Table 5. Dosage* of radiotherapy according to the FIGO stage

Dose (cGy)	Missing (*n*)	Stage					*P*-value	Total
		I	II	III	IVA	Other		
EBRT								
Total point A dose							<0.0001	
0–1999	0	7 (35%)	9 (8%)	6 (4%)	1	0		23 (8%)
2000–2999	0	7 (35%)	21 (21%)	14 (9%)	0	0		42 (14%)
3000–3999	1	3 (15%)	29 (28%)	79 (49%)	7 (28%)	0		118 (38%)
4000–4999	0	3 (15%)	22 (22%)	23 (14%)	9 (36%)	0		57 (18%)
5000+	0	0	21 (21%)	40 (24%)	8 (32%)	0		69 (22%)
Missing	2	9	2	3	0	1		17
Median		2180	3060	3240	4060			3220
Total point B dose							<0.0001	
0–1999	0	0	0	0	0	0		0
2000–2999	0	2 (10%)	1	1	0	0		4 (1%)
3000–3999	0	0	2	3 (2%)	2 (8%)	0		7 (2%)
4000–4999	0	10 (50%)	17 (17%)	29 (18%)	3 (12%)	0		59 (20%)
5000–5999	1	8 (40%)	81 (80%)	120 (76%)	17 (68%)	0		226 (74%)
6000+	0	0	0	5 (3%)	3 (12%)	0		8 (3%)
Missing	2	9	3	7	0	1		22
Median		4830	5000	5000	5000			5000
HDR-ICBT								
Total point A dose							0.33	
0–999	0	0	0	3 (2%)	1	0		4 (1%)
1000–1999	0	5 (18%)	25 (25%)	42 (28%)	8 (35%)	0		80 (26%)
2000–2999	1	14 (50%)	47 (48%)	70 (46%)	13 (56%)	0		144 (48%)
3000–3999	2	9 (32%)	27 (27%)	37 (24%)	1	1		75 (25%)
4000+	0	0	0	0	0	0		0
Missing	0	1	5	13	2	0		21
Median		2500	2400	2400	2177			2400
EBRT + HDR-ICBT								
Total point A dose							0.0002	
0–3999	0	12 (48%)	4 (4%)	5 (3%)	0	0		21 (7%)
4000–4999	0	4 (16%)	18 (19%)	14 (9%)	3 (13%)	0		39 (13%)
5000–5999	1	6 (24%)	35 (36%)	53 (35%)	3 (13%)	0		97 (33%)
6000–6999	0	2 (8%)	15 (15%)	53 (35%)	13 (57%)	0		83 (28%)
7000+	0	1	25 (26%)	26 (17%)	4 (17%)	0		56 (19%)
Missing	2	4	7	14	2	1		30
Median		4020	5600	6000	6390			5800

A total of 327 patients were treated with HDR-ICBT with a combination of tandem and vaginal applicator, or tandem only.
*Dose at left side.
HDR-ICBT, high-dose-rate intracavitary brachytherapy; EBRT, external beam radiotherapy.

Overall treatment time (OTT) could be calculated for all 591 patients. The median OTT including ICBT was 49 days. OTT exceeded 8 weeks (56 days) in 193 patients (33%), and 10 weeks (70 days) in 59 patients (10%). There was no significant variance in OTT by either institutional strata or FIGO stage. An unplanned treatment break occurred in 56 out of 565 patients (10%). Patients whose treatment period included consecutive national holidays (e.g. holidays from April 29 to May 5, the year end's and the New year's holidays) had significantly longer OTT ($P = 0.023$). The median OTT was 58 days for

patients with these national holidays during their treatment period (n = 140), and 48 days for those without (n = 451). Sixty-eight out of 193 patients (35%) with OTT >8 weeks were those whose treatment period included the consecutive national holidays.

Chemotherapy

Data on chemotherapy application were collected for 574 patients (97%). One hundred and forty patients (24%) received chemotherapy. Use of chemotherapy significantly varied according to FIGO stage (P = 0.001). Chemotherapy was administered in eight patients (15%) in stage I, 22 patients (13%) in stage II, 87 patients (32%) in stage III and 21 patients (28%) in stage IVA.

Neoadjuvant chemotherapy (NAC) prior to radiotherapy was given in 81 of 574 patients (14%). Twenty-eight of 574 patients (5%) were treated with concurrent chemoradiation. The most frequently used agent for concurrent chemoradiation was bleomycin/pepleomycin, and it was followed by oral 5-fluorouracil. No patients received cisplatin concurrently with radiotherapy.

DISCUSSION

This study demonstrated the national practice patterns for cervical cancer patients treated with radiotherapy without planned surgery between 1995 and 1997 in Japan. Several significant variances in the process according to the stratification of institutions were also observed.

Status of patient background, such as age and KPS, were unfavorable compared with the JPCS data of post-operative radiotherapy for the same period (3). This tendency was also observed when compared with the US PCS (4,5). This might imply that radiotherapy without surgery was mainly given to patients with unfavorable general conditions in Japan. This was also suggested by the distribution ratio of stage I/II patients. Whereas the ratio in the US PCS was ~70% (5,6), it was only 39% in this study. Many investigators demonstrated that definitive radiotherapy brought equivalent outcomes to radical surgery in respectable stage I/II disease (7). Furthermore, a randomized trial clearly confirmed this hypothesis in 1997 (8). The present study identified that patient backgrounds varied by institutional strata. In addition to the factors mentioned above, the hemoglobin value was found to affect the outcome. Several investigators indicated that the pre-treatment hemoglobin value was one of the important prognostic indicators for uterine cervical cancer patients treated with radiotherapy (9). Patients in A1 institutions tended to be favorable for these patient-related factors. This was consistent with the previous JPCS survey (2). This suggested that patients with definitive status tended to be treated at large academic institutions, when radical radiotherapy was attempted. Concerning histology, most patients (95%) had squamous cell carcinoma. The breakdown in histology was different from that of the JPCS data of post-operative radiotherapy (3) and the US PCS (1996–1999) (6). Squamous cell carcinoma was found in 83% of patients in both the JPCS post-operative radiotherapy data and the US PCS (3,6). This might reflect the majority opinion of Japanese gynecological oncologists, i.e. radiotherapy is less effective for cervical adenocarcinoma despite some encouraging treatment results of radical radiotherapy (10,11).

As mentioned above, >60% of the patients were stage III/IV in this survey. The distribution ratio was higher than that of the US PCS (5,6). However, this observation should be interpreted with caution. The incidence of hydronephrosis/non-functioning kidney (23%) in stage III patients demonstrated in this study was lower than that of the US PCS (41%) (5). This suggested that some type of overstaging migration existed in Japan. Eifel has stressed the importance of accurate staging closely adhering to the FIGO notes and rules (12,13). Besides the FIGO stage, we consider that tumor size assessment using MRI could be one of the effective means to evaluate and compare tumor status among different institutions and countries. Although MRI is not permitted to be used in the FIGO staging system, its usefulness in measuring cervical tumor diameter has been demonstrated in several studies (14,15). In evaluation of lymph node status, the present study showed that CT was most commonly used. The same observation was made in the US PCS (5,6). However, lymphangiography and surgical exploration were rarely performed in this survey. although certain numbers of patient were evaluated with these examinations in the USA (5,6). Pre-treatment studies should be investigated further in the next survey using a revised data format.

Several interesting findings were demonstrated regarding methods of EBRT. The most common category of beam energies was 10–14 MV. A beam energy of ≥15 MV was used in <10% of patients. Concerning beam arrangement, the majority of the patients were treated with AP–PA opposite portals. The four-field technique was rarely applied. These treatment parameters are quite different from those demonstrated in the US PCS. In the US PCS survey, a beam energy of ≥15 MV was most frequently used, and 80% of patients were treated with the four-field technique (5). One might claim that the process of EBRT observed in the JPCS is inappropriate to achieve proper dose distribution. However, we consider that the physique of patients, such as antero-posterior (AP) separation should be taken into account to evaluate the appropriateness of EBRT. While we did not directly collect the data of AP separation, height and weight of the patients were documented in this study. Median height and weight demonstrated in this series should be quite a lot smaller than those of the US patients. We consider that simple beam arrangement using medium beam energy might be sufficient for the majority of Japanese patients. However, this survey also revealed that 20–30% of the patients of A2 and B2 institutions were treated with linear accelerators of <6 MV or Co-60 machines. When only these insufficient beams can be used we consider that the four-box field technique should be applied, even for small patients. Although RTOG79-20 ha

demonstrated the therapeutic value of extended field radiotherapy (16), it had not penetrated into clinical practice during the surveyed period. This was also shown in the 1992–1994 US PCS survey (5). An MLB was used in ~70% of the patients during a part of their treatment course of EBRT. The rate was higher than that of the US PCS (5). A difference in the beam arrangements mentioned above might be one of the reasons. It is difficult to add the MLB for the four-field technique. The present study showed that facility type significantly affected the use of the MLB. We speculate that this closely relates to the application of ICBT.

