

## Influence of Age on the Pattern and Outcome of External Beam Radiotherapy for Clinically Localized Prostate Cancer

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and JAPANESE PATTERNS of CARE STUDY WORKING SUBGROUP of PROSTATE CANCER

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**Abstract.** *Background:* The influence of age on the patterns and outcomes of external beam radiotherapy for clinically localized prostate cancer patients was examined. *Materials and Methods:* The Japanese Patterns of Care Study surveys were used to compare the processes and outcomes of radical external beam radiotherapy in 140 elderly patients (>75 years old) and 304 younger patients (<75 years old). *Results:* Although the Karnofsky performance status was significantly different between elderly and younger patients, there were no significant differences in disease characteristics such as pretreatment PSA level, differentiation, Gleason combined score and clinical T stage. There were also no significant differences in the treatment characteristics such as CT-based treatment planning, conformal therapy, total radiation doses (both a median of 66.0 Gy) and hormonal therapy usage. Moreover, no significant differences in overall survival, biochemical relapse-free survival and late toxicity rates were observed between elderly and younger patients. *Conclusion:* Age did not influence the disease characteristics, patterns of external beam radiotherapy, survival and late toxicities for clinically localized prostate cancer patients. Therefore, radiotherapy could represent an important treatment modality for elderly patients as well as for younger ones.

Although treatment decision making in clinically localized prostate cancer is complex, most physicians consider age when deciding on treatment between the principal options of radiotherapy, surgery, hormonal therapy or observation (1-3). Surgery is often not offered to patients  $\geq 70$  years of age, while observation or hormonal therapy is frequently considered for patients  $\geq 75$  years of age. Radiotherapy also has been the treatment of choice for elderly patients, including those 75 years or older.

Life expectancy has increased steadily in industrialized countries during the past 100 years, and there is a growing demand to treat elderly prostate cancer patients (4, 5). At the beginning of the 1990s, the survival rates reported in several series of untreated patients (6, 7) created a consensus that elderly patients die with and not due to prostate cancer, but more recent studies are challenging this commonly held opinion. According to these new data, patients with adverse prognostic features and/or a life expectancy of more than 5 years, even patients aged 75 years or over, showed high mortality rates from prostate cancer (8-10). These assertions seem to justify the fact that elderly patients with prostate cancer undergo radical radiotherapy because the typical life expectancy in Japan is 10 years for 75-year-old men and 8 years for 80-year-old men (11). However, the role of radiotherapy for elderly patients, including those 75 years or older, has not been fully described.

Since 1996, the Japanese Patterns of Care Study (PCS) Working Group of Prostate Cancer has conducted a nationwide process survey for prostate cancer patients who underwent radiotherapy in Japan (12-18). Here, the PCS results were examined to answer specific questions about the process and outcome of external beam radiotherapy for elderly patients with prostate cancer ( $\geq 75$  years) as compared to younger patients (<75 years).

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*Key Words:* Patterns of care study, prostatic carcinoma, age, elderly patients, radiation therapy.

## Materials and Methods

The PCS national survey is a retrospective study designed to establish national practice for selected malignancies over a specific time-period (19, 20). In addition to documenting the practice, the PCS is important in developing and spreading national guidelines for cancer treatment. This helps to promote a higher quality care in the country (19-21). The PCS was imported to Japan from the United States in order to improve the quality of radiation oncology nationwide in Japan.

The PCS methodology has been described previously (19-21). In brief, the PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The PCS surveyors consisted of 20 radiation oncologists from academic institutions, with one radiation oncologist compiling data by reviewing the patients' charts for each institution. The following patient eligibility criteria were used: prostatic adenocarcinoma without evidence of distant metastasis; radiotherapy between 1996 and 1998 or between 1999 and 2001 with no prior radiotherapy; and no concurrent or prior diagnosis of another malignancy. Patients who had had prior prostatectomy and patients with hormone-refractory cancer were excluded from the analysis.

The PCS data used in the current study are the results of two Japanese national surveys conducted to evaluate prostate cancer patients treated with radical external beam radiotherapy in the 1996-1998 and 1999-2001 PCS. Because of appropriate random sampling, the results of these studies represent true Japanese national averages (19-21). Out of the 694 patients comprising the 1996-1998 and 1999-2001 PCS surveys, a total of 444 patients with clinically localized prostate cancer treated with radical external beam radiotherapy met the eligibility criteria and were selected for analysis (1996-1998 PCS: 161 patients, 38 institutions; 1999-2001 PCS: 283 patients, 66 institutions). The patients were categorized into two age groups:  $\geq 75$  years (140 patients) and  $< 75$  years (304 patients), and the comparison data were used to examine the influences of age on patient and disease characteristics, treatment characteristics, overall and biochemical relapse-free survival and late toxicities.

The median follow-up of all patients was 2.0 years (range, 0.1-6.3 years). Biochemical relapse-free survival was defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition (22). Statistical analyses were performed using the Statistical Analysis System at the PCS statistical center (23). Statistical significance was tested using the Chi-square test, Mann-Whitney *U*-test and the Kaplan-Meier method (24). A probability level of 0.05 was chosen for statistical significance. The Radiation Therapy Oncology Group (RTOG) late toxicity scales (25) were used to assess late toxicity.

