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Diffusion-weighted MRI and PSA Correlations in Patients with Prostate Cancer Treated with Radiation and Hormonal Therapy

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Abstract. *Aim: To investigate the correlation between signal intensity (SI) on diffusion-weighted imaging (DWI) and the levels of prostate-specific antigen (PSA) in patients with prostate cancer treated with radiation and hormonal therapy. Patients and Methods: Forty-four patients with prostate cancer treated with hormonal therapy and radiation therapy were evaluated. Areas with high SI on DWI were detected and the apparent diffusion co-efficient (ADC) values were measured. The ADC values and PSA levels were compared between patients with high-DWI SI and patients with a normal DWI signal. Results: Fourteen patients had high SI on DWI. The mean ADC value in these cancerous lesions was lower than in non-cancerous tissues. The mean PSA level in patients with high-DWI SI was significantly higher than in patients with a normal signal. Conclusion: The present results suggest that SI on DWI appears to correlate with PSA levels in patients with prostate cancer treated with radiation and hormonal therapy.*

Prostate-specific antigen (PSA) is widely used for screening, diagnosis, determination of prognosis, selection of appropriate treatment, and for predicting disease status after treatment of prostate cancer in men (1).

Magnetic resonance imaging (MRI) is now a major imaging modality for prostate cancer detection and localization. MRI techniques have recently progressed, and can provide good quality diffusion-weighted images (DWI), especially with the use of parallel imaging techniques. DWI can be used to detect malignant tumours. Several investigators have reported on the potential usefulness of DWI for detecting prostate cancer that is in part due to the lower apparent diffusion co-efficient (ADC) values of tumor compared to the non-cancerous regions of the prostate (2-6). DWI may also provide qualitative and quantitative information for measuring therapeutic response in patients with prostate cancer during and after radiotherapy. On the contrary, imaging methods have not been widely used in daily practice to assess the effect of hormonal therapy or disease status after hormonal therapy in patients with prostate cancer. Furthermore, few investigations have reported on the usefulness of DWI for assessment of the radiation and hormonal therapy response for prostate cancer (7-10).

In the present study, the performance of DWI for visualizing prostate cancer treated with radiation and hormonal therapy was investigated, and the correlation between the signal intensity (SI) on DWI and the PSA levels was examined.

Patients and Methods

Patients. This study was approved by our Institutional Review Board. Written informed consent was waived because of the retrospective nature of the analysis. Between May 2007 and April 2010, 44 patients with biopsy-proven prostate cancer underwent hormonal therapy prior to radiation therapy, and underwent MRI examinations before and after radiation therapy. The median patient age was 72 years (range=55-81 years). The median Gleason score was 7 (range=5-9). The mean PSA level before all therapy was 31.4 ng/ml (range=5-270 ng/ml). Nineteen of the men were at high risk, 17 were at intermediate risk, and eight were at low risk according to the classification by D'Amico *et al.* (11). The mean PSA level after the start of hormonal therapy and before radiation therapy was 0.66 ng/ml (range=0.01-10.31 ng/ml). Table I presents the patients' characteristics. The median interval from prostate biopsy to MRI examination was 7.5 months (range=0.5-96.1 months). The median interval from the start of hormonal therapy to the start of radiation therapy was 6.4 months (range=0.2-83.6 months). All MRI were carried out before radiation therapy and 3 to 4 months after the completion of therapy.

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Key Words: Prostate cancer, hormonal therapy, radiation therapy, diffusion-weighted MRI, prostate-specific antigen.

All patients received hormonal therapy with a luteinizing hormone releasing-hormone analog and an anti-androgen. Radiation therapy was administered at 2 Gy/fraction to a total dose of 72-76 Gy (mean dose=75.4 Gy) with the use of 10-MV modulated radiation therapy.

MRI techniques. All images were collected using a 1.5-T MRI system (Intera Achieva; Philips Healthcare, Best, the Netherlands), equipped with a five-channel phased-array coil. All patients underwent DWI in addition to imaging studies using a routine prostate MRI protocol. Axial T1- and T2-weighted images and coronal T2-weighted images with spectral pre-saturation with inversion recovery (SPIR) were acquired.

Imaging parameters for T1-weighted imaging were as follows: repetition time/echo time (TR/TE)=497/12 ms, echo-train length (ETL)=5, bandwidth (BW)=217.7 kHz, field of view (FOV)=22 cm, slice thickness/gap=4/1 mm, number of excitations (NEX)=4, matrix size=288×288, and sensitivity-encoding (SENSE) factor=2. The time required to acquire the T1-weighted image set was 2 minutes and 47 seconds.

Imaging parameters for turbo spin-echo T2-weighted imaging were as follows: TR/TE=4700/120 ms, ETL=11, BW= 145.9 kHz, FOV=22 cm, slice thickness/gap=4/1 mm, NEX=4, matrix size=288×288, and SENSE factor=2. The time required to acquire the T2-weighted image set was 2 minutes and 44 seconds.

Axial echo-planar DWI with STIR was performed using slice locations similar to those used for T1- and T2-weighted image sequences, respectively, using the following parameters: b values=0, 800 and 2,000 s/mm2, TR/TE=6000/80 ms, TI=160-170 ms, BW=41.4 kHz, FOV=25 cm, slice thickness/gap=4/0.6 mm, NEX=3, matrix size=80×80, and SENSE factor=2. Motion-probing gradients were applied in three orthogonal orientations. ADC maps were automatically constructed on a pixel-by-pixel basis (0, 800 and 2,000 s/mm^2). The time required to acquire the DWI set was 5 minutes and 6 seconds.

Image analysis. All images were retrospectively analyzed by consensus by two radiologists, each with 16 years of experience, who were unaware of the clinical findings. The two readers did know that all patients in the study had biopsy-proven prostate cancer.

The readers first reviewed the axial DWI images obtained for each case using a b-value of 2000 s/mm^2, in order to identify areas suspicious for cancer. An area with focal high-SI relative to that of the surrounding prostate tissue was regarded as a cancerous lesion by consensus of the two readers. These images were reviewed in conjunction with the axial T1-weighted images and axial and coronal T2-weighted images to localize hemorrhage. An area with normal SI on DWI was regarded as non-cancerous prostate tissue. An area with diffuse high-SI in the peripheral zone on DWI was also regarded as non-cancerous tissue, since that area might be affected by hormonal therapy. The ADC values of the cancerous lesions and non-cancerous prostate tissue were measured by placement of regions of interest (ROIs). When the ROIs were drawn, great care was taken to exclude both the neurovascular bundle and the urethra. ROIs of cancerous lesions were drawn on ADC maps to include as much of the lesions as possible with the use of T2-weighted images to assist in the identification of the detailed anatomy of the prostate. ADC values of the lesions were assessed twice in the same site, and the average ADC value was calculated. For non-cancerous prostate tissue of the peripheral zone and transition zone, ROI circles were drawn in three different areas, and the ADC values were averaged.

