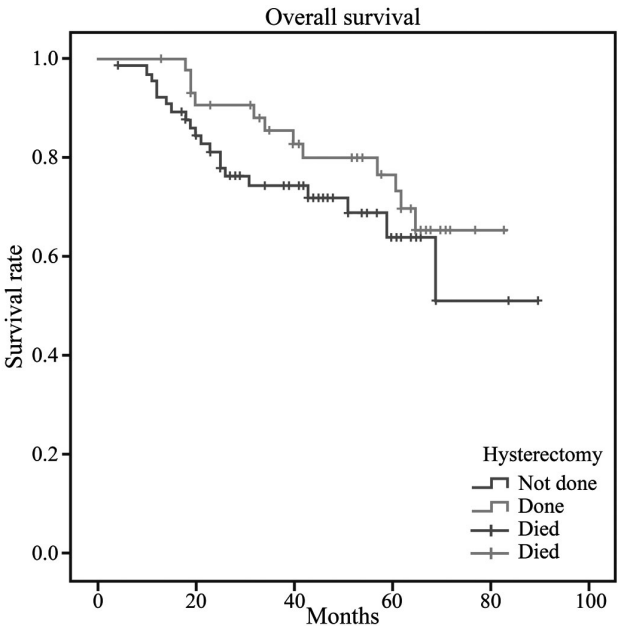

Figure 2. — Kaplan-Meier estimates of overall survival in patients with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin with or without hysterectomy.

After the completion of the radiation and chemotherapy following the operation, patients were examined by cytology, human papillomavirus (HPV) testing using Hybrid Capture 2, CT, and MRI. In cases with a lack of complete response, cytology positive result, or positive HPV test result following the six to nine chemotherapy cycles, additional chemotherapy was administered.

Toxicity was determined at follow-up evaluations. Post-treatment surveillance was done by complete physical examination every month during the first year, every two months in the second year, every three months in the third year, and every six months thereafter. CT imaging was performed every six to 12 months. Acute hematologic and non-hematologic toxicities were recorded based on the Common Toxicity Criteria (CTC) Version 4.0. Acute and late gastrointestinal and genitourinary tract toxicities were recorded using the RTOG/EORTC Late Radiation Morbidity Scoring Criteria.

The present authors used JMP, version 10.0.0 for statistical analyses. Demographic variables are reported as mean ± standard deviation. PFS and OS were analyzed by the Kaplan-Meier method and compared with respect to age, histopathology, stage, PS, and tumor size using log-rank tests. The Cox proportional hazards model was used to adjust for all prognostic factors in multivariable analysis, including survival, stage, tumor histology, PS, and tumor size. For all statistical tests, a p value < 0.05 was considered significant.

Results

During the study period, 110 patients underwent radiation, and 44 patients underwent simple hysterectomy. Mean follow-up duration was 45.0 ± 21.0 months. Basic patient characteristics and prevalence of all stages of cancer are shown in Table 1. All but seven patients completed their chemotherapy; two patients had grade 4 fatigue, two patients had grade 4 diarrhea, one patient wanted to stop chemotherapy, one patient experienced an outbreak of Guillain-Barré syndrome, and one patient experienced a cerebral infraction. The same patient who experienced a cerebral infraction did not complete the radiation therapy.

Table 2. — *Results of operations.*

Time (minutes)	81.8 ± 26.3
Bleeding (grams)	158.9 ± 139.1
Intra/postoperative complication	6 patients
Infection to stump (grade 3)	5
Stump disruption (grade 2)	2
Colon vaginal fistula (grade 2)	1
Residual cancer	17
Lymphatic invasion of residual cancer	5
Parametrial invasion of residual cancer	1

For all patients, the Kaplan-Meier estimates for PFS and OS with or without operation are shown in Figures 1 and 2, respectively; the three-year PFS and OS rates of patients with and without operation were 68% and 88%, and 65% and 72% (p = 0.76, and 0.26), respectively. Results of the operation are shown in Table 2.

In the univariate analysis, stage, PS, tumor size, and age

Table 3. — *Survival of patients according to various prognostic factors in univariate analysis.*

	PFS	*p*	OS	*p*
Stage		0.001*		0.022*
IB2-IIB	0.74		0.83	
IIIA-IVA	0.56		81	OS median:69
IVB	0.33	PFS median:11	48	OS median:32
Tumor histology		0.28		0.47
SCC	0.69		0.82	
Adenocarcinoma	0.53	PFS median:54	0.65	
Others	0.6		0.6	
PS		0		0.003*
1	0.72		0.81	
2	0.5	PFS median:17	0.67	OS median:59
3	0	PFS median:10	0.43	OS median:26
Tumor size		0.007*		0.02*
≤ 6 cm	0.75		0.83	
> 6 cm	0.47	PFS median:25	0.7	OS median:62
Age		0.21		0.011*
≤ 60	0.7		0.84	
> 60	0.59		0.66	OS median:61
Intracavitary therapy		0.045*		
Done	0.77		0.81	0.394
Not done	0.58		0.77	
Operation		0.76		0.301
Done	0.68		0.84	
Not done	0.65		0.72	
PAN swelling		0.5		0.493
Yes	0.58		0.79	OS median:62
No	0.67		0.78	
PLN swelling		0.016*		0.12
Yes	0.54	PFS median:52	0.66	
No	0.72		0.8	

