●有害事象

全脳照射では，照射中に頭痛，悪心，嘔吐を来すことがあります。また，長期経過例で意欲や活動性の低下が問題となる例がみられます。

B 骨転移

●概　念

骨転移後の生命予後は，一般的に1年未満と短く，それに伴う疼痛，姿勢保持困難，運動制限は，患者のQOLを低下させます。予後の短い骨転移の患者にとっては，生活に支障を来す症状を緩和して，もとの生活に復帰することが治療の主目的となります。

骨転移による疼痛は，癌病巣の骨膜浸潤，病的骨折に伴う骨膜破壊，転移病巣の増大に伴う骨髄内圧上昇と骨膜伸展などによる骨膜に分布する神経末端に由来するだけでなく，破骨細胞が関与している可能性も指摘され，癌関連化学物質，プロスタグランジン，サイトカインなどが複雑に関与し，また，精神心理的な要素も加わって引き起こされると考えられています。

●予後因子，病期分類

原発疾患，転移個数，転移部位，骨破壊の程度，内固定の有無，有効な全身治療の有無などが，骨転移の予後因子として挙げられます。生命予後はこれらの予後因子によって異なるので，予測される生存期間を考慮に入れ，適切な緩和治療を多角的に検討し選択することが重要です。

●標準治療

放射線治療やオピオイドなどの薬物療法だけでなく，化学療法，ホルモン療法，ビスフォスフォネート製剤，整形外科的固定術，画像診断的介入interventional radiology（IVR）などから最適な治療法の組合せを患者個別に選択します。また，不眠，不安，不定愁訴を緩和するための支持療法（抗不安薬，抗潰瘍薬，下剤，制吐薬，神経弛緩薬，副腎皮質ステロイド薬，理学療法，心理カウンセリング，リラクゼーション療法など）を積極的に行います。

●放射線治療

放射線治療の最大の利点は，癌病巣を縮小させ，局所的に病勢進行を抑えることです。

①疼痛軽減の目的

日常生活に不自由な程度の疼痛，特に体動などによって急激な増悪を示す突出痛を認める場合に行います。短期間に除痛効果を得るため，通常は1回線量を3Gy以上とします。一般的に放射線治療による除痛効果は，4～12週後に最大になります。疼痛緩和に用いられる放射線療法の照射線量は，正常組織の耐容線量より低い場合が多く，余裕を残しています。疼痛が再燃した場合に，前回照射から数か月の期間があれば，多くの例で再照射が可能です。再照射による疼痛緩和率は，初回治療ほどは高くないものの，50％程度は得られます。

②運動姿勢機能の保持（病的骨折の予防）

臼蓋部や長管骨など荷重により病的骨折の危険のある部位や，脊椎，下肢骨のように病的骨折を起こすと運動機能障害によって日常生活が著しく阻害される部位の骨転移に行われます。大線量多分割照射の方が石灰化率は高いとされ，30Gy/10回/2週以上の分割照射が推奨されています（表3-1）。荷重のかかる長管骨の骨皮質に50％以上の破壊がみられたとき，あるいは病変の長さが2.5cm以上に及ぶ場合は，病的骨折の危険が高いと考えられます。このような症例に対しては，整形外科

表3-1　代表的な分割法

線量・分割	提唱元
8Gy/1回	カナダ・オンタリオ・ガイドライン
24Gy/6回	オランダ骨転移試験
20Gy/5回/1週	米国放射線医会推奨
30Gy/10回/2週	米国放射線医会推奨
40Gy/15～20回/3～4週	米国放射線医会推奨

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CLINICAL INVESTIGATION

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

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Purpose: To delineate changing trends in radical external beam radiotherapy (EBRT) for prostate cancer in Japan.
Methods and Materials: Data from 841 patients with clinically localized prostate cancer treated with EBRT in the Japanese Patterns of Care Study (PCS) from 1996 to 2005 were analyzed.
Results: Significant increases in the proportions of patients with stage T1 to T2 disease and decrease in prostate-specific antigen values were observed. Also, there were significant increases in the percentages of patients treated with radiotherapy by their own choice. Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing to 70 Gy from 2003 to 2005. Moreover, conformal therapy was more frequently used from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and from 1999 to 2001 (50.2%). On the other hand, the percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and from 1999 to 2001 (89.7%). Compared with the PCS in the United States, patient characteristics and patterns of treatments from 2003 to 2005 have become more similar to those in the United States than those from 1996 to 1998 and those from 1999 to 2001.
Conclusions: This study indicates a trend toward increasing numbers of patients with early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipment among Japanese prostate cancer patients treated with EBRT during 1996 to 2005 survey periods. Patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. © 2010 Elsevier Inc.

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

INTRODUCTION

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

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

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Conflict of interest: none.

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

METHODS AND MATERIALS

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

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

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

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

RESULTS

Patient characteristics

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

Treatment characteristics

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

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

Table 1. Patient and disease characteristics

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

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

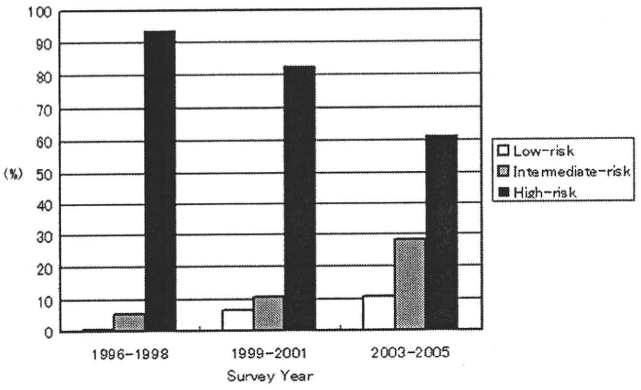

Fig. 1. Distribution of patients with prostate cancer according to risk group among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

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

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

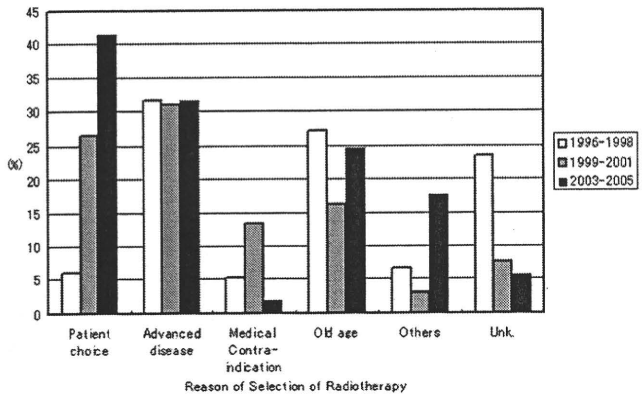

Fig. 2. Reasons of selection of EBRT for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

FTE radiation oncologists

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

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

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

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

DISCUSSION

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

Table 2. Treatment characteristics

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

Abbreviation: SD = standard deviation.

