

Definitive radiotherapy in elderly patients and patients with locally advanced cervical cancer with complications

H. Imafuku¹, Y. Ebina¹, K. Suzuki¹, S. Wakahashi¹, Y. Miyahara¹, K. Yoshida², H. Yamada¹

¹Department of Obstetrics and Gynecology, ²Department of Radiation Oncology, Kobe University Graduate School of Medicine, Kobe City (Japan)

Summary

Objective: To analyze the efficacy and toxicity of radiation therapy (RT) in elderly patients (>80-years-old) and patients with locally advanced cervical cancer with complications. **Materials and Methods:** Thirty-six patients treated with RT and 52 patients treated with concurrent chemoradiation therapy (CCRT) between 2010 and 2013 were included in this study. Treatment efficacy, treatment toxicity, overall survival, disease progression-free survival, and pelvic progression-free survival were analyzed. **Results:** The frequency of patients who had Grade 3-4 leukopenia in the CCRT group (57.6%) was significantly higher than that in the RT group (8.3%, $p < 0.01$). The complete response rates were 84% in the RT group ($n = 32$) and 90% in the CCRT group ($n = 51$) ($p = 0.498$). There was no statistical difference in overall survival, disease progression-free survival, and pelvic progression-free survival between the RT group and the CCRT group. **Conclusion:** Definitive RT in elderly and complicated cervical cancer patients was safe and effective.

Key words: Cervical cancer; Radiation therapy; Elderly patients; Patients with complications.

Introduction

An estimated 10,520 new cases of uterine cervical cancer were diagnosed in Japan in 2013, and an estimated 2,813 women died of the disease in 2015 [1]. The mortality rate associated with cervical cancer in Japan decreased from the 1960s until 1995; however, the incidence of cervical cancer slightly increased during this period [1]. The 2011 Japan Society of Gynecologic Oncology guidelines for the treatment of cervical cancer recommend radical hysterectomy or concurrent chemoradiation therapy (CCRT) for patients with FIGO IB2, IIA2, or IIB cervical cancer; they also recommend CCRT for patients with FIGO III and IVA cervical cancer [2]. Compared to radiation therapy (RT), the superiority of CCRT in treating invasive cervical cancer (IB2, IIA2, or IIB-IVA) has been previously demonstrated [3]. However, the incidence of acute hematological or gastrointestinal toxicity was higher in CCRT compared to that in RT [8]. No consensus has yet been reached with regards to the optimal treatment modality for elderly patients and those with cervical cancer with complications. In the present institution, elderly patients and those with severe complications were treated with definitive RT to decrease the adverse effects of treatment. In the present study, the authors retrospectively analyzed the efficacy and toxicity of RT in elderly patients and patients with locally advanced cervical cancer and complications, in comparison with the efficacy and toxicity of CCRT.

Materials and Methods

The patients in this retrospective study were identified from a database of patients who were diagnosed with uterine cervical cancer in Kobe University Hospital between 2010 and 2013. The study protocol was approved by the Kobe University School of Medicine Ethics Committee (No.170180). Written informed consents were obtained from the patients for publication of this study. The eligibility criteria were as follows: patients with pathologically confirmed cervical cancer, patients who were clinically diagnosed with FIGO IB-IVA cervical cancer, and patients who underwent definitive RT or CCRT. Patients who received palliative RT were excluded from this study. All the patients underwent comprehensive staging, including physical examination, CT, pelvic MRI, and PET-CT. Tumor diameter was assessed by MRI, and lymph node enlargement was defined as ≥ 10 mm in the shortest diameter assessed by CT/MRI. The pathological diagnosis was performed at the pathological division of the institution. CCRT was performed in younger patients (< 80 years) with good Eastern Cooperative Oncology Group performance status (ECOG-PS). The presence of medical complications was also considered.

In the database of 211 patients with cervical cancer, 89 patients satisfied the eligibility criteria. Based on the above criteria, 52 patients were treated with CCRT, and the remaining 36 patients received RT.

