Table 2. Connection between full-time and part-time RO data

Data of full-time ROs	
Total number	1,007
Number of full-time ROs excluded from this analysis*	53
Number of full-time ROs analyzed	954
Breakdown	
Number of ROs who worked as full-time staff at main facilities and as part-time staff at affiliated facilities	199
Number of ROs who conducted only radiotherapy-related work as full-time staff at individual facilities (FTE of the RO was 1.0)	275
Number of ROs who conducted radiotherapy-related and other work as full-time staff at individual facilities (FTE of the RO was less than 1.0)	480
Data of part-time ROs including duplicate ROs	
Total number	534
Number of ROs who worked as full-time staff at main facilities and as part-time staff at affiliated facilities (number of part-time ROs analyzed)	280
Number of ROs who worked as only part-time staff at the facilities (Number of part-time ROs excluded from this analysis)	254

Abbreviations: RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology service only).
* Data of full-time ROs who worked at facilities with few patients were excluded, as were duplicated data of full-time ROs.

RT hospitals. The percentages of white parts in Figures 1 (a-c) were 17.4%, 5.0%, and 32.0%.

In university hospitals, the mean FTE RO for main facilities was 0.73 and for affiliated facilities it was 0.10. The corresponding figures were 0.94 and 0.01 for cancer centers, and 0.67 and 0.01 for other RT hospitals. For university hospitals, the ratio of ROs working only in main facilities was 16.4%, and the corresponding figures for cancer centers and other RT hospitals were 79.5% and 31.7%, respectively. The ratio of ROs working mainly in university hospitals and part-time in affiliated facilities was 44.5%. The corresponding data were 6.5% of ROs working primarily in cancer centers and 7.5% of ROs working mainly in other RT hospitals.

Patient loads

Figure 2(a) shows the patient load per RO working mainly in university hospitals, cancer centers, and other RT hospitals. Of ROs working primarily in university hospitals, 40.1% treated more than 200 patients per year. The corresponding ratios were 74.4% of ROs working primarily in cancer centers and 36.5% of those working mainly in other RT hospitals. The average number of patients treated by ROs working primarily in university hospitals was 189.2, with the corresponding figures being 256.6 patients in cancer centers and 176.6 in other RT hospitals. Figure 2(b) shows the patient load per RO working primarily in university hospitals. Of ROs working in university hospitals and affiliated facilities, 65.9% treated more than 200 patients per year, and the percentage was 19.3% of ROs working only in university hospitals. The former treated an average of 249.1 patients and the latter 144.0 patients per year.

The geographic patterns

Figure 3 shows the geographic distribution for 47 prefectures of the mean annual number of patients (new plus repeat) per RO arranged in order of increasing population by all prefectures in Japan (9). The average annual number of patients per RO per quarter ranged from 143.1 to 203.4, with significant differences among quarters ($p < 0.0001$). Figure 4 shows the top 10 prefectures with ROs who treated more than 200 patients per year in descending order: Tokyo, Osaka, Kanagawa, Hokkaido, Chiba, Aichi, Fukuoka, Hyogo, Miyagi, and Hiroshima.

Relative practice index for patients of ROs

Figure 5(a) shows the average relative practice index for patients of ROs in university hospitals and affiliated facilities (ROs working mainly in university hospitals). The average practice index of RO for patients was 1.07 at university hospitals and 0.71 at affiliated facilities for a statistically significant difference ($p < 0.0001$). Figure 5(b) shows the average relative practice index for patients of ROs working only in university hospitals, only in cancer centers, and only in other RT hospitals. The respective indices for the three categories were 1.26, 1.02, and 1.01. There were significant differences in the indices between university hospitals and cancer centers ($p = 0.0278$) and between university hospitals and other RT hospitals ($p < 0.0001$). The difference between cancer

Table 3. Overview of analyzed data

Main facility category	Number of full-time ROs working at main facilities	Number of part-time ROs working at affiliated facilities					
		First*	Second*	Third*	Fourth*	Fifth*	Subtotal
University hospital	372	160	59	14	4	2	239
Cancer center	78	5	0	0	0	0	5
Other radiotherapy hospital	504	34	2	0	0	0	36
Total	954	199	61	14	4	2	280

Abbreviation: RO = radiation oncologist.
* First: first affiliated facilities; second: second affiliated facilities; third: third affiliated facilities; fourth: fourth affiliated facilities; fifth: fifth affiliated facilities.

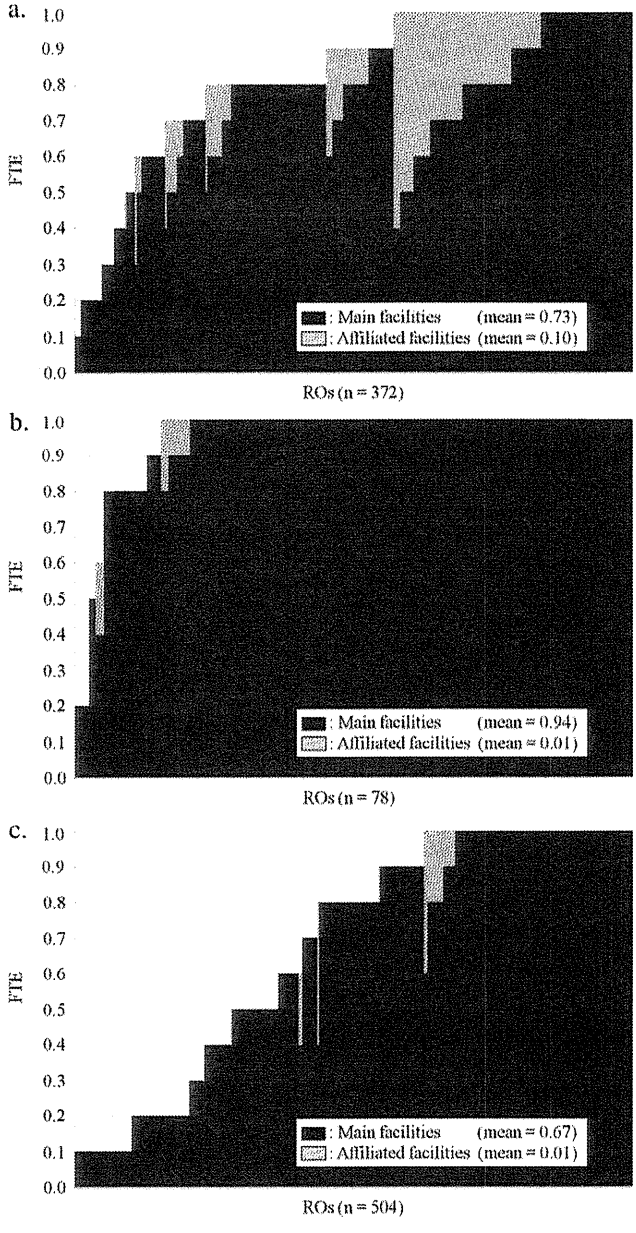

Fig. 1. Working patterns of ROs working mainly at (a) university hospitals, (b) cancer centers, and (c) other radiotherapy hospitals. Distribution of FTE ratio between main and affiliated facilities on each RO. Horizontal axis represents ROs in ascending order of own total FTE. *Abbreviations:* RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

centers and other RT hospitals was not significant ($p = 0.9459$).