Table I. *Characteristics of included patients.*

Characteristic	Value*
Age (years)	
Median	72
Range	55-81
Prostate-specific antigen level (ng/ml)**	
Mean	0.66
Range	0.01-10.31
Gleason score	
5	3
6	12
7	18
8	4
9	7

*Unless otherwise indicated, data represent the number of patients. **Before radiation therapy.

After radiation therapy, ADC values were measured for the cancerous lesions and non-cancerous prostate tissue. The ROI was drawn as much as possible in the same area that was initially used in the pre-radiotherapy images.

Statistical analysis. Statistical analysis was performed using the SPSS software (version 19.0J; SPSS Chicago, IL, USA). To compare the ADC values and PSA levels in patients with high SI on DWI and in patients with normal SI, the non-parametric Mann-Whitney test was used. The non-parametric Kruskal–Wallis test was used to compare the PSA levels in patients stratified by duration of hormonal therapy. The Wilcoxon signed rank test was used to compare the ADC values and PSA levels measured before and after radiation therapy. A correlation in the degree of change between serum PSA levels and ADC values was performed by use of the Pearson's correlation. A p-value of <0.05 was considered statistically significant.

Results

In 14 out of 44 patients, an area with high SI on DWI was detected (Figure 1). In these 14 patients, ten were at high risk and four were at intermediate risk for prostate cancer. The cancerous lesion was mainly detected within the peripheral zone in nine patients and in the transitional zone in five.

The mean ADC value of cancerous lesions was 0.76×10^{-3} mm^2/s, significantly smaller than that in non-cancerous prostate tissue ($1.07\times^{-3}$ mm^2/s) ($p<0.001$) (Figure 2a).

The mean PSA level in patients with high SI on DWI before radiation therapy was 1.88 ng/ml, significantly higher than that (0.08 ng/ml) in patients with normal SI on DWI ($p<0.001$) (Figure 2b).

The time from start of hormonal therapy to radiation therapy was within six months in 19 patients, six months to two years in 18, and more than two years in 7 patients. Mean PSA levels in the stratified patients were 1.07, 0.18 and 0.76 ng/ml respectively, and statistically significant differences were found ($p=0.001$).

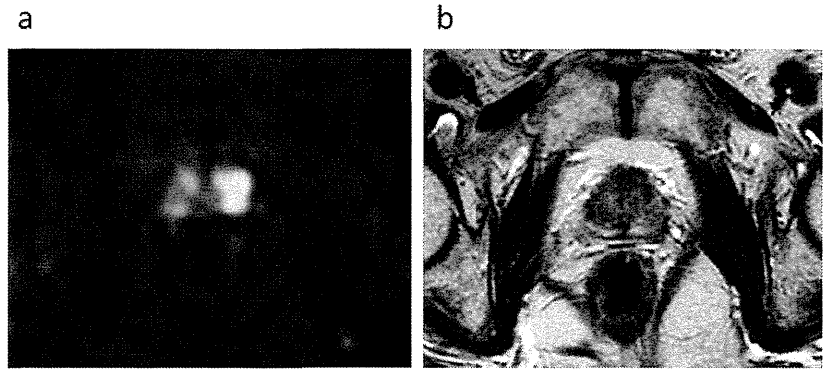

Figure 1. *A 74-year-old man with prostate cancer in the left peripheral zone. Prostate-specific antigen was 1.63 ng/ml before radiation therapy (160 ng/ml before all therapy) and the Gleason score was 8. T2-weighted image shows focal low-signal intensity in the left peripheral zone of the apex (a), and diffusion-weighted image shows focal high-signal intensity in the same region (b). The apparent diffusion co-efficient value of the lesion was* 0.642×10^{-3} *mm²/s.*

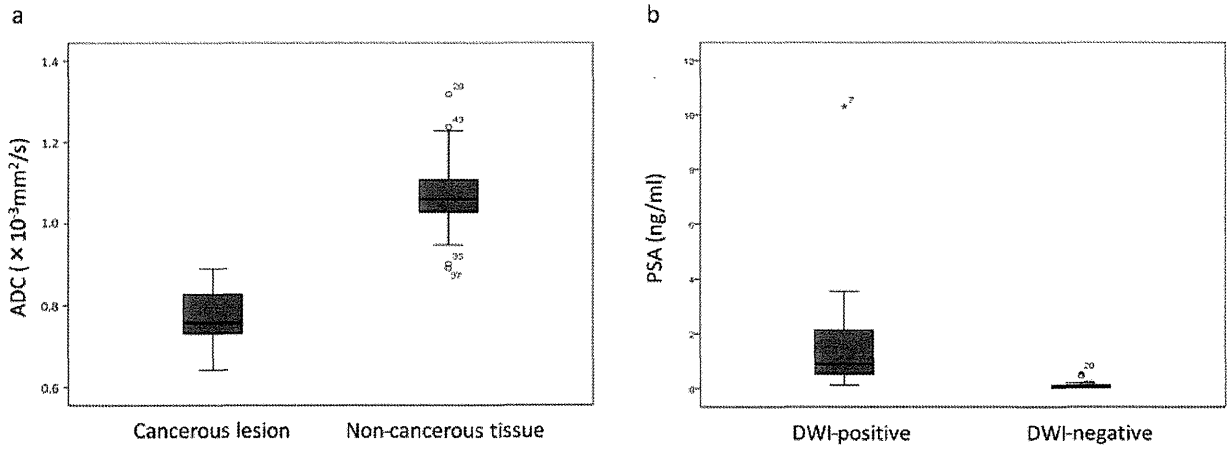

Figure 2. *Box and whisker plots illustrate the apparent diffusion co-efficient values (a) and prostate-specific antigen levels (b) in patients with high-signal lesion (the cancerous lesion) and normal signal (non-cancerous prostate tissue) on diffusion-weighted image. In this plot the horizontal lines outside each box indicate the minimum and maximum values, the box represent the value from the lower to upper quartile and is crossed by a line at the median value. Outliers are shown as dots.*

After radiation therapy, the mean ADC value of cancerous lesions increased significantly (1.02×10^{-3} mm²/s) (p=0.001) (Figure 3) and high-DWI SI disappeared. However, significant differences in the ADC values between cancerous lesions and non-cancerous tissue (1.14×10^{-3} mm²/s) remained. The mean ADC value of non-cancerous prostate tissue was statistically higher after radiation therapy (p<0.001), but the increase in the ratio was lower than in cancerous lesions.

