EJGO European Journal of Gynaecological Oncology

The prognosis of high-risk early-stage cervical cancer patients who did not receive postoperative concurrent chemoradiotherapy

H. Kuroda, S. Mabuchi, Y. Matsumoto, K. Kozasa, T. Sasano, R. Takahashi, E. Kobayashi, T. Kimura

Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Osaka (Japan)

Summary

Purpose of investigation. To investigate the prognosis of high-risk early-stage cervical cancer patients who did not receive postoperative concurrent chemoradiotherapy (CCRT). *Materials and Methods.* The characteristics and outcomes of high-risk early-stage cervical cancer patients who did not receive postoperative CCRT were collected. They were separated into two groups according to the type of adjuvant treatment: no further therapy (NFT group) or chemotherapy (chemotherapy group), and the clinico-pathological characteristics, recurrence rate, progression-free survival (PFS), and overall survival (OS) were investigated. *Results.* A total of 23 patients were included. After a median follow-up period of 115 months, 19 had developed recurrent disease, and 17 had died of disease progression. The median PFS and OS of all patients were ten and 29 months, respectively. The recurrence rate of the NFT group (n=10) was similar to that of the chemotherapy group (n=13) (80% *vs*. 85%, $p > 0.05$). Although the PFS and OS of the chemotherapy group were slightly longer than those of the NFT group, the differences were not statistically significant (PFS, 10 *vs*. 36 months, $p > 0.05$; OS, 28 *vs*. 59 months $p > 0.05$). *Conclusion.* High-risk early-stage cervical cancer patients who did not receive postoperative CCRT have dismal prognosis irrespective of the type of adjuvant treatment.

Key words: Survival; Cervical cancer; Radical hysterectomy; Adjuvant treatment; High-risk group.

Introduction

Early-stage cervical cancer (FIGO Stage IB1-IIA) can be treated with radical hysterectomy or definitive radiotherapy (RT), which achieve similar survival outcomes. In previous studies, the five-year survival rate of FIGO Stage IB-IIA cervical cancer patients that were treated with radical surgery ranged from 83-91%, which is comparable to the 74-91% reported for those treated with RT alone [1-3]. In addition, retrospective investigations of patients with FIGO Stage IIB disease have suggested that patients that are treated with radical hysterectomy exhibit similar treatment outcomes to those that are treated with definitive RT; i.e., estimated five-year survival rates of 64-69% [4, 5].

Risk factors that compromise the treatment outcomes of early-stage cervical cancer patients who are primarily treated with radical surgery have been intensively investigated [6-8]. Generally, patients with risk factors such as positive pelvic lymph nodes, parametrial invasion, or a positive surgical margin are regarded as being at high risk of recurrence (high-risk patients). Moreover, patients with tumors that are confined to the cervix who display risk factors such as a large tumor, lymphovascular space involvement (LVSI), or deep stromal invasion (DSI) are considered to be at intermediate risk of recurrence (intermediate-risk factors) [9-11].

A previous Gynecologic Oncology Group Phase III study (GOG 92) evaluated the role of adjuvant RT in intermediate-risk patients. In a comparison between pelvic RT versus no further therapy (NFT), the latter study demonstrated that adjuvant RT significantly reduced the risk of recurrence and prolonged progression-free survival (PFS) [12,13]. Currently, a prospective randomized study (GOG 0263) is investigating the role of concurrent chemoradiotherapy (CCRT) in intermediate-risk cervical cancer patients with regards to quality of life, long-term complications, and survival outcomes [14]. As for high-risk patients, a Gynecologic Oncology Group phase III study (GOG 109/ SWOG 8797) demonstrated that the addition of cisplatin-based concurrent chemotherapy to postoperative RT improved survival [15], and so platinum-based concurrent chemoradiotherapy has become the standard adjuvant treatment for early-stage cervical cancer.