*$p < 0.05$

Table 4. — *Survival of patients according to various prognostic factors in multivariate analysis.*

Prognostic factors	Hazard ratio	95% confidence interval	*p*
Stage			
IB2-IIB	1		
IIIA-IVA	1	0.3−3.0	0.91
IVB	1.01	0.3−3.7	0.98
PS			
1	1		
2	2.1	0.6−7.2	0.263
3	3.5	0.8−14.5	0.087
Tumor size			
≤ 6cm	1		
> 6cm	2.1	0.8−5.5	0.136
Age			
≤ 60	1		
> 60	2.6	1.2−5.7	0.014*

*$p < 0.05$

Table 5. — *Survival of patients regarding non-SCC according to various prognostic factors in univariate analysis.*

	PFS	*p*	OS	*p*
Stage		0		0.152
IB2-IIB	0.67		0.79	
IIIA-IVA	0.5	PFS median:13	0.5	OS median:25
IVB	0.33	PFS median:6	0.33	OS median:20
PS				0
1	0.57		0.7	
2 (n=0)				
3	0		0	OS median:10
Tumor size		0.079		0.25
≤ 6 cm	0.67		0.73	
> 6 cm	0.29	PFS median:8	0.53	
Age		0.744		0.57
≤ 60	0.53	PFS median:54	0.72	
> 60	0.57		0.57	
Intracavitary therapy		0.56		0.91
Done	0.6		0.69	
Not done	0.53	PFS median:54	0.6	
Operation		0.32		0.025*
Done	0.64		0.84	
Not done	0.375	PFS median:13	0.38	OS median:23
PAN swelling		0.36		0.49
Yes	1		1	
No	0.53	PFS median:54	0.62	
PLN swelling		0.36		0.72
Yes	0.5	PFS median:34	0.63	
No	0.57		0.7	

*$p < 0.05$

were significant factors (Table 3). Age was a significant factor in the multivariable analysis (hazard ratio, 2.6; $p = 0.01$, hazard ratio) (Table 4).

In non-SCC patients, in the univariate analysis, operation was only significant for OS (Table 5). OS of patients who did and did not undergo surgery was 84% and 38%, respectively ($p = 0.025$) (Figures 3 and 4). None of the patients with PS ≥ 2 survived. Multivariable analysis could not be conducted because there was only one patient with PS = 3 and she did not undergo surgery. Three of the eight patients who underwent surgery and had residual carcinoma at the time of operation died of the disease. On the contrary, all those patients who did not have residual carcinoma survived (six patients) ($p = 0.11$). All patients with residual disease who had lymphatic invasion died (two patients); however, one of the six patients with no lymphatic invasion died of the disease ($p = 0.0039$).

Regarding those with adenocarcinoma only, in the univariate analysis, PS and operation were significant factors (Table 6). OS of patients who did and did not undergo surgery was 100% and 29%, respectively ($p = 0.002$). Multivariable analysis could not be performed because there was only one patient with PS = 3 and she did not undergo the surgery. All those who underwent the surgery were alive 36 months postoperatively.

Acute toxicity grade 3 or 4 neutropenia, anemia, and diarrhea were detected in 59.1%, 4.5%, and 37.3% of the patients, respectively (Table 7). Late toxicity grade 3 or 4

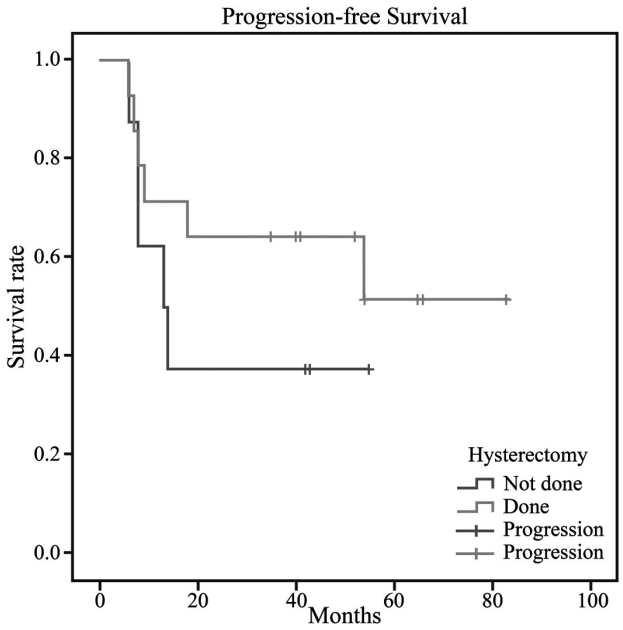

Figure 3. — Kaplan-Meier estimates of progression-free survival in patients of non-SCC with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin with or without hysterectomy.

