EJGO European Journal of Gynaecological Oncology

Outcomes of concurrent radiotherapy and weekly paclitaxel/carboplatin therapy in cervical cancer: a retrospective study

K. Chikazawa, S. Netsu, R. Konno

Department of Obstetrics and Gynecology, Jichi Medical University, Saitama (Japan)

Summary

Purpose of investigation: To determine if concurrent chemoradiotherapy (CCRT) with paclitaxel and carboplatin is effective, convenient, and tolerable for cervical cancer treatment. *Materials and Methods:* The authors retrospectively reviewed the medical records of 49 patients. Primary outcomes included progression-free survival (PFS) and overall survival (OS). The Cox proportional hazards model was adjusted for all prognostic factors in the multivariable analysis. *Results:* Over the median follow-up time of 32 months in a sample consisting of 87.8% (43/49) squamous cell carcinoma and 12.2% (6/49) adenocarcinoma, two-year PFS and OS rates were 67.2% and 80.9%, respectively. In univariate analyses, stage, histology, performance status, tumor size, and age were significant variables for OS; only histology was significant in the multivariable analysis. Acute toxicity grade 3 or 4 neutropenia (85.7%), diarrhea (32.7%), and late toxicity grade 3 or 4 (12.2%) were detected. *Conclusions:* For cervical cancer treatment, CCRT with paclitaxel/carboplatin is satisfactory.

Key words: Uterine cervical neoplasms; Chemoradiotherapy; Paclitaxel; Carboplatin; Survival.

Introduction

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

Although the primary drug choice is cisplatin, paclitaxel or carboplatin alone has been shown to be efficacious for CCRT [6-8]. Carboplatin induces the same platinum-DNA adduct formation as cisplatin, is easy to use, and does not require hydration [9]; furthermore, it results in lower nephrotoxicity and emetogenicity than cisplatin. The combination of paclitaxel and cisplatin chemoradiation reportedly results in only mild toxicity and a good response rate in patients with locally advanced cervical cancer [10, 11]. The combination of paclitaxel and carboplatin is also effective as chemotherapy [12, 13], with a good survival rate [14]; as a result, this combination is used as chemotherapy for advanced or recurrent cervical cancer in Japan. In CCRT, these drugs act together as a radiosensitizer as well as effective chemotherapy.

The use of CCRT in other cancers has resulted in shorter treatment durations and improved efficacy in terms of progression-free survival (PFS), overall survival (OS), toxicity, and complications [15-19]. The present institute utilizes CCRT with paclitaxel and carboplatin because hydration and hospitalization are not required, and there are a limited number of hospital beds in this hospital [20]. However, the ideal approach for multimodal therapy that includes chemotherapy and external beam therapy for the treatment of cervical cancer has not yet been established. It is unknown if there is increased efficacy against cancer with the use of two antineoplastic drugs or with the administration of CCRT. Therefore, the present retrospective study aimed at evaluating 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 June 2012 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) Stage IB2-IVB cervical cancer with histopathology of squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous carcinoma. Exclusion criteria included previous, partial treatment at another institution or history of another malignant disease.

Revised manuscript accepted for publication May 4, 2015

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVII, n. 4, 2016
doi: 10.12892/ejgo3101.2016

7847050 Canada Inc.
www.irog.net

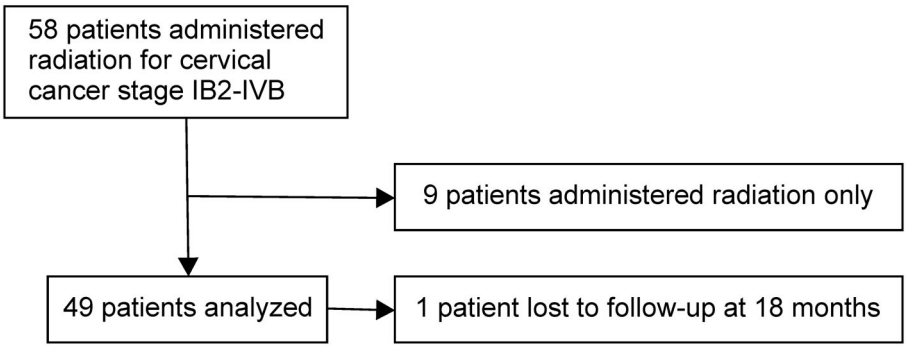

Figure 1. — Flowchart of enrollment of patients with Stage IB2-IVB cervical cancer.

