[3] Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer 2002;12(5):448–53.
[4] Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 2000;78(2):85–91.
[5] Goff BA, Goodman A, Muntz HG, Fuller Jr AF, Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol 1994;52(2):237–40.
[6] Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in stage IV endometrial carcinoma. Gynecol Oncol 1997;67(1):56–60.
[7] Shih KK, Yun E, Gardner GJ, Barakat RR, Chi DS, Leitao Jr MM. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. Gynecol Oncol 2011;122(3):608–11.
[8] Bristow RE, Duska LR, Montz FJ. The role of cytoreductive surgery in the management of stage IV uterine papillary serous carcinoma. Gynecol Oncol 2001;81(1):92–9.
[9] Thomas MB, Mariani A, Cliby WA, Keeney GL, Podratz KC, Dowdy SC. Role of cytoreduction in stage III and IV uterine papillary serous carcinoma. Gynecol Oncol 2007;107(2):190–3.
[10] Ueda Y, Enomoto T, Miyatake T, Egawa-Tanaka T, Ugaki H, Yoshino K, et al. Endometrial carcinoma with extra-abdominal metastasis: improved prognosis following cytoreductive surgery. Ann Surg Oncol 2010;17(4):1111–7.
[11] Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol 2010;118(1):14–8.
[12] Eto T, Saito T, Kasamatsu T, Nakanishi T, Yokota H, Satoh T, et al. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: a retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol 2012;127(2):338–44.
[13] Creasman W, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Cancer of the corpus uteri. FIGO 6th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2006;95(Suppl. 1):S105–43.
[14] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363(10):943–53.
[15] Vandenput I, Van Calster B, Capoen A, Leunen K, Berteloot P, Neven P, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer 2009;101(2):244–9.
[16] Cook AM, Lodge N, Blake P. Stage IV endometrial carcinoma: a 10 year review of patients. Br J Radiol 1999;72(857):485–8.
[17] Pliskow S, Penalver M, Averette HE. Stage III and stage IV endometrial carcinoma: a review of 41 cases. Gynecol Oncol 1990;38(2):210–5.
[18] Behbakht K, Yordan EL, Casey C, DeGeest K, Massad LS, Kirschner CV, et al. Prognostic indicators of survival in advanced endometrial cancer. Gynecol Oncol 1994;55(3):363–7.
[19] van Wijk FH, Huikeshoven FJ, Abdulkadir L, Ewing PC, Burger CW. Stage III and IV endometrial cancer: a 20-year review of patients. Int J Gynecol Cancer 2006;16(4):1648–55.
[20] Aalders JG, Abeler V, Kolstad P. Stage IV endometrial carcinoma: a clinical and histopathological study of 83 patients. Gynecol Oncol 1984;17(1):75–84.
[21] Landrum LM, Moore KN, Myers TK, Lanneau Jr GS, McMeekin DS, Walker JL, et al. Stage IVB endometrial cancer: does applying an ovarian cancer treatment paradigm result in similar outcomes? A case-control analysis. Gynecol Oncol 2009;112(2):337–41.
[22] Bonnefoi H, A'Hern RP, Fisher C, Macfarlane V, Barton D, Blake P, et al. Natural history of stage IV epithelial ovarian cancer. J Clin Oncol 1999;17(3):767–75.
[23] NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®). http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf; 2013. [cited Version 1.2013 18.3.2013]; Available from:.
[24] Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol 2007;18:409–20.
[25] Lambrou NC, Gomez-Marin O, Mirhashemi R, Beach H, Salom E, Almeida-Parra Z, et al. Optimal surgical cytoreduction in patients with stage III and stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol 2004;93(3):653–8.
[26] Memarzadeh S, Holschneider CH, Bristow RE, Jones NL, Fu YS, Karlan BY, et al. FIGO stage III and IV uterine papillary serous carcinoma: impact of residual disease on survival. Int J Gynecol Cancer 2002;12(5):454–8.
[27] Numazaki R, Miyagi E, Konnai K, Ikeda M, Yamamoto A, Onose R, et al. Analysis of stage IVB endometrial carcinoma patients with distant metastasis: a review of prognoses in 55 patients. Int J Clin Oncol 2009;14(4):344–50.
[28] Chambers JT, Chambers SK, Voynick IM, Schwartz PE. Neoadjuvant chemotherapy in stage X ovarian carcinoma. Gynecol Oncol 1990;37(3):327–31.
[29] Jacob JH, Gershenson DM, Morris M, Copeland LJ, Burke TW, Wharton JT. Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer. Gynecol Oncol 1991;42(2):146–50.

FULL PAPER

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Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery *vs* radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: a Japan Clinical Oncology Group trial (JCOG 0102)

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Background: A phase III trial was conducted to determine whether neoadjuvant chemotherapy (NACT) before radical surgery (RS) improves overall survival.

Methods: Patients with stage IB2, IIA2, or IIB squamous cell carcinoma of the uterine cervix were randomly assigned to receive either BOMP (bleomycin 7 mg days 1–5, vincristine 0.7 mg m^{-2} day 5, mitomycin 7 mg m^{-2} day 5, cisplatin 14 mg m^{-2} days 1–5, every 3 weeks for 2 to 4 cycles) plus RS (NACT group) or RS alone (RS group). Patients with pathological high-risk factors received postoperative radiotherapy (RT). The primary end point was overall survival.

Results: A total of 134 patients were randomly assigned to treatment. This study was prematurely terminated at the first planned interim analysis because overall survival in the NACT group was inferior to that in the RS group. Patients who received postoperative RT were significantly lower in the NACT group (58%) than in the RS group (80%; $P=0.015$). The 5-year overall survival was 70.0% in the NACT group and 74.4% in the RS group ($P=0.85$).

Conclusion: Neoadjuvant chemotherapy with BOMP regimen before RS did not improve overall survival, but reduced the number of patients who received postoperative RT.

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Treatment of International Federation of Gynaecology and Obstetrics (FIGO) stages IB2, IIA2, and IIB cervical cancer remains controversial. Bulky stage IIA (tumour diameter >4 cm) cervical cancer was revised to stage IIA2 (Pecorelli *et al*, 2009) in the FIGO staging system in 2009. Major treatment options include radical surgery (RS) with or without postoperative radiotherapy (RT), neoadjuvant chemotherapy (NACT) followed by RS with or without postoperative RT, and concurrent chemoradiotherapy (CCRT). Radical surgery usually entails type III radical hysterectomy (Piver *et al*, 1974) plus pelvic or para-aortic lymphadenectomy (or both). For stage IB2 and IIA2 cervical cancer, the National Comprehensive Cancer Network (NCCN Clinical Practice Guidelines, 2012) clinical guidelines mainly recommend CCRT (category 1) and, to a lesser degree, radical hysterectomy with pelvic lymphadenectomy and para-aortic lymph node sampling (category 2b). In Japan, however, more radical procedures, such as Okabayashi's (type III or IV) radical hysterectomy plus pelvic or para-aortic lymphadenectomy (or both), remain the standard treatment of choice for stages IB2, IIA2, and IIB cervical cancer (Fujii *et al*, 2007).

Before we started this study, only one randomised controlled trial conducted at a single centre had compared NACT plus RS with RS alone. In 1997, Sardi *et al* (1997) reported the results of a randomised trial that compared NACT plus RS with RS in 205 patients with stages IB squamous cell cervical cancer. Three courses of NACT with vincristine, bleomycin, and cisplatin (VBP) were given in NACT group. Overall survival at 8 years with NACT group was superior to RS group (81% *vs* 66%, $P<0.05$). In a subgroup analysis in patients with non-bulky tumours <4 cm, there was no significant difference between the two groups (82% *vs* 77%, NS).

Thus, NACT plus RS has emerged as a valid alternative investigational treatment. In 1998, one institution affiliated with our group confirmed that combination chemotherapy with bleomycin, vincristine, mitomycin, and cisplatin (BOMP) produced a high response rate (76%) in metastatic cervical cancer (Shimizu *et al*, 1998). We decided to use the BOMP regimen as NACT.

To clarify the potential benefits of NACT before RS, we undertook a phase III, randomised controlled trial to compare NACT plus RS with RS alone in patients with stages IB2, IIA2, and IIB cervical cancer.

PATIENTS AND METHODS

Eligibility criteria. Patients who had primary, previously untreated, histologically confirmed squamous cell carcinoma of the cervix with bulky FIGO stage IB2, IIA, and IIB disease (tumour diameter >4 cm on magnetic resonance imaging (MRI)) were eligible for this Japan Clinical Oncology Group (JCOG) study (JCOG 0102). In July 2003, the criteria were amended to patients with FIGO stage IB2, IIA2 (tumour diameter >4 cm by clinical measurement), and IIB (irrespective of tumour diameter) disease and additionally required the presence of target cervical lesions (>2 cm) on MRI according to the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. Patients who were suitable candidates for radical hysterectomy as described in the treatment schedule section were eligible. Patients were also required to be between 20 and 70 years of age, to have performance status of 0 or 1, and to have normal organ functions and normal electrocardiogram. Patients with any of the following conditions were excluded: synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ* or mucosal cancer; pregnancy; psychotic disease; active infection with fever; uncontrolled hypertension or diabetes mellitus; positive hepatitis B surface antigen; a history of heart failure, unstable angina, or myocardial infarction; interstitial pneumonitis or pulmonary fibrosis; or severe obesity, liver cirrhosis, or bleeding tendency. All patients gave informed consent before enrolment in this study, which was approved by the institutional review boards at the participating institutions (UMIN-CTR No. C000000194 and clinicaltrials.gov No. NCT00190528).

Treatment schedule

Neoadjuvant chemotherapy. Patients were randomly assigned to receive either NACT followed by RS or RS alone. The BOMP regimen for NACT comprised bleomycin (7 mg) as a 30-min intravenous infusion on days 1–5, vincristine (0.7 mg m^{-2}) as a bolus intravenous injection on day 5, mitomycin (7 mg m^{-2}) as a bolus intravenous injection on day 5, and cisplatin (14 mg m^{-2}) as a 30-min intravenous infusion on days 1–5 of a 21-day cycle. Patients initially received two cycles. Patients who had a complete response (CR) or partial response (PR) after two cycles of BOMP were given two additional cycles. Treatment was administered if the white cell count was $\geqslant$2000 per μl and the platelet count was $\geqslant$75 000 per μl. Treatment could be delayed for up to 2 weeks until these minimum criteria were met.

After NACT, the patients were clinically reassessed and classified as suitable or unsuitable for radical hysterectomy. The criteria for radical hysterectomy includes adequate organ function with good performance status. The unsuitable patients received RT, including whole pelvis RT and brachytherapy.

Surgery. The standard procedure used to perform radical hysterectomy in this study was based on Okabayashi's radical hysterectomy as reported by Kyoto Imperial University in 1921. This procedure involves wide extirpation of the parametrial tissue and separation of the posterior leaf of the vesicouterine ligament (Okabayashi, 1921). With the use of this technique, the surgeon can separate the bladder with the ureter completely away from the lateral side of the cervix and the vagina. This dissection facilitates resection of all periureteral tissue and any length (more than one-third) of the vagina and paravaginal tissues. Okabayashi's radical hysterectomy is thus classified as type III or IV radical hysterectomy (Okabayashi, 1921).

