trials, however, the patients treated with HDR-ICBT were not evaluated separately. It is unclear whether concurrent chemotherapy delivery with RT increases late complications [19]. In view of potential narrow therapeutic window of HDR-ICBT, the optimum RT dose should be carefully determined especially in the CCRT setting. Late RT complications, even when mild to moderate (i.e., Grades 1–2), significantly reduce quality of life [20]. Recently, image-guided brachytherapy (IGBT) using CT/MRI has been investigated in order to decrease late toxicity as well as improve local control [21].

Japanese centers use lower cumulative dose schedules than those of the US and Europe [2,3]. Favorable local control results have been obtained with these lower dose schedules in retrospective series of RT alone [22,23]. However, these lower dose schedules have not been accepted in the US and Europe given the lack of prospective data. In this situation, prospective clinical trials on the efficacy and safety of the CCRT using HDR-ICBT with the low cumulative dose schedules are encouraged.

Based on this background, we conducted a phase II multi-institutional clinical trial on CCRT for locally advanced cervical cancer patients. Herein, we report the data of outcomes and late toxicity observed in the trial.

Materials and methods

Study design

The JGOG1066 trial was a multicenter phase II prospective study aimed at evaluating the efficacy and late toxicity of CCRT using HDR-ICBT for locally advanced uterine cervical cancer patients. This study was designed by the JGOG Cervical Cancer Committee in collaboration with the Japanese radiation oncologists with expertise in the cervical cancer treatment. The study was approved by the JGOG Clinical Trial Review Committee, and the local institutional review boards (IRB) of the participating institutions. This trial is registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; number 000001042).

Patients

Patients with histologically proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix with International Federation of Gynecology and Obstetrics (FIGO) stages IIIA, IIIB, or IVA disease with no para-aortic lymphadenopathy (<10 mm) assessed by computed tomography (CT), performed within 4 weeks prior to entry were eligible. Histopathological evaluation of the para-aortic nodes (e.g., retroperitoneal surgical exploration) was not required. Eligibility criteria also included patient age between 20 and 70 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS)<2. Patients with prior therapy (radiotherapy, surgery or chemotherapy) for cervical cancer were ineligible. Patients were also required to have abdomen-pelvic CT, pelvic MRI (T2 weighted image), chest X-ray/CT, within 28 days before entry. All patients were required to give written informed consent prior to enrollment in this study.

Radiotherapy

Protocol radiotherapy (RT) consisted of a combination of whole pelvic (WP) EBRT and HDR-ICBT. Interstitial brachytherapy was not allowed.

WP-EBRT was delivered with a photon beam of 6 MV or greater. Both anteroposterior (AP)–posteroanterior (PA) and a four-field technique were permitted. Intensity modulated radiation therapy (IMRT) was not allowed. When the four-field technique was utilized, the portal arrangement was changed to the AP–PA technique after the midline block (MB) was inserted. A tissue heterogeneity correction was not applied in the dose calculation. WP-EBRT was delivered for 5 days during a week to achieve a total dose of 50 Gy/25 fractions or 50.4 Gy/28 fractions. The WP-EBRT was initially delivered without a MB. Subsequently, the next phase of WP-EBRT was administered through the same WP field with a MB width of 3 or 4 cm. The MB was formed with multileaf collimators (MLC) or a custom cerrobend block. Four radiotherapy schedules were provided for the protocol (Table 1). Because these schedules are biologically nearly equivalent, the choice of schedule was left to the treating radiation oncologist. The upper boarder of the pelvic field was L4–5, and the lower border was a transverse line below the obturator foramen or pubic symphysis or 2 cm inferior from caudal end of the tumor. The lateral borders of the AP/PA portals were 1.5 to 2 cm beyond the lateral margin of the bony pelvis. For the lateral field, the anterior border was placed at a horizontal line drawn 0.5 cm anterior to the symphysis pubis anteriorly and the posterior border was placed at least 1.5 cm posterior from the surface of the sacrum. Boost EBRT of 6–10 Gy/3–5 fractions was indicated for patients with nodular parametrial involvement to the pelvic walls and/or nodal metastases ($\geq$10 mm in shortest diameter).

The first HDR-ICBT was performed within 7 days after the MB insertion. HDR-ICBT was performed once a week with a fraction dose of 6 Gy prescribed at point A using Ir-192 afterloading machines. HDR-ICBT was not allowed on the same day as the EBRT. The total HDR-ICBT dose was determined by the timing of the MB insertion (Table 1). The cumulative linear quadratic equivalent doses (EQD2) [24] at point A, which were the summation of the EBRT doses without the MB and HDR-ICBT doses, ranged from 62 to 65 Gy. For patients who had an inadequate response to EBRT or failed tandem insertion, additional WP EBRT without the MB was allowed to a total dose of 50 or 50.4 Gy. The total HDR-ICBT dose was 11 Gy per 2 fractions (i.e., 6 Gy + 5 Gy or 5.5 Gy × 2) at point A for this situation. A tandem and ovoid combination was recommended except as restricted by the vaginal anatomy (e.g., narrow vagina) or significant (>1/2) vaginal disease. For these patients, a vaginal cylinder could be utilized. Source dwell patterns (i.e., times and positions) were determined according to the Manchester system [25]. A dose calculation was performed for each application, using two orthogonal radiographs. The isodose curves were plotted, and doses at the rectum and bladder were calculated according to the International Commission on Radiation Units and Measurements (ICRU) 38 criteria [26]. Three dimensional planning using CT and/or MRI was not applied.

For patients who could not receive HDR-ICBT appropriately even after the additional EBRT without MB to 50/50.4 Gy, a boost EBRT with reduced portals was given to a total dose ranging from 64.8 to 72 Gy. Treatment was to be completed within 56 days.

To maintain RT quality, the protocol included an integrated QA process. Credentialing of participating institutions and individual case reviews for all patients were performed. The details of the QA process and its results have been published elsewhere [27].

Table 1
Radiotherapy schedules.

External beam radiotherapy		HDR-ICBT	Total EQD2 at point A
WP	WP + MB		WP + HDR-ICBT
30 Gy/15 fs	20 Gy/10 fs	24 Gy/4 fs	62 Gy
30.6 Gy/17 fs	19.8 Gy/11 fs	24 Gy/4 fs	62 Gy
40 Gy/20 fs	10 Gy/5 fs	18 Gy/3 fs	64 Gy
41.4 Gy/23 fs	9 Gy/5 fs	18 Gy/3 fs	65 Gy

WP: whole pelvic radiotherapy, MB: midline block.
HDR-ICBT: high-dose-rate intracavitary brachytherapy.
EQD2: equivalent dose in 2 Gy per fraction.

Chemotherapy

Weekly cisplatin at a dose of 40 mg/m^2 (maximum dose of 70 mg/body) was administered for 5 courses during the radiotherapy period. The first course of cisplatin was administered on day 1 of radiotherapy. Cisplatin could be given on the same day of HDR-ICBT as well as EBRT.

Follow-up

Response was assessed by MRI T2 weighted images 3 months after the completion of treatment according to the RECIST criteria. Patients were followed every 3 months for the first 2 years. Follow-up included a pelvic examination with PAP smear and monitoring of tumor markers if initially elevated. CT scans of the abdomen and pelvis, and chest X-ray (or CT scan) were performed annually. Pelvic disease progression was defined as follows: pelvic recurrence after assessment of CR, pelvic disease progression with a >20% increase in the size of target lesions assessed by MRI T2WI, or initiation of salvage treatment (regardless of pathological findings) for pelvic disease.

Statistical design

This was a phase II trial with the primary endpoint of estimating 2-year cumulative progression-free survival rate (PFS). The secondary endpoints included the treatment completion rate (all, chemotherapy, and radiotherapy), adverse events (acute and late), compete response rate, 2-year cumulative overall survival rate (OS), 2-year cumulative pelvic disease progression-free rate (PDPF), and 2-year cumulative distant metastasis rate (DM). Details of feasibility and acute adverse events will be reported elsewhere (manuscript submitted for publication).

The sample size was initially calculated based on the following assumptions: an expected 2-year PFS rate of 60% versus the threshold value of 40% from the previous published data of RT alone series [28,29] and data of the US RCT's control arms [1]. CCRT would be considered superior to RT alone if the lower limit of the 95% confidence interval of the 2-year PFS rate exceeded the threshold value of 40%. To attain 90% power with a two-sided α error of 0.05, the minimum required sample size was estimated to be 68 patients. After the sample size was adjusted to allow for patient ineligibility or loss, the total sample size was 70 patients. We also performed a Monte-Carlo simulation to examine the effect of censoring on the power. We generated the exponential and Weibull random numbers to simulate censoring times, assumed the recruiting time and follow-up time of 2 years, and set the expected 2-year PFS rate to 60%. In various scenarios, we confirmed the lower limits of the 95% confidence intervals for 2-year PFS rates that exceeded the threshold value of 40% with the probability of more than 80%.

The cumulative outcomes and late complication curves were estimated by the Kaplan-Meier method. Differences in outcomes were compared using a log-rank test. PFS was measured from the time of registration until disease progression or death resulting from any cause. OS was measured from the time of registration until death resulting from any cause. Late adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Complete response was assessed following the Response Evaluation Criteria in Solid Tumors. All analyses were performed with SAS software, version 9.2.

Results

Patient characteristics

Seventy-two patients were enrolled from 25 institutions between March 2008 and January 2009. One patient was ineligible because she had para-aortic lymphadenopathy of 10 mm in the shortest diameter assessed on pretreatment abdominal CT. She never received treatment on protocol and was not included into the following analyses. Therefore, 71 patients formed the patient cohort for this report. The clinical characteristics of the 71 patients are listed in Table 2.

Feasibility

Sixty-three of the 71 patients (89%) completed the protocol treatment as planned. Chemotherapy was administered for the planned 5 courses in 65 patients (92%). Planned radiotherapy was completed in 68 patients (96%). One patient could not receive HDR-ICBT due to uterine perforation that occurred after 4 Gy of EBRT was delivered and the first administration of cisplatin. Subsequently, she was discontinued from the protocol treatment and received EBRT irradiation as a salvage treatment. Individual case reviews on RT QA revealed favorable compliance with the RT protocol [27]. The median total EQD2 (WP-EBRT + HDR-ICBT) at point A was 62 Gy (range, 49–65 Gy). Prescribed point A doses per protocol were delivered in 63 patients (89%): WP-EBRT 30 Gy + HDR-ICBT 24 Gy in 10 patients, WP-EBRT 30.6 Gy + HDR-ICBT 24 Gy in 30 patients, WP-EBRT 40 Gy + HDR-ICBT 18 Gy in 15 patients, WP-EBRT 41.4 Gy + HDR-ICBT 18 Gy in 6 patients, and WP-EBRT 50 Gy + HDR-ICBT 11 Gy in 2 patients. Boost EBRT was delivered to the parametrium in 28 patients, enlarged nodes in 22 patients, and both in 11 patients.