The following data were collected: age, histopathology, stage, Eastern Cooperative Oncology Group performance status (PS), tumor size, number of chemotherapy cycles, toxicities, and tumor response, 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 first 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 receive 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. Because the schedule for radiation is typically fully booked, 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.

The paclitaxel and carboplatin doses were 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, which is the primary method in the present institute for chemotherapy for cervical cancer [20, 21]. Chemotherapy was administered six to nine times during irradiation or after irradiation; before each cycle, $\geq$ 1,000 neutrophils and $\geq$ 100,000 blood platelets were obtained using growth factors in cases 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.

Following completion of the radiation and chemotherapy, 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 none chemotherapy cycles, additional chemotherapy was administered.

Response to treatment, using the RECIST guideline (version 1.1), and toxicity were determined at follow-up evaluations. Post-treatment surveillance was by complete physical examination every month during the first year, every two months for another year (year 2), every three months for another year (year 3), and every six months thereafter. Imaging was obtained by CT 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 between age, histopathology, stage, PS, and tumor size using log-rank tests because of the short study period. 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, 58 patients underwent radiation. Nine patients were excluded because they received only radiation, resulting in a sample size of 49 patients (Figure 1) with a mean age of 57.2 ± 10.5 years (Table 1). One patient was lost to follow-up at 18 months. The basic patient characteristics and prevalence of all stages are shown in Table 1.

There were only eight patients with Stage IVB cervical cancer (Table 1). All but four patients completed their chemotherapy; two patients had grade 4 fatigue, one patient experienced an outbreak of Guillain-Barré syndrome, and one patient experienced a cerebral infraction. An additional patient who experienced a cerebral infraction did not complete the radiation therapy. The total radiation dose was 57.0 ± 8.6 Gy; this included the one patient that did not complete the radiation therapy.

The follow-up lasted a median 32 months (range, four to 75 months). The Kaplan-Meier estimates for PFS and OS

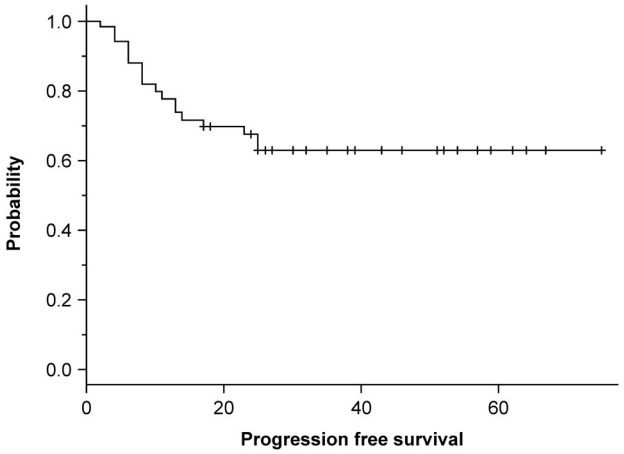

Figure 2. — Kaplan-Meier estimates of progression-free survival in patients with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin.

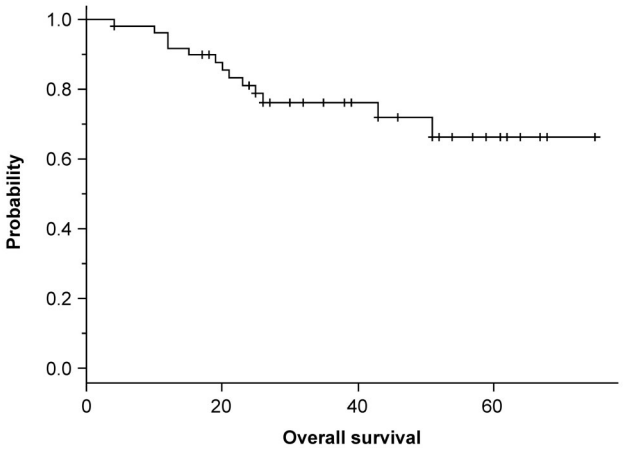

Figure 3. — Kaplan-Meier estimates of overall survival in patients with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin.