## Results

The patient and disease characteristics according to age group are shown in Table I. With regard to patient characteristics, the Karnofsky performance status (KPS) in elderly patients was significantly lower than that of younger patients ( $p=0.0040$ ). On the other hand, there were no significant differences in disease characteristics such as pretreatment PSA level ( $p=0.3290$ ), differentiation ( $p=0.1030$ ), Gleason combined score ( $p=0.1413$ ) and clinical T stage ( $p=0.6836$ ).

Table II indicates the treatment characteristics according to age group. There were no significant differences in the patterns of radiotherapy; such as CT-based treatment planning ( $p=0.5987$ ), conformal therapy ( $p=0.0759$ ), total radiation doses (both: median 66 Gy,  $p=0.1446$ ) and hormonal therapy usage ( $p=0.6758$ ).

At a median follow-up of 2.0 years, 17 patients had died of prostate cancer, 6 of intercurrent diseases, 3 of another cancer and 2 of unknown causes. The 2- and 5-year actuarial overall survival rates were 93.4% and 88.8% in elderly patients, and 95.5% and 84.3% in younger patients (Figure 1). There were no significant differences in overall survival between these groups ( $p=0.8524$ ). Biochemical failure was noted in 54 patients. The 2- and 5-year actuarial biochemical relapse-free survival rates were 90.8% and 90.8% in elderly patients, and 84.3% and 83.5% in younger patients (Figure 2). In addition, there were no significant differences in biochemical relapse-free survival between the elderly and younger patients ( $p=0.1362$ ).

Table III indicates the incidence of late toxicities ( $\geq$  Grade 2) in elderly and younger patients. Twenty out of 140 older patients (14.3%) and 37 out of 304 younger patients (12.2%) suffered late toxicities. There was one patient with grade 3 gastrointestinal toxicity in the younger age group. There were no significant differences in the incidence of late toxicities between elderly patients and younger patients (gastrointestinal:  $p=0.9599$ , genitourinary:  $p=0.0597$ ).

Among the elderly patients, the median total radiation dose was 66.0 Gy (range, 60-82 Gy) for patients treated with conformal therapy and 63.0 Gy (range, 30.6-80 Gy) for patients treated without conformal therapy ( $p<0.0001$ ). Moreover, 41% of patients with conformal therapy were treated with total doses of 70 Gy or more, while only 17.1% of patients without conformal therapy were treated with these dose levels ( $p<0.0001$ ). Although significantly higher total doses were delivered to patients with conformal therapy than those without conformal therapy, there were no significant differences ( $p=0.1152$ ) in the incidence of late toxicities between patients with conformal therapy (15.4%) and those without conformal therapy (9.8%).

## Discussion

The results of the current study indicated that age did not influence the disease characteristics for clinically localized prostate cancer patients who underwent external beam radiotherapy. Because of appropriate random sampling of the PCS surveys, the results of these studies represent true Japanese national averages. Several authors also compared elderly patients with younger patients and found no differences in the patient characteristics (5, 26, 27). Suzuki *et al.* indicated that elderly patients  $\geq 80$  years old presented

Table I. Patient and disease characteristics.

	Age group		Significance ( <i>p</i> )
	<75 (n=304)	≥75 (n=140)	
<b>Patient characteristics</b>			
Age (years)			
Median (Min-Max)	69.3 (46-74)	78.0 (75-92)	<0.001
KPS (%)			
≤80	68/291 (22.7)	47/130 (36.2)	0.004
90-100	231/299 (77.3)	83/130 (63.8)	
Missing	5	10	
Hypertension			
Yes	95/295 (32.2%)	39/137 (28.5%)	0.5502
Unknown	17/295 (5.8%)	11/137 (8.0%)	
Missing	9	3	
Angina			
Yes	30/295 (10.2%)	18/137 (13.1%)	0.598
Unknown	23/295 (7.8%)	12/137 (8.8%)	
Missing	9	3	
Myocardial infraction			
Yes	13/295 (4.4%)	11/137 (8.0%)	0.3101
Unknown	22/295 (7.5%)	10/137 (7.3%)	
Missing	9	3	
Hepatitis			
Yes	27/297 (9.1%)	7/137 (5.1%)	0.2922
Unknown	20/297 (6.7%)	12/137 (8.8%)	
Missing	7	3	
Liver cirrhosis			
Yes	4/294 (1.4%)	0/137 (0%)	0.225
Unknown	21/294 (7.1%)	14/137 (10.2%)	
Missing	10	3	
Diabetes			
Yes	34/296 (11.5%)	12/137 (8.8%)	
No	244/296 (82.4%)	112/137 (81.8%)	0.3362
Unknown	18/296 (6.1%)	13/137 (9.5%)	
Missing	8	3	
<b>Disease characteristics</b>			
Pretreatment PSA level (ng/ml, %)			
Median (Min-Max)	20.55 (0.8-900)	22.58 (0.3-856.9)	
<4	14/282 (5.0%)	11/132 (8.3%)	
4 ≤ <10	69/282 (24.4%)	24/132 (18.2%)	
10 ≤ <20	56/282 (19.9%)	26/132 (19.7%)	0.329
≥20	143/282 (50.8%)	71/132 (53.8%)	
Missing	22	8	
Differentiation			
Well	66/284 (23.2%)	20/139 (14.4%)	
Moderate	117/284 (41.2%)	55/139 (39.6%)	0.1030
Poor	84/284 (29.6%)	55/136 (39.6%)	
Unknown	15/284 (5.3%)	9/139 (6.5%)	
Other	2/284 (0.7%)	0	
Missing	20	1	
Gleason combined score (%)			
2-6	62/147 (42.2%)	26/47 (39.4%)	
7	41/147 (27.9%)	12/66 (18.2%)	0.1413
8-10	44/147 (30.0%)	28/66 (42.4%)	
Missing	157	74	