The uterine cervical cancer irradiation protocol at Kobe University Hospital has been described previously [10]. Briefly, the patients who received EBRT combined with HDR-ICBT were initially treated with whole pelvic irradiation using a box field and high-energy 10 MV X-ray photons from a linear accelerator with a daily fraction size of 1.8-02.0 Gy delivered five times per week. A centrally shielded field using anterior/posterior opposed portals was applied just before starting HDR-ICBT. The patients who received EBRT alone were also initially treated with whole pelvic

irradiation. A boost to the primary tumor was delivered using a three-dimensional conformal technique, and a pelvic lymph node boost was delivered using the anterior/posterior opposed portals. The median total dose of EBRT was 50.4 (range 16.2–61.2) Gy. The HDR-ICBT was performed with a microselectron HDR using a 192-Iridium remote afterload-ing system at one-week intervals during the period of EBRT. The median total dose to point A was 20.0 (range 4.5–31.0) Gy with a single fraction size of 4.0–6.5 Gy. A boost EBRT of 6–10 Gy per 3–5 fractions was applied to patients with nodal metastases, and for patients who could not receive appropriate HDR-ICBT, boost EBRT was planned. During the RT course, weekly monitoring of hemoglobin levels was required; blood transfusion was mandatory if the hemoglobin level was < 9 mg/dL.

For CCRT, chemotherapy consisted of cisplatin, administered weekly at a dose of 40 mg/m² intravenously during the RT period. This chemotherapy was concurrent with extended-field radiotherapy. Appropriate hydration and antiemetics were administered. Renal function and blood counts were examined prior to each cycle. During radiotherapy, or before the initiation of chemo-therapy, weekly physical examinations, complete blood counts, and liver and renal function tests were performed. If the white blood cell count was < 2,000/μl, granulocyte count was < 1,000/μl, platelet count was < 10 × 10⁴/μl, or creatinine clearance estimated by the Cockcroft–Gault Equation was < 50 mL/minute, chemotherapy was postponed until creatinine clearance improved ≥ 50 mL/minute. If chemotherapy was delayed by ≥ 2 weeks, chemotherapy was discontinued, but RT was continued.

In this study, a completion of RT was defined as irradiation for appropriate RT (EBRT and/or HDR-ICBT and/or boost EBRT). The response was assessed by images (CT, MRI, or PET-CT) 2–3 months after their treatment according to the RECIST criteria. We also referred to uterine cervix cytology.

After treatment, all the patients were followed-up by gynecological and radiation oncologists every 1–2 months during the first year. Further, follow-up was conducted every 3–6 months to detect recurrence and late toxicity. Gynecological examination was performed, and the tumor marker was checked at every visit. Radiographic examinations (CT scan or MRI) were performed as necessary. Pelvic recurrence was confirmed if the disease was detected in the irradiation field. Distant metastases were confirmed in areas outside of the pelvis.

Treatment toxicity was assessed weekly throughout the treatment period and scored according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 4.0). Acute toxicity was defined as those events that occurred within 90 days from the start of the treatment, and late toxicity was defined as those events that either occurred > 90 days from the start of the treatment or persisted beyond 90 days.

Patient survival was measured from the start of treatment to the date of the last follow-up examination. Those patients who did not complete the appropriate RT were excluded.

All statistical analyses were conducted using the statistical package R (ver. 3.2.0, www.r-project.org). The differences between the groups were tested for statistical significance using Fisher's exact test, Mann–Whitney U test, and Chi-squared test. Overall survival (OS), disease progression-free survival (PFS), and pelvic progression-free survival (PPFS) were estimated by the Kaplan–Meier method. Statistical significance was calculated using the log-rank test, and *p*-value < 0.05 was considered significant.

Results

The characteristics of the 88 patients are summarized in Table 1. Patient age in the RT group (median 80 years, range 43–91 years) was significantly more than that in the CCRT group (median 63 years, range 35–79 years) (*p* < 0.01). All 22 patients ≥