Although surgically treated cervical cancer patients who display intermediate-risk or high-risk factors are indicated to receive standard adjuvant pelvic RT with or without platinum-based concurrent chemotherapy, we sometimes encounter patients who refuse to receive it for various reasons, e.g., economic problems, fear of the side effects

Revised manuscript accepted for publication October 5, 2016

Table 1. — *Patient characteristics.*

		All patients n (%) (n=23)	NFT-group n (%) (n=10)	Chemotherapy group n (%) (n=13)	*p*-value
Age (years)	Mean ± SD (range)	54.9 ± 5.4 (20-77)	53.6 ± 7.0 (20-77)	55.9 ± 3.7 (41-71)	0.405
	< 60	16 (69.6%)	6 (60%)	10 (76.9%)	0,4143
	> 60	7 (30.4%)	4 (40%)	3 (23.1%)	
FIGO Stage	Ib1	2 (8.7%)	2 (20%)	0 (0%)	< 0.01
	Ib2	2 (8.7%)	2 (20%)	0 (0%)	
	IIa	1 (4.3%)	1 (10%)	0 (0%)	
	IIb	18 (78.3%)	5 (50%)	13 (100%)	
Histologic type	Squamous cell carcinoma	10 (43.5%)	8 (80%)	2 (15.4%)	< 0.01
	Adenocarcinoma	13 (56.5%)	2 (20%)	11 (84.6%)	
LVSI	No	1 (4.3%)	0 (0%)	1 (7.7%)	0.4299
	Yes	22 (95.7%)	10 (100%)	12 (92.3%)	
DSI	No	1 (4.3%)	1 (10%)	0 (0%)	0.2926
	Yes	22 (95.7%)	9 (90%)	13 (100%)	
Tumor size (mm)	< 40	7 (30.4%)	3 (30%)	4 (30.8%)	0.6795
	> 40	16 (69.6%)	7 (70%)	9 (69.2%)	
Lymph node metastasis	No	4 (17.4%)	2 (20%)	2 (15.4%)	0.8135
	Yes	19 (82.6%)	8 (80%)	11 (84.6%)	
Surgical margin	Negative	23 (100%)	10 (100%)	13 (100%)	0.2926
	Positive	0 (0%)	0 (0%)	0 (0%)	
Parametrial involvement	No	4 (17.4%)	4 (40%)	0 (0%)	<0.05
	Yes	19 (82.6%)	6 (60%)	13 (100%)	

NFT: no further therapy; SD: standard deviation; FIGO: the International Federation of Gynecology and Obstetrics; LVSI: lymphovascular space involvement; DSI: deep stromal invasion.

of radiation, or medical complications. Moreover, adjuvant chemotherapy has recently been employed for surgically treated cervical cancer at some institutions, even though it has not been demonstrated to have a clinical benefit in a prospective randomized study. Thus, some patients may wish to undergo adjuvant chemotherapy instead of adjuvant RT or chemoradiotherapy. Therefore, information regarding the oncological outcomes of surgically treated early-stage cervical cancer patients who do not receive the standard adjuvant treatment is practically important. Regarding intermediate-risk patients, in the GOG 92 study 39 out of 140 (28%) patients in the NFT group developed recurrence. In addition, the two-year recurrence-free rate of the NFT group was 79% [15]. However, due to the lack of a NFT-arm in the GOG109/SWOG8797 study, the prognosis of high-risk early-stage cervical cancer patients who do not receive postoperative CCRT remains unknown.

In the current study, the authors retrospectively investigated the prognosis of high-risk early-stage cervical cancer patients who did not receive standard adjuvant treatment.

Materials 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 patients who had undergone radical hysterectomy and pelvic lymphadenectomy for FIGO Stage IB-IIB cervical cancer between August 1997 and April 2014 was generated from the present institutional tumor registries. Then, through a chart review, patients whose pathological reports included any high-risk prognostic factors, including parametrial invasion, pelvic lymph node metastasis, or a positive surgical margin, but did not receive the standard adjuvant treatment, were identified. Informed consent was not obtained from patients, because of the retrospective nature of the study. However, confidentiality was maintained.

At the present institution, the histological classification of cervical cancer is performed by two pathologists based on the criteria outlined by the World Health Organization (WHO) for tumors of the uterine cervix. The patients were clinically staged according to the FIGO staging criteria without general anesthesia. The pretreatment work-up consisted of a complete medical history, a physical examination, a complete blood count, biochemistry panels, chest X-rays, CT of the abdomen and pelvis, MRI, and optional intravenous pyelography, cystoscopy, and rectosigmoidoscopy. In all patients, a preoperative para-aortic lymph node (PALN) evaluation was conducted by performing a CT scan of the abdomen as part of the initial evaluation.