Table I. continued

	Age group		Significance ( <i>p</i> )
	<75 (n=304)	≥75 (n=140)	
<b>Clinical T stage</b>			
TX	7/294 (2.4%)	3/137 (2.2%)	
T0	1/294 (0.7%)	0	
T1	18/294 (6.1%)	12/137 (8.8%)	
T2	110/294 (37.4%)	46/137 (33.6%)	0.6836
T3	125/294 (42.5%)	65/137 (47.4%)	
T4	26/294 (8.8%)	10/137 (7.3%)	
Unknown	7/294 (2.4%)	1/137 (0.7%)	
Missing	10	3	
<b>Clinical N stage</b>			
NX	11/292 (3.8%)	2/135 (1.5%)	
N0	246/292 (84.2%)	126/135 (93.3%)	
N1	27/292 (9.2%)	6/135 (4.4%)	0.0731
Unknown	8/292 (2.7%)	1/135 (0.7%)	
Missing	12	5	

KPS=Karnofsky performance status; PSA=prostate-specific antigen.

with similar histological grade and disease stage as younger patients (26). Geinitz *et al.* indicated that there were no significant differences in disease characteristics between patients of ≥75 years and <75 years (5). These results suggest that elderly patients present with similar disease characteristics as younger patients.

The results of the current study also indicated that age did not influence the patterns of external beam radiotherapy for clinically localized prostate cancer patients. Although the KPS of elderly patients was significantly lower than that of younger patients, treatment characteristics, such as CT-based treatment planning, conformal therapy, total radiation doses and hormonal therapy usage, were not significantly different. Several authors also compared elderly patients with younger patients and found no differences in the patterns of external beam radiotherapy (5, 26, 27). Geinitz *et al.* found that 3D conformal radiotherapy for prostate cancer with doses of 70 Gy was well tolerated in patients aged 75 years or older as well as in younger patients (5). Hanks *et al.* found that radiotherapy could be given to prostate cancer patients without age bias (27). These results suggest that elderly patients can tolerate standard external beam radiotherapy in the same way as younger patients.

In spite of the short median follow-up period, the results of the current study indicated that age did not influence the overall survival and biochemical relapse-free survival rates and incidence of late toxicities for clinically localized prostate cancer patients. Although intercurrent death would result in a poorer overall survival for patients 75 years or older, the overall survivals were similar between patients of

Table II. Treatment characteristics.

	Age group		Significance (p)
	<75 (n=304)	≥75 (n=140)	
<b>Radiotherapy</b>			
Energy (≥10 MV) (%)			
Yes	210/301 (70.0%)	95/139 (68.4%)	0.7636
Missing	3	1	
<b>CT-based treatment planning (%)</b>			
Yes	249/304 (81.9%)	114/139 (82.0%)	0.5987
Unknown	6/304 (2.0%)	1/139 (0.7%)	
Missing	0	1	
<b>Conformal therapy (%)</b>			
Yes	143/256 (55.9%)	78/119 (65.6%)	0.0759
Missing	48	21	
<b>All fields treated each day (%)</b>			
Yes	146/196 (74.5%)	69/87 (79.3%)	0.3811
Missing	108	53	
<b>Pelvic irradiation (%)</b>			
Yes	119/304 (39.1%)	52/140 (37.1%)	0.6781
<b>Radiation dose (cGy)</b>			
Median (Min-Max)	6600 (1400-7600)	6600 (3000-8200)	0.1446
Missing	0	1	
<b>Hormonal therapy</b>			
Yes	266/303 (87.8%)	125/139 (89.9%)	0.6758
Unknown	1/303 (0.3%)	0	
Missing	1	1	
<b>Content (%)</b>			
Orchiectomy	34/274 (12.4%)	15/127 (11.8%)	0.8368
Unknown	4/274 (1.5%)	1/127 (0.8%)	
Missing	30	13	
Estrogen agent	35/263 (13.3%)	13/123 (10.6%)	0.7609
Unknown	10/263 (3.8%)	7/123 (5.7%)	
Missing	41	17	
LH-RH agonist	226/281 (80.4%)	101/132 (76.5%)	0.0880
Unknown	9/281 (3.2%)	9/132 (6.8%)	
Missing	23	8	
Antiandrogen	190/282 (67.4%)	80/130 (61.5%)	0.6352
Unknown	15/282 (5.3%)	10/130 (7.7%)	
Missing	22	10	
<b>Period (%)</b>			
Before RT (77.3%)		243/285 (84.5%)	102/132
Unknown	0.0887		
Missing	1/285 (0.4%)	0	
During RT (78.9%)		230/284 (81.0%)	105/133
Unknown	0.6693		
Missing	6/284 (2.1%)	3/133 (2.3%)	
Missing	20	7	