After radiation therapy, the mean PSA level in patients with a high SI on DWI decreased significantly (0.2 ng/ml, p=0.002). The mean PSA level in patients with normal DWI signal did not change.

No correlation in the degree of changes between the PSA levels and ADC values was found (p>0.05).

Discussion

Several studies have shown that the ADC values of prostate cancer are lower than these of benign non-cancerous tissue (2-6), and, following treatment, tumor ADC values increase (7-10). This reflects increased water mobility through the loss of membrane integrity or an increase in the proportion of total extracellular fluid due to a decrease in cell size or number (12, 13).

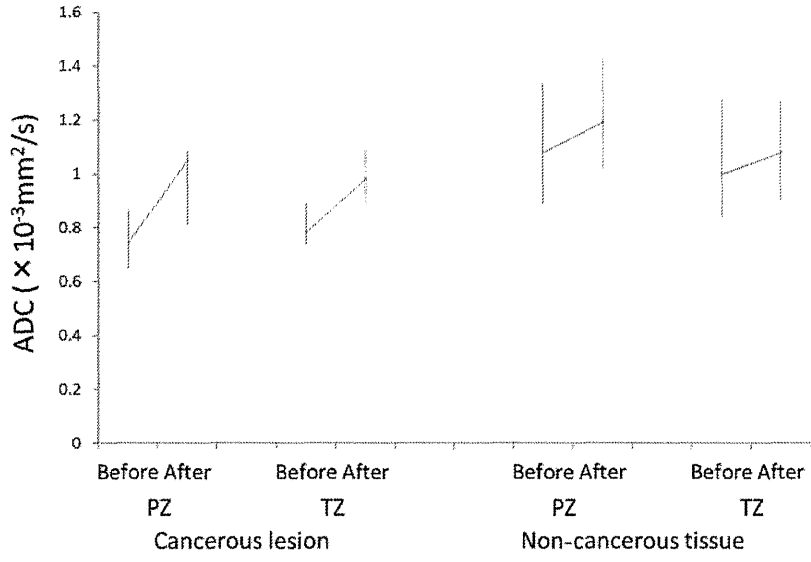

Figure 3. *Apparent diffusion co-efficient values of cancerous lesions and non-cancerous tissue before and after radiation therapy. ADC values of both cancerous lesions and non-cancerous tissue increased after radiation therapy, but the increase in the ratio of non-cancerous tissue was lower than that of cancerous lesions. PZ, Peripheral zone; TZ, transitional zone.*

The treatment effect of hormonal therapy for prostate cancer is usually evaluated with serum PSA. Imaging methods including MRI are not commonly used to monitor the treatment response in patients with prostate cancer because the measurement of PSA kinetics is simpler and more convenient. Nemoto *et al.* (10) reported that ADC values of prostate cancer increase after hormonal therapy.

In the present study, more than a quarter of the patients had areas with high SI on DWI that were regarded as cancerous lesions, despite hormonal therapy. In these patients, serum PSA levels were significantly higher than in patients with a normal DWI signal. This suggests that cancer viability remained in patients with high SI on DWI. ADC values increased significantly after radiation therapy in these patients, as has been seen in previous reports (7, 8). Thus, DWI could be used as an imaging biomarker to assess the therapeutic effect in patients with prostate cancer treated with hormonal and radiation therapy. Furthermore, as has been shown in previous reports (14-16), DWI might be used for predicting locally-recurrent prostate cancer after therapy.

The present results showed that the ADC values of non-cancerous prostate tissue also statistically increased after radiation therapy. As all patients received hormonal therapy prior to radiation therapy in the present study, the effect of hormonal therapy might remain during radiation therapy. These changes in ADC values might reflect the weakened hormonal therapy effect, especially in the peripheral zone. Several patients had an area with diffuse high-SI in the peripheral zone with relatively decreased volume and SI on T2-weighted images. These areas were excluded as cancerous lesions in order to avoid the hormonal therapy effect on normal tissue. In previous reports (17-19), histological findings in the prostate gland after hormonal therapy revealed marked glandular shrinkage, glandular atrophy, and fibrosis. These changes would be been expected to result in a smaller, darker prostate gland with relatively decreased ADC values before radiation therapy. Further investigation is needed for evaluating such ADC changes.

In the present study, all patients were treated with the same hormonal therapy but the different time from starting hormonal therapy to radiation therapy. The mean PSA levels were significantly higher in patients treated with hormonal therapy within six months or more than two years before radiotherapy. Possible reasons for this phenomenon include the following: the therapeutic effect of hormonal therapy may be inadequate when treated within six months, and PSA failure may arise when patients are treated for more than two years.

There are several limitations to this study. Firstly, no histopathological confirmation was obtained. Second, a *b* value of 2,000 s/mm^2 was used for DWI in spite of the fact that most previous reports have used a *b* value of 1,000 s/mm^2 for DWI, as is commonly used for other organs. Therefore, ADC values in the present study were relatively low compared with these of other studies; however, recent studies (20, 21) have shown that using a high *b* value of 2,000 s/mm^2 can

improve diagnostic performance in prostate cancer detection.

In conclusion, the present results suggest that SI on DWI appears to correlate with PSA levels for prostate cancer treated with radiation and hormonal therapy. ADC values appear to be useful for monitoring the therapeutic response of prostate cancer.