Table 1. — *Demographic and clinical characteristics of patients with Stage IB2-IVB cervical cancer.*

	Total sample (n = 49)
Age (years) (mean ± SD)	57.2 ± 10.5
Tumor size (cm) (mean ± SD)	60.0 ± 19.2 (range, 22–125)
Stage, n (adenocarcinoma)	49 (6)
IB2	8 (1)
IIA1	0
IIA2	4 (0)
IIB	14 (1)
IIIA	5 (2)
IIIB	7 (0)
IVA	3 (0)
IVB	8 (2)
Lymph node, n	
Positive	17
Negative	32
RALS, n	
Yes	28
No	21

RALS: remote afterloading system.

Table 2. — *Response rate to concurrent chemoradiotherapy with paclitaxel and carboplatin in patients with Stage IB2-IVB cervical cancer.*

Stage	n	CR+PR	CR	PR	SD	PD
IB2-IIB	24	100	22 (91.7)	2 (8.3)	0	0
IB2-IIB adenocarcinoma	2	100	1 (50)	1 (50)	0	0
IIIA-IVA SCC	13	92.3	9 (69.2)	3 (23.1)	0	1 (7.7)
IIIA-IVA adenocarcinoma	2	100	1 (50)	1 (50)	0	0
IVB SCC	6	83.3	3 (50)	1 (16.7)	0	2 (33.3)
IVB adenocarcinoma	2	100	1 (50)	0	0	1 (50)
Total	49	91.8	37 (75.5)	8 (16.3)	0	4 (8.2)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; SCC: squamous cell carcinoma.

are shown in Figures 2 and 3, respectively; the two-year PFS and OS rates were 67.2% and 80.9%. The estimated median PFS and OS rates were 55.1 months and 92.1 months, respectively. Of the patients with a complete or partial response (Table 2), 31.1% (14/45) of the patients experienced recurrence (n = 3, local; n = 9, distant; and n = 2, both local and distant). The distant metastases sites included para-aortic lymph nodes (35.7%, 5/14), lungs (28.6%, 4/14), and the liver (14.3%, 2/14).

In the univariable analysis, histology, PS, tumor size, and age were significant (Table 3); however, only histology was significant in the multivariable analysis (hazard ratio, 6.69; $p = 0.0271$) (Table 4). The PFS was 72% for SCC and 33% for adenocarcinoma.

Acute toxicity grade 3 or 4 neutropenia, anemia, and diarrhea were detected in 85.7%, 8.2%, and 32.7% of the patients, respectively (Table 5). Late toxicity grade 3 or 4 was detected in 12.2% of the patients. Vaginal fistula occurred in three patients, and perforation of the sigmoid colon occurred in one patient; all of these patients had a PS of 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, was satisfactory, with similar response, PFS, and OS rates to those of previous studies (Table 6) [2, 4, 22], even in patients with

Table 3. — *Relationships between prognostic factors and cervical cancer patient survival in univariable analyses.*

	PFS	*p*	OS	*p*
Stage		0.0096		0.0017
IB2-IIB	84.6		87.8	
IIIA-IVA	53.3		85.1	
IVB	37.5		37.5	
Tumor histology		0.0935		0.0061
SCC	71.9		85.6	
AdenoCa	33.3		33.3	
PS		< 0.0001		0.0006
1	78.8		86.2	
2	40		60	
3	0		60	
Tumor size				
≤ 6 cm	76.7		89.5	0.0371
> 6 cm	52.6	0.013	66.9	
Age (years)		0.654		0.0372
≤ 60	79.2		89.3	
> 60	59		68.2	
Intracavitary therapy				
Yes	82.1	0.008	88.7	
No	47.6		70.2	0.0649

PFS: progression-free survival; OS: overall survival;
SCC: squamous cell carcinoma; AdenoCa: adenocarcinoma;
PS: Eastern Cooperative Oncology Group performance status.