In this study, radical hysterectomy require removal of at least 3 cm of the vaginal and paravaginal tissues, and if the vagina was involved, removal of the vagina and vaginal tissues with a margin of at least 2 cm from the cancer. Twenty or more pelvic lymph nodes were required to dissect. If metastases to the para-aortic nodes were suspected, the para-aortic nodes were sampled or dissected. Radical surgery was performed within 3 weeks after randomisation in the RS group and within 8 weeks after the last administration of chemotherapy in the NACT group.

Postoperative RT. The protocol required that postoperative RT was started within 6 weeks after surgery. A total dose of 4500–5040 cGy was delivered to the whole pelvis in daily fractions of 180–200 cGy if patients had pelvic lymph node metastasis, parametrial involvement, or deep stromal invasion ($\geqslant$2/3). Extended-field external beam therapy, delivering a dose of 4500 cGy by a four-field technique, was administered to patients with positive para-aortic nodes. High-dose rate brachytherapy was delivered to the vaginal stump if patients had positive surgical margins.

Response and toxicity evaluation. Tumour response in the NAC group was assessed according to the RECIST guidelines (Therasse *et al*, 2000). Target lesions, including the primary cervical tumour, were measured by MRI. An independent response review committee evaluated all tumour responses after the investigators had completed their assessments.

Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0) (Trotti *et al*, 2000). Surgical morbidity was defined as adverse events related to surgery that occurred between the date of surgery

1 month postoperatively. Early and late adverse events of RT were respectively defined as adverse events that occurred within the first 90 days or more than 90 days after the completion of RT. Late adverse events were evaluated according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme in Appendix IV of NCI-CTC, version 2.0 (Trotti *et al*, 2000).

Statistical considerations. This was a randomised, multicentre, nonblinded, prospective, phase III study. After confirmation of the inclusion/exclusion criteria by telephone or fax to the JCOG Data Center, the patients were randomly assigned to treatment according to a minimisation procedure. Minimisation criteria were disease stage (I; II), age ($\leqslant$50 years; $>$50 years), and institution. The primary end point was overall survival. The secondary end points were progression-free survival, surgical morbidity, compliance with radical hysterectomy, omission of postoperative irradiation, early and late radiation-related morbidity, and rate of response to chemotherapy. Overall survival was measured from the date of registration to the date of death from any cause, and data were censored at the time of the last follow-up for surviving patients. Progression-free survival was measured from the date of randomisation to the date of the first event (i.e., confirmation of disease progression or death from any cause), and data were censored at the last date on which the absence of disease progression was confirmed.

We assumed that the 5-year survival rate would be 60% in the RS group and 75% in the NACT group. The planned sample size was 100 patients in each treatment group, with a one-sided α-level of 0.05, a power of 0.8, an accrual of 5.5 years, and a follow-up of 3.5 years (Schoenfeld and Richter, 1982). Two interim analyses were scheduled. The first interim analysis was done when 100 patients had been randomly assigned to treatment, and the second was done when all patients had been assigned treatment. Multiplicity was adjusted by the method proposed by the Southwest Oncology Group (Green *et al*, 1997). The significant levels were one-sided 0.005 at each interim analysis and one-sided 0.045 at the final analysis. Survival curves were estimated with the Kaplan–Meier method, and stratified log-rank tests were used to assess differences between treatment groups, stratified according to disease stage (I *vs* II) and age ($\leqslant$50 years *vs* $>$50 years). We used a Cox proportional hazard model to estimate treatment effects. All analyses were done on an intention-to-treat basis, except for toxicity. Toxicity analyses were restricted to patients who had received at any part of their assigned treatment. Although this trial was designed for one-sided hypothesis testing, follow-up results are reported with two-sided *P*-values because of the exploratory nature of the analysis. All analyses were carried out using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Enrolment in this study began on 1 December 2001. The first planned interim analysis was performed in July 2005 (Figure 1). Data from 108 patients enrolled by November 2004 were analysed. On the basis of this analysis, the Data and Safety Monitoring Committee (DSMC) recommended to prematurely terminate the study because overall survival in the NACT group was inferior to that in the RS group (HR, 2.11; multiplicity-adjusted 99% CI, 0.34–13.2), and the predicted probability of significant superiority in the NACT group at the end of the study as assessed by Spiegelhalter's method (Spiegelhalter *et al*, 1993) was extremely low (6.4%). The study was therefore closed on 1 August 2005.

Between December 2001 and August 2005, a total of 134 patients (67 in the NACT group and 67 in the RS group) were randomly assigned to treatment at 28 institutions. Table 1 summarises the baseline characteristics of the patients. One patient

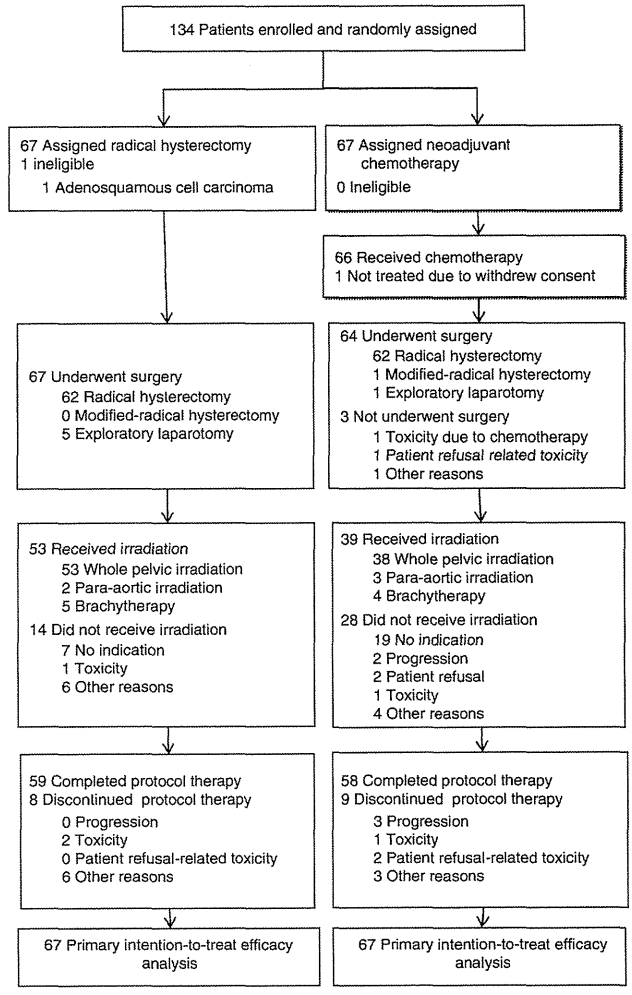


Figure 1. Trial profile.

in the RS group was ineligible because of an incorrect histopathological diagnosis of adenosquamous carcinoma on cervical biopsy before enrolment. Three patients in the NACT group who were given a diagnosis of squamous cell carcinoma on biopsy before enrolment were found to have adenosquamous carcinoma on evaluation of their surgical specimens. These patients were considered eligible.

Of the 67 patients randomly assigned to the NACT group, 66 received chemotherapy. One patient did not receive chemotherapy because of her refusal after registration. This patient underwent primary RS. The other 66 patients received at least two cycles of NACT. The overall response (CR + PR) rate was 70% (47 out of 67) on the investigators' assessment and 66% (44 out of 67) on independent central review (Table 2). Toxicity associated with chemotherapy is summarised in Table 3. Nearly all toxic effects were tolerable, and chemotherapy could be continued in all but three patients who discontinued treatment during the third or fourth cycle because of toxicity (persistent grade 3 thrombocytopenia in two patients and grade 3 skin toxicity in one patient). Grade 3 alkalosis with hypertension, thrombosis, atrial fibrillation, or skin ulceration occurred in one patient each, but these toxic effects were transient and soon resolved.

Of the 67 patients in each group, 62 (93%) underwent RS, suggesting that operability was similar in the groups. Five patients in the RS group and one in the NACT group underwent laparotomy for RS, but the procedure was terminated during surgery because of inoperable disease associated with conditions

Table 1. Patient characteristics

	Radical hysterectomy ($n=67$)		Neoadjuvant chemotherapy ($n=67$)	
	No. of patients	%	No. of patients	%
Age, years				
Median Range	46 22–67		47 28–70	
ECOG performance status				
0	59	88	62	93
1	8	12	5	8
FIGO stage				
IB2	26	39	24	36
IIA	7	10	5	8
IIB	34	51	38	57
Histology in biopsy				
Squamous cell	66	99	67	100
Adenosquamous cell	1	1	0	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynaecology and Obstetrics surgical staging system.

Table 2. Clinical response of neoadjuvant chemotherapy

Response category	Investigator assessment ($n=67$)	Independent central review ($n=67$)
CR	9 (13)	8 (12)
PR	38 (57)	36 (54)
SD	18 (27)	20 (30)
PD	0 (0)	0 (0)
NE	1 (1)	2 (3)
Overall response	47 (70)	44 (66)
95% CI	58–81	53–77

Abbreviations: CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease. Values are presented as *n* (%).

Table 3. Toxicity of chemotherapy ($n=66$)

	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukopenia	24	3	41
Neutropenia	21	15	56
Haemoglobin	11	5	24
Thrombocytopenia	18	0	27
Hyponatraemia	3	0	5
Hyperkalaemia	1	0	2
Nausea	11	—	17
Vomiting	4	0	6
Febrile neutropenia	2	0	3
Fatigue	3	0	5
Hypersensitivity	2	0	3

Table 4. Surgical findings

	Radical hysterectomy ($n=62$)		Neoadjuvant chemotherapy ($n=62$)	
	No. of patients	%	No. of patients	%
Tumour diameter (cm)				
Median Range	5.1 2.5–13.5		3 0–10.3	
Postsurgical T classification (pT)				
0–IB1	5	8	25	40
IB2–pT2B	57	92	34	55
>2B	0	0	3	5
Positive pelvic nodes	27	44	17	27
Invasion to muscle layer ⩾2/3	52	84	38	61
Parametrial invasion	28	45	25	40

such as pelvic wall involvement, disseminated tumours, or both. Median dissected lymph nodes were 47 (range 20–119) in the RS group and 45 (range 13–95) in the NACT group. Para-aortic lymph node sampling and dissection were respectively performed in 22 and 14 patients in the RS group and 20 and 14 patients in the NACT group. Median blood loss and operation time were respectively 950 ml and 5.5 h in the RS group and 1370 ml and 5.6 h in the NACT group.

Table 4 shows the pathological findings of surgical specimens obtained from patients who underwent RS. The median tumour diameter in the NACT group was smaller than that in the RS group (3.0 *vs* 5.1 cm). On postsurgical T classification (pT), downstaging to pT0-Ib1 was confirmed in 40% of the patients in the NACT group. The proportion of patients with positive pelvic nodes was lower but statistically not significant in the NACT group than in the RS group (27% *vs* 44%, $P=0.091$), whereas parametrial involvement was similar in both groups (40% *vs* 45%, $P=0.717$). The incidence of para-aortic lymph node metastasis was 2 and 1 in the RS group and NACT group, respectively.