The rectal and bladder dose calculation according to the ICRU 38 definition was performed for every fraction in 66 patients (93%). Median doses were 4.4 Gy (range, 2.6–9.4 Gy) for the bladder, and 4.3 Gy (range, 2.8–11.1 Gy) for the rectum. Median cumulative biologically effective doses (BEDs) (EBRT + HDR-ICBT) were 95 Gy_3 (range, 68–184 Gy_3) for the bladder, and 96 Gy_3 (range, 71–199 Gy_3) for the rectum. Nine out of 66 patients (14%) received over 120 Gy_3 for the rectum. The median overall treatment time was 50 days (range, 37 to 66 days) for 68 patients who completed the planned radiotherapy.

Table 2
Patient characteristics.

Clinical variable	n	%
Median age (range)	57 years (32–70 years)	
PS		
0	63	89
1	8	11
FIGO stage		
IIIA	3	4
IIIB	64	90
IVA	4	6
Histological diagnosis		
Squamous cell carcinoma	66	93
Adenosquamous carcinoma	2	3
Adenocarcinoma	3	4
Parametrial involvement (fixed to pelvic wall)		
No	4	6
Yes	67	94
Unilateral	47	66
Bilateral	20	28
Maximum tumor diameter (mm)[a]		
<40	16	22.5
40≤, <50	10	14
50≤, <60	16	22.5
60≤, <70	16	22.5
70≤, <80	6	8.5
80≤	7	10
Pelvic node enlargement[b]		
Yes	41	58
No	30	42

[a] Assessed by MRI T2WI.
[b] ≥10 mm in shortest diameter assessed by CT/MRI.

Efficacy and late toxicity

The median follow-up for the 71 patients was 28 months (range, 12 to 35 months). Fifty-six patients (79%) achieved a complete response and 25 patients had disease progression. Twenty-one patients had a pelvic recurrence: primary lesion in 14; pelvic node in 6; and pelvic peritoneum in 1. Seventeen patients developed distant metastases: para-aortic node in 11; lung in 4; bone in 2; liver in 1; and supraclavicular node in 1. The 2-year PFS rate was 66% (95% CI, 54% to 76%; Fig. 1). The 2-year OS, PDPF, and DM were 90% (95% CI, 80% to 95%), 73% (95% CI, 61% to 82%), and 25% (95% CI, 16% to 37%), respectively.

There were decreases in both PFS ($P=0.036$) and PDPF ($P=0.24$) with increased tumor diameter as assessed by MRI. The 2-year PFS and PDPF were, respectively, 77% and 85% for tumors <50 mm, 69% and 72% for tumors 50–70 mm, and 39% and 54% for tumors ≥70 mm. The 2-year DM was higher for patients with large diameter tumors (47% for ≥70 mm) compared with those with smaller diameter tumors (19% for <50 mm, 20% for 50–70 mm) ($P=0.067$). Patients with enlarged pelvic nodes (≥10 mm in the shortest diameter assessed by CT/MRI) had poorer PFS and PDPF, and higher DM than those with no enlarged nodes. The 2-year PFS, PDPF and DM were, respectively, 60%, 67% and 31% for the node positive patients and 71%, 78% and 20% for the node negative patients. There were no significant differences between these two groups for these endpoints.

Table 3 lists late adverse events. Only 3 patients (4%) suffered severe (≥grade 3) late toxicity. The 2-year cumulative late complication rates by grades were 24% for all grades, 9% for grade 1, 12% for grade 2, 3% for grade 3, and 0 for grades 4/5.

Table 3
Reported late adverse events (n=71).

Events	Grade (n)				3≤(%, 95% CI)
	1	2	3	4	
Gastrointestinal					
Colitis	2	5	0	0	0
Enteritis	1	1	0	0	0
Proctitis	3	2	0	0	0
Nausea	1	0	0	0	0
Vomiting	1	0	0	0	0
Other (hemorrhage, upper GI)	1	0	0	0	0
Renal/genitourinary					
Cystitis	2	5	1	0	1 (0–8)
Incontinence	0	1	0	0	0
Obstruction (ureter)	0	0	1	0	1 (0–8)
Urinary retention	0	1	0	0	0
Other					
Edema: limb	3	0	0	0	0
Creatinine	0	0	1	0	1 (0–8)
Pain (pelvis)	0	1	0	0	0

Discussion

This prospective multi-institutional phase II study (JGOG1066) demonstrated that CCRT using HDR-ICBT with a low cumulative dose schedule (EQD2 = 62–65 Gy prescribed at point A) achieved a 2-year PFS rate of 66% with a low incidence (4%) of severe late toxicity in stage III and IVA uterine cervical cancer patients. The lower limit of the 95% CI for PFS was 54%, which was higher than the threshold of 40%, confirming the superiority of CCRT over historical outcomes of RT alone, although the eligibility criteria regarding para-aortic node evaluation were different from the prior RCTs [1].

Although the cumulative doses prescribed at point A adopted in this study were remarkably lower than those used in global schedules, the pelvic control rate appeared to be comparable to previously reported data (Table 4). However, there remains room for improvement in local control, particularly for patients with large tumors (≥70 mm in the largest diameter) who frequently developed pelvic recurrences in this study. The data from previously published papers suggested that higher prescribed doses had no apparent impact for improving local control, but probably did increase the risk of severe late complications (Table 4).

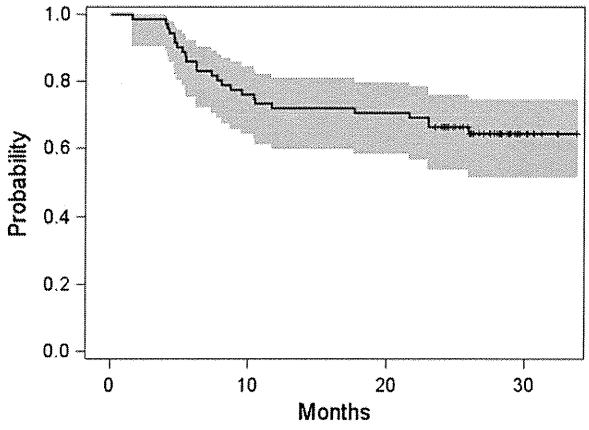

Fig. 1. Progression-free survival (PFS) of 71 eligible patients enrolled in JGOG1066.

In this study, 14% of the patients received over 120 Gy_3 at the ICRU38 rectal point, which is considered to be the threshold for developing severe proctitis [1]. We must bear in mind that these data, including those from our study, were for patients who were treated with ICBT that was planned only by a classical 2-dimensional (2-D) method, which prescribes doses at a single point A. Recently, 3-dimensional (3-D) image-guided brachytherapy (IGBT) using CT/MRI has become popular in clinical practice [30]. With IGBT, the actual tumor volume can be sufficiently covered with adequate prescribed doses while limiting the doses to surrounding organs at risk (OAR).

Dimopoulos et al. analyzed the dose–effect relationship between tumor diameter (at diagnosis and at time of HDR-ICBT) and local control for cases that were treated with IGBT [31]. They found a significant dose–effect relationship for local control within a dose range of 68 to 91 Gy using D90 HR-CTV for patients with large pretreatment tumor diameters and those with poor responses to EBRT [31]. A simple dose escalation for a single point A is an inappropriate approach to provide additional improvements in the therapeutic ratio. It is essential to investigate the therapeutic value of dose escalation using IGBT with careful monitoring of the doses to OAR, particularly for patients with large central tumors or, perhaps, those who responded poorly to prior EBRT.

In contrast, in this study, local control for patients with non-bulky tumors (<50 mm) was favorable (85%). Dimopoulos et al. showed excellent local control (97%) with no dose–effect relationship in patients with small tumors (2–5 cm) and those who had good responses to EBRT. Based on these results, they suggested that dose de-escalation with IGBT for these patient subsets might be appropriate [31]. Narayan et al. reported their experience with IGBT for cervical cancer [32]. Their goal with IGBT was to treat residual disease in the cervix and uterus after EBRT to a total dose of 80 Gy_{10}. They showed excellent local control with an average target dose of 79.2 Gy_{10} (resulting in 72 Gy_{10} at point A) for patients who had good responses to EBRT before ICBT and proper application of tandem applicator (i.e., inserted through the center of a cervical tumor) [32]. Unfortunately, for our study, we could not analyze local control based on both the response to EBRT and applicator laterality within a tumor, as we did not have a planned response evaluation or 3-D planning. A prospective study with IGBT to investigate local control with the prescribed doses used in this study is encouraged to determine whether dose de-escalation from global schedules is feasible for patients with

Table 4
Treatment results of cisplatin-based CCRT using HDR-ICBT for locally advanced cervical cancer.