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

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

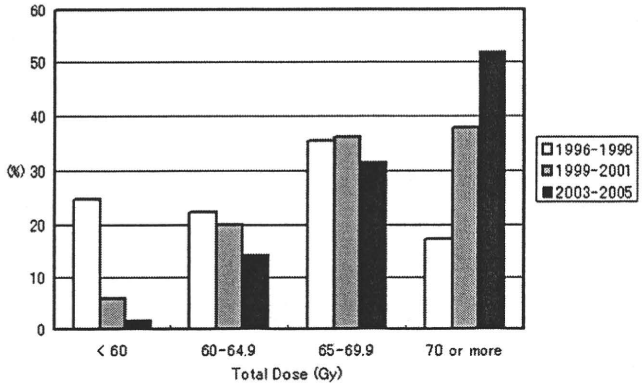

Fig. 3. Distributions of total radiation doses of external beam radiotherapy for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

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

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

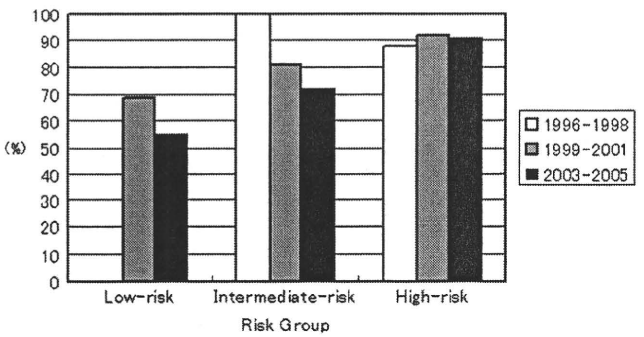

Fig. 4. Hormonal therapy distribution according to risk group for prostate cancer in Japan among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

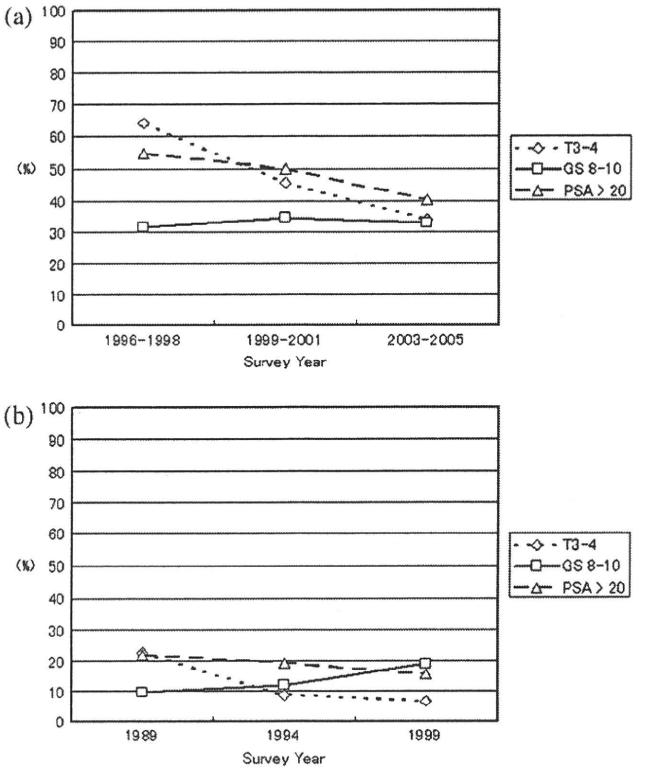

Fig. 5. (a) Changing trend in patient characteristics in Japan. (b) Changing trend in patient characteristic in the United States. (Data from ZelefskyMJ, Moughan J, Owen J, et al. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 patterns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

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

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

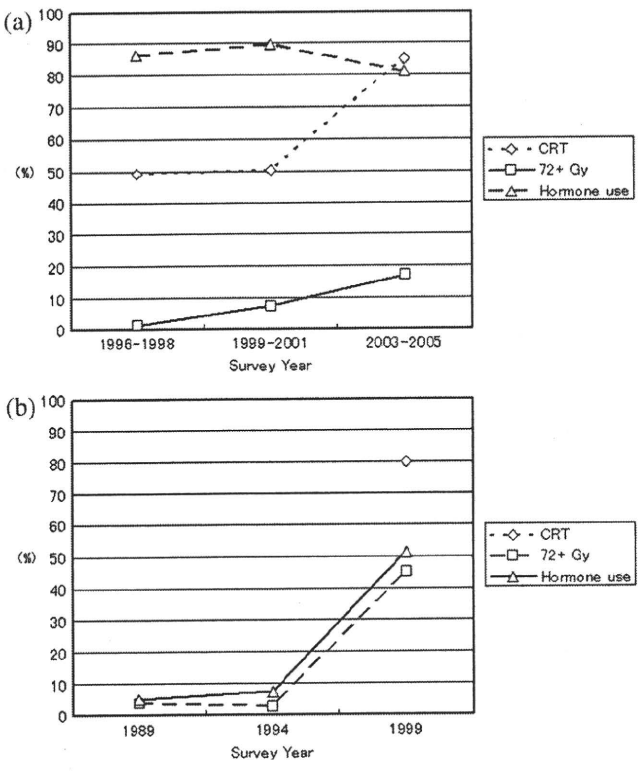

Fig. 6. (a) Changing trend in treatment characteristics in Japan. (b) Changing trend in patient characteristics in the United States. (*Data from* Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328.)

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

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

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

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

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

CONCLUSIONS

By comparing the PCS results of 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, we can delineate changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. Study data indicate a trend toward increasing early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipments, suggesting that radical EBRT is gaining acceptance as a first-line treatment for prostate cancer in Japan. Also, our results indicate that patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. In the future, to optimize the delivery of radiotherapy, more advanced equipment and more FTE radiation oncologists are warranted. Also, repeat surveys and point-by-point comparisons of results from other countries, such as the United States, will demonstrate how EBRT for prostate cancer has been developed and optimized for patients in Japan.

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Examination of fundamental characteristics of a polymer gel detector in a proton beam irradiation

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ABSTRACT

This paper was intended as a study of the radiological characteristics of a polymer gel detector in a clinical proton beam irradiation. The depth dose distributions in the detector were examined with regard of dose and dose rate dependences in the response. Our experimental results indicated that the dose response depended considerably on the depth from the incident position, and also the dose rate in the proton irradiation. We estimated the dose response at different depth of the incident proton beam from the depth-R_2 relations with various dose, and the spread-out depth dose in a single field irradiation derived from these dose responses obtained the good agreement with a planned dose distribution. In conclusion, our method with MAGAT type polymer gel is effective in a quality assurance of fundamental reproducibility test for three dimensional radiation therapy planning system, such as monitor unit verification and standard isodose verification using a single field proton beam. However the depth dose distribution should be evaluated depending on irradiation dose rate, SOBP width, and maximum energy.

1. Introduction

In the recent stereo-tactic irradiations and intensity-modulated radiotherapy treatments, a highly tailored multi-segmented X-ray beam can give precise radiation doses to the target volume. As results high radiation doses are allowed to be delivered to the tumor while sparing healthy tissue. These complex three dimensional (3D) radiation distributions can be determined by the 3D radiation therapy planning (RTP) system and also 3D optimizations with the computed tomography (CT) simulator. In order to perform the irradiations with extraordinary precision, it is essential to establish the method of direct 3D dose verifications.

A polymer gel detector is one of the detectors that have the potential to be a 3D dosimeter. It is a radiation sensitive detector utilizing a radiation-induced polymerization reaction of vinyl monomers. The polymerization degree depends on exposing dose, and the resulting polymers in the detector affect the mobility of the surrounding water molecules. Eventually, the 3D absorbed dose distribution in the detector can be estimated from the distribution of the spin–spin relaxation time (T_2) deduced by the magnetic resonance imaging (MRI) measurements.

Since a polymer gel detector has been introduced, its radiological characteristics in the irradiation of photons have been well investigated so far (e.g. reviewed by De Deene et al., 2006). However, a few studies on its characteristics have been reported with regard to the irradiation of high linear energy transfer (LET) particles including protons (Baker et al., 2009; Heufelder et al., 2003; Jirasek and Duzenli, 2002; Ramm et al., 2000). In their results, strong suppressions have been observed in the response of the polymer gel detector at the Bragg peak. Gustavsson et al. (2004) indicated from the comparison of their experimental data with the Monte Carlo calculated LET distribution that the decrease of relative detector sensitivity (D_{gel}/D_{diode}) at the Bragg peak in the irradiation of 133 MeV monoenergetic protons was due to the increase in LET. As another characteristic in the dose response of a polymer gel detector, dose rate dependence in X-ray irradiation, that the reduction of the dose sensitivity with increasing dose rate, has been reported.