Table II. continued

	Age group		Significance (p)
	<75 (n=304)	≥75 (n=140)	
<b>After RT</b>			
Unknown	216/282 (76.6%)	95/133 (71.4%)	0.4092
Missing	26/282 (9.2%)	13/133 (9.8%)	
Missing	22	7	
<b>Duration* (Years)</b>			
Median (Min-Max)	0.96 (0.0-4.8)	1.01 (0.0-4.5)	0.4822
<b>Chemotherapy</b>			
Yes	30/298 (10.1%)	7/135 (5.2%)	
No	264/298 (88.6%)	128/135 (94.8%)	0.0907
Unknown	4/298 (1.3%)	0	
Missing	6	5	

CT=computed tomography; RT=radiotherapy; LH-RH=Lutein hormone-releasing hormone.

Table III. Late toxicities.

	Age group		Significance (p)
	<75 (n=304)	≥75 (n=140)	
<b>Gastrointestinal (≥Grade 2)</b>			
Yes	34/298 (11.4%)	15/135 (11.1%)	
No	261/298 (87.6%)	119/135 (88.1%)	N.S. (0.9599)
Unknown	3/298 (3.0%)	1/135 (0.7%)	
Missing	6	5	
<b>Genitourinary (≥Grade 2)</b>			
Yes	3/193 (1.6%)	5/87 (5.7%)	
No	180/193 (93.2%)	74/87 (85.1%)	N.S. (0.0597)
Unknown	10/193 (5.2%)	8/87 (9.2%)	
Missing	111	53	

N.S.=Not significant.

≥75 years and those of 75 < years. Perhaps patients older than 75 who are selected for radiotherapy may be in better health than the average person in that age group. Previously, several authors also reported the favorable results of external beam radiotherapy for elderly patients. Villa *et al.* reviewed 183 elderly patients >70 years of age with localized prostate cancer, treated with radical external beam radiotherapy, and found that elderly patients with clinically localized prostate cancer can fare well when treated with radical irradiation, with very limited acute and late toxicity (28). Alibhai *et al.* indicated that potentially curative therapy, such as radiotherapy, results in significantly improved life expectancy and quality-adjusted

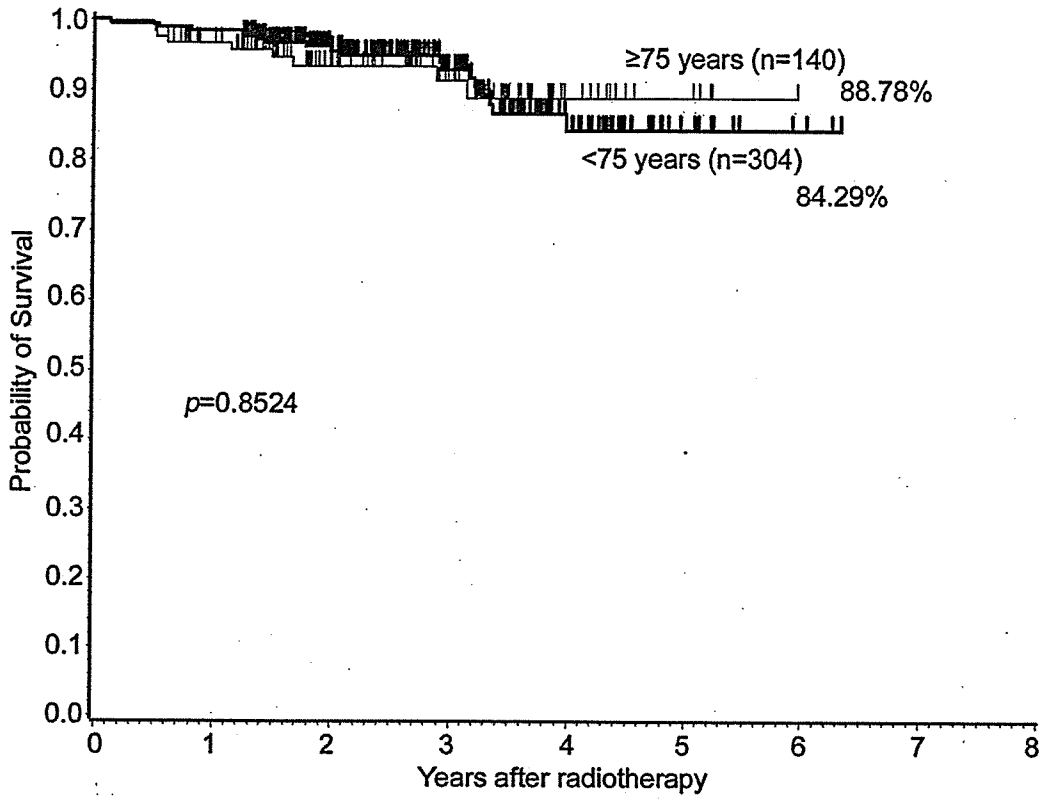


Figure 1. Overall survival curves for clinically localized prostate cancer patients according to age.

