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.

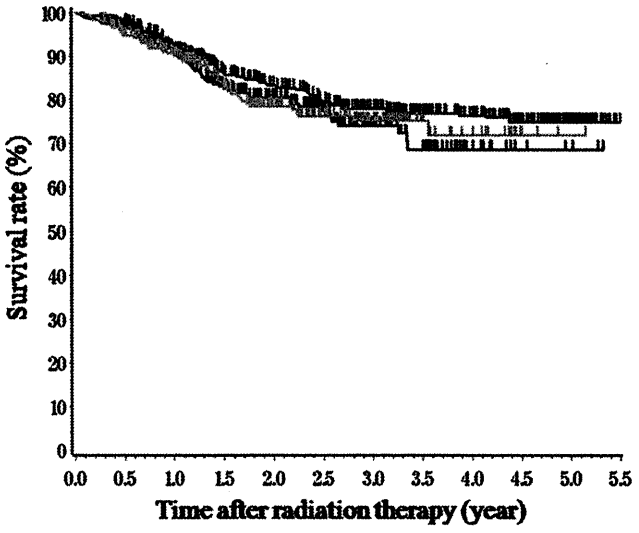

Fig. 1. Kaplan-Meier estimates of overall survival are shown for cervical cancer patients surveyed in the 1995–1997 (blue line, n = 573 patients), 1999–2001 (yellow line, n = 310 patients), and 2003–2005 (black line, n = 279 patients) patterns of care studies in Japan.

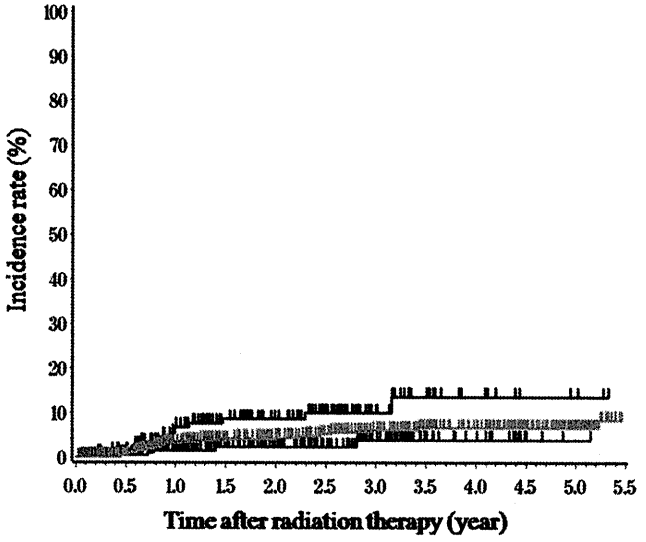

Fig. 2. The rate of developing late Grade 3 or higher toxicity are shown for cervical cancer patients surveyed in the 1995–1997 (blue, $n = 445$), 1999–2001 (yellow, $n = 224$), and 2003–2005 (black, $n = 166$) patterns of care studies in Japan.

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.

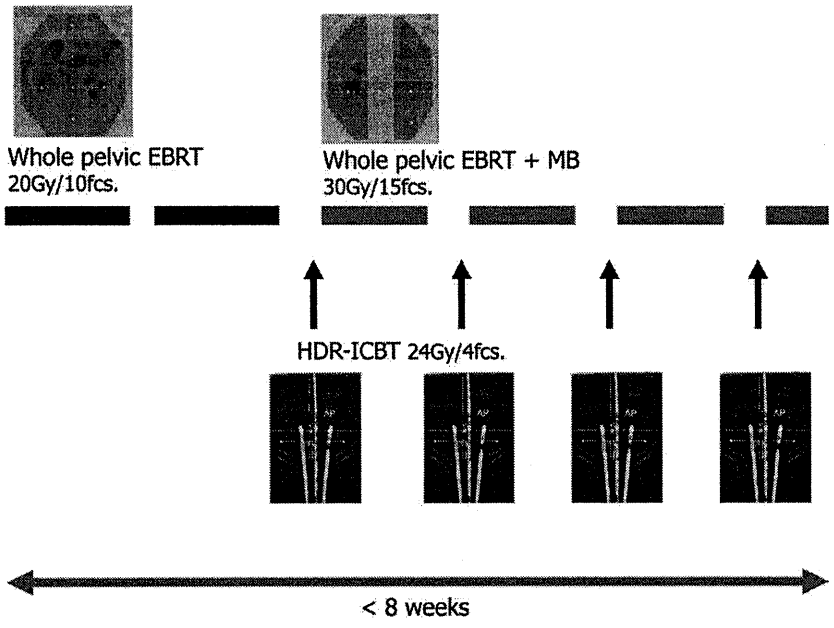

Fig. 1. Treatment schema.

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).