In this study, we focus the dose response at different depth positions from the beam entrance for a single field Bragg Peak irradiation scheme. Since LET and dose rate vary at each depth along a proton beam in a detector, single relation between dose and R_2 (dose-R_2 curves) is expected not to cover whole range of proton

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beam to estimate dose from observed R_2. First the dose-R_2 curves at each depth are deduced from the measurement of the depth-R_2 distribution of a clinical proton beam irradiation including the Bragg peak. Second we analyse the dose rate dependence in the dose response with the irradiation of protons to examine how it will relate to the suppression at the spread-out Bragg peak (SOBP). These preliminary results have been reported in Tominaga et al. (2009). Herein our recent results are presented, which include new data sets that were examined by the revised experimental method considering with a practical quality assurance. And also a dose distribution measured in a polymer gel detector is evaluated by comparison with a planned dose distribution. In addition, the diffusion kinetic "spur" model will be applied to give a phenomenological interpretation on both of LET effect and dose rate dependence.

2. Materials and methods

2.1. Polymer gel preparation

We prepared MAGAT type polymer gel detector (Bayreder et al., 2006) for this study. The recent studies have demonstrated that other polymer gel detectors, for example the PAG gel which compose of acrylamide with *N,N'*-methylene-bis-acrylamide as the monomer, had the advantages over the MAGAT gel in the various radiation properties such as the dependence on the dose rate and the dose integration (De Deene et al., 2006; Karlsson et al., 2007), nevertheless the MAGAT gel has over ten times steeper gradient in the dose–response relations than PAG gel's gradient, which is to advantage in the depth dose measurements.

The gel consists of distilled water, gelatin (300 Bloom, Sigma Aldrich) as gelling agent, methacrylic acid (99%, Wako) as a vinyl monomer, and tetrakis-hydroxy-methyl-phosphonium chloride (THPC) solution (80%, Sigma Aldrich) as an oxygen scavenger. Table 1 summarizes the composition for the gel of 1000 g. The details of procedure of the fabrication are described as follows. Gelatin was dissolved in a water-filled glass beaker at room temperature and left intact until it swelled from soaking. It was heated with a constant temperature at 60°C on a thermostatic water bath with gentle stirring. After the gelatin solution got clear and homogeneous, it was cooled down to 45°C. Methacrylic acid was added. Finally THPC solution was added at 40°C, and the mixture was stirred until it become homogeneous. The whole solution was filled into the whole set of cylindrical PMMA containers with 3 cm diameter and 20 cm length, and rectangular polyethylene terephthalate (PET) containers (8 cm × 8 cm × 17 cm). The container material inhibits the penetration of oxygen. All containers were completely filled with gel and over wrapped tightly with Parafilm (Pechiney Plastic Packaging Companys) after putting a rubber tap on the top. These containers were stored in an incubator at a fixed temperature (23°C) until the irradiation.

2.2. Irradiations

All samples were irradiated one day after gel preparation in a fixed horizontal 150 MeV proton beam at the facility of the Hyogolon Beam Medical Center. Preceding the irradiation to the samples, the ionization chamber setting with a water equivalent phantom was irradiated to determine the prescribed irradiation dose and dose rate at the monoenergetic Bragg peak and also at the center of the spread-out Bragg peak (SOBP). Then both monoenergetic and 3 cm spread-out depth dose in water were measured by the ionization chamber for reference.

The MAGAT gel's water equivalency in the physical characteristics has been evaluated by the calculations on the attenuation and ionization of radiations, and also by Monte Carlo calculations on the transport of electrons and photons in the gel and water (Venning et al., 2005; Haneda et al., 2007). In the performance of irradiations, a cylindrical gel detector was placed in water along the beam line including full proton's ionization range in the gel. First of all various doses from 1 to 20 Gy were delivered to examine the dose response of the detector. At this time, the dose rate of 4 Gy/min typically applied in treatments was fixed in SOBP irradiations and 10 Gy/min for the mono-peak irradiations. Secondary the dose rate was varied from 0.4 to 4 Gy/min at 4 Gy to examine the dose rate dependence on the response. The setting of a cylindrical gel detector during a performance of irradiation is pictured in Fig. 1. And for the purpose of comparison with RTP, a 150 MeV proton beam with a homogeneous dose of 4 Gy and dose rate of 4 Gy/min in 3 cm × 3 cm single field with 3 cm SOBP was delivered to the rectangular PET containers.

2.3. MRI analysis

After irradiations, all gel detectors were stored in the incubator again for one day before the measurements. MRI on the samples was conducted on a 1.5 T whole body scanner (SIEMENS, Magneton Symphony) equipped with a head coil. Coronal images through the

Table 1
Composition of 1000 g gel.

Chemical	Concentration
Water	85% (w/w)
Gelatin	10% (w/w)
Methacrylic acid	5% (w/w)
THPC	2 mM

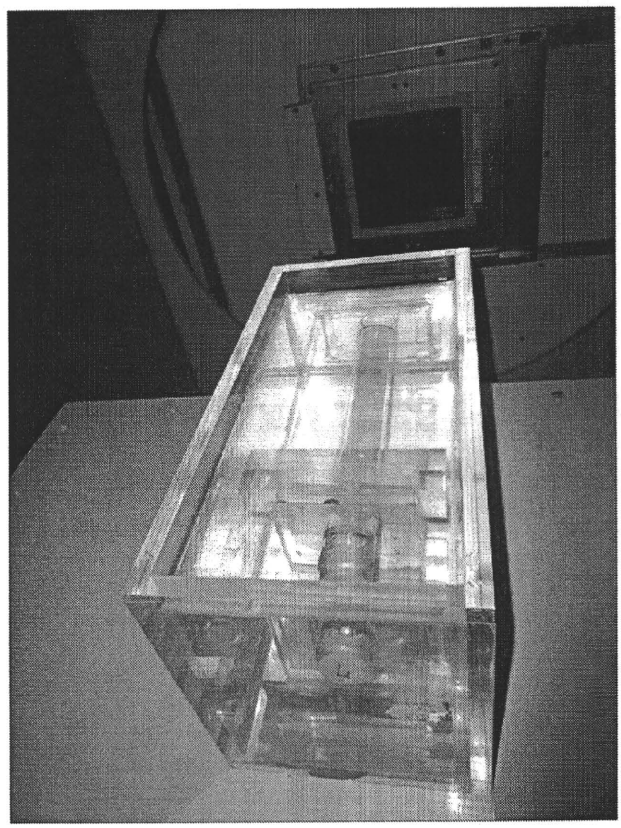

Fig. 1. Experimental set up for proton beam irradiations. A cylindrical MAGAT gel detector is placed at the center of an acrylic box full of water.

