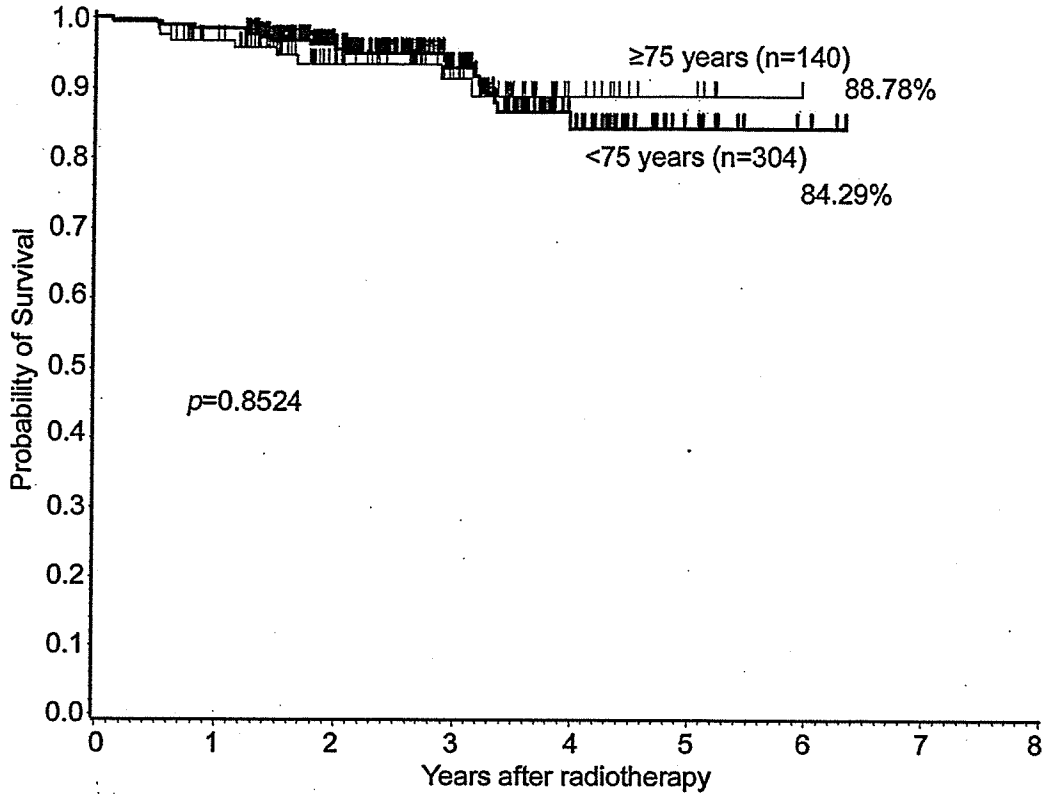

Figure 1. *Overall survival curves for clinically localized prostate cancer patients according to age.*