Authors	n	Stage	III, IVA/all	EBRT (Gy) at point A	HDR-ICBT (Gy/fr) at point A	Total EQD2 (Gy) at point A	Median OTT	Median F/U	PC[a]	PFS[a]	Late toxicity[a] G3 <=	Subject for PC, and comments
Retrospective study												
Toita et al. [5]	40	IIB–IIIB	65%	40	18/3	64	48d	37 m	91% (3y)	67% (3y)	3%[b]	All stages
Novetsky et al. [6]	77	IB2–IV	40%	45	18/2	73	–	3.5y	68% (5y)	61% (5y)	6%[b]	Stages III and IVA
Ozsaran et al. [7]	81	IB–IVA	19%	50.4	18/3	73	–	42 m	78% (5y)	77% (5y)	0	>4 cm tumors
Parker et al. [8]	92	IB1–IVA	30%	45	24/4	77	61d	26 m	67% (5y)	–	4%[b]	All stages
Chen et al. [9]	70	IIB–IIIB	31%	45	24/4	77	–	43 m	87% (4y)	–	14%	All stages
Lim et al. [10]	69	IB1–IVA	26%	45	27.5/5, 30/5[c]	80, 84	8.4w	27 m	70% (2y)	59% (2y)	6%[b]	All stages
Anker et al. [11]	65	IB1–IVA	20%	45	30/5	84	–	25 m	97% (3y)	76% (3y)	17% (3y)	All stages, including RT alone cases (8%)
Forrest et al. [12]	122	IB–IV	25%	45	30/5	84	51d	18 m	86%[b]	70% (2y)	14% (2y)	All stages, including RT alone cases (16%)
Souhami et al. [13]	50	IIA–IVA	60%	46	30/3	96	–	27 m	68%[b]	–	26%[b]	Stage IIIB
Prospective study												
RTOG0128 [14]	77	IB1–IVA	21%	45	30/5	85	45d	24 m	74% (2y)	69% (4y)	16%[b]	All stages, HDR-ICBT was used in 35% of cases
Present study	71	III–IVA	100%	30–40	18/3, 24/4	62–65	50d	28 m	73% (2y)	66% (2y)	3% (2y)	Stages III and IVA

Abbreviations: CCRT = concurrent chemoradiotherapy; EBRT = external beam radiotherapy; HDR-ICBT = high dose-rate intracavitary brachytherapy; EQD2 = linear quadratic equivalent dose; PC = pelvic control rate; PFS = progression-free survival; d = days; w = weeks; m = months; y = year; NS = not stated; RT = radiotherapy.
[a] Actuarial rate.
[b] Crude rate.
[c] Point H.

non-bulky tumors or those with tumors that show good response. We believe that dose de-escalation has the potential to decrease the incidence of lower grade complications as well as high grade complications, which would contribute to improving patients' quality of life [20].

Distant failures, including para-aortic node metastases were frequently observed in this study. The incidence of distant failure increased with increased tumor size as well. In this study, histopathological examinations and PET/CT were not done to rule out para-aortic node metastases. This might have been one of the causes for frequent distant failures, including PAN recurrences. Reducing distant failures is another challenge that must be faced in order to improve the outcomes of patients with locoregionally advanced cervical cancer. A meta-analysis suggested that there might be therapeutic value with additional systemic chemotherapy after CCRT [19]. A phase I study to determine the optimum dose for adjuvant chemotherapy after definitive CCRT is now underway (JGOG1068).

One limitation of this study was that all of the patients were Japanese. Japanese women are generally smaller than Western women. This might have affected the toxicity incidences and grades. In addition, possible genetic differences between Japanese and Westerners cannot be completely ruled out. As mentioned previously, another limitation was that we did not use IGBT. For future multi-institutional prospective studies with IGBT, another quality assurance program on RT will be necessary [27].

In conclusion, despite the limited follow-up periods, the results of this study demonstrated that CCRT using HDR-ICBT with low cumulative RT dose schedules achieved comparable outcomes to those attained with global dose schedules with a lower incidence of late toxicity for locally advanced uterine cervical cancer patients in a Japanese population. If the presented RT dose schedules presented here are integrated into the current global standards, it would encourage the participation of Japanese patients in ongoing global studies. To further improve these outcomes, investigations on appropriate RT dose with IGBT and additional systemic treatment are warranted.

Conflict of interest statement
No conflict of interest.

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CLINICAL INVESTIGATION **Gynecologic Cancer**

PROSPECTIVE MULTI-INSTITUTIONAL STUDY OF DEFINITIVE RADIOTHERAPY WITH HIGH-DOSE-RATE INTRACAVITARY BRACHYTHERAPY IN PATIENTS WITH NONBULKY (<4-CM) STAGE I AND II UTERINE CERVICAL CANCER (JAROG0401/JROSG04-2)

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Purpose: To determine the efficacy of a definitive radiotherapy protocol using high-dose-rate intracavitary brachytherapy (HDR-ICBT) with a low cumulative dose schedule in nonbulky early-stage cervical cancer patients, we conducted a prospective multi-institutional study.

Methods and Materials: Eligible patients had squamous cell carcinoma of the intact uterine cervix, Federation of Gynecologic Oncology and Obstetrics (FIGO) stages Ib1, IIa, and IIb, tumor size <40 mm in diameter (assessed by T2-weighted magnetic resonance imaging), and no pelvic/para-aortic lymphadenopathy. The treatment protocol consisted of whole-pelvis external beam radiotherapy (EBRT) of 20 Gy/10 fractions, pelvic EBRT with midline block of 30 Gy/15 fractions, and HDR-ICBT of 24 Gy/4 fractions (at point A). The cumulative biologically effective dose (BED) was 62 Gy_{10} ($\alpha/\beta = 10$) at point A. The primary endpoint was the 2-year pelvic disease progression-free (PDPF) rate. All patients received a radiotherapy quality assurance review.

Results: Between September 2004 and July 2007, 60 eligible patients were enrolled. Thirty-six patients were assessed with FIGO stage Ib1; 12 patients with stage IIa; and 12 patients with stage IIb. Median tumor diameter was 28 mm (range, 6–39 mm). Median overall treatment time was 43 days. Median follow-up was 49 months (range, 7–72 months). Seven patients developed recurrences: 3 patients had pelvic recurrences (2 central, 1 nodal), and 4 patients had distant metastases. The 2-year PDPF was 96% (95% confidence interval [CI], 92%–100%). The

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2-year disease-free and overall survival rates were 90% (95% CI, 82%–98%) and 95% (95% CI, 89%–100%), respectively. The 2-year late complication rates (according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer of Grade ≥1) were 18% (95% CI, 8%–28%) for large intestine/rectum, 4% (95% CI, 0%–8%) for small intestine, and 0% for bladder. No Grade ≥3 cases were observed for genitourinary/gastrointestinal late complications.

Conclusions: These results suggest that definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED, 62 Gy_{10} at point A) can provide excellent local control without severe toxicity in nonbulky (<4-cm) early-stage cervical cancer. © **2012 Elsevier Inc.**

Carcinoma of the cervix, Radiotherapy, High-dose-rate, Intracavitary brachytherapy, Dose response.

INTRODUCTION

Numerous retrospective studies of definitive radiotherapy (RT) have reported favorable local control with an acceptable level of toxicity for patients with early-stage cervical cancer (1–4). A randomized clinical trial (RCT) performed in Italy in the 1990s revealed no significant difference in overall survival between patients treated with surgery and those treated with definitive RT (5). As a result, definitive radiotherapy has been accepted as one of the treatment options for early-stage cervical cancer (6).

Standard definitive RT for uterine cervical cancer consists of external beam RT (EBRT) to the whole pelvis and intracavitary brachytherapy (ICBT) (6). Several RCTs have demonstrated that high-dose-rate ICBT (HDR-ICBT) achieves rates of local control and late toxicity that are similar to those of low-dose-rate ICBT (LDR-ICBT) (7,8). Therefore, HDR-ICBT will likely replace LDR-ICBT as the standard of treatment, with several advantages over the LDR-ICBT. Dosing schedules of HDR-ICBT (*i.e.*, total dose and fractions in combination with EBRT) differ substantially among various countries, both in clinical practice (3, 4, 7–20) and in published guidelines (21, 22). Table 1 lists various schedules for definitive RT with HDR-ICBT along with pelvic control rates for stage I and II cervical cancer (3, 4, 7–22). Immediately evident is the lack of a clear dose-response relationship between biologically effective dose (BED) at point A and pelvic control, which has been previously noted (23).

We have identified two possible factors that explain the lack of a clear dose-response relationship in these retrospective studies. The first is potential bias in the doses delivered to each patient; that is, patients with a poor response to RT might have received higher total doses than good responders. Second, most of these studies did not include tumor size assessment, which was another serious limitation for comparison among the various series. Tumor size is one of the most important parameters affecting local control in radiotherapy for cervical cancer and may vary widely even within the same Federation of Gynecologic Oncology and Obstetrics (FIGO) stage (24). Therefore, a prospective study based on appropriate tumor size assessment and a fixed dose schedule would seem warranted to determine an optimum dosing schedule of HDR-ICBT.

Magnetic resonance imaging (MRI) is one of the most useful imaging modalities to evaluate tumor size objectively in cervical cancer (25–27). Toita *et al.* (28) retrospectively analyzed the relationship between local control and tumor diameter as assessed by MRI in a small series. In that series, in patients with American Brachytherapy Society (ABS)-defined early disease (stage I/II, <4 cm) (22), the 3-year actuarial pelvic control rate was 96%, within the dose range of 48 Gy_{10} to 77 Gy_{10} (28). Pelvic control rates by BED values were 5 out of 5 (5/5) for 48 Gy_{10}, 7/7 for 62 Gy_{10} (α/β = 10), 2/2 for 68 Gy_{10}, and 8/9 for 77 Gy_{10} (28). As shown in Table 1, Japanese investigators have reported favorable pelvic control rates with a total BED of 46 to 68 Gy_{10} despite no objective tumor size assessment. These findings suggest that a cumulative dose of 46 to 68 Gy_{10} may be adequate to achieve local control of nonbulky (<4-cm) early-stage cervical cancer.

Based on the above background data, the Japanese Radiation Oncology Study Group (JROSG; http://www.jrosg.jp) conducted a prospective multi-institutional study to assess the efficacy and toxicity of a definitive RT schedule with low cumulative doses in patients with nonbulky stage I and II uterine cervical cancer. We report herein the endpoint results of that prospective study.

METHODS AND MATERIALS

Patient eligibility criteria

Eligible patients had histologically proven squamous cell carcinoma of the intact uterine cervix and FIGO stage Ib1, IIa, or IIb disease. Study patients were between 20 and 85 years of age. A complete physical examination, a pelvic examination performed without anesthesia, and a chest X-ray were required to determine the clinical stage. Patients also were required to have cervical tumors less than 40 mm in diameter, assessed by T_2-weighted MRI, and negative pelvic and para-aortic lymph nodes (less than 10 mm in shortest diameter), as determined by computed tomography (CT). The CT and MRI studies had to be preformed within 4 weeks of entry. Patients were also required to have a Zubrod performance score (PS) of 0 to 2 and adequate bone marrow function: white blood cell count ≥3,000/mm^3, absolute neutrophil count ≥1,000/mm^3, and hemoglobin level ≥8.0 g/L (data after transfusion would be acceptable). All patients provided written informed consent.