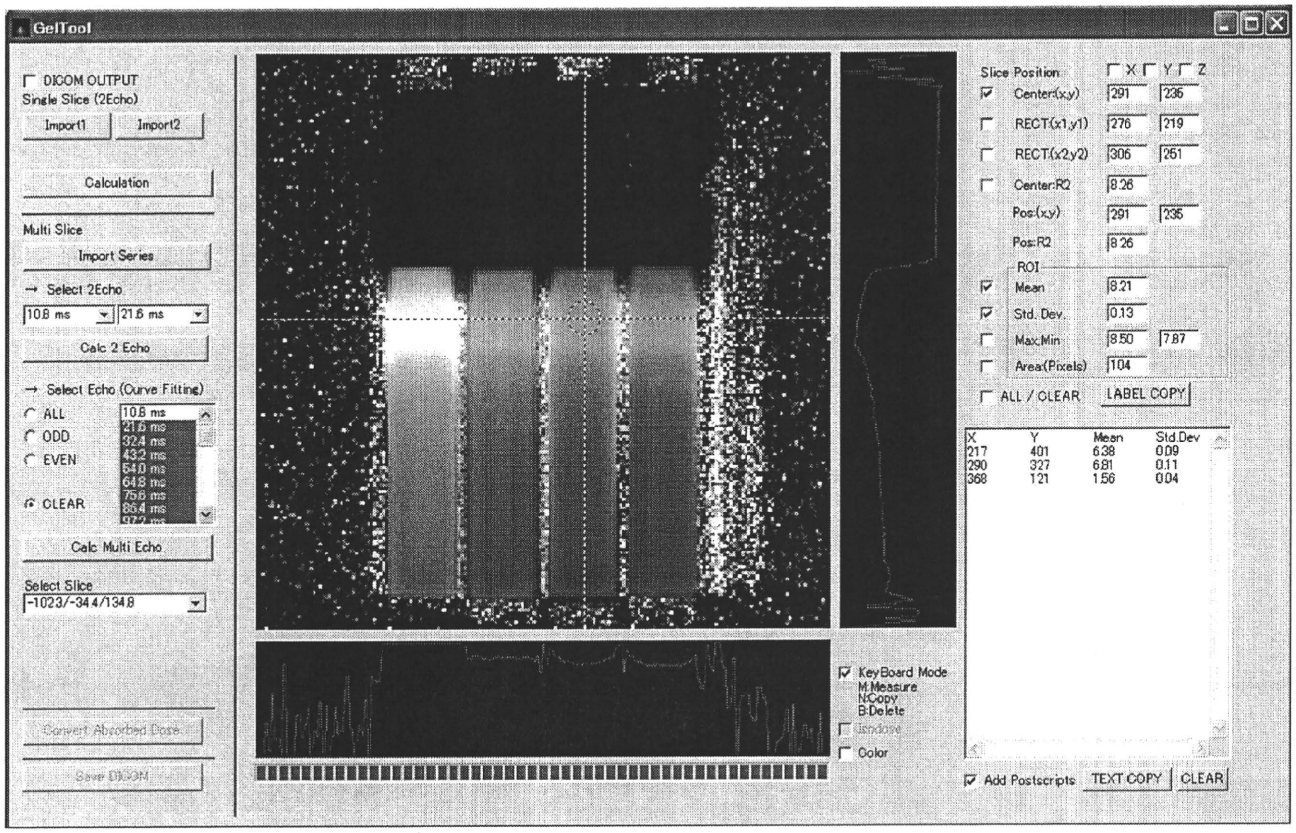

Fig. 2. Interface of GELTOOL. GELTOOL is an in-house written software to convert a measured image in DICOM format to R_2 images data for the statistical analysis by PC. As an example, the images at the coronal planes of four cylindrical samples are shown in the center of the display.

center of the cylindrical container for dose-R_2 experiments or transverse and sagittal images of the rectangular container for RTP experiment were acquired with multiple spin-echo pulse sequence. The acquisition parameters are as follows: number of echoes = 32, inter-echo time = 10.8 ms, *TR* = 5 s, *FOV* = 220 mm, matrix size = 192 × 192, slice thickness = 5 mm and number of acquisition = 1. DICOM format data from MRI were converted to PC for the calculation of the spin–spin relaxation rates (R_2) images by an in-house written software GELTOOL (Fig. 2) on a pixel-by-pixel basis. Considering the shortest T_2 relaxation time (40 ms), the R_2 values were derived algebraically from the signal intensity in the 17 images (*TE* = 21.6–194.4 ms) by fitting to a monoexponential function (De Deene and Baldock, 2002). In the case of dose-R_2 experiments, the R_2 values were adopted an average of 5 pixels in the same depth. The standard errors of R_2 were less than 3%.

3. Results

3.1. Depth-R_2 relations in the gel detector

Fig. 3 shows the depth-R_2 relations in the cylindrical gel detector at post irradiations with various amount of dose. The distributions in the case of monoenergetic protons are presented in Fig. 3 (left), and that in the case of 3 cm spread-out depth dose of protons are in

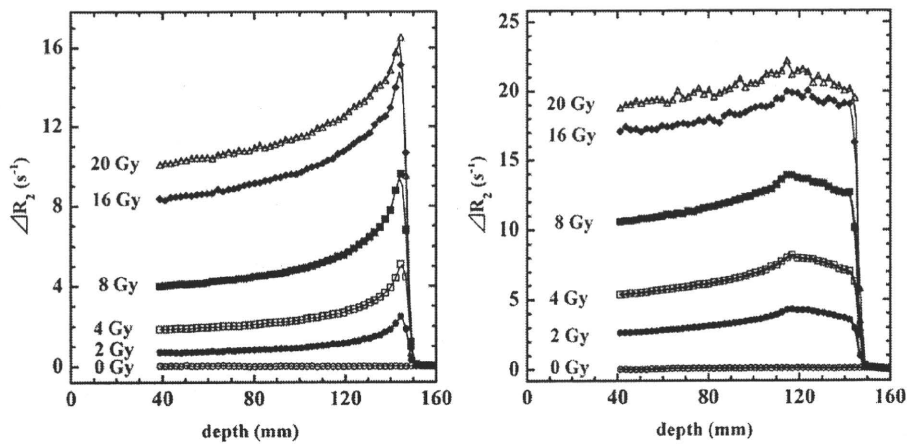

Fig. 3. The depth-ΔR_2 data for monoenergetic depth distributions (left) and spread-out depth ΔR_2 (right) of a 150 MeV proton beam with various dose in a cylindrical MAGAT gel detector.

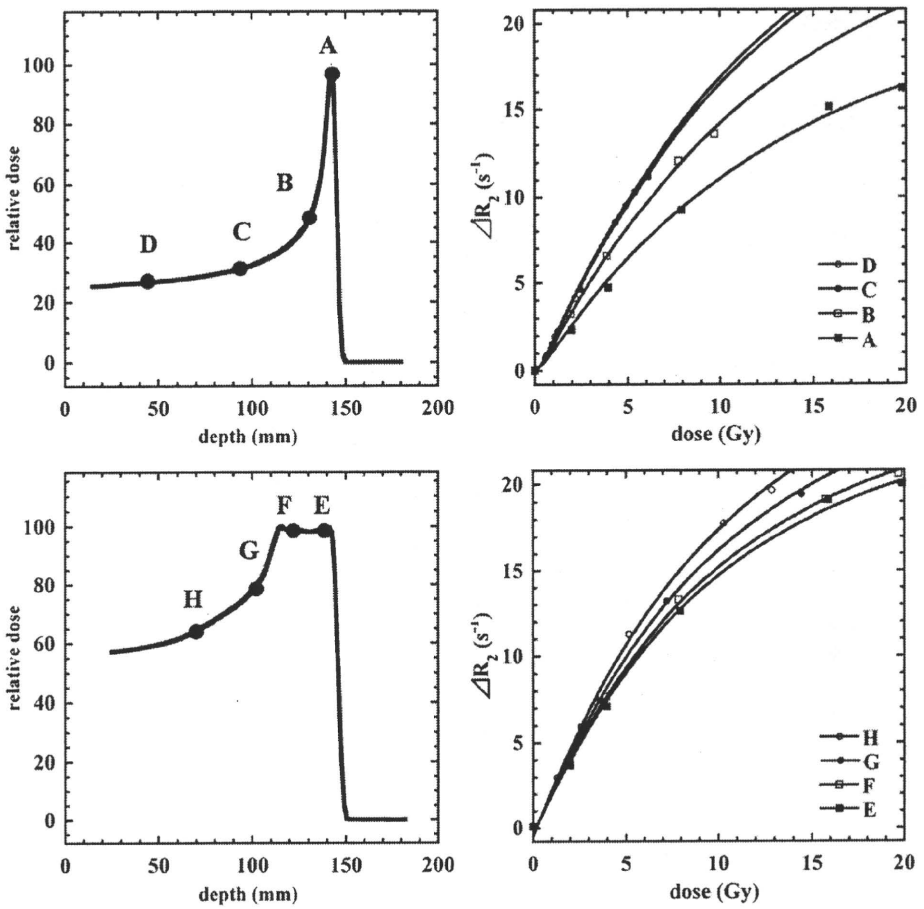

Fig. 4. Left: depth dose profiles from ionization chamber. Right: data from MAGAT polymer gel dosimetry. Top: Monoenergetic Bragg Peak. Bottom: SOBP. For polymer gel data the dose induced difference in ΔR_2 at various depths in a MAGAT gel detector is shown for 150 MeV protons. The fitted lines in the right figures are indicated by letters, which correspond to the different positions in depth dose shown in the left figures. The positions indicated by letters are as follows, A: 142 mm, B: 130 mm, C: 93 mm, D: 43 mm, E: 139 mm, F: 121 mm, G: 101 mm and H: 69 mm.