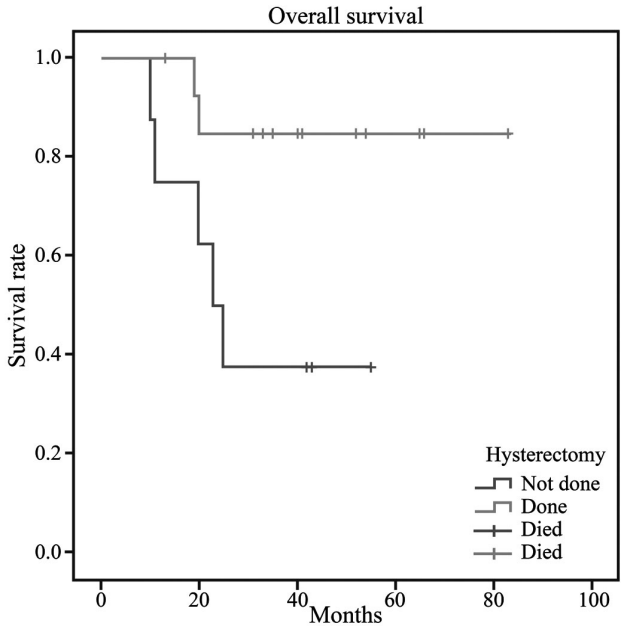

Figure 4. — Kaplan-Meier estimates of overall survival in patients of non-SCC with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin with or without hysterectomy.

Table 6. — *Survival of patients about adenocarcinoma according to various prognostic factors in univariate analysis.*

	PFS	*p*	OS	*p*
Stage		0.001*		0.125
IB2-IIB	0.67		0.83	
IIIA-IVA	0.5	PFS median:13	0.5	OS median:25
IVB	0	PFS median:6	0.33	OS median:20
PS		0.006*		< 0.0001*
1	0.56		0.74	
2	n=0			
3	0	PFS median:6	0	OS median:10
Tumor size		0.008*		0.074
≤ 6cm	0.73		0.82	
> 6 cm	0.17	PFS median:8	0.44	OS median:23
Age		0.87		0.24
≤ 60	0.55		0.81	
> 60	0.5	PFS median:14	0.5	OS median:25
Intracavitary therapy	0.95			0.5
Done	0.5	PFS median:14	0.5	OS median:25
Not done	0.54		0.76	
Operation		0.091		
Done	0.7		1	0.002*
Not done	0.29	PFS median:13	0.29	OS median:22
PAN swelling		0.49		0.77
Yes	0.33	PFS median:18	0.7	
No	0.57		0.67	
PLN swelling		0.41		0.65
Yes	0.4	PFS median:52	0.6	
No	0.58		0.73	

*$p < 0.05$

urogenital disorder and gastrointestinal disorder were detected in 0.9% and 1.8% of the patients, respectively. Vaginal fistula occurred in four patients, and perforation of the sigmoid colon in one patient; four of these five patients had PS = 3. One patient developed septic shock, but she was treated with antibiotics and recovered.

Discussion

In the present study, treatment of cervical cancer with CCRT, including paclitaxel and carboplatin following simple hysterectomy was tolerable. Overall, hysterectomy had no significant impact on the outcomes of patients with Stages IB2 to IVB cervical cancer. However, simple hysterectomy significantly improved prognosis in non-SCC cervical cancer patients.

Past reports about CCRT following hysterectomy have given inconsistent results [6-13]. The present authors speculate that the reason for this was that in those studies, the study population mainly comprised SCC patients and only few non-SCC patients. Treatment of Stages III adenocarcinoma with operation was superior to that with CCRT. After CCRT, central recurrence was higher in non-SCC patients [16, 17]; therefore, in the present study, CCRT following hysterectomy improved prognosis and OS in non-SCC.

CCRT followed by simple hysterectomy was feasible. Intra/postoperative complications occurred in 13.6% (6/44) patients. This percentage was relatively lower than those in

Table 7. — *Incidence and types of acute complications.*

Grade	0	1	2	3	4
Hematologic					
Neutropenia	7.3 (8/110)	4.5 (5/110)	29.1 (32/110)	51.8 (57/110)	7.3 (8/110)
Anemia	7.3 (8/110)	55.5 (61/110)	32.7 (36/110)	2.7 (3/110)	1.8 (2/110)
Thrombocytopenia	70.9 (78/110)	16.4 (18/110)	8.2 (9/110)	0.9 (1/110)	3.6 (4/110)
Non-hematologic					
Vomiting	71.8 (79/110)	15.5 (17/110)	10.9 (12/110)	0.9 (1/110)	0.9 (1/110)
Diarrhea	2.7 (3/110)	37.3 (41/110)	22.7 (25/110)	28.2 (31/110)	9.1 (10/110)

Incidence and types of late complications.