Protocol treatment

The treatment is shown in Fig. 1, consisting of a combination of EBRT and HDR-ICBT. Interstitial brachytherapy was not allowed. Chemotherapy was also not permitted. EBRT was delivered to a total dose of 50 Gy in 25 fractions over 5 to 6 weeks. The initial 20 Gy was delivered to the whole pelvis. After that, 30 Gy was administered through the same whole-pelvis field with a midline block (MB) 3 to 4 cm in width. The MB was formed with multileaf collimators (MLC) or a custom cerrobend block. The first HDR-ICBT was performed within 10 days after the initial 20 Gy of EBRT. If HDR-ICBT could not be performed in this time interval, the protocol was

Table 1. Schedules and doses of definitive radiotherapy using HDR-ICBT for stage I and/or II cervical cancer

Study (country) (ref)	EBRT (Gy)	HDR-ICBT dose (Gy/fr) or dose range at point A	Total BED (Gy_{10}) or BED range at point A	% or % range of pelvic control (follow-up)	Median follow-up	Comments
Reports						
Nakano *et al.* (Japan) (4)	0–20	29/5–23/4	46–62	86[§]	22 years	Stage IB and II (small)
Teshima *et al.* (Japan) (7)	20	28/4–30/4	63–66	87[§]	11 years	Stage I and II (all)
Hareyama *et al.* (Japan) (8)	0–30	29/5–23/4	46–68	89 (5 years)[‡]	47 months	Stage II (all)
Wang *et al.* (Taiwan) (9)	39.6–45	24/5	82–88	87–94 (5 years)[‡]	5 years	Stage I and II (all)
Wong *et al.* (China) (10)	40	21/3–24/4	84–86	79–89 (5 years)[‡]	4.7 years	Stage I and II (all)
Ozsaran *et al.* (Turkey) (11)	50.4	18/3	88	73 (5 years)[‡]	42 months	CCRT data; stage I and II (all) = 82%
Lee *et al.* (Korea) (3)	40	39/13	95 (median)	95[§]	60 months	Stage IB
Souhami *et al.* (Canada) (12)	45	24/3	96	80–88[§]	50 months	Including CCRT data
Petereit *et al.* (US) (13)	40–50*	45.5–49.5/5[†]	96 (median)[†]	88 (3 years)[‡]	22 months	Stage I and II (≤5 cm)
Sood *et al.* (US) (14)	45	18/2	87	77 (3 years)[§]	3 years	Stage I and II (all): 87%
Anker *et al.* (US) (15)	45	30/5	101	97 (3 years)[‡]	25 months	Including CCRT data; stage I and II (all) = 80%
Patterns of care						
Toita *et al.* (Japan) (16)	30	22–23/4	70–72	–	–	Stage I and II (all)
Jones *et al.* (UK) (17)	40–60	7.5/1–42/6	61–96	–	–	Small volume
Pearce *et al.* (Canada) (18)	45	30/5	101	–	–	Same in all stages
Erickson *et al.* (US) (19)	NS	NS	103 (median)	–	–	All stages combined
Dyk *et al.* (Australia, New Zealand) (20)	45–60	18/3–30/5	73–94	–	–	All stages combined
Recommendations						
Okawa (Japan) (21)	0, 20	29/5, 23/4	46, 60	–	–	Stage I and II (small)
Nag *et al.* (US [ABS]) (22)	20, 45	48/8, 30/5	101	–	–	Stage I and II (nonbulky, <4cm)

Abbreviations: EBRT = external beam radiotherapy; HDR-ICBT = high dose-rate intracavitary brachytherapy; BED = biologically effective dose CCRT = concurrent chemoradiotherapy; fr = fraction; NS = not stated; ABS = American Brachytherapy Society.

* 1.7 Gy/fr.

† Point M.

‡ Actuarial rate.

§ Crude rate.

terminated, and any subsequent treatments (*e.g.*, additional whole-pelvis EBRT without the MB) were at the discretion of the treating physician. Treatment was to be completed within 56 days.

All patients were treated with a photon beam of 6 MV or greater. Both anteroposterior (AP)-posteroanterior (PA) and a four-field techniques were allowed. When the four-field technique was utilized, the portal arrangement was changed to the AP/PA technique after the MB was inserted. A tissue heterogeneity correction was not used in the dose calculation. The upper border of the pelvic field was L4-L5, and the lower border was a transverse line below the obturator foramen. The lateral borders of the AP/PA fields were 1 to 2 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the anterior border was placed at a horizontal line drawn 1 cm anterior to the symphysis pubis anteriorly and a vertical line at the posterior border of the sacrum posteriorly. The upper and lower borders were the same as those for the AP/PA fields. The fields were shaped to shield normal tissues, using a custom block or MLC. Prophylactic para-aortic radiotherapy was not allowed.

HDR-ICBT was performed once per week, administering 24 Gy to point A in four fractions with Ir-192 afterloading machines.

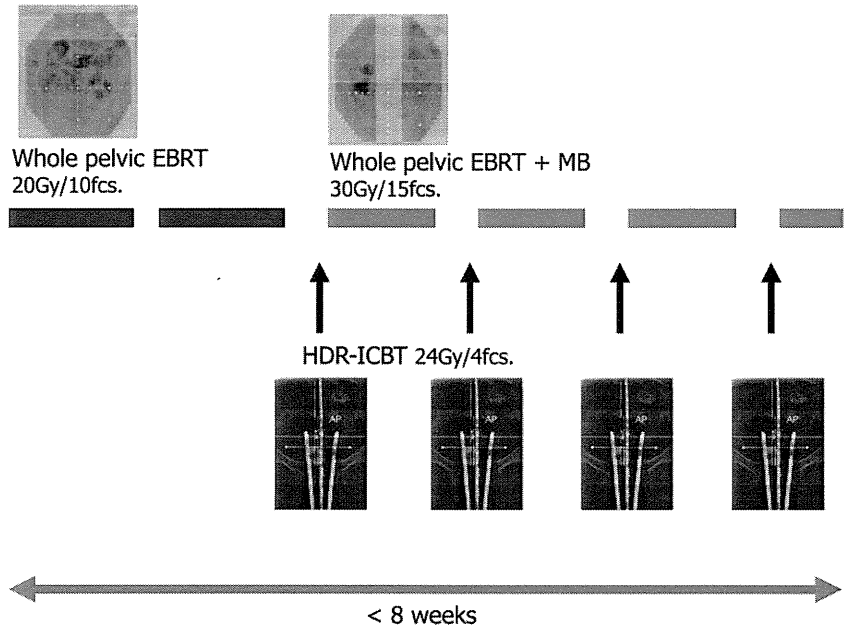

Fig. 1. Treatment schema.

HDR-ICBT delivery was not allowed on the same day as the EBRT. A combination of tandem and ovoid applicators was recommended except as restricted by the vaginal anatomy (*e.g.*, narrow vagina) or significant vaginal disease invasion. Source dwell patterns (*i.e.*, times and positions) were determined according to the Manchester system(29). For determining point A, two alternative rules were established on the basis of the topographical relationships between the tandem and ovoid applicators (30). First, for two A points (left and right), the point associated with the lower dose was to be designated as the prescribed point A. The second rule pertained to the point of origin for the determination of point A. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) would be selected as the geographic origin of the point A. In the event the external os was located caudally to the cranial ovoid surface (*e.g.*, roomy vaginal vault), a coordinate of the vaginal vault surface was to be designated as the origin of the vertical level to point A. The concept behind the latter definition is essentially the same as that for point H, proposed by the ABS (22). Dosimetry was performed before each application,using two orthogonal radiographs. The isodoses were plotted, and the doses to the rectum and bladder were calculated according to International Commission on Radiation Units and Measurements (ICRU) 38 criteria (31). Three-dimensional planning with CT and/or MRI was not utilized.

RT was postponed until adverse effects resolved, if one or more of the following adverse events was observed: Grade 4 hematologic toxicity; Grade ≥3 diarrhea, cystitis, nausea, and/or dermatitis; and PS ≥3. If the grade of the toxicities did not decrease after 3 weeks, the planned treatment was terminated.

Quality assurance (QA) reviews of the RT were performed by the QA committee for all patients entered. Treatment charts and radiological data and figures were submitted and reviewed. The results have been published elsewhere (30). Tumor diameter was also reevaluated for all patients at the time of the QA meetings.

Evaluation

Acute side effects were scored according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Late toxicity was scored by Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity criteria. Patients visited every 3 months during the first 2 years and then every 6 months or annually. Follow-up was to include assessment of late toxicity, pelvic examination, CT of the abdomen and pelvis (every 6 months), MRI of the pelvis (every 6 months), and chest X-ray (every 6 months).

Statistical analysis

The study was approved by the JROSG Protocol Review Committee and the local institutional review boards of the participating institutions.

The primary purpose of this study was to determine if the RT protocol could achieve a local control rate comparable to those previously reported in several retrospective studies. The primary endpoint of this study was the 2-year pelvic disease progression-free (PDPF) rate. Sample size was calculated on the basis of the primary endpoint. We set the expected level for the 2-year PDPF at 85%. To achieve the result within a 95% confidence interval (CI, 75%–95%)for the 2-year PDPF, we calculated that 54 patients would have to be recruited over 3 years, based on the Brookmeyer-Crowly method (32). After the sample size was adjusted by 10% to allow for patient ineligibility or loss, the total sample size was 60 patients.

The secondary endpoints were acute toxicity, treatment completion rate, late complication rate, 2-year disease-specific survival (DSS) rate, 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate, and site of recurrence. The PDPF, DSS, DFS, and OS endpoints were measured from the date of treatment start to the date of the events. Estimates of survival distribution and late complication probability were calculated by the Kaplan-Meier method. All analyses were performed using SAS version 8.02 software (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

Between September 2004 and July 2007, 60 patients were enrolled from 13 institutions. No patient was assessed as

Table 2. Patient characteristics

Characteristics	No. of patients (%)
Age (years)	
Median	73
Range	37–84
<60	11 (18)
60–70	11 (18)
70–80	31 (52)
>80	7 (12)
Performance status	
0	31
1	28
2	1
FIGO stage	
Ib1	36 (60)
IIa	12 (20)
IIb	12 (20)
Tumor size (mm)	
Median	28
Range	6–39
<10	2 (3)
10–19	5 (8)
20–29	23 (39)
30–39	22 (37)
Unable to measure	8 (13)

ineligible. Therefore, 60 patients formed the patient cohort for the analysis. Pretreatment characteristics for the eligible patients are listed in Table 2.