Table 1. Patient characteristic

Clinical variable	RT (N=36)	CCRT (n=52)	
Age, years	80 (43–91)*	63.5 (35–79)*	<i>P</i> <0.01
FIGO stage			
IB	9 (25%)	5 (9.6%)	
II	8 (22.2%)	23 (44.2%)	<i>P</i> =0.07
III	17 (47.2%)	23 (44.2%)	
IVA	2 (5.6%)	1 (2.0%)	
Histological type			
Squamous cell carcinoma (SCC)	32 (88.9%)	46 (88.5%)	<i>P</i> = 0.95
Non-SCC	4 (11%)	6 (11.5%)	
Maximum tumor diameter (mm)**	50 (11–90)*	46 (13–81)*	<i>p</i> =0.71
Lymph node enlargement***			
Pelvic node positive	7 (19.4%)	21 (40.4%)	<i>P</i> =0.03
Para-aorta node positive	1 (2.8%)	5 (9.6%)	<i>P</i> =0.21

* median, range

** Assessed by MRI T2-weighted image

***>= 10 mm in shorter diameter assessed by CT or MRI

Table 2. Acute treatment related toxicity according to treatment modality (CTC-AE version 4.0)

Events	RT (N=36)			CCRT (N=52)		
	G2	G3	G4	G2	G3	G4
Leukopenia	13 (36.1%)	3 (8.3%)	0	15 (28.8%)	27 (51.9%)	3
Anemia	14 (38.9%)	1 (2.7%)	0	27 (51.9%)	8 (15.4%)	0
Thrombocytopenia	0	1 (2.7%)	0	6 (11.5%)	1 (1.9%)	0
Diarrhea	3 (8.3%)	2 (5.6%)	0	4 (7.7%)	0	0

80 years of age received RT. The remaining 14 patients received RT for the following medical complications: renal failure because of hydronephrosis caused by cervical cancer invasion (*n* = 3), renal failure due to comorbid renal disease (*n* = 3), cerebral infarction (*n* = 2), PS 3 due to femoral neck fracture (*n* = 1), rheumatoid arthritis and posttreatment malignant lymphoma (*n* = 1), history of cancer in other organs (*n* = 1), complete blindness (*n* = 1), visual disturbance with hearing impairment (*n* = 1), and integration disorder syndrome (*n* = 1). The rate of pelvic lymph node enlargement in the CCRT group was significantly higher than that in the RT group (*p* < 0.05).

The frequency of acute treatment-related toxicity is shown in Table 2. The frequency of patients with Grade 3–4 leukopenia in the CCRT group (57.6%) was significantly higher than that in the RT group (8.3%, *p* < 0.01). There was no significant difference in the frequency of acute treatment-related toxicity in patients with Grade 3–4 anemia between the CCRT and RT groups (*p* = 0.07). In the CCRT group, one patient had Grade 4 hyponatremia owing

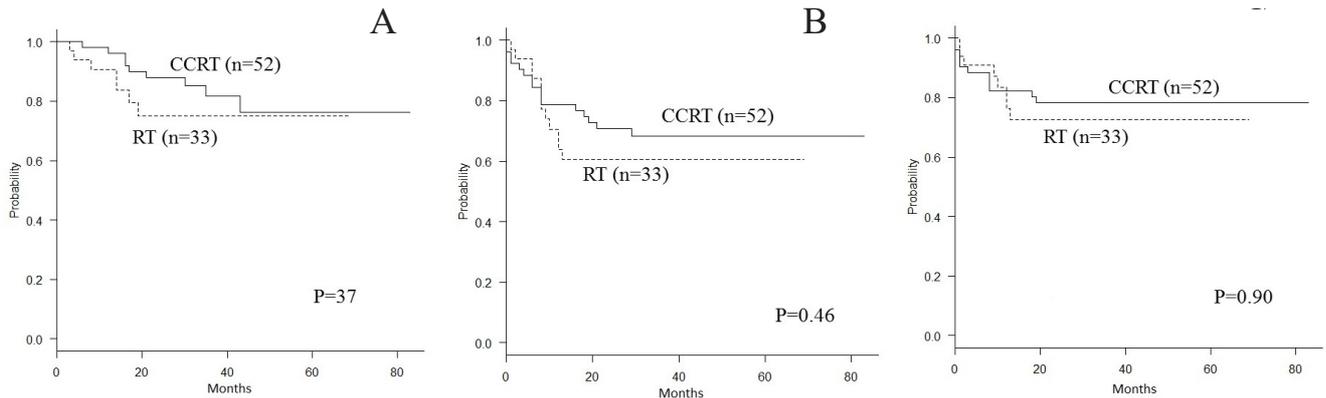


Figure 1. — Overall survival (A), PFS (B), and pelvic progression-free survival (C) of women with cervical cancer after definitive radiation therapy (RT) or concurrent chemoradiation therapy (CCRT).