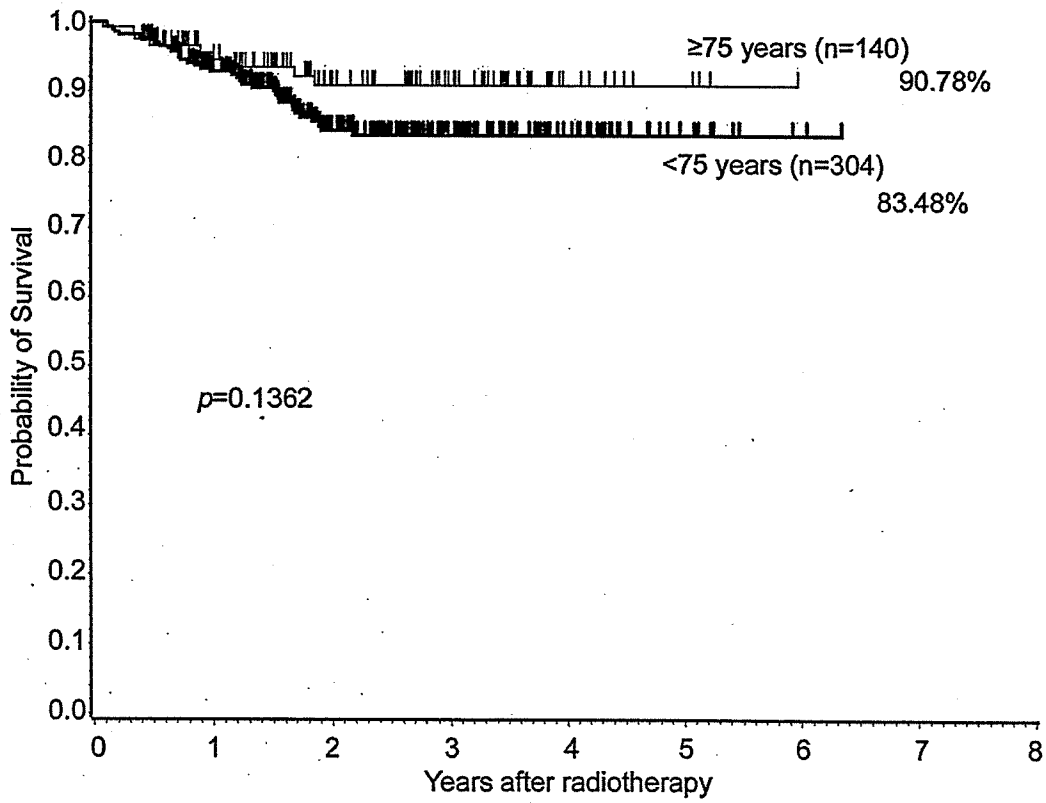

Figure 2. *Biochemical relapse-free survival curves for clinically localized prostate cancer patients according to age.*

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 ≥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 toxicitiy.

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.

Acknowledgements

Supported by Grants-in-Aid for Cancer Research (Grant No. 14-6) from the Ministry of Health, Labor and Welfare of Japan.

We thank all the radiation oncologists who participated in this study. Their efforts to provide information made these surveys possible. We are grateful for the continuous and thoughtful support we have received from the U.S. PCS committee for nine years.

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Received November 29, 2005
Accepted January 20, 2006

ANTICANCER RESEARCH *26*: 575-580 (2006)

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

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.

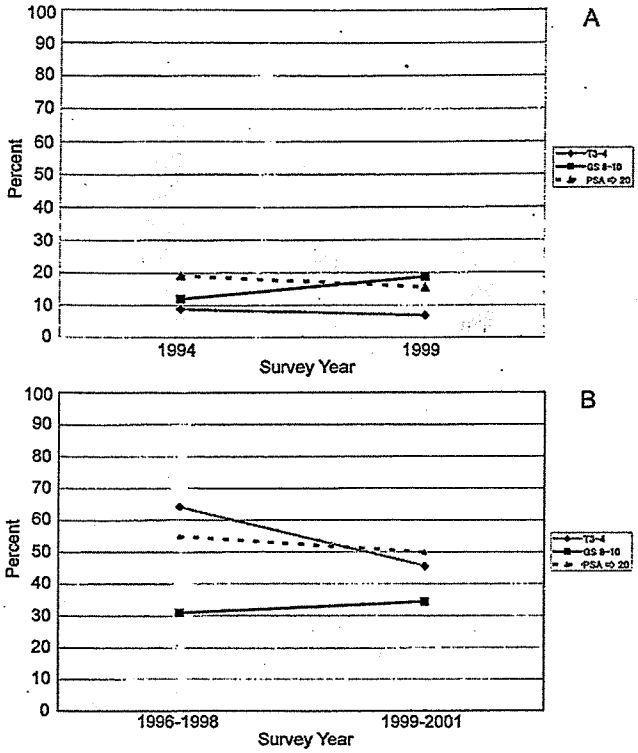

Figure 1. *Changing trend in disease characteristics in Japan and the United States. In the United States, the proportions of T3-4, Gleason sore of 8-10, and PSA ≥20 ng/mL were all below 20% in the periods 1994 and 1999 (Figure 1A). On the other hand, in Japan, the proportions of these adverse factors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

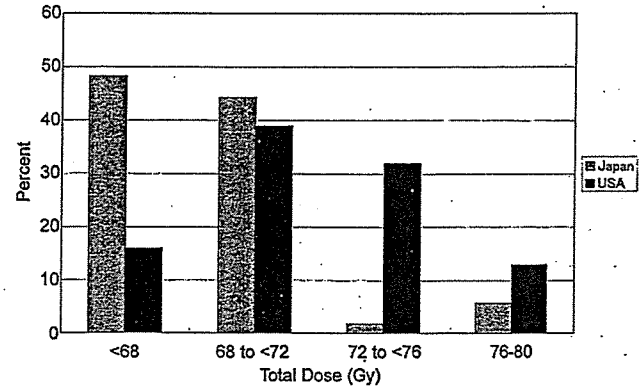

Figure 2. *Radiation dose distribution in Japan and the United States. The distributions of total dose to the prostate in the United States were significantly higher ($p<0.00001$) than those in Japan.*