DISCUSSION

In the United States, most RT facilities are supported by full-time ROs, with an FTE of 1.0 for most ROs working at their own facilities. In Japan, on the other hand, more than a half of the facilities still rely on part-time ROs. The main reason of this discrepancy is a shortage of ROs. Between 2005 and 2007, the increase in the number of cancer

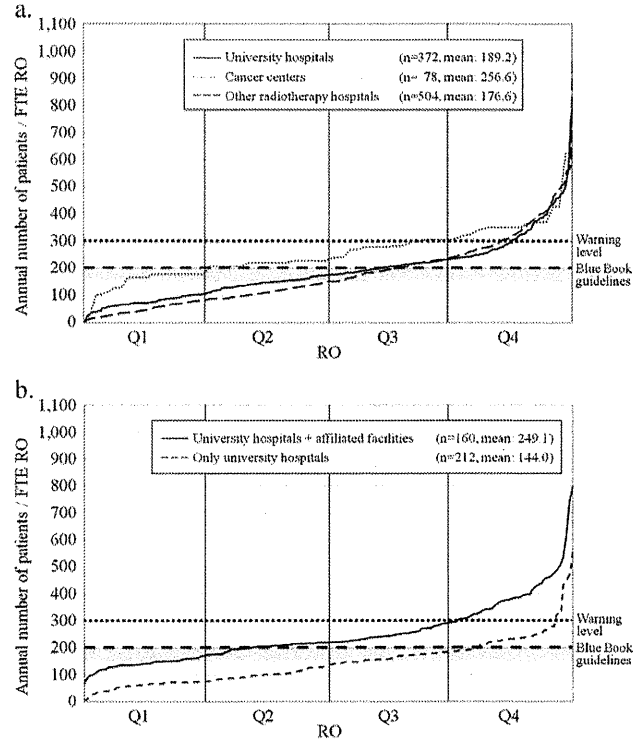

Fig. 2. Distribution of annual patient load/RO. (a) RO working mainly in university hospitals, cancer centers, and other radiotherapy hospitals. (b) RO working mainly in university hospitals. Horizontal axis represents ROs in ascending order of annual numbers of patients/RO. Q1: 0–25%, Q2: 26–50%, Q3: 51–75%, Q4: 76–100%. *Abbreviations:* RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

patients requiring RT (7.3%) was higher than that in the number of FTE ROs (6.7%) (1). To make up for the shortage of ROs, most ROs in university hospitals must work part-time at affiliated hospitals, as is evident from the date shown in Figure 1. White parts of Figure 1 (a: 17.4%, b: 5.0% c: 32.0%) represent three types of data: (a) FTE data of ROs who were not provided in the survey questionnaire; (b) FTE data of part-time ROs whose identification data could not connect to those of full-time ROs; (c) FTE data of ROs working in nonradiation oncology services. In this survey, the data of type (a) and (b) were missing data and the data of type (c) were not collected. In other RT hospitals, the FTE of most ROs working in their own facilities is low and these ROs do not work part-time at other hospitals. There are two reasons for this. First, diagnosticians partly provide RT as ROs in their own hospitals and, second, other specialists (such as brain surgeons using gamma knife) partly function as ROs to provide RT. Because those facilities have few cancer patients, their patient load is less than that of university hospitals and cancer centers. These findings are evident from Figure 2(a). There was a major difference in the working patterns of ROs between university hospitals and cancer centers. FTE at their own facilities of most ROs working in university hospitals is less than 1.0, whereas that of most ROs working in cancer centers is 1.0,

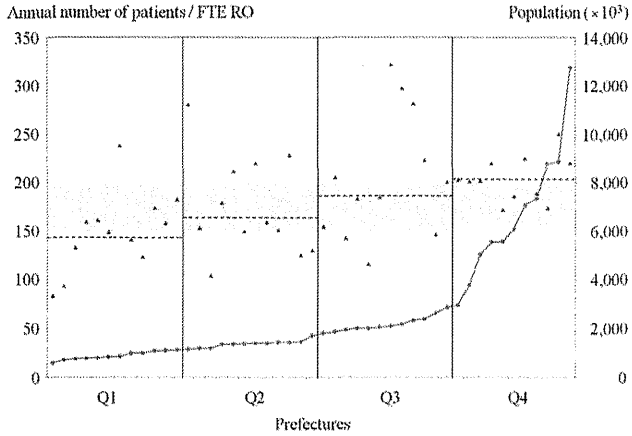

Fig. 3. Geographic distribution for 47 prefectures of annual number of patients (new plus repeat) per RO in ascending order of prefectural population. Q1: 0–25%; Q2: 26–50%; Q3: 51–75%; Q4: 76–100%. Triangles represent average annual number of patients per RO for each prefecture. Blue circles show prefectural population. Horizontal broken lines indicate the average annual number of patients per RO per quarter. The shaded area represents the Japanese Blue Book guideline (150–200 patients per RO). *Abbreviations:* RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

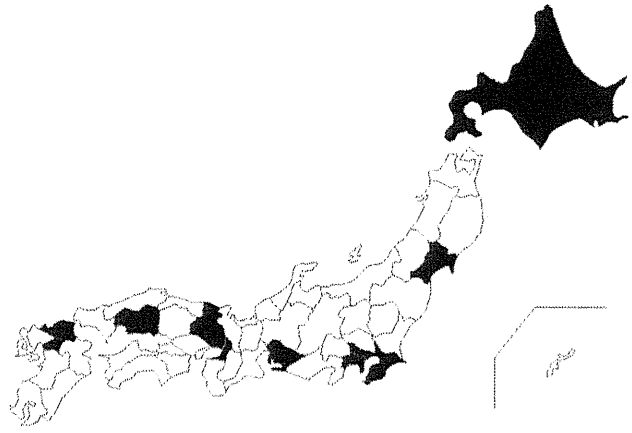

Fig. 4. The top 10 prefectures with ROs who treated more than 200 patients in descending order: Tokyo, Osaka, Kanagawa, Hokkaido, Chiba, Aichi, Fukuoka, Hyogo, Miyagi, and Hiroshima. *Abbreviation:* RO = radiation oncologist.

the same as in the United States and European countries. The shortage of ROs is not the only reason for the problems facing Japan. The pay system of ROs is another important reason. The salary of ROs in Japan is low because specialist medical fees for ROs are not covered by the Japanese healthcare insurance system. Moreover, the salary of ROs in university hospitals is lower than in other types of facilities, so that most of these ROs must work part-time at affiliated hospitals to earn a living. One advantage of this system, however, is that advanced technology is introduced sooner and faster in affiliated hospitals.