The US PCS has demonstrated that the use of ICBT significantly improved survival and reduced local failures over EBRT alone (17,18). Nevertheless, the utilization rate of ICBT was lower than expected in the present study. The utilization varied significantly according to the types of institution. We consider that this relates to the problems of institutional infrastructure of radiotherapy in Japan (19). Inoue revealed that brachytherapy equipment and the number of staff were insufficient especially in small non-academic institutions in Japan (19). This survey demonstrated that most patients were treated with HDR-ICBT in all institutional strata. In contrast, the latest US PCS survey (1996–1999) showed that only 12% of the patients were treated with HDR-ICBT (6). We consider that this is one of the most remarkable differences between the USA and Japan. Concerning brachytherapy sources, Co-60 was mostly used, followed by Ir-192. Ir-192 was used more frequently in A1 institutions compared with other strata. In 2002, a quality assurance committee of the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) recommended that old HDR machines with Co-60 sources should be replaced with the new type of HDR machines (20). In consequence, the use of Ir-192 sources would be increasing. It is important to note that ICBT applicator insertion was performed without any sedation for about half of the patients. Furthermore, the methods are deemed to be almost insufficient even for sedated patients, such as those receiving orally or rectally administrated NSAIDs. The American Brachytherapy Society (ABS) recommended routine conscious sedation for HDR-ICBT applicator insertions whenever possible (21). The fraction size of HDR-ICBT was within 800 cGy for almost all patients in this survey. This met the recommendation of the ABS and the Gynecologic Oncology Group (GOG) (21,22). The ABS proposed some other technical issues concerning HDR insertion, such as a method of normal tissue displacement, and dose specification (21). These issues should be monitored in detail to assess the quality of ICBT in the next JPCS survey.

We found that there was an obvious difference in total radiation dose of EBRT and HDR-ICBT between the USA and Japan. Although simple dose summation of EBRT and HDR-ICBT is not appropriate, the median total point A dose was 7480 cGy in the US PCS (5) and 5800 cGy in this JPCS series. We consider that this is also one of the remarkable differences in the treatment process between the two countries. This discrepancy was also observed in previously published clinical studies (23–26). We think that it may be closely related to the difference in standard treatment schedules in both countries. A Japanese guideline of radiotherapy has been established for the treatment of uterine cervical cancer by the Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Radiological Society (JRS) in 1987. Its English version came out in 1999 (27). Total doses of EBRT and HDR-ICBT used for patients in this survey were almost the same as the recommended schedules in the guideline. We consider that the majority of patients in this survey were treated in accordance with the guideline. In contrast, the ABS recommended doses are higher than those of the Japanese guideline (21). We consider that there are no conclusive clinical data regarding the optimum radiotherapy schedule for uterine cervical cancer. The outcome analysis using PCS data could be one of the measures to solve this problem.

Several investigators indicated that prolonged OTT reduced the pelvic control rate for patients with uterine cervical cancer (28,29). The ABS recommended that the OTT should be kept within 8 weeks (21). The median OTT of this study (49 days) was shorter than that of the US PCS (63 days) (5). However, the OTT exceeded 8 weeks for >30% of the patients in this JPCS series. Further effort should be made to shorten the OTT. The present analysis revealed that consecutive national holidays had a negative influence on the OTT. We consider this to be one of the important problems to be solved.

Approximately one-quarter of the patient received chemotherapy in this survey. Although several randomized clinical trials (RCTs) had failed to demonstrate any positive prognostic value of NAC prior to radiotherapy in the early 1990s (30), this study showed that not a small number of patients were treated with NAC. This indicated that the negative results had not yet penetrated into clinical practice during this period in Japan. On the other hand, concurrent chemoradiotherapy was applied to only 5% of the patients. In 1999, several RCTs demonstrated the survival benefit of concurrent chemoradiotherapy compared with radiotherapy alone (31). We consider that the increasing application of concurrent chemoradiotherapy will be observed in the next JPCS survey.

In conclusion, the JPCS established the national practice patterns of care for uterine cervical cancer patients treated with radiotherapy without planned surgery between 1995 and 1997 within Japan. This survey demonstrated that the institutional strata significantly affected several practice patterns. Some practice patterns were remarkably different from those established by the US PCS. Further improvements in pre-treatment evaluation including staging, and the method of EBRT and ICBT are necessary.

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Radical External Beam Radiotherapy for Clinically Localized Prostate Cancer in Japan: Changing Trends in the Patterns of Care Process Survey Between 1996-1998 and 1999-2001

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Abstract. *Background: This report presents results of a study delineating changing trends in radical external beam radiotherapy usage for prostate cancer between the 1996-1998 and 1999-2001 Patterns of Care Study (PCS) survey periods in Japan. Materials and Methods: Out of the 694 patients comprising the 1996-1998 and 1999-2001 PCS surveys, the current study analyzed data for 444 patients with clinically localized prostate cancer treated with external beam radiotherapy (1996-1998 PCS: 161 patients; 1999-2001 PCS: 283 patients). Results: Significantly higher percentages of patients had earlier T stages (T1-T2: 48.2%) and well-differentiated tumors (23.6%) between 1999 and 2001 than between 1996 and 1998 (T1-T2: 34.6%, well-differentiated tumors: 15.1%). Although only 5.9% of patients were treated with radiotherapy by their own choice during 1996-1998, a larger proportion (26.5%) chose this treatment during 1999-2001. The median radiation dose was 65.0 Gy during 1996-1998, increasing to 68.4 Gy during 1999-2001. Moreover, the incidence of total treatment doses of ≥70 Gy was higher during 1999-2001 (38.0%) than during 1996-1998 (17.5%). On the other hand, the percentage of patients receiving conformal therapy during 1996-1998 (49.1%) was almost the same as during 1999-2001 (50.2%). The median numbers of full-time equivalent (FTE) radiation oncologists increased in academic institutions (1.8 in 1996-1998; 2.4 in 1999-2001), while those in non-academic institutions remained low (0.5 in 1996-1998; 0.45 in 1999-2001). Conclusion: In Japan, fewer prostate cancer patients treated with radical external beam radiotherapy had advanced diseases. Increasing percentages of patients chose radiotherapy and received increased radiation doses, which might reflect the growing acceptance of radical external beam radiotherapy as a first-line treatment for prostate cancer in Japan.*

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Key Words: Patterns of Care Study, prostate cancer, radical external beam radiotherapy.

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, the PCS is important in 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, the PCS methodology was imported to Japan from the United States (5, 6). The Japanese PCS Working Group of Prostate Cancer started a nationwide process survey of patients treated with radiotherapy between 1996 and 1998 (7, 8). Subsequently, the Working Group conducted a second PCS of patients treated with radiotherapy between 1999 and 2001, and previously reported preliminary results of this second PCS for prostate cancer patients in Japan treated with radical external beam radiotherapy (9-11).