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Analysis of late toxicity associated with external beam radiation therapy for prostate cancer with uniform setting of classical 4-field 70 Gy in 35 fractions: a survey study by the Osaka Urological Tumor Radiotherapy Study Group

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We aimed to analyse late toxicity associated with external beam radiation therapy (EBRT) for prostate cancer using uniform dose-fractionation and beam arrangement, with the focus on the effect of 3D (CT) simulation and portal field size. We collected data concerning patients with localized prostate adenocarcinoma who had been treated with EBRT at five institutions in Osaka, Japan, between 1998 and 2006. All had been treated with 70 Gy in 35 fractions, using the classical 4-field technique with gantry angles of 0°, 90°, 180° and 270°. Late toxicity was evaluated strictly in terms of the Common Terminology Criteria for Adverse Events Version 4.0. In total, 362 patients were analysed, with a median follow-up of 4.5 years (range 1.0–11.6). The 5-year overall and cause-specific survival rates were 93% and 96%, respectively. The mean ± SD portal field size in the right–left, superior–inferior, and anterior–posterior directions was, respectively, 10.8 ± 1.1, 10.2 ± 1.0 and 8.8 ± 0.9 cm for 2D simulation, and 8.4 ± 1.2, 8.2 ± 1.0 and 7.7 ± 1.0 cm for 3D simulation ($P < 0.001$). No Grade 4 or 5 late toxicity was observed. The actuarial 5-year Grade 2–3 genitourinary and gastrointestinal (GI) late toxicity rates were 6% and 14%, respectively, while the corresponding late rectal bleeding rate was 23% for 2D simulation and 7% for 3D simulation ($P < 0.001$). With a uniform setting of classical 4-field 70 Gy/35 fractions, the use of CT simulation and the resultant reduction in portal field size were significantly associated with reduced late GI toxicity, especially with less rectal bleeding.

Keywords: prostate cancer; late toxicity; portal field size; CT simulation; external beam radiation therapy

INTRODUCTION

Since radiotherapy for prostate cancer is a standard treatment option for localized prostate cancer, its toxicity should be clearly addressed. In a previous survey study conducted from 1995 to 2006 in Osaka, Japan, which was intended to clarify time trends in radiotherapy and its biochemical relapse-free survival (bRFS) outcomes, we made the interesting discovery that 87% of patients had been treated with a highly uniform mode of radiotherapy, that is,

with classical 4-field 70 Gy in 35 fractions [1]. While that study was being conducted, CT simulation was introduced and developed, and almost all institutions had replaced 2D simulation with 3D simulation by 2006. This resulted in a reduction in the size of the portal field. We realized that we could obtain very pure data for an investigation of the relationship between portal field size and late toxicity rate, especially for rectal bleeding, in view of the uniform setting of dose-fractionation and beam arrangement. The findings of this investigation are the main subject of this article. Dearnaley *et al.* had already conducted a prospective randomized trial comparing 1.0 and 1.5 cm margins, and concluded that a larger margin was associated with significantly higher incidence of toxicities [2]. However, their study included only 126 patients, who had been assigned to 2×2 arms (64 Gy and 74 Gy groups, and 1.0 and 1.5 cm margin groups). Moreover, their treatment planning included two phases comprising a 3-field phase and a 6-field phase. We aimed to repeat the investigation with a larger Japanese patient cohort, treated with more uniform dose-fractionation and beam arrangement, although in a retrospective manner.

MATERIALS AND METHODS

A brief summary of the previous survey study

In our previous study [1], data were collected for 652 consecutive patients with clinically localized prostate cancer (T1-4N0M0), who had been treated with definitive external beam radiotherapy (EBRT) of 60 Gy or more at one of the 11 participating institutions, mainly in Osaka, Japan, from 1995 through 2006. Of the 652 patients, 436 met the enrolment criteria and were analysed. The main findings were: (i) the number of radiotherapy patients showed a 10-fold increase over 10 years; (ii) the dominant dose-fractionation was 70 Gy/35 fractions (87%); (iii) hormone therapy had been administered to 95% of the patients; (iv) the 3- and 5-year bRFS rates were 85% and 70%, respectively; (v) toxicity data was not available.

An interesting finding was that as many as 87% of the patients had received radiotherapy in a highly uniform manner, that is, with the classical 4-field technique using a dose-fractionation schedule of 70 Gy/35 fractions. We therefore planned the second survey by focusing on detailed late toxicity data and irradiation field data obtained with a uniform setting of 4-field 70 Gy/35 fractions.

Data collection

Five institutions participated in the present study. Data collected for the 362 patients who are the subject of this study are described in the Results section.

All the data were collected by physicians (radiation oncologists or urologists), who are also the authors of this paper, and no non-physician surveyors took any part in this study. Detailed information was collected about portal field size and other parameters of radiotherapy. Late toxicity grading was performed by retrospectively reviewing medical charts, strictly according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The concrete description of each relevant CTCAE Term was gathered as Tables 1 and 2, which had been distributed to the surveyors as references. All data were sent to Osaka University, analysed by the first author, and finally reviewed and approved by all the authors.

Statistical Analysis

The unpaired *t* test was used to compare the averages of the two groups, while Fisher's exact test was used to compare the proportions. Kaplan-Meier curves were obtained for survival and toxicity rates, and the log-rank test was used to compare them. A P-value <0.05 was deemed statistically significant. Statistical analysis was performed with PASW Statistics 18 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Data for a total of 362 patients, all of whom had been treated for T1-4N0M0 adenocarcinoma of the prostate between 1998 and 2006, were collected from five representative institutions in Osaka, Japan. Postoperative cases were not included. None of the patients had been irradiated to the elective lymph node region, and all had been treated with the classical 4-field technique using 70 Gy in 35 fractions with gantry angles of 0°, 90°, 180° and 270°.

The median and mean ages of the patients were both 70 years (range, 49–82). The median follow-up period was 4.5 years (range, 1.0–11.6), with a minimum of 1 year. The actuarial 5-year overall and prostate cancer-specific survival rates were 93% and 96%, respectively (Fig. 1).

Neoadjuvant hormone therapy had been administered to 328 patients (91%), 35 of whom (11 %) had been considered hormone-refractory at the time of radiotherapy. Adjuvant hormone therapy had been administered to 276 of the total of 362 patients (76%), and 179 of them (65%) had already discontinued the therapy at the time of this survey. The median durations of neoadjuvant and adjuvant hormone therapy were 8 months (range, 1–150) and 24 months (range, 1–129), respectively.