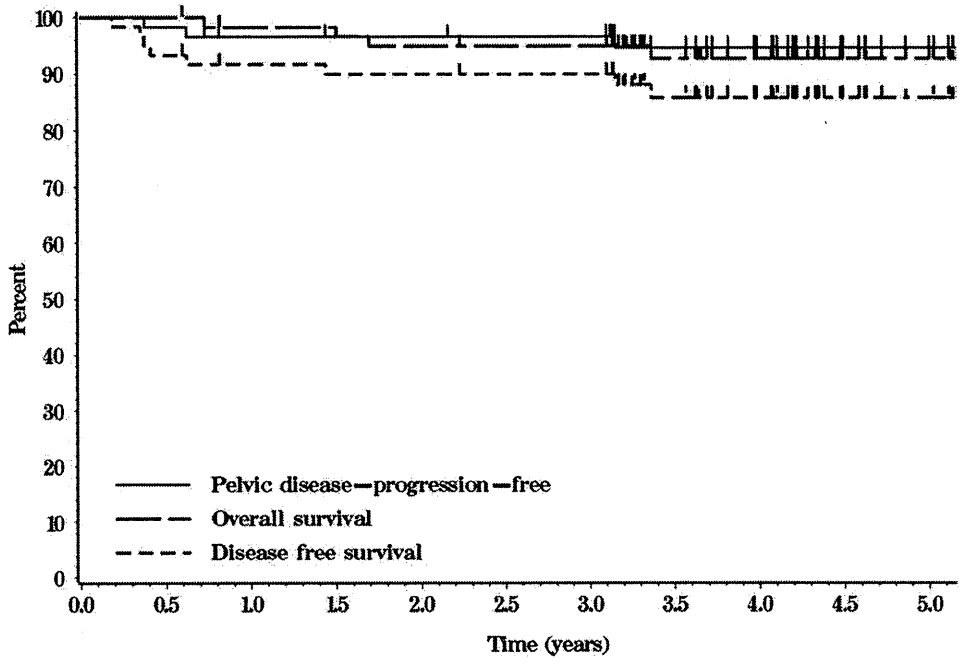

Fig. 2. PDPF survival, OS, and DFS are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

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,

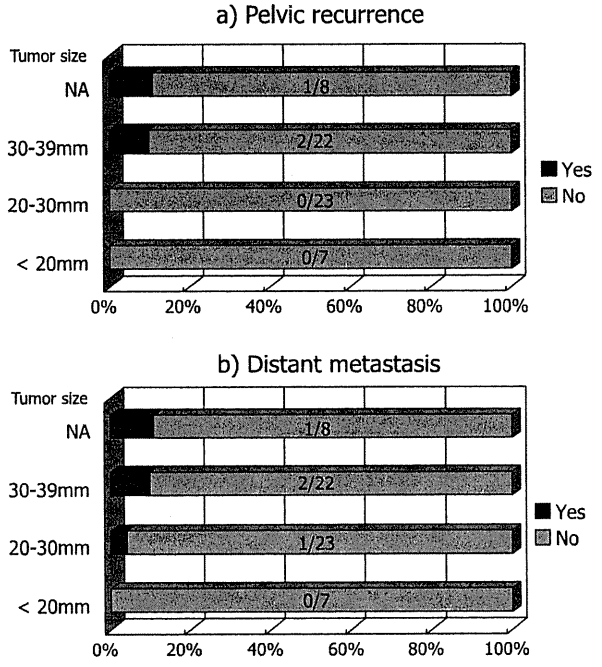

Fig. 3. Recurrence rate as a function of tumor size is shown for (a) pelvic recurrence and (b) distant metastasis. NA = not assessed (invisible on MRI).

Table 4. Late toxicities

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

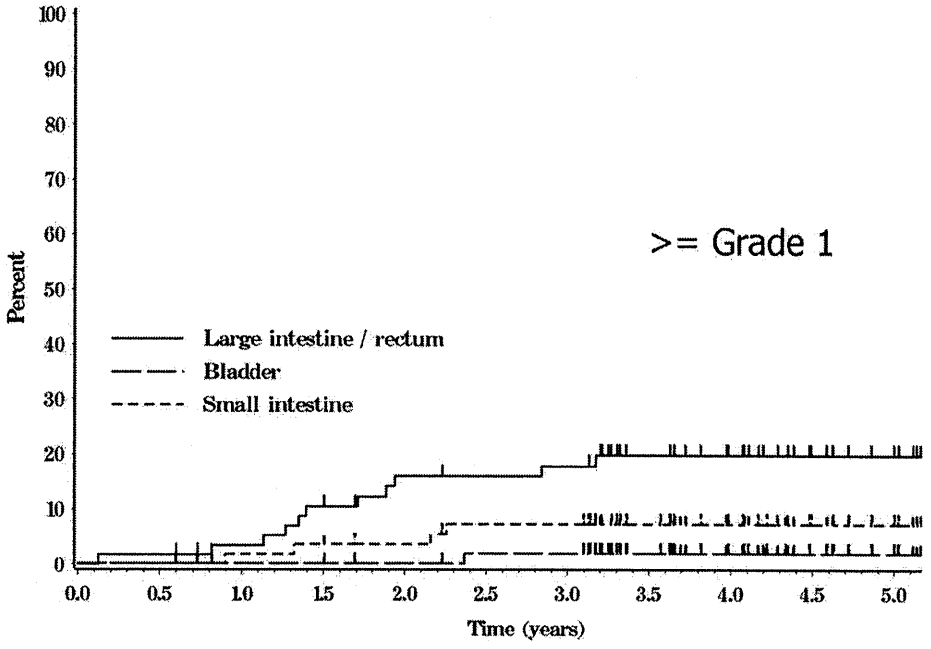

Fig. 4. Late complications (Grade ≥1) are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

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 **Prostate**

RADICAL EXTERNAL BEAM RADIOTHERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER IN JAPAN: CHANGING TRENDS IN THE PATTERNS OF CARE PROCESS SURVEY