Acute toxicity and compliance

Forty-four patients (72%) were treated on an inpatient basis. The acute toxicity profiles during and after the protocol treatment period (within 90 days) are shown in Table 3. Only one patient experienced toxicity necessitating treatment rest (Grade 3 diarrhea); however, per the patient's treating physician, no protocol treatment postponement was adopted. Eleven patients had treatment rest (median, 4 days; range, 1–7 days). Five patients had treatment rest because of national holidays; 4 patients because of machine trouble; 1 patient because of heart disease; and 1 patient because of preference. Overall treatment time (OTT) ranged from 38 to 55 days, with a median of 43 days. All 60 patients (100%) completed the planned protocol treatment.

Efficacy

Two patients (3%) were lost to follow-up (at 7 and 10 months) within the 24-month follow-up interval. The remaining 58 patients were followed beyond the planned 24 months. The median follow-up time for all 60 patients was 49 months (range, 7–72 months).

Table 3. Acute toxicities

	No. of patients by toxicity grade (n = 60)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	17	16	3	0
Neutropenia	15	5	3	0
Anemia	14	2	0	0
Thrombocytopenia	13	0	0	0
Dermatitis	17	4	0	0
Nausea	10	0	0	0
Diarrhea	25	11	1	0
Cystitis	8	5	0	0

Three patients experienced pelvic recurrence: 2 patients had central recurrence, and 1 patient had recurrence in lymph nodes. The estimated 2-year and 3-year PDPF rates were both 96% (95% CI, 92%–100%) (Fig. 2). Five patients developed distant metastases: 4 patients had metastases without pelvic recurrence, and 1 patient had metastases after pelvic recurrence. These cases included recurrence in paraaortic lymph nodes (1 patient), lung (1 patient), liver and subcutaneous tissue (1 patient), and multiple osseous lesions and nodes (2 patients).

Figure 3 shows the incidence of pelvic recurrence and distant recurrence as a function of tumor size subcategories. No pelvic recurrences occurred in patients with tumors less than 30 mm in diameter. The incidence of distant metastasis rose as tumor diameter increased.

Of the 5 patient deaths recorded, 4 patients died from cervical cancer, and 1 patient without cervical cancer recurrence died from an unrelated cause. The estimated 2-year and 3-year DFS rates were both 90% (95% CI, 82%–98%), and the estimated 2-year and 3-year OS rates were both 95% (95% CI, 89%–100%) (Fig. 2).

Dose to organs at risk and late toxicity

In ICBT, median calculated doses to the rectum and bladder according to the ICRU 38 definition were 4.9 Gy (range, 2.2–10.5 Gy) and 4.8 Gy (range, 2.1–12.1 Gy), respectively. Table 4 lists gastrointestinal and genitourinary late toxicity profiles. No patient suffered severe gastrointestinal or genitourinary late toxicities (Grade ≥3). The estimated 2-year and 3-years rates for late toxicities (Grade 1–2) were 16% (95% CI, 6%–26%) and 18% (95% CI, 8%–28%) for the large intestine and rectum, respectively; 0% and 2% (95% CI, 0%–5%), respectively, for the bladder; and 4% (95% CI, 0%–8%) and 7% (95% CI, 4%–14%), respectively, for the small intestine (Fig. 4).

DISCUSSION

To our knowledge, this is the first multi-institutional prospective study to evaluate the efficacy and toxicity of a defined radiotherapy schedule with HDR-ICBT for uterine cervical cancer. Our prospective study demonstrated good 2-year and 3-year PDPF rates of 96% (95% CI, 92%–100%) and an acceptable level of toxicity in 60 patients with nonbulky (<4-cm, assessed by MRI) stage I and II cervical cancer. These results suggest the clinical validity of previously reported results of other Japanese studies (4, 7, 8, 28).

The study by Petereit and Pearcey (23) questioned the published favorable data from Japanese investigators with low cumulative radiotherapy doses, noting that the doses in those Japanese series were less than tumoricidal. The BED of 62 Gy_{10} utilized in our study is equivalent to the 52 Gy used in conventional fractionated radiotherapy (33).

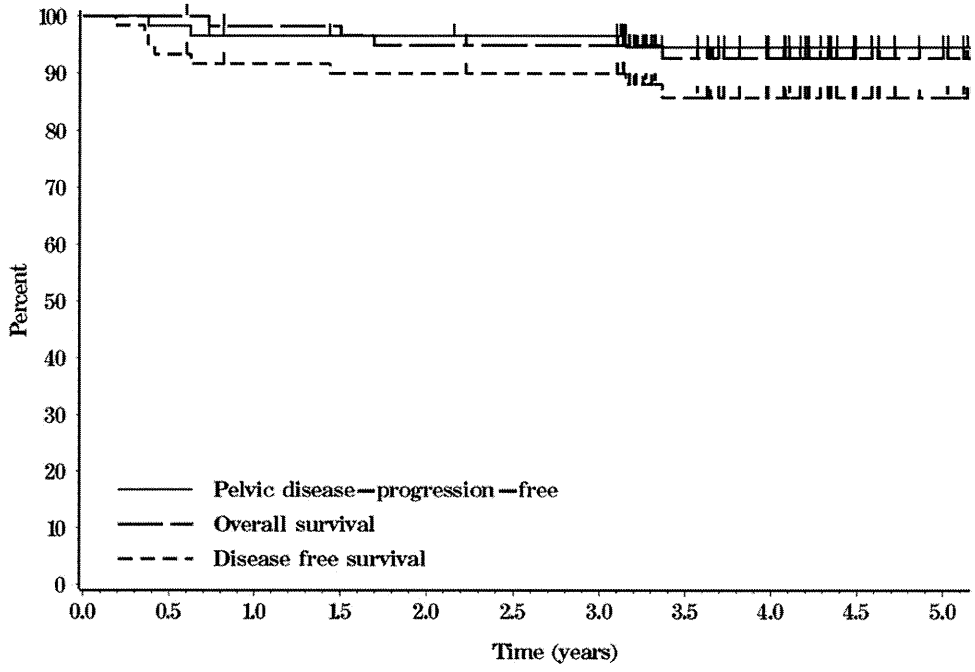

Fig. 2. PDPF survival, OS, and DFS are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

As Petereit and Pearcey (23) claimed, 52 Gy is the minimum dose for eradicating subclinical microscopic disease (*i.e.*, low risk clinical target volume). However, in the definitive radiotherapy for cervical cancer, the dose distribution of ICBT with a steep dose gradient should be taken into account in analyzing dose response on local control. In some patients with small volume tumor, the minimum dose delivered to the tumor might be higher than a prescribed point A dose.

In addition to radiation physics issues, radiobiological parameters need to be taken into account to explain the favorable local control results, despite the low radiation dose delivered in our study. One potentially significant parameter is the short OTT in our study. The OTT has been reported to be one of the most important treatment factors affecting local control of cervical cancer (34). In our study, the relatively short median OTT (median, 43 days) might have positively affected the local control results. Fowler and colleagues (35) proposed a linear quadratic formula that takes time factors in account. Several investigators have demonstrated that the repopulation rate of cervical cancer cells increases at around 21 to 28 days after starting EBRT (36). Our treatment protocol specified that HDR-ICBT was to start at 2 to 3 weeks. Additionally, tumor cell heterogeneity in radiosensitivity and tumor volume have been implicated as important factors affecting tumor control probability in sophisticated radiobiological models (37). In our series, no patients with small tumors (<2–3 cm) developed local recurrence. This finding is supportive of the hypothesis that a lower dose might be sufficient for eradicating cancer cells in small volume tumors,

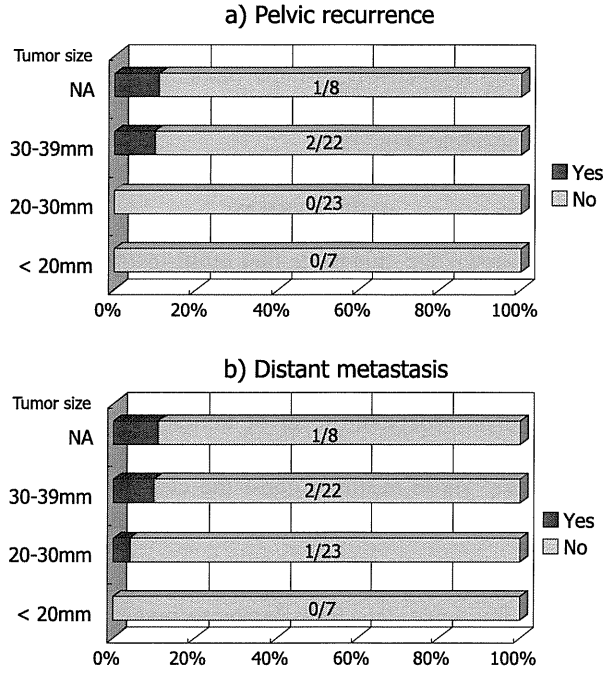

Fig. 3. Recurrence rate as a function of tumor size is shown for (a) pelvic recurrence and (b) distant metastasis. NA = not assessed (invisible on MRI).

Table 4. Late toxicities

Toxicity	No. of patients by toxicity grade (n = 60)			
	Grade 1	Grade 2	Grade 3	Grade 4
Small intestine	3	1	0	0
Large intestine/rectum	9	2	0	0
Bladder	0	1	0	0

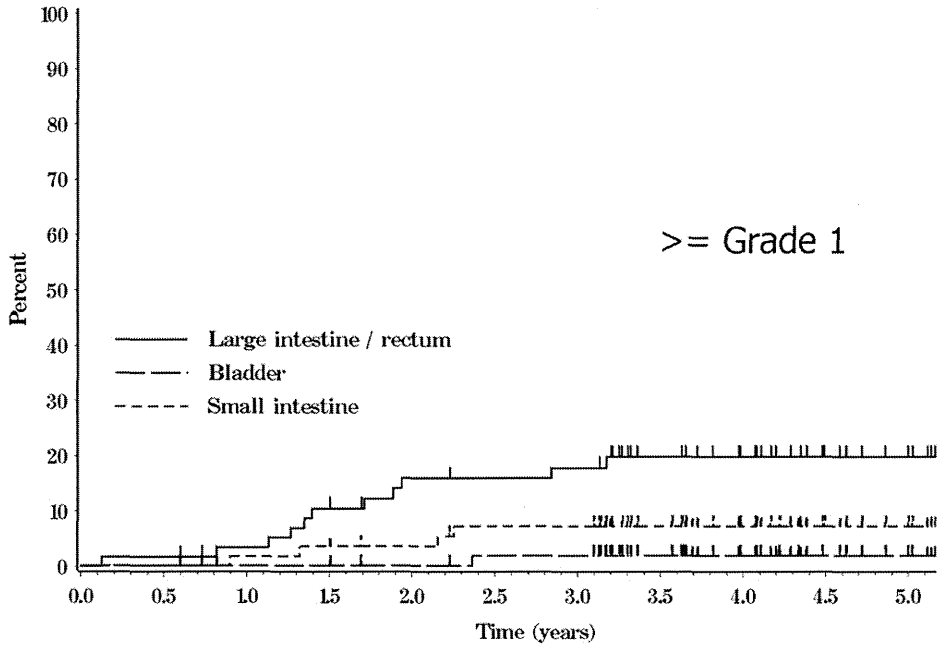

Fig. 4. Late complications (Grade ≥1) are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

even if such a low dose is not effective in treating bulky tumors.