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Table I. *Patient and disease characteristics.*

		PCS		Significance (p)
		1996-1998 (n=161)	1999-2001 (n=283)	
Institutions		82	66	
Age	(median, years)	70.4(46.5-89.8)	72.0(49.7-92.2)	0.0677
	(mean±SD)	70.8±8.1	71.8±6.6	0.151
KPS	(median, %)	90(40-100)	90(50-100)	0.0108
	(mean+SD)	87.0±8.9	89.1±7.2	0.0252
	Missing	7	8	
Pretreatment PSA level (%)				
	median	21.95(0.3-900.0)	19.99(0.6-856.9)	0.9657
	mean+SD	51.5±93.5	54.1±99.5	0.5341
	<10	41/146(28.1%)	77/268(28.7%)	
	10-19.9	25/146(17.1%)	57/268(21.3%)	
	≥20	80/146(55.0%)	134/268(50.0%)	
	Missing	15	15	
Differentiation				
	Well	24/159(15.1%)	62/264(23.6%)	
	Moderate	79/159(50.0%)	93/264(35.2%)	0.0209
	Poor	46/159(28.9%)	93/264(35.2%)	
	Unknown	10/159(6.3%)	16/264(6.0%)	
	Missing	2	19	
Gleason combined score (%)				
	2-6	11/42(26.2%)	77/171(45.0%)	
	7	18/42(42.9%)	35/171(20.5%)	0.0074
	8-10	13/42(31.0%)	59/171(34.5%)	
	Missing	119	112	
T-stage (%)				
	TX-T0	1/159(0.6%)	10/272(3.7%)	
	T1	8/159(5.0%)	22/272(8.1%)	0.0022
	T2	47/159(29.6%)	109/272(40.1%)	
	T3-4	102/159(64.2%)	124/272(45.6%)	
	Uknown	1/159(0.6%)	7/272(2.6%)	
	Missing	2	11	
N-stage (%)				
	NX-N0	136/157(86.6%)	249/270(92.2%)	
	N1	18/157(11.5%)	15/270(5.6%)	0.0873
	Uknown	3/157(1.9%)	6/270(2.2%)	
	Missing	4	13	
Reason for selection of RT (%)				
	Patient choice	8/136(5.9%)	71/268(26.5%)	
	Advanced or high-risk disease	43/136(31.7%)	83/268(31.0%)	
	Medical contraindication	7/136(5.2%)	36/268(13.5%)	<0.0001
	Old age	37/136(27.2%)	44/268(16.5%)	
	Others	9/136(6.6%)	8/268(3.0%)	
	N/A or uknown	32/136(23.5%)	20/268(7.5%)	
	Missing	25	15	

KPS=Karnofsky performance status; PSA=prostate-specific antigen; RT=radiotherapy

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 in total cancer death also showed an increase from 0.9% in 1960 to 4.2% in 2000 (12). Since entering the prostate-specific antigen (PSA) era, prostate cancers are being detected at earlier stages of disease, offering these early-stage patients a better chance of successful treatment. Moreover, the use of radical external beam radiotherapy for prostate cancer has been rapidly increasing recently, as significant new radiation treatment planning technology and methodology has 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, the results of our analysis of changes in the process of care for prostate cancer patients, treated with radical external beam radiotherapy between the 1996-1998 and 1999-2001 survey periods in Japan, are presented.

Materials and Methods

The 1996-1998 PCS and the 1999-2001 PCS surveys in Japan contain detailed information about a total of 694 patients with prostate cancer treated with radiotherapy during the respective survey periods (1996-1998 PCS: 307 patients; 1999-2001PCS: 387 patients). The PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The Japanese PCS employed an original data format developed in collaboration with the American College of Radiology (ACR, Philadelphia, PA, USA). The PCS surveyors comprised 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 utilized an Internet mailing list including all the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee.

Out of the 694 patients comprising the 1996-1998 and 1999-2001 PCS 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: i) hormone-refractory cancer; ii) evidence of distant metastasis; iii) concurrent or prior diagnosis of any other malignancy; iv) prior radiotherapy; v) prior prostatectomy. A total of 444 patients with clinically localized prostate cancer treated with radical external beam radiotherapy met these eligibility criteria and were selected for analysis (1996-1998 PCS: 161 patients, 82 institutions; 1999-2001 PCS: 283 patients, 66 institutions).

The criteria for both the 1996-1998 and 1999-2001 institutional stratification have been detailed elsewhere (9, 13,14). In brief, the PCS stratified Japanese institutions into: academic institutions (university hospital or cancer center) and non-academic institutions (other hospitals).

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University, Japan (15). Statistical significance was tested using the Chi-square test,

Table II. *Treatment characteristics.*

	PCS		Significance (*p*)
	1996-1998 (n=161)	1999-2001 (n=283)	
Radiotherapy Energy (≥10 MV) (%)			
Yes	98/161(60.9%)	207/279(74.2%)	0.0035
Missing	0	4	
Were portal films or electric portal images used (%)			
Yes	–	211/280(75.3%)	
Missing	–	3	
All field treated each day (%)			
Yes	–	215/283(76.0%)	
CT-based treatment planning (%)			
Yes	130/161(80.8%)	241/282(85.5%)	0.1957
Missing	0	1	
Conformal radiotherapy (%)			
Yes	79/161(49.1%)	142/283(50.2%)	0.8223
Pelvic irradiation (%)			
Yes	69/161(42.9%)	102/283(36.0%)	0.156
Readiation dose (cGy)			
A+B (Total)			
Median (range)	6500(2200-7400)	6840(1400-8200)	<0.0001
(mean±SD)	6090.9±990.5	6600.8±732.0	<0.0001
A Median (Min-Max)	6500(2200-7400)	6600(1400-8200)	<0.0001
(mean±SD)	6250.9±976.8	6610.3±776.5	<0.0001
B Median (Min-Max)	5940(3400-7000)	6900(3000-8000)	<0.0001
(mean±SD)	5622.4±885.6	6587.5±684.1	<0.0001
Hormonal therapy (%)			
Yes	138/160(86.3%)	253/282(89.7%)	0.2685
No	21/160(13.0%)	29/283(10.3%)	
Unknown	1/160(0.63%)	0/283(0%)	
Missing	1	1	
Chemotherapy			
Yes	20/159(12.6%)	17/274(6.2%)	0.0603
No	137/159(86.1%)	255/274(92.3%)	
Unknown	2/159(1.3%)	2/274(0.7%)	
Missing	2	9	

Student's *t*-test and Mann-Whitney *U*-test. A probability level of 0.05 was chosen for statistical significance.

Results

Patient and disease characteristics. The patient and disease characteristics for the 1996-1998 and the 1999-2001 PCS surveys are shown in Table I. Significantly higher percentages of patients had earlier T stages (T1-T2: 48.2%, $p=0.0022$) and well-differentiated tumors (23.6%, $p=0.0209$) between 1999 and 2001 than between 1996 and 1998 (T1-T2: 34.6%, well-differentiated tumors: 15.1%). The reasons for selecting radiotherapy during these different periods are also listed in Table I. During 1996-1998, only 5.9% (8 out of 136) of the patients received radiotherapy through their own choice, compared with the 26.5% (71 out of 268) of patients who chose radiotherapy between 1999 and 2001. This change in the rate of "patient choice" was significantly different ($p<0.0001$).

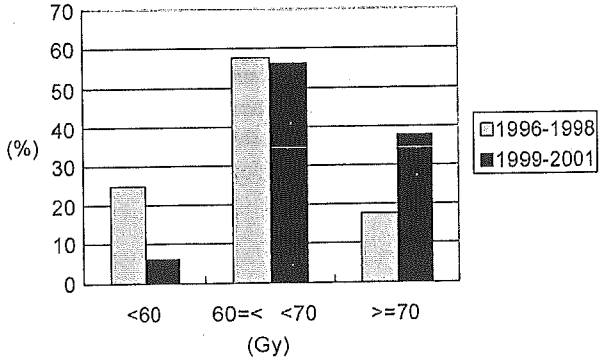

Figure 1. *Distribution of external irradiation doses for prostate cancer during the 1996-1998 and 1999-2001 survey periods.*

Treatment characteristics. The treatment characteristics are shown in Table II. The frequency of radiation energies ≥10 MV was significantly higher ($p=0.0035$) in the 1999-2001 PCS (74.2%) compared with the 1996-1998 PCS (60.9%). On the other hand, the rates of CT-based treatment planning ($p=0.1957$) and conformal radiotherapy administration ($p=0.8223$) did not differ significantly between the two survey periods. For instance, the frequency of conformal therapy during 1996-1998 (49.1%) was almost the same as during 1999-2001 (50.2%). The median radiation doses during 1996-1998 and 1999-2001 were 65 Gy and 68.4 Gy, respectively. Stratifying patients by total dosage revealed that 25% of patients received total radiation doses below 60 Gy during the 1996-1998 PCS *versus* 6.1% during 1999-2001, whereas 38% of patients received total doses ≥70 Gy during 1999-2001 *versus* 17.5% during 1996-1998 (Figure 1). Increased radiation doses were predominantly administered in non-academic institutions (Table II).

During both the 1996-1998 and 1999-2001 survey periods, hormonal therapy was commonly used before, during and after radiotherapy for a mean duration of 1.01±1.04 years and 1.31±1.03 years, respectively (83.6% of patients in 1996-1998; 88.9% of patients in 1999-2001, $p=0.2685$). In contrast, chemotherapy was infrequently administered during both periods (1996-1998: 12.6%; 1999-2001: 6.2%, $p=0.0603$).