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Purpose: To delineate changing trends in radical external beam radiotherapy (EBRT) for prostate cancer in Japan.
Methods and Materials: Data from 841 patients with clinically localized prostate cancer treated with EBRT in the Japanese Patterns of Care Study (PCS) from 1996 to 2005 were analyzed.
Results: Significant increases in the proportions of patients with stage T1 to T2 disease and decrease in prostate-specific antigen values were observed. Also, there were significant increases in the percentages of patients treated with radiotherapy by their own choice. Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing to 70 Gy from 2003 to 2005. Moreover, conformal therapy was more frequently used from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and from 1999 to 2001 (50.2%). On the other hand, the percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and from 1999 to 2001 (89.7%). Compared with the PCS in the United States, patient characteristics and patterns of treatments from 2003 to 2005 have become more similar to those in the United States than those from 1996 to 1998 and those from 1999 to 2001.
Conclusions: This study indicates a trend toward increasing numbers of patients with early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipment among Japanese prostate cancer patients treated with EBRT during 1996 to 2005 survey periods. Patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. © 2011 Elsevier Inc.

Patterns of care study, Prostate cancer, Radical external beam radiotherapy, Changing trend.

INTRODUCTION

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish the national practice process of therapies for selected malignancies over a specific time period (1–3). In addition to documenting the practice process, data from PCS surveys are important for developing and disseminating national guidelines for cancer treatment that help promote a more uniform care process in the country. The PCS is also designed to complement the role of clinical trials in enhancing the standard of care for cancer patients (1, 4).

To improve the quality of radiation oncology, PCS methodology has been imported to Japan from the United States. The Japanese PCS Working Group of Prostate Cancer started a nationwide process survey of patients treated with radiotherapy between 1996 and 1998 (5, 6). Subsequently, the Working Group conducted a second PCS of patients treated with radiotherapy between 1999 and 2001 and previously reported the results of this second PCS for prostate cancer patients in Japan treated with radiotherapy (7–18). At present, we have conducted a third PCS of patients treated with radiotherapy from 2003 to 2005 (19).

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Over the past 10 years, remarkable changes have occurred in prostate cancer treatment policy in Japan. The number of deaths due to prostate cancer has been on a steep increase, especially in elderly patients. The proportion of prostate cancer deaths to total cancer deaths also showed an increase from 0.9% in 1960 to 4.2% in 2000 (20). Since the introduction of prostate-specific antigen (PSA) screening, prostate cancer cases are being detected at earlier stages of disease, which allows early-stage patients a better chance of successful treatment and reduction of death from prostate cancer (21, 22). Moreover, recently, the use of radical external beam radiotherapy (EBRT) for prostate cancer has increased rapidly, as significant new radiation treatment planning technologies and methodologies have become available. Therefore, to optimally treat Japanese prostate cancer patients, it is important to accurately delineate the intrinsic changes taking place in the national practice process of radiotherapy for prostate cancer in Japan. In this report, we present the results of our analysis of the time-dependent transition of the process of care for prostate cancer patients treated with radical EBRT in the time periods from 1996 to 1998, 1999 to 2001, and 2003 to 2005.

METHODS AND MATERIALS

PCS surveys from 1996 to 1998, 1999 to 2001, and 2003 to 2005 in Japan contain detailed information about a total of 1,286 patients with prostate cancer treated with radiotherapy during the respective survey periods (307 patients were treated in 1996-1998; 387 patients in 1999-2001 PCS; and 592 patients in 2003-2005). PCS methodology has been described previously (1–4). Briefly, the PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The Japanese PCS used an original data format developed in collaboration with the American College of Radiology (Philadelphia, PA). The PCS surveyors consisted of 20 radiation oncologists from academic institutions. For each institution, one radiation oncologist collected data by reviewing patients' charts. To validate the quality of the collected data, the PCS used an Internet mailing list including all of the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee.

Of the 1,286 patients comprising the PCS 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, patients with a diagnosis of adenocarcinoma of the prostate were eligible for inclusion in the present study unless they had one or more of the following conditions: (*1*) hormone-refractory cancer; (*2*) evidence of distant metastasis; (*3*) concurrent or prior diagnosis of any other malignancy; (*4*) prior radiotherapy; (*5*) or prior prostatectomy. In the current study, we considered the exclusion of patients with concurrent or prior diagnosis of nonmelanoma skin cancer would not affect the results of our PCS survey because the incidence of nonmelanoma skin cancers in Japan has been low compared to those in Western countries. A total of 841 patients with clinically localized prostate cancer treated with EBRT met these eligibility criteria and were selected for analysis (1996-1998 PCS included 161 patients from 51 institutions; 1999-2001 PCS included 283 patients from 66 institutions; and 2003-2005 PCS included 397 patients from 61 institutions). Criteria for institutional categories in the 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys have been detailed elsewhere (10, 11). Briefly, the PCS divided Japanese institutions into academic institutions (university hospital or cancer center) and nonacademic institutions (other hospitals).

In the current study, we used the risk groups utilized by D'Amico *et al.* (23), based on serum PSA level, biopsy, Gleason combined score, and 1992 American Joint Commission on Cancer (AJCC) clinical tumor category. Low-risk patients had a PSA of 10 μg/l or less, a Gleason score of 6 or less, and a 1992 tumor category of stage T1c or T2a. Intermediate-risk patients had PSA levels of 10.1 to 20 μg/l or a Gleason combined score of 7 or a 1992 AJCC tumor category of stage T2b. High-risk patients had a PSA level of more than 20 μg/l or a Gleason combined score of 8 or a 1992 AJCC tumor category of stage T2c.

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University (24). Statistical significance was tested using the chi-square test, Student's *t* test, and the Mann-Whitney U test. A probability level of 0.05 was chosen for statistical significance.