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

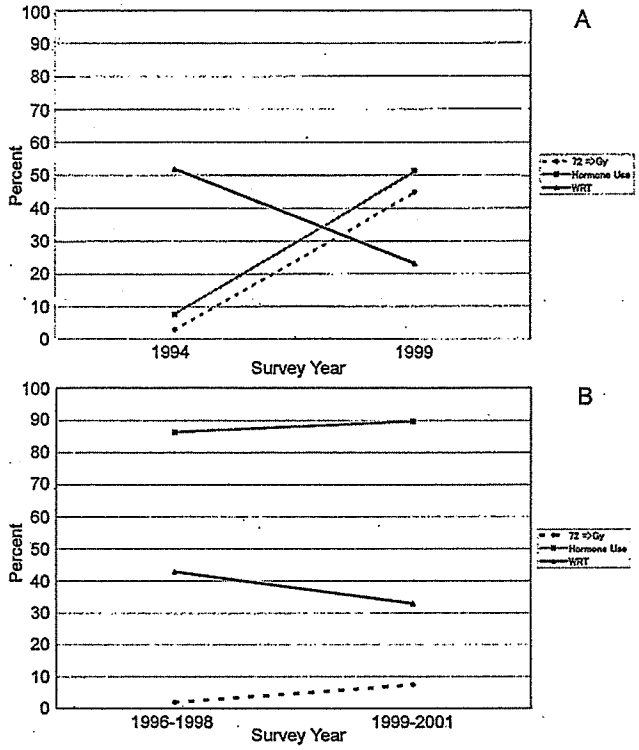

Figure 3. *Changing trends in the treatment characteristics in Japan and the United States. There were marked changes concerning the percentage of higher prescribed radiation doses (≥72 Gy), whole pelvic radiation therapy (WRT) and hormone use in the United States from 1994 to 1999 (Figure 3A). In contrast,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

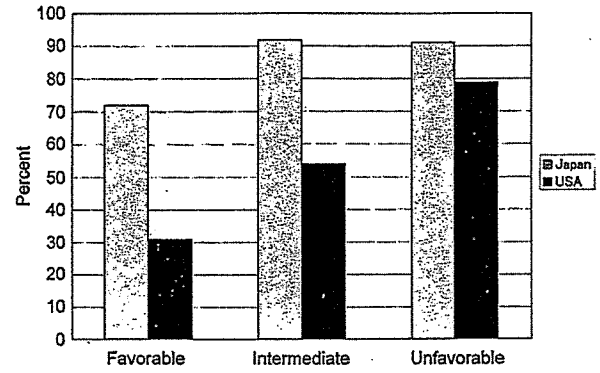

Figure 4. *Hormonal therapy distribution according to the risk groups for prostate cancer patients in Japan and in the United States.*

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.

Acknowledgements

This work was supported by Grants-in-Aid for Cancer Research (Grant No. 14-6) from the Ministry of Health, Labor and Welfare of Japan. We thank all the radiation oncologists who participated in this study. Their provision of information made these surveys possible. We are also grateful for the continuous thoughtful support we have received from the U.S. PCS committee for the last 9 years.

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Received August 22, 2005
Accepted October 7, 2005

Jpn J Clin Oncol 2006;36(1)40–45
doi:10.1093/jjco/hyi216

Radical External Beam Radiotherapy for Prostate Cancer in Japan: Results of the 1999–2001 Patterns of Care Process Survey

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Received September 27, 2005; accepted November 16, 2005; published online January 17, 2006

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 (A1: 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 ≥430 patients yearly; A2, academic institutions with <430 patients; B1, non-academic institutions (other hospitals) with ≥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 ≥ 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 ≥ 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 χ^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 ≥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 ≥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 ≥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