The geographic patterns demonstrated significant differences in the patient load among prefectures, ranging from 83.2 to 321.4 patients per RO. There were more ROs in metropolitan than other areas. However, the number of ROs who had more than 200 patients (new plus repeat) was strongly associated with population (correlation coefficient: 0.94), so that the number of ROs in metropolitan area remained insufficient.

Gomi *et al.* reported that the survival rate of patients treated in academic RT facilities (university hospitals and cancer centers) was better than that of those treated in nonacademic RT facilities in Japan (10). In this study, the proportion of facilities with part-time ROs in nonacademic RT facilities group was higher than that in academic RT facilities group. Part-time ROs have less care time per patient because they had a limit to working hours. On the basis of the presented evidence, the relative practice index for patients of ROs was calculated as one way to valuate quality of cancer care in this study. Concerning ROs working primarily in university hospitals, the average relative practice index for patients in affiliated facilities was less than that in main facilities (university hospitals). Teshima *et al.* reported that academic RT facilities (university hospitals and cancer centers) had better equipments and manpower than nonacademic RT facilities (1). Therefore, ROs at large-scale university hospitals might be given sufficient support because large-scale university hospitals tend to have state-of-the-art equipment, practice leading-edge medical treatment techniques, and employ enough medical staff members. On the other hand, ROs of most affiliated facilities could provide only minimal cancer care because these facilities

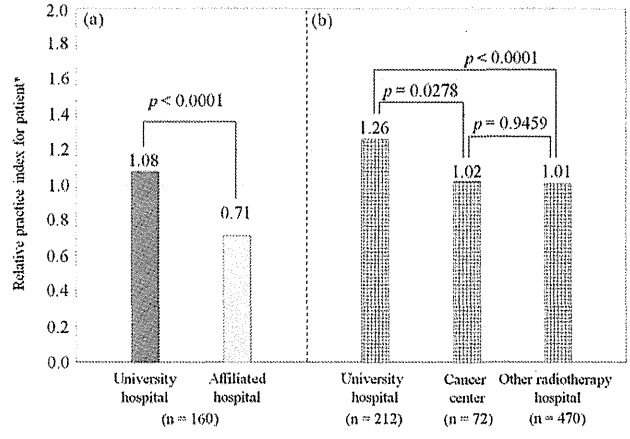

Fig. 5. Relative practice index for patients of ROs. (a) Relative practice index for patients in university hospitals and affiliated hospitals (targeted ROs were working mainly in university hospitals and part-time in affiliated hospitals). (b) Relative practice index for patients in university hospitals, cancer centers, and other radiotherapy hospitals (targeted ROs were working only in university hospitals or cancer centers only or only in other radiotherapy hospitals). *The formula used for calculating relative practice index for patients is: $\frac{\sum_{k=1}^{n} f_k}{\sum_{k=1}^{n} a_k} \times 200$ n: number of facilities that the RO works in (n = 1, 2, 3, …, k). f_k : FTE of the RO in facility k a_k : annual number of patients per RO in facility k. *Abbreviations:* RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

tend to lack sufficient equipment and medical staff. Moreover, commuting between large-scale university hospitals and affiliated facilities resulted in a waste of time and in tiredness. Therefore, the quality of cancer care in affiliated facilities was worse than that in large-scale university hospitals. Although the annual number of patients per RO in cancer centers was higher than that in university hospitals and other RT hospitals, the average relative practice index for patients of ROs working only in cancer centers was lower than that for patients of ROs working only in university hospitals and equal to that for patients of ROs working only in other RT hospitals. It can thus be concluded that ROs in cancer centers worked efficiently.

The utilization rate of RT for new cancer patients in Japan is much lower than that in European countries and the United States. Because there are enough RT facilities distributed nationwide in Japan, an increase in the number of Ros would likely result in a spectacular improvement in the utilization rate of RT for new cancer patients. To increase the number of ROs, it is necessary to improve the work environment and conditions for radiation oncology in medical care facilities. One, feasible suggestion is for RT facilities to set up a new department of radiation oncology, so that the position of RO will be established at every such facility and the status of radiation oncology will improve as a result. In addition, the Cancer Control Act was approved in 2006 and the Basic Plan to Promote Cancer Control Program was approved by the Japanese Cabinet in 2007 to promote RT and education for ROs as well as other RT staff members. For the implementation of this law and plan, the availability of basic data of RO working conditions is essential. As a start, an education program called "Cancer Professional Training Plan" was started in April 2008 with the support of the Ministry of Education, Culture, Sports, Science and Technology.

Quality of cancer care was evaluated in this study with the aid of the relative practice index for patients. However, data concerning the processes and outcomes for cancer care using RT should be used for a more accurate evaluation of cancer care. In the United States, the National Cancer Data Base has been collecting data for cancer care. The data of National Cancer Data Base are useful for quality evaluation of cancer care (11, 12). Furthermore, PCS has been performed every 4 or 5 years since 1973 for a survey of the structure, processes, and outcomes of radiation oncology facilities (13). As PCS evolved into Quality Research in Radiation Oncology, periodic assessments of radiation oncology have been conducted for evaluation of practice quality on a national basis. In Japan, the structure, processes and outcomes for cancer care using RT have been investigated by PCS every 4 years (7, 8). The Japanese PCS has evaluated the quality of cancer care with RT and provided evidence of the disparity in quality of RT among facilities (14–18). However, these data are insufficient because PCS is a two-stage cluster sampling survey. We have recently established a database system based on available radiation oncology data and the collection of cancer care data by means of this system is now in preparation.

This study based on the JASTRO structure survey has indicated that the current national medical care system may impede fostering of true specialization of radiation oncologists in Japan because it is suffering from systemic fatigue. Although private hospitals make much money by receiving fee-for-service reimbursement, public hospitals face major deficit problems. It is therefore necessary to redistribute the burden of medical costs. On the other hand, the Japanese medical care system is beneficial for patients and national finances. Japan has had a universal health insurance system since 1961. Even though the per-capita medical costs in Japan were less than half of those in the United States and the medical costs in relation to the gross domestic product in Japan were about half of those in the United States as of 2007 (19), the outcome of cancer treatment in Japan is the same or better than in the United States. It is therefore very important to collect at regular intervals detailed information about all cancer care facilities for evaluation of quality of care and medical care systems for cancer. In Japan, the JASTRO structure survey has collected structural data of radiation oncology. Furthermore, a database system for the collection of data regarding the processes and outcomes for cancer care has recently been established in Japan as well as an information infrastructure for evaluation of the quality of care in radiation oncology.