RESULTS

Patient characteristics

Patient characteristics for the PCS surveys from 1996 to 1998, 1999 to 2001, and 2003 to 2005 are shown in Table 1. There were significant increases over time in the proportion of patients with stage T1 to T2 disease (34.6% of patients in the 1996-1998 PCS; 48.2% of patients in the1999-2001 PCS; and 61.4% of patients in the 2003-2005 PCS) and decreases in median PSA values at diagnosis (: 22.0 ng/ml in the 1996-1998 PCS; 20.0 ng/ml in the 1999-2001 PCS; and 14.9 ng/ml in the 2003-2005 PCS). Data for the Gleason combined score were missing for 73.9% (119/161) of the patients in the 1996 to 1998 PCS and for 39.6% (112/283) of the patients in the 1999 to 2001 PCS, while only 5.5% (22/397) of patients were missing in the 2003 to 2005 PCS. The number of patients in the low-risk group increased gradually over time, while the number of patients in the high-risk group decreased gradually (Fig. 1). Table 1 and Fig. 2 indicate the reasons for selecting radiotherapy during these different time periods. There were significant increases over time in the number of patients treated with radiotherapy by their own choice (5.9% of patients in the 1996-1998 PCS; 26.5% of patients in the 1999-2001 PCS; and 41.4% of patients in the 2003-2005). This change in the rate of "patient choice" was significantly different ($p < 0.0001$).

Treatment characteristics

Treatment characteristics are shown in Table 2. The frequencies of radiation energies >10 MV, the use of portal or electronic portal images, and all field treatment each day increased gradually from 1996 to 1998 to 2003 to 2005. Also, the frequency of computed tomography (CT)-based treatment planning was 90.9% in 2003 to 2005, but 80.7% in 1996 to 1998, and 85.5% in 1999 to 2001. Moreover, the frequency of conformal therapy increased more rapidly from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and 1999 to 2001 (50.2%).

Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Stratifying patients by

Table 1. Patient and disease characteristics

Patient characteristic	PCS survey 1996-1998 (n = 161 patients)	PCS survey 1999-2001 (n = 283 patients)	PCS survey 2003-2005 (n = 397 patients)	Significance (p value)
Institution	51	66	61	
Median age, years (range)	70.4 (46.5–89.8)	71.8 (49.7–92.2)	72.1 (50.7–87.7)	0.4556
Mean age ± SD	70.8 ± 8.1	71.8 ± 6.6	71.5 ± 6.1	0.3446
Median KPS % (range)	90 (40–100)	90 (50–100)	90 (60–100)	<0.0001
Mean ± SD	87.0 ± 8.9	89.1 ± 7.1	90.9 ± 8.5	<0.0001
Missing data	7	8	0	
Pretreatment PSA level (%)				
Median PSA level (range)	21.95 (0.3–900.0)	19.99 (0.6–856.9)	14.94 (0.7–3,058.0)	0.0176
Mean PSA level ± SD	51.5 ± 93.5	54.1 ± 99.5	48.2 ± 179.2	0.8719
<10	41/146 (28.1%)	77/268 (28.7%)	121/391 (30.9%)	0.0066
10-19.9	25/146 (17.1%)	57/268 (21.3%)	113/391 (28.9%)	
≥20	80/146 (54.8%)	134/268 (50.0%)	157/391 (40.2%)	
Missing data	15	15	6	
Lower pretreatment PSA level (%)				
<4	17/146 (11.6%)	8/268 (3.0%)	9/391 (2.3%)	<0.0001
≥4	129/146 (88.4%)	260/268 (97.0%)	382/391 (97.7%)	
Missing data	15	15	6	
Differentiation (no. patients/total) (%)				
Well	24/159 (15.1%)	62/264 (23.5%)	67/376 (17.8%)	0.0148
Moderate	79/159 (49.7%)	93/264 (35.2%)	152/376 (40.4%)	
Poor	46/159 (28.9%)	93/264 (35.2%)	99/376 (26.3%)	
Other	0/159 (0.0%)	2/264 (0.8%)	7/376 (1.9%)	
Unknown	10/159 (6.3%)	14/264 (5.3%)	51/376 (13.6%)	
Missing data	2	19	21	
Gleason combined score (%)				
2-6	11/42 (26.2%)	77/171 (45.0%)	118/375 (31.5%)	0.0014
7	18/42 (42.9%)	35/171 (20.5%)	134/375 (35.7%)	
8-10	13/42 (31.0%)	59/171 (34.5%)	123/375 (32.8%)	
Missing data	119	112	22	
T stage (no. patients/total) (%)				
TX-T0	1/159 (0.6%)	10/272 (3.7%)	1/394 (0.3%)	<0.0001
T1	8/159 (5.0%)	22/272 (8.1%)	88/394 (22.3%)	
T2	47/159 (29.6%)	109/272 (40.1%)	154/394 (39.1%)	
T3-T4	102/159 (64.2%)	124/272 (45.6%)	134/394 (34.0%)	
Unknown	1/159 (0.6%)	7/272 (2.6%)	17/394 (4.3%)	
Missing data	2	11	3	
N stage (no. patients/total) (%)				
NX-N0	136/157 (86.6%)	249/270 (92.2%)	372/394 (94.4%)	0.0038
N1	18/157 (11.5%)	15/270 (5.6%)	12/394 (3.0%)	
Unknown	3/157 (1.9%)	6/270 (2.2%)	10/394 (2.5%)	
Missing data	4	13	3	
Risk group (no. patients/total) (%)				
Low risk	1/127 (0.8%)	16/242 (6.6%)	40/381 (10.5%)	< 0.0001
Intermediate risk	7/127 (5.5%)	26/242 (10.7%)	107/381 (28.1%)	
High risk	119/127 (93.7%)	200/242 (82.6%)	234/381 (61.4%)	
Missing patient data	34	41	16	
Reason for selection of RT (no. patients/total) (%)				
Patient choice	8/136 (5.9%)	71/268 (26.5%)	159/384 (41.4%)	
Advanced or high-risk disease	43/136 (31.6%)	83/268 (31.0%)	121/384 (31.5%)	
Intercurrent disease	0/136 (0.0%)	0/268 (0.0%)	62/384 (16.1%)	
Medical contraindication	7/136 (5.1%)	36/268 (13.4%)	0/384 (0.0%)	
Old age	37/136 (27.2%)	44/268 (16.4%)	94/384 (24.5%)	
Other	9/136 (6.6%)	8/268 (3.0%)	6/384 (1.6%)	
NA or unknown	32/136 (23.5%)	26/268 (9.7%)	27/384 (7.0%)	
Missing data	25	15	13	

