INTRODUCTION

The medical care systems of the United States and Japan are very different, which influences the personnel cost of medical staff. In radiation oncology, too, there is thus a major difference in personnel distribution between the United States and Japan. Most radiotherapy facilities in the United States are supported by full-time radiation oncologists (ROs), whereas the majority of radiotherapy facilities in Japan still rely on part-time ROs. Radiotherapy facilities with less than one full-time equivalent (FTE) RO on their staff still account for 56% nationwide (1). The Cancer Control Act was implemented in Japan in 2007 in response to patients' urgent petitions to the government (2). This act strongly advocates the promotion of radiotherapy (RT) and an increase in the number of ROs and medical physicists. However, a shortage of ROs still remains a major concern in Japan and will remain so for the foreseeable future.

The Japanese Society of Therapeutic Radiology and Oncology (JASTRO) has conducted national structure surveys of RT facilities in Japan every 2 years since 1990 (1, 3). The structure of radiation oncology in Japan has improved in terms of equipment and its functions in response to the increasing number of cancer patients who require RT.

In this study, we used the data of the JASTRO structure survey of 2007 to evaluate the actual work environment of radiation oncologists in Japan in terms of working pattern, patient load, and the quality of cancer care based on the relative time spent on patient care.

MATERIALS AND METHODS

Between March and December 2008, JASTRO carried out a national structure survey of radiation oncology in the form of a questionnaire in 2007 (1). The questionnaire consisted of questions about the number of treatment machines and modality by type, the number of personnel by job category, the number of patients by type, and the site. The response rate was 721 of 765 (94.2%) from all actual RT facilities in Japan.

Table 1 shows the overview of radiation oncology in Japan. University hospitals accounted for 15.8% of all RT facilities and had 40.0% of the total full-time ROs and treated 29.5% of all patients. The corresponding data were 4.0%, 7.8%, and 10.2% for cancer centers, and 80.2%, 52.2%, and 60.3% for other RT hospitals, respectively. "Full-time/part-time" indicates the employment pattern of RO. In Japan, even full-time ROs must work part-time in smaller facilities such as other RT hospitals. We considered these numbers to be inappropriate for accurate assessment of personnel. For this survey, we therefore collected FTE (40 h/week for radiation oncology services only) data depending on hours worked in clinical RT of each RO. For example, if an RO works 3 days at a university hospital and 2 days at an affiliated hospital each week, FTE of the RO at the university hospital is 0.6 and at an affiliated hospital it is 0.4. The FTE of a facility that has three ROs with 0.8, 0.4, and 0.6 is calculated as 1.8 in total.

This survey collected the work situation data of a total of 1,007 full-time ROs and 534 part-time ROs. The data of full-time ROs were crosschecked with those of part-time ROs by using their identification data. Table 2 shows the result of crosschecking between data of full-time ROs and data of part-time ROs. In this study, data of 954 ROs were analyzed. Table 3 shows an overview of the analyzed data. In ROs working mainly in university hospitals, there are two ROs who worked at a maximum of six facilities (main facilities and five affiliated facilities) SAS 8.02 (SAS Institute Inc., Cary, NC) (4) was used for the statistical analysis, and the statistical significance was tested by means of the Student's *t*-test or analysis of variance.

The Japanese Blue Book guidelines (5, 6) for structure of radiation oncology in Japan based on Patterns of Care Study (PCS) data were used as the standard for comparison with the results of this study. PCS in Japan have been used since 1996 and have disclosed significant differences in the quality of RT by the type of facilities and their caseloads (7, 8). The standard guidelines for annual patient load per FTE RO have been set at 200 (warning level 300).

To evaluate quality of cancer care provided by ROs, the relative practice index for patients was calculated by the following expression.

$$\frac{\sum_{k=1}^{n} f_k}{\sum_{k=1}^{n} a_k} \times 200$$

in which n is the number of facilities that the RO works in (n = 1, 2, 3, ..., k), f_k is the FTE of the RO in facility k, and a_k is the annual number of patients per RO in facility k

Calculation method of coefficient "200:"

1) Number of weeks per year = (365–15)/7 = 50 weeks
   ※ Japan has 15 national holidays a year
2) 1.0 FTE = 40 h/week
3) Annual working hours of FTE 1.0 = 50 × 40 h = 2,000 h
4) Relative practice index for patients was normalized using the Blue Book guideline of 200 patients/FTE RO. For this guideline, care time per patient was set at 10 hours (2,000 h/200 patients).
5) Coefficient was 200 (2000/10).