Table 1. Patient and disease characteristics

	Type of institutions		Significance (*P*)
	A (n = 165)	B (n = 118)	
Age (years)			
Median (range)	72 (58–92)	71 (49–89)	0.2248
KPS (%)			
Median (range)	90 (70–100)	90 (50–100)	0.0002
Missing	5	3	
Pretreatment PSA level (ng/ml, %)			
Median (range)	19.0 (0.6–856.9)	23.0 (0.8–660)	
mean ± SD	47.2 ± 90.7	64.2 ± 110.9	0.5364
<4	4/160 (2.5%)	4/108 (3.7%)	
≤4 to <10	46/160 (28.8%)	23/108 (21.3%)	
≤10 to <20	34/160 (21.2%)	23/108 (21.3%)	0.5364
≥20	76/160 (47.5%)	58/108 (53.7%)	
Missing	5	10	
Differentiation			
Well	33/156 (21.2%)	29/108 (26.9%)	
Moderate	57/156 (36.5%)	36/108 (33.3%)	0.6401
Poor	55/156 (35.3%)	38/108 (35.2%)	
unknown	11/156 (7.0%)	5/108 (4.6%)	
Missing	9	10	
Gleason combined score (%)			
2–6	32/70 (45.7%)	16/47 (34.0%)	
7	13/70 (18.6%)	13/47 (27.7%)	0.3624
8–10	25/70 (35.7%)	18/47 (38.3%)	
Missing	31	33	
Clinical T stage			
TX	6/162 (3.7%)	3/110 (2.7%)	
T0	0/162 (0.0%)	1/110 (0.9%)	
T1	14/162 (8.6%)	8/110 (7.3%)	
T2	58/162 (35.8%)	51/110 (46.4%)	0.5228
T3	72/162 (44.4%)	37/110 (33.6%)	
T4	8/162 (4.9%)	7/110 (6.4%)	
Unknown	4/162 (2.4%)	3/110 (2.7%)	
Missing	3	8	
Clinical N stage			
NX	1/162 (0.6%)	5/108 (4.6%)	
N0	150/162 (92.6%)	93/108 (86.1%)	
N1	9/162 (5.6%)	6/108 (5.6%)	0.0794
Unknown	2/162 (1.2%)	4/108 (3.7%)	
Missing	3	10	
*Risk group (%)			
Favorable	24/152 (15.8%)	12/96 (12.5%)	
Intermediate	50/152 (32.9%)	37/96 (38.5%)	0.5950
Unfavorable	78/152 (51.3%)	47/96 (49.0%)	
Missing	13	22	
Reason for selecting radiotherapy			
Patient preference	41/152 (27.0%)	30/116 (25.9%)	
Advanced or high-risk disease	41/152 (27.0%)	42/116 (36.2%)	
Medical contraindication	21/152 (13.8%)	15/116 (12.9%)	0.0218
Old age	27/152 (17.8%)	17/116 (14.7%)	
Others	2/152 (1.3%)	6/116 (5.2%)	
N/A or Unknown	17/152 (11.2%)	3/116 (2.6%)	
Missing	13	2	

KPS = Karnofsky performance status; PSA = prostate-specific antigen
*Favorable = meet all conditions below; Intermediate = meet 2 conditions; Unfavorable = meet only 1 or no conditions
(1) PSA ≤ 10 (2) not poorly differentiation (3) T stage < 3
Institution types: A, academic; B, non-academic.

prostate gland, seminal vesicle and pelvic lymph nodes) was used in 26.2% of patients in A institutions and 42.4% of patients in B institutions (P = 0.0087). The median number of full-time equivalent (FTE) radiation oncologists was 2.4 in A institutions but only 0.4 in B1 institutions (P < 0.0001).

Hormonal therapy was commonly used before, during and after radiotherapy for a mean duration of 1.4 ± 1.0 years (A: 89.0%, B: 90.7%). Luteinizing hormone-releasing hormone (LH-RH) agonists and antiandrogens were frequently used as hormonal agents. In contrast, the use of chemotherapy was uncommon (A: 7.9%, B: 3.6%).

The percentages of patients with favorable, intermediate and unfavorable tumors were 15.2%, 37.0% and 47.9%, respectively. The percentages of patients with favorable, intermediate and unfavorable tumors treated with hormonal therapy were 72.2%, 93.1% and 92.0%, respectively. The use of hormonal therapy did not significantly differ between A and B institutions (Fig. 3, P = 0.12). Many patients with a favorable prognosis (A: 62.5%, B: 91.7%, P = 0.0655) received hormonal therapy, and most patients with unfavorable risk (A: 93.6%, B: 91.6%) also received hormonal therapy.

DISCUSSION

The 1999–2001 PCS revealed that more than 80% of Japanese patients treated with radical external beam radiotherapy had intermediate or unfavorable risk diseases, and that institutional type did not significantly affect disease characteristics, such as pretreatment PSA levels, Gleason combined score and T stage. In the current study, the higher rate of missing data in Gleason combined score was observed. During the period between 1999 and 2001, many Japanese physicians may consider the Gleason combined score less important for prostate cancer treatment.