Abbreviations: KPS = karnofsky performance status; PSA = prostate-specific antigen; RT = radiotherapy; NA = data not available; SD = standard deviation.

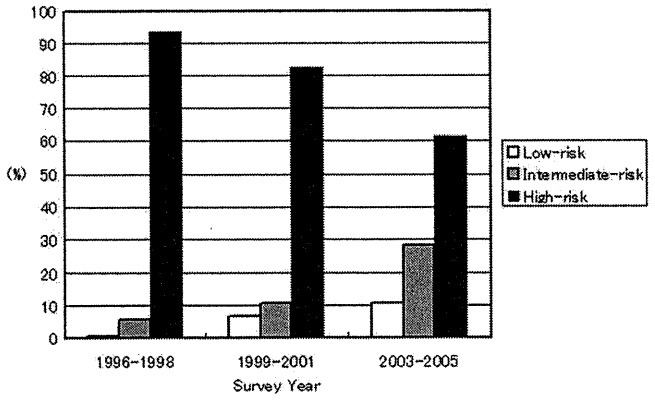

Fig. 1. Distribution of patients with prostate cancer according to risk group among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

total dosage revealed that 24.8% of patients received total radiation doses below 60 Gy in the 1996 to 1998 PCS, decreasing to only 2.0% from 2003 to 2005. Also, only 17.4% of patients received total doses of >70 Gy from 1996 to 1998, which increased dramatically to 52.0% from 2003 to 2005 (Fig. 3). Increased radiation doses were administered predominantly in academic institutions (Table 2).

The percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and that from 1999 to 2001 (89.7%). Hormonal therapy was used before, during, and after radiotherapy for a mean duration of 30.1 ± 29.8 months, 43.9 ± 36.7 months, and 40.6 ± 34.3 months, respectively (86.3% of patients in 1996-1998; 89.7% of patients in 1999-2001; and 81.1% in 2003-2005). The proportion of patients receiving hormone therapy was analyzed according to risk group. Most patients in the intermediate- and high-risk groups were treated with hormone therapy during 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods (Fig. 4). In the low risk-group, approximately 50% to 70% of patients were treated with hormone therapy in the periods 1999 to 2001 and 2003 to 2005. We could not precisely analyze the incidence of low-risk patients treated with hormone therapy during the 1996 to 1998 period because only 1 patient, who was not treated with hormone therapy, was available for this analysis.

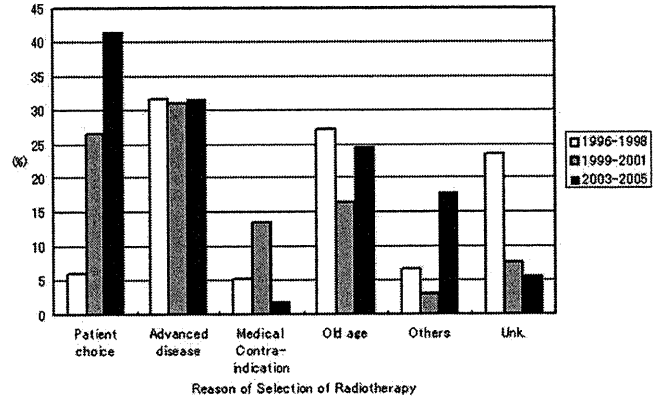

Fig. 2. Reasons of selection of EBRT for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

FTE radiation oncologists

For academic institutions, the mean numbers of full-time equivalent (FTE) radiation oncologists increased gradually over time (results of the surveys for 1996-1998, 1999-2001, and 2003-2005 were 2.13, 2.36, and 2.86, respectively). For nonacademic institutions, the mean numbers of FTE radiation oncologists also increased gradually over time (results for 1996-1998, 1999-2001, and 2003-2005 were 0.57, 0.62, and 0.75, respectively), but the numbers were extremely low compared with those in academic institutions.

Comparisons of changing trends in patient and treatment characteristics between Japan and the United States

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics by using the US PCS data reported by Zelefsky *et al.* (25). In Japan, the proportions of patients with stage T3 to T4 disease and PSA levels >20 ng/ml decreased gradually from 1996 to 1998 to 2003 to 2005, but the proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were over 30% among the three surveys (Fig. 5a). On the other hand, in the United States, the proportions of patients with T3 to T4 disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 disease, a PSA of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b).