All patients were treated with radical hysterectomy (type III) and pelvic lymphadenectomy, as reported previously [16, 17]. The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes. Intraoperative assessments of the PALN were routinely performed by palpation. When PALN metastasis was suspected on a preoperative CT scan or during intraoperative palpation, a biopsy was performed for confirmation. Patients who had biopsy-confirmed PALN metastasis were excluded from the study.

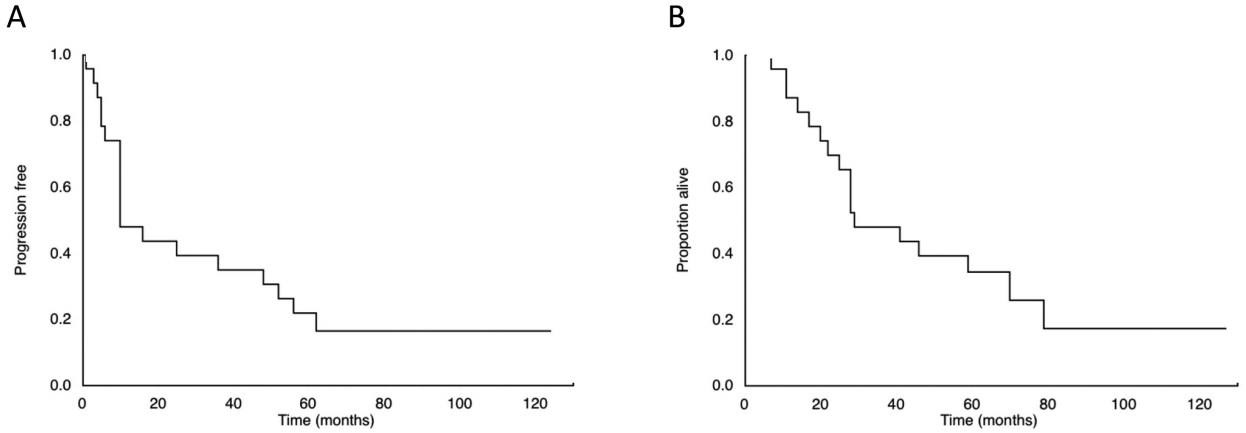

Figure 1. — Kaplan-Meier estimates of the survival of all high-risk early-stage cervical cancer patients who did not receive postoperative concurrent chemoradiotherapy. A) Progression-free survival. B) Overall survival.