Fig. 3 (right). In the figure, its vertical axis represents the net R_2 value (ΔR_2), which was subtracted background R_2 from the R_2 of irradiated gel. A spatial uniformity in background R_2 has been confirmed by taking the images of un-irradiated cylindrical gel detectors in advance. The depth-ΔR_2 relations shown in Fig. 3 are corresponding to the depth dose distributions, and yet the relations between ΔR_2 and irradiation dose (dose-ΔR_2 curves) are required to convert each other. It must be noted that the absorbed dose given in the figure are the values at the center of SOBP where the prescribed dose has been calibrated by ionization chamber. The incident protons lose their velocity and kinetic energy gradually in the gel due to the inelastic collisions with bound electrons. As the consequence, the yield of water radicals induced by the ionization along their pass seems to depend on their kinetic energy, namely the

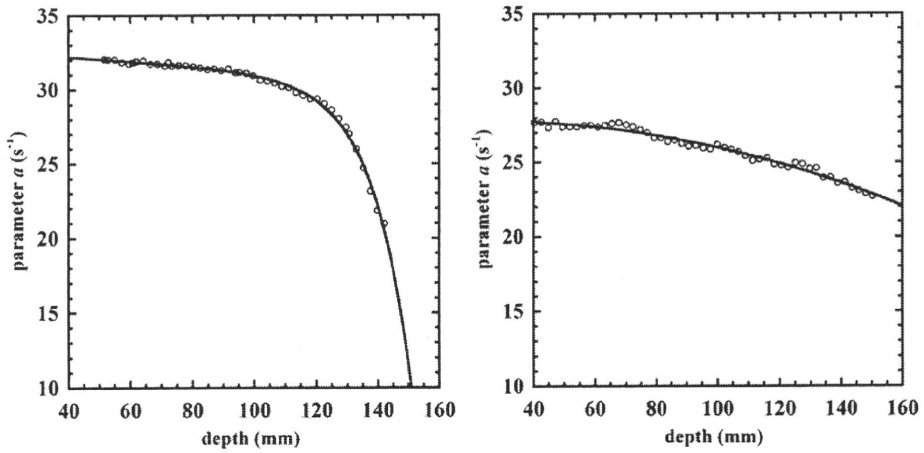

Fig. 5. The calculated "a" [s^{-1}] values at various depths in a MAGAT gel detector for 150 MeV protons. The data are fitted by the bi-exponential function as follows, Left: $\Delta R_2 = a \cdot (1 - \exp(-0.077 \cdot (dose - 0.26))) + 0.66 \cdot \exp(-3.7 \cdot dose)$ for monoenergetic beam. Right: $\Delta R_2 = a \cdot (1 - \exp(-0.10 \cdot (dose - 0.050))) + 0.0010 \exp(-0.50\ dose)$ for SOBP beam.

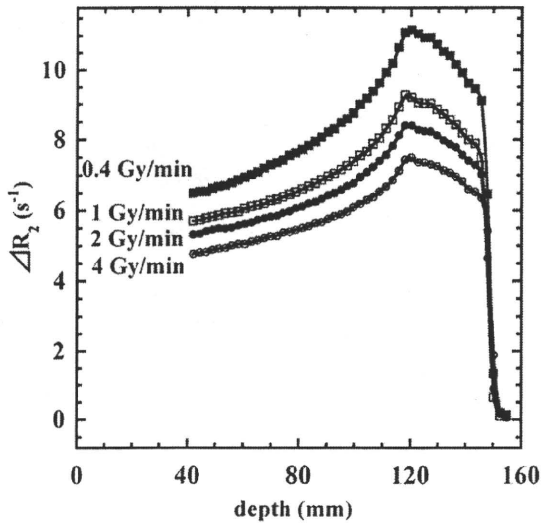

Fig. 6. Spread-out depth-ΔR_2 relations of a 4 Gy proton beam with various dose rates in a cylindrical MAGAT gel detector.

density of radicals would increase along the pass with the decrease of proton's kinetic energy. It is quite likely that this fact would affect the variation in the initiation of polymerization reaction and the probability of their termination reactions in the gel. Thus it is reasonable to suppose that the dose response of the gel detector depends on a kinetic energy of proton, in other words, depends on the depth from the incidence position in the detector. That corresponds to LET effect in the dose response. In the mean time no significant difference in the dose response for 6 MV and 25 MV photon beam has been observed by De Deene et al. (2006). Fig. 4 shows the dose response (ΔR_2) at different depth of the incident beam for the detector irradiated with monoenergetic and spread-out depth dose of protons.

The details of procedure how these curves were derived from the depth-ΔR_2 relations are described as follows. First the origin of the depth coordinates, z_0 mm, is found at the first pixel whose ΔR_2 is equal to the background level following the edge of SOBP, and set z_0 to 150 mm, which corresponds to the depth coordinates in mm at the bottom end of SOBP on the percentage depth dose (PDD) derived from ion-chamber measurements. The depth coordinates

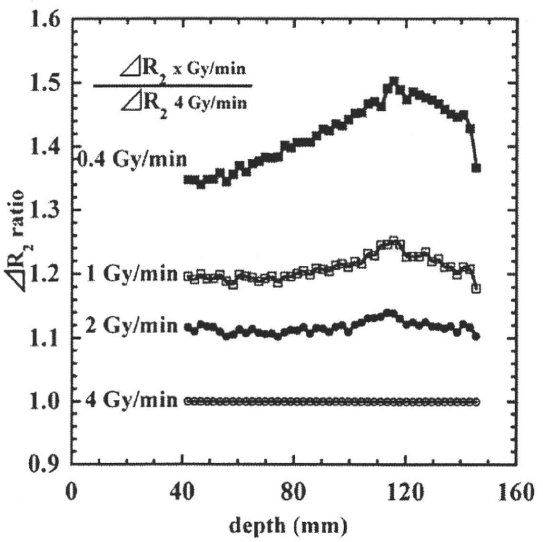

Fig. 7. The same result as in Fig. 6 normalized to ΔR_2 at 4 Gy/min.

of all depth-ΔR_2 relations can be determined identically within the accuracy of 1.15 mm (one pixel size) by means of this process. The depth coordinate of each pixel is found in increments by 1.15 mm toward the beam entrance. Next the absorbed dose of each pixel at the depth coordinate, z mm, was calculated from PDD as follows,

$$Dose(z) = \frac{\int_{z-\Delta z/2}^{z+\Delta z/2} PDD(z)\cdot Dose_{\max} dz}{100\cdot\Delta z} \quad (1)$$

where $Dose_{max}$ represents maximum dose at Bragg peak for a monoenergetic beam, or at the center of SOBP for a spread-out depth dose beam, and $PDD(z)$ is a function of z that presents the percentage depth dose, and Δz corresponds to pixel size. This procedure is applied to all depth-ΔR_2 relations, and finally the dose-ΔR_2 relation at any z coordinates were derived from a combination of all depth-ΔR_2 relations of corresponding pixel to the position.