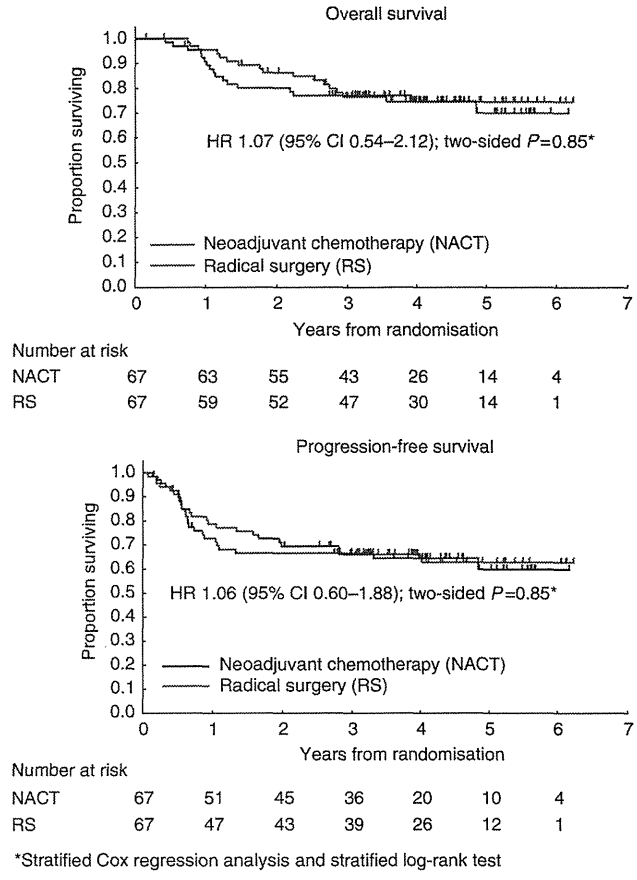
As for surgical morbidity, ureteral or bladder injuries occurred and were repaired during surgery in two patients in the RS group and two in the NACT group. A ureterovaginal fistula developed postoperatively in another patient in the RS group. Grade 3 wound infections occurred in one patient in the RS group and two patients in the NACT group. Grade 3 dysuria developed in one patient in the RS group. Grade 3 disseminated intravascular coagulation occurred in one patient in the NACT group. The incidences of pneumonia, bowel obstruction, and haemorrhage during the first month after surgery were similar in both treatment groups (0, 3, and 0 patients in the RS group *vs* 1, 2, and 1 patients in the NACT group).

The proportion of patients who met the criteria for post-operative radiation (i.e., lymph node metastasis, parametrial involvement, or deep stromal invasion >2/3) was significantly lower in the NACT group (48 (72%) of 67) than in the RS group (59 (89%) of 66; $P=0.015$), and the patients who received

Table 5. Radiation morbidity

	Radical hysterectomy ($n=66$)			Neoadjuvant chemotherapy ($n=67$)		
	Grade 3	Grade 4	Grade 3 or 4 (%)	Grade 3	Grade 4	Grade 3 or 4 (%)
Early adverse events						
Leukocytes	0	0	0	1	0	1
Haemoglobin	0	0	0	2	1	4
Thrombocytes	0	0	0	1	0	1
Diarrhoea	5	0	8	2	0	3
Nausea	0	—	0	1	—	1
Vomiting	0	0	0	1	0	1
Lymphedema	1	0	2	0	0	0
Dysuria	1	—	2	0	—	0
Urinary retention	9	0	14	5	0	7
Late adverse events[a]						
Lymphedema	2	0	3	5	0	7
Urinary retention	7	0	11	3	1	6
Vesicovaginal fistula	1	0	2	1	1	3
Bowel obstruction	6	0	9	1	2	4

[a]Late adverse events were defined as the adverse events that were observed more than 90 days after radiation therapy.



*Stratified Cox regression analysis and stratified log-rank test

Figure 2. Survival curves of all randomised patients.

radiation in the NACT group (39 (58%) of 67) were lower than those in the RS group (53 (79%) of 67; $P=0.015$). Postoperative RT to the whole pelvis, RT to the para-aortic region, and brachytherapy were respectively given to 53, 2, and 5 patients in the RS group and 38, 3, and 4 patients in the NACT group. Early adverse events (within 90 days after radiation) occurred in 70% (46 of 66) of the patients in the RS group and 55% (37 of 67; $P=0.108$) of the patients in the NACT group. Grade 3 or 4 haematologic toxicity was more common in the NACT group than in the RS group (Table 5), whereas nonhaematologic toxic effects such as diarrhoea or urinary retention were more common in the RS group than in the NACT group. Late adverse events (90 days or more after radiation) occurred in 65% (43 of 66) of the patients in the RS group and 42% (28 of 67; $P=0.009$) of the patients in the NACT group. The incidence of grade 3 or 4 lymphedema was slightly higher in the NACT group than in the RS group, whereas urinary retention and bowel obstruction were more common in the RS group than in the NACT group. One patient in the NACT group died of perforation and necrosis of the small intestine 215 days after the last dose of radiation. This death was considered treatment related.

At the time of final follow-up (May 2008), with a median follow-up of 49 months for patients with censored data, there had been 17 deaths in the NACT group and 16 in the RS group. The 5-year overall survival was 70.0% in the NACT group and 74.4% in the RS group (Figure 2; hazard ratio (HR) by Cox regression analysis, 1.07; 95% CI, 0.54–2.12; two-sided $P=0.85$, stratified log-rank test). The 5-year progression-free survival was 59.9% in the NACT group and 62.7% in the RS group (Figure 2; HR, 1.06; 95% CI, 0.60–1.88; two-sided $P=0.85$, stratified log-rank test). On subgroup analyses among patients with stage IB2 disease, the 5-year overall survival and progression-free survival were, respectively, 82.9% and 71.2% in the RS group ($n=25$) and 78.4% and 60.5% in the NACT group ($n=25$), and among patients with stages IIA2 and IIB disease, the 5-year overall survival and progression-free survival were 69.5% and 58.4% in the RS group ($n=42$) and 65.3% and 59.3% in the NACT group ($n=42$).

DISCUSSION

Our study concluded that NACT with BOMP before RS did not improve overall survival of patients with stages IB2, IIA2, and IIB cervical cancer. However, NACT was associated with a reduced proportion of patients who received postoperative RT.

The benefits of NACT followed by surgery as compared with surgery alone were addressed in a Cochrane meta-analysis (Rydzewska *et al*, 2010) of six phase III trials (FIGO stage of the subjects: Sardi's trial (Sardi *et al*, 1997), IB1 + IB2; Napolitano's trial (Napolitano *et al*, 2003), IB-IIIB; Cai's trial (Cai *et al*, 2006), IB1 + IB2; Katsumata's trial (present study) (Katsumata *et al*, 2006), IB2, IIA2, IIB; Eddy's trial (Eddy *et al*, 2007), IB2; Chen's trial (Chen *et al*, 2008), IB2-IIB) of 1036 patients, including our immature survival data, after a median follow-up of 34 months. Progression-free survival was significantly improved by NACT + RS (HR = 0.76, 95% CI, 0.62–0.94). However, the improvement in overall survival with NACT plus RS was not statistically significant (HR = 0.85, 95% CI, 0.67–1.07). Only Sardi's trial showed a statistically significant benefit of NACT in terms of overall survival (HR = 0.53, 95% CI, 0.31–0.92) (Sardi *et al*, 1997). Among the six trials, Eddy's GOG trial (Eddy *et al*, 2007) and our trial

demonstrated no survival benefit of NACT (HR = 1.01, 95% CI, 0.68–1.49 and HR = 1.12, 95% CI, 0.56–2.22). Why the results differed substantially among trials remains unclear. The meta-analysis concluded that the type of drugs used or how they were given had no effect on the overall results. Moreover, the results were similar in women with early-stage disease and those with more advanced cancer.

The clinical response rate of 67% reported in this study is lower than the rate of 84% obtained in patients with stage IB2 disease in Sardi's trial (quick VBP regimen: intravenous vincristine 1 mg m^{-2}, bleomycin 25 mg m^{-2} on days 1–3 and cisplatin 50 mg m^{-2} every 10 days for 3 cycles), but higher than the rate of 52% obtained in Eddy's GOG trial (quick VP regimen, intravenous vincristine 1 mg m^{-2} and cisplatin 50 mg m^{-2} every 10 days for 3 cycles). A previous meta-analysis of Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration (2003) reported that the timing and dose intensity of cisplatin-based NACT appear to have an important impact on the benefits of such treatment despite some unexplained heterogeneity between the trials in their design and results.

It is very difficult to compare the radicality of RS among trials in the Cochrane meta-analysis. Two of the trials (Napolitano's and Sardi's trials) reported markedly increased rates of radical resection with NACT, whereas no difference was found in the three trials (Cai's, Chen's, and Eddy's trials). In the present study, the rate of RS was similar in NACT group and RS group (93%). The 5-year survival rate of patients with stage IB2 disease in the RS group of Sardi's trial was only 60%, whereas the 4-year survival rate of patients with stage IB2 disease in the RS group of our study was 82%. Perhaps more radical surgery eliminates the survival benefits of NACT.

Concurrent chemoradiotherapy has been considered as current standard adjuvant therapy after RS for patients with high-risk factors for recurrence since 2000 (Peters *et al*, 2000). The role of NACT for high-risk patients who will receive chemoradiotherapy after RS is unclear. Radiotherapy alone was administered in previous NACT trials including our study. Therefore, concurrent chemoradiotherapy should be included when conducting the future NACT trial.

Optimal regimens for NACT have yet to be defined. Among the six trials included in the Cochrane meta-analysis, four trials used cisplatin-based chemotherapy combined with vincristine, three trials used bleomycin, and two trials used 5-fluorouracil or mitomycin because these trials were started between 1987 and 2001. Cisplatin-based chemotherapy combined with ifosphamide, paclitaxel, and topotecan may be more effective for cervical cancer (Omura *et al*, 1997; Moore *et al*, 2004; Long *et al*, 2005). Paclitaxel combined with cisplatin was associated with a higher response rate and better progression-free survival in patients with metastatic cervical cancer (Moore *et al*, 2004), and one phase III trial reported that a combination of paclitaxel, cisplatin, and ifosphamide had a significantly higher response rate than cisplatin and ifosphamide (Buda *et al*, 2005). To clarify the benefits of neoadjuvant chemotherapy, more potent regimens of chemotherapy should be explored.

In this study, the proportion of patients who received postoperative RT was significantly lower in the NACT group than in the RS group (58% *vs* 80%). In Eddy's GOG trial, the rate of postoperative RT was small, but not significantly lower in the NACT group than in the RS group (45% *vs* 52%). When we compared improvements in extrauterine pathological findings associated with NACT between these studies, the reduction in the proportion of patients with positive pelvic nodes was more apparent in the present study than in the GOG trial (from 44% to 29% *vs* from 39% to 32%). Improvements in other extrauterine pathological findings such as positive para-aortic nodes, parametrial involvement, and positive surgical margins were marginal in both studies. The decreased incidence of positive pelvic nodes in our trial most likely influenced the rate of postoperative RT in the NACT group.