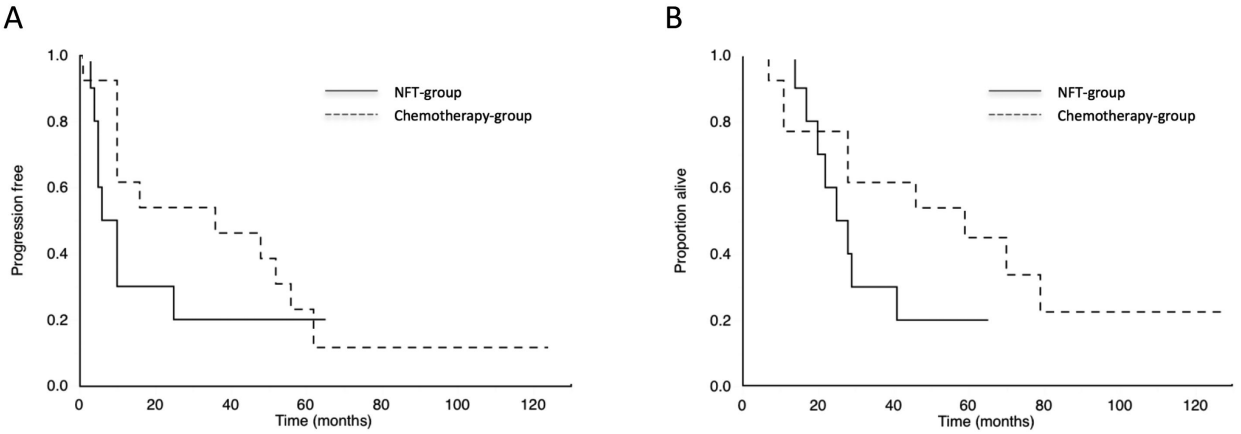

Figure 2. — Kaplan-Meier estimates of the survival of all high-risk early-stage cervical cancer patients who did not receive postoperative concurrent chemoradiotherapy according to the type of adjuvant treatment (the NFT group *vs*. the chemotherapy-group). A) Progression-free survival. B) Overall survival. The patients in the chemotherapy group exhibited slightly longer survival than those in the NFT group. However, the differences were not statistically significant (PFS: $p = 0.4007$; OS: $p = 0.1860$).
NFT: no further therapy; PFS: progression-free survival; OS: overall survival.

At the present institution, postoperative chemoradiotherapy is indicated for all patients whose pathological reports display any one of the following high-risk prognostic factors: parametrial invasion, pelvic lymph node metastasis, or a positive surgical margin [18-20]. However, patients who refused CCRT were treated with platinum-based chemotherapy (the chemotherapy group; n=13) or no further therapy (the NFT group; n=10). The chemotherapeutic regimens used for adjuvant chemotherapy were carboplatin plus paclitaxel in five patients, carboplatin, paclitaxel, and epirubicin in six patients, nedaplatin and irinotecan in one patient, and cisplatin and etoposide in one patient.

Postoperatively, the patients were followed-up regularly by gynecological oncologists, as reported previously [21]. When recurrence was suspected, a biopsy was taken for confirmation whenever possible. The median duration of the follow-up period was 115 (range: 19-218) months in all patients, 140 (range: 19-218) months in the NFT group, and 101 (range: 53-137) months in the chemotherapy group.

Recurrent disease was treated in accordance with the institutional treatment guidelines: single distant recurrent tumors were treated with salvage external beam RT or salvage surgery. Patients that suffered from recurrence in the central pelvis were treated with salvage surgery or, when possible, with interstitial brachytherapy [22]. Patients with pelvic sidewall disease or multiple recurrent lesions were treated with platinum-based chemotherapy [23]. Patients with single distant tumors that could not be salvaged by surgery or RT were also treated with platinum-based chemotherapy. Patients who refused salvage chemotherapy or RT were treated with palliative care alone.

Continuous data were compared between the groups using the

Table 2. — *The recurrence rates and the mortality rate.*

	All patients (n=23)	NFT-group (n=10)	Chemotherapy-group (n=13)	*p*-value
Recurrence rate	83%	80%	85%	0.8135
Mortality rate	70%	80%	69%	0.5964

NFT: no further therapy.

Student's *t*-test, Wilcoxon rank-sum test, or median test, as appropriate. Frequency counts and proportions were compared between the groups using the chi-square test or a two-tailed Fisher's exact test, as appropriate. PFS was defined as the time from the date of the primary diagnosis to the date of the first physical or radiographic evidence of disease progression. Overall survival (OS) was defined as the time from the date of the primary diagnosis to the date of death or the last follow-up visit. The survival analysis was based on the Kaplan-Meier method and was compared using the log-rank test. *P*-values of < 0.05 were considered to be statistically significant. All analyses were performed using the software JMP, version 11.0.

Results

A total of 23 consecutive patients with cervical cancer were included in this retrospective study. The clinicopathological characteristics of the patients are summarized in Table 1. The median age of the patients was 57 years. Of the 23 patients, two, three, and 18 had Stage IB1, Stage IB2-IIA, and Stage IIB disease, respectively. Histologically, ten patients (43.5%) had squamous cell carcinoma and 13 (56.5%) had tumors that exhibited a non-squamous histology. Sixteen patients had tumors with a maximum tumor diameter of ≥ 40 mm. Of the 23 patients, ten received no further treatment (NFT) and 13 received postoperative adjuvant chemotherapy.

At the time of this analysis, 19 of the 23 patients had developed recurrence (Table 2). The site of the recurrence was the central pelvis in nine patients, the pelvic lymph nodes in seven patients, distant lymph nodes in three patients, PALN in one patient, and distant organs in six patients (Table 3). Except for two patients who developed pelvic recurrent lesions that could be salvaged by RT, all patients who developed recurrence died of disease progression. The median PFS and OS periods were ten and 29 months, respectively (Figure 1). After a median follow-up period of 115 months, five patients were disease-free and one was alive with disease.