Full-time equivalent (FTE) radiation oncologists. In the 1996-1998 PCS, the median number of full-time equivalent (FTE) radiation oncologists was 1.8 in academic institutions and only 0.5 in non-academic institutions. In the 1999-2001 PCS, the median number of FTE radiation oncologists in academic institutions rose slightly to 2.4, but remained low at 0.45 in non-academic institutions.

Discussion

The current study indicates that, in Japan, significantly higher percentages of patients had early primary stage disease and well-differentiated tumors during 1999-2001 than during 1996-1998. Theses results suggest that the likelihood of earlier-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 a first-line therapy for prostate cancer (16-18). Because of the prevailing use of PSA and the increasing number of patients treated with radiotherapy in Japanese institutions (19), the opportunities for treating early-stage prostate cancer patients with radical external beam radiotherapy should increase even more in the future.

The current study also revealed a remarkable change in the selection criteria for radiotherapy in Japan between the 1996-1998 and 1999-2001 survey periods. Only 6.6% of the patients were treated with radiotherapy through their own choice in 1996-1998, whereas 26.5% of patients chose radiotherapy in 1999-2001. External beam radiotherapy did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an inadequate number of radiation oncology centers prevented earlier dissemination of this type of therapy. However, in conjunction with significant improvements in the availability of new radiation treatment planning technology and methodology, Japanese patients are becoming increasingly aware of the effectiveness of radiotherapy for prostate cancer (20). Therefore, the increasing percentage of patients choosing radiotherapy might reflect growing acceptance of radical external beam radiotherapy as a first-line therapy for prostate cancer patients in Japan.

Moreover, the radiotherapy strategy appears to have changed between the 1996-1998 and 1999-2001 survey periods. Radiation doses were higher in the 1999-2001 PCS (median, 68.4 Gy) than in the 1996-1998 PCS (65 Gy). The percentage of patients receiving radiation doses below 60 Gy dropped from 25.0% during 1996-1998 to only 6.1% during 1999-2001 (Figure 1). Conversely, the percent of patients treated with total doses of >70 Gy increased from 17.5% during 1996-1998 to 38.0% during 1999-2001, indicating that lower radiation doses were more common in the first period, while higher doses prevailed in the second. The U.S. PCS results indicate that many prostate cancer patients have been treated with total doses of ≥70 Gy in the United States (18, 21). The use of increasing radiation doses in Japan might reflect the widespread dissemination of clinical trial results (22, 23), as well at a growing acceptance by radiation oncologists and urologists of radical external beam radiotherapy as first-line treatment for prostate cancer (24).

However, the national practice process of radiotherapy in Japan reflects structural immaturity, especially in terms of equipment and personnel. The rates of CT-based treatment planning and conformal radiotherapy administration, technology that not only improves the target volume dose distribution but also concomitantly reduces the normal tissue dose (25), did not significantly differ between the 1996-1998 and 1999-2001 survey periods. It is particularly noteworthy that the conformal therapy rates remained low (approximately 50%) during these periods. The 1999 U.S. PCS indicated that 80% of patients were treated with conformal therapy in the United States (22). With regard to personnel, the median number of FTE radiation oncologists slightly increased in academic institutions, but remained low in non-academic institutions. However, publication data documenting a progressive increase in the number of prostate cancer patients treated with radiotherapy has increased in every institution (19) demonstrates a need for Japanese institutions, both academic and non-academic, to upgrade their radiation equipment and to recruit more radiation oncologists.

By comparing the results of the 1996-1998 PCS and 1999-2001 PCS surveys, we can delineate the changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. The study data indicate a trend towards less advanced diseases from 1999-2001 to 1996-1998 and suggest that radical external beam radiotherapy is gaining acceptance as first-line treatment for prostate cancer in Japan.

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Radical External Beam Radiotherapy for Clinically Localized Prostate Cancer in Japan: Differences in the Patterns of Care between Japan and the United States

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Abstract. *The current study focused on the differences in the patterns of care between Japan and the United States for clinically localized prostate cancer patients treated with radical external beam radiotherapy. Materials and Methods: Results from the 1999-2001 Japanese Patterns of Care Study (PCS) survey were compared with those of the 1999 PCS in the United States. In addition, the changing trends in the patterns of care between Japan and the United States were also analyzed. Results: Patients in Japan were found to have more advanced primary disease than patients in the United States: with higher PSA levels, advanced T stages and a Gleason combined score of 8-10. These patient characteristics in both countries have not changed from previous PCS studies. The prescribed dose of radiotherapy to the primary tumor was significantly higher in the United States and there was a rapid increase in patients treated with higher prescription dose levels (≥72 Gy) in the United States, while only a small number of patients received these dose levels in Japan. Hormonal therapy was used more frequently in Japan than in the United States, and the percentage of patients receiving hormonal therapy has remained high for several years in Japan. Furthermore, most of the patients in the favorable risk group in Japan were treated with hormonal therapy, contrary to those in the United States. Conclusion: Japanese prostate cancer patients treated with radical external beam radiotherapy were found to have more advanced disease than those in the United States and these trends have continued for the last few years. Patterns of care for prostate cancer in Japan are considerably different from those in the United States, especially in terms of the radiation dose and the use of hormonal therapy. Moreover, the changing trends in the patterns of care are also different between the two countries.*

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Key Words: Patterns of care study, prostatic carcinoma, radiation therapy, hormone therapy.

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish national practice processes for selected malignancies over a specific time-period (1-3). In addition to documenting the practice process, the PCS is important in developing and disseminating national guidelines for cancer treatment that help promote a high-quality process of care 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, the PCS was imported to Japan from the United States (5, 6). The Japanese PCS Working Group of Prostate Cancer started a nationwide survey for patients who underwent radiotherapy between 1996 and 1998 (7, 8). Subsequently, a second PCS of Japanese patients treated between 1999 and 2001 was conducted, for which the results concerning radical external beam radiotherapy for prostate cancer patients have been reported (9-12).

In Japan, the number of deaths due to prostate cancer has been increasing steeply, especially in elderly patients. The proportion of prostate cancer deaths in total cancer deaths also increased from 0.9% in 1960 to 4.2% in 2000 (13). Since

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entering the prostate-specific antigen (PSA) era, clinicians are detecting disease at an earlier stage, and the rates of successful treatment for early-stage patients are at historical highs. Moreover, radiotherapy has become much more common because a significant amount of new treatment planning technology and methodology has become available. Therefore, the optimal management of radiotherapy for prostate cancer patients has become a major concern in Japan. However, national practice processes have not been properly evaluated due to limited information. In July 2002, PCS audits for prostate cancer patients treated between 1999 and 2001 commenced, and data were collected for 283 patients who received radical external beam radiotherapy. Here, the results of the Japanese PCS study were compared with those of the U.S. PCS study and the differences in the patterns of care between Japan and the United States were identified. In addition, the changing trends in the patterns of radiotherapy for prostate cancer in these countries were compared.

Materials and Methods

The 1999-2001 Japanese PCS consisted of an extramural audit survey of 66 institutions using stratified 2-stage cluster sampling (2). Data were collected for 528 patients with prostate cancer who received radiotherapy. The PCS group developed an original data format in collaboration with the American College of Radiology (ACR, Philadelphia, PA, USA). The following patient eligibility criteria were used: prostatic adenocarcinoma without evidence of distant metastasis; radiotherapy between 1999 and 2001 with no prior radiotherapy; no concurrent or prior diagnosis of another malignancy. Patients who had prior prostatectomy and patients with hormone-refractory cancer were excluded from the analysis. The PCS surveyors were 20 radiation oncologists from academic institutions. For each institution surveyed, one radiation oncologist visited and surveyed data by reviewing the patients' charts. In order to validate data quality, the PCS utilized an internet mailing list including all the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee. Among the 528 patients identified, 283 patients who received radical external beam radiotherapy were selected for analysis, and the results for these patients are reported.

In the current study, the results of the PCS in Japan (1999-2001) were compared with those of the PCS in the United States (1999). Regarding risk, the 1999 U.S. PCS identified the following as adverse features: PSA >10 ng/mL; Gleason combined score >6; and T stage ≥3. On this basis, the U.S. PCS categorized patients into the following risk groups: favorable – zero adverse features; intermediate – one adverse feature; unfavorable – 2 or more adverse features (14). Because data for the Gleason combined score were missing for 40% (112/283) of our study patients, we substituted tumor differentiation for the Gleason combined score as one of the adverse features. Thus, the set of adverse features for Japanese patients was the following: PSA >10 ng/mL; poorly-differentiated disease; T stage ≥3. Japanese patients were then categorized into the following risk groups: favorable – zero adverse features; intermediate – one adverse feature; unfavorable – 2 or more adverse features.