Table 2. Treatment characteristics

	Type of institutions		Significance (*P*)
	A (n = 165)	B (n = 118)	
Radiotherapy			
Energy (≥10 MV) (%)			
Yes	132/156 (84.6%)	65/109 (59.6%)	<0.0001
Missing	9	9	
CT-based treatment planning (%)			
Yes	150/164 (91.5%)	91/118 (77.1%)	0.0007
Missing	1	0	
Conformal therapy (%)			
Yes	92/163 (56.4%)	28/116 (24.1%)	<0.0001
Missing	2	2	
Usage of portal films or electric portal images (%)			
Yes	146/162 (90.1%)	65/118 (55.1%)	<0.0001
Missing	3	0	
All fields treatment for each day (%)			
Yes	143/165 (86.7%)	72/118 (61.0%)	<0.0001
Pelvic irradiation (%)			
Yes	43/164 (26.2%)	50/118 (42.4%)	0.0087
Missing	1	0	
Radiation dose (cGy)			
Median (range)	6600 (1400–8200)	6900 (3000–8000)	
Mean ± SD	6610.3 ± 766.5	6592.6 ± 681.9	<0.0001
Missing	1	0	
Higher prescription dose levels (≥72 Gy) (%)			
Yes	18/164 (11.0%)	3/118 (2.5%)	0.2482
Missing	1	0	
Hormonal therapy			
Yes	146/164 (89.0%)	107/118 (90.7%)	0.6520
Missing	1	0	
Content (%)			
Orchiectomy	19/153 (12.4%)	13/97 (13.4%)	0.4382
Missing	12	21	
Estrogen agent	7/145 (4.8%)	23/98 (23.5%)	0.0008
Missing	20	20	
LH-RH agonist	121/153 (79.1%)	94/109 (86.2%)	0.4297
Missing	12	9	
Antiandrogen	104/155 (67.1%)	80/108 (74.1%)	0.2516
Missing	10	10	
Period (%)			
Before RT	131/155 (84.5%)	94/109 (86.2%)	0.6978
Missing	10	9	
During RT	122/155 (78.7%)	101/110 (91.8%)	0.0277
Missing	10	8	
After RT	115/154 (74.7%)	87/110 (79.1%)	0.0001
Missing	11	8	
Duration* (Years)			
Median (range)	0.97 (0.1–4.8)	1.27 (0.2–4.5)	
Mean ± SD	1.4 ± 1.3	1.5 ± 1.1	0.4822
Chemotherapy			
Yes	13/164 (7.9%)	4/110 (3.6%)	0.3418
Missing	1	8	

CT = computed tomography; RT = radiotherapy; LH-RH = Lutein hormone-releasing hormone.
Institution types: A, academic; B, non-academic.

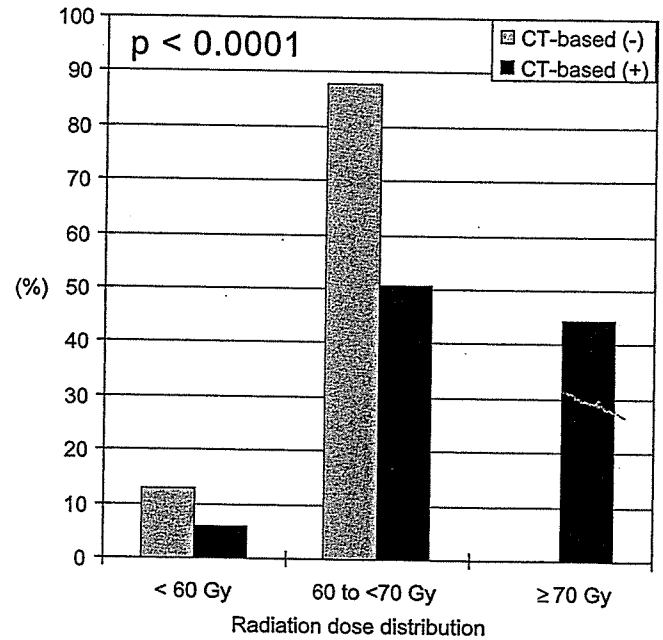

Figure 1. Radiation dose distribution for Japanese prostate cancer patients as a function of use of CT-based treatment planning.

The current study also demonstrated significant variations in radiotherapy practice patterns according to the type of institution, specifically in the beam energies utilized and in the use of a CT-based treatment planning and conformal therapy. These practice differences indicate that the quality of radiotherapy was significantly higher in academic institutions than in non-academic institutions. The lower rate of pelvic irradiation in academic institutions than in non-academic institutions may also reflect the more frequent use of CT-based treatment planning and conformal therapy in academic institutions. Similarly, two other Japanese PCS studies of esophageal cancer and cervical cancer have also identified significant differences in treatment patterns between academic and non-academic institutions (5,6).