2D simulation was performed for 127 patients, all of whom had been treated between 1998 and 2003. The other 235 had been treated using 3D simulation with a CT-simulator between 1998 and 2006. Of the five institutions, three had a 1 cm-width multileaf collimator (MLC), one a 2-cm MLC and one a 1-cm MLC until 2006, which was then replaced with a 0.5-cm MLC. The energy of the anterior-posterior beam was 10 MV at four institutions, and 20 MV at one. The energy of the lateral beams was 10 MV at three institutions, and 18 MV and 20 MV at one each. A

Table 1. Late genitourinary toxicity scale extracted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Renal and urinary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	–	–	–
Definition: A disorder characterized by urination at short intervals.					
Urinary incontinence	Occasional (e.g. with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g. clamp, collagen injections); operative intervention indicated; limiting self care ADL	–	–
Definition: A disorder characterized by inability to control the flow of urine from the bladder.					
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g. hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Continued

Table 1. *Continued*

Renal and urinary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	–	–	–
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	–	–	–	–
Definition: A disorder characterized by a change in the color of the urine.					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Table 2. Late gastrointestinal toxicity scale extracted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region.					
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin.					
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region.					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the anus.					
Anal necrosis	–	–	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by necrotic process occurring in the anal region.					
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–
Definition; A disorder characterized by a sensation of marked discomfort in the anal region.					
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention	Life-threatening consequences; urgent operative intervention indicated	Death

Continued

Table 2. *Continued*

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
			indicated; TPN or hospitalization indicated		
Definition: A disorder characterized by a narrowing of the lumen of the anal canal.					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	–	–
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by bleeding from the hemorrhoids.					
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	–	–
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileus	–	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g. rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum.					
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site.					
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharge from the anus.					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the rectum.					
Rectal necrosis	–	–	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall.					
Rectal obstruction	Asymptomatic; clinical or	Symptomatic; altered GI	Hospitalization indicated;	Life-threatening consequences;	Death

Continued

Table 2. *Continued*

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
	diagnostic observations only; intervention not indicated	function; limiting instrumental ADL	elective operative intervention indicated; limiting self care ADL; disabling	urgent operative intervention indicated	
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region.					
Rectal perforation	–	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall.					
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum.					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

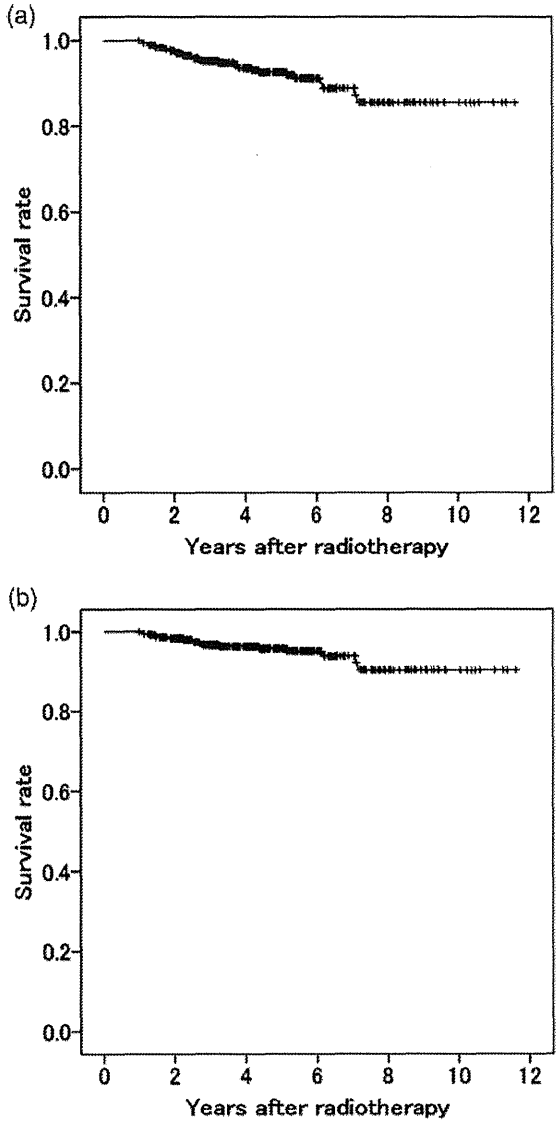

Fig. 1. (a) The 5-year overall survival rate was 93%. (b) The 5-year prostate cancer-specific survival rate was 96%.

field-shrinking technique was used for almost all patients (357 of 362, or 99%), once for 340 (94%) and twice for the other 17 (5%). The first shrinking was performed at 60 Gy for 219 patients (61%), at 50 Gy for 76 (21%), at 40 Gy for 42 (12%), and at other doses for 20 patients (6%). The second shrinking was performed at 60 Gy for 12 patients (71%), at 66 Gy for 4 (24%), and at 50 Gy for 1 (6%).

For the original irradiation field, three institutions defined the clinical target volume (CTV) as the prostate plus the whole seminal vesicle (SV), and the other two institutions as the prostate plus a part of SV. As for the shrinking field, three institutions defined the CTV as the prostate plus a part of SV, and the other two as the prostate only. In the original field, the median margin (distance from the CTV to the block edge) was 1.5 cm (range, 1.5–3.0) except for in the posterior (rectal) direction, where it was 1.3 cm (range, 1.0–2.0). As for the shrinking field, the median margin was 1.3 cm (range, 1.0–2.0) except for in the posterior direction, where it was 0.8 cm (range, 0.6–1.5). In 2D simulation, a Foley catheter was placed and contrast medium was administered into the bladder and rectum for visualization, trying to keep the definition of CTV and field margin described as above as much as possible. Retrograde urethrography was not performed routinely.

The use of the CT-simulator significantly reduced the irradiation field size compared to that used for 2D simulation (Table 3). The mean ± standard deviation (SD) of the distance between block edges in the right–left (RL) direction was 10.8 ± 1.1 cm for 2D simulation compared to 8.4 ± 1.2 cm for 3D (CT) simulation ($P < 0.001$). The corresponding values in the superior–inferior (SI) direction were 10.2 ± 1.0 cm and 8.2 ± 1.0 cm ($P < 0.001$), and in the anterior–posterior (AP) direction 8.8 ± 0.9 cm and 7.7 ± 1.0 cm ($P < 0.001$).