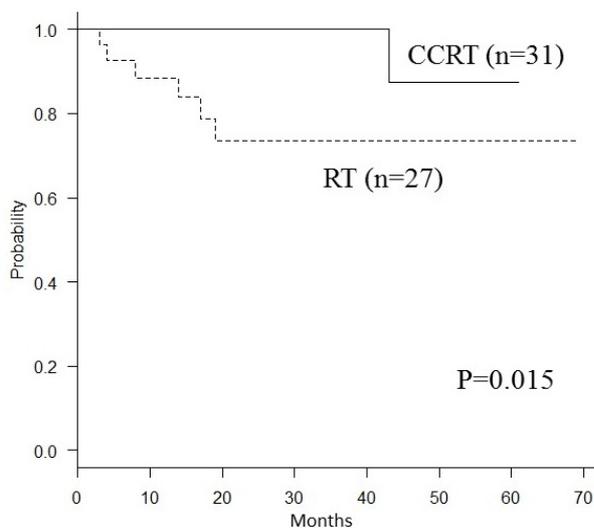


Figure 2. — Overall survival of women with node negative cervical cancer after definitive radiation therapy (RT) or concurrent chemoradiation therapy (CCRT).

to renal tubular disorders. There were no patients with febrile neutropenia, Grade 4 thrombocytopenia, or Grade 3–4 renal insufficiency.

In the RT group, 30 patients (81%) received initial planned EBRT and HDR-ICBT. Five patients did not receive HDR-ICBT for the following reasons: pyometra ($n = 1$), perforation of the uterus by the tandem ($n = 1$), impossible insertion of the tandem ($n = 2$), and patient's refusal of ICBT ($n = 1$). All the patients received boost EBRT instead of HDR-ICBT. Therefore, 33 patients (92%) had completed the appropriate RT. Three patients discontinued RT; one discontinued after 41.4 Gy EBRT and three HDR-ICBT due to severe diarrhea and appetite loss. One patient discontinued after 19.8 Gy EBRT due to severe ileus caused by collagen disease. The remaining patient refused RT after 27 Gy EBRT.

In the CCRT group, 51 (98%) patients were administered

EBRT and HDR-ICBT as initially planned. One remaining patient was administered only two HDR-ICBT due to pyometra after the second HDR-ICBT. Therefore, that patient was administered boost EBRT instead of HDR-ICBT. All the patients had completed RT. In the CCRT group, 34 patients (65.4%) received chemotherapy for > 4 cycles. However, nine patients received cycles, two patients received two cycles, and seven patients received only one cycle. The reasons for chemotherapy discontinuation were as follows: creatinine clearance < 50 mL/minute ($n = 9$), hematologic toxicity ($n = 4$), sudden thrombocytopenia because of hepatic cirrhosis ($n = 1$), appetite loss ($n = 1$), cardiac failure because of hydration ($n = 1$), and unknown reasons ($n = 2$).

Of the initial 88 patients, responses were assessed in 83 patients. Complete response (CR) rates were 84% in the RT group ($n = 32$) and 90% in the CCRT group ($n = 51$) ($p = 0.498$). In the RT group, three patients had partial response (PR) and two patients displayed progressive disease (PD). In the CCRT group, three patients had PR and two patients had PD. All four patients with PD were consistent in presenting with distant metastasis despite the presence of CR/PR in the pelvis.

Of the initial 88 patients, the survival analysis was conducted for 85 patients. Three patients in the RT group who did not have appropriate RT were excluded. The median follow-up period for all patients was 31 (range 3–83) months.