The plots in the figure are fitted by the bi-exponential function as follows,

$$\Delta R_2 = a\cdot(1-\exp(-b\cdot(dose-c))) + d\cdot\exp(-e\cdot dose) \quad (2)$$

where parameter "a" and "b" would relate to the maximum spin–spin relaxation rate at the high dose range, and also a gradient at the middle dose range where ΔR_2 is proportional to dose. While parameter "c" and second exponential function would relate to the "induction" effect, which is generally seen as gently slope of response curve of polymer gel detector at the low dose range (De Deene et al., 2006). In optimizing each parameter, we firstly fixed all parameter except "a" in the expression (2) to plausible constant values by independent on the depth and secondary determined the value of "a" at the depth of each pixel by the method of least squares. Relationship between the value of "a" and the depth in the gel detector for monoenergetic and SOBP beams are shown in Fig. 5.

3.2. Dose rate dependence on the dose response

Fig. 6 shows the series of SOBP of protons with increasing dose rate from 0.4 Gy/min to 4 Gy/min in the irradiation at 4 Gy. As shown in the figure, it is clear that absolute values of ΔR_2 strongly depend on dose rate such that ΔR_2 increase with decreasing dose rate. The ratios of ΔR_2 at each dose rate to ΔR_2 at 4 Gy/min appear within Fig. 7, which makes clear the effect of dose rate dependence regarding to each depth. As the figure indicates that the effect increases moderately with increasing the depth to the front of SOBP, and turns to decrease at SOBP. These results lead us to the speculation that the dose rate dependence, which is attributed to incident proton-induced radicals reacting with other nearby proton-induced radical, is dominant on the way of SOBP, while the LET effect, which is due to the reaction within single proton-induced radicals, starts to contribute at the remaining depth to the edge of SOBP (3 cm). In our previously reported results on depth-R_2 distributions with 6 cm SOBP (Fig. 6 in Tominaga et al., 2009), similar tendencies were observed in dose sensitivity, and the reduction of the dose sensitivity exhibited remarkably at the depth from a half of SOBP to the edge (3 cm), which are consistent with present results.

3.3. Comparison of the dose distribution with a radiation treatment-planning

These characteristics of the gel detector on the dose response described above lead us to the remark on the dose estimation from ΔR_2 in the irradiation of protons. That is, the multiple dose-ΔR_2

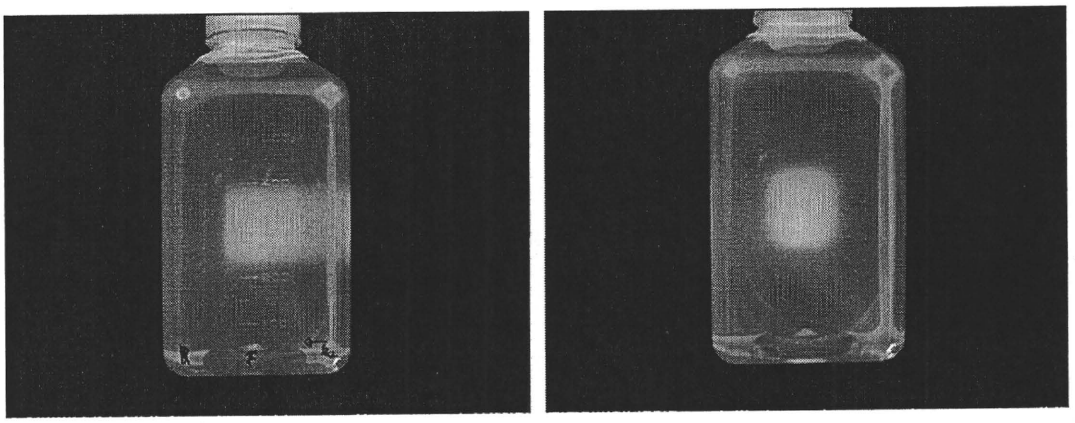

Fig. 8. Side and front view of a rectangular MAGAT gel detector after irradiation with a proton. beam (150 MeV) using a homogeneous dose of 4 Gy in 3 cm × 3 cm single field with 3 cm SOBP.

curves have to be applied with taking account of the depth from the incidence position instead of applying a single dose-ΔR_2 curve to the irradiated field entirely. With this issue in mind, we attempted to compare the dose distribution estimated from the measurement of a gel detector with a planned one. In the RTP, a planning target volume (PTV) was determined to 3 cm × 3 cm × 3 cm inside a rectangular PET container with setting to the center of PTV by the use of CT value data. CT scanning of the container with MAGAT gel was performed in advance. Fig. 8 shows the view of the sample after irradiation. The origin and the depth coordinate of each pixel were found as same as mentioned above. The dose-ΔR_2 relations calculated for pixel by pixel of each depth were applied to ΔR_2 of pixel at its corresponding depth for dose estimation on a longitudinal plane, and single dose-ΔR_2 relation was applied for dose estimation on a transverse plane. Dose distributions at longitudinal and transverse planes at the center of SOBP in a rectangular gel detector are displayed in Fig. 9 with the calculated distributions by RTP. The figures indicate that the measured dose distribution is well consistent with the calculated distribution.

4. Discussions

The diffusion kinetic model for a "spur", defined as a localized microscopic area involving several water radicals (Yamaguchi et al.,

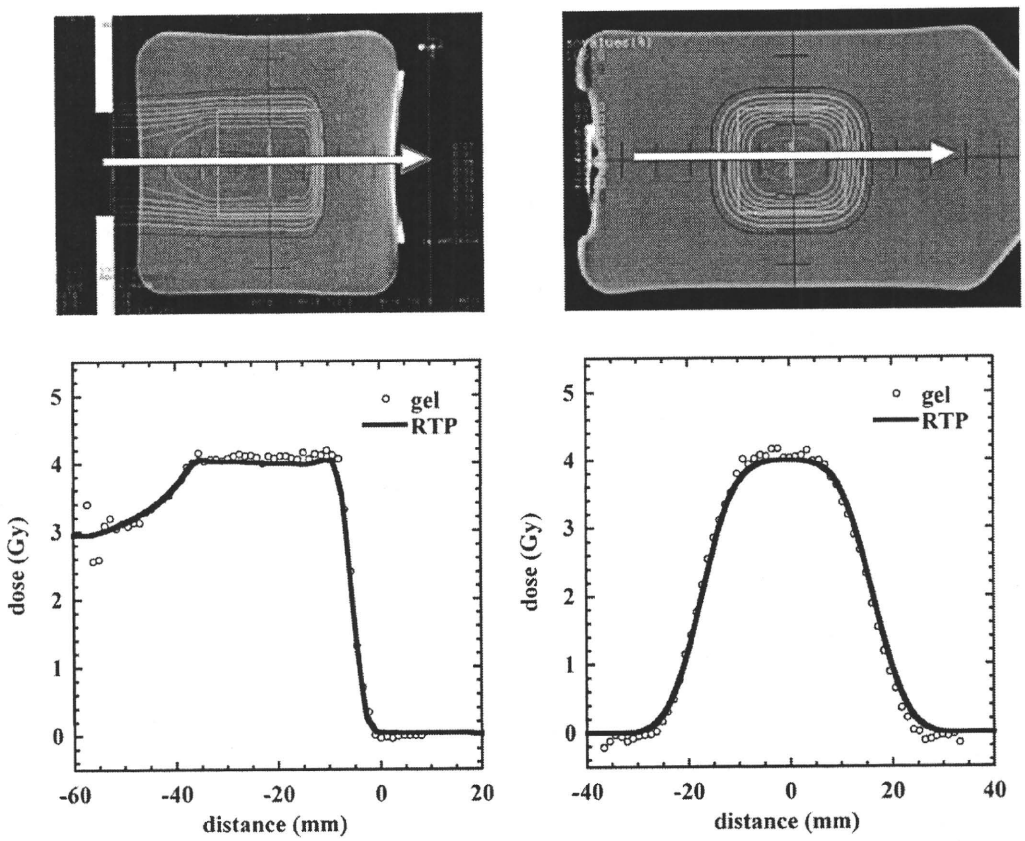

Fig. 9. Dose distributions at longitudinal and transverse planes at the center of SOBP in the rectangular MAGAT gel detector. Top: CT images with RTP dose distribution for front (right) and side (left) view. The arrows in the pictures correspond to the dose profiles from MRI as shown in the lower figures. Bottom: The solid line indicates expected distribution as calculated with RTP.