In conclusion, our survey found that ROs working in university hospitals and their affiliated facilities treated more patients than did other ROs. In terms of patient care time only, the quality of cancer care in affiliated facilities might be worse than that in university hospitals. Under the current national insurance system, working patterns of ROs in academic facilities in Japan tend to impede the fostering of true specialization of radiation oncologists.

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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.

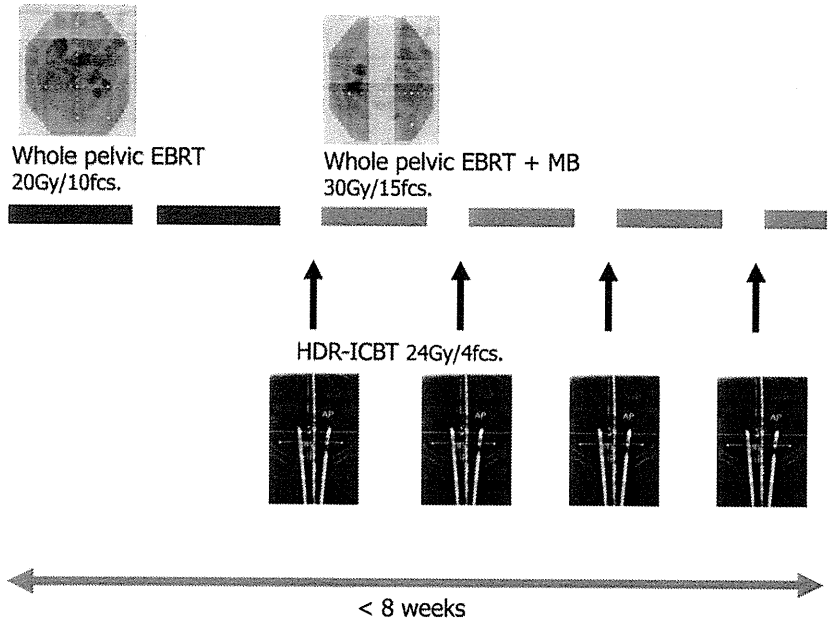

Fig. 1. Treatment schema.

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).

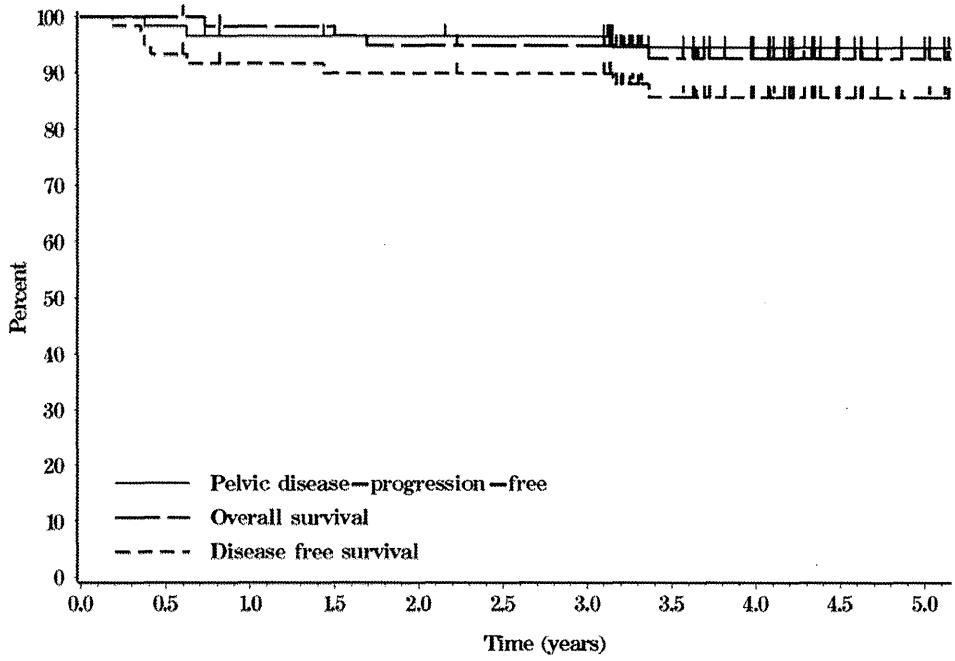

Fig. 2. PDPF survival, OS, and DFS are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

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,

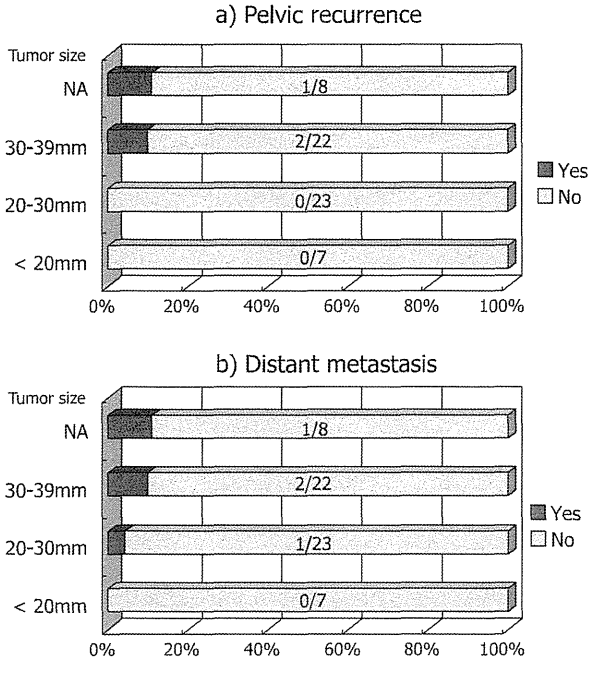

Fig. 3. Recurrence rate as a function of tumor size is shown for (a) pelvic recurrence and (b) distant metastasis. NA = not assessed (invisible on MRI).