In the RT group ($n = 33$), the five-year OS, PFS, and PPFS rates were 75%, 60%, and 73%, respectively. In the CCRT group ($n = 52$), the five-year OS, PFS, and PPFS rates were 76%, 68%, and 78%, respectively. There was no difference in OS between the RT and CCRT groups ($p = 0.371$). (Figure 1A) Similarly, there were no differences in PFS and PPFS between the RT and CCRT groups ($p = 0.461$ and 0.647 , respectively). (Figures 1B, C)

The rate of PPFS was significantly higher in patients with tumor diameter < 40 mm than in those with tumor diameter ≥ 40 mm ($p < 0.05$). However, there were no significant

differences in the OS and PFS between a tumor diameter < 40 mm and ≥ 40 mm ($p = 0.055$ and $p = 0.087$, respectively). Likewise, there were no differences in the OS, PFS, and PPFS between the RT and CCRT groups for patients with tumor diameter < 40 mm or ≥ 40 mm.

The rates of OS, PFS, and PPFS were significantly higher in the node negative patients than in the node positive patients ($p = 0.036$, 0.002 , and 0.004 , respectively). For the node negative patients, the rates of OS (Figure 2), PFS, and PPFS were higher in the CCRT group than in the RT group ($p = 0.015$, 0.028 and 0.047 , respectively). For the node positive patients, there were no significant differences in OS, PFS, and PPFS between the RT and CCRT groups ($p = 0.596$, 0.635 , and 0.615 , respectively).

Discussion

In the present study, the authors found that definitive RT was less toxic and effective in elderly patients and those with cervical cancer with complications. CCRT consists of pelvic RT with concurrent cisplatin-based chemotherapy and brachytherapy; it is a standard treatment for locoregionally advanced cervical cancer [11, 12]. A phase II study of CCRT (JGOG1066) showed that it was eligible and evaluable for compliance and severe toxicity and achieved comparable outcomes for Japanese patients. However, the JGOG1066 study focused on patients aged 20–70 years [13, 14]. Other reports of CCRT using weekly cisplatin were reported in patients younger than 79 years [15–20]. There are only few studies with relatively small number of cases that investigated cervical cancer in older patients [22–29]. The results of these studies are very heterogeneous.

A systematic review of acute toxicity showed that Grade 1–2 hematologic toxicities and Grade 3–4 hematological and gastrointestinal toxicities were higher in the CCRT group than in the RT group. A two-fold increase in white blood cell count, a three-fold increase in platelet toxicity, and a two-fold increase in gastrointestinal toxicity were observed in the CCRT group [9]. Keys *et al.* reported that 35% of patients in the CCRT group had Grade 3–4 adverse effects compared to 13% of the RT group [8]. These reactions almost exclusively comprised transient hematologic effects (21% in the CCRT group and 2% in the RT group) and gastrointestinal effects (14% in the CCRT group and 5% in the RT group) [8]. In the present study, the frequency of Grade 3–4 leukopenia in the RT group was lower than that in the CCRT group.

Elderly women with cervical cancer tolerated RT with acceptable morbidity and survival; moreover, age did not influence tumor control or the survival benefit provided by RT when adequate treatment was delivered [10, 25, 26, 30, 31]. RT for patients >70 years was completed as initially scheduled in 98.2% of patients; brachytherapy was not completed in 1.8% of patients for psychological problems due to insufficient mobility in bed [32]. In another report,

curative RT for patients with cervical cancer who were >70 years was completed as planned in 68% and stopped prematurely in 3% of the patients [30]. In the present study, the initially scheduled RT was completed in 81% of the patients, and appropriate RT was completed in 92% of the RT group. Thus, definitive RT was safely performed in elderly patients and those with complications. In addition, there were no significant differences in OS, PFS or PPFS between the RT and CCRT groups.

In contrast, the previously randomized controlled trials utilized low dose-rate ICBT (LDR-ICBT) [4, 8, 17], high dose-rate ICBT (HDR-ICBT) in Japan. Retrospective analysis on HDR-ICBT showed no significant differences between CCRT and RT in OS and disease-free survival for Japanese women with locally advanced cervical cancer [18]. Further randomized trials of RT and CCRT with HDR-ICBT are necessary to elucidate the optimal therapy for advanced cervical cancer.

In conclusion, definitive RT in elderly patients and patients with complicated cervical cancer was safe and effective. A limitation of this study was its retrospective nature and relatively small number of patients. Further studies are necessary to confirm the conclusions of the present study.