Regarding treatment characteristics, in Japan, the proportions of patients receiving conformal radiotherapy and higher radiation doses (72 Gy or more) increased, as 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005. On the other hand, use of hormone therapy was over 80% during the survey periods (Fig.6a). In the United States, the proportions of patients receiving hormone therapy and higher radiation doses (72 Gy or more) increased continuously over the survey periods, and the proportions of patients receiving hormone therapy and higher radiation doses were approximately 45% to 50% (Fig. 6b). Concerning conformal therapy in the United States, 80% of patients were treated with conformal radiotherapy in 1999, which was almost the same frequency as patients treated from 2003 to 2005 in Japan.

DISCUSSION

Results of the current study indicate that there were significant increases in the proportions of prostate cancer patients with stage T1 to T2 disease and lower initial PSA values in the 1996 to 2005 survey periods in Japan. Numbers of patients in the low-risk group increased gradually, while

Table 2. Treatment characteristics

Treatment	PCS survey 1996-1998 (n = 161)	1999-2001 (n = 283)	2003-2005 (n = 397)	Significance (p value)
Received radiotherapy				
Energy (≥10 MV) (%)				
Yes (no. patients/total) (%)	98/161 (60.9%)	208/279 (74.6%)	312/386 (80.8%)	<0.0001
Missing data	0	4	11	
Portal films or electric portal images used (%)				
Yes (no. patients/total) (%)		210/280 (75.4%)	388/397 (97.7%)	<0.0001
Missing data		3	0	
All fields treated each day (%)				
Yes (no. patients/total) (%)	44/65 (67.7%)	215/283 (76.0%)	363/397 (91.4%)	<0.0001
Missing data	96	0	0	
CT-based treatment planning (%)				
Yes (no. patients/total) (%)	130/161 (80.7%)	241/282 (85.5%)	361/397 (90.9%)	0.0006
Missing	0	1	0	
Received conformal radiotherapy (%)				
Yes (no. patients/total) (%)	79/161 (49.1%)	142/283 (50.2%)	337/397 (84.9%)	<0.0001
Received pelvic irradiation (%)				
Yes (no. patients/total) (%)	69/161 (42.9%)	102/283 (36.0%)	95/397 (23.9%)	<0.0001
Radiation dose (cGy)				
A+B (total)				
Median (range)	6,500 (2,200–7,400)	6,840 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,090.9 ± 990.5	6,602.9 ± 731.1	6,764.0 ± 621.9	<0.0001
A median (min-max)	6,500 (2,200–7,400)	6,600 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,250.9 ± 976.8	6,610.3 ± 766.5	6,855.8 ± 708.0	<0.0001
B median (min-max)	5,940 (3,400–7,000)	6,900 (3,000–8,000)	6,600 (3,000–7,640)	<0.0001
Mean ± SD	5,622.4 ± 885.6	6,592.6 ± 681.9	6,654.9 ± 480.5	<0.0001
Prescription dose levels (Gy) (no. patients/total) (%)				
<60	40/161 (24.8%)	17/282 (6.0%)	8/396 (2.0%)	<0.0001
60-65	36/161 (22.4%)	56/282 (19.9%)	57/396 (14.4%)	
65-70	57/161 (35.4%)	102/282 (36.2%)	125/396 (31.6%)	
≥70	28/161 (17.4%)	107/282 (37.9%)	206/396 (52.0%)	
Missing data	0	1	1	
Higher prescription dose levels (no. patients/total) (%)				
<72	159/161 (98.8%)	261/282 (92.6%)	329/396 (83.1%)	<0.0001
≥72	2/161 (1.2%)	21/282 (7.4%)	67/396 (16.9%)	
Missing data	0	1	1	
Received hormone therapy (%)				
Yes (no. patients/total) (%)	138/160 (86.3%)	253/282 (89.7%)	321/396 (81.1%)	0.0284
No (no. patients/total) (%)	21/160 (13.1%)	29/282 (10.3%)	73/396 (18.4%)	
Unknown	1/160 (0.6%)	0/282 (0.0%)	2/396 (0.5%)	
Missing data	1	1	1	
Received chemotherapy				
Yes (no. patients/total) (%)	20/159 (12.6%)	17/274 (6.2%)	5/394 (1.3%)	<0.0001
No (no. patients/total) (%)	137/159 (86.2%)	255/274 (93.1%)	387/394 (98.2%)	
Unknown	2/159 (1.3%)	2/274 (0.7%)	2/394 (0.5%)	
Missing data	2	9	3	

Abbreviation: SD = standard deviation.

numbers of patients in the high-risk group decreased gradually. These results suggest that the likelihood of early-stage prostate cancer patients being treated with radiotherapy is greater than ever before in Japan. In the United States, most of the prostate cancer patients have early-stage tumors, and radiotherapy has been recognized as the first-line therapy for prostate cancer (25–28). Because of the prevailing use of PSA screening and the increasing number of patients treated with radiotherapy in Japanese institutions (29), the opportunities for treating early-stage prostate cancer patients with radical EBRT should increase even more in the future.