Table I. *Patient and disease characteristics: comparison of PCS results between Japan and the United States*

	Japan/1999-2001	United States/1999*
No. of institutions	76	58
No. of patients	283	392
Patient characteristics		
Age (years)		
Median (Min-Max)	72 (49-92)	71.0 (49-86)
Mean	71.8±6.6	70.8
Pretreatment PSA level (ng/ml)		
Med (Min-Max)	20.0 (0.3-856.9)	-
mean±SD	90.0±7.1	
<10	77/268 (28.7%)	60.5%
10-20	57/268 (21.3%)	23%
≥20	134/268 (50.0%)	15.50%
Missing	15	1%
Gleason combined score		
2-6	77/171 (45.0%)	54.3%
7	35/171 (20.5%)	25.8%
8-10	59/171 (34.5%)	18.8%
Missing	112	1.1%
T stage		
TX-T0	10/272 (3.7%)	7.8%
T1	22/272 (8.1%)	43.9%
T2	109/272 (40.1%)	33.7%
T3-4	124/272 (45.6%)	6.8%
Unknown	7/272 (2.6%)	7.8%
Missing	11	
Risk group (%)		
Favorable	36/248 (14.5%)**	38.3%***
Intermediate	87/248 (35.1%)**	37.7%***
Unfavorable	125/248 (50.4%)**	24.0%***
Missing	35	-
Treatment characteristics		
Energy (>10 MV) (%)		
Yes	197/265 (74.3%)	73.0%
Missing	18	
CT-based treatment planning		
Yes	241/282 (85.5%)	95.0%
Missing	1	
Conformal therapy		
Yes	120/279 (43.0%)	80.0%
Missing	4	
Radiation dose (cGy)		
Median (Min-Max)	6840 (1400-8200)	-
mean±SD	6602.9 + 731.1	-
Missing	1	
Higher prescription dose levels (≥72 Gy)		
Yes	21/282 (7.5%)	43.0%
Missing	1	
Administration of pelvic irradiation		
Yes	93/282 (33.0%)	23.2%
Missing	1	
Hormonal therapy		
Yes	253/282 (89.7%)	51.3%
Missing	1.0	

*Zelefsky *et al:* Int J Radiat Oncol Biol Phys *59*: 1053-1106, 2004. PSA = prostate-specific antigen. **Favorable = zero adverse feature; Intermediate = one adverse feature; Unfavorable = 2 or more adverse features. Adverse features: PSA >10 ng/mL; Gleason combined score >6; and T stage ≥3. ***Favorable = zero adverse features; Intermediate = one adverse feature; Unfavorable = 2 or more adverse features. Adverse features: PSA >10 ng/mL; poorly-differentiated; and T stage ≥3.

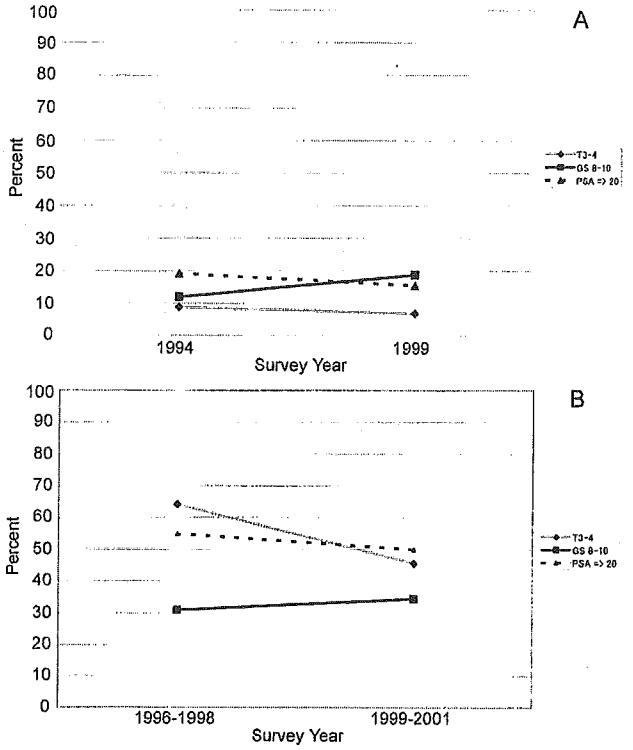

Figure 1. *Changing trend in disease characteristics in Japan and the United States. In the United States, the proportions of T3-4, Gleason sore of 8-10, and PSA ≥20 ng/mL were all below 20% in the periods 1994 and 1999 (Figure 1A). On the other hand, in Japan, the proportions of these adverse factors were all over 30% in the periods 1996-1998 and 1999-2001 (Figure 1B).*

The differences in the changing trends in the patterns of care between Japan and the United States were also analyzed. Results of the 1996-1998 PCS in Japan (7) and the 1994 PCS in the United States (14, 15) were used as a baseline for the patterns of care.

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University, Japan (16). Statistical significance was tested using the Chi-square test and the Student's *t*-test. A p value <0.05 was considered statistically significant.

Results

Comparison of patient characteristics between Japan and the United States. Comparisons of patient characteristics between Japan (1999-2001) and the United States (1999) are shown in Table I. The patients in Japan were found to have more advanced primary disease than those in the United States with higher PSA levels (≥20 ng/ml), advanced T stages (T3-4) and a Gleason combined score of 8-10. Regarding the risk groups, the percentage of Japanese patients with favorable, intermediate and unfavorable tumors were 14.5%, 35.1% and 50.4%, respectively, compared to 38.3%, 37.7% and 24.0%, respectively, in the United States.

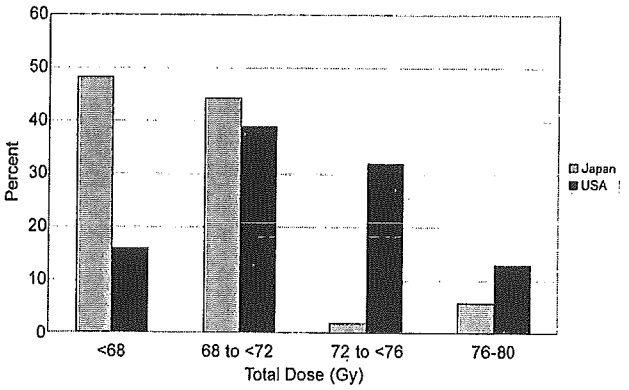

Figure 2. *Radiation dose distribution in Japan and the United States. The distributions of total dose to the prostate in the United States were significantly higher ($p<0.00001$) than those in Japan.*

By comparing the results from the previous PCS (1996-1998 Japan PCS and 1994 U.S. PCS), Japanese patients have continued to exhibit advanced disease for several years, while the proportion of U.S. patients with advanced disease has remained low from 1994 to 1999 (Figure 1A and 1B).

Comparison of patterns of radiotherapy. With regard to technique, conformal radiotherapy was administered to 43% of the patients in Japan and to 80% of the patients in the United States (Table I). The distributions of total radiation dose to the prostate in the United States were significantly higher ($p<0.00001$) than those in Japan (Figure 2). In the United States, there was a rapid increase in patients treated with higher prescription dose levels (≥72 Gy) compared to the 1994 PCS results and almost half (44.5%) of patients were treated with these higher doses in 1999 (Figure 3A). In contrast, only a small number of patients (7.5%) received these dose levels in Japan between 1996-1998 and 1999-2001 (Figure 3B). Whole pelvic radiation therapy (WRT) was less frequently performed in both countries (33% of the patients in Japan and 23.2% of the patients in the United States).

The analysis of changing trends in the higher prescribed radiation doses and radiation field (use of WRT) indicates that a marked change in these parameters occurred in the United States between 1994 to 1999, while only moderate or minor changes occurred in Japan between 1996-1998 and 1999-2001 (Figure 3A and 3B).