RESULTS

Working patterns

Figure 1 shows working patterns of ROs working mainly in (a) university hospitals, (b) cancer centers, and (c) other

Table 1. Categorization of radiotherapy facilities in Japan

Facility category	Number of facilities	New patients	Total patients (new + repeat)	Full-time ROs		Part-time ROs	
				n	FTE	*n*	FTE
University hospital	114	50,351	60,555	403	293.0	70	21.6
Cancer center	29	16,794	20,968	78	73.7	14	2.5
Other radiotherapy hospital	578	103,084	123,564	526	351.8	450	83.7
Total	721	170,229	205,087	1,007	718.5	534	107.8

Abbreviations: RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

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.

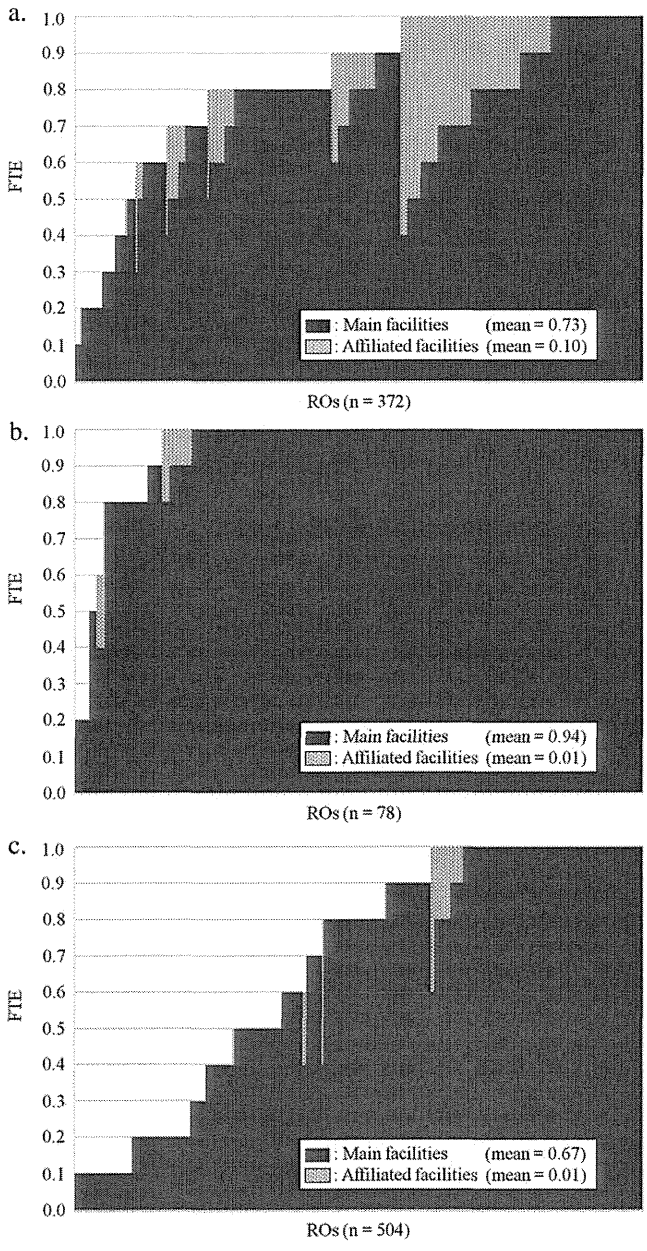

Fig. 1. Working patterns of ROs working mainly at (a) university hospitals, (b) cancer centers, and (c) other radiotherapy hospitals. Distribution of FTE ratio between main and affiliated facilities on each RO. Horizontal axis represents ROs in ascending order of own total FTE. *Abbreviations:* RO = 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