Recently, Matsumura *et al* (2010) reported that NACT followed by surgery plus postoperative chemotherapy with cisplatin/irnotecan or nedaplatin/irinotecan, but not RT, is a viable option for the treatment of stage IB2-IIB cervical cancer. This treatment offers the advantage of eliminating radiation-induced morbidity

In conclusion, NACT before RS did not improve overall survival in patients with stages IB2, IIA2, and IIB locally advanced cervical cancer. However, NACT did reduce the proportion of patients who received postoperative RT. Further trials are warranted to clarify the potential benefits of NACT in locally advanced cervical cancer, once new drugs or new combination regimens are shown to be effective as NACT, postoperative adjuvant chemotherapy, or both. Two ongoing randomised phase III trials (EORTC 55994; NCT00193739) are comparing NACT followed by surgery with concurrent chemoradiation. The results of these trials may play an important role in determining whether NACT before surgery is a valid alternative to chemoradiation.

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REFERENCES

Buda A, Fossati R, Colombo N, Fei F, Floriani I, Gueli Alletti D, Katsaros D, Landoni F, Lissoni A, Malzoni C, Sartori E, Scollo P, Torri V, Zola P, Mangioni C (2005) Randomized trial of neoadjuvant chemotherapy comparing paclitaxel, ifosfamide, and cisplatin with ifosfamide and cisplatin followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the SNAP01 (Studio Neo-Adjuvante Portio) Italian Collaborative Study. *J Clin Oncol* **23**(18): 4137–4145.

Cai HB, Chen HZ, Yin HH (2006) Randomized study of preoperative chemotherapy versus primary surgery for stage IB cervical cancer. *J Obstet Gynaecol Res* **32**(3): 315–323.

Chen H, Liang C, Zhang L, Huang S, Wu X (2008) Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study. *Gynecol Oncol* **110**(3): 308–315.

Eddy GL, Bundy BN, Creasman WT, Spirtos NM, Mannel RS, Hannigan E, O'Connor D (2007) Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. *Gynecol Oncol* **106**(2): 362–369.

EORTC 55994. http://www.cancer.gov/clinicaltrials/search/view?cdrid=69375&version=healthprofessional.

Fujii S, Takakura K, Matsumura N, Higuchi T, Yura S, Mandai M, Baba T, Yoshioka S (2007) Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. *Gynecol Oncol* **107**(1): 4–13.

Green S, Benedetti J, Crowley J (1997) Interim Analysis and Data Monitoring Committee. *Clinical Trials in Oncology*, 1st edn, pp 80–99. Chapman & Hall/CRC.

Katsumata N, Yoshikawa H, Hirakawa T, Saito T, Kuzuya K, Fujii T, Hiura M, Tsunematsu R, Fukuda H, Kamura T (2006) Phase III randomized trial of neoadjuvant chemotherapy (NAC) followed by radical hysterectomy (RH) versus RH for bulky stage I/II cervical cancer (JCOG 0102). *Proc Am Soc Clin Oncol* **24**((No 18S)): abstract 5013.

Long 3rd HJ, Bundy BN, Grendys Jr EC, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV (2005) Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine

cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* **23**(21): 4626–4633.

Matsumura M, Takeshima N, Ota T, Omatsu K, Sakamoto K, Kawamata Y, Umayahara K, Tanaka H, Akiyama F, Takizawa K (2010) Neoadjuvant chemotherapy followed by radical hysterectomy plus postoperative chemotherapy but no radiotherapy for Stage IB2-IIB cervical cancer–irinotecan and platinum chemotherapy. *Gynecol Oncol* **119**(2): 212–216.

Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF, Rocereto TF (2004) 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* **22**(15): 3113–3119.

Napolitano U, Imperato F, Mossa B, Framarino ML, Marziani R, Marzetti L (2003) The role of neoadjuvant chemotherapy for squamous cell cervical cancer (Ib-IIIb): a long-term randomized trial. *Eur J Gynaecol Oncol* **24**(1): 51–59.

NCCN Clinical Practice Guidelines (2012) Oncology-Cervical Cancer, version I. *National Comprehensive Cancer Network*. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.

NCT00193739. http://clinicaltrials.gov/ct2/show/NCT00193739?term=NCT00193739.

Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration (2003) Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. *Eur J Cancer* **39**(17): 2470–2486.

Okabayashi H (1921) Radical abdominal hysterectomy for cancer of the cervixuteri, modification of the Takayama operation. *Surg Gynecol Obstet* **33**: 335–341.

Omura GA, Blessing JA, Vaccarello L, Berman ML, Clarke-Pearson DL, Mutch DG, Anderson B (1997) Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* **15**(1): 165–171.

Pecorelli S, Zigliani L, Odicino F (2009) Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* **105**(2): 107–108.

Peters 3rd WA, Liu PY, Barrett 2nd RJ, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon Jr W, Alberts DS (2000) 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* **18**(8): 1606–1613.

Piver MS, Rutledge F, Smith JP (1974) Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol* **44**(2): 265–272.

Rydzewska L, Tierney J, Vale CL, Symonds PR (2010) Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. *Cochrane Database Syst Rev* (1): CD007406.

Sardi JE, Giaroli A, Sananes C, Ferreira M, Soderini A, Bermudez A, Snaidas L, Vighi S, Gomez Rueda N, di Paola G (1997) Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. *Gynecol Oncol* **67**(1): 61–69.

Schoenfeld DA, Richter JR (1982) Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* **38**(1): 163–170.

Shimizu Y, Akiyama F, Umezawa S, Ishiya T, Utsugi K, Hasumi K (1998) Combination of consecutive low-dose cisplatin with bleomycin, vincristine, and mitomycin for recurrent cervical carcinoma. *J Clin Oncol* **16**(5): 1869–1878.

Spiegelhalter DJ, Freedman LS, Parmar MK (1993) Applying Bayesian ideas in drug development and clinical trials. *Stat Med* **12**(15-16): 1501–1511 discussion 1513–7.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* **92**(3): 205–216.

Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, Gunderson L, McCormick B, Morrisintegral M, Rich T, Shipley W, Curran W (2000) Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* **47**(1): 13–47.

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APPENDIX

Institutions that participated in this study:

Hokkaido University, Sapporo Medical University, Tohoku University, Tsukuba University, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, National Cancer Center Hospital, The Jikei University Hospital, The Cancer Institute Hospital, Tokyo University, Juntendo University, Niigata Cancer Center, Nagaoka Red Cross Hospital, Shinsyu University, Aichi Cancer Center Hospital, National Hospital Organization Nagoya Medical Center, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Disease, Tottori University, Kure Medical Center, Shikoku Cancer Center, National Kyushu Cancer Center, Kurume University, Kyushu University, Saga University, Kagoshima City Hospital.

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Radiation Therapy for Stage IVA Cervical Cancer

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Abstract. *Background: To evaluate the outcome and discover predictive factors for patients with stage IVA cervical cancer treated with definitive radiation therapy. Patients and Methods: We retrospectively reviewed 34 patients with stage IVA cervical cancer who received definitive radiation therapy between 1992 and 2009. Results: On univariate analysis, statistically significant prognostic factors for improved local control rate (LCR) were absence of pyometra (p=0.037) and equivalent dose in 2 Gy fractions (EQD_2) at point A greater than 60 Gy (p=0.023). Prognostic factors for improved progression-free survival (PFS) were absence of pelvic lymph node metastasis at initial presentation (p=0.014), and EQD2 at point A greater than 60 Gy (p=0.023). Conclusion: Patients with stage IVA disease had poor median survival. However adequate radiation dose to point A produced favorable LCR and PFS, therefore efforts should be made to increase the point A dose.*

Classical radiation dose distribution of intracavity brachytherapy for cervical cancer was developed to avoid the bladder and rectum as much as possible because these structures can cause severe late morbidities when large amounts of radiation are delivered. However, the dose distribution is usually extended laterally in order to cover parametrial disease spread (1, 2). The International Federation of Gynecology and Obstetrics (FIGO) stage IVA cervical cancer is defined as tumor which directly invades the mucosa of the bladder or rectum (3). Therefore, it is quite challenging to treat such locally advanced cervical cancer by classical radiation therapy techniques. There are limited reports focusing on clinical results of FIGO stage IVA cervical cancer (4-6), which are considered to be far advanced, but for which there remains a chance for cure in contrast to stage IVB disease with distant metastasis. The purpose of the current retrospective study was to evaluate patient outcome and prognostic factors in stage IVA cervical cancer treated by definitive radiation therapy.

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Key Words: Radiation therapy, cervical cancer, FIGO IVA, bladder invasion, rectum invasion, EQD2.

Patients and Methods

The medical records of patients treated with definitive radiation therapy for pathologically-proven primary invasive cervical cancer at the National Cancer Center Hospital, Tokyo, Japan, between 1992 and 2009 were reviewed retrospectively. From 1992 to 2009, 407 patients with cervical cancer were treated with curative radiation therapy, with or without chemotherapy. The eligible patients for the present study consisted of cystoscopically- or colonoscopically-proven clinical stage T4A cervical cancer. Those patients who had been diagnosed with disease of less advanced than stage T4A tumor but which were revealed intra-operatively as being unresectable due to bladder wall invasion were not included in this analysis. Patients who had distant metastasis including para-aortic lymph node metastasis, who received palliative radiation therapy of less than 50 Gy, and who underwent surgery were excluded from this study. Nine patients without staging computed tomography (CT) were also excluded because status regarding pelvic and para-aorta lymph node metastasis was not obtained. A total of 34 females treated with definitive external-beam radiotherapy (EBRT), with or without high-dose-rate intracavitary brachytherapy (HDR-ICBT), were admitted to this retrospective analysis. All patients underwent pelvic examination, cystoscopy, pyeloureterography, chest X-ray/CT, pelvic CT/magnetic resonance image (MRI), and blood test. Maximum tumor diameters were measured based on the CT/MRI findings. All biopsy specimens were diagnosed at the Department of Pathology of National Cancer Center Hospital.

Treatment. Principles of management of cervical cancer at this Institute were described elsewhere (7). The treatment policy for locally advanced cervical cancer is concurrent chemoradiation therapy (cCRT) with a chemotherapy regimen of weekly cisplatin (40 mg/m^2/week), cisplatin (50 mg/m^2/3 weeks)-plus-oral S-1 (80-120 mg/body/day), or daily nedaplatin (10 mg/body/day). Concurrent chemoradiotherapy was not performed in patients with insufficient renal function, age over 75 years, or those treated by extended radiation fields for the whole pelvis and para-aortic lymph

node (PALN) region. Supportive treatments, such as blood transfusions, were encouraged during radiotherapy.