In our study, acute and late toxicities were also evaluated prospectively. We assessed the incidence and grade of acute toxicities among our study patients as acceptable. Regarding late toxicities, no patient suffered severe gastrointestinal or genitourinary complications (Grade ≥3). We would consider this outcome to be a positive consequence of the low cumulative doses delivered to the central pelvis.

One potential limitation to our study was that the application of a MB might have introduced some degree of uncertainty with respect to the EBRT dose to the cervical tumor (38). This uncertainty resulted from the difficulty in confirming that the MB completely covered the cervix in every patient during every EBRT fraction in this study. Recently, onboard CT images have now become routinely available in clinical practice. Daily confirmation with this imaging device is feasible to confirm that an MB completely covers the cervical lesion.

CONCLUSIONS

In conclusion, the results of our study suggest that definitive radiotherapy consisting of whole-pelvis EBRT of 20 Gy/10 fractions, pelvic EBRT with an MB of 30 Gy/15 fractions, and HDR-ICBT of 24 Gy/4 fractions at point A (BED 62 Gy_{10}) is an effective and safe treatment for stage I and II cervical cancer patients with small (<4-cm) tumor diameter. Recently, the value of dose-volume histogram parameters for predicting local control in MR image-guided BT has been investigated for treating cervical cancer (39, 40). A future prospective study with the novel image-guided BT method using appropriate dose-volume histogram parameters is encouraged to confirm the findings of the present study in the near future.

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Patterns of Radiotherapy Practice for Patients With Cervical Cancer in Japan, 2003–2005: Changing Trends in the Pattern of Care Process

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Summary

This study reports changes in the patterns of practice of definitive radiotherapy for cervical cancer in Japan since 1995 by comparing 3 patterns of care surveys. There has been a significant trend toward use of concurrent chemotherapy consistent with randomized trial data. External beam radiation has became progressively more standardized. Intracavitary brachytherapy, however, still has not reached consistent levels of quality.

Purpose: The patterns of care study (PCS) of radiotherapy for cervical cancer in Japan over the last 10 years was reviewed.

Methods and Materials: The Japanese PCS working group analyzed data from 1,200 patients (1995–1997, 591 patients; 1999–2001, 324 patients; 2003–2005, 285 patients) with cervical cancer treated with definitive radiotherapy in Japan.

Results: Patients in the 2001–2003 survey were significantly younger than those in the 1999–2001 study ($p < 0.0001$). Histology, performance status, and International Federation of Gynecology and Obstetrics stage were not significantly different among the three survey periods. Use of combinations of chemotherapy has increased significantly during those periods (1995–1997, 24%; 1999–2001, 33%; 2003–2005, 54%; $p < 0.0001$). The ratio of patients receiving concurrent chemotherapy has also dramatically increased (1995–1997, 20%; 1999–2001, 54%; 2003–2005, 83%; $p < 0.0001$). As for external beam radiotherapy (EBRT), the application rate of four-field portals has greatly increased over the three survey periods (1995–1997, 2%; 1999–2001, 7%; 2003–2005, 21%; $p < 0.0001$). In addition, the use of an appropriate beam energy for EBRT has shown an increase (1995–1997, 67%; 1999–2001, 74%; 2003–2005, 81%; $p = 0.064$). As for intracavitary brachytherapy (ICBT), an iridium source has become increasingly popular (1995–1997, 27%; 1999–2001, 42%; 2003–2005, 84%; $p < 0.0001$). Among the three surveys, the ratio of patients receiving ICBT (1995–1997, 77%; 1999–2001, 82%; 2003–2005, 78%) has not changed. Although

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follow-up was inadequate in each survey, no significant survival differences were observed ($p = 0.36$), and rates of late Grade 3 or higher toxicity were significantly different ($p = 0.016$). **Conclusions:** The Japanese PCS has monitored consistent improvements over the past 10 years in the application of chemotherapy, timing of chemotherapy, and EBRT methods. However, there is still room for improvement, especially in the clinical practice of ICBT.

Keywords: Cervix, Chemotherapy, Japan, Patterns of care study, Radiotherapy

Introduction

In Japan, the number of uterine cervical cancers decreased from the 1980s to 2000 but has been steadily increasing since then (1). The age-adjusted mortality rate due to cervical cancer has also shown an increase, especially in the younger generation in Japan (3). Radiation therapy is established as an integral component for cervical cancer. Over the past 10 years, some changes have occurred in the cervical cancer radiotherapy policy in Japan. Given the increases in cervical cancer and age-adjusted mortality rates, to optimally treat Japanese cervical cancer patients, it is important to accurately delineate intrinsic changes taking place in the national practice process of radiotherapy for cervical cancer in Japan. The patterns of care study (PCS) (2) initially surveyed radiotherapy practice in the United States. In the United States, PCS has been conducted for more than 30 years, and the structure, process, and outcomes of radiotherapy, as well as various problems in clinical practice, have been identified for cervical cancer (4, 5). The Japanese PCS began in 1996 and used the same methods (6). We previously reported Japanese PCS results for radiotherapy practice in cervical cancer patients treated in 1995–1997 and 1999–2001 (7, 8). We report here the corresponding results for 2003–2005, and the changes in radiotherapy practice that occurred over the years from the 1995–1997, 1999–2001, and 2003–2005 survey periods are also examined.

Methods and Materials

Between 2006 and 2008, the Japanese PCS working group conducted a third national survey of patients with uterine cervical cancer treated with radiotherapy. Patients who were eligible for the survey (*1*) had carcinoma, (*2*) were treated between January 2003 and December 2005, and (*3*) had no distant metastasis, (*4*) no prior or concurrent malignancy, (*5*) no gross para-aortic lymph node metastasis, and (*6*) no previous pelvic radiotherapy. Sixty-one of 640 institutions were selected for this survey by using a stratified two-staged cluster sampling method. Before the random sampling, all institutions were divided into four groups. Institutions were classified by type and number of patients treated with radiotherapy. The Japanese PCS working group stratified Japanese institutions as A1, academic institutions treating ≥430 patients annually; A2, academic institutions treating <430 patients; B1, nonacademic institutions treating ≥130 patients annually; and B2, nonacademic institutions treating <130 patients. Detailed criteria for stratification have been shown elsewhere (6). The Japanese PCS surveyors performed on-site chart reviews at each participating facility, using an originally developed database format for cervical cancer. Data collection included patient characteristics, details of the pretreatment workup, therapeutic information, and treatment outcome. The Japanese PCS collected clinical data for 487 patients with cervical cancer, who were treated with radiotherapy from 61 institutions. In this study, 285 patients treated with radiotherapy without planned surgery were analyzed. These included 114 patients from A1 institutions, 87 patients from A2 institutions, 50 patients from B1 institutions, and 34 patients from B2 institutions. There were unknown and missing data in the tables because no valid data were found in the given resources.

In addition, the current study compared data for three Japanese PCS surveys of 1,200 patients (1995–1997, 591 patients; 1999–2001, 324 patients; 2003–2005, 285 patients) with cervical cancer treated with radiotherapy with curative intent. Methods for the 1995–1997 and 1999–2001 PCS were the same as those for the 2003–2005 study. Ratios were calculated without unknown or missing data. Statistical significance was tested using the chi-square test.

Results

Patient characteristics in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

Table 1 shows characteristics of the 285 patients in the 2003–2005 survey and changes in radiotherapy practice over the 1995–1997, 1999–2001, and 2003–2005 survey periods. The ages of the analyzed cohorts were significantly different among the three survey periods ($p < 0.0001$). The ages of the analyzed cohort were not different between the 1995–1997 and 1999–2001 surveys ($p = 0.34$) but were significantly different between the 1999–2001 and 2003–2005 surveys ($p < 0.0001$). Karnofsky performance status (KPS), histology, and International Federation of Gynecology and Obstetrics (FIGO) stages were not significantly different among the three survey periods, as shown in Table 1.

EBRT in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

In the 2003–2005 survey, EBRT was performed in 283 patients (99%). Major treatment parameters for pelvic EBRT in the 2003–2005 survey are shown in Table 2. Treatment parameters in the 2003–2005 survey other than those shown in Table 2 are as follows. In 220 cases (78%), multileaf collimators were used to shape the portals. For 265 patients (94%), the planning target volume included the whole pelvic region. The upper border of the pelvic field was at level of the L4–L5 interspace in 245 of the 265 patients (92%). Only 6 patients (2%) received extended field radiotherapy that included the para-aortic region. The median radiation treatment time was 6.0 weeks (range, 1.1–13.0 weeks). The median radiation treatment time exceeded 8 weeks in 7 patients (3%).

Table 1 Patient and tumor characteristics of patients with uterine cervical cancer treated with radiotherapy in each surveillance period

Characteristic	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Age (years)				<0.0001
Range	28–94	26–100	25–95	
Median	70	71	67	
KPS				0.21
≤70	133 (23)	64 (21)	52 (18)	
80–90	421 (72)	217 (72)	193 (68)	
100	28 (5)	21 (7)	40 (14)	
Unknown/missing	9 (–)	22 (–)	0 (–)	
Histology				0.99
Squamous cell	554 (95)	300 (94)	257 (92)	
Adenocarcinoma	23 (4)	14 (4)	14 (5)	
Adenosquamous cell	4 (1)	4 (1)	5 (2)	
Other	4 (1)	2 (1)	3 (1)	
Unknown/missing	6 (–)	4 (–)	6 (–)	
FIGO stage				0.89
I	57 (10)	43 (14)	27 (10)	
II	171 (29)	102 (34)	85 (30)	
III	280 (48)	122 (40)	132 (46)	
IVA	75 (13)	35 (12)	41 (14)	
Other	5 (1)	0 (0)	0 (0)	
Unknown/missing	3 (–)	22 (–)	1 (–)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; KPS = Karnofsky performance status.