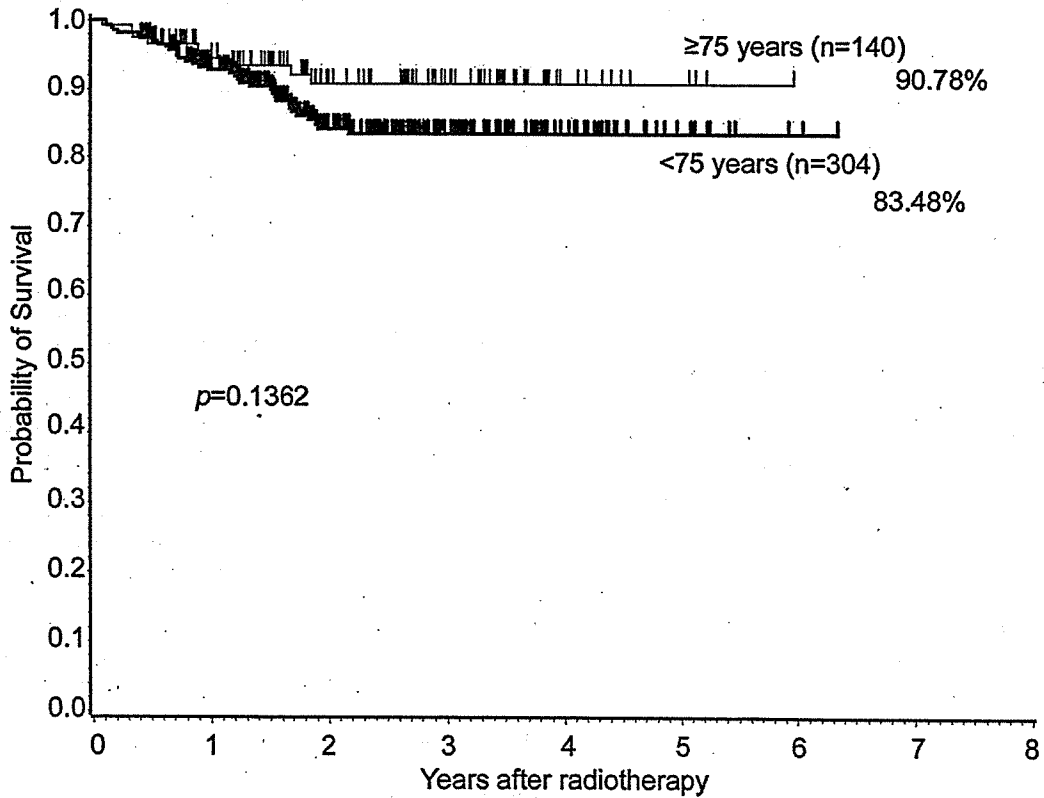


Figure 2. Biochemical relapse-free survival curves for clinically localized prostate cancer patients according to age.

life expectancy for older men with few co-morbidities and moderately- or poorly-differentiated localized prostate cancer (29). Huguein *et al.* retrospectively studied 59 patients aged  $\geq 75$  years who had received conventional radiotherapy for prostate cancer (4). The authors did not observe significant differences in late toxicity or quality of life between elderly and matched younger groups. In the current study, there were also no significant differences in the incidences of late toxicities between elderly patients and younger patients. A trend for more genitourinary toxicity in the elderly ( $p=0.0597$ ) may suggest that older men had more baseline problems urinating than their younger counterparts. These results suggest that radiotherapy can be administered to elderly patients with favorable outcomes and also with little late toxicity.

For elderly patients, although significantly higher total doses were delivered to patients with conformal therapy than those without conformal therapy, there were no significant differences in the incidence of late toxicities between these two groups. In order to reduce the risk of late toxicities, appropriate treatment planning should be used when treating elderly patients with external beam radiotherapy. Modern radiotherapy requires 3D conformal therapy or intensity modulated radiation therapy (IMRT) to improve the target dose distribution while reducing the normal tissue dose (30-32), thus also reducing the possible negative impact of the treatment on the quality of life of these patients. Geinitz *et al.* observed no serious late toxicity in patients aged 75 years or more when treated with 3D conformal therapy for prostate cancer using doses of 70 Gy (5). Hanks *et al.* found that the advantage of 3D conformal therapy was apparent for elderly patients in whom acute symptoms were reduced compared with those produced by conventional radiotherapy (27). These results suggest that 3D conformal therapy or IMRT may represent the gold standard for prostate gland irradiation for elderly patients. However, longer follow-ups are needed to ascertain the safety of these treatments for elderly patients.

In conclusion, age did not influence the disease characteristics and patterns of external beam radiotherapy for clinically localized prostate cancer patients. Moreover, the overall and biochemical relapse-free survival rates and late toxicities did not significantly differ between these groups. Therefore, external beam radiotherapy could represent an important modality for elderly patients as well as for younger patients. Appropriately selected elderly patients with prostate cancer can attain the same success after radiation treatment as do younger ones.

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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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and JAPANESE PATTERNS OF CARE STUDY  
WORKING SUBGROUP OF PROSTATE CANCER

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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  $\geq 70$  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.

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



Table I. Patient and disease characteristics.