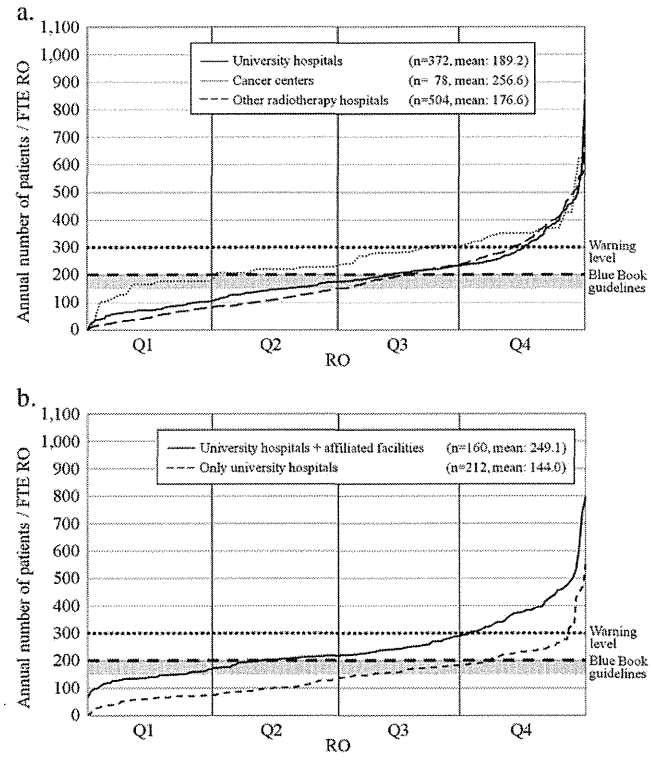

Fig. 2. Distribution of annual patient load/RO. (a) RO working mainly in university hospitals, cancer centers, and other radiotherapy hospitals. (b) RO working mainly in university hospitals. Horizontal axis represents ROs in ascending order of annual numbers of patients/RO. Q1: 0–25%, Q2: 26–50%, Q3: 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,

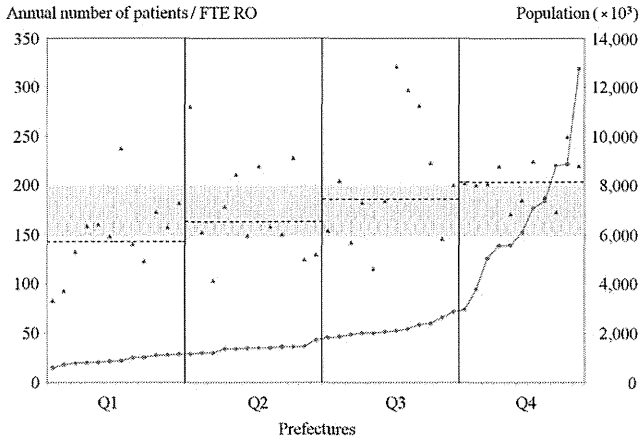

Fig. 3. Geographic distribution for 47 prefectures of annual number of patients (new plus repeat) per RO in ascending order of prefectural population. Q1: 0–25%; Q2: 26–50%; Q3: 51–75%; Q4: 76–100%. Triangles represent average annual number of patients per RO for each prefecture. Blue circles show prefectural 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).

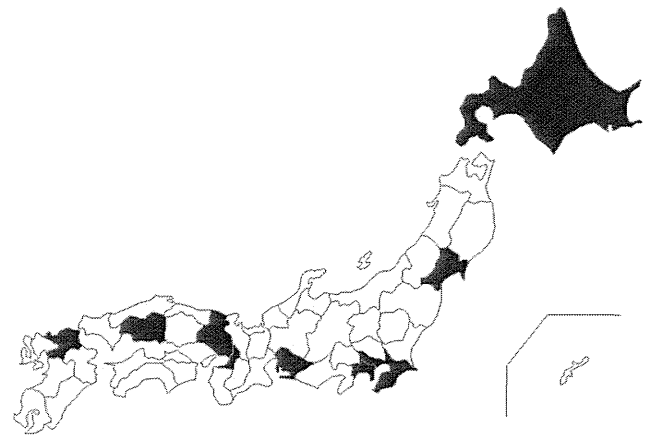

Fig. 4. The top 10 prefectures with ROs who treated more than 200 patients in descending order: Tokyo, Osaka, Kanagawa, Hokkaido, Chiba, Aichi, Fukuoka, Hyogo, Miyagi, and Hiroshima. *Abbreviation:* RO = radiation oncologist.

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

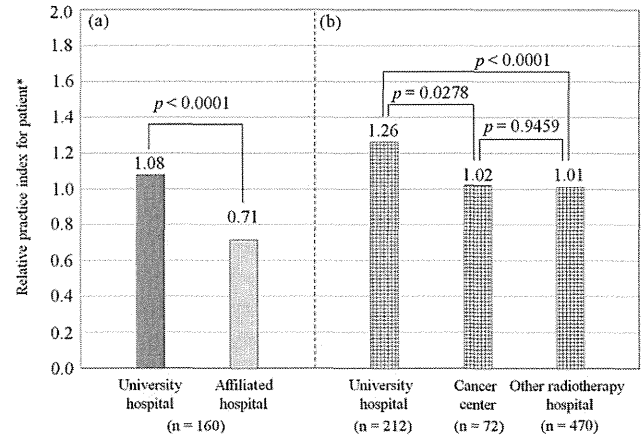

Fig. 5. Relative practice index for patients of ROs. (a) Relative practice index for patients in university hospitals and affiliated hospitals (targeted ROs were working mainly in university hospitals and part-time in affiliated hospitals). (b) Relative practice index for patients in university hospitals, 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

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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Conflict of interest: none.