Changes in radiotherapy practice over the 1995–1997, 1999–2001, and 2003–2005 survey periods are also shown in Table 2. The ratio of appropriate EBRT beam energy levels of more than or equal to 10 MV showed a tendency to increase over the three surveys (1995–1997, 67%; 1999–2001, 74%; 2003–2005, 81%; $p = 0.064$). In addition, application of four-field portals greatly increased over the three surveys ($p < 0.0001$). Use of a midline block, single-daily fraction doses, and total point A doses were not significantly different among the three survey periods.

ICBT in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

No patient surveyed received interstitial brachytherapy in the 2003–2005 survey. Fifty-nine patients (27%) received ICBT at another facility. Details of ICBT in the 2003–2005 survey are shown in Table 3. In most patients, all high-dose-rate ICBT (HDR-ICBT) procedures (applicator insertion, radiograph generation, and treatment) were performed in the same room, but these data for dose calculations for the rectum and bladder and the ICBT method showed a considerable rate of unknown or missing data.

Changes in ICBT practice over the years are also shown in Table 3. A ratio of Ir-192 source showed a significant increase among the three surveys ($p < 0.0001$). The number of patients who received no supportive medication before or during the applicator insertion significantly decreased over the three survey periods ($p < 0.0001$), but conscious sedation was still used for a few patients. The use of ICBT, dose rate, method of ICBT, and single-daily fraction dose were not different among the three survey periods. The use of *in vivo* dosimetry and International Commission on Radiation Units and Measurements (ICRU) report 38 calculations for bladder and rectum were not different among the three survey periods, although these data also showed an appreciable rate of unknown or missing data.

Chemotherapy in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

In the 2003–2005 survey, chemotherapy was given to 149 patients (54%), as shown in Table 4. Neoadjuvant chemotherapy was given to 16 patients before they received radiation therapy (11%), and 124 patients (83%) were treated with concurrent chemoradiation (CCRT). Weekly cisplatin was the agent most frequently used with CCRT (45%), and cisplatin was the most common agent in CCRT (55%) regimens.

Changes in chemotherapy practice over the years are also shown in Table 4. Application of chemotherapy significantly increased over the three survey periods ($p < 0.0001$). In addition, concurrent use of chemotherapy with radiotherapy has dramatically increased ($p < 0.0001$). On the other hand, the ratio of neoadjuvant chemotherapy in the most recent survey (2003–2005, 11%) decreased compared to those of 1995–1997 (58%) and 1999–2001 (50%).

Comparison of outcomes and toxicity between the 1995–1997, 1999–2001, and 2003–2005 surveys

Overall survival rates of patients in each survey are shown in Figure 1. Two-year survival rates in the 1995–1997, 1999–2001,

Table 2 Treatment parameters of pelvic external beam radiotherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameters	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Beam energy				0.064
Co-60 and 3–5 MV	96 (17)	32 (11)	20 (7)	
6–9 MV	82 (14)	45 (15)	30 (11)	
10–14 MV	338 (59)	220 (71)	191 (70)	
≥15 MV	45 (8)	9 (3)	31 (11)	
Other	10 (2)	0 (0)	1 (0)	
Unknown/ missing	20 (–)	2 (–)	12 (–)	
Technique				<0.0001
AP-PA	560 (98)	269 (87)	205 (75)	
Four-field box	11 (2)	21 (7)	57 (21)	
Other	1 (0)	17 (6)	11 (4)	
Unknown/ missing	19 (–)	1 (–)	12 (–)	
Midline block				0.56
Yes	386 (69)	215 (75)	186 (69)	
No	171 (31)	72 (25)	82 (31)	
Unknown/ missing	34 (–)	1 (–)	17 (–)	
Daily fraction size (Gy)				0.10
<1.8	13 (2)	25 (8)	3 (1)	
1.8	259 (45)	135 (44)	142 (51)	
>1.8 to <2	0 (0)	2 (1)	8 (3)	
2	299 (52)	137 (45)	120 (43)	
>2	3 (1)	6 (2)	4 (2)	
Unknown/ missing	17 (–)	3 (–)	8 (–)	
Total point A dose (Gy)				0.39
0–20	23 (8)	13 (5)	23 (9)	
20–30	42 (14)	40 (14)	58 (21)	
30–40	119 (38)	121 (42)	128 (47)	
40–50	57 (18)	62 (22)	46 (11)	
>50	69 (22)	49 (17)	17 (17)	
Unknown/ missing	17 (–)	39 (–)	12 (–)	
Median	32.2	32.4	32.4	

Abbreviations: AP-PA = opposing anteroposterior-posteroanterior; EBRT = external beam radiotherapy.

and 2003–2005 surveys were 83.4%, 78.4%, and 80.5%, respectively, with a median follow-up of only 2.4, 1.4, and 1.7 years, respectively, in the three studies. These differences did not reach a statistically significant level (p = 0.36).

Rates of developing late Grade 3 or higher toxicity of cervical cancer patients surveyed in each survey are shown in Figure 2. Two-year rates of developing late Grade 3 or higher toxicity in the 1995–1997, 1999–2001, and 2003–2005 surveys were 4.4%, 2.3%, and 8.5%, with a median follow-up of only 2.3, 1.4, and 1.7 years, respectively, in the three studies. Rates of late toxicity were significantly different (p = 0.016).

Discussion

The current study showed that, in Japan, a significant increase was observed in the rate of patients who received chemotherapy over the three periods of 1995–1997, 1999–2001, and 2003–2005. Several RCTs conducted in the 1990s demonstrated that CCRT reduced mortality risk in cervical cancer patients compared with radiotherapy alone (9). The current study showed that a combination of chemotherapy with radiotherapy has become widely used in Japan, similar to the change in the United States in the late 1990s. Concurrent use of chemotherapy also significantly increased over the three survey periods. Our study suggests that more appropriate management of uterine cervical cancer has been adopted in Japan. On the other hand, more than half of the patients (125 patients did not receive chemotherapy; and 25 of the patients who did receive chemotherapy did not receive CCRT) were not treated with CCRT in the 2003–2005 survey, although not all of these patients needed CCRT. Some Japanese physicians remain cautious about employing CCRT as a standard treatment for two reasons. The first reason concerns the feasibility of using the standard chemotherapy of weekly cisplatin concurrently with radiotherapy. Several reports have found Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 dosages of cisplatin might not be feasible for Japanese patients (10). The second reason is that there are limited data for CCRT using HDR-ICBT. A large amount of data concerning excellent outcomes and acceptable toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data are limited (11). Therefore, a prospective study (Japanese Gynecologic Oncology Group study 1066) was undertaken to evaluate toxicities and outcomes in patients treated with CCRT by using the standard dosage/schedule of cisplatin and the standard Japanese radiotherapy dosage schedules for HDR-ICBT (12). On the other hand, whereas several RCTs revealed the negative therapeutic value of neoadjuvant chemotherapy in the mid-1990s, more than 10% of patients were still treated with this strategy during the most recent survey period. However, the current study showed that the ratio of neoadjuvant chemotherapy decreased in the recent survey (2003–2005, 11%) compared to those in the 1995–1997 (58%) and 1999–2001 (50%) surveys. Cisplatin was the agent most commonly used in CCRT (55%) in the 2003–2005 survey. Previous recommendations have been limited to platinum-based chemoradiotherapy, but a recently released individual patient data meta-analysis (13) has shown a significant benefit also associated with non-platinum regimens, specifically those containing 5-fluorouracil and/or mitomycin-C, although those results are not based on a direct comparison. Therefore, detailed information about chemotherapy regimens other than cisplatin will need to be evaluated in future PCS surveys of radiotherapy for cervical cancer.

The current study showed that the four-field technique was gradually applied more frequently over the three survey periods and that the ratio of the four-field technique during the 2003–2005 period was 21%. However, most patients were still treated with the opposing anteroposterior (AP-PA) technique in

Table 3 Details of intracavitary brachytherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameter	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
ICBT given				0.66
Yes	454 (77)	265 (82)	222 (78)	
No	132 (23)	58 (18)	63 (22)	
Unknown/missing	5 (–)	1 (–)	0 (–)	
Dose rate				0.47
HDR	386 (89)	215 (89)	205 (93)	
LDR	37 (9)	27 (11)	13 (6)	
Other	10 (2)	0 (0)	2 (1)	
Unknown/missing	21 (–)	23 (–)	65 (–)	
Source				<0.0001
Ir-192	113 (27)	102 (42)	183 (84)	
Co-60	269 (64)	112 (46)	23 (11)	
Cs-137	33 (8)	21 (9)	12 (5)	
Ra-226	9 (2)	7 (3)	0 (0)	
Unknown/missing	33 (–)	23 (–)	67 (–)	
Method of ICBT				0.65
Tandem plus vaginal applicator	352 (87)	202 (83)	190 (89)	
Tandem only	30 (8)	26 (11)	14 (7)	
Vaginal applicator	22 (5)	16 (6)	6 (3)	
Others	0 (0)	0 (0)	3 (1)	
Unknown/missing	50 (–)	21 (–)	9 (–)	
Applicator				0.025
Rigid	NA	166 (72)	158 (85)	
Nonrigid	NA	66 (28)	27 (15)	
Unknown/missing	NA	33 (–)	100 (–)	
In vivo dosimetry: bladder				0.73
Yes	NA	8 (4)	9 (5)	
No	NA	207 (96)	171 (95)	
Unknown/missing	NA	50 (–)	105 (–)	
In vivo dosimetry: rectum				0.24
Yes	NA	71 (33)	75 (41)	
No	NA	145 (67)	108 (59)	
Unknown/missing	NA	49 (–)	102 (–)	
ICRU 38: bladder				0.12
Yes	NA	48 (25)	57 (35)	
No	NA	146 (75)	106 (65)	
Unknown/missing	NA	71 (–)	122 (–)	
ICRU 38: rectum				0.38
Yes	NA	65 (34)	68 (40)	
No	NA	128 (66)	104 (60)	
Unknown/missing	NA	72 (–)	113 (–)	
Preparation				<0.0001
None	199 (53)	90 (54)	33 (19)	
NSAIDs administered orally/rectally	107 (28)	68 (41)	86 (49)	
IV conscious sedation	29 (8)	5 (3)	7 (4)	
Others	2 (1)	3 (2)	49 (28)	
Unknown/missing	117 (–)	99 (–)	110 (–)	
All procedures performed in the same room*				0.58
Yes	NA	167 (94)	157 (92)	
No	NA	11 (6)	13 (8)	
Unknown/missing	NA	37 (–)	115 (–)	
Each fraction was planned*				0.16
Yes	NA	159 (76)	157 (84)	
No	NA	49 (24)	30 (16)	
Unknown/missing	NA	7 (–)	98 (–)	