	PCS		Signifi- cance (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%)	0.0209
Moderate	79/159(50.0%)	93/264(35.2%)	
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%)	0.0074
7	18/42(42.9%)	35/171(20.5%)	
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%)	0.0022
T1	8/159(5.0%)	22/272(8.1%)	
T2	47/159(29.6%)	109/272(40.1%)	
T3-4	102/159(64.2%)	124/272(45.6%)	
Unknown	1/159(0.6%)	7/272(2.6%)	
Missing	2	11	
N-stage (%)			
NX-N0	136/157(86.6%)	249/270(92.2%)	0.0873
N1	18/157(11.5%)	15/270(5.6%)	
Unknown	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%)	<0.0001
Advanced or high-risk disease	43/136(31.7%)	83/268(31.0%)	
Medical contraindication	7/136(5.2%)	36/268(13.5%)	
Old age	37/136(27.2%)	44/268(16.5%)	
Others	9/136(6.6%)	8/268(3.0%)	
N/A or unknown	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 ( $\geq 10$ 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
Radiation dose (cGy)			
A+B (Total)			
Median (range)	6500(2200-7400)	6840(1400-8200)	<0.0001
(mean $\pm$ SD)	6090.9 $\pm$ 990.5	6600.8 $\pm$ 732.0	<0.0001
A			
Median (Min-Max)	6500(2200-7400)	6600(1400-8200)	<0.0001
(mean $\pm$ SD)	6250.9 $\pm$ 976.8	6610.3 $\pm$ 776.5	<0.0001
B			
Median (Min-Max)	5940(3400-7000)	6900(3000-8000)	<0.0001
(mean $\pm$ SD)	5622.4 $\pm$ 885.6	6587.5 $\pm$ 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

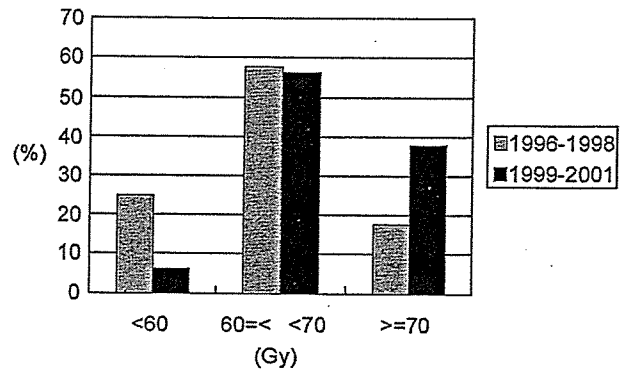


Figure 1. Distribution of external irradiation doses for prostate cancer during the 1996-1998 and 1999-2001 survey periods.

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 ( $p<0.0001$ ).

*Treatment characteristics.* The treatment characteristics are shown in Table II. The frequency of radiation energies  $\geq 10$  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  $\geq 70$  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  $1.01\pm 1.04$  years and  $1.31\pm 1.03$  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. These 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  $\geq 70$  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 as 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 ( $\geq 72$  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.*

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

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	-

\*Zelevsky *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.

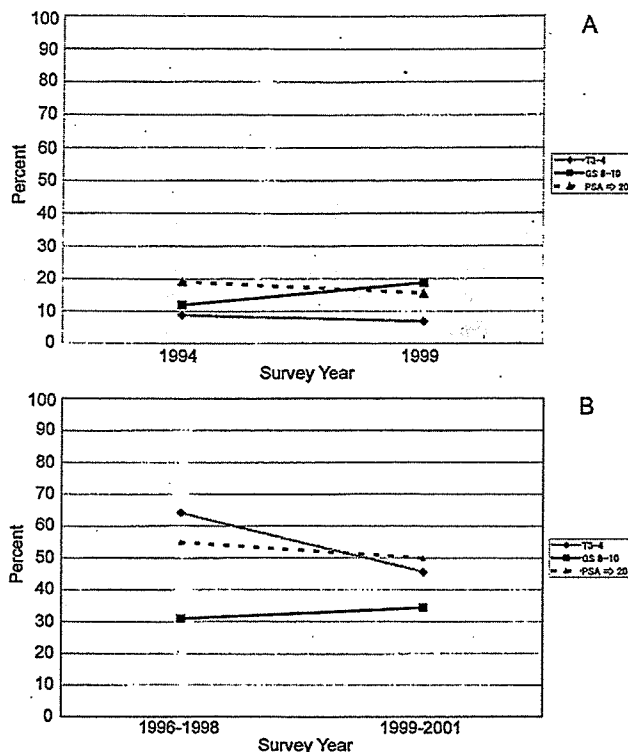


Figure 1. Changing trend in disease characteristics in Japan and the United States. In the United States, the proportions of T3-4, Gleason score of 8-10, and PSA  $\geq 20$  ng/mL were all below 20% in the periods 1994 and 1999 (Figure 1A). On the other hand, in Japan, the proportions of these adverse 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 ( $\geq 20$  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.