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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. © 2012 Elsevier Inc.

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 $\geq$430 patients annually; A2, academic institutions treating <430 patients; B1, nonacademic institutions treating $\geq$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

	No. of patients (%)			
Parameters	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.

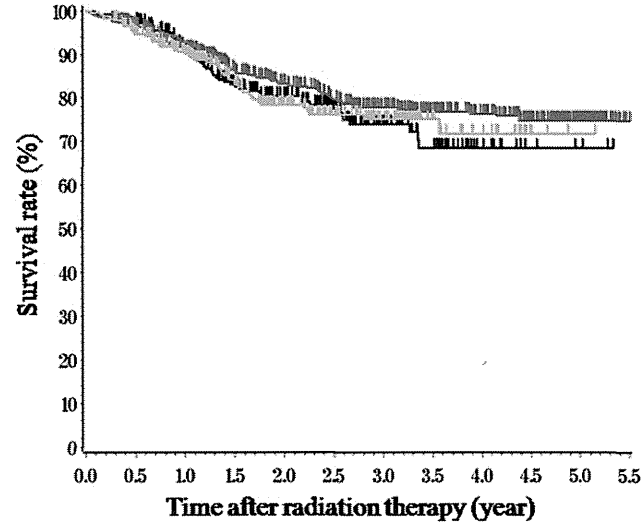

Fig. 1. Kaplan-Meier estimates of overall survival are shown for cervical cancer patients surveyed in the 1995–1997 (blue line, n = 573 patients), 1999–2001 (yellow line, n = 310 patients), and 2003–2005 (black line, n = 279 patients) patterns of care studies in Japan.

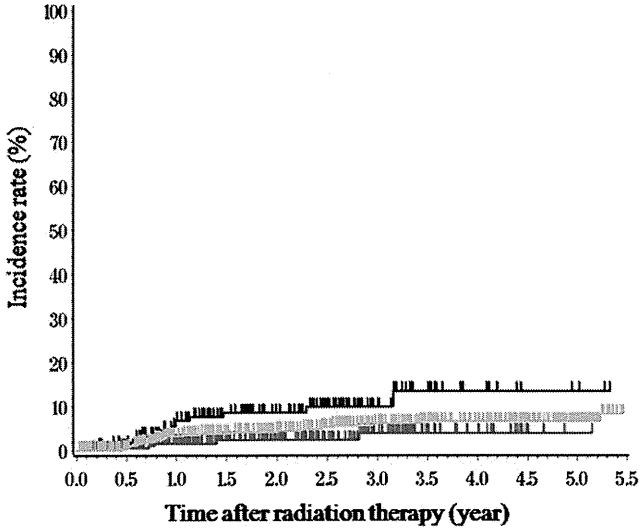

Fig. 2. The rate of developing late Grade 3 or higher toxicity are shown for cervical cancer patients surveyed in the 1995–1997 (blue, $n = 445$), 1999–2001 (yellow, $n = 224$), and 2003–2005 (black, $n = 166$) patterns of care studies in Japan.

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.

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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.