References

- [1] Hori M., Matsuda T., Shibata A., Katanoda K., Sobue T., Nishimoto H.: "Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project". *Jpn. J. Clin. Oncol.*, 2015, 45, 884.
- [2] Ebina Y., Yaegashi N., Katabuchi H., Nagase S., Udagawa Y., Hachisuga T., Saito T., *et al.*: "Japan Society of Gynecologic Oncology guidelines 2011 for the treatment of uterine cervical cancer". *Int. J. Clin. Oncol.*, 2015, 20, 240.
- [3] Eifel P.J., Winter K., Morris M., Levenback C., Grigsby P.W., Cooper J., Rotman M., *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.
- [4] Morris M., Eifel P.J., Lu J., Grigsby P.W., Levenback C., Stevens R.E., Rotman M., *et al.*: "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer". *The New England journal of medicine*, 1999, 340, 1137–43.
- [5] Of, O.: "Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials". *J. Clin. Oncol.*, 2008, 26, 5802.
- [6] Rose P.G., Bundy B.N., Watkins E.B., Thigpen J.T., Deppe G., Maiman M.A., Pearson D. L.C., *et al.*: "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *The New England journal of medicine*, 1999, 340, 1144.
- [7] Whitney C.W., Sause W., Bundy B.N., Malfetano J.H., Hannigan E.V., Fowler W.C., Jr., Pearson D. L.C., *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.
- [8] Keys H.M., Bundy B.N., Stehman F.B., Mudders L.L., Chafe W.E., Suggs C.L., 3rd, Walker J.L., *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.
- [9] Kirwan J.M., Symonds P., Green J.A., Tierney J., Collingwood M., Williams C.J.: "A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer". *Radiother. Oncol.*, 2003, 68, 217.
- [10] Yoshida K., Sasaki R., Nishimura H., Miyawaki D., Kawabe T., Okamoto Y., Nakabayashi K., *et al.*: "Radiotherapy for Japanese elderly patients with cervical cancer: preliminary survival outcomes and evaluation of treatment-related toxicity". *Arch. Gynecol. Obstet.*, 2011, 284, 1007.
- [11] Monk B.J., Tewari K.S., Koh W.J.: "Multimodality Therapy for Locally Advanced Cervical Carcinoma: State of the Art and Future Directions." *J. Clin. Oncol.* 2007, 25, 2952.
- [12] Robin T.P., Amini A., Scheffer T.E., Behbakht K., Fisher C.M.: "Disparities in standard of care treatment and associated survival decrement in patients with locally advanced cervical cancer". *Gynecol. Oncol.*, 2016, 143, 319.
- [13] Toita T., Kitagawa R., Hamano T., Umayahara K., Hirashima Y., Aoki Y., Oguchi M., *et al.*: "Feasibility and acute toxicity of Concurrent Chemoradiotherapy (CCRT) with high-dose rate intracavitary brachytherapy (HDR-ICBT) and 40-mg/m² weekly cisplatin for Japanese patients with cervical cancer: results of a Multi-Institutional Phase 2 Study (JGOG1066)". *Int. J. Gynecol. Cancer*, 2012, 22, 1420.
- [14] Toita T., Kitagawa R., Hamano T., Umayahara K., Hirashima Y., Aoki Y., Oguchi M., *et al.*: "Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule". *Gynecol. Oncol.*, 2012, 126, 211.
- [15] Chen S.W., Liang J.A., Hung Y.C., Yeh L.S., Chang W.C., Lin W.C., Yang S.N., *et al.*: "Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications". *Int. J. Radiat. Oncol. Biol. Phys.*, 2006, 66, 1370.
- [16] Kuroda Y., Murakami N., Morota M., Sekii S., Takahashi K., Inaba K., Matahara H., *et al.*: "Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer". *J. Radiat. Res.*, 2012, 53, 588.
- [17] Pearcey R., Brundage M., Drouin P., Jeffrey J., Johnston D., Lukka H., MacLean G., *et al.*: "Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix". *J. Clin. Oncol.*, 2002, 20, 966.