Findings for toxicity are shown in Table 4. The maximum CTCAE Version 4.0 Grade toxicity was observed in the form of late genitourinary (GU) toxicity, late gastrointestinal (GI) toxicity including rectal bleeding, and late rectal bleeding alone. No Grade 4 or 5 late toxicity was observed; 5 patients (1%) suffered Grade 3 GU late toxicity and 10 (3%) Grade 3 GI late toxicity, all of which consisted of rectal bleeding; 14 patients (4%) suffered Grade 2 GU late toxicity and 35 (10%) Grade 2 late GI toxicity, 32 (9%) of which consisted of rectal bleeding. The actuarial 2-, 3-, and 5-year Grade 1–3 GU late toxicity rates were 13%, 17% and 23%, respectively, and the corresponding figures for Grade 2–3 were 2%, 4% and 6% (Fig. 2). The 2-, 3-, and 5-year Grade 1–3 GI late toxicity rates were 30%, 33% and 36%, respectively, and the corresponding figures for Grade 2–3 were 13%, 14% and 14% (Fig. 3). The 2-, 3-, and 5-year Grade 1–3 late rectal bleeding rates were 26%, 30% and 31%, respectively, and the corresponding figures for Grade 2–3 were 12%, 13% and 13%.

When the patients were divided into a 2D- and a 3D-simulation group, the respective 2-, 3- and 5-year Grade 1–3 GI toxicity rates were 35%, 38% and 41% for 2D, and 27%, 31% and 32% for 3D ($P = 0.083$). The corresponding figures for Grade 2–3 were 21%, 23% and 23% for 2D, and 9%, 9% and 9% for 3D ($P < 0.001$) (Table 3). Similarly, the respective 2-, 3- and 5-year Grade 1–3 rectal bleeding rates were 33%, 38% and 38% for 2D, and 23%, 26% and 28% for 3D ($P = 0.015$), and the corresponding figures for Grade 2–3 were 21%, 23% and 23% for 2D, and 7%, 7% and 7% for 3D ($P < 0.001$) (Fig. 4).

Table 3. Comparison of 2D simulation and 3D (CT) simulation

	2D ($n = 127$)	3D ($n = 235$)	*P*
Median follow–up period (range) (year)	5.9 (1.1–11.6)	4.0 (1.0–8.0)	<0.001
Hormone therapy			<0.001
None	1 (1%)	30 (13%)	
Neoadjuvant only	7 (6%)	43 (18%)	
Adjuvant only	1 (1%)	1 (0%)	
Both neoadjuvant and adjuvant	118 (93%)	161 (69%)	
Multileaf collimator width			<0.001
0.5 cm	0 (0%)	5 (2%)	
1.0 cm	127 (100%)	155 (66%)	
2.0 cm	0 (0%)	75 (32%)	
Portal filed size (cm)[a]			
Right-left (RL)	10.8 ± 1.1	8.4 ± 1.2	<0.001
Superior-inferior (SI)	10.2 ± 1.0	8.2 ± 1.0	<0.001
Anterior-posterior (AP)	8.8 ± 0.9	7.7 ± 1.0	<0.001
Grade 1–3 late gastrointesitinal toxicity rate (%)			0.083
at 2 years	35	27	
at 3 years	38	31	
at 5 years	41	32	
Grade 2–3 late gastrointesitinal toxicity rate (%)			<0.001
at 2 years	21	9	
at 3 years	23	9	
at 5 years	23	9	
Grade 1–3 late rectal bleeding rate (%)			0.015
at 2 years	33	23	
at 3 years	38	26	
at 5 years	38	28	
Grade 2–3 late rectal bleeding rate (%)			<0.001
at 2 years	21	7	
at 3 years	23	7	
at 5 years	23	7	

[a]Mean ± standard deviation.
Grade: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
Late gastrointestinal toxicity included late rectal bleeding.

DISCUSSION

To describe and analyse late toxicity is of the utmost importance for the use of radiation therapy for the treatment of prostate cancer. A number of publications have dealt with late toxicity in prostate radiotherapy [2–13]. However, most of these studies examined mixed populations with respect to prescribed dose, dose fractionation, or beam arrangements (for example, number of beam ports and their gantry angles). Therefore, the quantity of pure data for the effect of portal field size on late toxicity has been insufficient.

In Japan, prostate cancer was not considered to be a commonly occurring cancer until around 2000. Moreover, radical prostatectomy was preferred to radiotherapy by most urologists until that time [14]. However, the rate of prostate cancer incidence has been rapidly increasing recently [15], and at the same time, definitive radiotherapy has become

Table 4. Grade of late toxicity

	Late genitourinary toxicity		Late gastrointestinal toxicity		Late rectal bleeding	
	n	%	*n*	%	*n*	%
Grade 3	5	1	10	3	10	3
Grade 2	14	4	35	10	32	9
Grade 1	59	16	79	22	66	18
Grade 0	281	78	235	65	251	69
Missing	3	1	3	1	3	1
Total	362	100	362	101	362	100

Grade: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
Late gastrointestinal toxicity included late rectal bleeding.

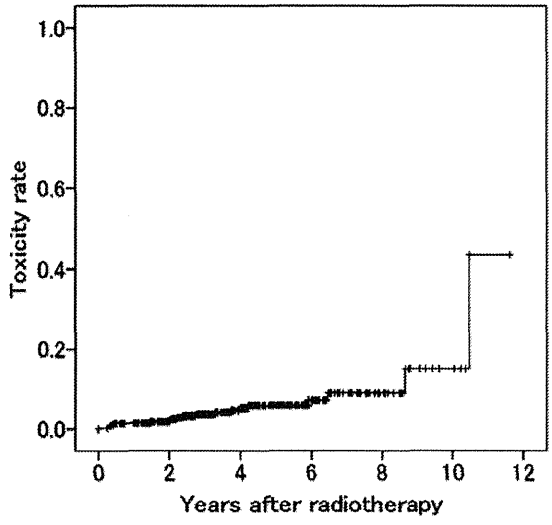

Fig. 2. Grade 2–3 late genitourinary toxicity. The 2-, 3- and 5-year toxicity rates were 2%, 4% and 6%, respectively.