(*continued on next page*)

Table 3 *(continued)*

Parameter	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Single-point A dose of HDR-ICBT (cGy)				<0.0001
0–499	16 (5)	43 (20)	14 (7)	
500–599	100 (33)	79 (37)	59 (29)	
600–699	145 (47)	48 (22)	123 (59)	
700–799	43 (14)	15 (7)	10 (5)	
>800	2 (1)	2 (1)	1 (1)	
Unknown/missing	21 (–)	28 (–)	65 (–)	
Median	600	524	600	
Total point A dose of HDR-ICBT (Gy)				<0.0001
0–10	4 (1)	5 (3)	6 (3)	
10–20	80 (26)	58 (31)	71 (34)	
20–30	145 (48)	113 (61)	127 (61)	
30–40	77 (25)	8 (4)	4 (2)	
>40	0 (0)	1 (0)	0 (0)	
Unknown/missing	21 (–)	24 (–)	64 (–)	
Median	24.0	20.3	24.0	

Abbreviations: HDR = high-dose rate; ICBT = intracavitary brachytherapy; ICRU = International Commission on Radiation Units and Measurements; LDR = low-dose rate; NA = not applicable; NSAIDs = nonsteroidal anti-inflammatory inflammatory drugs.
* A total of 222 patients were treated with HDR-ICBT.

Japan, and rates of the use of the four-field technique remained low during the latest period. According to a report of the status of Japanese radiation oncology, one of the problems for the national practice process of radiotherapy in Japan was structural immaturity, especially in terms of personnel (14). Results of our study indicated that radiotherapy characteristics are still developing in Japan. The current study also revealed a change in the beam energy used for radiotherapy in Japan over the three survey periods. Only 7% of the patients were treated with Co-60 and 3 to 5 MV in 2003–2005, whereas these energies were used in 17% of patients in 1995–1997 and 11% of patients in 1999–2001. In addition, the use of appropriate beam energies of 10 to 14 MV and ≥15 MV increased over the three survey periods. In conjunction with the increased numbers of full-time equivalent radiation oncologists in both academic and nonacademic institutions (15),

Table 4 Details of chemotherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameters	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Chemotherapy given				<0.0001
Yes	140 (24)	104 (33)	149 (54)	
No	434 (76)	213 (67)	125 (46)	
Unknown/missing	17 (–)	7 (–)	11 (–)	
Timing*				<0.0001
Neoadjuvant	81 (58)	52 (50)	16 (11)	
Concurrent	28 (20)	56 (54)	124 (83)	
Adjuvant	31 (22)	15 (14)	34 (23)	
Agent†				NA
CDDP weekly	NA	NA	49 (45)	
CDDP daily	NA	NA	5 (5)	
CDDP plus 5-FU	NA	NA	6 (5)	
Others	NA	NA	49 (45)	
Unknown/missing	NA	NA	15 (–)	

Abbreviations: 5-FU = 5-fluorouracil; CDDP = cisplatin; NA = not applicable.
* Some patients overlap in the timing column.
† The indicated agent was used for patients who received concurrent chemotherapy.

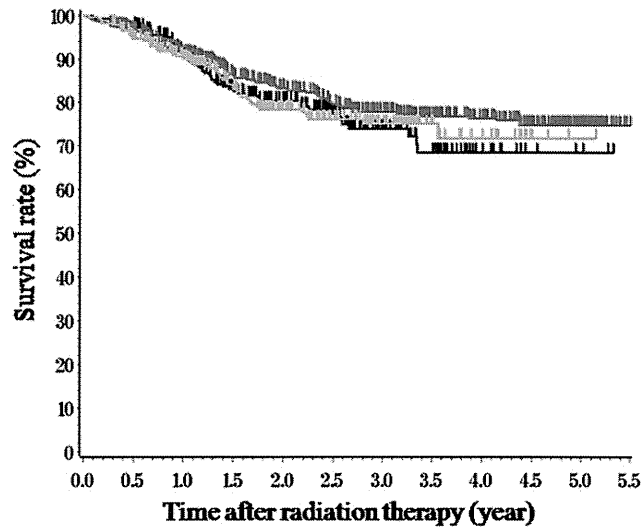

Fig. 1. Kaplan-Meier estimates of overall survival are shown for cervical cancer patients surveyed in the 1995–1997 (blue line, n = 573 patients), 1999–2001 (yellow line, n = 310 patients), and 2003–2005 (black line, n = 279 patients) patterns of care studies in Japan.

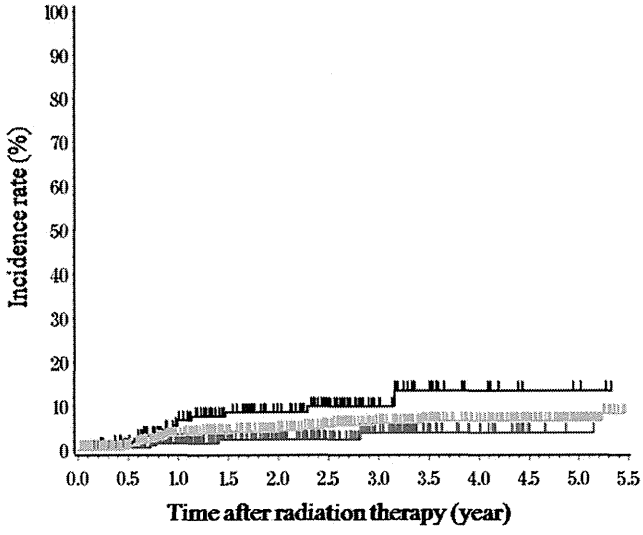

Fig. 2. The rate of developing late Grade 3 or higher toxicity are shown for cervical cancer patients surveyed in the 1995–1997 (blue, $n = 445$), 1999–2001 (yellow, $n = 224$), and 2003–2005 (black, $n = 166$) patterns of care studies in Japan.

Japanese cervical cancer patients are increasingly undergoing more appropriate methods.

The ratio of patients receiving ICBT did not increase over the three surveys. A considerable number of patients, 22%, were still not given ICBT during 2003–2005, and the application rate was lower in Japan than in the United States (4, 5). Therefore, ICBT should be applied more routinely for cervical cancer patients treated with definitive radiotherapy in Japan. One reason for the fact that some patients were not given ICBT might have been insufficient equipment, because 27% of patients received ICBT at another institution compared with 8.5% in the United States (16). The use of Ir-192 in 2003–2005 increased significantly compared with that in 1995–1997 and 1999–2001. The rapid increase in the use of Ir-192 might have been due to the result of the Japanese Society for Therapeutic Radiology and Oncology recommendation in the early 2000s that stated Co-60 should be avoided as a remote afterloading brachytherapy source in Japan because of source attenuation consistent with age. The American Brachytherapy Society (ABS) made a number of recommendations regarding HDR-ICBT techniques (17). Doses to the rectum were more often determined by using a dosimeter than by ICRU 38 reference point calculations. In fact, many studies showed that late rectal complications can be predicted by calculated doses at the ICRU 38 reference points (18). According to the ABS survey, rectal/bladder doses were evaluated in 80% or more patients at U.S. institutions, where HDR radiation was performed (19). However, our study showed that doses to the rectum and bladder in ICBT were evaluated, at most, in 40% of patients in Japan, and this status has significant scope for further improvement. Because accurate insertion can hardly be achieved if patients experience discomfort in ICBT, the ABS also recommends conscious sedation for HDR-ICBT applicator insertions (17). The current study showed that the number of patients who received no supportive medication before or during the applicator insertion significantly decreased, but conscious sedation was still used for a few patients. Although there are some limitations to the interpretation of these data due to an appreciable rate of unknown or missing data, we believe that additional improvements in the management of ICBT are still needed.

The current study also showed that patients' ages in the 1999–2001 survey were significantly different than those in the 2003–2005 survey, and the median age of 71 years old in the 2003–2005 survey was younger than that of the median age of 67 years old in the 1999–2001 survey. We think this may be due to the recent change in the age-specific incidence rate of cervical cancer in Japan. The age-specific incidence rate of cervical cancer in women over 40 years old has fallen gradually since the 1980s, while that in patients under 40 has gradually increased (21). Thus, the percentage of younger patients treated with radiotherapy may have increased. Konno *et al.* (22) organized the critical public health issues about cervical cancer in Japan in their cervical cancer working group report. In Japan, a national program for screening of cervical cancer was enacted in 1982. However, Organization for Economic Cooperation and Development data showed high rates of cervical cancer screening coverage in the United States and Europe but low coverage in Japan (23.4%) (20). With regard to cervical cancer prevention in Japan, in 1983, the government passed a Health and Medical Service Law for the Aged, leaving screening up to regional governments. A human papilloma virus vaccine was licensed in 2009 in Japan.

No significant survival improvement in patient outcome was observed among the three surveys. On the other hand, rates of late toxicity were significantly different in each study. One possible cause for these differences was the dramatic increase in the use of CCRT over the three survey periods. However, the current study has limitations in terms of outcome and toxicity analysis because of an inadequate follow-up time and significant variations in follow-up information according to institutional stratification (6). Therefore, we cannot draw any conclusions about Japanese radiotherapy practice in cervical cancer from these outcome and toxicity data.

Conclusions

In conclusion, we reported the status of definitive radiotherapy for uterine cervical cancer in Japan between 2003 and 2005 and examined the changes over the years in radiotherapy practice in the 1995–1997, 1999–2001, and 2003–2005 survey periods. By comparing the results of previous surveys with those of the 2003–2005 PCS survey, we delineated the changes in the process of care for cervical cancer patients treated with radiotherapy in Japan. Study data indicate a significant trend toward a combination of chemotherapy and concurrent use of chemotherapy and radiation therapy due to the adoption of recommendations found in RCTs. EBRT conditions such as beam energy and technique were gradually standardized to more appropriate methods over the three periods. Regarding ICBT, the patterns of both clinical procedure and quality assessment have still not reached sufficient quality. We believe that the three surveys of Japanese patterns of care for cervical cancer clearly show distinct improvements, while several problems remain to be resolved.

References

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