Practice processes in non-academic institutions in Japan were closely related to structural immaturity, especially in

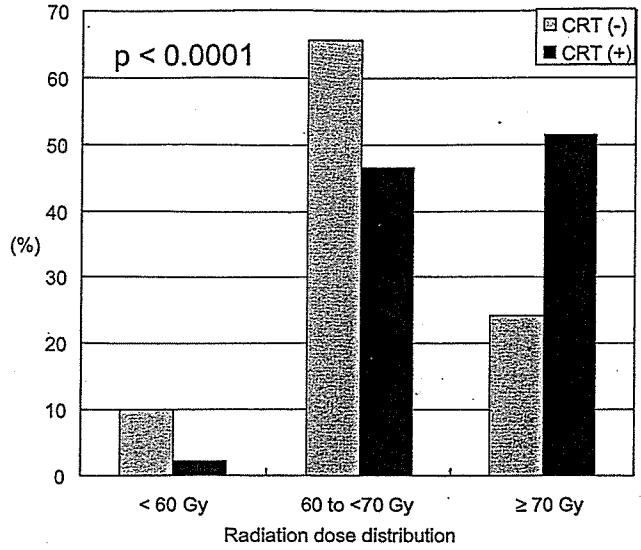

Figure 2. Radiation dose distribution for Japanese prostate cancer patients as a function of use of conformal therapy (CRT).

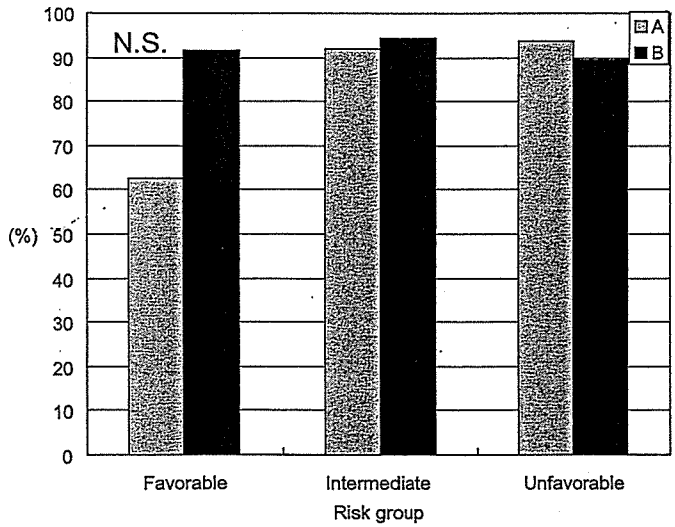

Figure 3. Hormonal therapy distribution as a function of disease risk for A (academic) and B (non-academic) institutions. Favorable meets all conditions below. Intermediate meets 2 conditions. Unfavorable meets only 1 or no conditions. (1) PSA ≤ 10 (2) not poorly differentiation (3) T stage < 3.

terms of equipment and personnel. Concerning treatment equipment and radiotherapy technique, lower rates of beam energy ≥10 MV, usage of portal films or electric portal images, and all fields treatment for each day were observed in non-academic institutions. Moreover, in non-academic institutions, only 77.1% of patients received CT-based treatment planning and 24.1% of patients received conformal therapy, compared with 91.5% and 56.4%, respectively, in academic institutions. The use of CT-based treatment planning and conformal radiotherapy significantly influenced total radiation dose. In the United States, the overall quality of radiotherapy for prostate cancer has been improving for years and has been higher than that in Japan: 95% of US patients received CT-based treatment planning and 80% received conformal therapy in the 1999 US PCS (15,17–20). On the other hand, radiotherapy for prostate cancer was still developing in Japan during the period when this national survey was conducted. Therefore, in order to provide high-quality radiotherapy in Japan, facilities need appropriate treatment planning capabilities. Modern radiotherapy requires CT-based treatment planning or conformal therapy to improve target dose distribution while reducing normal tissue dose (21).

The 1999–2001 PCS survey also revealed that the median number of FTE radiation oncologists employed by non-academic institutions to manage their many patients was lower than the median number employed by academic institutions (A: 2.4, B: 0.4, $P < 0.0001$). At the same time, the number of patients treated with radiotherapy has continually increased in every institutional type, with an overall increase of 140% over the past 10 years (22). These trends call for increasing the number of FTE radiation oncologists on duty especially in non-academic institutions.