Table 4. — *Relationships between prognostic factors and cervical cancer patient survival in multivariable analysis*

		Hazard radio	95% CI	*p*
Stage	IB2-IIB	1		
	IIIA-IVA	1.51	0.19–10.88	0.68
	IVB	9.93	0.93–129.38	0.0579
Tumor histology	SCC	1		
	AdenoCa	6.69	1.35–35.08	0.0271
PS	1	1		
	2	5.52	0.69–35.64	0.0994
	3	5.34	0.90–38.90	0.0661
Tumor size	≤ 6 cm	1		
	> 6 cm	1.93	0.43–8.05	0.3733
Age (years)	≤ 60	1		
	> 60	3.04	0.66–15.31	0.15
Intracavitary therapy	No	1		
	Yes	0.97	0.11–9.51	0.9784

CI, confidence interval; SCC, squamous cell carcinoma; AdenoCa, adenocarcinoma; PS, Eastern Cooperative Oncology Group performance status.

Table 5. — *Incidence and types of acute and late complications in patients with cervical cancer who underwent concurrent chemoradiotherapy with paclitaxel and carboplatin.*

	Grade				
	0	1	2	3	4
Acute					
Hematologic (neutropenia)	2	3	9	31	4
Hematologic (anemia)	3	22	20	4	0
Thrombocytopenia	42	6	1	0	0
Non-hematologic (vomiting)	36	8	4	0	1
Non-hematologic (diarrhea)	1	19	13	13	3
Late					
Urogenital disorder	34	3	11	1	0
Gastrointestinal disorder	42	0	5	1	1
Lymphedema	49	0	0	0	0
Neuropathy	34	11	1	3	0

Table 6. — *Progression-free survival and overall survival rates reported in previous studies of the use of concurrent chemoradiotherapy with paclitaxel and carboplatin in cervical cancer.*

Reference	Progression-free survival	Overall survival
Keys, *et al.* (1999) [2]	79	85
Eifel, *et al.* (2004) [4]	Not available	73
Whitney, *et al.* (1999) [22]	57	55

Stage III-IV cancer [4]. Regarding adverse effects, neutropenia tended to occur more frequently than previously reported, while gastrointestinal effects were less frequent [2,4,5,22]. Weekly administration of paclitaxel and carboplatin might be tolerable and effective in patients with stage IB2-IVB cervical cancer.

Similar to the results of the present study, a combination of paclitaxel and carboplatin has been reported to be effective chemotherapy [12, 13] as well as acting as a radiosensitizer. A previous *in vitro* study demonstrated an additive effect with concomitant paclitaxel and radiation for SCC [6]. In addition, a phase I study of weekly paclitaxel and carboplatin with concurrent radiotherapy demonstrated similar PFS and OS to those of cisplatin [23]. Furthermore, another member of the taxane family, docetaxel, enhances the efficacy of antivascular therapy when administered weekly; in addition, it confers metronomic chemotherapeutic effects [24]. Therefore, the present treatment may also function as antivascular therapy.

Carboplatin can be administered to patients with severe renal insufficiency [25] and demonstrates lower nephrotoxicity and emetogenicity than cisplatin [9]. Given the relative frequency of neutropenia and gastrointestinal effects in the present study, the authors believe that the regimen they utilized is suitable for outpatients, without requiring hospitalization.

PS and chemotherapy have been reported as independent prognostic factors for survival [26], and there was a tendency in the present study for PS to be a prognostic factor for survival. With a good PS, CCRT can be considered. The combination of taxane and platinum may extend PFS without affecting quality of life [27]. Furthermore, the therapeutic effects of weekly paclitaxel and carboplatin are similar to those of cisplatin [28, 29]. Stage IVB cancer tended to be related with poor survival

outcomes in the present study; however, Stage IIIA-IVA patients may benefit from this CCRT regimen. All of the patients with recurring Stage IVB cancer died, but patients with Stage IIIA-IVA cancer survived with additional treatment. The cancer in these stages (IIIA-IVA) invades locally, while cancers of higher stages spread principally through the lymphatic system; therefore, chemotherapy may be important in these patients [30], and the present regimen may be useful for treating Stage IVB cervical cancer [26].