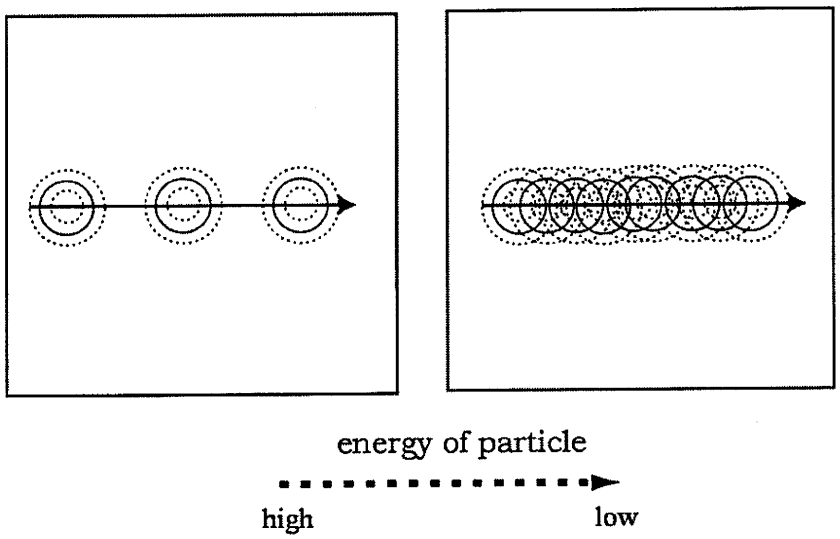

Fig. 10. Illustration of the spur model to interpret the energy dependence of the dose response. The density of spurs on a trajectory corresponds to the amount of ionization. The solid arrow represents a single proton track. The solid and dotted circles visualize the propagation of a spur. The distance between successive initial spurs decreases and the interactions of radicals increase abruptly with increasing LET.

2005), gives a reasonable account of the physical interpretation of the energy dependence for a dose response of the gel detector. Though it is just an empirical model that has been applied to the Monte Carlo simulations of the radiation chemistry occurring in a typical spur produced in the radiolysis, it is helpful to picture the phenomenological behavior of radicals in a gel detector. In the model, a spur is initially produced along the paths of an incident particle and secondary electrons, and propagates into a medium like a diffusion of elementary wave. It is also assumed that an initial spur would have constant size and include same number of radical. The radical inside the spur reacts only to other radicals in the nearby spur when both diffusing spurs interact with each other. As the distance of producing successive spurs along a track depends on kinetic energy of an objective particle, the yields of radical depend on the localized energy loss along its trajectory. With the energy loss advances, the interactions of radicals increase abruptly owing to decrease of distance between the spurs. This behavior of radicals must affect the yield of polymerization and the diffusion of produced polymers in the gel, and as the consequence, the dose response would be suppressed gradually as incident proton energy decreases. As the illustration in Fig. 10 shows, the energy dependence for the dose response is caused by the interactions among the spurs created along a single truck trajectory. With regard to a photon or electron beam, because of the electron's elastic scattering and the random movement in the material, an each individual electron has a unique path length and energy no matter the depth. Therefore, no evident dependence on the beam energy is observed for the dose response in these irradiations. Next we speculate about the dose rate dependence for the dose response by the spur model. The images of the model at high and low dose rate irradiations are illustrated in Fig. 11. In the higher dose rate irradiation, the interactions between radicals occur more frequently due to the decrease of distance between the spurs created along the adjacent protons. And as the result, the dose response would be

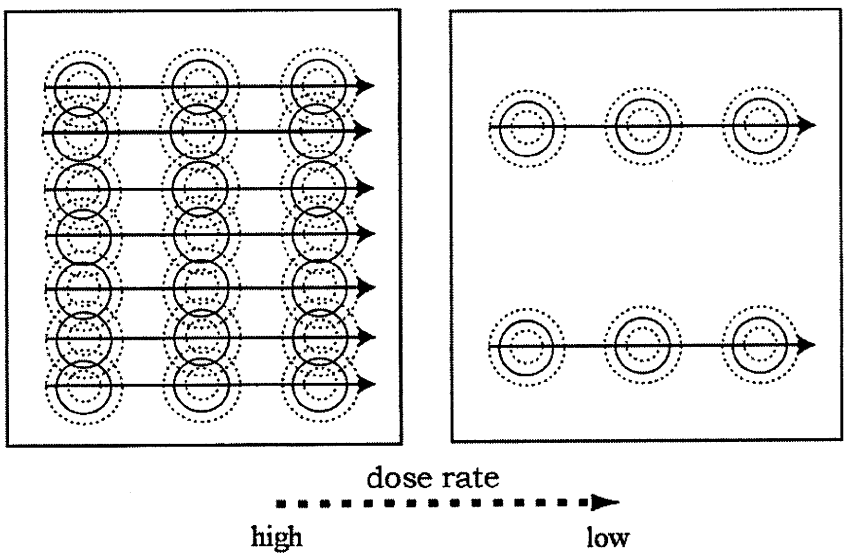

Fig. 11. Illustration of the spur model to interpret the dose-rate dependence of the dose response. The higher the dose rate, the more spurs interact with each other.

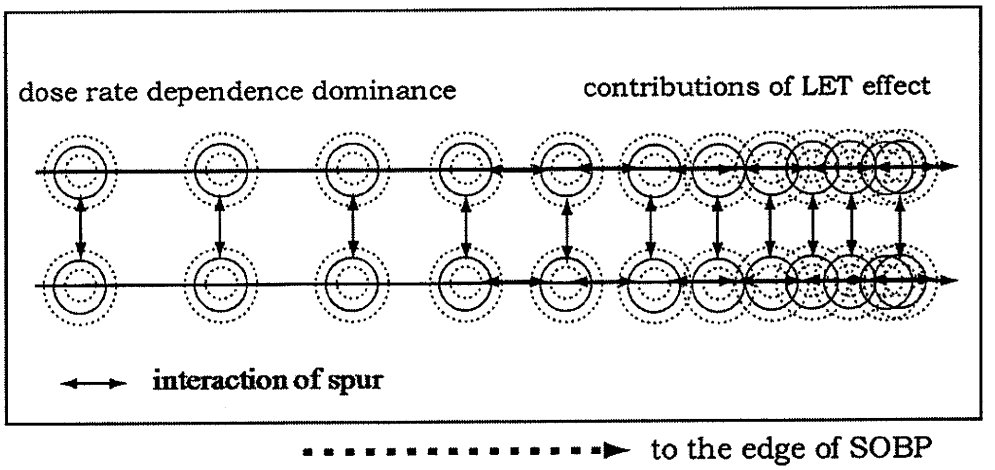

Fig. 12. Illustration of the spur model to interpret the evidence at the end of SOBP. A spur at the end of SOBP starts to interact with the neighboring spur originated from same incident proton.

suppressed gradually as the dose rate increases. As long as the dose rate dependence is caused by the incident trajectory congestion, this effect is observed even in the irradiation of photon beam (Bayreder et al., 2006). This model is also applied to interpret the evidence of the variation in the efficiency of dose rate dependence as to the depth (Fig. 7). That is, the effect increase with increasing the depth from a beam entrance due to increasing the number of spur per unit volume, however it turns to decrease at SOBP due to increasing the contribution of interaction with the neighboring spur originated from same incident proton, LET effect, which is not depend on the dose rate (Fig. 12).