Comparison of patterns of hormonal therapy. With regard to hormonal therapy, 89.7% of the patients in Japan and 51.3% in the United States received hormonal therapy. The mean duration of hormonal therapy in Japan was 1.4±1.0 years. The percentages of patients with favorable, intermediate and unfavorable tumors treated with hormonal therapy in Japan were 72.0%, 91.8% and 91.1%, respectively, compared to

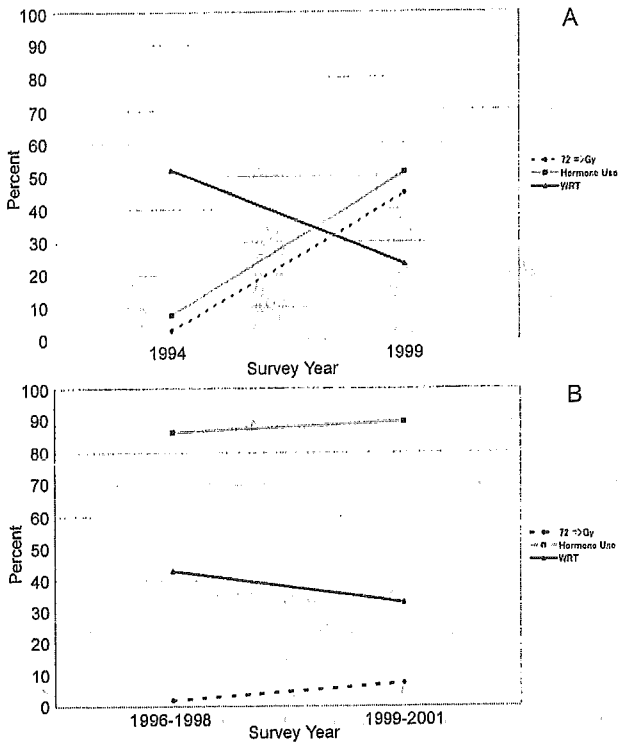

Figure 3. *Changing trends in the treatment characteristics in Japan and the United States. There were marked changes concerning the percentage of higher prescribed radiation doses (≥72 Gy), whole pelvic radiation therapy (WRT) and hormone use in the United States from 1994 to 1999 (Figure 3A). In contrast, only moderate or minor changes in the proportions of patients undergoing these treatments were observed in Japan between 1996-1998 and 1999-2001 (Figure 3B).*

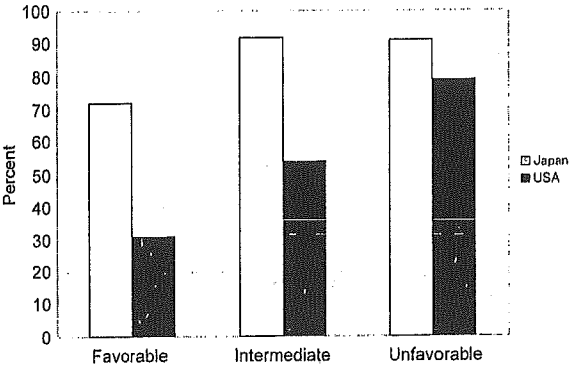

Figure 4. *Hormonal therapy distribution according to the risk groups for prostate cancer patients in Japan and in the United States.*

31%, 54% and 79%, respectively, in the United States (Figure 4). Most of the patients (72.0%) in the favorable risk group in Japan were treated with hormonal therapy, while only 31% of these patients received hormonal therapy in the United States. On the other hand, 80-90% of patients in the unfavorable risk group were treated with radiotherapy in conjunction with hormonal therapy in both Japan (91.1%) and the United States (79%).

The analysis of changing trends in the use of hormone therapy indicated that a rapid increase was observed in the United States from 1994 to 1999, while only minor changes in the proportion of patients receiving hormonal treatment were observed in Japan between 1996-1998 and 1999-2001 (Figure 3A and 3B).

Discussion

The results of the current study indicate that patients in Japan had more advanced diseases compared to patients in the United States. Japanese patients had higher pretreatment PSA levels, advanced T stage and a Gleason score of 8-10 such that the proportion of Japanese patients in the unfavorable risk group was 50.4% compared to 24% in the United States. Moreover, these trends for more advanced disease in Japan compared to the United States continued for several years (Figure 1A and 1B). These results indicate that higher proportions of patients with advanced disease were treated with radical external beam radiotherapy in Japan than in the United States. However, it is not known whether these differences between patients in Japan and the United States resulted from differences in access to medical care or to biological differences within the tumors themselves. Further investigation of the different disease characteristics between individuals in the two countries would be informative.

The current study also indicates that there were many differences in the patterns of radiotherapy between Japan and the United States. The radiation doses employed in the United States were significantly higher than those used in Japan, with almost half (44.5%) of the patients in the United States being treated with higher prescription dose levels (≥72 Gy). This practice in the United States probably reflects the penetration into clinical practice of various reports published in the 1990's indicating that higher radiation doses were associated with a statistically significant improvement in outcome (17, 18). On the other hand, a minority of patients in Japan were treated with higher doses (≥72 Gy), with only 7.5% receiving these higher doses in the period 1999-2001. One reason for this may be the lower incidence of conformal therapy. Conformal radiotherapy was administered to 85% of patients in the United States while only 43% of the Japanese patients received this treatment. The processes in Japanese institutions were closely related to structural

immaturity in terms of equipment (9-12). Therefore, in order to provide good quality radiotherapy in Japan, facilities need appropriate treatment planning capability. Modern radiotherapy requires CT-based treatment planning and conformal therapy in order to improve the target dose distribution, while concomitantly reducing the dose to normal tissues (19). Another reason may be the high incidence of hormonal therapy in Japan. At present, many Japanese radiation oncologists may consider the higher dose levels (≥72 Gy) unnecessary for prostate cancer patients when combined with long-term hormonal therapy.

With regard to the patterns of hormonal therapy, the combination of radiotherapy with hormonal therapy was almost routinely (89.7% of the patients surveyed) administered to Japanese patients treated between 1999 and 2001 compared to 51.3% in the United States in 1999. The percentage of patients receiving hormonal therapy remained high in Japan in the periods 1996-1998 and 1999-2001, while there was a rapid increase in the use of hormonal therapy in the United States from 1994 to 1999.

Furthermore, the administration of hormonal therapy to favorable risk patients was considerably different in Japan compared to the United States as only 30% of these patients in the United States, were treated with hormonal therapy (Figure 1). Several studies from the United States have indicated that radical radiotherapy alone could control the disease in patients with a favorable risk status. Zietman *et al.* 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 (20). Hanks *et al.* found that prostate cancer patients with a pretreatment PSA level <10 ng/ml did not benefit from a dose escalation above 70 Gy (21). Therefore, radical external beam radiotherapy without hormonal therapy has been the primary treatment for patients in the United States with favorable risk diseases. On the other hand, 72% of the patients in the favorable risk group in Japan were treated with long-term hormonal therapy (Figure 1). The high rate of health insurance coverage may explain the frequent administration of hormonal therapy in Japan (22). However, hormonal therapy was found to be unnecessary for favorable risk patients in the United States (20, 21). Therefore, radical external beam radiotherapy without hormonal therapy should also be the treatment of choice for favorable risk patients in Japan.

In conclusion, a comparison of the Japanese and U.S. PCS results revealed several differences in the patterns of care between these two countries. Higher proportions of patients with advanced disease were treated with radical external beam radiotherapy in Japan compared to the United States, and this trend has continued for the last few years. The patterns of care for prostate cancer in Japan are significantly different from those in the United States, especially in terms of radiation dose and the use of hormonal therapy. Moreover, the changing trends in the patterns of care are also different between these countries. In the United States, radiotherapy for prostate cancer has become widely applied as an established treatment, while it was still developing in Japan during the period of the national survey. Repeat surveys and point-by-point comparisons with results from other countries, such as the United States, will demonstrate how external beam radiotherapy for prostate cancer has been developed and optimized for patients in Japan.

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CLINICAL ARTICLE

Clinical aspects and prognosis of pelvic recurrence of cervical carcinoma

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Abstract

Objective: To identify which patients with locally recurrent cervical carcinoma are potentially curable. *Method:* A total of 664 stage IB-IVA patients were examined following surgery or radiotherapy. *Result:* Among the 664 patients, 193 (29%) developed recurrence. Sixty-seven (35%) of these recurrences were located in the pelvis alone. Among these 67 recurrences, 24 (35%) were central recurrences and the remaining 43 (65%) were pelvic side-wall recurrences. Of the 24 patients with central recurrences, 8 were salvaged. Of these 8 patients, 3 underwent pelvic exenteration, and 5 received optimal radiotherapy. The recurrent tumor in these 5 survivors who received radiotherapy had consisted of a small (<2 cm) tumor. All 43 patients with pelvic wall recurrence developed progressive disease. *Conclusion:* The following patients are potentially curable: patients with a resectable, centrally located tumor who are candidates for pelvic exenteration, and patients with a small central recurrence for whom complete radiation therapy is feasible.