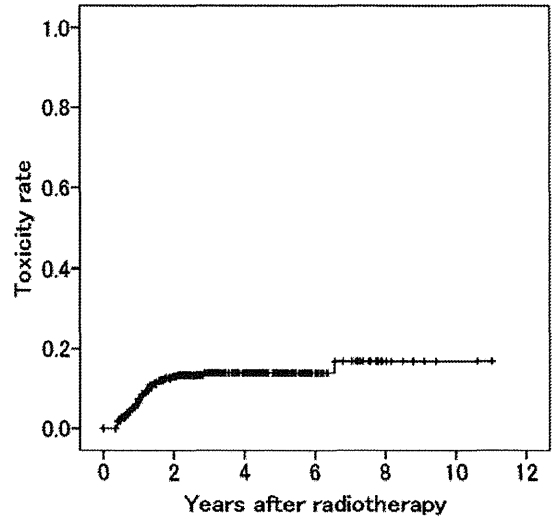

Fig. 3. Grade 2–3 late gastrointestinal toxicity. The 2-, 3- and 5-year toxicity rates were 13%, 14% and 14%, respectively.

the prevailing treatment mode. For these reasons, quite a few institutions did not have much experience with definitive radiotherapy for prostate cancer around 2000, when the subjects of our study were treated (1998–2006). Five representative institutions in the Osaka area, where radiation oncologists who had been trained at Osaka University were employed, participated in this study. These oncologists principally followed the same procedure as the one used at Osaka University, that is, the classical 4-field technique using anterior–posterior and lateral beams with 70 Gy in 35 fractions regardless of T-stage, Gleason Score or pretreatment prostate-specific antigen level. In fact, we found that 378 of all 436 patients (87%) enrolled in the previous survey study of ours had been treated with the same dose-fractionation of 70 Gy in 35 fractions. In view of this finding, we decided to embark upon this second survey to investigate solely the relationship between portal field size and late toxicity for a uniform setting of dose and beam arrangements.

To the best of our knowledge, our study cohort is one of the largest series treated with a uniform dose-fractionation and irradiation technique (classical 4-field technique). Moreover, all the institutions changed their simulation method from simple X-ray film-based simulation (2D) to CT simulation (3D) by the end of data acquisition for this study, which enabled us to compare the field size of 3D and 2D simulation. The results were very clear and easy to understand: 3D simulation reduced the field size significantly, as well as the rate of GI late toxicity, especially rectal bleeding. The reason for this improvement is deemed

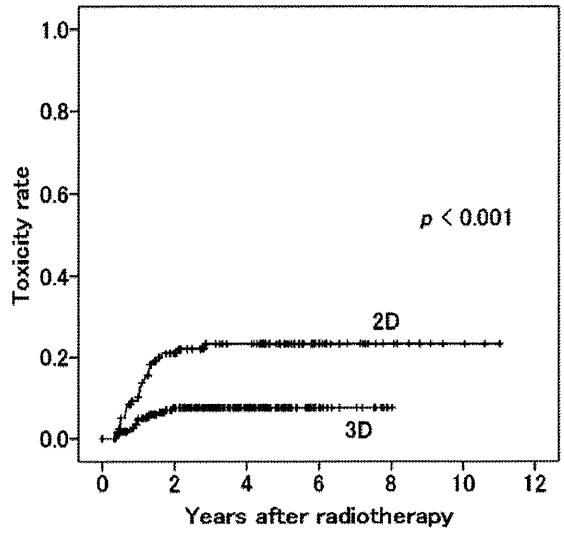

Fig. 4. Grade 2–3 late rectal bleeding. The 2-, 3- and 5-year occurrence rates were 21%, 23% and 23% for 2D simulation, and 7%, 7% and 7% for 3D simulation, respectively ($P < 0.001$).

to be simply that with the smaller irradiation field the rectum could be largely avoided. There might be a speculation that not only field sizes but also the width of the MLC made an impact on the toxicities. We analysed the influence of the width of the MLC, but no statistically significant impact was detected (data not shown), we think because the number of patients treated with other than 1 cm-width MLC was too small compared to the 1 cm-width group. This issue should be addressed with other cohorts in other studies.

A strength of this study may well be that the surveyors were all physicians: no non-physicians participated. Moreover, they were mostly the same physicians that had treated the patients who were the subject of this paper. This makes a high degree of accuracy likely for the data collection, although it should be noted that this study was of a retrospective nature. On the other hand, a variation was observed in the incidence rate of Grade 1 toxicity among the five institutions as follows; 14–33% for 5-year Grade 1 GU late toxicity, 17–36% for GI and 13–30% for rectal bleeding. This variation might indicate that the incidence rate of Grade 1 depended on and was influenced by the physicians who followed up patients, especially in a retrospective analysis; therefore, the significance of the figures presented as Grade 1 toxicity should be considered as relatively low.

The rate of Grade 2–3 late toxicity detected in our study was similar to, or slightly higher than, the findings of other studies in the literature. Dearnaley *et al.* [6] reported that, in their randomized controlled trial in which all patients were treated with 64 Gy, radiation-induced Grade 2 or higher proctitis and bleeding occurred in 5% in the conformal group compared to 15% in the conventional group ($P = 0.01$). They found no difference between groups in bladder function after treatment (20 vs. 23% for Grade 2 or more, $P = 0.61$). It should be noted, however, that the toxicity scales used for their study were the Radiation Therapy Oncology Group (RTOG) criteria [16]. Morris *et al.* [7] conducted an evidence-based review of 3-dimensional conformal radiotherapy (3D-CRT) as part of an American Society for Radiation Oncology (ASTRO) outcomes initiative. In the Task Force Conclusion, they stated that 3D-CRT reduces late morbidity, particularly GI late morbidity, with the dose to the rectum limited. No benefits in terms of GU symptoms or sexual function were observed. Their conclusion thus shows good agreement with ours. Zelefsky *et al.*, in their reports of the long-term results for 3D-CRT [8] and intensity-modulated radiotherapy (IMRT) [9] noted that, with 3D-CRT, the 5-year actuarial likelihood of Grade 2 and 3 late GI toxicities was 11% and 0.75%, respectively, while the corresponding findings for GU were 10% and 3%. With IMRT, the 10-year actuarial likelihood of Grade 2 and 3 late GI toxicities was 2% and 1%, respectively, while the corresponding findings for GU were 11% and 5%. The shapes of their actuarial toxicity curves resembled those of ours. That is, the GI toxicity curve reached a plateau at 2 or 3 years after radiotherapy, while the GU toxicity curve gradually rose until 10 years or more after radiotherapy. However, none of these studies provided detailed information on portal field size or its relation to late toxicity.

Dearnaley *et al.* had addressed this issue by a prospective randomized trial comparing 1.0 and 1.5 cm margins, arriving at the conclusion that the larger margin had been associated with the significantly higher incidence of toxicities [2]. However, their study had included only 126 patients, who had been assigned to 2×2 arms (64 Gy and 74 Gy groups, and, 1.0 and 1.5 cm margin groups). Moreover, their treatment planning had included two phases comprising a 3-field (anterior and left/right lateral or posterior oblique fields) phase and a 6-field (left and right, anterior/posterior oblique and lateral fields) phase. Although those patients had been randomly assigned, such critical heterogeneity of the cohort in total dose (64 Gy and 74 Gy) and treatment planning approach (3-field and 6-field) might make the interpretation complicated in terms of reproducibility. We considered that our current study could still add information and complement the conclusion drawn by Dearnaley *et al.*, because it included a significantly larger number of patients (362 patients) and the treatment was in a more homogeneous manner (all with 70 Gy by 4-field) in spite of its weakness as a retrospective study.