In the current study, the data for a Gleason combined score were missing for 73.9% of the patients in the 1996 to 1998 PCS and 39.6% of the patients in the 1999 to 2001 PCS, while data for only 5.5% of the patients in 2003 to 2005 PCS were missing. These results suggest that previously in Japan, physicians did not realize the importance of the

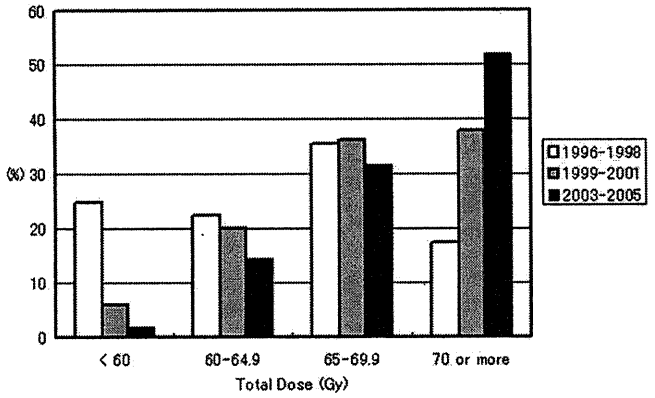

Fig. 3. Distributions of total radiation doses of external beam radiotherapy for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

Gleason combined score, but recently, they are becoming aware that the Gleason combined score is of critical importance in the evaluation and management of prostate cancer patients. Further studies are required to confirm whether physicians in Japan will routinely use the Gleason combined score in the management of prostate cancer patients in future.

The current study also revealed a remarkable change in the reason for choosing radiotherapy in Japan among the 1996 to 2005 survey periods. Only 5.9% of the patients were treated with radiotherapy by their own choice from 1996 to 1998, but 41.4% of patients chose radiotherapy from 2003 to 2005. EBRT did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an insufficient number of radiation oncology centers capable of delivering appropriate treatment prevented earlier dissemination of this type of therapy. However, in conjunction with significant improvements in the availability of new radiation treatment planning technologies and methodologies for treatment planning and delivery, Japanese patients are becoming increasingly aware of the effectiveness of radiotherapy for prostate cancer (30, 31). Therefore, the increasing percentage of patients choosing radiotherapy might reflect a growing acceptance of radical external EBRT as one of the main treatments for prostate cancer patients in Japan.

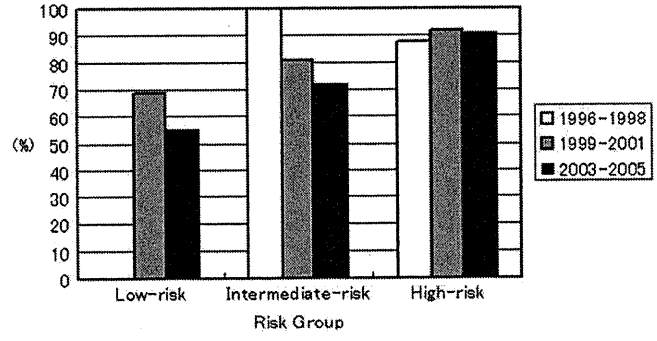

Fig. 4. Hormonal therapy distribution according to risk group for prostate cancer in Japan among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

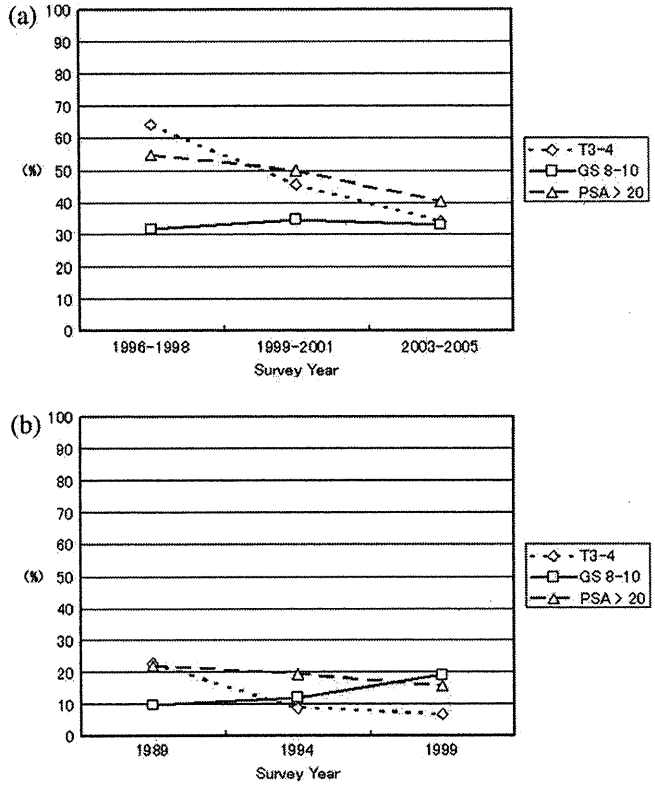

Fig. 5. (a) Changing trend in patient characteristics in Japan. (b) Changing trend in patient characteristic in the United States. (Data from ZelefskyMJ, Moughan J, Owen J, et al. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 patterns of care survey for prostate cancer. Int J Radiat Oncol Biol Phys 2004;59:1053-1061)

Moreover, the radiotherapy strategy appears to have changed among the 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods. The frequency of CT-based treatment planning increased up to 90.9% in 2003 to 2005, and the usage of conformal therapy increased rapidly from 2003 to 2005 (84.9%). The median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Also, the proportions of patients receiving total radiation doses below 60 Gy decreased, while the proportions of patients receiving total doses of >70 Gy increased rapidly during the survey period (Fig. 3). These results indicate that patients receiving lower radiation doses with obsolete treatment equipment was more common between 1996 and 1998, while higher doses with high-technology radiation equipment prevailed between 2003 and 2005. US PCS results indicate that many prostate cancer patients have been routinely treated with total doses of >70 Gy in the United States (25, 28). The use of increasing radiation doses in Japan might reflect the widespread dissemination of clinical trial results (32–35) and also a growing acceptance by radiation oncologists and urologists that radical EBRT is effective for treating prostate cancer (30, 31).