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

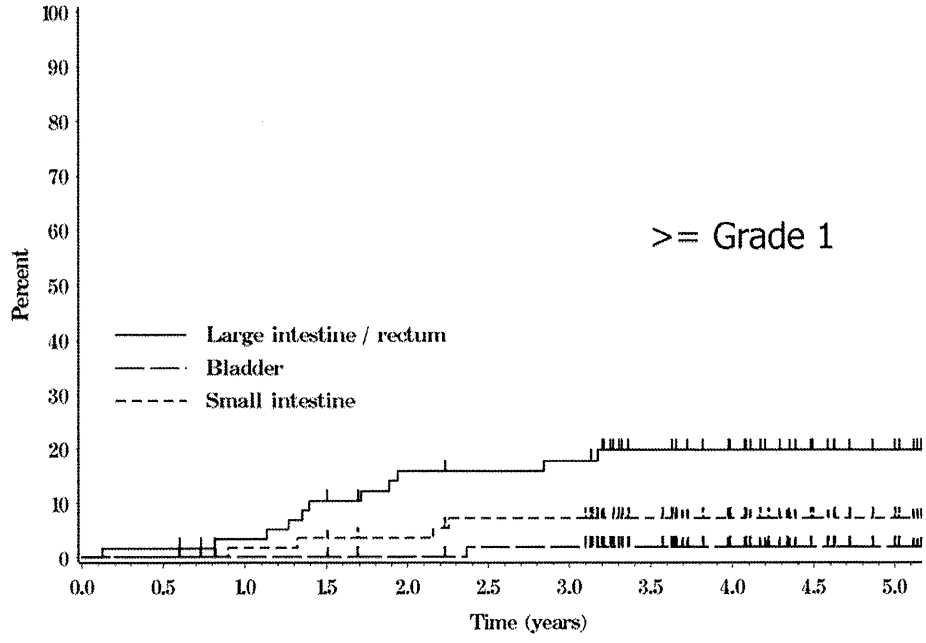

Fig. 4. Late complications (Grade ≥1) are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

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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Clinical Investigation: Gynecologic Cancer

Insufficiency Fractures After Pelvic Radiation Therapy for Uterine Cervical Cancer: An Analysis of Subjects in a Prospective Multi-institutional Trial, and Cooperative Study of the Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG)

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Summary

We analyzed subjects of a prospective multi-institutional study to investigate pelvic insufficiency fractures (IF) after definitive pelvic radiation therapy for early-stage uterine cervical cancer. The 2-year overall cumulative incidence of both symptomatic and asymptomatic IF was 36.9%, and the cumulative incidence of symptomatic IF was 16.1%. Higher age (>70 years) and low body weight (<50 kg) were thought to be risk factors for pelvic IF.

Purpose: To investigate pelvic insufficiency fractures (IF) after definitive pelvic radiation therapy for early-stage uterine cervical cancer, by analyzing subjects of a prospective, multi-institutional study.

Materials and Methods: Between September 2004 and July 2007, 59 eligible patients were analyzed. The median age was 73 years (range, 37-84 years). The International Federation of Gynecologic Oncology and Obstetrics stages were Ib1 in 35, IIa in 12, and IIb in 12 patients. Patients were treated with the constant method, which consisted of whole-pelvic external-beam radiation therapy of 50 Gy/25 fractions and high-dose-rate intracavitary brachytherapy of 24 Gy/4 fractions without chemotherapy. After radiation therapy the patients were evaluated by both pelvic CT and pelvic MRI at 3, 6, 12, 18, and 24 months. Diagnosis of IF was made when the patients had both CT and MRI findings, neither recurrent tumor lesions nor traumatic histories. The CT findings of IF were defined as fracture lines or sclerotic linear changes in the bones, and MRI findings of IF were defined as signal intensity changes in the bones, both on T1- and T2-weighted images.

Results: The median follow-up was 24 months. The 2-year pelvic IF cumulative occurrence rate was 36.9% (21 patients). Using Common Terminology Criteria for Adverse Events version 3.0, grade 1, 2, and 3 IF were seen in 12 (21%), 6 (10%), and 3 patients (5%), respectively. Sixteen patients had multiple fractures, so IF were identified at 44 sites. The pelvic IF were frequently seen at the sacroileal joints (32 sites, 72%). Nine patients complained of pain. All patients' pains were palliated by rest or non-narcotic analgesic drugs. Higher age (>70 years) and low body weight (<50 kg) were thought to be risk factors for pelvic IF ($P = .007$ and $P = .013$, Cox hazard test).

Conclusions: Cervical cancer patients with higher age and low body weight may be at some risk for the development of pelvic IF after pelvic radiation therapy.

Introduction

Insufficiency fractures (IF) are a type of stress fracture, occurring after normal or physiologic stress on bone with decreased mineralization and elastic resistance (1). Insufficiency fractures of the pelvic bones are thought to be associated with postmenopausal or corticosteroid-induced osteoporosis (1, 2). Pelvic radiation therapy (RT) also can affect the development of pelvic IF, although the precise pathogenesis is as yet unclear (1, 2). Although some investigators (3-5) have reported that pelvic IF are an uncommon adverse event in irradiated patients with gynecologic cancer, others (6-10) have reported that radiation-induced pelvic IF were frequently observed in women after RT. It seems that the precise incidence of IF is unclear. The findings on conventional radiographs are usually subtle (2, 10) and may be misleading. The fractures usually show increased uptake on radionuclide bone scans. A pattern of increased uptake in the body of the sacrum and in one or both sacrum alae (1, 2, 11) is indicative of a fracture, but increased uptake may also be present in metastases and sacroiliac joint osteoarthritis (12). The importance of understanding a pelvic IF lies in the potential for its misdiagnosis as bony metastases. Computed tomography (CT) is capable of displaying fracture lines and/or sclerotic changes associated with IF (8, 9, 11), whereas magnetic resonance imaging (MRI) is highly sensitive for revealing the reactive bone marrow changes associated with IF (9, 13).

Not only for unresectable locally advanced stages, RT has played an important role in the treatment of early-stage cervical cancer. Originally, to determine the efficacy of definitive RT 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 (JAROG0401/JROSG04-2) (14). Two-year pelvic disease progression-free rate was the primary endpoint, and late complication including IF was one of the secondary endpoints in the study (14). At first, IF was evaluated by only symptomatic features. However, we noticed that some follow-up imaging features after RT had shown IF of pelvic bones in several asymptomatic patients. Therefore, we planned this additional study to assess pelvic IF by adding a minute imaging evaluation prospectively, without changing the schedule and methods of the follow-up CT and MRI in the protocol.

The purpose of this study was to investigate the incidence of radiation-induced pelvic IF using CT and MRI and to investigate the risk factors and radiation doses associated with IF, as well as the distribution of IF sites among patients with this complication. In our study, patients were treated with the constant RT method described in the protocol and followed with CT and MRI regularly. To our knowledge, this is the first multi-institutional prospective analysis on IF.

Methods and Materials

Patient eligibility criteria

The women enrolled in these analyses were a group of patients with cervical carcinoma who were treated with a protocol JAROG0401/JROSG04-2) (14). Eligible patients had histologically proven squamous cell carcinoma of the intact uterine cervix with International Federation of Gynecologic Oncology and Obstetrics (FIGO) stage Ib1/IIa/IIb disease and were aged 20-80 years. A complete physical examination, pelvic examination performed without anesthesia, and chest X-ray were required to determine the clinical stage. Patients were required to have cervical tumors <40 mm in diameter as assessed by T2-weighted MRI and negative pelvic and paraortic lymph nodes (<10 mm in shortest diameter) as

determined by CT. All patients were required to give their written informed consent.