1. Introduction

Over the past 20 years, there has been remarkable progress in diagnostic imaging and in the identification of serial tumor markers that can detect tumor recurrence at an early stage, and advances in new chemotherapeutic agents and new surgical and radiotherapeutic approaches have been introduced. Despite these advances, the overall prognosis of patients with locally recurrent cervical cancer is very poor and optimal treatment for recurrent disease is still problematic [1]. In nearly all cases, treatment for local recurrence should be considered palliative, and a very small proportion of these patients is cured. In fact, 10–15% of patients with stage IB-IIA disease who undergo radical hysterectomy will develop recurrence, and 50–60% of these recurrences will be located in the

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pelvis alone [2,3]. Also, 20–50% of patients with stage II–III disease who undergo radiotherapy will relapse locally [4,5]. This retrospective study was undertaken to identify which patients with locally recurrent cervical carcinoma are potentially curable, to design new therapeutic strategies for dealing with these locally recurrent cervical carcinoma cases in the future, and to improve their prognosis.

2. Patients and methods

2.1. Patients

The medical records of 664 patients with stage IB-IVA cervical carcinoma who were treated at the Gynecology Division of National Cancer Center Hospital in Tokyo, between 1989 and 2000 were reviewed. Four patients who were lost to follow-up and 14 patients with persistent disease were excluded. All of the patients were staged according to the FIGO staging system, and histological typing was performed according to the criteria of the WHO International Histological Classification of Tumors. Follow-up continued through September 2003. Survival curves were obtained by the Kaplan–Meier method, and patients who died of other causes were included as deaths in the survival analysis.

2.2. Treatment

Our standard treatment for primary invasive cervical carcinoma was as follows. Patients with stage IB, IIA or IIB cervical carcinoma were appropriately treated with either radical hysterectomy or radiotherapy with equivalent results. In patients with lymph node metastasis or parametrial invasion (pT2b), following surgery, adjuvant radiotherapy to the whole pelvis was administered. The daily dose ranged from 1.8 Gy to 2 Gy, 5 fractions/week, and the dose for the whole pelvis was 50 Gy with opposed anterior and posterior fields. Primary radiotherapy was composed of external-beam plus high-dose-rate intracavitary irradiation. A remote afterloading system of 192Ir with Tandem and Ovoid applicators was employed. Extra-beam radiotherapy with a total dose of 50 Gy was administered over 5 weeks in daily fractions to the pelvis, and the applicator (6 Gy/A-point) was applied with 4–5 insertions at weekly intervals. Various combinations of external and intracavitary irradiation were tailored based on the size and distribution of the tumor. The choice of treatment modality depended on the age of the patient, presence of comorbid conditions, and histologic subtype. For patients with advanced stage carcinoma of FIGO IIIA, IIIB, or IVA, primary radiotherapy using external-beam radiation and high-dose-rate brachytherapy was employed. Following the primary treatment, asymptomatic patients underwent pelvic examination, Pap smear, chest radiograph, and determination of serial tumor markers every 4–6 months. Symptomatic patients underwent appropriate examinations where indicated by ultrasonography, computed tomography, and/or magnetic resonance imaging.

Our management of local recurrence of cervical carcinoma was generally as follows: (1) patients with recurrent disease arising in the previously irradiated pelvis received chemotherapy or palliative care, except for patients with central recurrence who were candidates for pelvic exenteration; (2) radiotherapy was used to treat recurrent disease in patients who had no prior history of receiving radiotherapy.

3. Results

3.1. Patient characteristics

The clinical characteristics of the 664 patients with primary cervical carcinoma are summarized in Table 1. Among the 353 patients with stage IB disease, surgery was performed in 326 patients (92%), of whom 89 (27%) subsequently received postoperative adjuvant radiotherapy. The remaining 27 patients (8%) with stage IB disease received primary radiotherapy. Of the 65 patients with stage IIA disease, surgery was performed in 45 patients (69%), of whom 18 (40%) subsequently received

Table 1 Patients characteristics, n=664

Mean age	52 years	(range, 22–86)
Histologic subtypes	Squamous	493 (74%)
	Adeno	117 (18%)
	Adenosquamous	38 (6%)
	Others	16 (2%)
FIGO stage	IB	353 (53%)
	IIA	65 (10%)
	IIB	108 (16%)
	IIIA	3 (0.5%)
	IIIB	119 (18%)
	IVA	16 (2.5%)
Treatment modalities	Surgery	471 (71%)
	Radical hysterectomy	419
	Simple hysterectomy	46
	Pelvic exenteration	6
	Postoperative adjuvant radiotherapy	156
	Radiotherapy	193 (29%)

postoperative adjuvant radiotherapy, and primary radiotherapy was performed in 20 patients (31%). Of the 108 patients with stage IIB disease, surgery was performed in 79 patients (73%), of whom 43 (54%) subsequently received postoperative adjuvant radiotherapy, and primary radiotherapy was performed in 29 patients (27%). Among the 117 patients with stage IIIA, IIIB, and IVA disease, 96 patients were treated with primary radiotherapy using external-beam radiation and high-dose-rate brachytherapy as described above, and 21 patients received the surgical approach. The 664 patients were followed for 1–166 months, and the median follow-up time was 68 months.

3.2. Survival and prognosis

The cumulative 5-year survival rate among patients with stage IB, IIA, IIB, IIIA, IIIB, or IVA primary cervical carcinoma was 84%, 78%, 65%, 67%, 54%, and 38%, respectively. Among the 664 patients, 193 patients (29%) suffered tumor recurrence. Of these 193 recurrences, 67 (35%) were located in the pelvis alone, 109 (56%) outside the pelvis, 13 (7%) intra- and extra-pelvis, and the remaining 4 in an unknown location.

Of the 67 patients with pelvic recurrence, 26 patients had FIGO stage IB disease, 6 had stage IIA, 13 had stage IIB, 1 had stage IIIA, 18 had stage IIIB, and 3 had stage IVA. Thirty-nine patients underwent radical hysterectomy, 1 underwent simple hysterectomy, and 2 underwent total pelvic exenteration. In total, 42 patients (63%) received surgical treatment. Among them, adjuvant external beam radiotherapy to the whole pelvis (total dose of 50 Gy) was administered postoperatively to the 12 patients (29%) who had parametrial invasion and/or lymph node metastasis. The remaining 25 patients (37%) received primary radiotherapy composed of external-beam plus high-dose-rate intracavitary irradiation. The histologic subtypes were squamous cell carcinoma in 46 cases (67%), adenocarcinoma in 14 cases (21%), the adenosquamous type in 4 cases (6%), the glassy cell type in 2 cases (3%), and the undifferentiated type in one case (1%).

Table 2 summarizes the location of the 67 pelvic recurrences, whether the recurrent tumor was located inside or outside of the previously irradiated field among patients who had undergone radiotherapy for treatment of primary cervical carcinoma, the treatment modality for the recurrence, and outcome. The 24 patients with central recurrence had undergone the following treatments for their primary cervical carcinoma: 11 patients had undergone surgery alone, 2 patients had undergone surgery followed by postoperative adjuvant radiotherapy, and the remaining 11 patients had undergone primary radiotherapy alone. Therefore, 13 patients with central recur-

Table 2 Clinical states of patients with pelvic recurrence, n=67

Location of tumor	n (%)	Prior radiotherapy	n	Treatment modality for recurrence	n	Status[a]	n (mo)[b]
Central pelvis	24 (35%)	Outside the irradiated field[c]	4	Radiotherapy	4	NED[d]	1 (71)
		Inside the irradiated field[e]	9	Radiotherapy	3	NED	1 (62)
				Pelvic exenteration	2	NED	1 (142)
				Palliative surgery	2		
				Not done	2		
		Not done[f]	11	Radiotherapy	8	NED	3 (70, 78, 86)
				Pelvic exenteration	3	NED	2 (61, 24)
Pelvic wall involvement	43 (65%)	Inside the irradiated field	25	Radiotherapy	5		
				Pelvic exenteration	1		
				Palliative surgery	1	AWD[g]	1 (34)
				Chemotherapy	6	AWD	2 (17, 23)
				Not done	12		
		Not done	18	Radiotherapy	9		
				Pelvic exenteration	2		
				Chemotherapy	4		
				Not done	3		

[a] Blank represents dead of disease.
[b] Survival after initial treatment.
[c] The recurrent tumor was located outside the field of irradiation that had been performed for the initial treatment.
[d] No evidence of disease.
[e] The recurrent tumor was located inside the field of irradiation that had been performed for the initial treatment.
[f] Patients who did not receive radiotherapy for treatment of initial therapy.
[g] Alive with disease.

rence had previously undergone radiotherapy for treatment of their primary carcinoma. Nine of the centrally recurrent tumors arose in the previously irradiated field, while 4 arose outside the irradiated field. These 4 tumors were located in the lower vagina outside the previously irradiated field. Among the 24 patients with central recurrence, 8 patients (33%) were alive without disease after salvage therapy and the remaining 16 patients died of disease.