Radiotherapy. The common EBRT portals included the cervix, as well as the parametrium, the upper part of vagina down to the level of lower border of the obturator foramens, and the draining pelvic lymph nodes up to the level of the common iliac (L4/5 junction). If the primary lesion involved the lower third of the vagina, inguinal regions were also included in the EBRT fields. Patients with inguinal lymph node involvement were excluded from this study. The initial 30-40 Gy was delivered to the whole pelvis with a 4-field box or the anterior-posterior technique and then pelvic irradiation was administered with a central shield (CS) being employed to reduce exposure of organs at risk (OARs). The dose of the whole pelvic irradiation was dependent upon tumor shrinkage, with late responding tumors being irradiated to a higher dose by whole pelvic irradiation. The total pelvic side wall dose was 50 Gy in 25 fractions. Two-dimensional conventional radiotherapy (2DCRT) was employed between 1992 and 2005, and three-dimensional conformal radiotherapy (3DCRT) was used between 2005 and 2009. After the CS was inserted, high-dose rate intracavitary brachytherapy (HDR-ICBT) was performed in 1-2 sessions/week, but EBRT and HDR-ICBT were not carried out on the same day. All brachytherapy was carried out by 192Ir remote after loading system (RALS, MicroSelectron HDR™; Nucletron, Veennendaal, the Netherlands). ICBT with tandem and ovoid applicators was performed with a prescribed dose of 6 Gy in point A using the Manchester method. For dose calculation of ICBT, Plato® (Nucletron) was used. A tandem-cylinder was used only in cases with a vaginal involvement of more than one-third of the total vaginal length or with an extraordinarily narrow vagina. Advanced tumors which did not shrink adequately to initiate HDR-ICBT after whole-pelvic EBRT were usually treated solely by EBRT with shrunk boost fields up to 60-66 Gy.

Follow-up. All patients were evaluated weekly during radiotherapy through physical examination and blood tests. CT and/or MRI scans and cytology were performed 1-3 months after radiotherapy, and physical examination and blood tests were performed regularly every 1-6 months. Disease progression was defined by the response evaluation criteria in solid tumors (RECIST) version 1.1 (8).

Statistical analysis. Information on potential prognostic factors, such as age, initial tumor diameter, vaginal invasion, parametrial invasion, uterine corpus invasion, pyometra, pelvic lymph node metastasis, PALN metastasis, hydronephrosis, tumor pathology, use of concurrent chemotherapy, type of radiation therapy applied, total treatment time, and total point A dose was retrieved from medical charts and CT/MRI findings. Overall survival (OS) rate was estimated from the start of radiation therapy to the date of death, or of the last follow-up. Progression-free survival (PFS) rate was estimated to the date of any disease relapse considered as an event. Patients without relapse who died of another disease or were still alive were censored at the time of death or last follow-up. Local failure includes central and parametrial relapses. The local control rate (LCR) was censored at the time of local failure, death, non-local relapse, or last follow-up. OS, PFS, and LCR were calculated by the Kaplan–Meier method. As a measure of radiotherapeutic intensity, we used the equivalent dose in 2 Gy fractions (EQD2) calculated from the total irradiated dose (D) and each dose (d) with α/β for 10 Gy using the following formula (9);

Table I. *Patients' characteristics.*

Characteristic	No. of patients
Median age, years (range)	62 (32-80)
Invasion of	
Badder	32
Rectum	2
Vaginal invasion	
Yes	29
No	5
Parametrial invasion	
Yes	34
No	0
Corpus invasion	
Yes	29
No	5
Pyometra	
Yes	10
No	24
Pelvic LN metastasis	
Yes	12
No	22
Hydronephrosis	
Yes	23
No	11
Pathology	
Squamous cell carcinoma	32
Adenocarcinoma	2
Median initial tumor size, cm (range)	6.7 (3.9-10)
Median pre-treatment Hb, mg/dl (range)	11.6 (6.4-14.6)
Median pre-treatment SCC, ng/ml (range)	15.4 (0.5-167.4)

LN: Lymph node.

$$EQD2 = D\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

The survival curves were compared by the log-rank test. For univariate analysis, all of the variables were dichotomized at the median. Statistical significance was set to less than 0.05. All statistical analyses were performed using SPSS Statistics version 18.0 (SAS Institute, Tokyo, Japan).

Results

Patients' characteristics are summarized in Table I. Between 1992 and 2009, nine patients were clinically diagnosed with tumors of less than T4A but surgically of T4A because of direct tumor invasion of the bladder wall. These patients were excluded from the current study. Thirty-four patients were all diagnosed clinically as having T4A tumor either by cystoscopy or colonoscopic findings without distant metastasis. In the current study, the frequency of cases with bladder invasion was much higher than those with rectal invasion (32 *vs.* 2). All the patients had parametrial invasion,

Table II. *Treatment details.*

EBRT alone, n	8
Median total dose, Gy (range)	55.2 (50-66)
EBRT + ICBT, n	26
Median central pelvic dose, Gy (range)	40 (30-50.4)
Median pelvic side wall dose, Gy (range)	50 (50-60)
Applicator type	
Tandem, ovoid	18
Tandem, cylinder	8
Median ICBT dose, Gy (range)	15 (12-24)
Concurrent chemotherapy	
Yes	17
No	17
Median TTT, weeks (range)	6.3 (5.0-12.4)
Median EQD_2 of point A, Gy (range)	63 (50-74)

EBRT: External-beam radiation therapy; ICBT: intracavitary brachytherapy; TTT: total treatment time; EQD2: equivalent dose in 2 Gy fractions.

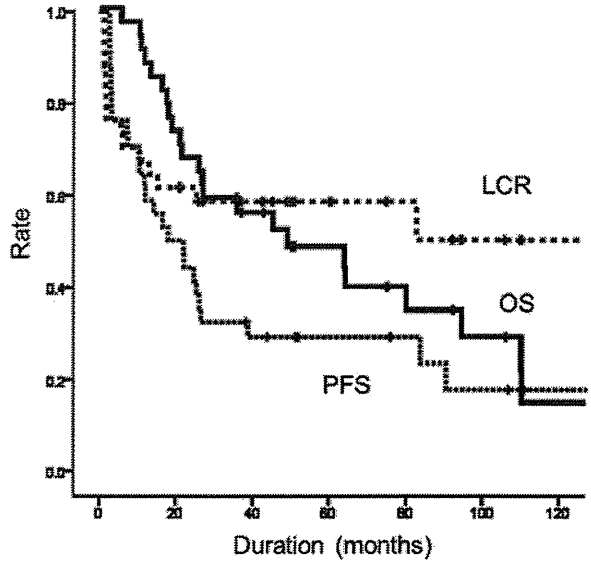

Figure 1. *Kaplan–Meier curves for local control rate (LCR), progression-free survival (PFS) and overall survival (OS).*

and most had vaginal and corpus invasion. Twenty-three patients had hydronephrosis at the time of diagnosis and four patients required urinary tract diversion during radiotherapy because of bilateral hydronephrosis. One patient had vesicovaginal fistula at initial presentation. Treatment characteristics are shown in Table II. Eight patients were treated solely by EBRT because tumor shrinkage was inadequate to start HDR-ICBT or because the external os of the uterus could not be found for ICBT. Tandem ovoid applicators were used in the majority of patients (18 out of 26 patients) treated by a combination of EBRT and HDR-ICBT. Concurrent chemotherapy was used in 17 patients who were under 75 years old and with adequate kidney function and good performance status; in these, the combined chemotherapeutic agents used were cisplatin in 12 patients (70.6%), cisplatin-plus-oral S-1 in two (11.8%), and nedaplatin in three (17.6%). Follow-up period was calculated from the start of radiation therapy. After a median follow-up period of 50.9 months (range: 35.7-191 months) for those who were alive at the time of the analysis (November 2012), 5-year OS, PFS, and LCR were 48.3%, 29.1% and 58.7%, respectively. The median survival time (MST) was estimated to be 49 months (95% confidence interval, 7.9-90.1, Figure 1). At the time of analysis, 11 patients were still alive and seven were alive without disease recurrence, while 21 patients had died from recurrent disease and 2 from other causes. Twenty-six out of 34 patients (76.5%) experienced persistent disease or disease recurrence after definitive radiotherapy. Local failure was the most common reason for disease progression, with 15 out of 34 patients (44.1%) experiencing local failure. Regional lymph node failure was rare (3/34, 8.9%), with distant metastasis being more frequent (8/34, 23.5%) than regional failure. Among 15 patients who experienced local treatment failure, eight patients required urinary tract diversion because of direct tumor invasion of the base of the bladder, and three and one patient experienced vesicovaginal and rectovaginal fistula, respectively.

Univariate analysis was performed on eight different variables to evaluate their potential effect on LCR, PFS, and OS after radiotherapy (Table III). On univariate analysis, statistically significant prognostic factors for improved LCR were absence of pyometra (p=0.037) and EQD2 at point A greater than 60 Gy (p=0.023). The prognostic factors for improved PFS were absence of pelvic lymph node metastasis at initial presentation (p=0.014), and EQD2 at point A greater than 60 Gy (p=0.023). None of the variables was found to be a significant prognostic factor predicting OS, but a trend towards a favorable OS was noted for EQD2 at point A greater than 60 Gy (p=0.078). Figure 2 shows a boxplot of the EQD2 of point A stratified by event for LCR, PFS and OS.

Treatment-related toxicities. Toxicities during and after radiotherapy are listed in Table IV. Hematological toxicity was relatively mild and there was only one case of grade 4 leukopenia. One patient developed sigmoidal colon rupture one month after radiotherapy and required colostomy but is still alive without disease recurrence. One patient died due to obstruction of the gastrointestinal tract. This patient first developed local recurrence in the lower part of the vagina four months after radiotherapy and local relapse was controlled by further HDR-ICBT of 30 Gy in five fractions using a vaginal cylinder. This patient again developed secondary local recurrence in the uterine cervix and was

Table III. *Results of univariate analysis for local control rate, progression-free survival, and overall survival.*

			LCR		PFS		OS	
Variants		n	3 years	*p*-Value	3 years	*p*-Value	3 years	*p*-Value
All patients		34	58.7		32.4		55.7	
Age	<60 years	15	60.0	0.954	26.7	0.377	45.7	0.523
	≥60 years	19	57.9		36.8		63.2	
Pyometra	Yes	10	30.0	0.037*	20.0	0.433	30.0	0.218
	No	24	70.8		37.5		66.7	
Pelvic LN metastasis	Yes	12	58.3	0.959	8.3	0.014*	40.0	0.151
	No	22	59.1		45.5		63.6	
Hydronephrosis	Yes	23	51.8	0.201	21.7	0.169	51.8	0.091
	No	11	72.7		54.5		63.6	
Brachytherapy	Yes	26	61.5	0.513	38.5	0.110	61.5	0.323
	No	8	50.0		12.5		37.5	
cCRT	Yes	18	55.0	0.761	38.9	0.950	55.0	0.443
	Yo	16	62.5		25.0		56.3	
EQD_2 at point A	<60 Gy	12	41.7	0.023*	16.7	0.023*	41.7	0.078
	≥60 Gy	22	67.9		40.9		63.6	
TTT	<6.5 weeks	21	61.9	0.837	38.1	0.306	66.7	0.282
	≥6.5 weeks	13	53.8		23.1		36.9	

EQD2: Equivalent dose in 2 Gy fractions; cCRT: concurrent chemoradiotherapy; LN: lymph node; TTT; total treatment time.

salvaged by a third treatment with HDR-ICBT of 24 Gy in four fractions. This patient developed ileus 44 months after the third HDR-ICBT and died without evidence of disease relapse. One patient developed grade 4 cystitis four months after radiotherapy but anti-coagulant for deep vein thrombosis was used, therefore there is a possibility that such medication might exacerbate the severity of cystitis. After the cessation of anti-coagulant, cystitis subsided by itself. There was no radiation-related vesicovaginal or rectovaginal fistula formation.