5. Conclusion

In this work, we have concerned about the dose response of a MAGAT gel detector at different depth positions from the beam entrance for a single field Bragg Peak irradiation scheme in the irradiation of a clinical proton beam. Our experimental results showed that a dose response of the gel detector was considerably depending on the energy of an incident proton and its dose rate in the irradiation. The diffusion kinetic "spur" model interpreted these evidences phenomenologically. We have deduced the dose response relations at each depth from the depth-ΔR_2 relations, and applied them to the dose estimation of SOBP. The results obtained the good agreement with a planned dose distribution at longitudinal and transverse planes at the center in a single field irradiation. These results show that our method with MAGAT type polymer gel is effective in a quality assurance of fundamental reproducibility test for 3D treatment-planning system, such as monitor unit verification and standard isodose verification using a single field proton beam. And it is applicable in principle to various environmental irradiation conditions, but depth-ΔR_2 distributions should be evaluated again in order to make corrections in the dose response for the used gels under the condition.

A further direction of this study will be to examine the detail on the dose integration property of the gel detector in the multiple field irradiations to establish the presented method for direct 3D dose verification, and to investigate the dose response of other gel detector to a proton beam for the development of a better gel dosimeter in proton therapy.

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CLINICAL INVESTIGATION **Radiation Oncology Practice**

JAPANESE STRUCTURE SURVEY OF RADIATION ONCOLOGY IN 2007 BASED ON INSTITUTIONAL STRATIFICATION OF PATTERNS OF CARE STUDY

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Purpose: To evaluate the ongoing structure of radiation oncology in Japan in terms of equipment, personnel, patient load, and geographic distribution to identify and improve any deficiencies.

Methods and Materials: A questionnaire-based national structure survey was conducted from March to December 2008 by the Japanese Society of Therapeutic Radiology and Oncology (JASTRO). These data were analyzed in terms of the institutional stratification of the Patterns of Care Study.

Results: The total numbers of new cancer patients and total cancer patients (new and repeat) treated with radiation in 2007 were estimated at 181,000 and 218,000, respectively. There were 807 linear accelerator, 15 telecobalt, 46 Gamma Knife, 45 ^{60}Co remote-controlled after-loading, and 123 ^{192}Ir remote-controlled after-loading systems in actual use. The linear accelerator systems used dual-energy function in 539 units (66.8%), three-dimensional conformal radiation therapy in 555 (68.8%), and intensity-modulated radiation therapy in 235 (29.1%). There were 477 JASTRO-certified radiation oncologists, 826.3 full-time equivalent (FTE) radiation oncologists, 68.4 FTE medical physicists, and 1,634 FTE radiation therapists. The number of interstitial radiotherapy (RT) administrations for prostate, stereotactic body radiotherapy, and intensity-modulated radiation therapy increased significantly. Patterns of Care Study stratification can clearly identify the maturity of structures based on their academic nature and caseload. Geographically, the more JASTRO-certified physicians there were in a given area, the more RT tended to be used for cancer patients.

Conclusions: The Japanese structure has clearly improved during the past 17 years in terms of equipment and its use, although a shortage of personnel and variations in maturity disclosed by Patterns of Care Study stratification were still problematic in 2007. © **2010 Elsevier Inc.**

Structure survey, Radiotherapy facility, Radiotherapy personnel, Radiotherapy equipment, Caseload.

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Conflict of interest: none.

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INTRODUCTION

The medical care systems of the United States and Japan have very different backgrounds. In 1990 the Patterns of Care Study (PCS) conducted a survey of the structure of radiation oncology facilities in 1989 for the entire census of facilities in the United States (1). In 1991 the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) conducted the first national survey of the structure of radiotherapy (RT) facilities in Japan based on their status in 1990, with the results reported by Tsunemoto (2). The first comparison of these two national structure surveys to illustrate and identify similarities and differences in 1989–1990 was conducted by Teshima *et al.* (3) and reported in 1996. The resultant international exchange of information proved especially valuable for Japan, because we could improve our own structure of radiation oncology based on those data.

The Japanese structure has gradually improved in terms of a greater number of cancer patients who are treated with radiation as well as public awareness of the importance of RT. The Japanese Society of Therapeutic Radiology and Oncology has conducted national structure surveys every 2 years since 1990 (4), and in 2006 an anticancer law was enacted in Japan, which strongly advocates the promotion of RT and an increase in the number of radiation oncologists (ROs) and medical physicists. The Japanese Ministry of Education, Sciences, and Sports is supporting the education of these specialists at university medical hospitals. Findings of international comparisons and the consecutive structural data gathered and published by JASTRO have been useful for an understanding of our current position and future direction (4, 5). In this report the recent structure of radiation oncology in Japan is analyzed and compared with the data of 2005 (5).

METHODS AND MATERIALS

From March to December 2008, JASTRO conducted a questionnaire based on the national structure survey of radiation oncology in 2007. The questionnaire dealt with the number of treatment machines by type, number of personnel by category, and number of patients by type, site, and treatment modality. To measure variables over a longer period of time, data for the calendar year 2007 were also requested. The response rate was 721 of 765 active facilities (94.2%). The data from 573 institutions (79.5%) were registered in the International Directory of Radiotherapy Centres in Vienna, Austria, in October 2008.

The PCS was introduced in Japan in 1996 (6–15). The Japanese PCS used methods similar to those of the American version, which used structural stratification to analyze national averages for the data in each survey item by means of two-stage cluster sampling. We stratified RT facilities throughout the country into four categories for the regular structure surveys. This stratification was based on academic conditions and the annual number of patients treated with radiation at each institution, because academic institutions require and have access to more resources for education and training whereas the annual caseload also constitutes essential information related to structure. For the study reported here, the following institutional stratification was used: A1, university hospitals/cancer centers treating 440 patients or more per year; A2, university hospitals/cancer centers treating 439 patients or fewer per year; B1, other national/public hospitals treating 140 patients or more per year; and B2, other national hospital/public hospitals treating 139 patients or fewer per year.

We used SAS 8.02 (SAS Institute, Cary, NC) (16) for statistical analyses, and statistical significance was tested by means of chi-square test, Student *t* test, or analysis of variance.

RESULTS

Current situation of radiation oncology in Japan

Table 1 shows that the numbers of new patients and total patients (new plus repeat) undergoing radiation in 2007 were estimated at 181,000 and 218,000, respectively, showing a 7.3% increase over 2005 (5). According to the PCS stratification of institutions, 40.1% of the patients were treated at academic institutions (Categories A1 and A2), even though these academic institutions constituted only 18.6% of the 765 RT facilities nationwide.

Table 1. Patterns of Care Study stratification of radiotherapy facilities in Japan

Institution category	Description	Facilities (*n*)	New patients (*n*)	Average new patients/facility* (*n*)	Total patients (new + repeat) (*n*)	Comparison with data of 2005† (%)	Average total patients/facility* (*n*)	Comparison with data of 2005† (%)
A1	UH and CC (≥440 patients/y)	71	49,866	702.3	60,398	10.0	850.7	2.3
A2	UH and CC (<440 patients/y)	71	17,974	253.2	21,867	2.1	308.0	−3.6
B1	Other (≥140 patients/y)	288	78,154	271.4	94,188	6.1	327.0	6.8
B2	Other (<140 patients/y)	291	24,235	83.3	28,634	9.6	98.4	8.8
Total		721	170,229‡	236.1	205,087‡	7.3	284.4	5.9

Abbreviations: UH = university hospital; CC = cancer center hospital; Other = other national, city, or public hospital.

* $p < 0.0001$.

† Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{data\ of\ 2007\ (n) - data\ of\ 2005\ (n)}{data\ of\ 2005\ (n)} \times 100\ (\%)$.

‡ The number of radiotherapy institutions was 765 in 2007, and the number of new patients was estimated at approximately 181,000; the corresponding number of total patients (new plus repeat) was 218,000.