Treatment

The treatment protocol has been described in detail previously (14). The treatment protocol consists of a combination of external-beam radiation therapy (EBRT) and HDR-ICBT. Interstitial brachytherapy and chemotherapy were not allowed. External-beam radiation therapy was delivered to a total dose of 50 Gy in 25 fractions over 5-6 weeks. The early part with 20 Gy was delivered to the whole pelvis. After that, 30 Gy was administered through the same whole-pelvic field with a midline block (MB) of 3- to 4-cm width. The MB was formed with multileaf collimators or custom cerrobend block. The first HDR-ICBT was performed within 10 days after the initial 20 Gy of EBRT. Treatment was to be completed within 56 days.

All patients were treated with a photon beam of 10 MV or greater. Both anteroposterior/posteroanterior (AP/PA) and a 4-field technique were allowed. In cases in which the 4-field technique was used, the portal arrangement was changed to the AP/PA technique after the insertion of the MB. Tissue heterogeneity correction was not used in the dose calculation. The upper border of the pelvic field was L4/5, and the lower border was a transverse line below the obturator foramen. The lateral borders of the AP/PA fields were 1-2 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 the AP/PA fields. The fields were shaped to shield normal tissues using a custom block or multileaf collimators. Prophylactic paraortic RT was not allowed.

High-dose-rate intracavitary brachytherapy using a tandem and 2 ovoids was performed once per week giving 24 Gy to point A in 4 fractions with ^{192}Ir afterloading machines.

Evaluation

After RT the patients were evaluated by both pelvic CT and pelvic MRI at 3, 6, 12, 18, and 24 months. Diagnosis of IF was made when the patients had positive findings on both CT and MRI, without recurrent tumor lesions or traumatic histories. Computed tomography findings of IF were defined as fracture lines or sclerotic linear changes in the bones, and MRI findings of IF were defined as signal intensity changes in the bones of >5 mm both on T1 and T2-weighted images (Fig. 1). All CT and MR images were evaluated together by 4 investigators. The cumulative occurrence rate of IF was calculated by the Kaplan-Meier method. Risk factors that could affect the incidence of IF (age, stage, body weight, simulation, beam technique, energy of X-ray, and location of facilities) were assessed by log-rank test and Cox hazard test. Statistical analyses were performed with SPSS 16.0 (SPSS, Chicago, IL).

The patients were also evaluated by CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 every 3 months from 3-30 months. Clinical characteristics, including sites of IF and doses administered to IF lesions, were identified by a review of the medical records and imaging studies of the participating facilities, including isodose curves of pelvic RT.

The study was approved by the Protocol Review Committee of our study group and the local institutional review board of participating institutions.

Results

Patients

Between September 2004 and July 2007, 60 patients were enrolled from 13 institutions. One patient was considered ineligible, leaving 59 patients in the final patient cohort.

The median age was 73 years (range, 37-84 years). The eligible patients had squamous cell carcinoma of the uterine cervix, and the FIGO stages were Ib1 in 35, IIa in 12, and IIb in 12 patients. No patients had pelvic/paraortic lymphadenopathy. The median follow-up was 24 months.

Incidents and clinical characteristics of IF

A total of 21 patients were diagnosed with IF after RT. The 2-year overall cumulative incidence of both symptomatic and asymptomatic IF was 36.9% (Fig. 2). On CTCAE version 3.0, grade 1, 2, and 3 were seen in 12 (21.4%), 6 (10.2%), and 3 patients (5.3%), respectively.

On univariate analysis by log-rank test, age >70 years (P=.004) and body weight <50 kg (P=.007) were thought to be risk factors of pelvic IF. Multivariate analysis by Cox hazard test showed that age >70 years (P=.007) and body weight <50 kg (P=.013) were significant predisposing factors for developing IF (Table).

The cumulative incidence of symptomatic IF at 2 years was 16.1% (9 patients) in all patients (Fig. 2). Nine patients complained of pelvic or back pain. The pain was palliated by rest or non-narcotic analgesic drugs in all 9 cases, and no patients required surgical intervention. Sixteen patients had multiple fractures, so the pelvic IF was identified at 44 sites. The symptomatic patients had from 1-4 IF sites (mean 2.7 sites), and the asymptomatic patients had 1 or 2 IF sites (mean 1.7 sites). The pelvic IF was seen at the sacroileal (SI) joints (32 sites, 72%), pubis (9 sites, 20%), acetabula (2 sites, 4%), and lumbar spine (1 site, 2%) (Fig. 3).

The external-beam doses of all 44 IF sites were calculated from the isodose curves. It was estimated that the median dose was 49 Gy and the mean dose was 46 Gy (range, 23-50 Gy). The doses of 38 IF sites (86%) were estimated at >45 Gy.

Discussion

Insufficiency fractures occur most often in elderly women with postmenopausal osteoporosis (2). Other predisposing factors include rheumatoid arthritis, corticosteroid therapy, heparin use, diabetes mellitus, low body weight, current smoking, and RT (15). Fu et al (16) reported that the incidence of IF increased when the dose was above the threshold of 45 Gy. However, there have been no tolerance dose data for IF. In conventional pelvic RT, the irradiated dose of the pelvic bone is usually 45-50 Gy, and the development of IF after pelvic RT at this level has been considered a rare complication (3-5).

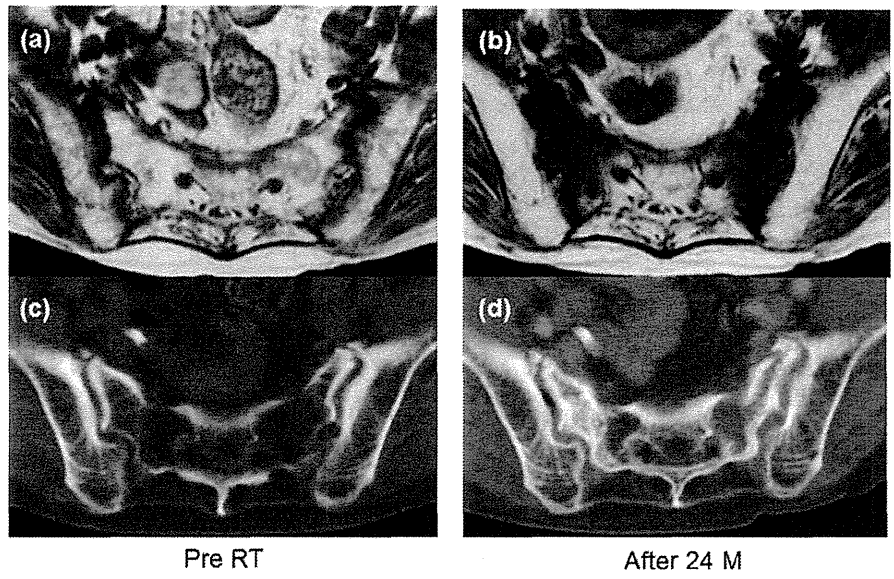

Fig. 1. Pelvic MRI shows low signal intensity in both sacroiliac joints (b) after radiotherapy (RT). Pelvic bone window CT shows (d) cortical fractures and sclerotic changes in the bilateral sacroiliac joints. M = month.