The current study demonstrated the almost routine administration of hormonal therapy (A institutions: 89.0%, B institutions: 90.7%) to Japanese patients treated between 1999 and 2001. Moreover, the percentage of favorable risk patients receiving hormonal therapy remains high in Japan despite the results of several US studies indicating that radical radiotherapy alone can control disease in favorable risk patients. Pollack et al. (23) indicated that a total dose of 70 Gy was sufficient to control disease with a pretreatment PSA level <10 ng/mL. Hanks et al. (24) found that patients with pretreatment PSA < 10 ng/ml did not benefit from dose escalation >70 Gy. Therefore, the primary non-surgical treatment practice for US patients with favorable risk disease is radical external beam radiotherapy without hormonal therapy unlike the practice we identified in Japan. One major reason for the frequent use of hormonal therapy in Japan may be the high rate of health insurance coverage for Japanese people (25). However, in line with current treatment practice in the United States, we propose that radical external beam radiotherapy alone should also be the treatment of choice for favorable risk patients in Japan.

In contrast, a growing body of evidence suggests that radiotherapy with hormonal therapy is more effective than radiotherapy alone for high-risk patients. For instance, the results of various randomized trials by the Radiation Therapy Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC) demonstrated that combining radiotherapy with hormonal therapy was advantageous for high-risk patients with clinically localized prostate cancer (26,27). The 1999 US PCS reported that 79% of radiotherapy patients with unfavorable risk disease received hormonal therapy in the United States, reflecting the penetration and growing acceptance of clinical trial results demonstrating the efficacy of combination treatment approaches (15). In Japan, the 1999–2001 PCS also found that radiotherapy combined with hormonal therapy represents the standard care for patients with unfavorable risk disease,

with over 90% of such patients receiving combination therapy. Based upon clinical study data and the US PCS data, radiotherapy combined with hormonal therapy for Japanese patients with unfavorable risk disease appears to be a reasonable practice.

In summary, our analysis of the 1999–2001 PCS data revealed that most prostate cancer patients treated in Japan with radical external beam radiotherapy have advanced diseases and that institutional type significantly influences radiotherapy practice patterns. Differences in practice patterns must not be disregarded when they can negatively influence outcome. The impact of these practice differences on outcome should be examined in a future study. The current study also demonstrated that radiotherapy was commonly combined with hormonal therapy regardless of institution type and disease risk group. Therefore, the optimal use of hormonal therapy also needs to be addressed in future studies.

Acknowledgments

Supported by Grants-in-Aid for Cancer Research (Grant No. 14-6) from the Ministry of Health, Labor and Welfare of Japan. We thank all radiation oncologists who participated in this study. Their efforts to provide information to us make these surveys possible. We are grateful for the continuous thoughtful support we have received from the US PCS committee for 9 years.

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乳腺疾患の臨床

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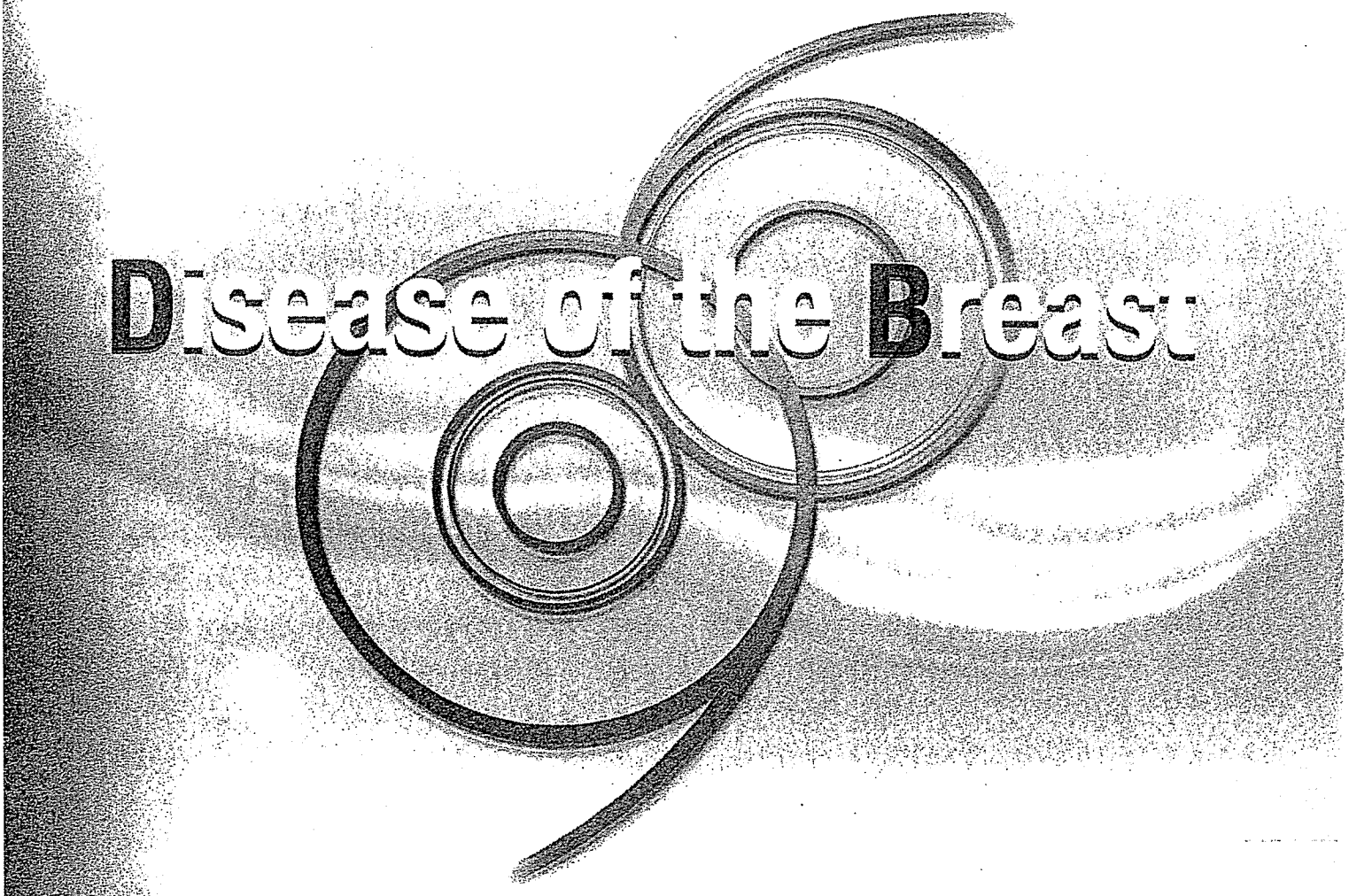