The authors next examined the patients' oncological outcomes according to the type of adjuvant treatment administered. As shown in Table 2, eight out of ten patients developed recurrence in the NFT group. In the chemotherapy group, recurrent lesions were observed in 11 out of 13 patients. The recurrence rates of the two groups were similar (80% *vs*. 85%, $p = 0.8135$). As shown in Figure 2, PFS and OS were slightly longer in the chemotherapy group than in the NFT group, but the differences were not statistically significant (five-year PFS, 0.2 *vs*. 0.2308; 50% PFS, ten vs. 36 months, $p = 0.4007$; five-year OS, 0.4 *vs*. 0.4487; 50% OS, 28 *vs*. 59 months, $p = 0.1860$).

Discussion

The current study showed that high-risk early-stage cervical cancer patients who do not receive the standard adjuvant treatment; i.e., CCRT, have a dismal prognosis. The recurrence rate of this group was 83%, and their estimated five-year PFS and OS rates were 22% and 34%, respectively. When the authors examined survival outcomes according to the type of adjuvant treatment administered, they found that the NFT and chemotherapy groups exhibited similar recurrence rates, PFS, and OS (Figure 2 and Table 2).

The oncological outcomes observed in these patients were significantly worse than those reported in a previous randomized controlled trial comparing adjuvant RT versus adjuvant CCRT in high-risk early-stage cervical cancer patients (the GOG109/SWOG8797 study) [15]. Thus, it is indicated that radical surgery alone is not sufficient for high-risk early-stage cervical cancer.

In the present authors' previous study, high-risk patients who received adjuvant platinum-based CCRT demonstrated estimated five-year PFS and OS rates of 72.0%, and 78.2%, respectively [19]. In addition, high-risk patients who received adjuvant RT alone displayed estimated five-year PFS and OS rates of 44.3% and 60.0%, respectively [19]. These oncological outcomes [15, 19] were significantly better than those observed in the chemotherapy and NFT groups in the current study. Collectively, these results indicate that postoperative CCRT, the standard adjuvant treatment, is strongly recommended for high-risk early-stage cervical cancer patients.

Recently, a retrospective study that included a relatively small number of patients suggested that adjuvant chemotherapy exhibits a good toxicity profile and might be effective in surgically-treated cervical cancer patients [24]. However, as the majority of patients in the study were classified into the intermediate-risk group, little information is available regarding the role of adjuvant chemotherapy in high-risk patients. Moreover, a Japanese group previously suggested that adjuvant chemotherapy is of limited use in node-positive cervical cancer patients [25]. In the latter study, of the 21 node-positive cervical adenocarcinoma patients that received adjuvant platinum-based chemotherapy, nine developed recurrence, and the five-year disease-free survival rate was estimated to be 57% [26]. As the findings of the current study indicate that the prognosis of high-risk cervical cancer patients is not improved by the addition of adjuvant chemotherapy, the present authors consider that adjuvant chemotherapy should be employed sparingly in this patient population until its clinical benefit has been

Table 3. — *The sites of recurrence after initial surgery.*

	All patients n n=19	(%)	NFT-group n n=8	(%)	Chemotherapy-group n n=11	(%)	*p*-value
Pelvic central	5	26	2	25	3	27	0.9569
Pelvic nodes	3	16	1	13	2	18	0.794
Distant nodes	0	0	0	0	0	0	-
Peritoneal disseminations	2	11	1	13	1	9.1	0.8767
Visceral organs	1	5.3	1	13	0	0	0.2864
Pelvic central and Visceral organs	2	11	0	0	2	18	0.2446
Pelvic central, distant nodes, and peritoneal disseminations	1	5.3	1	13	0	0	0.2864
Pelvic central, pelvic nodes, distant nodes, and visceral organs	1	5.3	0	0	1	9.1	0.4555
Pelvic nodes and distant nodes	1	5.3	0	0	1	9.1	0.4555
Pelvic nodes and peritoneal disseminations	1	5.3	0	0	1	9.1	0.4555
Pelvic nodes and visceral organs	1	5.3	1	13	0	0	0.2864
Peritoneal disseminations and visceral organs	1	5.3	1	13	0	0	0.2864
Pelvic recurrence	8	42	3	38	5	45	0.7724
Distant recurrences	1	5.3	1	13	0	0	0.2864
Both recurrences	10	53	4	50	6	55	0.8863

NFT: no further therapy.

demonstrated in a randomized controlled study.