The main criticism of our study might be that the kind of data on which it is based is so classical that no direct clinical indicators such as V_{40Gy} or V_{65Gy} of the rectum, could

be provided as dose-volume constraints for modern 3D treatment planning for 3D-CRT or IMRT. However, the authors believe that the data presented here are still meaningful in terms of (i) describing a certain era of Japanese standard practice, (ii) providing radiation oncologists and treatment planners with a valuable reference because of the clear correspondence between a given portal field size (as a final block-to-block distance that would be relevant even for the most up-to-date irradiation technology) and a given rate of late toxicity, and (iii) providing suggestions for newly emerging irradiation technique in terms of a tolerance level that should not be exceeded, as detailed next.

CONCLUSION

In conclusion, we investigated late toxicity associated with EBRT for prostate cancer under conditions of a uniform setting of classical 4-field 70 Gy in 35 fractions. The use of CT simulation and the resultant reduction in the portal field size were significantly associated with diminished GI late toxicity, especially with less rectal bleeding. Typically, the field size was significantly reduced from $10.8 \times 10.2 \times 8.8$ cm (2D simulation) to $8.4 \times 8.2 \times 7.7$ cm (3D simulation), and at the same time, the rate of Grade 2–3 late rectal bleeding was significantly reduced from 23% to 7%. In view of the high overall and cause-specific survival rates observed in our study, any novel innovative radiotherapy should not exceed a late toxicity level of 7% for Grade 2–3 rectal bleeding in order to improve the quality of life of the patients or at least keep it the same as with "classical radiotherapy".

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Treatment Outcome of Elderly Patients With Glioblastoma who Received Combination Therapy

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Objectives: Large population-based registries in Western countries show that the treatment strategy for glioblastoma multiforme (GBM) in elderly patients is likely less intensive. The purpose of this study was to clarify the treatment outcome of elderly patients with GBM and to explore appropriate treatment strategies.

Methods: We analyzed records from 86 patients (median age, 59 y; range, 9 to 77 y) diagnosed and histologically confirmed to have GBM, between January 1991 and June 2006 at our institutions; 14 elderly patients (range, 71 to 77 y) and 72 younger patients (range, 9 to 70 y). Fifty-two patients underwent total or subtotal resection and 34 patients underwent partial resection or biopsy. The median radiation dose was 54 Gy and 79 patients (92%) received anticancer agents.

Results: Among the 51 patients in recursive partitioning analysis (RPA) classes 5 and 6, the median survival time of the 12 elderly and 39 younger patients were 10.5 months [95% confidence interval, 5.8-12.8] and 11.7 months (95% confidence interval, 9.3-13.0), respectively ($P = 0.32$). Multivariate analysis showed only RPA class as an independent prognostic factor for overall survival rate ($P = 0.009$), whereas age ($P = 0.85$), total radiation dose ($P = 0.052$), and treatment with anticancer agents ($P = 0.32$) were not.

Conclusions: After adjustment for RPA class, the treatment outcome of patients aged >70 years was equal to that of younger patients. Definitive treatment should not be withheld based on age alone.

Key Words: glioblastoma, prognostic factor, radiotherapy, elderly patients

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Glioblastoma multiforme (GBM) is the most common glioma, occurring more often in patients in their 60s and 70s.[1,2] GBM is a rapidly progressive brain tumor, and the standard of care includes surgery, postoperative radiotherapy, and systemic chemotherapy.[1,3–6] In most clinical trials, the optimal treatment has been offered to only a selected subgroup of patients with GBM, such as those aged <70 years and with a good performance status (PS).[4,7] There is little information to define the standard of care for elderly patients with GBM.[6,8,9] Large population-based cancer registries in Western countries show that the treatment strategy for GBM in patients aged >70 years is likely to be less intensive and more palliative.[1,10] Data from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results program showed that a total of 1412 patients with GBM (35%) received neither radiation nor chemotherapy, and patients who were elderly, unmarried, or had more comorbidities were less likely to receive radiotherapy and chemotherapy.[10,11] The cancer registry in Switzerland showed that although 56% of patients with GBM, aged 65 to 74 years, underwent surgery followed by radiotherapy, radiotherapy alone, or surgery alone, only 25% of the patients aged >75 years underwent surgery and/or radiotherapy.[12]

Some retrospective studies have shown that aggressive treatment is associated with prolonged survival in elderly patients with GBM. A study at the Memorial Sloan-Kettering Cancer Center demonstrated that, similar to studies in younger patients with GBM, age, PS, and extension of surgery were independent prognostic factors for treatment outcome of elderly patients, and emphasized that age alone should not disqualify patients from aggressive-combined treatment.[10] Results from the Cleveland Clinic showed that elderly patients aged >70 years with good PS, treated aggressively with maximal resection and definitive radiotherapy survived longer than those who received palliative radiotherapy and biopsy.[8] More prospective and retrospective studies are needed to establish the standard of care for elderly patients with GBM.

The purpose of this retrospective study was to clarify the treatment outcome of patients with GBM aged >70 years who received combination therapy, and to explore appropriate treatment strategies for elderly patients.

MATERIALS AND METHODS

We analyzed records from 86 patients (median age, 59 y; range, 9 to 77 y) who were diagnosed and histologically confirmed to have GBM between January 1991 and June 2006 at our institutions. Fourteen patients were aged >70 years (elderly patients; range, 71 to 77 y) and 72 patients were aged ≤70 years (younger patients; range, 9 to 70 y). Forty-six patients (53%) had good PS scores (0 to 1), whereas 40 (47%) had poor PS scores (2 to 4). The median preoperative tumor size was 4.5 cm (range, 1.4 to 8 cm; Table 1). Fifty-two patients (60%) underwent total or subtotal resection, and 34 (40%) underwent partial resection or biopsy. There was no difference in extension of surgery between elderly and younger patients ($P = 0.55$). O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was not assessed in all patients.

Radiotherapy started within 6 weeks postoperatively. As a basic procedure, clinical target volume was based on

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