Discussion

Stage IVA cervical cancer is infrequent and according to the FIGO annual report 2006 only 3.1% of patients were diagnosed as stage IVA (10, 11). Limited literature exists specifically dealing with stage IVA cervical cancer. In the current study, we evaluated 34 patients with stage IVA disease who were treated with definitive radiation therapy between 1992 and 2009. The MST of 49 months of the entire patient cohort was poor and only seven out of 34 patients were alive without disease progression at the time of analysis (November 2012). As was also shown in the literature (4-6), most stage IVA tumors were diagnosed based on bladder involvement in this study. Patients with stage IVA disease not only had disease directly invading neighboring organs, but they also had several poor prognostic factors, such as parametrial invasion, corpus invasion and hydronephrosis (Table I). It can be considered that the poor prognosis of

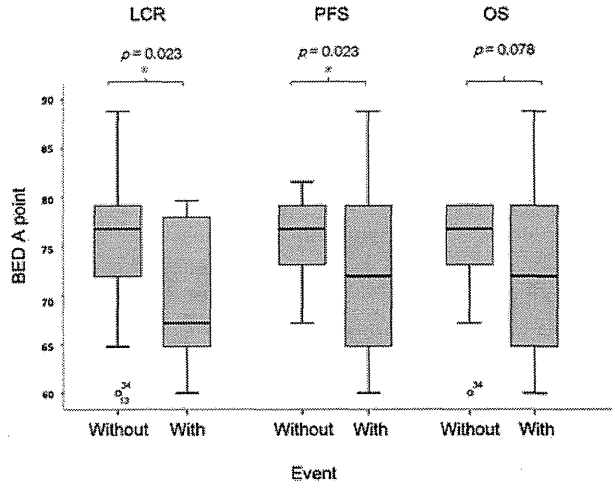

Figure 2. *A boxplot of the equivalent dose in 2 Gy fractions (EQD2) of point A stratified by event for local control rate (LCR), progression-free survival (PFS) and overall survival (OS).*

patients with stage IVA disease was not only due to direct invasion to neighboring organs, but also to the co-existence of such prognostic factors. In this study, local recurrence was the most frequent pattern of disease progression. Therefore, improvement in the initial local therapy might contribute to prolongation of OS. The presence of pyometra at the time of diagnosis was found to be a predictive factor for unfavorable

Table IV. *Toxicity during and after radiotherapy.*

Toxicity	Grade					
	0	1	2	3	4	5
Hematological acute toxicity						
Leukopenia	3	16	8	6	1	0
Anemia	2	9	12	11	0	0
Thrombocytopenia	11	19	3	1	0	0
Non-hematological acute toxicity						
Gastrointestinal toxicity	9	4	16	5	0	0
Genitourinary toxicity	32	0	2	0	0	0
Non-hematological late toxicity						
Gastrointestinal toxicity	24	3	5	0	1	1
Genitourinary toxicity	29	1	1	2	1	0

LCR (p=0.037, Table III). Pyometra was considered to be an adverse factor for radiation therapy (12) because hypoxic region surrounding inflammation were found to be radioresistant, therefore quick and adequate drainage is imperative for prompt recovery from inflammation. A cumulative EQD_2 of point A greater than 60 Gy was also found to be a predictive factor for favorable LCR and PFS. Although the majority of patients received the combination of EBRT and ICBT, the cumulative EQD_2 of point A is relatively low at 63 Gy (range=50-74 Gy) presumably because of the lack of experience using high dose ICBT in the past, the total dose of ICBT was slightly lower than the one used in recent years. Although prognosis of stage IVA cervical cancer is devastating, unlike stage IVB disease, some of patients with tumor stage IVA can be cured with definitive radiation therapy. Therefore it is important to deliver an adequate dose.

Stage IVA cervical carcinoma is associated with fistula formation (5, 6). In this study, there was no fistula formation for patients whose disease was controlled by radiation therapy; however among 15 patients who experienced local recurrence, three and one patient experienced vesicovaginal and rectovaginal fistula, respectively. In addition, eight out of 15 patients required urinary tract diversion because of direct tumor invasion of the base of the bladder. Therefore in order to achieve local control, an adequate radiation dose is necessary for stage IVA disease. Pinn-Bingham *et al.* reported an excellent local control for advanced cervical carcinoma, including seven cases of stage IVA using HDR interstitial brachytherapy (ISBT) with a LCR for the entire patient cohort of 85.3% (13). Patients with locally advanced cervical carcinoma for whom ICBT is unsuitable should be treated by HDR-ISBT in order to deliver an adequate dose. However, there are patients whose disease does not respond well to EBRT and even HDR-ISBT is unsuitable because of bulky disease. In such patients, an EBRT boost over 60 Gy should be delivered. Matsuura *et al.* reported favorable local control of stage IVA cervical cancer treated by only EBRT with a 3-year LCR of 57.1% (14). The National Cancer Center Institute Alert of 1999 recommended cisplatin-based cCRT for patients requiring primary radiation therapy for cervical carcinoma. This was based on the results of five randomized trials that evaluated cisplatin-based chemotherapy with radiation for various stages of cervical carcinoma (15-19). Improvement in local control was demonstrated in all of these studies. However, whether addition of chemotherapy will be beneficial for patients with stage IVA disease has not been validated. No impact of cisplatin-based chemotherapy on the outcome of the patients with stage IVA disease was observed in this study. This was presumably due to the small sample size (4, 10). Patients with stage IVA disease had a poor prognosis, with only 3-year survival of only 55.7%. However, an adequate radiation dose to point A confers favorable LCR and PFS, therefore efforts must be made to deliver as great a dosage as possible.

Acknowledgements

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References

1 Bethesda M: Dose and volume specification for reporting intracavitary therapy in gynecology. Int Comm Radiat Units Measure *38*: 1-20, 1985.
2 Tod M and Meredith WJ: Treatment of cancer of the cervix uteri, a revised Manchester method. Br J Radiol *26*: 252-257, 1953.
3 Pecorelli S, Zigliani L and Odicino F: Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet *105*: 107-108, 2009.
4 Rose PG, Ali S, Whitney CW, Lanciano R and Stehman FB: Outcome of stage IVA cervical cancer patients with disease limited to the pelvis in the era of chemoradiation: A Gynecologic Oncology Group study. Gynecol Oncol *121*: 542-545, 2011.
5 Moore KN, Gold MA, McMeekin DS and Zorn KK: Vesicovaginal fistula formation in patients with Stage IVA cervical carcinoma. Gynecol Oncol *106*: 498-501, 2007.
6 Biewenga P, Mutsaerts MA, Stalpers LJ, Buist MR, Schilthuis MS and van der Velden J: Can we predict vesicovaginal or rectovaginal fistula formation in patients with stage IVA cervical cancer? Int J Gynecol Cancer *20*: 471-475, 2010.
7 Kuroda Y, Murakami N, Morota M, Sekii S, Takahashi K, Inaba K, Mayahara H, Ito Y, Yoshimura R, Sumi M, Kagami Y, Katsumata N, Kasamatsu T and Itami J: Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer. J Radiat Res *53*: 588-593, 2012.
8 Eisenhauer EA, Therasse P, Bogaerts J, Schwarts LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009.

9 Bentzen SM, Dörr W, Gahbauer R, Howell RW, Joiner MC, Jones B, Jones DT, van der Kogel AJ, Wambersie A and Whitmore G: Bioeffect modeling and equieffective dose concepts in radiation oncology – teminology, quantities and units. Radiother Oncol *105*: 266-268, 2012.
10 Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, Ngan HY and Pecorelli S: Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet *95(Suppl 1)*: S43-103, 2006.
11 Aoki Y: 51st Annual report; 5-year overall survival for cervical cancer, corpus cancer, and ovarian cancer treated in 2003 in Japan. Acta Obstetrica et Gynecologica Japonica *64*: 1078-1141, 2012.
12 Yu GR and Yan YZ: Pyometra and radiotherapy of cancer of the uterine cervix – analysis of 282 patients. Zhonghua Zhong Liu Za Zhi *9*: 379-381, 1987 in Chinese.
13 Pinn-Bingham M, Puthawala AA, Syed AM, Sharma A, Disaia P, Berman M, Tewari KS, Randall-Whitis L, Mahmood U, Ramsinghani N, Kuo J, Chen WP and McLaren CE: Outcomes of high-dose-rate interstitial brachytherapy in the treatment of locally advanced cervical cancer: Long-term results. Int J Radiat Oncol Biol Phys *85*: 714-720, 2012.
14 Matsuura K, Okabe T, Fujita K, Tanimoto H, Akagi Y and Kagemoto M: Clinical results of external beam radiotherapy alone with a concomitant boost program or with conventional fractionation for cervical cancer patients who did not receive intracavitary brachytherapy. J Radiat Res *53*: 900-905, 2012.
15 Whitney CW, Sause W, Bundy BN, Malferano JH, Hannigan EV, Fowler WC Jr., Clarke-Pearson DL and Liao SY: 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 *17*: 1339-1348, 1999.
16 Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL and Insalaco S: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med *340*: 1144-1153, 1999.
17 Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL and Gersell D: Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med *340*: 1154-1161, 1999.
18 Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, Rotman M, Gershenson DM and Mutch DG: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med *340*: 1137-1143, 1999.
19 Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W Jr. and Alberts DS: 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 *18*: 1606-1613, 2000.

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Radiation therapy for primary vaginal carcinoma

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Brachytherapy plays a significant role in the management of cervical cancer, but the clinical significance of brachytherapy in the management of vaginal cancer remains to be defined. Thus, a single institutional experience in the treatment of primary invasive vaginal carcinoma was reviewed to define the role of brachytherapy. We retrospectively reviewed the charts of 36 patients with primary vaginal carcinoma who received definitive radiotherapy between 1992 and 2010. The treatment modalities included high-dose-rate intracavitary brachytherapy alone (HDR-ICBT; two patients), external beam radiation therapy alone (EBRT; 14 patients), a combination of EBRT and HDR-ICBT (10 patients), or high-dose-rate interstitial brachytherapy (HDR-ISBT; 10 patients). The median follow-up was 35.2 months. The 2-year local control rate (LCR), disease-free survival (DFS), and overall survival (OS) were 68.8%, 55.3% and 73.9%, respectively. The 2-year LCR for Stage I, II, III and IV was 100%, 87.5%, 51.5% and 0%, respectively ($P = 0.007$). In subgroup analysis consisting only of T2–T3 disease, the use of HDR-ISBT showed marginal significance for favorable 5-year LCR (88.9% vs 46.9%, $P = 0.064$). One patient each developed Grade 2 proctitis, Grade 2 cystitis, and a vaginal ulcer. We conclude that brachytherapy can play a central role in radiation therapy for primary vaginal cancer. Combining EBRT and HDR-ISBT for T2–T3 disease resulted in good local control.