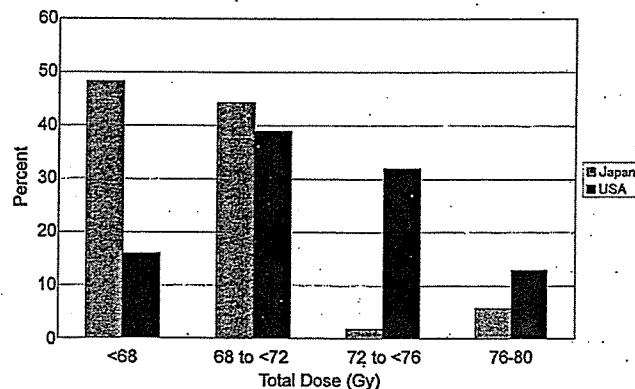


Figure 2. Radiation dose distribution in Japan and the United States. The distributions of total dose to the prostate in the United States were significantly higher ( $p < 0.00001$ ) than those in Japan.

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 ( $\geq 72$  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  $1.4 \pm 1.0$  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

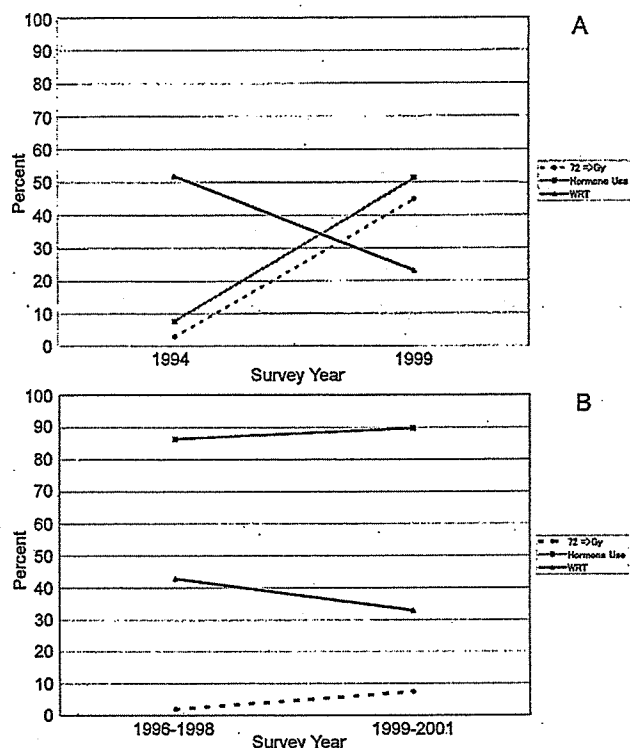


Figure 3. Changing trends in the treatment characteristics in Japan and the United States. There were marked changes concerning the percentage of higher prescribed radiation doses ( $\geq 72$  Gy), whole pelvic radiation therapy (WRT) and hormone use in the United States from 1994 to 1999 (Figure 3A). 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).

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

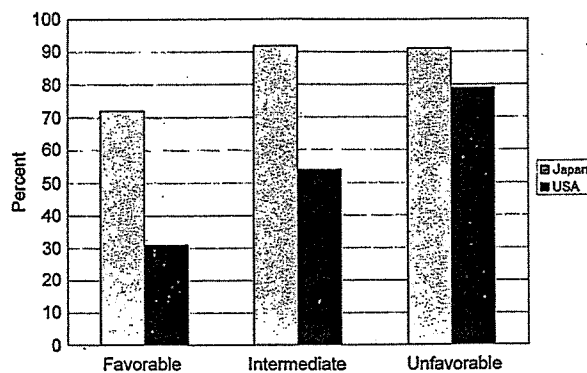


Figure 4. Hormonal therapy distribution according to the risk groups for prostate cancer patients in Japan and in the United States.

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 ( $\geq 72$  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 ( $\geq 72$  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 ( $\geq 72$  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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## Radical External Beam Radiotherapy for Prostate Cancer in Japan: Results of the 1999-2001 Patterns of Care Process Survey

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**Background:** The Patterns of Care Study evaluated standards of practice for patients with clinically localized prostate cancer treated with radiotherapy in Japan. This study examined the influence of institutional stratification on care for patients receiving radical external beam radiotherapy.

**Methods:** A national survey of 66 institutions was conducted using two-stage cluster sampling, and detailed information was accumulated on 283 patients who received radiotherapy between 1999 and 2001.

**Results:** In A (academic) and B (non-academic) institutions, more than 80% of patients had intermediate or unfavorable risk disease. Although there were no significant differences in disease characteristics between A and B institutions, institutional stratification significantly affected radiotherapy practice patterns, such as the use of a CT-based treatment planning (A: 91.5%, B: 77.1%;  $P = 0.0007$ ) and the use of conformal therapy (A: 56.4%, B: 24.1%;  $P < 0.0001$ ). CT-based treatment planning and conformal therapy significantly influenced total radiation dose ( $P < 0.0001$  for each). Hormonal therapy was commonly used in both A and B institutions (A: 89.0%, B: 90.7%). Many patients with a favorable prognosis (A: 62.5%, B: 91.7%) received hormonal therapy, and most patients with unfavorable risk disease (A: 93.6%, B: 91.6%) also received hormonal therapy.

**Conclusion:** During the period 1999-2001, the majority of prostate cancer patients treated in Japan with radical external beam radiotherapy had advanced diseases. Institutional stratification significantly affected radiotherapy practice patterns, with the notable exception that radiotherapy was commonly combined with hormonal therapy regardless of the institutional stratification and individual risk.