The 43 patients with recurrence with pelvic wall involvement had undergone the following treatments for their primary cervical carcinoma: 18 patients had undergone surgery alone, 11 patients had undergone surgery followed by postoperative adjuvant radiotherapy, and 14 patients had undergone primary radiotherapy alone. All 43 patients with recurrent tumor involving the pelvic side-wall developed tumor progression. Forty patients died of disease, and 3 were alive with disease and were receiving palliative care at the end of the follow-up period. After tumor recurrence in the pelvic-side-wall, 10 patients were treated with one of the following chemotherapy regimens: cisplatin (Briplatin; Bristol-Myers Squibb, NY, USA) + 5-fluorouracil(5-FU; Kyowa Hakko Kogyo, Tokyo, Japan), bleomycin hydrochloride (Bleomycin; Nippon Kayaku, Tokyo, Japan) + vincristine sulfate (Oncovin; Eli Lilly Japan, Kobe, Japan) + mitomycin c (Mitomycin; Kyowa Hakko Kogyo, Tokyo, Japan) + cisplatin, carboplatin (Paraplatin; Bristol-Myers Squibb, NY, USA) + irinotecan hydrochloride (Campto; Yakult Honsya, Tokyo, Japan), or paclitaxel (Taxol; Bristol-Myers Squibb, NY, USA) + carboplatin. Among the 67 patients with pelvic recurrence, the 5-year survival rate after the development of pelvic recurrence was 15% and the median survival time was 12 months.

Table 3 shows details of the clinicopathological states of the 8 survivors who suffered central recurrence and were alive without disease after salvage therapy. Four patients could receive complete radiation therapy composed of external beam plus brachytherapy; 3 of the 4 patients had no prior history of radiotherapy (Case 4, 5, and 6) and one had a recurrent tumor originating outside the previously irradiated field (Case 2). These 4 tumors were less than approximately 2 cm in diameter and/or spread on the surface of the vaginal wall. Three of the 8 survivors had undergone pelvic exenteration for treatment of the recurrent tumor. Two of them had not received prior radiotherapy, and their histologic subtypes were glassy cell type and endometrioid adenocarcinoma (Case 7 and 8). The remaining one patient who was a candidate for pelvic exenteration, received intracavitary brachytherapy even though she had a history of prior radiotherapy because she refused surgery (Case 2). Although she was alive without disease for 50 months at the end of follow-up, she suffered severe radiation cystitis as a late complication of irradiation at 12 months.

4. Discussion

Our review demonstrated that patients with locally recurrent cervical carcinoma have a poor outcome, similar to previous studies. Only 13% of the recurrent patients with IB-IIB disease and 11% of the recurrent patients with IIIB disease were cured. According to the results of our study, patients who are potentially curable are limited to the following recurrence patterns.

First, a recurrent tumor that is located centrally in the pelvis, is associated with better

Table 3 Clinical states of patients with no evidence of disease after salvage therapy for cervical carcinoma

Patient no.	FIGO stage	Histological subtype	Primary therapy	Recurrent site	Recurrence free interval (mo)	Salvage therapy	Survival after recurrence (mo)
1	IIA	Squamous	Radiotherapy	Cervix, Bladder	7	Anterior exenteration	135
2	IIIB	Squamous	Radiotherapy	Vaginal wall	21	Radiotherapy	50
3	IB	Adenosquamous	Radical hysterectomy+ radiotherapy	Vaginal stump	12	Radiotherapy	50
4	IB	Squamous	Radical hysterectomy	Vaginal stump	7	Radiotherapy	79
5	IB	Squamous	Radical hysterectomy	Vaginal wall	2	Radiotherapy	76
6	IB	Adenosquamous	Radical hysterectomy	Vaginal wall	18	Radiotherapy	52
7	IB	Adenocarcinoma	Radical hysterectomy	Rectum, Bladder	26	Total exenteration	35
8	IIIb	Glassy cell	Anterior exenteration+ chemotherapy	Rectum	44	Posterior exenteration	80

prognosis. All of our patients in whom the tumor was fixed to the pelvic side-wall developed progressive disease. Although the patients who had not previously received radiotherapy could receive optimal doses of radiation, there were no long-term survivors. As pelvic exenteration is not indicated for tumors involving the pelvic wall, and as chemotherapy for recurrent cervical cancer should be considered as a palliative treatment, no curative approach exists for recurrence in the pelvic side-wall. It has been discussed that pelvic side-wall recurrence which indicates metastatic systemic disease, is biologically different from central recurrence. On the other hand, the efficacy of combined surgery and radiotherapy on small-size lateral recurrences was reported, and was equivalent to its efficacy on central recurrences [6,7]. In this method, maximum tumor resection and intraoperative radiotherapy using the applicator of high-dose-rate brachytherapy are performed. This method is not widely accepted, and further studies are needed.

Secondly, based on the results of the present study, patients with central recurrence who are either (1) a candidate for pelvic exenteration or (2) a candidate for complete radiotherapy, are potentially curable. Pelvic exenteration is the only potentially curative approach for central recurrence in patients who had previously undergone radiotherapy. The overall 5-year survival rate after exenteration varied between approximately 20 and 60%, and the operative mortality was less than 10% in the literature [8–11]. In our 27 years' experience in performing pelvic exenteration in patients with recurrent cervical carcinoma (between 1973 and 2000) including the patients in the present study, the 5-year survival rate was 36% and the procedure-related mortality was 6%. The preoperative status of the patient is related to survival. Leg edema, sciatic pain, and urethral obstruction in patients with recurrent cervical carcinoma almost always indicate pelvic side-wall involvement and lead to abortion of extensively planned procedures. A short interval from primary therapy to recurrence (within one year) and nodal metastasis are also poor prognostic factors [1,12]. As for histologic subtypes, Crozier et al. [13] reported that central recurrence of cervical adenocarcinoma could be successfully treated with pelvic exenteration and was associated with a survival rate similar to that of squamous carcinoma. In the present study, 2 out of the 3 patients who were successfully treated with exenteration had non-squamous cell carcinoma. Pelvic exenteration is a traumatic operation for patients, and selection of patients for this procedure should be carefully performed in preoperative assessment and at the time of laparotomy [14]. On the other hand, since this exenterative procedure offers the only possibility for cure in patients with central recurrence after optimal radiotherapy, gynecologic oncologists should not miss this only chance for saving the patient's life.

For patients who develop central recurrence outside the initial irradiated field, radiotherapy can provide long-term local control. Above all, under ideal conditions, curable treatment can be achieved. Survival is greatly influenced by tumor size, and a small tumor originating on the surface of the vagina is highly curable. Ito et al. [15] reported that among patients with recurrent cervical cancer of the vaginal stump that was treated with high-dose-rate intracavitary brachytherapy with or without external irradiation, the 10-year survival rate of patients who had a small (no palpable tumor), medium (less than 3 cm), or large (3 cm or more) tumor was 72, 48, and 0%, respectively. In the present study, all survivors who received optimal radiotherapy for their centrally recurrent tumor satisfied the ideal conditions, that is, they had either an unpalpable tumor or a small tumor of the vagina.

Patients who do not meet the criteria for curable treatment mentioned above were compelled to receive palliative treatment such as chemotherapy, palliative surgery, palliative radiotherapy, or palliative care. Although various agents have been investigated as a single-drug regimen or in combined regimens, chemotherapy for the treatment of local recurrence is considered to be palliative at present [16]. Although cisplatin is the most effective single agent, only 25% of patients show a clinical response. Several phase II studies have been performed to assess the effectiveness of gemcitabine, paclitaxel, vinorelvine, and camptothecines, and the overall response rate to these new drugs ranged between 8 and 25% [17]. Several recent phase II studies on combination chemotherapy with cisplatin and these new drugs demonstrated an overall response rate of 41 to 64% [17]. Nevertheless, it is uncertain whether chemotherapy has a palliative effect and whether it prolongs the survival of patients with locally recurrent cervical carcinoma, and oncologists should assess the potential benefit to each patient before administration.

The prognosis of patients with locally recurrent cervical carcinoma is very poor; however, the following patients are potentially curable: patients with a resectable, centrally located tumor who are candidates for pelvic exenteration; and patients with a small central recurrence for whom complete