However, several recent studies (6-10) showed that the incidence of IF after pelvic RT might have been underestimated in gynecologic patients. Among these studies, the cumulative incidence of symptomatic IF at 2 years was 11.1%-14.9%, and that at 5 years was 8.2%-17.9%. In our series the cumulative incidence of IF was 36.9% at 2 years in all patients and 16.1% in symptomatic patients. The results of this study showed a relatively higher incidence of IF compared with previously reported data (2-10); however, the rate of occurrence of symptomatic IF was in accordance with other recent studies (6-10). In their prospective MRI study, Blomlie et al (13) reported that 89% of patients (16 of 18) had findings compatible with IF after pelvic RT. They showed that signal changes of MRI in pelvic bones were seen until 24 months after the end of RT, and 56% of patients (10 of 18) complained of pelvic pain. Abe et al (11) showed a 34% incidence of IF after pelvic RT using bone scintigraphy. We performed CT and MRI during the follow-up at least 2 times per year, so as to detect asymptomatic patients (12 of 21, 57.1%) with IF.

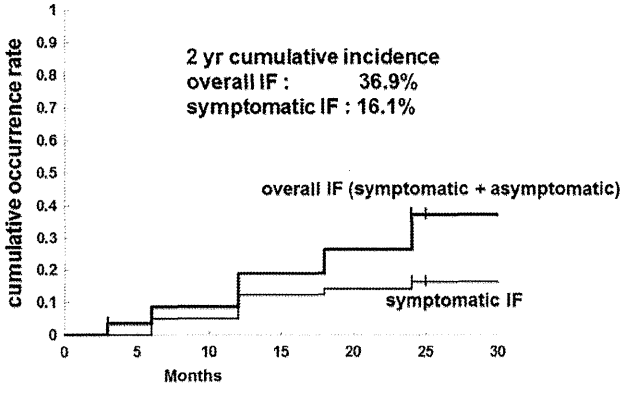

Fig. 2. Graph shows the overall incidence of both symptomatic and asymptomatic insufficiency fractures (IF) (thick line) and the incidence of symptomatic insufficiency fractures (thin line) after pelvic radiotherapy for cervical cancer.

The characteristics of irradiated patients can affect the incidence of IF. As revealed in our study, older patients receiving pelvic RT are more susceptible to the development of IF. In our study the incidence of IF at 2 years in patients aged >70 years was 52.8%, almost all the patients were elderly (the median age was 73 years), and all but 4 of the patients were postmenopausal. In the study by Ogino et al (6) all IF patients were postmenopausal, whereas in the study by Baxter et al (8) some of the patients were aged >65 years.

Our study showed that the SI joints are the most commonly involved site of pelvic IF, which agrees with the reports of several previous investigators (7, 9, 10). In our study most fractures were located at the SI joints; a solitary pubic bone fracture was seen in only 1 patient, and solitary acetabulum fracture was not seen. These findings indicated that initial mechanical failure of the sacrum causes other subsequent pelvic bone fracture (10, 13).

As has been reported by many investigators (2, 4, 6, 7, 13), our study showed that the symptoms of all patients were resolved after conservative management based on analgesics and rest. The extent of the lesions may correlate with the severity of symptoms. In the series reported by Blomlie et al (13), all patients without pain had smaller lesions (<1 cm^2) on MRI, and it was suggested that small fractures might not be painful. In our study symptomatic patients were more likely to have IF at multiple sites of pelvic bone (mean 2.7 sites) than asymptomatic patients (mean 1.7 sites).

The risk factors of osteoporosis are closely correlated with the development of IF (3, 6). Blomlie et al (13) showed that 95% of patients with IF reported in the literature were postmenopausal women. Ikushima et al (7) reported that the mean age of patients who developed IF was significantly higher than that of other patients (69 years vs 59 years, $P<.01$). Ogino et al (6) showed that low body weight (≤49 kg) and more than 3 deliveries were significant factors for the development of symptomatic IF. In our study, both low body weight (<50 kg) and older age (>70 years) were significant predisposing factors for IF in multivariate analysis. Many medical illnesses or medications, such as rheumatoid arthritis, hyperthyroidism, and corticosteroids, are also reported as risk factors for osteoporosis.

Table Risk factors associated with the development of IF

Variable	IF/n	*P*	
		Univariate	Multivariate
Age (y)		.004*	.007*
≤70	4/26		
>70	17/33		
Weight (kg)		.007*	.013*
<50	15/29		
≥50	6/30		
Stage		.347	.368
I	12/35		
II	9/24		
Simulation		.249	.271
X-ray	13/30		
CT	8/29		
Beam technique		.192	.211
AP/PA	15/35		
4-field	6/24		
Energy of X-ray		.928	.931
10 MV	14/40		
>10 MV	7/19		
Facilities		.932	.569
East	11/31		
West	10/28		

Abbreviations: AP/PA = anteroposterior/posteroanterior parallel opposing field; IF = insufficiency fracture.
* $P<.05$.

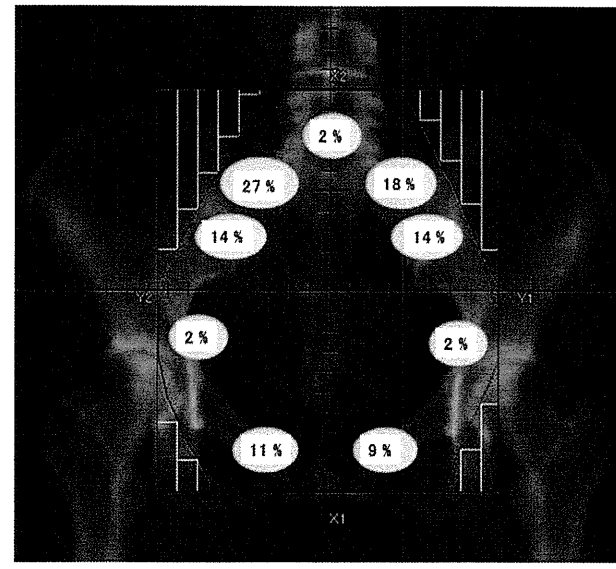

Fig. 3. Schematic shows the distribution of insufficiency fractures in our study population. Some patients had multiple fractures.

In our study, no patients had a history of either rheumatoid arthritis or hyperthyroidism.