The limitations of this study need to be addressed. The first is that it was conducted at a single institution and included a relatively small number of patients. The authors intend to verify their clinical findings in collaborative multi-institutional investigations in the future. The second is the retrospective nature of the current study. As this report covers a long period, there have been changes in the patient work-up, surgical procedures, the choice of adjuvant treatment, the choice of salvage treatment for recurrent disease, and supportive care during the study, which might have affected patient survival. To eliminate these potential biases, prospective multi-institutional investigations need to be conducted.

Conclusion

In conclusion, high-risk early-stage cervical cancer patients who do not receive standard adjuvant treatment have a dismal prognosis. Until its clinical benefit has been demonstrated in a prospective randomized study, postoperative adjuvant chemotherapy cannot be recommended for this patient population.

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] Morley G.W., Seski J.C.: "Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasion)". *Am. J. Obstet. Gynecol.*, 1976, *126*, 785.

[3] Perez C.A., Camel H.M., Kao M.S., Hederman M.A.: "Randomized study of preoperative radiation and surgery or irradiation alone in the treatment of stage IB and IIA carcinoma of the uterine cervix: final report". *Gynecol. Oncol.*, 1987, *27*, 129.

[4] Benedet J.L., Odicino F., Maisonneuve P., Beller U., Creasman W.T., Heintz A.P., *et al.*: "Carcinoma of the cervix uteri". Int. J. Gynaecol. Obstet., 2003, *83*, 41.

[5] Kasamatsu T., Onda T., Sawada M., Kato T., Ikeda S.: "Radical hysterectomy for FIGO stage IIB cervical cancer: clinicopathological characteristics and prognostic evaluation". *Gynecol. Oncol.*, 2009, *114*, 69.

[6] Delgado G., Bundy B., Zaino R., Sevin B.U., Creasman W.T., Major F.: "Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 1990, *38*, 352.

[7] Fuller A.F. Jr., Elliott N., Kosloff C., Hoskins W.J., Lewis J.L. Jr.: "Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix". *Gynecol. Oncol.*, 1989, *33*, 34.

[8] Samlal R.A., van der Velden J., Schilthuis M.S., Gonzalez Gonzalez D., Ten Kate F.J., Hart A.A., *et al.*: "Identification of high-risk groups among node-positive patients with stage IB and IIA cervical carcinoma". *Gynecol. Oncol.*, 1997, *64*, 463.

[9] Kim K., Kang S.B., Chung H.H., Kim J.W., Park N.H., Song Y.S.: "Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors". *Eur. J. Surg. Oncol.*, 2009, *35*, 192.

[10] Ryu S.Y., Park S.I., Nam B.H., Cho C.K., Kim K., Kim B.J., *et al.*: "Is adjuvant chemoradiotherapy overtreatment in cervical cancer patients with intermediate risk factors?" *Int. J. Radiat. Oncol. Biol. Phys.*, 2011, *79*, 794.

[11] Song S., Song C., Kim H.J., Wu H.G., Kim J.H., Park N.H., et al.: "20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: impact of treatment period and concurrent chemotherapy". *Gynecol. Oncol.*, 2012, *124*, 63.

[12] Rotman M., Sedlis A., Piedmonte M.R., Bundy B., Lentz S.S., Muderspach L.I., *et al.*: "A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prog-

nostic features: follow-up of a gynecologic oncology group study". *Int. J. Radiat. Oncol. Biol. Phys.*, 2006, *65*, 169.

[13] Sedlis A., Bundy B.N., Rotman M.Z., Lentz S.S., Muderspach L.I., Zaino R.J.: "A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study". *Gynecol. Oncol.*, 1999, *73*, 177.

[14] NCT01101451. National Cancer Institute: "Radiation Therapy With or Without Chemotherapy in Patients With Stage I or Stage II Cervical Cancer Who Previously Underwent Surgery". Available at: www.cancer.gov/clinicaltrials/search/view?cdrid=670125&version=HealthProfessional&protocolsearchid=10780359

[15] Peters W.A. 3rd., Liu P.Y., Barrett R.J. 2nd., Stock R.J., Monk B.J., Berek J.S., *et al.*: "Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix". *J. Clin. Oncol.*, 2000, *18*, 1606.