Adverse effects included bone marrow suppression, with particularly high rates of neutropenia in the present study. Because the data are retrospective and from clinical practice instead of phase I study, 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 [23]. In addition, 34.7% (17/49) of the patients were older than 60 years, and the condition of the patients was particularly poor, with 85.7% (42/49) of the patients experiencing at least grade 3 neutropenia and 16.7% (7/49) of the patients with a PS of 2 or 3. Therefore, future clinical trials are needed to determine the optimal dose to avoid neutropenia and bone marrow suppression.

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 appropriate protocols should be followed to evaluate adverse effects. Because of the small number of patients with Stage IVB cancer, the results might not generalize to patients with more advanced cancers, and further study should be conducted to gather data in these patients.

The present results indicate that weekly administration of paclitaxel and carboplatin as part of CCRT might be effective for the treatment of cervical cancer. The response, PFS, and OS rates were acceptable, and there were less frequent adverse gastrointestinal effects than previously reported. Future studies should be conducted to compare the efficacy of cisplatin alone with paclitaxel/carboplatin as part of CCRT for the treatment of cervical cancer.

References

[1] Landoni F., Maneo A., Colombo A., Placa F., Milani R., Perego P., *et al.*: "Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer". *Lancet,* 1997, *350*, 535.

[2] Keys H.M., Bundy B.N., Stehman F.B., Muderspach L.I., Chafe W.E., Suggs C.L. 3rd, *et al.*: "Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma". *N. Engl. J. Med.,* 1999, *340*, 1154.

[3] Morris M., Eifel P.J., Lu J., Grigsby P.W., Levenback C., Stevens R.E., *et al.*: "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer". *N. Engl. J. Med.,* 1999, *340*, 1137.

[4] Eifel P.J., Winter K., Morris M., Levenback C., Grigsby P.W., Cooper J., *et al.*: "Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01". *J. Clin. Oncol.,* 2004, *22*, 872.

[5] Rose P.G., Bundy B.N., Watkins E.B., Thigpen J.T., Deppe G., Maiman M.A., *et al.*: "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *N. Engl. J. Med.,* 1999, *340*, 1144.

[6] Jaakkola M., Rantanen V., Grénman S., Kulmala J., Grénman R.: "In vitro concurrent paclitaxel and radiation of four vulvar squamous cell carcinoma cell lines". *Cancer.,* 1996, *77*, 1940.

[7] Sangkittipaiboon S.: "Long-term outcomes of concurrent chemoradiotherapy with weekly carboplatin in locally-advanced carcinoma of the uterine cervix patients". *J. Med. Assoc. Thai.,* 2014, *97*, 12.

[8] Katanyoo K., Tangjitgamol S., Chongthanakorn M., Tantivatana T., Manusirivithaya S., Rongsriyam K., Cholpaisal A.: "Treatment outcomes of concurrent weekly carboplatin with radiation therapy in locally advanced cervical cancer patients". *Gynecol. Oncol.,* 2011, *123*, 571

[9] Go R.S., Adjei A.A.: "Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin". *J. Clin. Oncol.,* 1999, *17*, 409.

[10] Chen M.D., Paley P.J., Potish R.A., Twiggs L.B.: "Phase I trial of taxol as a radiation sensitizer with cisplatin in advanced cervical cancer". *Gynecol. Oncol.,* 1997, *67*, 131.

[11] Pignata S., Frezza P., Tramontana S., Perrone F., Tambaro R., Casella G., *et al.*: "Phase I study with weekly cisplatin-paclitaxel and concurrent radiotherapy in patients with carcinoma of the cervix uteri". *Ann. Oncol.,* 2000, *11*, 455.

[12] Singh R.B., Chander S., Mohanti B.K., Pathy S., Kumar S., Bhatla N., *et al.*: "Neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation in locally advanced cervical carcinoma: a pilot study". *Gynecol. Oncol.,* 2013, *129*, 124

[13] Torfs S., Cadron I., Amant F., Leunen K., Berteloot P., Vergote I.: "Evaluation of paclitaxel/carboplatin in a dose dense or weekly regimen in 66 patients with recurrent or primary metastatic cervical cancer". *Eur. J. Cancer.,* 2012, *48*, 1332

[14] Higgins R., Bussey M., Naumann W., Hall J., Tait D., Haake M.: "Concurrent carboplatin and paclitaxel with pelvic radiation therapy in the primary treatment of cervical cancer". *Am. J. Obstet. Gynecol.,* 2007, *197*, 205.e1.