Keywords: primary vaginal cancer; radiation therapy; high-dose-rate brachytherapy; intracavitary brachytherapy; interstitial brachytherapy

INTRODUCTION

The most common carcinoma affecting the vagina is metastatic from other primary gynecologic and non-gynecologic sites, including the cervix, endometrium, colon and rectum, ovary, and vulva. Primary vaginal cancer is considered to be a rare entity, accounting for only 2% of gynecologic malignancies [1, 2]. To diagnose primary vaginal cancer it is necessary to fulfill the following two conditions: the cervix and vulva must be free of disease [3]; and if a hysterectomy has been performed within five years for a uterine tumor, the histopathological findings must differ from that of the uterine tumor. Squamous cell carcinomas account for the majority of primary vaginal carcinomas. Other histological subtypes of vaginal carcinomas include adenocarcinoma, adenosquamous carcinoma, small cell carcinoma, melanoma, lymphoma and sarcoma. Most patients with vaginal carcinomas are in their sixth and seventh decades of life, with only 10% of cases occurring in patients ≤ 40 years of age; however, vaginal cancer is increasingly diagnosed in younger women, possibly because of human papillomavirus (HPV) infections [4].

There have been no prospective randomized trials with a focus on vaginal cancer treatments. Therefore, the management of vaginal cancer is not standardized, as is the treatment of cervical cancer. Small vaginal cancers, particularly those involving the apex of the vagina, may be treated successfully with surgical excision alone; however, definitive organ-sparing surgery is technically difficult for more advanced or distal lesions, which are usually treated with radiation therapy.

Before 2008, radiation therapy techniques applied to advanced primary vaginal cancer at the National Cancer Center Hospital in Tokyo, Japan, consisted of a combination of external beam radiation therapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT), or EBRT

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alone. After 2008, high-dose-rate interstitial brachytherapy (HDR-ISBT) was introduced. The purpose of this report is to retrospectively analyze the results of radiation therapy for primary vaginal cancer, and to determine whether or not the difference in radiation therapy technique affects disease control.

MATERIALS AND METHODS

The medical records of all patients treated with definitive radiation therapy for primary invasive carcinoma of the vagina at the National Cancer Center Hospital in Tokyo, Japan between February 1992 and November 2010 were reviewed retrospectively. Patients whose tumors involved the external os of the cervix or vulva were excluded [5]. Patients who had a hysterectomy for primary invasive uterine carcinoma with the same histology as vaginal cancer, patients who had distant metastases, and patients with histologic findings consistent with a sarcoma or melanoma were also excluded. Patients who had non-invasive carcinoma of the vagina, and patients who underwent EBRT post-operatively after hysterectomy for apical vaginal cancer, were excluded. A total of 36 patients with primary carcinoma of the vagina with a histopathological diagnosis of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and small cell carcinoma were included in this study.

All patients underwent a routine metastatic work-up, including a complete blood count, renal function testing, liver function testing, chest X-ray/CT, and pelvic CT/MRI. These patients were then evaluated jointly by gynecological oncologists and radiation oncologists for the purpose of staging and to determine the optimal treatment modality. Tumor size was determined by CT/MRI imaging. For superficial disease that could not be visualized with imaging studies, tumor size was determined by physical examination. With the exception of two patients who were treated by HDR-ICBT alone, the remaining 34 patients received EBRT. The common EBRT portals included the entire vagina, as well as the paracolpium, parametrium, and draining pelvic lymph nodes up to the level of the common iliac (L4/5 junction). If the primary lesion involved the lower one-third of the vagina or there were clinically palpable inguinal nodes, the inguinal regions were also included in the EBRT fields. Superficial tumors were treated by HDR-ICBT with or without EBRT. When HDR-ICBT was used in combination with EBRT, the treatment schedule was similar to the radiation therapy schedule for the treatment of cervical cancer in Japan [6, 7]. The initial 20–40 Gy was delivered to the whole pelvis, then pelvic irradiation with a central shield ensued. The total dose delivered to the pelvic side wall was up to 50 Gy using conventional fractionation. HDR-ICBT was delivered after pelvic irradiation with a central shield at 6–10 Gy/fraction to 5 mm under the vaginal surface, for a total of 2–5 fractions. Before 2008, HDR-ISBT was not used routinely in the treatment of vaginal cancer in our department. Advanced tumors that did not shrink sufficiently for HDR-ICBT after 40–50 Gy of pelvic irradiation were usually treated solely with EBRT with smaller boost fields of 60–70 Gy. For patients treated solely with EBRT, the median dose was 60 Gy (range, 49.6–70 Gy). For patients treated with a combination of EBRT and brachytherapy, the median EBRT dose for the central pelvis was 38 Gy (range, 20–50 Gy), the median EBRT dose for the pelvic side wall was 50 Gy (range, 36–50 Gy), the median ICBT dose was 18 Gy (range, 12–30 Gy), and the median ICBT dose per fraction was 6 Gy (range, 6–10 Gy). Of the two patients who were treated solely by ICBT, one patient was irradiated with 24 Gy in four fractions (6 Gy per fraction), and one patient was irradiated with 32 Gy in four fractions (8 Gy per fraction). After 2008, HDR-ISBT has been used routinely in the treatment of vaginal cancer in combination with EBRT. The detailed procedure for gynecological HDR-ISBT is described elsewhere [8]. In brief, a transperineal needle applicator insertion with transrectal ultrasound (TRUS) or CT image guidance was performed under general and epidural anesthesia or saddle block with the patient in the lithotomy position. After the needle applicator insertion, HDR-ISBT was performed twice daily, with each fraction 6 h apart. For advanced disease, a Syed-Neblett template™ (Alpha Omega Services, Bellflower, CA, USA) was used to sufficiently cover lateral disease spread. For localized disease with limited paracolpium or parametrium invasion, free-handed needle applicator insertion with a vaginal applicator was used with fewer needles inserted compared with the Syed-Neblett template™. The gross target volume (GTV) was defined based on the CT image obtained after needle insertion, as well as on physical examination immediately before needle insertion, the intra-operative TRUS image, and the most recent MRI. The dwell time of Ir-192 and the dose distribution of HDR-ISBT was calculated by geometric optimization and graphical modification to enclose the GTV by the prescription dose. The median HDR-ISBT dose was 24 Gy (range, 22–32 Gy) and the median HDR-ISBT dose per fraction was 6 Gy (range, 4–6 Gy). HDR-ICBT and ISBT were performed with a MicroSelectron HDR™ (Nucletron, Veenendaal, The Netherlands). Before 2010, administration of concurrent chemotherapy (cCRT) was not routinely used because there was no evidence that strongly favored utilization of cCRT for vaginal cancer; thus, the administration of cCRT was at the discretion of the attending physician and the most common agent used was cisplatin. After 2010, weekly cisplatin (40 mg/m^2) was used for bulky tumors (>4 cm) or patients with N1 disease, as is done for patients with cervical cancer.

After completion of radiotherapy, gynecological examinations were performed every 2–3 months for the initial

two years, every 4–6 months for years 3–5, and once or twice a year thereafter. Suspected persistent or recurrent disease was confirmed by a biopsy whenever possible. Treatment failures were classified as local, pelvic, or distant. Local failures were defined as persistent or recurrences located within the vagina or paracolpium. Pelvic failures were defined as recurrences in the pelvic or inguinal lymph nodes. Recurrences that involved the para-aortic nodes area were considered to be distant failures.

The local control rate (LCR), disease-free survival (DFS), and overall survival (OS) were calculated using the Kaplan Meier method [9] with all time intervals measured from the date of initiation of radiation therapy. The relationships between tumor characteristics and treatment variables, and LCR, DFS, and OS were analyzed by univariate analysis. The associations between tumor characteristics and treatment modality, and treatment modality and complications were evaluated with a chi-square test. A P-value < 0.05 was considered statistically significant. The continuous variables were dichotomized to give the lowest P-values in the log-rank test [10]. All statistical analyses were performed using SPSS™ (version 18.0; SPSS, Inc., Chicago, IL, USA).

This retrospective study was approved by the Institutional Review Board.

RESULTS

There were 36 patients who met the eligibility criteria; 24 patients were alive at the time of the analysis in May 2012 and 23 patients were free from loco-regional recurrence. The median follow-up length of all living patients and those who were treated by HDR-ISBT was 35.2 months (range, 12.3–151.3 months) and 29.3 months (range, 15.9–39.4 months), respectively. The pretreatment characteristics of the 36 patients are summarized in Table 1. The median age was 59 years (range, 25–94 years). Greater than one-half of the patients presented with T1 and T2 disease. Lymph node metastasis was noted in 10 patients. Five patients had undergone a hysterectomy for benign or non-invasive disease. Five patients had adenocarcinomas, one had an adenosquamous cell carcinoma, and one had a small cell carcinoma. The remaining 29 patients were diagnosed based on pathologic evaluation as squamous cell carcinoma. The median tumor size at diagnosis was 3.6 cm (range, 1.0–11 cm). Figure 1 shows the distribution of the initial tumor location in the vagina. The involvement of the upper one-third of the vagina and lateral wall involvement were most frequent (26/36 [72.2%] and 29/36 [80.6%], respectively). Table 2 shows the methods of treatment according to T classification. All patients with T1 disease were treated by brachytherapy with or without EBRT. No ICBT was applied for patients with T3–4 disease. Either EBRT alone or a combination of EBRT and ISBT was used for patients with T3 disease, while all patients with T4 disease were treated with EBRT alone. The tumor characteristics and treatment methods according to tumor histology are summarized in Table 3. Non-squamous cell carcinomas were more advanced compared with squamous cell carcinomas ($P = 0.006$, Table 3). Although there were no variables which were biased statistically because of the small number of patients, there was a tendency that non-squamous cell carcinomas was treated more frequently by EBRT alone than squamous cell carcinomas.

The 2-year LCR, DFS and OS were 68.8%, 55.3% and 73.9%, respectively. The 2-year LCR was 100% for Stage I, 87.5% for Stage II, 51.5% for Stage III, and 0% for Stage IV ($P = 0.007$, Table 1). The LCR was significantly unfavorable for patients with a non-squamous cell carcinoma histologic diagnosis (81.9% vs 14.3%, $P < 0.001$). In T2–T3 patients, in which EBRT alone or a combination of EBRT and HDR-ICBT/ISBT was used, HDR-ISBT had a marginally favorable LCR (88.9% vs 46.9%, $P = 0.064$, Fig. 2). In another analysis of the T1–T3 patients who had received EBRT and HDR-ICBT/ISBT, the 2-year LCR for EBRT + HDR-ICBT and EBRT + HDR-ISBT was identical (90%; $P = 0.970$). As shown in Table 1, the treatment result was not influenced by the treatment period (before or after 2008), when HDR-ISBT was introduced routinely for advanced disease.

Of the 36 patients in the current study, 17 (47.2 %) had persistent disease or recurrences; Fig. 3 shows the sites of initial failure of the 17 patients. Local recurrence was the most frequent site of recurrence.

One patient developed Grade 2 proctitis 8 months after radiation therapy and one patient developed Grade 2 cystitis 36.4 months after radiation therapy. Vaginal complications were assessed for 23 patients who did not have loco-regional recurrences (Table 4). Vaginal adhesions were noted in nine patients and were the most frequent complication; however, most of the adhesions were lysed with manual manipulation. Two patients each had vaginal atresia and strictures. A vaginal ulcer developed in one patient 17.3 months after radiation therapy, and healed with conservative treatment. No vesicovaginal or rectovaginal fistulae formed, and no patients with hemorrhagic cystitis required a blood transfusion. As shown in Table 4, the correlation between vaginal complications and administration of brachytherapy was analyzed using a chi-square test; the incidence of vaginal complications was not influenced by brachytherapy; rather there was a trend that patients treated with EBRT alone were more likely to develop vaginal adhesions ($P = 0.056$, Table 4). One patient developed a sacral bone fracture 11 months after radiation therapy.