[16] Mabuchi S., Okazawa M., Isohashi F., Matsuo K., Ohta Y., Suzuki O., *et al.*: "Radical hysterectomy with adjuvant radiotherapy versus definitive radiotherapy alone for FIGO stage IIB cervical cancer". *Gynecol. Oncol.*, 2011, *123*, 241.

[17] Mabuchi S., Okazawa M., Matsuo K., Kawano M., Suzuki O., Miyatake T., *et al.*: "Impact of histological subtype on survival of patients with surgically-treated stage IA2-IIB cervical cancer: Adenocarcinoma versus squamous cell carcinoma". *Gynecol. Oncol.*, 2012, *127*, 114.

[18] Isohashi F., Mabuchi S., Yoshioka Y., Seo Y., Suzuki O., Tamari K., *et al.*: "Intensity-modulated radiation therapy versus three-dimensional conformal radiation therapy with concurrent nedaplatin-based chemotherapy after radical hysterectomy for uterine cervical cancer: comparison of outcomes, complications, and dose-volume histogram parameters". *Radiat. Oncol.*, 2015, *10*, 180.

[19] Okazawa M., Mabuchi S., Isohashi F., Suzuki O., Yoshioka Y., Sasano T., *et al.*: "Impact of the addition of concurrent chemotherapy to pelvic radiotherapy in surgically treated stage IB1-IIB cervical cancer patients with intermediate-risk or high-risk factors: a 13-year experience". *Int. J. Gynecol. Cancer*, 2013, *23*, 567.

[20] Mabuchi S., Morishige K., Isohashi F., Yoshioka Y., Takeda T., Yamamoto T., *et al.*: "Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors". *Gynecol. Oncol.*, 2009, *115*, 482.

[21] Mabuchi S., Isohashi F., Maruoka S., Hisamatsu T., Takiuchi T., Yoshioka Y., Kimura T.: "Post-treatment follow-up procedures in cervical cancer patients previously treated with radiotherapy". *Arch. Gynecol. Obstet.*, 2012, *286*, 179.

[22] Mabuchi S., Isohashi F., Yoshioka Y., Temma K., Takeda T., Yamamoto T., *et al.*: "Prognostic factors for survival in patients with recurrent cervical cancer previously treated with radiotherapy". *Int. J. Gynecol. Cancer*, 2010, *20*, 834.

[23] Mabuchi S., Takahashi R., Isohashi F., Yokoi T., Okazawa M., Sasano T., Maruoka S., *et al.*: "Reirradiation using high-dose-rate interstitial brachytherapy for locally recurrent cervical cancer: a single institutional experience". *Int. J. Gynecol. Cancer*, 2014, *24*, 141.

[24] Hisamatsu T., Mabuchi S., Yoshino K., Fujita M., Enomoto T., Hamasaki T., Kimura T.: "Prediction of progression-free survival and response to paclitaxel plus carboplatin in patients with recurrent or advanced cervical cancer". *Int. J. Gynecol. Cancer*, 2012, *22*, 623.

[25] Jung P.S., Kim D.Y., Lee S.W., Park J.Y., Suh D.S., Kim J.H.: "Clinical Role of Adjuvant Chemotherapy after Radical Hysterectomy for FIGO Stage IB-IIA Cervical Cancer: Comparison with Adjuvant RT/CCRT Using Inverse-Probability-of-Treatment Weighting". *PLoS One*, 2015, *10*, e0132298.

[26] Takeshima N., Utsugi K., Hasumi K., Takizawa K.: "Postoperative adjuvant chemotherapy for node-positive cervical adenocarcinoma". *Int. J. Gynecol. Cancer*, 2009, *19*, 277.

Corresponding Author:
S. MABUCHI, M.D., PH.D.
Department of Obstetrics and Gynecology
Osaka University Graduate School of Medicine
2-2 Yamadaoka
Suita, Osaka 565-0871 (Japan)
e-mail: smabuchi@gyne.med.osaka-u.ac.jp