- [18] Sakata K., Sakurai H., Suzuki Y., Katoh S., Ohno T., Toita T., Kataoka M., *et al.*: "Results of concomitant chemoradiation for cervical cancer using high dose rate intracavitary brachytherapy: study of JROSG (Japan Radiation Oncology Study Group)". *Acta. Oncol.*, 2008, 47, 434.
- [19] Serkies K., Jassem J.: "Concurrent weekly cisplatin and radiotherapy in routine management of cervical cancer: a report on patient compliance and acute toxicity". *Int. J. Radiat. Oncol. Biol. Phys.*, 2004, 60, 814.
- [20] Tharavichitkul E., Pinitpatcharalerd A., Lorvidhaya V., Kamnerdsupaphon P., Pukanhaphan N., Sukthomya V., Chitapanarax I., *et al.*: "Impact of Incomplete Plan to Treatment Results of Concurrent Weekly Cisplatin and Radiotherapy in Locally Advanced Cervical Cancer". *J. Radiat. Res.*, 2011, 52, 9.
- [21] Alvarez R.D., Soong S.J., Kinney W.K., Reid G.C., Schray M.F., Podratz K.C., Morley G. W., *et al.*: "Identification of prognostic factors and risk groups in patients found to have nodal metastasis at the time of radical hysterectomy for early-stage squamous carcinoma of the cervix". *Gynecol. Oncol.*, 1989, 35, 130.
- [22] Chen S.W., Liang J.A., Yang S.N., Lin F.J.: "High dose-rate brachytherapy for elderly patients with uterine cervical cancer". *Jpn. J. Clin. Oncol.*, 2003, 33, 221.
- [23] Goodheart M., Jacobson G., Smith B.J., Zhou L.: "Chemoradiation for invasive cervical cancer in elderly patients: outcomes and morbidity". *Int. J. Gynecol. Cancer*, 2008, 18, 95.
- [24] Hata M., Koike I., Miyagi E., Numazaki R., Asai-Sato M., Kasuya T., Kaizu H., *et al.*: "Radiation Therapy for Very Elderly Patients Aged 80 Years and Older With Squamous Cell Carcinoma of the Uterine Cervix". *Am. J. Clinical Oncol.*, 2017, 40, 178.
- [25] Ikushima H., Takegawa Y., Osaki K., Furutani S., Yamashita K., Kawanaka T., Kubo A., *et al.*: "Radiation therapy for cervical cancer in the elderly". *Gynecol. Oncol.*, 2007, 107, 339.
- [26] Mitchell P.A., Waggoner S., Rotmensch J., Mundt A.J.: "Cervical cancer in the elderly treated with radiation therapy". *Gynecol. Oncol.*, 1998, 71, 291.
- [27] Nosaka K., Shibata K., Utsumi F., Yoshida K., Niimi K., Sekiya R., Suzuki S., *et al.*: "Feasibility and benefit of concurrent chemoradiotherapy for elderly patients with uterine cervical cancer". *Tumori.*, 2016, 102, 600.
- [28] Park J.H., Kim Y.S., Ahn S.D., Choi E.K., Shin S.S., Kim Y.T., Kim Y.M., *et al.*: "Concurrent chemoradiotherapy or radiotherapy alone for locally advanced cervical cancer in elderly women". *Tumori.*, 2010, 96, 959.
- [29] Sablinska B.: "Carcinoma of the uterine cervix in women over 70 years of age". *Gynecol Oncol.*, 1979, 7, 128.
- [30] Lindegaard J.C., Thranov I.R., Engelholm S.A.: "Radiotherapy in the management of cervical cancer in elderly patients". *Radiother. Oncol.*, 2000, 56, 9.
- [31] Minagawa Y., Kigawa J., Itamochi H., Terakawa N.: "The outcome of radiation therapy in elderly patients with advanced cervical cancer". *Int J Gynaecol Obstet.*, 1997, 58, 305.
- [32] Magne N., Mancy N.C., Chajon E., Duvillard P., Pautier P., Castaigne D., Lhomme C., *et al.*: "Patterns of care and outcome in elderly cervical cancer patients: a special focus on brachytherapy". *Radiother. Oncol.*, 2009, 91, 197.

Corresponding Author:

H. IMAFUKU, M.D.

Department of Obstetrics and Gynecology

Kobe University Graduate School of Medicine

7-5-1 Kusunoki-cho

Chuo-ku, Kobe 650-0017 (Japan)

e-mail: ima1210@med.kobe-u.ac.jp