It is well known that radiation toxicity is strongly correlated with irradiated volume and dose. In our study, both the 4-field box technique and the AP/PA parallel opposing technique were used. In the 4-field box technique, lateral portals could spare the irradiated volume of the small bowel and rectum and also spare the irradiated volume of the posterior portion of the sacrum and SI joints. Oh et al (9) reported that the incidence of IF was higher in patients receiving the AP/PA technique than in those receiving the 4-field box technique in univariate analysis. In our study there was no significant difference between the 2 techniques. However, in our study these techniques differed only until 20 Gy of EBRT, and the following 30 Gy of EBRT was administered through the same whole-pelvic field with MB.

Patients who received a higher irradiated dose to the pelvic bone had a greater risk of IF. In our study the external-beam doses of all 44 IF sites were estimated to have a median dose of 49 Gy, and the doses of 38 IF sites (86%) were estimated at >45 Gy. There might be a threshold dose for IF at approximately 45 Gy, as reported by Fu et al (16). Oh et al (9) reported that the risk factors of IF were receiving a higher dose (>50.4 Gy) and receiving curative RT. In our study all patients received 50 Gy by EBRT and received an additional dose of HDR-ICBT. Fu et al (16) calculated the contribution of the brachytherapy dose to the pelvic bone and estimated it to be approximately 10% of the central brachytherapy dose. It was uncertain whether this small additional dose of HDR-ICBT to the pelvic bones was one of the causes of the higher occurrence of IF in our study.

Concurrent chemoradiation therapy is used frequently in gynecologic cancer for increasing tumor control, but it is well known that it also increases radiation toxicity. Thus many investigators have thought that combination therapy with radiation and chemotherapy might increase the risk of IF, but there have been few studies to evaluate this (17). Jenkins et al (17) reported that combined treatment with radiation and chemotherapy might predispose to pelvic fracture in patients with cervical cancer.

Oh et al (9) suggested 2 approaches to reduce the risk of IF. The first approach is to improve the osseous environment by treatment of osteoporosis, and the second approach is to reduce radiation toxicity (9). Sambrook et al (18) reported that bisphosphonate has been used as an effective agent for treatment of osteoporosis, and Guise et al (19) reported that it has also been shown to be effective to reduce cancer-induced bone loss. Further study is required to determine whether it can reduce the risk of IF in patients with high-risk factors such as older age and lower body weight.

The irradiated volume and dose to the sacrum and SI joints might correlate with the risk of IF. Ogino et al (6) suggested that a multibeam arrangement by CT planning could shield the posterior portion of the sacrum and SI joints without inadequate coverage of the target volume. Intensity modulated radiation therapy (IMRT) can reduce the irradiated dose and volume of normal tissue (20). It may be difficult to achieve significant sparing to reduce the risk of IF because of its proximity to the target volume; however, bone-sparing IMRT may reduce the radiation dose to the pelvic bones and result in a decrease in the occurrence of IF.

There were some limitations to our study. First, we could not evaluate the presence and severity of osteoporosis in patients before treatment. This might have led to under- or overestimation of the true prevalence of pelvic IF.

Second, we did not obtain a short-time-inversion-recovery (STIR) sequence on MRI. Blomlie et al (13) reported that STIR imaging may be the best sequence for visualizing insufficiency fractures, but we did not use this technique because STIR imaging does not provide good contrast between gynecologic organs and the surrounding tissues.

Third, there is no histologic proof that a pelvic IF is indeed just that and not a pathologic fracture within a metastatic or other bone

lesion. However, many investigators (10-13) have emphasized that an appropriate reading of CT, MRI, and/or bone scan is able to definitively diagnose IF. And some investigators (10) have reported that biopsy of a lesion is not recommended because of the high probability of fracture and low diagnostic efficiency.

In conclusion, the development of IF is not a rare complication of standard pelvic RT for cervical cancer, especially in elderly women with low body weight. If patients complain of pelvic pain after pelvic RT for gynecologic malignancies, pelvic IF must be considered in the differential diagnosis. The symptoms of most patients are resolved after conservative management based on analgesics and rest. Knowledge of the IF is useful to rule out bone metastases and thus avoid inappropriate treatment. We plan to conduct a further prospective study in such patients to evaluate whether treatment of osteoporosis using bisphosphonate or sparing bones by using IMRT can decrease the risk of development of IF.

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Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy

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What's known on the subject? and What does the study add?

- It is known that a prostate cancer gene 3 (PCA3) urine assay is superior to serum PSA level or PSA-related indices for predicting a positive biopsy result in European and US men.
- This is the first report on PCA3 in a large cohort of Japanese men. The diagnostic value of the PCA3 score in Japanese men was similar to those reported in European and US men. The study concludes that a combination of PSA density and PCA3 score may be useful for selecting patients who could avoid an unnecessary biopsy.

Objective

- To examine the diagnostic performance of the prostate cancer gene 3 (PCA3) score for prostate cancer in Japanese men undergoing prostate biopsy.

Patients and Methods

- This Japanese, multicentre study included 647 Asian men who underwent extended prostate biopsy with elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE).
- Urine samples were collected after DRE.
- The PCA3 score was determined using a PROGENSA PCA3 assay and correlated with biopsy outcome. Its diagnostic accuracy was compared with that of serum PSA level, prostate volume (PV), PSA density (PSAD), and free/total PSA ratio (f/t PSA).

Results

- A total of 633 urine samples were successfully analysed (the informative rate was 98%). Median PSA was 7.6 ng/mL.
- Biopsy revealed cancer in 264 men (41.7%). The PCA3 score for men with prostate cancer was significantly higher than that for men with negative biopsies (median PCA3 score: 49 vs. 18; $P < 0.001$). The rate of positive biopsy was 16.0% in men with a PCA3 score of <20 and 60.6% in those with a PCA3 score of ≥50.
- Using a PCA3 score threshold of 35, sensitivity and specificity were 66.5 and 71.6%, respectively.
- The area under the curve of the PCA3 score was significantly higher than that of the f/t PSA in men with PSA 4–10 ng/mL (0.742 vs 0.647; $P < 0.05$).
- In men with PSAD < 0.15 and PCA3 < 20, only three (4.2%) out of 72 men had prostate cancer.

Conclusions

- The PCA3 score was significantly superior to f/t PSA in predicting a positive biopsy result for prostate cancer in Japanese men with PSA 4–10 ng/mL.
- The combination of PSAD and PCA3 score may be useful for selecting patients who could avoid an unnecessary biopsy.

Keywords

Japanese men, PCA3 urine assay, prostate cancer

Introduction

Serum PSA level has been widely used to detect prostate cancer [1]. It is organ-specific, but not cancer-specific. Several conditions, including BPH and prostatitis, may be associated with an elevated PSA level. An elevated PSA level is likely to be associated with prostate cancer, but the low specificity of PSA limits its use as a screening test and