*Key words: patterns of care study - prostatic carcinoma - type of institution - radiation therapy - hormone therapy*

### INTRODUCTION

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 practice process, the PCS is important for the development and spread of national guidelines for cancer treatment. PCS results should help to promote

a high-quality care process in Japan and complement the role of clinical trials (1,4).

To improve the quality of radiation oncology, PCS was imported to Japan from the United States (5,6). The Japanese PCS Working Group of Prostate Cancer started a nationwide process 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. We have previously reported the preliminary results of the second PCS for radical external beam radiotherapy for prostate cancer patients (9-11).

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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 among total cancer deaths also showed an increase from 0.9% in 1960 to 4.2% in 2000 (12). Since entering the prostate-specific antigen (PSA) era, clinicians are detecting earlier stage disease, and the rates of successful treatment for early-stage patients are increasing in Japan (13). Moreover, radiotherapy has become much more common because a significant amount of new treatment planning technology and methodology has become available. Therefore, optimal management of radiotherapy for prostate cancer patients has become a major concern in Japan. However, we have not been able to properly evaluate national practice processes owing to limited information. In July 2002, PCS audits for prostate cancer patients treated between 1999 and 2001 began, and data were collected for 283 patients who received radical external beam radiotherapy. In the current study, we have analyzed results of radical external beam radiotherapy for clinically localized prostate cancer and focused on how institutional stratification influences the patient characteristics, disease characteristics and patterns of radiotherapy in Japan.

## PATIENTS AND METHODS

The 1999–2001 Japanese PCS consisted of an extramural audit survey of 66 institutions using stratified two-stage cluster sampling. 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). The following patient eligibility criteria were used: prostatic adenocarcinoma without evidence of distant metastasis; radiotherapy between 1999 and 2001 with no prior radiotherapy; and no concurrent or prior diagnosis of another malignancy. Patients who had prior prostatectomy and patients with hormone-refractory cancer were also excluded for this analysis. The PCS surveyors were 20 radiation oncologists from academic institutions. For each institution surveyed, one radiation oncologist visited and surveyed data by reviewing 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.

Using the 1999 facilities master list (14), the 1999–2001 PCS stratified institutions as follows: A1, academic institutions (university hospital or cancer center) with  $\geq 430$  patients yearly; A2, academic institutions with  $< 430$  patients; B1, non-academic institutions (other hospitals) with  $\geq 130$  patients yearly; and B2, non-academic institutions with  $< 130$  patients. Among the 528 patients identified, 283 patients who received radical external beam radiotherapy were selected for analysis, and results for these patients are reported.

Regarding risk, the 1999 US PCS identified the following as adverse features: PSA  $> 10$  ng/ml; Gleason combined score  $> 6$ ; and T stage  $\geq 3$ . On the basis of this, the US

PCS categorized patients into the following risk groups: favorable—zero adverse features; intermediate—one adverse feature; unfavorable—two or more adverse features (15). Because data for the Gleason combined score were missing for 47% (132/283) 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 consisted of the following: PSA  $> 10$  ng/ml; poorly-differentiated disease; and T stage  $\geq 3$ . Japanese patients were then categorized into the following risk groups: favorable—zero adverse features; intermediate—one adverse feature; unfavorable—two or more adverse features.

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University (16). Statistical significance was tested using the  $\chi^2$ -test and the Student's *t*-test. A *P*-value  $< 0.05$  was considered statistically significant.

## RESULTS

### PATIENT AND DISEASE CHARACTERISTICS

Patient and disease characteristics are shown in Table 1, stratified by institution type (academic versus non-academic). No significant differences in disease characteristics were observed, including pretreatment PSA level, tumor differentiation, Gleason combined score and T stage. In both A (academic) and B (non-academic) institutions, more than 80% of patients had intermediate or unfavorable risk diseases. Major reasons for selecting radiotherapy included patient preference, advanced or high-risk disease, medical contraindication and old age.

### TREATMENT CHARACTERISTICS

Institutional and therapy characteristics are shown in Table 2. Not unexpectedly, institutional type was closely related to radiation oncology infrastructure (e.g. equipment and personnel), which in turn significantly affected radiotherapy practice patterns, such as beam energy  $\geq 10$  MV (A: 86.4%, B: 59.6%;  $P < 0.0001$ ), usage of portal films or electric portal images (A: 90.1%, B: 55.1%;  $P < 0.0001$ ), all fields treatment for each day (A: 86.7%, B: 61.0%;  $P < 0.0001$ ), usage of a CT-based treatment planning (A: 91.5%, B: 77.1%;  $P = 0.0007$ ) and use of conformal therapy (A: 56.4%, B: 24.1%;  $P < 0.0001$ ). Use of CT-based treatment planning and conformal radiotherapy significantly influenced total radiation dose (Figs 1 and 2;  $P < 0.0001$  for each). The only patients who received total radiation doses  $\geq 70$  Gy were patients who had CT-based treatment planning. Significantly, more patients who had conformal therapy (compared with those who did not have conformal radiotherapy) received total radiation doses  $\geq 70$  Gy. Portal films or electronic portal images were used for 90.1% in A institutions and 55.1% in B institutions ( $P < 0.0001$ ). All fields were treated each day for 86.7% in A institutions and 55.1% in B institutions ( $P < 0.0001$ ). Pelvic irradiation (clinical target volume is