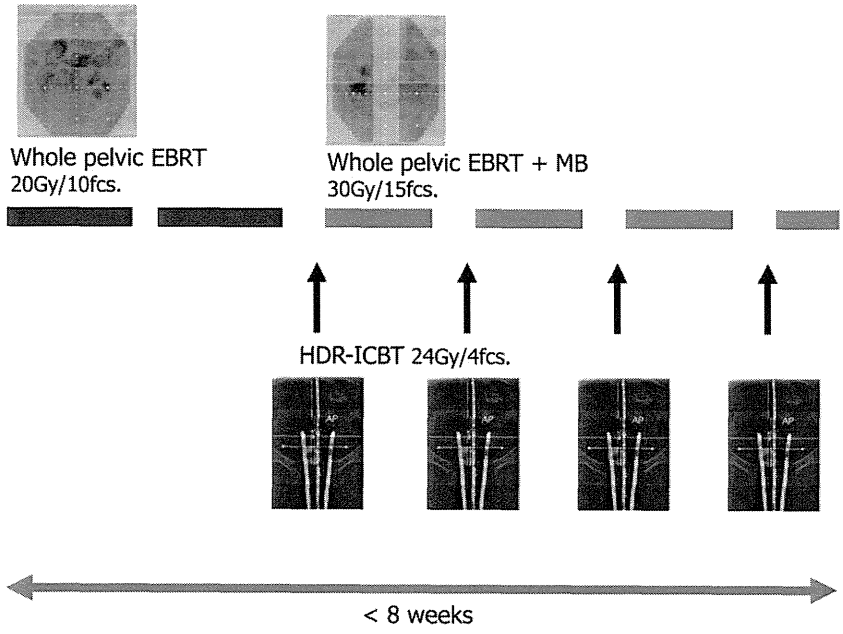

Fig. 1. Treatment schema.

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).

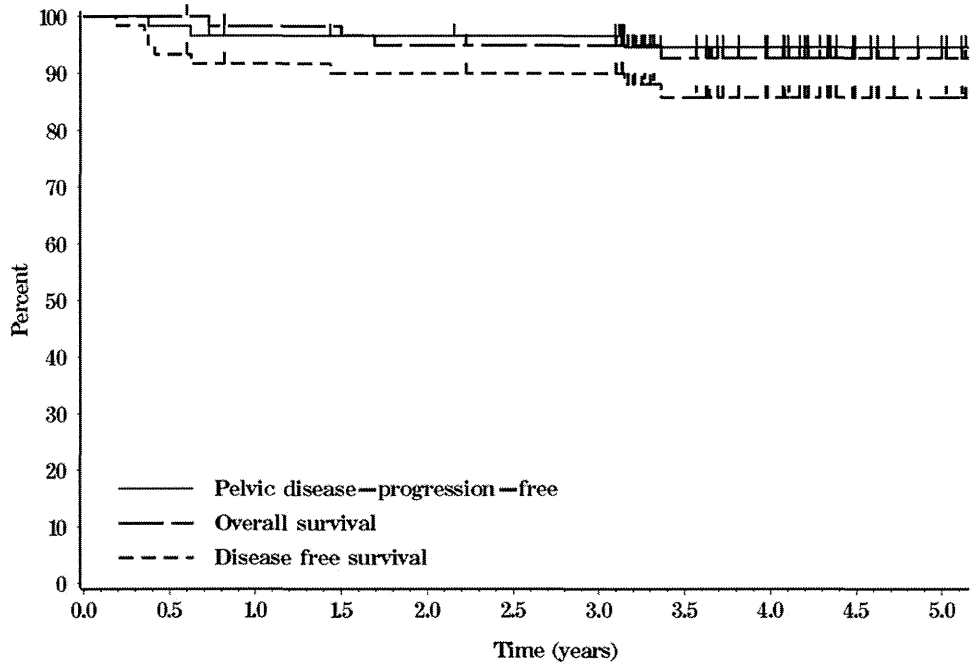

Fig. 2. PDPF survival, OS, and DFS are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

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,

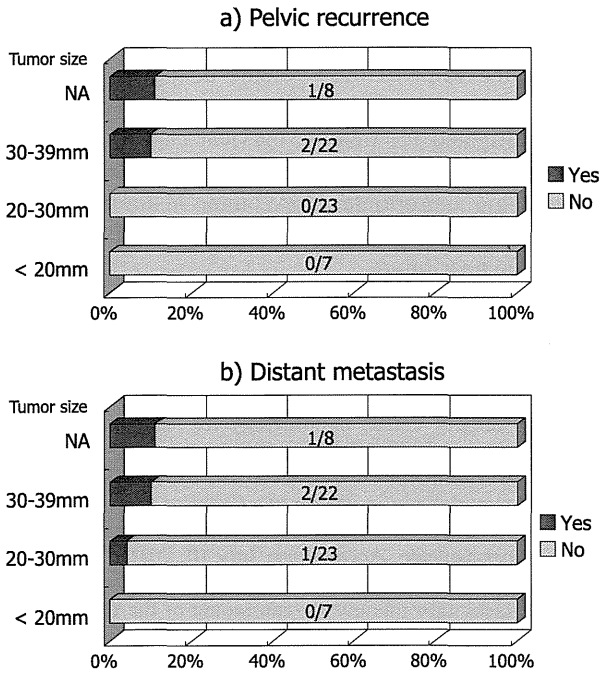

Fig. 3. Recurrence rate as a function of tumor size is shown for (a) pelvic recurrence and (b) distant metastasis. NA = not assessed (invisible on MRI).

Table 4. Late toxicities

	No. of patients by toxicity grade (n = 60)			
Toxicity	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