金原出版株式会社

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(執筆順)

4. 骨転移・脳転移の放射線治療

はじめに　乳癌の他臓器転移において最も頻度が高いのは骨転移であり，遠隔転移の約6割を占め，肺，肝，脳転移[1]がこれに続く。放射線治療の対象となるのは主に骨および脳転移であり，放射線治療についてその目的，適応，方法を概説する。

A 骨転移に対する放射線治療

1 乳癌骨転移の特徴と放射線治療

骨転移部位は血流の多い赤色髄に多く，椎体（腰椎，胸椎，頸椎の順），骨盤骨，肋骨，大腿骨に多く生じる。乳癌骨転移単独例の平均生存期間は28カ月との報告もあり，長期生存も期待可能である[2]。脊椎転移342症例の後ろ向き研究では，原発部位が乳癌であることは，全身状態良好，内臓転移がないことと並んで予後良好因子の一つとされており[3]，QOLの維持を目的とした放射線治療の果たす役割は大きい。

2 放射線治療の目的

骨転移に対する放射線治療の目的は，疼痛の軽減，病的骨折の予防，脊髄圧迫による麻痺の予防と改善である。有痛性骨転移は原則的に放射線治療の適応となるが，無痛性であっても臼蓋部や長管骨，脊椎などの荷重がかかり，運動障害を起こし得る部位に生じた転移に対しては放射線治療の適応がある。一般に骨転移に対する放射線治療では，50～80%に疼痛の緩和が得られ，およそ20～50%の症例には完全除痛が得られると報告されている[4][5]。

3 放射線治療の方法

単純X線写真で溶骨性変化および造骨性変化の範囲，骨シンチグラフィで全身骨の転移部位の検索，CTまたはMRIで骨破壊の程度と骨外病変の範囲を把握した上で治療計画を行う。

日常臨床ではX線シミュレーターを用いて，病変の部位によって症例ごとに1門～多門の照射法を選択する。CTシミュレーターも徐々に普及し，正常臓器の線量を考慮した照射法，範囲設定を正確に把握できるようになった。骨盤骨や肋骨などは腸管や肺への照射をできるだけ避けるよう注意が必要である。

4 疼痛緩和における線量・分割方法

骨転移による疼痛緩和は，根治治療に必要とされる線量より低線量で目的を達することが示されているが，その総線量・分割方法に関して統一した見解はない。

わが国では30Gy/10回/2週が最も浸透した照射法であると思われるが，近年除痛目的として8Gy/1回照射を支持する報告が相次いでおり[6]~[8]，標準治療として広く用いられるものと思われる。Radiation Therapy Oncology Group（RTOG）9714では，長期予後が期待できる乳癌および前立腺癌からの骨転移例のみを対象として，8Gy/1回