Results of the current study indicate that hormone therapy was commonly used in conjunction with radiotherapy during the survey period in Japan. Moreover, it was not only

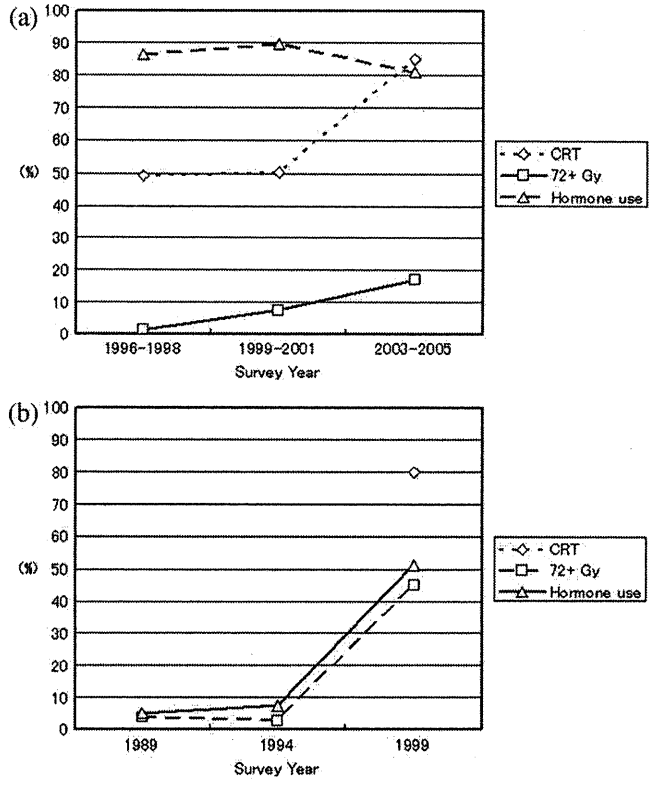

Fig. 6. (a) Changing trend in treatment characteristics in Japan. (b) Changing trend in patient characteristics in the United States. (*Data from* Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328.)

patients in the intermediate- and high-risk groups but also patients in the low-risk group who were frequently treated with hormone therapy during 1999 to 2001 and 2003 to 2005 (Fig. 4). However, several studies from the United States have indicated that radical radiotherapy alone could control the disease in low-risk patients. Zietman *et al.* (34) indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was less than 10 ng/ml. Hanks *et al.* (35) found that prostate cancer patients with a pretreatment PSA level of <10 ng/ml did not benefit from a dose escalation above 70 Gy (35). Therefore, radical EBRT without hormone therapy has been the primary treatment for patients in the United States with low-risk diseases. The high rate of health insurance coverage for Japanese people may explain the frequent administration of hormone therapy in Japan (36). Another reason may be that at present, many Japanese radiation oncologists may consider the higher dose levels (>72 Gy) unnecessary for prostate cancer patients when combined with long-term hormone therapy. Therefore, radical EBRT without hormone therapy should also be the treatment of choice for low-risk patients in Japan.

In the current study, the mean numbers of FTE radiation oncologists increased gradually over time in both academic and nonacademic institutions. However, the median number of FTE radiation oncologists remained low, especially in nonacademic institutions. Publication data documenting a progressive increase in the number of prostate cancer patients treated with radiotherapy in every institution, demonstrating a need for both academic and nonacademic Japanese institutions to upgrade their radiation equipment and to recruit more radiation oncologists (29).

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics. In Japan, proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were all over 30%, but proportions of patients with T3 to T4 disease and a PSA level of >20 ng/ml decreased gradually during the survey period (Fig. 5a). In the United States, the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b). These results indicate that although patients in Japan had more advanced disease than those in the United States, patient characteristics in Japan have been changing, becoming more similar to patients in the United States. Further studies are required to confirm this finding.

Concerning treatment characteristics: in Japan, proportions of patients receiving conformal radiotherapy and higher radiation doses have been increasing, and 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005 (Fig. 6a). In the United States, conformal therapy was administered to 85% of patients in 1999, and higher radiation doses (72 Gy or more) have increased continuously from 1989 to 1999 (Fig. 6b). These results indicate that although radiotherapy characteristics were still developing in Japan compared to the United States, the proportions of modern radiotherapy have been increasing both in Japan and the United States during the survey period.

The percentage of patients receiving hormone therapy remained high during the periods from 1996 to 1998 to 2003 to 2005 in Japan. On the other hand, there was a rapid increase in the use of hormone therapy in the United States from 1994 to 1999. The significantly increased use of hormone therapy for high-risk patients in the United States reflects the penetration and growing acceptance of clinical trial results that have demonstrated the efficacy of these treatment approaches (32, 33). The randomized Radiation Therapy Oncology Group 8610 trial demonstrated an increase in disease-free survival at 2 years (76% vs. 62% survival) for locally advanced prostate cancer patients treated with neoadjuvant total androgen blockade plus radiation compared to those treated with radiation therapy alone (33). In Japan, hormone therapy was administered to approximately 90% of patients with high-risk disease, and these high rates of hormone therapy have continued for several years. Therefore, radiotherapy in conjunction with hormone therapy appears to be an accepted approach for the unfavorable risk group in Japan and in the United States.