[15] Pritchard R.S., Anthony S.P.: "Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis". *Ann. Intern. Med.,* 1996, *125*, 723.

[16] "Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group". *BMJ,* 1995, *311*, 899.

[17] Marino P., Preatoni A., Cantoni A.: "Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis". *Cancer,* 1995, *76*, 593.

[18] Herskovic A., Martz K., al-Sarraf M., Leichman L., Brindle J., Vaitkevicius V., *et al.*: "Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus". *N. Engl. J. Med.,* 1992, *326*, 1593.

[19] al-Sarraf M., Martz K., Herskovic A., Leichman L., Brindle J.S., Vaitkevicius V.K., *et al.*: "Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study". *J. Clin. Oncol.,* 1997, *15*, 277.

[20] Kurihara M., Sakamoto H., Ohta Y., Takami T., Takami M., Nakayama Y., *et al.*: "Patient compliance and the quality of life are well maintained in weekly paclitaxel and carboplatin therapy for advanced gynecologic cancers in Japanese women (in Japanese)". *Gan. To. Kagaku. Ryoho.,* 2001, *28*, 55.

[21] de Vos F.Y., Bos A.M., Gietema J.A., Pras E., Van der Zee A.G., de Vries E.G., Willemse P.H.: "Paclitaxel and carboplatin concurrent with radiotherapy for primary cervical cancer". *Anticancer Res.,* 2004, *24*, 345

[22] Whitney C.W., Sause W., Bundy B.N., Malfetano J.H., Hannigan E.V., Fowler W.C. Jr., *et al.*: "Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study". *J. Clin. Oncol*., 1999, *17*, 1339.

[23] Rao G.G., Rogers P., Drake R.D., Nguyen P., Coleman R.L.: "Phase I clinical trial of weekly paclitaxel, weekly carboplatin, and concurrent radiotherapy for primary cervical cancer". *Gynecol. Oncol.,* 2005, *96*, 168.

[24] Kamat A.A., Kim T.J., Landen C.N. Jr., Lu C., Han L.Y., Lin Y.G., *et al.*: "Metronomic chemotherapy enhances the efficacy of antivascular therapy in ovarian cancer". *Cancer. Res.,* 2007, *67*, 281.

[25] Motzer R.J., Niedzwiecki D., Isaacs M., Menendez-Botet C., Tong W.P., Flombaum C., *et al.*: "Carboplatin-based chemotherapy with pharmacokinetic analysis for patients with hemodialysis-dependent renal insufficiency". *Cancer Chemother. Pharmacol.,* 1990, *27*, 234.

[26] Nishio S., Katsumata N., Matsumoto K., Tanabe H., Yonemori K., Kohno T., *et al.*: "Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma". *Oncol. Rep.,* 2008, *19*, 497.

[27] Moore D.H., Blessing J.A., McQuellon R.P., Thaler H.T., Cella D., Benda J., *et al.*: "Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study". *J. Clin. Oncol.,* 2004, *22*, 3113.

[28] Schuette W., Blankenburg T., Guschall W., Dittrich I., Schroeder M., Schweisfurth H., *et al.*: "Multicenter randomized trial for stage IIIB/IV non-small-cell lung cancer using every-3-week versus weekly paclitaxel/carboplatin". *Clin. Lung. Cancer.,* 2006, *7*, 338.

[29] van der Burg M.E., van der Gaast A., Vergote I., Burger C.W., van Doorn H.C., de Wit R., *et al.*: "What is the role of dose-dense therapy?" *Int. J. Gynecol. Cancer.,* 2005, *15*, 233.

[30] Kurman R.J., Hedrick Ellenson L., Ronnett B.M., (eds): "Blaustein's pathology of the female genital pathology," 6th ed. Pennsylvania: Springer, 2011.

Address reprint requests to:
K. CHIKAZAWA, M.D.
Department of Obstetrics and Gynecology
Jichi Medical University
Saitama Medical Center
1-847 Amanuma, Omiya, Saitama
Saitama 330-8503 (Japan)
e-mail: kendokenro@hotmail.com