DISCUSSION

Carcinoma of the vagina is a rare gynecological malignancy that primarily affects the elderly. Because of the

Table 1. Patient, tumor and treatment characteristics and correlation with outcome

Characteristic	*n* (%)	2-year LCR (%)	*P*	2-year DFS (%)	*P*	2-year OS (%)	*P*
Age							
<60	18 (50)	77.8	0.343	55.6	0.848	72.2	0.811
≥60	18 (50)	60		55		76.2	
Previous hysterectomy							
yes	5 (13.9)	60	0.416	60	0.928	60	0.456
no	31 (86.1)	70.3		54.6		76.2	
Stage							
I	9 (25)	100	0.007*	80	0.003*	100	0.053
II	8 (22.2)	87.5		75		62.5	
III	17 (47.2)	51.5		29.4		69.1	
IV	2 (5.6)	0		0		0	
T-Stage							
T1	9 (25)	100	0.013*	80	0.03*	100	0.051
T2	13 (36.1)	76.9		46.2		59.8	
T3	12 (33.3)	48.6		41.7		73.3	
T4	2 (5.6)	0		0		0	
N-Stage							
N0	26 (72.2)	68.5	0.804	64.9	0.062	68.4	0.071
N1	10 (27.8)	70		30		60	
Histology							
Scc	29 (80.6)	81.9	<0.001*	68.6	<0.001*	82.1	0.01*
non-Scc	7 (19.4)	14.3		0		42.9	
Tumor size							
<4 cm	20 (55.6)	80	0.133	65	0.241	74.1	0.758
≥4 cm	16 (44.4)	54.7		43.8		74	
Brachytherapy (HDR-ICBT/ISBT)							
yes	22 (61.1)	90.9	0.001*	77.3	0.001*	86.4	0.008*
no	14 (38.9)	32.1		21.4		53	
HDR-ISBT (T2–T3)							
yes	9	88.9	0.064	55.6	0.313	88.9	0.196
no	18	46.9		36.5		52.1	
Concurrent chemotherapy							
yes	7 (19.4)	64.3	0.773	28.6	0.298	71.4	0.472
no	29 (80.6)	69		62.1		74.3	
Treated period							
before 2008	23 (63.9)	60.2	0.178	51.8	0.561	68.6	0.2
after 2008	13 (36.1)	84.6		61.5		83.9	

LCR = local control rate, DFS = disease-free survival, OS = overall survival, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

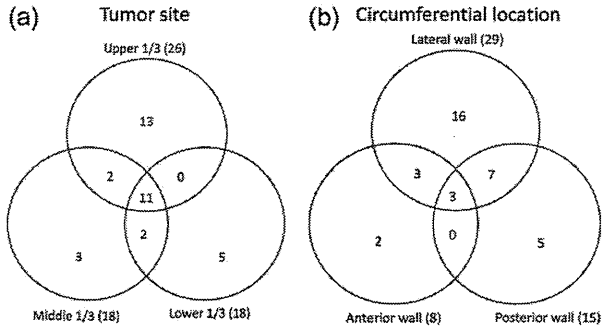

Fig. 1. Distribution of initial location of the tumor in the vagina. (a) Tumor site. (b) Circumferential location.

Table 2. Methods of treatment according to T classification

Treatment methods	T1	T2	T3	T4
EBRT only	0	4	8	2
HDR-ICBT only	2	0	0	0
EBRT + HDR-ICBT	6	4	0	0
EBRT + HDR-ISBT	1	5	4	0
Concurrent chemotherapy	0	2	4	1

EBRT = external beam radiation therapy, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

Table 3. Tumor characteristics and treatment methods according to tumor histology

Treatment methods	Scc (29)	Non-Scc (7)	*P*
Age (mean)	62.5	57.9	0.441
Stage I–II	17	0	0.006*
Stage III–IV	12	7	
T-Stage T1–2	20	2	0.064
T-Stage T3–4	9	5	
N stage N0	22	4	0.37
N stage N1	7	3	
Tumor size (mean)	3.6	5.6	0.148
EBRT only	9	5	0.064
Brachytherapy ± EBRT	20	2	
Concurrent chemotherapy	6	1	0.701

EBRT = external beam radiation therapy, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

rarity of vaginal carcinoma, there have been no randomized clinical trials involving patients with virginal carcinoma and it is difficult to make robust treatment recommendations

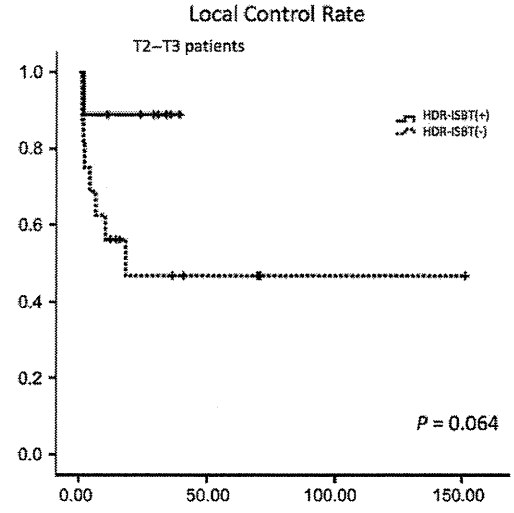

Fig. 2. Local control rate stratified by HDR-ISBT for 25 patients with T2–3 disease.

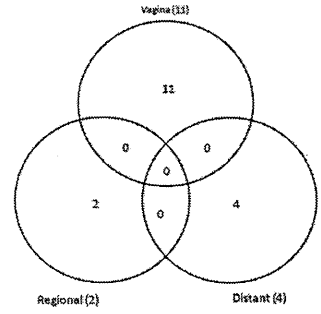

Fig. 3. Patterns of relapse for entire patients. There were 17 relapses in this cohort. There was a local-regional component in 76% of relapses.

Table 4. Vaginal complications according to the administration of brachytherapy

		Brachytherapy		
	Total	yes (18)	no (5)	*P*
Vaginal adhesion	9	5	4	0.056
Vaginal atresia	2	1	1	0.395
Vaginal stricture	2	1	1	0.395
Vaginal ulcer	1	1	0	0.783

for patients with primary vaginal cancer. However, radiation therapy is considered to play a significant role in the management of primary vaginal cancer. In one of the largest series, Frank *et al.* [11] reported the clinical results of 193 patients with primary vaginal squamous cell

carcinomas treated with carefully tailored primary radiation therapy as showing excellent pelvic control. The 5-year pelvic disease control rate was 86% for Stage I, 84% for Stage II, and 71% for combined Stages III and IVA. The study published by Frank *et al.* [11], however, had several limitations, which are as follows: the retrospective nature of the study; the small number of patients; the heterogeneity of the patient's backgrounds; the treatment modalities used, which presumably included selection bias; and the short follow-up period. Therefore, the results have to be interpreted with caution. However, after careful analysis, several findings were derived from the current study. In the current study, the use of HDR-ISBT in patients with T2–T3 primary vaginal cancer was associated with favorable local control. This result was consistent with the report by Leung *et al.* [12], in which the addition of interstitial brachytherapy to EBRT was shown to have a significant favorable effect on clinical outcome. Seeger *et al.* [13] also reported favorable results for ISBT for primary carcinoma of the vagina and vulva, with no local recurrences of vaginal cancer with a median follow-up period of 27 months. In contrast, Nonaka *et al.* [14] reported the results of 26 patients with primary vaginal carcinoma who were treated mainly with HDR-ICBT with or without EBRT. Specifically, the 5-year pelvic control rate (PCR) for Stage I was 86%, whereas the 5-year PCR for Stages II and III was 50% and 57%, respectively [14]. Similarly, Hegemann *et al.* [15] reported the results of EBRT with or without ICBT for primary vaginal cancer and found that the median survival for Stage III/IV was unfavorable compared to Stage I/II (26.8 months and 58.1 months, respectively), suggesting that it is difficult to control thicker tumors with HDR-ICBT. In the current study, there was no difference in the LCR between HDR-ICRT and HDR-ISBT in patients withT1–T3 tumors, most likely because patient selection was performed properly; indeed, HDR-ICBT was applied only for thin tumors. The recently published American Brachytherapy Society guidelines for vaginal cancer recommend using ISBT for vaginal tumors ≥0.5 cm thick at the time of brachytherapy [16]. However, the follow-up period for those patients treated with HDR-ISBT in the current study was rather short, thus it is important to interpret this result with caution. Unfortunately, the treatment results did not differ significantly between treatment periods in this study, presumably because of the small number of patients analyzed and the short follow-up period for patients treated after 2008 (Table 1).

In seven patients with non-squamous cell carcinoma, six had Stage III and one had Stage IV disease, and only one of the patients received a combination of EBRT and HDR-ISBT, which was a relatively favorable factor for advanced disease in this analysis, while the remaining patients underwent only EBRT. As shown in Table 3, the treatment modality did not differ significantly between tumor pathologies, although non-squamous cell carcinomas were more likely to be treated by EBRT alone. The administration of chemotherapy did not differ significantly between tumor pathologies. However, non-squamous cell carcinomas were significantly more advanced at the time of initial presentation compared with squamous cell carcinomas ($P = 0.06$, Table 3). This observation explains, in part, the reason why patients with non-squamous cell carcinomas had such poor outcomes. In the current retrospective study, non-squamous cell carcinoma histology was shown to be a strongly negative factor for local control, which was consistent with the largest retrospective analysis of 301 patients with primary vaginal cancer that included 30 adenocarcinomas [17]. Specifically, the analysis showed that adenocarcinomas have twice the rates of local and metastatic relapse compared with squamous cell carcinomas. Whether or not the routine application of HDR-ISBT in patients with advanced non-squamous cell carcinomas can improve outcomes warrants an additional study.

Because of the small number of patients in the current study, it is difficult to discuss the role of chemotherapy in patients with primary vaginal carcinoma. Distant metastases were frequent in the current study, and the addition of chemotherapy concurrent with radiotherapy might add survival benefit in patients with advanced primary vaginal cancer, as occurs in patients with cervical cancer. In contrast, in vaginal cancer patients the perineum is more likely to be included in the radiation field compared with cervical cancer patients. Therefore, skin toxicities caused by chemoradiation should be prospectively assessed as well as the survival benefits.

Only a small number of patients had late complications in the current study; even HDR-ISBT and the administration of brachytherapy for vaginal cancer did not increase the incidence of complications (Table 4); however, further observation is required.

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REFERENCES

1. Ball HG, Berman ML. Management of primary vaginal carcinoma. *Gynecol Oncol* 1982;**14**:154–63.
2. Peters WA, III, Kumar NB, Morley GW. Carcinoma of the vagina. Factors influencing treatment outcome. *Cancer* 1985;**55**:892–7.
3. Pecorelli S, Benedet JL, Creasman WT *et al.* FIGO staging of gynecologic cancer. 1994–1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. *Int J Gynaecol Obstet* 1999;**65**:243–9.