Grade	0	1	2	3	4
Urogenital disorder	70.0 (77/110)	4.5 (5/110)	24.6 (27/110)	0.9 (1/110)	0
Gastrointestinal disorder	74.5 (82/110)	5.5 (6/110)	18.2 (20/110)	0.9 (1/110)	0.9 (1/110)
Lymphedema	97.3 (107/110)	0	2.7 (3/110)	0	0
Neuropathy	80.0 (88/110)	13.6 (15/110)	4.6 (5/110)	1.8 (2/110)	0

Table 8. — *Intra/postoperative complication rate.*

Reference no.	%
9	20.3−32.0
10	16.7
14	12.6
15	11.2

previous reports (Table 8) [9, 10, 14, 15]. As mentioned, this treatment was accompanied by a high prevalence of adverse events, including hematologic toxicity and diarrhea; therefore, aggressiveness of CCRT might be high. However, rate of intra/post-operative complication was low. This might be a benefit of simple hysterectomy. Considering the improved prognosis in non-SCC patients, radical surgery might not be needed after CCRT with paclitaxel and carboplatin. In the present study, patients with lymphatic invasion who underwent hysterectomy had poorer prognosis than those without lymphatic invasion. This could not be resolved with radical surgery. If we perform parametrial invasion with radical surgery, it might not improve OS because the patient may have lymphatic invasion that cannot be treated with hysterectomy. Therefore, this factor cannot be resolved by surgery. It needs to be resolved with chemotherapy. The present authors thought that they did not require radical surgery after CCRT.

Paclitaxel and carboplatin might be useful for CCRT in non-SCC patients. As the present authors have reported in the past, this regimen was feasible and satisfactory for PFS and OS [18]. Moreover, paclitaxel had high response rate for adenocarcinoma [19]. Combination of paclitaxel and carboplatin resulted in a higher response rate [20]. This effect of chemotherapy might be useful in CCRT for non-SCC. It might be helpful as neoadjuvant therapy in the surgical group for this study.

PS and chemotherapy have been reported as independent prognostic factors for survival [21], and in the present study, PS was found to be a prognostic factor for survival. With a good PS, CCRT can be considered. In addition, in non-SCC patients, CCRT followed by hysterectomy can be considered. The combination of taxane and platinum may extend PFS without affecting the quality of life [22]. Furthermore, the therapeutic effects of weekly paclitaxel and carboplatin are similar to those of cisplatin [23, 24]. Stage IVB cancer tended to be related to poor survival outcomes in the present study; however, Stage IIIA-IVA patients may benefit from this CCRT regimen. The present authors speculate that patients with Stage IVB cancer may also benefit. Six of the 11 patients with Stage IVB cancer survived in this study. Among these, three had adenocarcinoma and one patient who underwent hysterectomy survived. The cancer in Stage IVB invades not only locally, but also spreads principally through the lymphatic system; therefore, chemotherapy may be important in these patients [25], and the present regimen may be useful for treating Stage IVB cervical cancer [21].

Adverse events included bone marrow suppression, with particularly high rates of neutropenia in the present study. The data are retrospective and from cases in clinical practice instead of those in a phase I study; therefore, the doses chosen by the physicians might not reflect the optimal doses; it is possible that the doses were too high, resulting in toxicity. The outcomes of a phase I trial were published after these patients were treated. In addition, 33.67% (37/110) of the patients were older than 60 years, and 11.8% (13/110) of the patients had a PS of 2 or 3, so the condition of the patients was particularly poor.

This study has certain limitations. First, because the present study was retrospective in nature, randomized controlled trials should be conducted to reduce potential selection bias in determining PFS and OS. Strict and ap-

propriate protocols should be followed to evaluate adverse effects. The results cannot be generalized to patients with more advanced cancers because of the small number of patients with Stage IVB cancer. Further studies should be conducted to collect more data on these patients.

The present results indicate that treatment of cervical cancer with CCRT, including paclitaxel and carboplatin followed by simple hysterectomy, was tolerable. Hysterectomy had no significant impact on the outcomes of patients with Stages IB2 to IVB SCC cervical cancer. However, simple hysterectomy significantly improved prognosis in non-SCC cervical cancer. Future prospective studies should be conducted to compare the efficacy of CCRT followed by simple hysterectomy for the treatment of non-SCC cervical cancer.

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